Adverse pathologic characteristics in the small renal mass: implications for active surveillance

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Introduction: *Evidence has demonstrated that tumor size is related to adverse oncologic outcomes in small renal tumors (≤ 4 cm). We evaluated the association of adverse pathologic features (APF) with tumor size and survival in patients with a small renal mass (SRM).*

Materials and methods: *We retrospectively reviewed the pathologic characteristics of 380 surgically resected SRMs from a single institution. APFs included lymphovascular invasion, coagulative necrosis, sarcomatoid/rhabdoid features, papillary type II histology, and perinephric fat/renal sinus invasion. The number and type of APFs were compared with tumor size. Survival analysis was performed using the Kaplan-Meier method.*

Results: *There were 244 (64.2%) males and 136 (35.8%) females. The median age was 61 years, and median tumor size was 2.7 cm. The median follow up time was 65 months. A significant association was found between tumor size and presence of APFs ($p = 0.018$). At least 1 APF could be found in 22%, 32%, 36%, and 49% of tumors ≤ 1 cm, 1 cm-2 cm, 2 cm-3 cm, and 3 cm-4 cm, respectively. There were no differences in overall survival or recurrence free survival when compared by tumor size at diagnosis ($p = 0.22$ and 0.15 respectively). Compared to patients with ≤ 1 APFs, disease specific survival was worse for patients with ≥ 2 APFs ($p < 0.002$).*

Conclusion: *Our data support that aggressive tumor biology in a SRM is associated with greater size. In patients with a SRM, the decision to pursue active surveillance and the trigger for intervention should take tumor size and APFs into consideration as this may have future oncologic implications.*

Key Words: small renal mass, renal biopsy, renal histology, renal cell carcinoma

Introduction

The increased use of cross-sectional imaging has led to a rising number of incidentally detected small renal masses (SRM) less than 4 cm.[1] It has been established that up to 20%-30% of SRMs are benign on final pathology after resection.[2] In addition, the majority of these tumors are indolent in nature.[3] Many studies have consistently shown that without surgical intervention, the majority of small renal tumors are not destined to spread and have excellent outcomes.[4]

The median age at diagnosis of renal cell carcinoma (RCC) is 64 years and as such, many patients are found to have significant, coexisting comorbidities.[5] A previous analysis of concomitant comorbidities at diagnosis demonstrated that nearly half of patients with a localized renal tumor have a Charlson Comorbidity

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index of ≥ 1.[6] Thus, many patients undergoing surgical management of SRMs are at risk for worsening their quality of life with further adverse health outcomes after surgery.[7]

As evidence regarding the slow growth rate and low metastatic potential of SRMs has expanded, so has the role of active surveillance. This approach has demonstrated favorable outcomes as several studies have shown that most tumors on active surveillance have a slow growth rate (median of 1 mm-2 mm a year) with only a 1% risk of distant progression.[3,8,9] In the most recent guideline statement, the American Urological Association considers active surveillance to be a recommendation for infirm or elderly patients presenting with a clinical T1 renal mass.[10] In this population, intervention may not improve overall survival, and curative treatment may be unnecessary.[11]

While active surveillance is certainly feasible for specific patient populations, it does not guarantee that treatment can be avoided indefinitely as patients often undergo delayed treatment due to tumor growth characteristics or patient anxiety.[12,13] Unfortunately, there are currently no universally accepted guidelines for determining the need for delayed intervention.

It is recognized that the risk of malignancy, high-grade disease, and recurrence after treatment increases with tumor size. However, there has been limited work on small renal tumors and the frequency of adverse pathologic features (APF) that are associated with risk of recurrence and cancer-specific death. The objective of this study is to evaluate the association between the number of APFs with tumor size and survival in patients with a SRM.

