ORIGINAL RESEARCH

Tumour location as a predictor of benign disease in the management of renal masses

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Abstract

Objective: To investigate the association between tumour location and the proportion of benign disease in renal masses presumed to be renal cell carcinoma (RCC) preoperatively.
Methods: This Institutional Review Board approved study includes 196 patients who underwent surgical treatment for renal masses <5 cm at our institution by a single surgeon between January 2002 and June 2009. Based on preoperative imaging, each mass was designated as central (touching or encroaching upon the renal collecting system and/or renal sinus) or peripheral. The association between tumour location and benign pathology was determined using univariate and multiple logistic regression, including tumour size and patient sex in the model.
Results: The proportion of histologically confirmed benign disease in this series was 11.2%. The proportion of benign disease by location was 5.9% and 19.5% for central and peripheral masses, respectively. The effect of location was found to have a significant prognostic value ($p = 0.0273$) with an adjusted odds ratio of 3.51 (95% CI = 1.38-19.62) for the odds of a benign diagnosis in peripheral compared to central tumours. Tumour size and patient sex were not significant predictors of benign pathology ($p = 0.483$ and 0.191, respectively).
Conclusions: Peripherally located renal masses are more likely to be benign than centrally located renal masses. This information may be used when selecting strategies for the management of renal masses presumed to be RCC.

Résumé

Objectif : Étudier le lien entre l'emplacement de la tumeur et le taux de maladie bénigne en présence de masse rénales qu'on suppose être un hypernéphrome avant l'intervention chirurgicale.
Méthodologie : L'étude approuvée par le Conseil d'examen de l'établissement comptait 196 patients qui ont subi un traitement chirurgical en raison de masses rénales de < 5 cm; toutes les interventions ont été effectuées par le même chirurgien entre janvier 2002 et juin 2009. Selon les images obtenues avant l'opération, chaque masse était considérée comme étant centrale (touchant ou envahissant le système collecteur et/ou le sinus rénal) ou péri-phérique. Le lien entre l'emplacement de la tumeur et le caractère bénin a été déterminé à l'aide de régressions logistiques univariées et multivariées, dont la taille de la tumeur et le sexe du patient.
Résultats : La proportion de tumeurs bénignes confirmées par examen histologique dans cette série était de 11,2 %. Le taux de tumeurs bénignes en fonction de l'emplacement était de 5,9 % et de 19,5 % pour les masses centrales et périphériques, respective-ment. L'emplacement s'est révélé avoir une valeur pronostique significative ($p = 0,0273$), avec un rapport de cotes ajusté de 3,51 (IC à 95 % = 1,38 à 19,62) pour la probabilité d'un diagnostic de tumeur bénigne en périphérie en comparaison avec un emplace-ment central. La taille de la tumeur et le sexe du patient n'étaient pas des facteurs de prédiction significatifs d'une pathologie bénigne ($p = 0,483$ et 0,191, respectivement).
Conclusions : Les masses rénales en périphérie sont plus suscep-tibles d'être bénignes que les masses rénales centrales. Ces don-nées peuvent être utiles au moment de choisir la stratégie de prise en charge des masses rénales supposées être un hypernéphrome.

Introduction

Renal cell carcinoma (RCC) is the most lethal of all uro-logical cancers. It accounts for 3% of all cancer diagnoses, making it the tenth most common cancer and the thirteenth most common cause of cancer-related death.[1] The incidence of RCC is increasing at 2% to 3% per year.[2]

Over 70% of renal masses are diagnosed incidentally while still small in volume[3] with the standard of care being removal with a partial or radical nephrectomy.[4] Although most masses are found to be RCC on final histology, high proportions of benign disease have also been identified (up to 46% for small renal masses[5]). Because of this, urologists need more preoperative predictors of pathology to aid in decision-making.

Several studies have linked the likelihood of benign pathology with preoperative factors, such as age,[6] sex,[6-9] smoking history[6] and tumour size.[5-7,10-13] However, making a definitive diagnosis remains difficult. Recently, 2 studies have reported a higher proportion of benign disease for renal masses located on the periphery of the kidney compared to those located centrally within the kidney or at the renal hilum.[14,15] Both of these studies reported this as a secondary finding and did not control for possible confounding vari-ables. We evaluated tumour location as a predictor of benign

pathology in patients who underwent surgical management of renal masses presumed to be RCC. To the best of our knowledge, this is the first study to look at the association between tumour location and pathological diagnosis while controlling for other tumour and patient characteristics.

