

# Is tumor size a reliable predictor of histopathological characteristics of renal cell carcinoma?

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## Abstract

**Objectives:** To determine whether smaller tumor size is associated with less-aggressiveness in renal cell carcinoma (RCC).

**Materials and Methods:** Series records of 505 patients diagnosed with RCC were retrospectively reviewed and the data concerning tumor size and pathological information were extracted and analyzed.

**Results:** Five hundred and eight RCCs were identified. The mean tumor size was  $5.02 \pm 2.70$  cm. No correlation was detected between the size of tumor and the histological subtype. The overall nuclear grade distribution was 57.1% and 42.9% for low-grade and high-grade disease, respectively. Each 1 cm increase in tumor size was associated with a significant increase in the odds ratio of high-grade disease by 1.46. 91.1% were found low-stage lesions and the odds ratio for the association of high-stage disease with each 1 cm increase in tumor size was 1.67. Multinomial models revealed that each 1 cm increase in the tumor size was associated with a 35% increase in renal capsule involvement and 66% renal vascular invasion. The cut-off point of tumor size in renal vascular invasion was 5.6 cm.

**Conclusion:** Tumor size is not an independent predictor for the histological subtype of RCC. However, it is closely correlated to histopathological features, with the indications that the greater the tumor size, the more aggressive potential the RCC is.

**Key Words:** Pathology, renal cell carcinoma, size

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## INTRODUCTION

In the last two decades, increasing using of cross-sectional imaging modalities has led to an increased incidence of serendipitously discovered renal cell carcinoma (RCCs) trending small size.<sup>[1]</sup> The management toward these small tumors is also changing. Nephron-sparing surgery (NSS) is frequently recommended for selected candidates with small

renal mass.<sup>[2]</sup> Modern techniques provide the patients with other minimal invasive procedures as well, such as ablation and active surveillance. Recent data from a series of 105 patients who underwent radiofrequency ablation showed a short-term tumor control of 90%.<sup>[3]</sup> For elderly or infirm patients with a short life expectancy or those with masses that are 1 cm in diameter or smaller, active surveillance is also an attractive option.<sup>[4]</sup> However, on decision making, the pathological characteristics are not available because pre-operative biopsy is not routinely performed and is considerably false-negative. Are these options being supported histopathologically? Can we predict that the RCCs we detected are an aggressive tumor that will grow fast, invade adjacent structures and produce metastasis or an indolent one? Is bigger tumor associated with higher aggressiveness or vice versa? The dilemma is whether a weakened constitutional patient with a newly diagnosed

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renal mass that is diagnosed as malignant from radiographic characteristics under active surgical intervention bring much more benefits than surveillance? Although previous studies have demonstrated that risk of high-grade tumors increased with tumor size,<sup>[5,6]</sup> Hu reported that smaller tumors (<3 cm) were of significant percentage to have high nuclear and high Tumor, lymph nodes and metastasis (TNM) stage (2002 TNM classification) with no difference on comparison with larger tumors (3–5 cm).<sup>[7]</sup> To clarify these issues and provide more evidence for pre-operative prediction and decision making, we conducted this study by examining a series of RCCs resected in our institution and determining whether the tumor may be small with high grade or very huge with low grade.

## MATERIALS AND METHODS

We retrospectively reviewed the records of patients who underwent radical nephrectomy or NSS for renal tumors with confirmed pathological diagnosis of RCCs between January 2008 and June 2010. Patients with cystic lesion, pre-operative arterial embolization, positive surgical margins or known hereditary disease such as Von Hippel-Lindau and tuberous sclerosis were excluded. The tumor size was defined as the largest transaxial diameter on specimen. All histopathological specimens were reviewed by urological pathologists and histological subtype was classified following the 2004 WHO classification of RCCs. Papillary RCCs was defined as a tumor with largest diameter larger than 5 mm, and those of less than 5 mm considered papillary adenoma were excluded. The Fuhrman nuclear grading system and the 2009 updated TNM classification system were applied to all the RCCs.<sup>[8]</sup> In cases with intermediate nuclear grade, lesions were assigned into the higher of the two grades. Tumors of Fuhrman I/II were considered low-grade disease and tumors of Fuhrman III/IV were considered high-grade disease. Similarly, tumors of T1/2 were categorized into low-stage disease and of T3/4 were considered high-stage disease. In patients with multiple unilateral tumors of the same histological subtype, the largest tumor was included. In patients with multiple unilateral tumors of different subtypes or bilateral tumors, all tumors were included.