Materials and methods

Study population and data collection

We retrospectively reviewed a single institution database consisting of a consecutive series of partial and radical nephrectomies performed from 1989 to 2004 for RCC.[14] Study inclusion criteria were surgical resection of pathologically confirmed RCC (partial or radical nephrectomy), adequate tissue available for central pathological review, and adequate radiographic and/or clinical follow up data available. Exclusion criteria were pathologically confirmed urothelial carcinoma or any benign lesion and known advanced metastatic or nodal disease. Subject data were extracted from charts by certified registrars. Data collected included elements such as patient age, gender, race, date of diagnosis, therapy, length of follow up, and clinical outcome. Charts were retrospectively reviewed to determine date of recurrence and vital status, which included cause of death.

Pathological study

All specimens were re-reviewed by a single pathologist blinded to clinical outcome data. The primary tumor size was recorded from the initial surgical pathology report. All available tumor slides were reviewed at high power at 40X for the following APFs: high nuclear grade, lymphovascular invasion (LVI), coagulative necrosis, sarcomatoid features, rhabdoid features, papillary type II histology, and perinephric fat/renal sinus invasion.[15] The histological type and specific pathologic features were recorded according to the 2004 World Health Organization classification and morphologic characteristic subtypes of papillary RCC.[16,17] TNM stage was recorded according to the 2002 AJCC TNM scheme and conventional Fuhrman grade (1 to 4).

Statistical analysis

Pathologic characteristics were compared by 1 cm intervals of tumor size. Relationships between size and pathologic variables were analyzed by the chi-square, Fisher's exact, and ANOVA tests. Survival analyses were performed by considering the date of surgery as the time of diagnosis. For bilateral tumors, only the first operated tumor was considered. Recurrence free survival (RFS) was defined as the time from diagnosis to the date of documented local or distant recurrence. Disease-specific survival (DSS) was defined as time from diagnosis to death from disease, and overall survival (OS) was defined as time to death from any cause. In our survival analysis, patients were censored if alive and/or disease-free at date of last contact (all analyses) or if death occurred from other causes (for RFS and DSS). Survival analyses were performed using the Kaplan-Meier method, and differences between patient subgroups were compared with the log rank test.

Results

A total of 380 patients with SRMs that were pathologically confirmed to be RCC were included in the analysis. Table 1 summarizes patient and tumor characteristics. There were 244 (64.2%) males and 136 (35.8%) females. The median age was 61 (range 27-89) years. The median tumor size was 2.7 cm. Clear cell histology was found in 283 (74.5%) cases, papillary type 1 histology was found in 42 (11%) cases, and papillary type 2 histology was found in 33 (8.7%) cases. Pathologic staging found 353 (92.9%) cases of T1a disease and 27 (7.1%) cases of T3a and T3b disease. Coagulative tumor necrosis was found in 75 (19.7%) specimens, high Fuhrman grade in 59 (15.5%), LVI in 10 (2.6%), sarcomatoid features in 3 (< 1%), and rhabdoid features in 2 (< 1%). There

TABLE 1. **Patient and tumor characteristics**

Category	Criteria	Value
Sex	Men	244 (64.2%)
	Women	136 (35.8%)
Age	Mean/median	60.4/61
	Age	27-89
Follow up (months)	Mean/median	66/55
	IQR	34-87
Histology	Clear cell	283 (74%)
	Type 1 papillary	42 (11%)
	Type 2 papillary	33 (9%)
	Chromophobe	9 (2%)
	Multilocular cystic	5 (1%)
	Unclassified	8 (2%)
Pathologic stage	pT1a	353 (93%)
	pT3a/b	27 (7%)
Size	≤ 1 cm	18 (5%)
	> 1 to ≤ 2	93 (24%)
	> 2 to ≤ 3	143 (38%)
	> 3 to ≤ 4	123 (33%)
Fuhrman grade	1	75 (20%)
	2	246 (64%)
	3	52 (14%)
	4	7 (2%)
Lymphovascular invasion	No	370 (97%)
	Yes	10 (3%)
Necrosis	No	306 (81%)
	Yes	74 (19%)
Sarcomatoid features	No	377 (99%)
	Yes	3 (1%)
Rhabdoid features	No	378 (99%)
	Yes	2 (1%)
Tumor recurrence	No	356 (94%)
	Yes	24 (6%)
Died of RCC	No	365 (96%)
	Yes	15 (4%)

