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The fate of small renal masses, less then 1 cm size: outcome study

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ABSTRACT

Purpose: We evaluated the outcome and etiologies of small renal masses (less than 1 cm in size) discovered incidentally on 2 consecutive CTs that investigated non-urologic abdominal complaints.

Materials and Methods: A retrospective search for incidentally discovered small renal masses, less then 1 cm in size, was carried out in the files of 6 major US medical centers. 4822 such lesions had been reported over a 12 year period. A search of these patients' records revealed 1082 subsequent new CTs for non urologic complaints, allowing the assessment of the fate of the masses. Lesions enlarging, of ambivalent contour or enhancement were examined by a third multiphasic MDCT. The findings were interpreted by 2 blinded radiologists.

Results: Six hundred and four masses could no longer be identified, 231 were significantly smaller, 113 unchanged in size and 134 larger. Of the disappearing lesions 448 were located in the medulla, 94 both in medulla and cortex and 62 in cortex. Multiphasic MDCTs obtained in 308 masses enlarging, unchanged in size or of ambivalent appearance, revealed 7 neoplasms, 45 inflammatory lesions, 8 abscesses and 62 renal medullary necrosis. Concurrent antibiotic therapy of GI conditions may have caused some of the 496 lesions to disappear.

Conclusion: It is questionable whether the small number of malignant neoplasms (0.4%), inflammatory lesions (5%) and renal medullary necrosis (6%) justify routine follow-up CTs and exposure to radiation. The delay in intervention in neoplastic lesions probably didn't influence tumor-free survival potential and clinical symptoms would soon have revealed inflammatory conditions. With exception of ambivalent lesions, clinical surveillance appears adequate.

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INTRODUCTION

The expanded use of CT to assess abdominal disorders has identified a large number of unsuspected small renal masses, less than 1 cm in size (1,2). However, to date, there are no data available of their outcome and pathologic diagnosis.

Unless diagnosed as cysts (based on cortical location, contours, base density of - 5 to +10 HU and lack of enhancement) these masses could not be further categorized by CT.

Surgical data from the recent urologic literature suggest that only 19.6 - 43% of up to 4 cm lesions are benign (3-5). However, the differentia-

tion of benign and malignant lesions is difficult. Neither size nor growth rate are reliable predictors of malignancy (1, 6-10). In fact, even in lesions with a "0" growth rate, an 83% incidence of malignancy has been reported (7). Recent reports have shown similar tumor-free survival rates of patients treated by surgery regardless whether the size of the lesion was 1.5 cm or 4 cm. This favored the option of surveillance of small lesions particularly in elderly patients with co-morbidities (1,3,11-14). Moreover, histologically aggressive behavior of lesions can be identified by biopsy, which is advocated by some when pursuing surveillance (15,16).

We have undertaken this retrospective study of our files to identify underlying pathology and particularly neoplastic etiology as well as treatable conditions of these masses.

MATERIALS AND METHODS

Study Design

Waivers were obtained from the respective Institutional Review Boards for a retrospective review of the charts to identify lesions of interest. The reports of all CTs obtained to evaluate non-urologic abdominal complaints and conditions were reviewed for the incidental diagnosis of small renal mass (less then 1 cm).

Four thousand eight hundred and twenty-two such renal lesions were observed in the files of Tulane Health Science Center, (1995-2005) LSU Medical Center, Charity Hospital, VA Hospital, all in N.O, (1995-2000) SUNY Downstate Medical School, Brooklyn, N.Y, (1998-2007) and Johns Hopkins Medical Institutions, Bayview, Baltimore, (2005-2007). All patients with a history of prior or existing neoplastic disease were excluded. To establish the fate of these mass lesions we then searched the files of the 4822 patients for any subsequent CTs obtained for non-urologic abdominal conditions, and identified 1082 such CTs carried out in the ensuing 4-36 months period (13.2 months mean).

