Renal tumour size measured radiologically before surgery is an unreliable variable for predicting histopathological features: benign tumours are not necessarily small

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OBJECTIVE

To compare histopathological findings as a function of radiological tumour size, as published data suggest that small renal tumours are often benign and large tumours are renal cell cancer (RCC).

PATIENTS AND METHODS

Data from 543 surgically treated patients with solid renal tumours were analysed retrospectively. Tumour size measured by computed tomography (CT) before surgery was stratified into seven subgroups (cm): 0–2, 2.1–3, 3.1–4, 4.1–5, 5.1–6, 6.1–7 and >7, and correlated with final histology.

RESULTS

In all, 80 lesions (14.7%) were benign on final histology; tumour size did not correlate with benign histology ($P = 0.660$). Histopathological tumour size was not statistically significant different ($P = 0.521$) from measured tumour size on CT, and there was no statistical significance between CT and histopathological tumour size ($P = 0.528$). Only 13 (17%) of lesions were correctly defined as benign on CT before surgery, whereas 67 (83%) were considered to be suspicious for malignant disease. Only one patient with a tumour correctly defined as benign had a radical nephrectomy; by contrast, 28 of 67 (42%) had a radical nephrectomy for benign lesions not correctly identified as benign on CT before surgery ($P < 0.001$).

CONCLUSION

Substantially many renal masses are benign, independent of tumour size. Radical nephrectomy could potentially have been avoided in 42% of patients with benign renal tumours. These data provide a good argument for the use of a more refined preoperative diagnostic evaluation, in particular needle biopsy.

KEYWORDS

angiomyolipoma, Fuhrman classification, oncocytomas, renal cell cancer, small renal masses

INTRODUCTION

In large series of solid renal masses, the incidence of benign lesions was 12.8% [1] to 16.9% [2]. There has been a greater incidence of all stages of RCC, with the greatest increase in patients with localized tumours, probably caused by stage migration as a result of earlier detection [3]. However, significantly many of these lesions are actually benign tumours, especially oncocytomas and angiomyolipomas with low fat content, which remain difficult to differentiate from RCC, even when the most advanced cross-sectional imaging techniques are used [4]. The increase in incidentally detected small renal tumours has led to an increase in the incidence of benign renal masses and probably to an associated increase in the number of unnecessary surgical interventions for benign renal tumours.

Tumour size was therefore retrospectively correlated with histopathological features in renal tumours removed surgically over a 10-year period. The relationship between tumour diameter, as measured before surgery by helical CT on two-dimensional imaging, was correlated with histopathological features of the tumours.

PATIENTS AND METHODS

Data of all patients who had solid renal tumours at diagnosis, and that were removed surgically between September 1994 and December 2004 at our institution, were analysed retrospectively. Only patients with complete pathological and radiological documentation were included in the study. Patients with known hereditary disease like Von Hippel-Lindau and tuberous sclerosis were excluded. All histopathological specimens were reviewed by the same pathology team (supervised by M.S.) and were classified using the Heidelberg system [5].

Papillary adenoma was defined as a low-grade papillary tumour of <5 mm in greatest diameter, and larger lesions were defined as papillary RCC [6]. Oncocytoma was defined as a benign renal epithelial neoplasm, consisting of oncocytes with a granular eosinophilic cytoplasm and round and regular nuclei. Classic angiomyolipomas were defined as composed of mature fat cells, abnormal vascular tissue and smooth muscle.