Tumor size was analyzed as a continuous variable and as a categorical variable; stratifying into different size range with the intervals of 1 cm. Size of the tumors was categorized into 4 cm or less, 4–7 cm and larger than 7 cm as well. All categorical variables were analyzed by the two-tailed Fisher exact test, Chi-square test or MU test, as appropriate. All continuous variables were analyzed by either the two-tailed Student's *t* test or one-way analysis of variance, as appropriate. The relationship between tumor size and histological subtype, nuclear grading, TNM classification and other related histopathological features were analyzed by means of a logistic regression model. OR value was also evaluated in the correlated histopathological features

according to tumor size. Statistical analyses were performed using SPSS software package version 13.0 (Statistical Package for Social Science™, Chicago, IL, USA) and  $P < 0.05$  was considered to be statistically significant throughout this study.

## RESULTS

A total of 508 RCCs were identified in 505 patients for one patient with bilateral tumors and another two had unilateral tumors with different subtypes. Mean age for all patients was 54.12 years (10–87 years) and no difference was found in age between male and female (55.62 vs 51.56;  $P = 0.135$ ) patients. A summary of other demographic information was presented in Table 1. Renal capsule was found to be involved in 289 tumors. In stage T3, 24 out of the 41 patients had vascular invasion and the rest were of perinephric fat involvement. All five T4 patients were detected with tumors extended into the ipsilateral adrenal gland. Twenty-seven patients were found with confirmed renal vascular invasion. No Greta's fascia was found to be involved. All tumors were screened with no nodes' or distant metastasis.

The mean tumor size for all 508 tumors was  $5.02 \pm 2.70$  cm (1–20.5 cm). Table 2 depicted the proportion of different subtypes of RCCs according to tumor size. 82.7% of the included tumors were clear cell; there was statistical discrepancy in the proportion between clear cell and non-clear cell RCCs

**Table 1: Demographic information of all patients and tumors**

	No. of patients/tumors	Tumor size	P value
No. of patients	505		0.419
Male	318	4.95 ± 2.52 cm	
Female	187	5.12 ± 2.99 cm	
No. of tumors	508		0.578
Side			
Left	272	5.08 ± 2.75 cm	
Right	236	4.95 ± 2.64 cm	
Histological subtype			0.003
Clear cell	420	4.91 ± 2.55 cm	
Papillary cell	19	4.92 ± 2.86 cm	
Chromphobe cell	10	8.17 ± 4.02 cm	
Unclassified	10	8.35 ± 4.42 cm	
Multiple cystic	3	3.400 ± 96 cm	
XP11.2 translocation	1		
Unclear	45		
Fuhrman grading			<0.001
I	24	3.43 ± 1.74 cm	
II	266	4.33 ± 1.98 cm	
III	185	5.69 ± 2.86 cm	
IV	31	7.97 ± 4.16 cm	
Unclear	2		
TNM staging			<0.001
T1	403	4.06 ± 1.44 cm	
T2	59	9.65 ± 1.89 cm	
T3	41	7.44 ± 4.13 cm	
T4	5	8.80 ± 3.47 cm	
Surgery			<0.001
RS <sup>†</sup>	415	5.41 ± 2.78 cm	
NSS <sup>‡</sup>	93	3.26 ± 1.22 cm	

<sup>†</sup>radical surgery; <sup>‡</sup>nephron sparing surgery

in different size range with an interval of 1 cm ( $P=0.01$ ). However, the logistic regression model indicated that the histological subtype odds associated with the increase of 1 cm in tumor size was 1.07 (95% CI: 0.94–1.21). The distribution of histopathological subtype according to tumor size showed a marked variation in number of cases and statistical significance was detected between clear cell, papillary, chromphobe and other subtypes with  $P=0.047$ .