Since these studies were investigating abdominal symptoms and complaints (mostly gastrointestinal (41 %), biliary (27%), pancreatic (26%) and retroperitoneal & vascular (6%)), oral contrast had been administered in at least one of the two CTs in 93% of the patients; intravenous contrast in 91%. Eighty-four percent of the studies were 2 phase CTs, 9% 3 phase and 7% single phase nonenhanced CTs. Since the two CTs that were compared may have been obtained for different reasons, the techniques often differed. The accuracy of diagnosis may vary for different enhancement phases. Variability in equipment and interpreters may be another shortcoming of our study design. A third follow-up, 3 or 4 phase MDCT was performed to assess 308 renal mass lesions which were larger, unchanged in size or of ambivalent appearance (ill-defined margins, rim enhancement) on the second CT. These CTs were limited to the kidneys, generating 2.5, 3.7 mm thick slices, some with 1.5 mm axial and coronal reconstructions. Technical factors: 100 ml nonionic contrast medium at a flow rate of 4-5 ml/sec, 100-140 KV, 180-320 MAS, 6 cm table movement. Phases: Pre-enhancement, late arterial cortico-medullary phase at 12-16 second scan delay, parenchymal phase with 40-60 second scan delay, and sometimes excretory phase with a 4-12 minute delay. An identical protocol was performed in all our institutions. The studies were interpreted by 2 experienced uro-radiologists, blinded to prior interpretations and clinical findings.

Statistical analysis was carried out using X 2 test to assess outcomes for different locations.

The lesions varied from 2-10 mm in size (6.2 mm mean), 805/1082 (75%) were solitary, 277/1082 (25%) multiple (2-5); their sum-total volume never exceeded 2.9 ml, 28 were located in both kidneys. Seven hundred fifty-seven (70%) patients were male, 308 (28%) female, and 17 (2%) children, aged 16 to 82 years (39 years mean).

RESULTS

Six hundred and four (55.8%) of the 1082 lesions shown on the first CT could no longer be identified. Two hundred and thirty-one renal masses (21.3%) were significantly smaller, 113 (0.4%) unchanged in size (cross-sectional diameter) and 134 (12.4%) larger (Table-1). Four hundred forty-eight (41.4%) of the disappearing le-

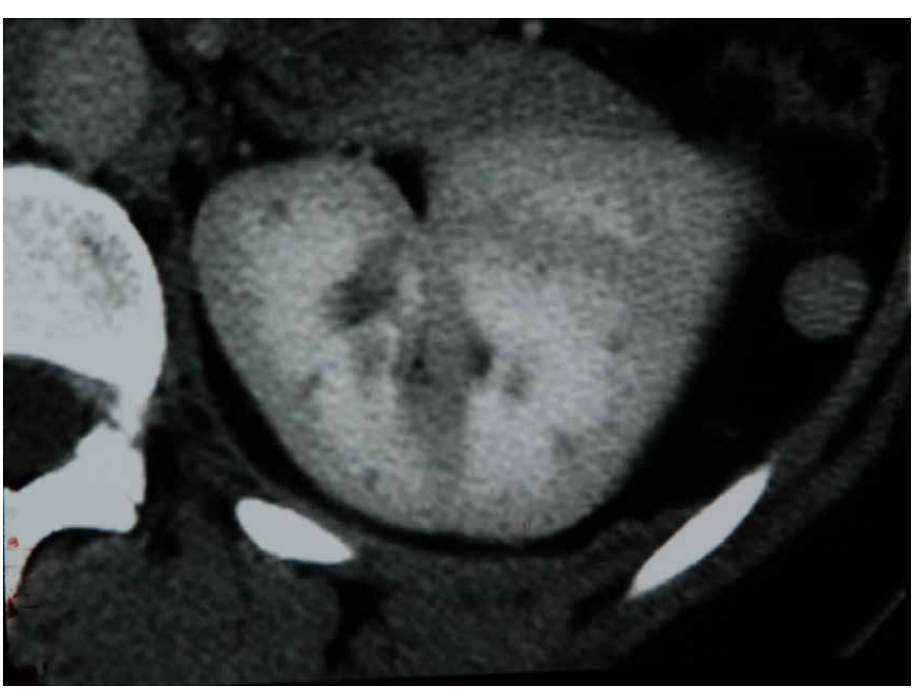
Table 1 - Location and Outcome of 1082 Small Renal Masses on Follow-up CT (after 4-26 months).