The following clinical, CT and histopathological data were collected from the case files: surgery date and type of operation; age of patient; site, location and size of the tumour as determined by preoperative CT; histological type and

TABLE 1 The demographic characteristics and the distribution of oncocytomas, angiomyolipomas, leiomyomas, adenoma and other benign lesions, stratified by tumour size

	Tumour size, cm								
Variable	0–2	2.1–3	3.1–4	4.1–5	5.1–6	6.1–7	>7	≤4	>4
N (%) patients	59 (10.9)	93 (17.1)	103 (19)	90 (16.5)	51 (9.4)	50 (9.2)	97 (17.9)	255 (46.9)	288 (53.1)
Mean (SD) age, years	60.8 (12.5)	61.3 (13.5)	61.8 (14.1)	62.3 (12.6)	61.4 (15.9)	64.4 (13.1)	64.2 (11.9)	61.4 (13.5)	62.4 (13.5)
N (%) RCC	47 (79.7)	74 (79.6)	88 (85.4)	80 (88.9)	43 (84.3)	48 (96.0)	83 (91.1)	209 (81.9)	254 (88.2)
N (%) NSS	50 (85)	59 (63)	36 (35)	14 (16)	4 (7.8)	5 (10)	5 (5.1)	145 (57)	28 (9.7)
Distribution									
Oncocytoma	2	9	10	7	3	1	4*		
Angiomyolipoma	5	4	4	3	3	–	9†		
Leiomyoma	1	4	–	–	–	–	–		
Adenoma	4	–	–	–	–	–	–		
Others¶	–	2	1	–	2	1	1		
Overall	12	19	15	10	8	2	14‡		

*P = *0.89, †0.30 and ‡0.66. ¶Three papillary adenoma and one metanephric adenoma, two abscesses (2.4 cm and 5.1 cm); one haematoma (3.6 cm and 7 cm); one giant cell fibroblastoma (7.3 cm); one lipoma (6 cm); and one haemangioma (3 cm).*

diameter, and in cases of RCC, stage (TNM classification 1997) [7], grade (Fuhrman classification) [8] and histological subtype (Heidelberg classification) [5]. Tumour size as determined from CT was stratified into seven subgroups with a 1-cm interval, i.e. 0–2, 2.1–3, 3.1–4, 4.1–5, 5.1–6, 6.1–7 and >7 cm.

The chi-square test was used to test the hypothesis that rates were the same in each sample category. The Pearson chi-square test, which tests the hypothesis that response rates are the same in each sample category, was calculated by summing the squares of the differences between observed and expected cell counts. The nonparametric Wilcoxon test (two groups) or the Kruskal–Wallis test (more than two groups) were used for testing whether distributions across factor levels were centred at the same locations. Continuous data are shown as the mean (SD).

RESULTS

Between September 1994 and December 2004, 543 renal tumour-bearing kidneys were treated surgically and had complete radiological and pathological documentation; 370 kidneys (68.1%) were removed by radical nephrectomy and 173 (31.9%) had nephron-sparing surgery (NSS). The mean tumour size and patient age were 5.09 (2.87) cm and 62 (13.5) years, respectively. Table 1 shows the data stratified by tumour size; in 47% of patients (255) the tumour was ≤4 cm on preoperative helical CT.

Overall, RCC was found in 463 tumours (85.3%); the rate of RCC was significantly higher in tumours of >4 cm (254, 88.2%) than those ≤4 cm (209, 81.9%; $P = 0.028$). With larger tumours, advanced stages (≥pT3a) and higher grade (G3/G4) were significantly more common ($P < 0.001$). RCCs were detected in 62.9% of men and in 48% of left kidneys.

In all, 80 tumours were confirmed as benign (Table 1); the distribution of RCC and benign lesions according to tumour size is shown in Fig. 1a. The mean patient age in this group was 61.2 (15.0) years; 46% were men and in 46% the lesions were on the left side. Overall, benign lesions, at 4.7 (3.4) cm, were significantly smaller than RCC lesions, at 5.2 (2.7) cm ($P = 0.011$). The median (range) tumour diameter was 3.8 (1.4–16) cm.