The proportion of different Fuhrman grade and TNM stage according to different tumor size was demonstrated in Table 3. The percentage of Fuhrman grade according to tumor size varied significantly ( $P<0.001$ ). The proportion of low-grade disease decreased from 75.9% for those of 2 cm or less to 31.2% for tumor of larger than 7 cm; high-grade disease accounted for 29.7% and 50.6% in tumors no larger than 4 cm and 4–7 cm, respectively. There was a significant increase in the percentage of high-grade disease by 46% for each 1 cm increase in tumor size (OR=1.46, 95% CI: 1.31–1.63). With respect to TNM staging, the tumors of 2 cm or less are all low-stage disease (100%), and in those larger than 7 cm, the low-stage disease accounts for 76.6% ( $P<0.001$ ). In tumors of 4 cm or less, the percentage of high-stage disease was 3.5%, and for those of 4–7 cm, larger than 7 cm, the rate of high-stage disease was 10.5% and 23.4%, respectively. The odds ratio for the association of high-stage disease with tumor size was 1.67 (95% CI: 1.39–2.00), indicating that each 1 cm increase in tumor size was associated with a 67% increase of high-stage

disease. The clear cell subtype group had an 8.1% high-stage disease; papillary cell and chromphobe cell subtype groups had 10.5% and 10% of high-stage disease, respectively.

The mean size for tumors with and without renal capsule infiltration was  $5.57 \pm 2.94$  cm and  $4.29 \pm 2.13$  cm, respectively ( $P<0.001$ ). Among all tumors, the percentage of renal capsule filtration increased from 17.2% for those of 2 cm or less to 75.6% for tumors of 7 cm or larger. Each 1 cm increase in the tumor size was associated with a 35% increase in the odds of renal capsule filtration (OR=1.35,  $P<0.001$ , 95% CI: 1.21–1.50). Twenty-seven tumors were found with confirmed diagnosis of renal vascular invasion. There was no vascular invasion in tumors of 1–2 cm, but 14.1% in those of 7 cm or larger. Each 1 cm increase in tumor size increased the odds of positive renal vascular invasion by 66% (OR=1.66,  $P<0.001$ , 95% CI: 1.31–2.09).

The receiver operating characteristic curves demonstrated that the size of the tumor was a strong predictor of renal vascular invasion and that 5.6 cm was the cut-off point (area under the curve was 0.748, 95% CI: 0.655–0.840) with a sensitivity of 75% and specificity of 73.4%. With respect to renal capsule infiltration, the cut-off value was 4.25 cm (area under the curve was 0.612, 95% CI: 0.561–0.664) with a sensitivity of 53.6% and specificity of 36.2%.

**DISCUSSION**

Clinically, RCCs are a radiographic diagnosis and often recommended to intervention. Increased use of cross-sectional imaging techniques lead to more frequency of incidentally found RCCs and the smaller size trend.<sup>[1]</sup> This requires changing in the management of RCCs, particularly in an era of increased interests in minimal invasive procedures.

There are several factors that will exert potential influence on decision making, of which the most important factor is tumor size. The tumor size is a major component of TNM staging system, and those localized tumors of tumor size less than

**Table 2: Summary of the distribution of histopathological subtype according to tumor size**

Lesion size (cm)	Clear cell (%)	Papillary cell (%)	Chromphobe cell (%)	Others (%)
1 to ≤2	18	4	0	7
2 to ≤3	82	2	0	9
3 to ≤4	120	3	2	12
4 to ≤5	60	2	2	8
5 to ≤6	55	4	1	7
6 to ≤7	27	0	0	5
>7	58	4	5	11
Total	420 (82.7)	19 (3.7)	10 (2.0)	59 (11.6)