Methods

After obtaining institutional research ethics board approval, we identified 196 consecutive patients who underwent surgical removal of a renal mass less than 5 cm in maximum diameter by a single surgeon (RAR) between January 2002 and June 2009. All patients had a solitary renal mass which was presumed to be RCC on preoperative imaging and treatments included laparoscopic and open partial and radical nephrectomies.

Patient charts and imaging were reviewed and clinical-pathological data were collected. From postoperative histology reports, renal masses were broadly categorized as malignant (RCC) or benign. Malignant lesions included clear cell, papillary and chromophobe tumours. Benign lesions included oncocytomas, angiomyolipomas, renal cysts and a leiomyoma. Each mass was classified as either central (C) or peripheral (P) by a urologic oncologist who reviewed the preoperative computed tomography or magnetic resonance imaging scans and was blinded to the primary endpoint. A central mass was defined as one which extended into the kidney in direct contact with or invading into the renal collecting system and/or renal sinus. Renal masses which had no contact with the renal collecting system and/or renal sinus were defined as peripheral. This definition of C/P was adapted from Frank and colleagues.[14] For the purpose of this study, it was decided to classify hilar tumours (those in contact with the renal hilum) as central in location as it is frequently difficult to separate the central component of many hilar masses.

The total proportion of benign disease and the proportion of benign disease according to renal location were calculated. The association between tumour location (C compared to P) and benign pathology was determined using univariate logistic regression and multiple logistic regression, including tumour size and patient sex in the model. Statistical analysis was performed using SPSS 17 (IBM, Somers, NY) statistical software.

Results

The median age of the entire cohort was 61 years (range 24-90) and 116 patients (59.2%) were male. In 164 patients (83.7%), the renal mass was an incidental finding with only 25 patients (12.8%) presenting with hematuria and 7 (3.6%) with pain attributable to the renal mass. All patients had a renal mass which enhanced on preoperative imaging, except for 2 (1.0%) who did not receive contrast. One hundred and forty-nine patients (76.0%) were treated with open or laparoscopic partial nephrectomies. There were no conversions to radical nephrectomy in patients who were scheduled for partial nephrectomies. There were 119 patients (60.7%) with a C mass and 77 (39.3%) with a P mass. Table 1 shows patient characteristics by tumour location.

Histopathological analysis revealed that 22 tumours (11.2%) were benign. The number of benign tumours by location was 7 (5.9%) for C masses and 15 (19.5%) for P masses. In univariate analysis, the proportion of benign disease was significantly higher for P compared with C tumours ($p = 0.0052$). Smaller tumours were more likely to be benign ($p = 0.043$), and no difference was found in the proportion of benign lesions between sexes ($p = 0.169$). Table 2 shows the unadjusted odds ratios in univariate analysis.

When controlling for tumour size and patient sex in multiple logistic regression analysis, the proportion of benign disease remained significantly higher for P compared with C

Table 1. Patient characteristics by tumour location

	Overall N (%)	Central N (%)	Peripheral N (%)
N	196	119	77
Median age, years (range)	61 (24-90)	61 (24-90)	61 (25-78)
Male (%)	116 (59.2)	69 (58.0)	47 (61.0)
Clinical presentation			
Incidental (%)	164 (83.7)	97 (81.5)	67 (87.0)
Hematuria (%)	25 (12.8)	16 (13.4)	9 (11.6)
Pain (%)	7 (3.6)	6 (5.0)	1 (1.3)
Treatment type			
Laparoscopic partial nephrectomy	92 (46.9)	44 (37.0)	48 (62.3)
Open partial nephrectomy	57 (29.1)	40 (33.6)	17 (22.1)
Laparoscopic radical nephrectomy	47 (24.0)	35 (29.4)	12 (15.6)
Open radical nephrectomy	0	0	0
Mean preoperative size in cm (range)	3.0 (1.0-4.8)	3.3 (1.0-4.8)	2.6 (1.0-4.6)
Mean pathological size in cm (range)	2.9 (0.6-6.5)	3.2 (1.2-5.5)	2.5 (0.6-6.5)