The distribution of benign lesions stratified by radiological tumour size is shown in Fig. 1b. In tumours of ≤4 cm the incidence of benign lesions was 30%, 22% and 19.9% in tumours of 0–2, 2–3 and 3–4 cm ($P = 0.660$). In tumours of >4 cm the incidence of benign lesions was 18.3%, 6.5%, 11.4% and 14.3% for tumours of 4–5, 5–6, 6–7 and >7 cm ($P = 0.125$), respectively. In larger tumours (>4 cm) the incidence (10%) of benign lesions was significantly lower than in smaller renal tumours (≤4 cm; 20%; $P = 0.005$).

Although there was a trend towards histopathological tumour size being less than tumour size measured before surgery by CT, the differences were not statistically significant ($P = 0.521$; Table 2).

According to the preoperative helical CT report, only 13 (17%) of the benign tumours were correctly defined as benign lesions, with the remainder identified as suspected malignant tumour. The mean tumour diameter of tumours correctly defined as benign was 5.65 (2.1) cm. The histology of the correctly identified benign lesions was angiomyolipoma in 10, leiomyoma in one and oncocytoma in two.

Benign lesions incorrectly defined as RCC (83%) on preoperative CT had a mean size of 3.9 (2.0) cm, which was not significantly different from those correctly defined as benign ($P = 0.235$). Histologically these were oncocytoma in 34, angiomyolipoma in 18, leiomyoma in four and adenoma in four.

Only one patient with a correctly identified benign lesion (central oncocytoma of 5.2 cm) had a radical nephrectomy. By contrast, 28 of 67 patients (42%) with benign lesions incorrectly identified as malignant by CT had a radical nephrectomy.

According to CT diameter, 34 benign lesions were ≥4 cm; the remaining 46 were ≤4 cm. The mean tumour size for small benign lesions (≤4 cm) and larger benign lesions (>4 cm) was 2.8 (0.82) and 6.6 (2.4) cm, respectively. The benign lesions had no correlation with lesion diameter ($P = 0.660$).

DISCUSSION

There are recent reports on the expectant, conservative management of small renal masses in high-risk surgical candidates. This might reflect the large proportion of small renal masses that are found to be benign or low-grade RCCs [9,10], as a histopathological diagnosis is usually not available. There is a general view that small renal masses might be benign and larger renal masses are RCC. Frank *et al.* [1] reported retrospectively that 30%, 22% and 19.9% of renal lesions of <2, <3 and <4 cm were benign. However, even with large renal masses, a substantial proportion has been shown to be of benign histology [1,10]. If benign lesions could be accurately identified before surgery this could alter the surgical approach to these lesions, as NSS is the goal even for larger tumours.

Based on the present findings, tumour size alone does not provide adequate information for deciding the optimum surgical treatment. Although the percentage of benign renal tumours was significantly less in tumours of >4 cm than ≤4 cm, the proportion of benign lesions was significant in both groups (10% and 20%, respectively). We found that 17.5% of the benign lesions were >7 cm. The distribution of benign lesion had the same percentage in tumours of ≤4 cm and >7 cm (Fig. 1b), although the percentage of RCC increased with tumour size (Fig. 1a).

As well documented elsewhere [11], and underlined by this contemporary series, helical CT is not able to differentiate RCC from benign lesions with adequate accuracy. In the present series, only 17% of all benign lesions were correctly identified as benign on preoperative CT; most of these were angiomyolipomas (77%). Most angiomyolipomas contain sufficient fat [11] to be diagnosed as such, but ≈5% of angiomyolipomas have minimal or no fat and are therefore misdiagnosed on CT [12]. Tuncali *et al.* [13] reported that 30% of benign lesions referred for percutaneous ablative treatment were low fat angiomyolipomas.