Chi-square: 25.539;  $P=0.047$

**Table 3: Summary of the distribution of Fuhrman grading and TNM staging**

Tumor size (cm)	No. of Fuhrman grade					No. of TNM stage	
	I (%)	II (%)	III (%)	IV (%)	Unknown (%)	T1/T2 (%)	T3/T4 (%)
1 to ≤2	5	17	7	0	2	29	0
2 to ≤3	8	64	20	0		92	0
3 to ≤4	5	83	43	7		129	9
4 to ≤5	3	35	30	3		69	4
5 to ≤6	1	37	26	3		58	9
6 to ≤7	0	8	19	5		27	5
>7	2	22	40	13		59	18
Total	24 (4.7)	266 (52.4)	185 (36.4)	31 (6.1)	2 (0.4)	463 (91.1)	45 (8.9)

Fuhrman grade: Chi-square: 76.089,  $P<0.001$ ; with each 1 cm increase in tumor size, the increase in percentage to be high-grade disease is 46% (OR=1.46,  $P<0.001$ ). TNM stage: Chi-square: 36.651;  $P<0.001$ , with each 1 cm increase in tumor size, the increase in percentage to be high-stage disease is 67% (OR=1.67,  $P<0.001$ )

7 cm or larger were considered T1, T2 disease.<sup>[8]</sup> Unfortunately, based on the present findings, tumor size alone does not provide adequate information for deciding the optimum treatment option. Besides tumor size, the biological behavior is another critical factor. For those receiving minimally invasive procedures, especially the active watching and ablation, the pathological features of the tumors were not available and the fine needle biopsy is not routinely performed with considerable false diagnosis; thus, better understanding of the relationship between tumor size and corresponding pathological features is needed.

To our knowledge, the clear cell is more aggressive and associated poorer prognosis than papillary and chromophobe cell subtypes.<sup>[9]</sup> Zhang also confirmed that faster-growing tumors were more likely to be clear cell carcinoma.<sup>[10]</sup> Although significance was detected in the distribution of histopathological subtype according to tumor size, the odds of clear cell subtype to non-clear cell subtype is 1.07, with 95% CI (0.94–1.21), indicating that tumor size is not a predictive value in histological subtype differentiation. The mean size of papillary cell is much larger than that of clear cell, and this is contradictory to the common conception that larger tumor size is associated with higher malignancy. This finding was not consistent with that of Frank as well,<sup>[11]</sup> but perfectly matched with corresponding curves showed in another study with the largest included patients.<sup>[12]</sup> It may be explained that the less-aggressive, slower-growing tumors are present in the pre-clinical stage for a longer time before being detected.

Few studies have demonstrated that odds associated with increased percentage in each 1 cm increase in tumor size were 1.13–1.32.<sup>[11–13]</sup> Tabibi and his colleagues have presented a similar relationship between smaller tumors and favorable histopathological features as well.<sup>[14]</sup> We confirmed these findings, but with a higher odds ratio of 1.46 due to a larger mean size of the included tumors. We firstly presented the relationship between tumor size and primary T staging. The odds of primary T stage increased by 67% with each 1 cm increase in tumor size, and in size of larger than 7 cm, the high-stage disease accounted for 23.4%. These findings indicate that the greater the tumor size, the higher is the malignancy of the tumor.

Although most localized RCC had a low grade in this study, the significant percentage of small lesions found to have high Fuhrman grade suggests that many of these lesions would have progressed to regional metastasis and would have become a potential source of morbidity and mortality, and tumor resection is required. Although radical nephrectomy is still considered a standard procedure for treating RCCs, in the era of increased interest in minimal invasive procedure, management of RCCs is changing. Currently, 4 cm in tumor size is widely accepted as the cut-off point for NSS in selected patients. Our data revealed that in lesions of 4 cm or smaller, the great

majority were still low-grade and low-stage disease, supporting the proposition that for small renal masses, NSS is sufficient for this procedure, yielding oncologically comparable results, low morbidity, excellent disease-free survival rates and low local recurrence rates.<sup>[15–18]</sup> However, only 30.1% underwent NSS in our institution, which is consistent with reports suggesting that NSS is underused for small ( $\leq 4$  cm) renal masses,<sup>[19,20]</sup> with the indication that urological surgeons are still too conservative and this novel procedures should be advocated greatly.