Outcome		Location		
	Number	Medulla	Medulla and Cortex	Cortex
All	1082	616(56.9%)	186(17.2%)	280(25.9%)
Disappeared	604(55.8%)	445(73.8%)	94(15.8%)	62(10.3%)
Smaller	231(21.3%)	47(20.3%)	41(17.7%)	143(61.9%)
Unchanged	113(10.4%)	52(46%)	30(26.5%)	31(27.4%)
Larger	134(12.4%)	69(51.2%)	21(15.4%)	44(33.4%)

sions had been located in the medulla, 94 (8.7%) in both medulla and cortex and 62 (5.7%) in cortex (Figure-1). Almost 73% of solitary medullary masses disappeared compared to 22% of solitary cortical masses (p = 0.0001); a significant finding. Among the lesions unchanged in size, 52 (4.8%) were located in the medulla, 30 (2.7%) in both cortex and medulla and 31 (2.9%) in cortex; of those larger, 69 (6.4%) were located in medulla, 21 (1.9%) in both cortex and medulla and 44 (4.1%) in cortex (Table-1). There were no significant differences in outcomes for different locations of small renal masses (X 2 test, p = 0.0001).

Location in the medulla, pre-enhancement density of 14-26 HU, lack of or heterogeneous enhancement in the late arterial, cortico-medullary

Figure 1 – This parenchymal phase CT demonstrates innumerable small, non-enhancing masses in the medulla.



and parenchymal phase, and demonstration of an ill-defined enhancing perimeter rim, led to the presumptive diagnosis of renal medullary necrosis (RMN) in 22 of the enlarging, 4 of unchanged size and 36 of shrinking mass lesions (Figures 1 and 2).

Enhancement of the rim of lesions in the cortico-medullary and parenchymal phase, sometimes layering debris in its center, prompted the diagnosis of abscess in 8 mass lesions, 4 in the medulla, 2 in cortex and 2 involving both cortex and medulla. Five decreased while under antibiotic therapy and 3 increased in size until treated by percutaneous drainage. Histologic and bacteriologic proof was available in all 8 lesions (Table-2).

Figure 2 – On pre-enhancement CT(left) one can not identify a parenchymal lesion. However, the parenchymal phase CT(right) shows a non-enhancing mass in the right medullary pyramid. The finding of a mass identifiable only on post-enhancement phases, but isodense on pre-enhancement phase, is pathognomonic for renal medullary necrosis (RMN).

