A classification tree for the prediction of benign versus malignant disease in patients with small renal masses

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Introduction: *To develop a classification tree for the preoperative prediction of benign versus malignant disease in patients with small renal masses.*

Materials and methods: *This is a retrospective study including 395 consecutive patients who underwent surgical treatment for a renal mass < 5 cm in maximum diameter between July 1st 2001 and June 30th 2010. A classification tree to predict the risk of having a benign renal mass preoperatively was developed using recursive partitioning analysis for repeated measures outcomes. Age, sex, volume on preoperative imaging, tumor location (central/peripheral), degree of endophytic component (1%-100%), and tumor axis position were used as potential predictors to develop the model.*

Results: *Forty-five patients (11.4%) were found to have a benign mass postoperatively. A classification tree has been developed which can predict the risk of benign disease with an accuracy of 88.9% (95% CI: 85.3 to 91.8). The significant prognostic factors in the classification tree are tumor volume, degree of endophytic component and symptoms at diagnosis. As an example of its utilization, a renal mass with a volume of < 5.67 cm^3 that is < 45% endophytic has a 52.6% chance of having benign pathology. Conversely, a renal mass with a volume ≥ 5.67 cm^3 that is ≥ 35% endophytic has only a 5.3% possibility of being benign.*

Conclusions: *A classification tree to predict the risk of benign disease in small renal masses has been developed to aid the clinician when deciding on treatment strategies for small renal masses.*

Key Words: benign, diagnosis, prognosis, renal cell carcinoma, renal mass, pathology

Introduction

Renal cell carcinoma (RCC) is the most common solid neoplasm of the kidney and, currently, the only curative treatment remains surgery with either radical or partial nephrectomy. Unfortunately, both of these treatments carry a significant risk of perioperative morbidity[1,2] and predispose the patient to chronic renal failure and its sequelae.[3,4]

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Although most renal masses are found to be RCC on final pathology, some authors have reported a high incidence of benign disease in patients with small renal masses (SRMs) of up to 46%.[5] This unacceptably high rate of benign disease leads to unnecessary surgeries in generally elderly patients with multiple comorbidities. Our group and others have looked at various predictors of benign disease, but most of these studies have used traditional regression models.[6-12] Only two groups have developed predictive tools to aid in the prognostication of tumor histology. These are in the form of complex nomograms which are not used in routine practice.[13] Other groups have explored the utility of preoperative renal mass biopsy. Although improved techniques of renal mass biopsy have resulted in higher tissue yield and diagnostic

accuracy,[14] the rates of technical failure, inaccurate pathological diagnosis and complications are still significant.[15] Therefore, the preoperative prediction of renal mass histology remains a significant challenge. The purpose of this study was to create an accurate and easily applicable classification tree for the prediction of benign and malignant disease in SRMs. To our knowledge, this is a novel approach to this diagnostic dilemma.

Materials and methods

Patient selection and data collection

This institutional review board approved retrospective study includes 395 consecutive patients who underwent surgical treatment for a renal mass < 5 cm in maximum diameter between July 1st 2001 and June 30th 2010. Patients were identified from an institutionally maintained prospective database of patients with renal masses and from physician records. All patients were > 18 years of age and had a renal mass felt to represent RCC based on preoperative imaging characteristics (computed tomography, ultrasound, or magnetic resonance imaging). Surgical treatments included partial and radical nephrectomy performed by open or laparoscopic approaches.

Patient records and preoperative images were reviewed to collect clinical and radiographic data. Potential clinical predictive factors used to develop the classification tree included age, sex, and symptoms at diagnosis. Symptoms included pain attributable to the renal mass, hematuria, and/or a palpable mass. Potential radiographic predictive factors included tumor volume, tumor location (central or peripheral), degree of endophytic component (1%-100%), and tumor axis location. Tumor volume was calculated in one of three ways depending on the number of available dimensions: 1) for three dimensions, the formula for ellipsoid volume was used (0.5326xyz), 2) for two dimensions, the formula 0.5326xy(x+y/2) was used, and 3) for one dimension, the formula for volume of a sphere was used ((4/3)(3.14)(x/2)^3) which is equivalent to 0.5326x^3. A central tumor was defined as one that extended into the kidney in direct contact with or invading into the collecting system and/or renal sinus. All other renal masses were defined as peripheral. This definition was adapted from Frank et al.[16] Degree of endophytic component was recorded as the percentage of the tumor that was within the normal contour of the kidney. Tumor axis location was designated according to three renal axis: 1) upper pole, interpolar, or lower pole, 2) medial or lateral and 3) anterior or posterior. Pathology reports were reviewed to determine final diagnosis and each mass was classified as malignant or benign accordingly.