Although radical nephrectomy is still considered a standard procedure for treating RCC, recent studies show that in tumours of ≤4 cm in diameter, NSS yields oncologically comparable results, with low morbidity, excellent disease-free survival rates of 89–98%, and low local recurrence rates of 0–7.3% [14–17]. Thus, NSS has become the standard treatment for these lesions [14–17]. However, recent reports suggest that NSS is underused for even small (≤4 cm) renal masses, i.e. in the USA for <20% [18] and in England for <4% [19]. In the present series 57% of tumours of ≤4 cm were treated by NSS. Although there was no statistical difference in tumour size between those correctly and incorrectly defined as benign on CT, one of 13 and 28 of 67 (43%) of the present patients were treated by an unnecessary radical nephrectomy, respectively. In the series of Frank *et al.* [1] 65% (244/376) of benign lesions were treated by radical nephrectomy. If NSS is suggested for RCC up to 7 cm in diameter [20] the decision for it seems imperative for benign tumours, especially as radical nephrectomy is a significant risk factor for developing chronic kidney disease [21].

If about half of all patients harbouring a benign renal tumour lose otherwise functioning kidney parenchyma with no oncological benefit, it is strongly arguable that it is time to re-evaluate the treatment policy. Moreover, more reliable evaluation of lesions before therapy appears to be even

FIG. 1. Distribution of ***a,*** *RCC and benign lesions, and* ***b,*** *benign lesions, according to tumour size, measured by CT before surgery, for the present study (in* ***a,*** *orange, RCC; and magenta, benign; orange in* ***b****) and that of Frank* et al. *[1] (yellow, RCC; green, benign in* ***a****; yellow in* ***b****, data for pathological size).*