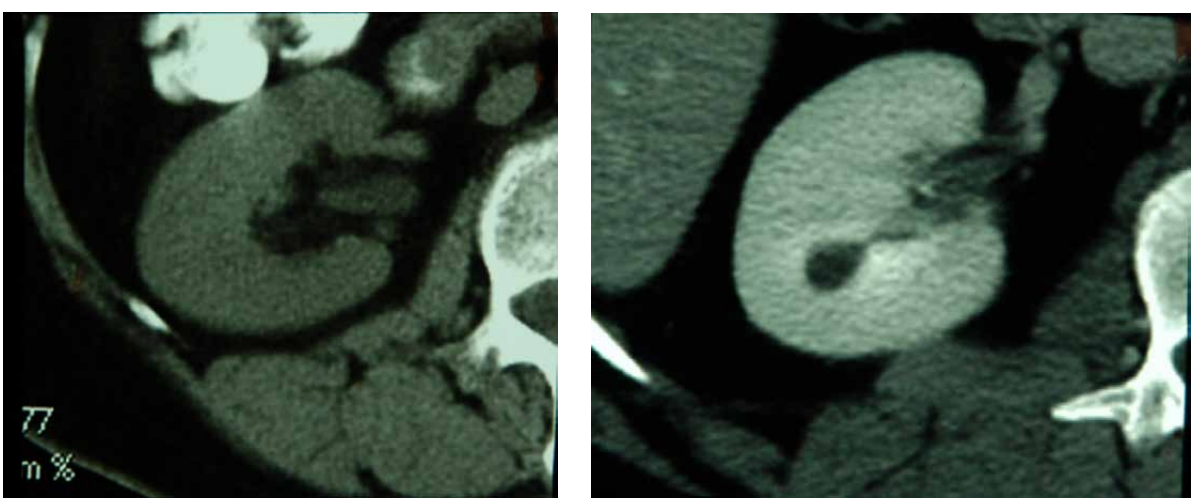


Table 2 - Significant and Potentially Treatable Conditions Observed Among 1082 Small Renal Masses.

		Pathologic Diagnosis						
Location	Size	Inflammatory	Abscess	RCC	AML	Metastasis	Fibroma	RMN
Cortex	Smaller	4	1	-	-	-	-	-
	Larger	12	1	2	2	-	1	-
Medulla	Smaller	4	1	-	-	-	-	36
	Unchanged	14	1	-	-	-	-	-
	Larger	-	2	-	-	-	-	22
Cortex and Medulla	Smaller	8	1	-	-	-	-	-
	Larger	3	1	-	-	2	-	-
	Unchanged	-	-	-	-	-	-	4

While none of these patients presented with findings of urinary tract pathology, urine WBC/hpf was 8-12 in 3 at the time of the second CT work-up. This finding was ignored because of the established diagnosis of inflammatory sigmoid-colon disease. However, within 10 days, urine culture (N = 8) and blood culture (N = 3) became positive.

Poor and heterogeneous enhancement of 45 renal masses suggested an underlying inflammatory etiology. A pale or non-enhancing center on the cortico-medullary phase suggested edema or early necrosis, while enhancement in the periphery and immediately adjacent tissues in the parenchymal phase was consistent with inflammatory hyperemia. WBC was elevated in 28 patients, urine analysis showed 5-10 WBC/hpf in 3 patients. The laboratory findings seemed consistent with the diagnosed inflammatory disease of bowel, pancreas or gallbladder, and a urinary tract infection was not considered. Within 2 weeks, urine cultures turned positive in 12 patients; urine analysis (WBC/hpf) was positive in 44 patients.

Eighteen of these lesions were found in the medulla, 16 in cortical location and 11 involved both cortex and medulla (Table-3). Fifteen of 45 (33.3%) had decreased in size, while 30 (66.6%) increased or remained unchanged in size (Tables 2 and 3). Antibiotic therapy used to treat inflammatory abdominal conditions between the first and second CT could have contributed to shrinkage of 15 of these lesions (Table-3). Ultimately, all patients were treated with urinary tract antibiotics and the masses disappeared, though a small pyelonephritic scar persevered in 14 patients.

Based on progressive enlargement (projected growth rate of 1.32 & 1.52 cm/year), and characteristic enhancement during the early cortico-medullary phase to 142 and

Table 3 - Outcome of 247 Enlarging or Unchanged In Size Small Renal Masses Reexamined by Multiphase MDCT.

Size Diagnosis	Medulla	Medulla and Cortex	Cortex
Larger	**69**	**21**	**44**
Cyst/IL*	41	16	26
Inflammatory	4	3	12
Abscess	2	-	1
Neoplasms	-	2	5
RMN	22	-	-
Unchanged	**52**	**30**	**31**
Cyst/IL*	37	20	25
Abscess	1	1	-
Inflammatory	14	5	6
RMN	-	4	-
Smaller	**47**	**41**	**143**
Abscess	1	1	1
Inflammatory	-	3	9
RMN	36	-	-
Cyst/IL*	10	37	133

*IL = Indeterminate Lesion, features suggestive of cyst.