Table 2. Univariate logistic regression

	Benign N (%)	Malignant N (%)	Odds ratio (95% CI)	*p* value
N	22 (11.2)	174 (88.8)		
Tumour location			3.89 (1.49 – 10.0)	0.005
Central (%)	7 (5.9)	112 (94.1)		
Peripheral (%)	15 (19.5)	62 (80.5)		
Mean preoperative size (range)	2.6 (1.0 – 4.3)	3.1 (1.0 – 4.8)	0.61 (0.38 – 0.98)	0.043
Patient sex			1.87 (0.77 – 4.57)	0.169
Male (%)	10 (8.6)	106 (91.4)		
Female (%)	12 (15.0)	68 (85.0)		
Mean patient age (range)	60 (39 – 78)	59 (24 – 90)	1.01 (0.97 – 1.05)	0.583
Clinical presentation			2.08 (0.46 – 9.4)	0.339
Incidental (%)	20 (90.9)	144 (82.8)		
Symptomatic (%)	2 (9.1)	30 (17.2)		

tumours (*p* = 0.017), but tumour size and patient sex were not significant predictors of benign pathology (*p* = 0.483 and 0.191, respectively). The adjusted odds ratio was 3.51(95% CI 1.25-9.80) for the odds of a benign diagnosis in P compared to C tumours. When a cut-off point of 4 cm was evaluated, the findings of this study continued to show a significant difference in the proportion of benign disease according to tumour location (*p* = 0.013) and tumour size and patient sex remained non-significant (*p* = 0.977 and 0.110, respectively). Table 3 shows all adjusted odds ratios in multiple logistic regression.

Discussion

The current study identified that the odds of a renal mass having benign pathology is 3.5 times higher for peripherally located renal masses as compared with those located centrally within the kidney. These results are consistent with those reported in 2 other studies. In a series by Frank and colleagues, the proportion of benign disease in peripheral and central tumours was 34% and 20%, respectively (*p* = 0.002).[14] Venkatesh and colleagues reported that 45%, 14%, 25% and 14% of exophytic, mesophytic, endophytic and hilar renal masses were benign, respectively (*p* < 0.05).[15] Both of these studies only included patients who underwent laparoscopic partial nephrectomy.

The total proportion of benign disease in the current series was 11.2% for renal masses <5 cm which were thought to be RCC preoperatively. Numerous studies have reported a higher proportion of benign pathology for small renal masses treated surgically.[6,9,11,12,16-19] In a series by Schachter and colleagues, 26.3% of masses ≤4 cm were benign.[12] Similarly,

Pahernik and colleagues reported a proportion of benign disease of 24.4% in a series of 504 patients treated with partial nephrectomy over 25 years.[19] However, a few contemporary series have reported an incidence of benign disease similar to ours.[7,20] In a study by Klatte and colleagues, which included 1208 patients with renal masses ≤4 cm, 12% had benign disease.[20] Fujii and colleagues found that 11% of renal masses were benign in patients treated with partial nephrectomy for presumed RCC.[7] They suggest that this may be due to a smaller proportion of oncocytomas in Japanese patients (2.8%) compared with the 5% reported in western countries. The proportion of oncocytomas in our study, however, was 5.7%.

Traditionally, tumour size has been highlighted as the only reliable preoperative factor for prediction of malignant histology. As demonstrated in this series of tumours smaller than 5 cm, and in this era of incidental detection of small renal masses, tumour size has lost its independent ability to predict the presence of malignant pathology. The high number of benign renal lesions diagnosed postoperatively highlights the unreliability of currently used imaging methods in predicting malignancy. Better preoperative diagnostic methods are needed to reduce the number of major surgeries performed unnecessarily. One option is to produce an algorithm which predicts the likelihood of a tumour being malignant or benign. One such algorithm was produced by Lane et al which included age, sex, tumour size, smoking history and symptoms at diagnoses.[6] With this algorithm, the authors were able to predict the probability of a benign diagnosis within ± 4%, and with further research into factors associated with tumour pathology, these algorithms can be improved upon. Another option is to employ preoperative needle core biopsy for select lesions, which has been shown to be an accurate method for pathological diagnosis.[21] Based on the findings from this study where peripheral renal lesions carry a significant probability of having benign pathology, we suggest that preoperative biopsy of these lesions may be warranted.

Table 3. Adjusted odds ratios in multiple logistic regression

	Adjusted odds ratio (95% CI)	*p* value
Tumour location	3.51 (1.25 – 9.80)	0.017
Preoperative size	0.84 (0.51 – 1.38)	0.483
Patient sex	1.87 (0.73 – 4.80)	0.191

Several possible limitations of this study warrant discussion. The choice of 5 cm as a size cut-off may seem unusual. This was chosen because, from our experience, tumours larger than this are difficult to classify by location and the vast majority start to include a central component. In addition, most of the incidentally detected renal masses are <5 cm in size, exactly the masses that generate this diagnostic and management dilemma. Although central tumours were larger than peripheral tumours, this was accounted for in the multiple logistic regression. Another potential limitation of this study is that it only included patients with renal masses who were treated surgically, and did not include all patients with renal masses <5 cm who were treated at our institution during the study period. In the same period of time, 7 patients underwent radio frequency ablation and 68 patients underwent active surveillance. Treatment with these later modalities was chosen because these patients had significant comorbidities; this decision was not based on imaging characteristics of their renal masses. Of these 75 patients, only 8 underwent renal biopsies and histological confirmation of benign/malignant disease. We believe that the chances of selection bias were diminished by selecting all consecutive patients who underwent surgical management of their disease during the study period.