Statistical analysis

Recursive partitioning analysis (RPA) for repeated measures outcomes[17,18] was used to develop a classification tree model for the prediction of tumor histology (benign versus malignant) using the potential predictive factors listed above as covariates. Briefly, starting with the complete data set (the parent node), the algorithm automatically ranks all possible dichotomous splits of the data for each of the covariates and selects the split with the most homogenous subsets (children nodes) with regards to the variable of interest. The splitting procedure is then applied to each new group separately with the objective of partitioning the subsets into homogeneous groups while keeping the tree reasonably small. Splitting is continued until an overlarge tree is grown. The splitting procedure stops when all the records belong to the same class of response variable (malignant or benign) or all the records have identical attribute values (explanatory variables). The classification tree was developed automatically using the rpart package[19] in the R language for statistical computing.[20]

The overgrown full classification tree was developed and subsequently pruned in order to obtain a simpler while still predictive classification tree. The model was then validated using the 10-fold cross-validation routine in rpart. Sensitivity, specificity, accuracy, and positive and negative predictive values were calculated using a confusion matrix.

Results

Patient characteristics and histopathological outcomes

The median age of the cohort was 61 years (range 24-90) and 217 (55%) patients were male. The diagnosis of a renal mass was incidental in 81% of patients with the remainder experiencing hematuria and/or pain. Based on preoperative imaging, the median maximum renal mass diameter was 3.1 cm (range 1.0 cm-4.9 cm) with a median tumor volume of 14.38 cm^3 (range: 0.53 cm^3-62.66 cm^3). Table 1 shows patient and preoperative tumor characteristics for all patients.

Histopathological examination of the surgical specimens revealed that 350 (89.6%) masses were malignant and 45 (11.4%) were benign. The most common malignant lesion was clear cell carcinoma and the most common benign lesion was oncocytoma. Table 2 depicts histopathological findings for all masses.

TABLE 1. **Patient and tumor characteristics**

	Total	Benign	Malignant
N	395	45 (11.4%)	350 (89.2%)
Median age in in years (range)	61 (24-90)	60 (39-90)	61 (24-90)
Sex			
Male	217 (55%)	17 (37.8%)	200 (57%)
Female	178 (45%)	28 (62.2%)	150 (43%)
Presentation			
Incidental	320 (81%)	40 (90%)	280 (80%)
Symptoms	75 (19%)	5 (10%)	70 (20%)
Median diameter (range)	3.1 cm (1.0-4.9)	2.6 cm (1.0-4.6)	3.2 cm (1.0-4.9)
Median tumor volume (range)	14.4 cm^3 (0.5-62.7)	10.2 cm^3 (0.5-51.8)	14.4 cm^3 (0.5-62.7)
Tumor location			
Central	252 (64%)	17 (37.8%)	235 (67%)
Peripheral	143 (36%)	28 (62.2%)	115 (33%)
Surgical procedure			
Laparoscopic	303 (77%)	34 (76%)	269 (77%)
Open	92 (23%)	11 (24%)	81 (23%)
Partial nephrectomy	223 (57%)	24 (53%)	199 (57%)
Radical nephrectomy	172 (44%)	21 (47%)	151 (43%)