RCC = renal cell carcinoma

were a total of 18 SRMs that measured ≤ 1 cm (4.7%), 93 (24.5%) that measured > 1 cm to ≤ 2 cm, 143 (37.6%) that measured > 2 cm to ≤ 3 cm, and 123 (32.4%) that measured > 3 cm to ≤ 4 cm. A total of 233 (61.3%), 95 (25.0%), and 52 (13.7%) tumors had zero, one, and two or more APF's respectively. The median follow up time was 65 months (IQR 34-87). A total of 24 patients had recurrence, 15 patients died from RCC, and 88 patients died from other causes.

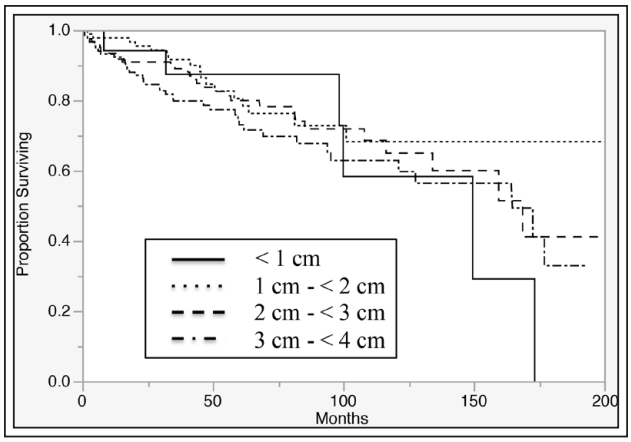

Figure 1. Overall survival stratified by tumor size (p = 0.22).

Aggressive pathologic characteristics by tumor size are shown in Table 2. High nuclear grade increased with tumor size (p = 0.02) from 11% for tumors ≤ 1 cm to 24% in tumors between 3 cm-4 cm. The frequency of papillary type 2 histology and LVI did not increase with larger tumor size (p = 0.93 and 0.6, respectively). There was a trend towards increased stage (pT3) and necrosis with larger tumor size, however, this association did not reach statistical significance (p = 0.09 and 0.11, respectively). There was a significant association between tumor size and the presence of APFs (p = 0.018). At least one APF could be found in 22%, 32%, 36%, and 49% of tumors ≤ 1 cm, > 1 cm to ≤ 2 cm, > 2 cm to ≤ 3 cm, and > 3 cm to ≤ 4 cm, respectively. The mean number of APFs also increased by tumor size (p = 0.008). Two or more APFs were identified in 1/18 (5.6%), 6/93 (6.5%), 13/143 (9.1%), 22/126 (17.5%) in tumors ≤ 1 cm,

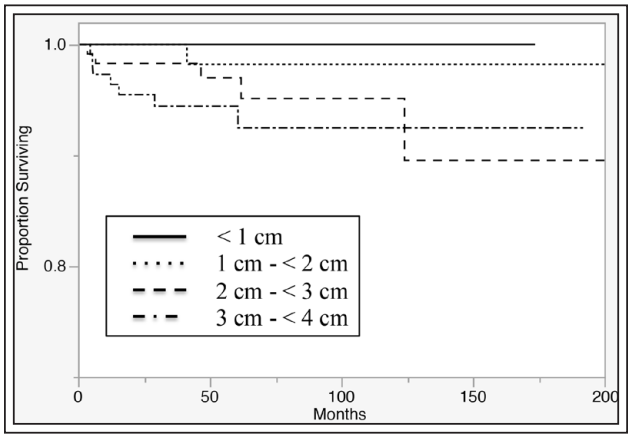

Figure 2. Recurrence free survival stratified by tumor size (p = .15).