Conclusion

Peripherally located renal masses are 3.5 times more likely to have benign pathology than centrally located renal tumours. In addition, in this era of incidentally detected smaller renal masses, tumour size appears to have lost its predictive ability. This information may be used when selecting strategies for the management of renal masses presumed to be RCC.

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References

1. Canadian Cancer Society. Available at: www.cancer.ca. Accessed April 17th, 2010.
2. Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev* 2008;34:193-205.
3. Schlomer B, Figenshau RS, Yan Y, et al. Pathological features of renal neoplasms classified by size and symptomatology. *J Urol* 2006;176:1317-20.
4. Touijer K, Jacqmin D, Kavoussi LR, et al. The expanding role of partial nephrectomy: a critical analysis of indications, results, and complications. *Eur Urol* 2010;57:214-22.
5. Frank I, Blute ML, Cheville JC, et al. Solid renal tumours: an analysis of pathological features related to tumour size. *J Urol* 2003;170:2217-20.
6. Lane BR, Babineau D, Kattan MW, et al. A preoperative prognostic nomogram for solid enhancing renal tumours 7 cm or less amenable to partial nephrectomy. *J Urol* 2007;178:429-44.
7. Murphy AM, Buck AM, Benson MC, et al. Increasing detection rate of benign renal tumours: evaluation of factors predicting for benign tumour histologic features during past two decades. *Urology* 2009;73:1293-7.
8. Fujii Y, Komai Y, Saito K, et al. Incidence of benign pathologic lesions at partial nephrectomy for presumed RCC renal masses: Japanese dual-center experience with 176 consecutive patients. *Urology* 2008;72:598-602.
9. Snyder ME, Bach A, Kattan MW, et al. Incidence of benign lesions for clinically localized renal masses smaller than 7 cm in radiological diameter: influence of sex. *J Urol* 2006;176:2391-5.
10. Duchene DA, Lotan Y, Cadeddu JA, et al. Histopathology of surgically managed renal tumours: analysis of a contemporary series. *Urology* 2003;62:827-30.
11. Glassman D, Chawla SN, Waldman I, et al. Correlation of pathology with tumour size of renal masses. *Can J Urol* 2007;14:3616-20.
12. Schachter LR, Cookson MS, Chang SS, et al. Second prize: frequency of benign renal cortical tumours and histologic subtypes based on size in a contemporary series: what to tell our patients. *J Endourol* 2007;21 819-23.
13. Thompson RH, Kurta JM, Kaag M, et al. Tumour size is associated with malignant potential in renal cell carcinoma cases. *J Urol* 2009;181:2033-6.
14. Frank I, Colombo JR Jr, Rubinstein M, et al. Laparoscopic partial nephrectomy for centrally located renal tumours. *J Urol* 2006;175:849-52.
15. Venkatesh R, Weld K, Ames CD, et al. Laparoscopic partial nephrectomy for renal masses: effect of tumour location. *Urology* 2006;67:1169-74.
16. Kutikov A, Fossett LK, Ramchandani P, et al. Incidence of benign pathologic findings at partial nephrectomy for solitary renal mass presumed to be renal cell carcinoma on preoperative imaging. *Urology* 2006;68:737-40.
17. Remzi M, Memarsadeghi M. Small incidental renal tumours. Evaluation and biological parameters. *Urologe A* 2007;46:478, 480-4.
18. Remzi M, Ozsoy M, Klingler HC, et al. Are small renal tumours harmless? Analysis of histopathological features according to tumours 4 cm or less in diameter. *J Urol* 2006;176:896-9.
19. Pahernik S, Roos F, Hampel C, et al. Nephron sparing surgery for renal cell carcinoma with normal contralateral kidney: 25 years of experience. *J Urol* 2006;175:2027-31.
20. Klatte T, Patard JJ, de Martino M, et al. Tumour size does not predict risk of metastatic disease or prognosis of small renal cell carcinomas. *J Urol* 2008;179:1719-26.
21. Shannon BA, Cohen RJ, de Bruto H, et al. The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. *J Urol* 2008;180:1257-61.

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