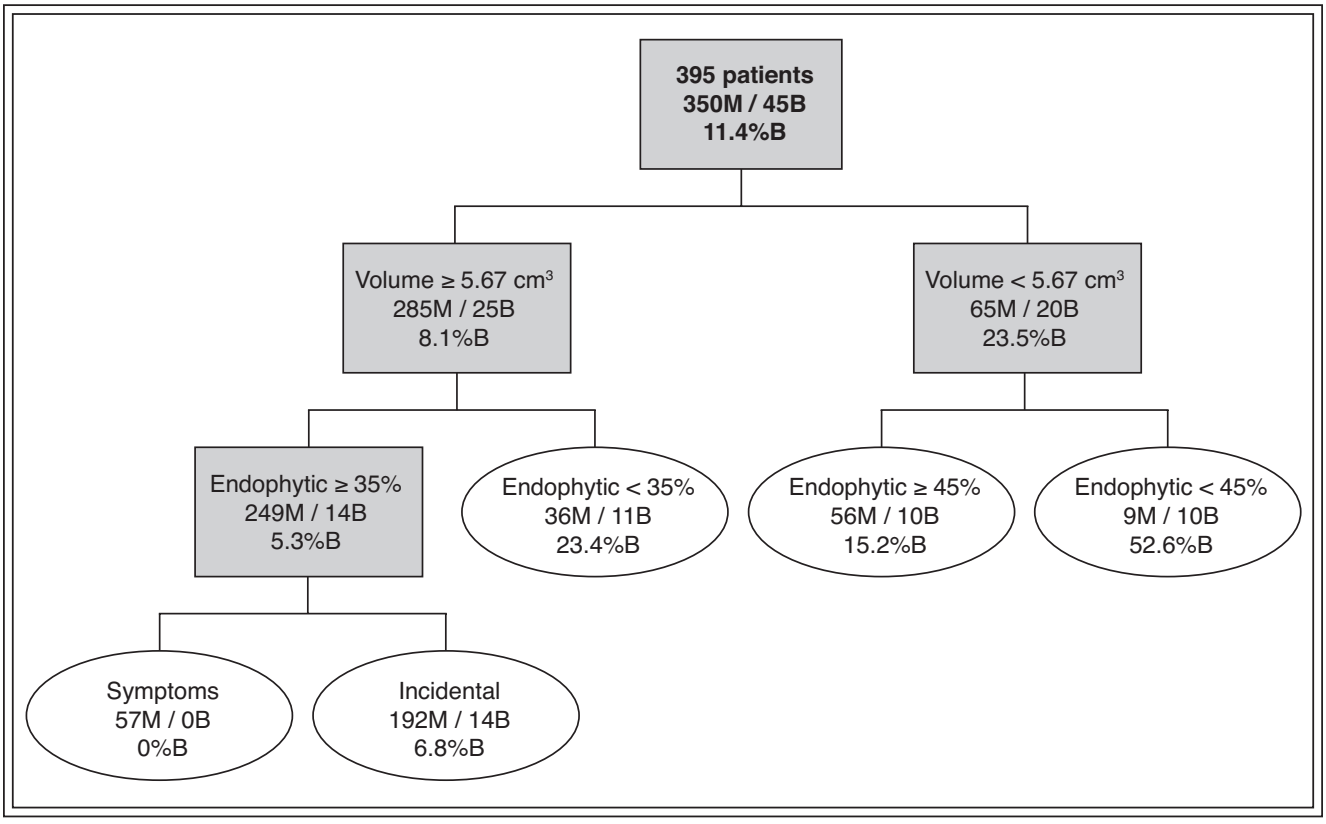

Figure 1. Classification tree for predicting the risk of benign disease in small renal masses. B = benign, M = malignant.

TABLE 2. **Histopathological findings**

Benign	45 (11.4%)
Oncocytoma	20 (5.1%)
Angiomyolipoma	11 (2.8%)
Benign cyst	6 (1.5%)
Metanephric adenoma	5 (1.3%)
Leiomyoma	1 (0.3%)
Cystic nephroma	1 (0.3%)
Granular Cell	1 (0.3%)
Malignant	350 (88.6%)
Clear cell	264 (66.8%)
Papillary	68 (17.2%)
Chromophobe	17 (4.3%)
Mucinous spindle cell	1 (0.25%)
Vascular invasion	11 (2.8%)
Fat invasion	18 (4.6%)
Fuhrman grade	
1	39 (11.7%)
2	177 (53.3%)
3	100 (30.1%)
4	16 (4.8%)
Pathological T stage	
1a	250 (71.7%)
1b	86 (24.6%)
3a	14 (3.7%)
Positive margins	9 (2.3%)

Classification tree

The pruned classification tree is shown in Figure 1. Following the tree downwards, the first split is according to tumor volume with a cut off of 5.67 cm^3 (maximum tumor diameter = 2.2 cm) optimally separating renal masses with benign and malignant histology. After this split, the right side of the tree (with a greater proportion of benign disease) splits additionally according to the degree of endophytic component with an optimal cut off of 45%. Similarly, the left side of the tree splits with according to the degree of endophytic component with an optimal cut off of 35%. The far left of the tree (volume ≥ 5.67, degree of endophytic component ≥ 35%) then splits a final time according to symptoms at presentation.

The calculated overall accuracy of this classification tree is 88.9% (95% CI: 85.3 to 91.8). The sensitivity and specificity are 96.6% and 35.6%, respectively, with a positive predictive value and negative predictive value of 92.1% and 57.1%.

Discussion

SRMs are a growing problem, and their incidence is rising mostly at the expense of incidental findings in the elderly.[21] It has become apparent over the past decade that not all of these small masses are malignant and, among those that are, not all of them need to be treated. The treatment of these masses is complex and can lead to significant morbidity as a result of perioperative complications or reduction in renal function. Based on these facts, it is becoming increasingly clear that many of these SRMs are over treated. However, the preoperative identification of patients who have benign or indolent disease remains a significant challenge.