TABLE 2. **Pathologic features by tumor size**

Category	≤ 1 cm (n = 18)	> 1 to ≤ 2 (n = 93)	> 2 to ≤ 3 (n = 143)	> 3 to ≤ 4 (n = 126)	p value
High nuclear grade	2 (11%)	11 (12%)	16 (11%)	30 (24%)	0.02
LVI	0 (0%)	1 (1%)	5 (4%)	4 (3%)	0.6
Necrosis	1 (6%)	14 (15%)	28 (20%)	32 (25%)	0.11
Sarcomatoid features	0	2 (2%)	0	1 (1%)	0.26
Rhabdoid features	0	0	0	2 (2%)	0.32
Type II papillary	2 (11%)	9 (10%)	11 (8%)	11 (9%)	0.93
Stage T3	0 (0%)	2 (2%)	8 (6%)	12 (10%)	0.09
Any adverse features	4 (22%)	30 (32%)	51 (36%)	62 (49%)	0.018
Mean # of adverse features	0.28	0.42	0.48	0.73	0.008
2 or more adverse features	1 (5.6%)	6 (6.5%)	13 (9.1%)	22 (17.5%)	0.039

LVI = lymphovascular invasion

> 1 cm to ≤ 2 cm, > 2 cm to ≤ 3 cm, and > 3 cm to ≤ 4 cm, respectively (p = 0.039).

The 5 and 10-year overall survivals were 79% and 64%, respectively. RFS at 5 and 10-years were 97% and 95%, respectively. DSS for the entire cohort at 5 and 10-years were 99% and 96%, respectively. There was no difference in overall survival, Figure 1, or RFS, Figure 2, when stratifying patients by tumor size (p = 0.22 and 0.15, respectively). DSS appeared worse for patients with one or more APF compared to those without any APF (p = 0.08). Those with ≤ 1 APF had worse DSS when compared to patients with ≥ 2 APFs (p < 0.002), Figure 3.

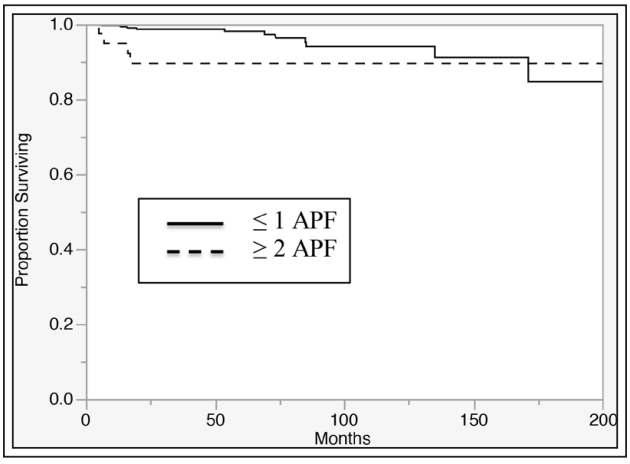

Figure 3. Disease specific survival by # of APF ≤1 versus ≥ 2 (p < 0.002).

Discussion

Management options for the SRM include partial and radical nephrectomy, ablative therapies, and active surveillance. Active surveillance has increasingly become a treatment option for older patients or those with significant comorbidities.[18] However, active surveillance does not come without risk as there is a possibility for tumor progression. In a multicenter clinical trial conducted by Jewett et al, 27 of 178 patients (15.1%) on active surveillance for a SRM (cT1a) progressed, 25 (14%) patients progressed locally with 9 receiving delayed intervention, and 2 (1%) patients demonstrated distant progression.[12] If a reliable marker to preoperatively identify tumors with aggressive features existed, appropriate candidates for active surveillance could be selected. Such a marker would likely increase utilization of active surveillance as many patients select treatment due to the clinical uncertainty over the natural history of the SRM. The characteristics that best define which patients will benefit most from active surveillance are still not clear. Active surveillance for tumors ≤ 4 cm is considered an option based on the American Urological Association guidelines, however, there are no established criteria based on high level evidence to support the ideal size to survey.[10]

We hypothesized that larger size, even among smaller tumors, would have an increased risk of containing specific APFs that would be associated with aggressive biologic potential. Our results demonstrate that increasing tumor size is associated

with higher grade, the presence of tumor necrosis, and more advanced stage (pT3a). We did not find that the presence of any APFs influenced survival after nephrectomy. This is likely due to the small number of cancer events, as only 6.3% and 3.9% of patients developed tumor recurrence or kidney cancer mortality, respectively. Whether these characteristics would be associated with progression during active surveillance is unknown. Our findings suggest that aggressive tumor biology is clearly associated with increasing size at diagnosis and should be considered when evaluating and counseling a patient with a SRM.