Hsu and Remzi reported that tumor size of 3 cm was the cut-off in localized tumors, and lesions larger than 3 cm were of much higher likelihood of aggressive biological behavior.<sup>[21,22]</sup> Contrarily, our study revealed that tumors of size between 3 cm and 6 cm still harbored nearly 60% low-grade disease and 86.6–93% harbored low-stage disease. These findings were consistent with that observed by Rothman.<sup>[12]</sup> Moreover, for RCCs with size 5–6 cm, the percentage of renal vascular invasion being detected was 5%, and the cut-off value was 5.6 cm, indicating that renal tumors of size smaller than 4 cm is relatively indolent and, for those, NSS is an appropriate choice. Under some circumstances, the upper limit of tumor size being included for NSS could be extended, because, recently, other studies also reported that NSS was suggested for RCCs up to 7 cm in diameter with the same therapeutic effect and a lower risk for developing chronic kidney disease.<sup>[23,24]</sup>

Comparing with a previous study that reported that size of the tumor was a reliable predictor of capsule infiltration with a cut-off value of 55 mm on the specimen, our data did not reveal the same results.<sup>[25]</sup> However, our study demonstrated that tumor size was useful in the vascular invasion prediction, with the cut-off value of 5.6 cm. Based on our findings, tumors of 4 cm or smaller are mostly low-grade and low-stage disease with a low rate of vascular invasion and capsule infiltration. As illustrated in a meta-analysis by Chawla, which presented a series of 286 lesions undergoing active surveillance with mean tumor size of 2.6 cm and mean follow-up period of 34 months, only one lesions progressed to distant metastasis.<sup>[26]</sup> For those patients with small tumors accompanying infirmed physical condition or short life expectancy, active surveillance is still an attractive option. For those with small renal tumors unwilling to receiving surgery or those that cannot make through surgery, ablation still can be taken into consideration, as this therapy means have already been proven to be of favorable short-term tumor control.<sup>[3,27,28]</sup>

Thompson reported a method to predict the risk of malignancy by the product of multiple percentages.<sup>[13]</sup> It seemed useful during the initial consultation and deciding a management approach. For example, if a patient presents with a renal tumor that is between 3 and 4 cm in size, our data suggests that there is a 87.6% chance of a clear cell RCC and he could be further



informed a 63.7% and 93.5% chance to have low-grade and low-stage disease. Therefore, these data can be useful in the initial consultation and management decision making.

There are several limitations to this study that merit discussion. Our data represented a retrospective review of records in our single center. Moreover, we only included those that underwent resection with confirmed diagnosis of RCCs, and excluded patients receiving active surveillance or ablation and especially those with non-RCC, the histopathological diagnosis of which may have a direct impact on management. Patients with nodes or distant metastasis were also excluded. This makes the application of our result only proper for those suspected malignant. The histological diagnosis and grading was not obtained from a single pathologist and intra- or extraobserver bias could not be excluded.

## CONCLUSION

The data in our study revealed that tumor size closely correlated to Fuhrman grade, TNM stage, renal capsule involvement and renal vascular invasion. Tumor with greater size is always associated with higher risk to be high-grade and higher stage disease. The increase of tumor size accompanied a significant higher percentage of renal capsule involvement and renal vascular invasion as well. However, it is not a reliable predictor in differentiating tumor histopathological subtype and renal capsule infiltration, but is useful in vascular involvement evaluation. Additionally, for tumors with small size, our data still harbor a significant part of high-grade disease and also provided strong support to the conception that NSS is an appropriate treatment for patients with small renal tumor (tumor size of 4 cm or less), and for those infirmed with short life expectancy, conservative or less-active interventions are also favorable.

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