Herein the predictive ability of patient and tumor characteristics to differentiate between benign and malignant histology was explored and a prediction tool was developed. This classification tree predicts the percentage chance that a patient with a SRM has benign or malignant disease. Tumour volume, degree of endophytic component, and symptoms at diagnosis were determined to be significant predictors of benign disease and incorporated into this tree. As an example of its utilization, a renal mass with a volume of < 5.67 cm^3 that is < 45% endophytic has a 52.6% chance of having benign pathology. Conversely, a renal mass with a volume ≥ 5.67 cm^3 that is ≥ 35% endophytic has only a 5.3% possibility of being benign. A patient with similar characteristics but who presented with symptoms at diagnosis has a 0% chance of having a benign tumor. The risk of harboring malignant disease between these three hypothetical patients is clearly different and this finding can be of help when deciding which patients should undergo further evaluation before exposing them to morbid surgical procedures.

In the past, several groups have reported on the ability of isolated clinical and radiological characteristics to predict benign disease.[5-10,12,22] However, only two other groups have developed predictive tools to determine the risk of benign versus malignant disease for SRMs.[7,13] Kutikov et al reported on the use the R.E.N.A.L nephrometry scoring system to evaluate whether radiographic features correlated with histology and high grade disease.[13] They found that nephrometry score correlated with both histology ($p < 0.0001$) and grade ($p < 0.0001$) and created a nomogram incorporating age, sex, and nephrometry score for predicting both histology and grade. However, within the nephrometry score, size was the dominant predictor with the other components adding only marginally to the value of the nomogram. By including parameters individually in our model we have avoided

adding unnecessary confounders. Similarly, Lane et al also developed a nomogram for the prediction of benign disease in renal masses incorporating age, sex, symptoms at diagnosis, smoking history, and tumor size.[7] Their nomogram proved to be reasonably accurate with predicted probabilities of benign disease within 4% of actual probabilities. Although these nomograms are available to the clinician, the classification tree we have developed provides another tool for the clinician to use and also reports on a novel approach to the diagnostic dilemma of small renal masses. This classification tree may be particularly useful in the elderly and significant comorbid in whom a high probability of benign disease may make the decision to provide no active treatment easier.

Another method employed for the detection of benign disease preoperatively is renal mass biopsy. The use of biopsy in the preoperative diagnosis of SRMs has increased substantially in recent years due to significant improvements in both techniques and histopathology. The reported sensitivity and specificity of renal mass biopsy has been as high as 100% with up to 90% accuracy.[23] In a study by Volpe et al including 100 patients, 84 renal mass biopsies were diagnostic with 66 and 18 patients having malignant and benign disease, respectively.[14] Renal mass biopsy also appears to be a safe procedure. A systematic review by Lane et al showed that in contemporary series, minor complications are rare (< 5%), and catastrophic complications and mortality (no reported cases) are exceedingly rare.[15] Despite these improvements, renal mass biopsy still has limitations with significant rates of technical failure and indeterminate diagnosis.[15,24] In a recent study by Menogue et al including 268 renal mass biopsies, the rate of non-diagnostic biopsy was 20%.[24] At present, we believe that pretreatment renal mass biopsy has a growing role in the management of kidney cancer but due to technical and histopathology limitations, a blanket approach to biopsying all renal masses is not supported. Perhaps a better approach would be to use a prognostic tool such as this classification tree to determine which patients should receive renal mass biopsy. For example, patients harboring a mass that has a high risk of benign disease could be biopsied while those with a high malignant potential could proceed directly to surgery.

There are limitations to this study that warrant discussion. The specificity of this classification tree is relatively low. The main reason for this is the fact that the proportion of benign disease (10%) in the cohort is relatively low. This low event rate endpoint makes difficult any statistical modeling. However, the high sensitivity is favorable, as it will prevent malignant tumors from being misclassified as benign. This study also lacks external validation. Currently, external validation using an external cohort of patients is ongoing and results will be forthcoming. Finally, this study used tumor volume as a measure of tumor size. Although most existing literature uses maximum tumor diameter, we hypothesize that volume is a more accurate reflection of tumor size as not all tumors are spherical and that this is a benefit of this study rather than a limitation.

Conclusion

A classification tree has been developed to aid the clinician in the prediction of benign versus malignant disease in patients with SRMs. This classification tree will be useful when deciding on treatment strategies for SRMs, and may be helpful in determining who should receive renal mass biopsy. □

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