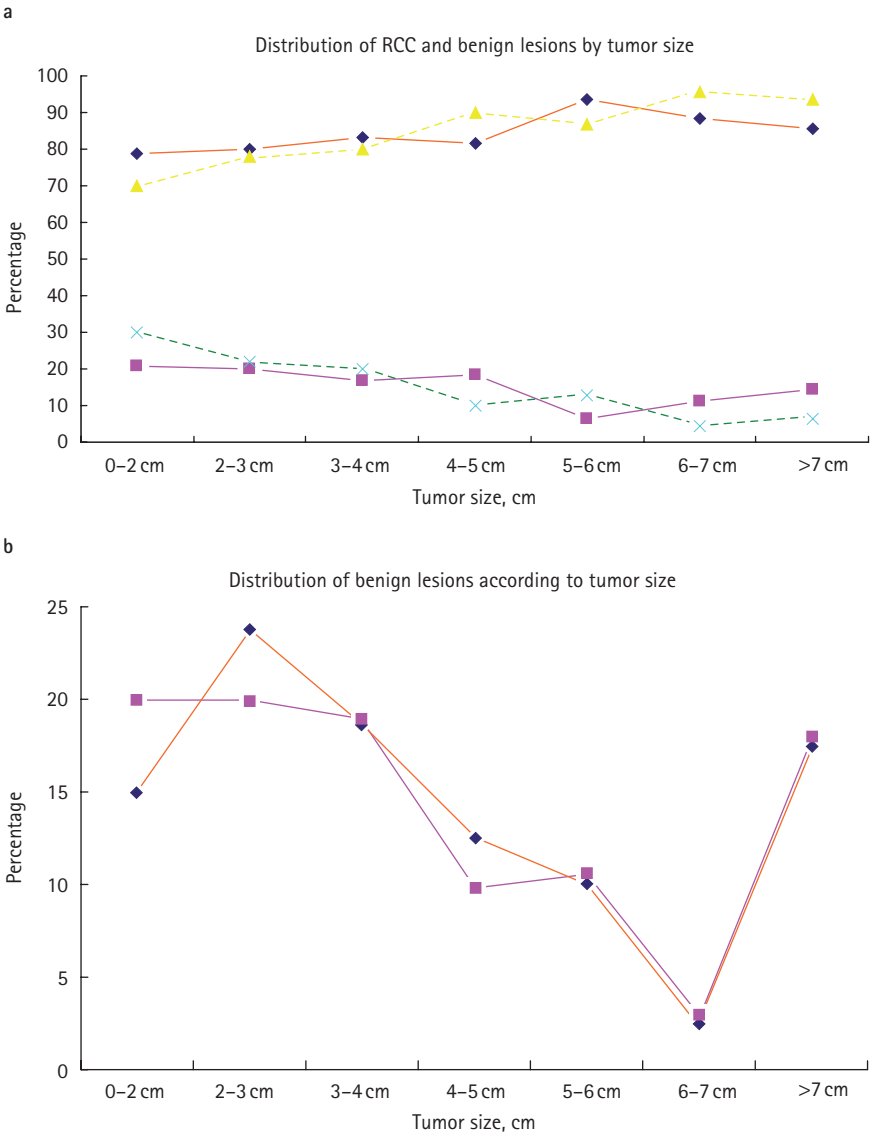

TABLE 2 Comparison of tumour size measured on helical CT vs histopathological tumour size for benign lesions

Lesion	No. of lesions	CT size, cm	Histological size, cm	Difference*, cm	P
Mean (SD) and median (range)					
Oncocytoma	36	4.1 (2)	3.8 (2.2)	+0.1 (1.2)	0.547
		3.7 (1.5–10)	3.1 (1.4–11.5)	+0.2 (–5.5, +2.3)	
Angiomyolipoma	28	5.4 (4.9)	5.3 (5.3)	+0.12 (1.2)	0.944
		3.5, (1.4–24)	4 (0.9–26)	0.0 (–2, +4)	
Leiomyoma	5	2.2 (0.28)	1.5 (0.7)	–0.7 (0.98)	0.345
		2, (2–2.4)	2 (1–2)	0.7 (0–1.4)	
Adenoma†	4	0.3 (0.2)			
		0.3 (0.1–0.5)			
Others†	7				

**Defined as (CT tumour size – histological tumour size). †see Table 1.*

more important with the advent of less-invasive treatments for tumours of ≤3 cm, such as ablation with radiofrequency [22], high-intensity focused ultrasound [23] and cryotherapy [24]. Tuncali *et al.* [25] reported that a substantial number of tumours (10 of 27, 37%) referred for radiofrequency ablation (mean tumour size 2.2 cm) were benign. The ongoing discussion about expectant 'watchful waiting' management in comorbid patients assessed as poor candidates for surgery further underlines the need for better identification of low-risk tumours [26]. The most promising option is image-guided biopsy. Neuzillet *et al.* [27] showed that CT-guided fine-needle percutaneous biopsy had an accuracy of 92% and 70% for defining histological tumour type and Fuhrman grade, respectively, with no substantial morbidity. They showed that in nearly half of patients a radical nephrectomy could be avoided. The specificity of percutaneous renal biopsy for differentiating between RCC and benign lesions is 80–92% [28]. Advances in cytological techniques, particularly immunocytochemistry, have contributed to the increasing ability to diagnose both benign and malignant tumours percutaneously. Percutaneous biopsy is a safe and accurate procedure with imaging guidance and both fine- and large needle-based techniques [28].

The main argument for surgery even in lesions suspected to be benign, such as oncocytomas, is the lack of accurate preoperative diagnostic tools and the lack of data on the natural history of oncocytoma. The first report that followed histopathologically confirmed oncocytoma showed that surgery was needed at a mean follow-up of 30 (19.8) months in six of 15 patients, because of initial tumour burden, tumour growth of >0.5 cm/year, and patient preference in one, four, and one case of surgery, respectively. Patients who had surgery were significantly younger (mean age 45.5 years) than the remaining nine patients (mean age 65.6 years) with no surgery. This study also showed the tendency of oncocytomas to grow, albeit at a variable velocity [29]. Even with the correct histological distinction, the larger benign lesions should be treated in time, so that the option of NSS is not missed.

In conclusion, substantially many renal masses are benign, independent of tumour size. The results of this retrospective analysis showed that radical nephrectomy could have been avoided in 42% of patients with benign renal tumours. This provides a strong argument for more refined preoperative evaluation, mainly by percutaneous image-guided needle biopsy.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **NSS**, nephron-sparing surgery.