A number of studies have established that in cohorts of kidney tumors of all sizes, increasing size raises the risk of malignancy and risk of higher grade/stage.[19-22] Similarly, studies have examined the association between size and APFs within the SRM. Remzi et al analyzed 287 solid renal tumors ≤ 4 cm and found that for each 1 cm increase in tumor diameter, there was a significant increase in the likelihood of high Fuhrman grade (3 or 4) and advanced tumor stage (≥ pT3a).[23] Subsequently, Pahernik and colleagues reviewed 548 SRMs (≤ 4 cm) that were confirmed to be RCC and also found a statistically significant association between advance stage and tumor grade with each 1 cm increment in tumor diameter.[24] In addition to the association with APFs that signify risk of progression, it has been documented that SRMs with a larger size are more commonly identified to have synchronous metastatic disease.[25-27] Our report contributes further evidence that increased size among SRMs is associated with an increased likelihood of harboring APFs, however, our data are unique in that we provide a more detailed pathologic description and include specific histopathologic findings such as necrosis, LVI, and papillary subtype histology, all of which are known to influence prognosis.

Assessment of the performance of a pre-treatment renal tumor biopsy for predicting APFs at time of nephrectomy will be critical for assessing the utility of this modality for the selection of patients for active surveillance. In recent years, some authors have argued that renal tumor biopsy should be performed for every SRM, citing a high diagnostic rate (> 90%) with minimal procedural morbidity and a negligible risk of tumor track seeding.[2] Although renal tumor biopsy can be performed without difficulty, the characterization of several APFs may be challenging with a limited amount of sample tissue. The accuracy of the Furhman grade based on biopsy has been reported to be only 46%-85%, which may limit the evaluation of high grade features on a biopsy.[28] As the overall Fuhrman grade is designated from the highest grade present in the tumor, under grading is commonly seen due to grade heterogeneity.[29] How reliable several core biopsies are at predicting pathologic characteristics such as tumor necrosis, the papillary subtype, LVI, or sarcomatoid and rhabdoid features is unclear, but deserves further study and is ongoing at our center.

Currently, there are no standardized criteria for when to perform delayed treatment in patients on active surveillance. Once active surveillance has begun, periodic monitoring with cross sectional imaging can be helpful as tumor growth kinetics have played a role in determining the need for intervention. Suggested criteria for intervention based on imaging have been inconsistent among various centers. Some of the recommended triggers for intervention have included tumor growth of > 0.5 cm per year, doubling time < 12 months, or reaching a specific tumor diameter; some authors have argued 3 cm, while others have suggested 4 cm.[30,31] In this study, 49% of tumors that were ≥ 3 cm had at least one APF, while 17.5% had 2 or more APFs. Our data may indicate that patients on active surveillance for renal tumors above 3 cm may have an increased risk of distant progression before or after treatment as these tumors are much more likely to contain aggressive biologic characteristics.

While our analysis is the first to comprehensively evaluate the presence of APFs in the SRM, several limitations must be addressed. Our study was retrospective, and as such was limited by the inherent bias present in any analysis of this type. Only renal tumors that were microscopically confirmed to be RCC were assessed. As we did not include benign masses in our analysis, our ability to accurately predict the risk of APFs prior to confirmation of kidney cancer is limited. Additionally, we did not have specific information on tumor location or radiographic features, which may also be useful to predict aggressiveness.[32]

Conclusions

Aggressive tumor biology in patients with a SRM (cT1a) is associated with size and may impact the risk of progression for patients under surveillance. Tumors that were 3 cm-4cm in size were found to have at least one adverse pathologic feature in 49% of cases, which represented the highest percentage of all size groups. Whether a renal tumor biopsy can identify adverse pathologic features within a SRM should be pursued, as identification of these features may influence treatment decisions. □

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