164HU respectively, two renal cell carcinomas were identified on 4 phase MDCTs (Table-2). A rapid growth rate (1.44 cm/year) of 2 mass lesions involving cortex and medulla, enhancing from 30 and 32 to 120HU in parenchymal phase, prompted exploration and segmental resection. Metastatic carcinomas (lung = 1, colon = 1) were found (Table-3). Presence of fat on MDCT in lesions enlarging at a rate of 0.2 & 1.1 cm/year respectively led to diagnosis of angiomyolipoma in 2 patients. Hemorrhage into the lesions may have obscured the fat on the first 2 CTs (Table-3). One enlarging cortical mass (32 HU) with morphology favoring a benign neoplasm was biopsied and a fibroma diagnosed (Table-3). The diagnoses were confirmed in 6 patients by histopathology of the resected specimen, and in one by core biopsy specimen.

Benign cysts were diagnosed in 87 enlarging or stationary cortical and cortical and medullary masses, and 72 shrinking cortical masses based on established CT criteria. Two enlarging cysts, with 34 and 42 HU were thought to represent hemorrhagic cysts. The diagnosis was confirmed by unroofing in one, aspiration in 8 and follow-up imaging in the remainder.

Seven hundred and three of 1082 (65%) patients had been placed on broad-spectrum antibiotics in the period between the first and the second CT, to treat intestinal and biliary infections (Table-4). Collateral impact on GU tract organisms could not be excluded. Four hundred and ninety-six lesions disappeared or decreased in size, while 115 enlarged and 93 remained stationary in size. Fourteen were diagnosed as RMN based on imaging criteria, 10 as inflammatory masses and 2 as abscesses (Table-3). The impact of antibiotics is uncertain; in untreated patients, 89.4% of masses disappeared or got smaller versus 70.6% in treated patients (p = 0.0001). Another 339 lesions decreased in size or disappeared in patients who were not on antibiotic therapy.

DISCUSSION

The once universally held opinion that radical nephrectomy is the sole modality to manage renal cell carcinoma is now widely challenged (9). Partial nephrectomy, open or laparoscopic technique, cryoablation, radiofrequency (RF) ablation and ultrasonic ablation have proven equally effective in the management of suitable neoplasms (5,8,16-19). RF and cryoablation in particular have achieved recurrence-free survival rates of up to 98.7% (16-19). The most recent guidelines of the AUA call for a more conservative approach to the management of small renal masses (20). The now well established fact that tumor-free survival is achievable by resection irrespective of whether a renal cell carcinoma is of 1 ½ cm or 4 cm size, eliminates the urgency of surgical intervention for a small carcinoma (8,9,11). This led to the concept of surveillance of small renal mass lesions and assessment of indolent or aggressive behavior, indicated by rate of growth, intensity of enhancement on early cortico-medullary phase CTs (tumor neo-vascularity) and by spiking of

Table 4 - Outcome of Small Renal Masses in 703 Patients Treated with Antibiotics for Inflammatory.

Conditions of the Gastrointestinal or Biliary Tract and Pancreas versus 339 untreated Patients.

Outcome	# Treated with Antibiotics	# Untreated
Disappeared/Smaller	496	339
Unchanged	92	21
Larger	115	19
Total #	703	379

their rim (6,7,9,10,12). In older patients and those with medical co-morbidities this provides a period to establish and observe benign or indolent nature of the mass lesion without significantly reducing potential for tumor-free survival by delaying surgery. The guided biopsy for assessing histologic aggressiveness of lesions, which is the major factor determining frequency of reexamination, is well stablished (14,15,17). MDCTs and guided biopsy seem to provide adequate criteria for follow-up (14,15). As of date the significance of renal masses less then 1 cm in size and their appropriate management remain an open question (1,2,8). However, recent reports suggest a high incidence of malignancy of such lesions, particularly if located in cortex (8,21). Hence, a more frequent interval follow-up surveillance by ultrasound may be appropriate for such cortical mass lesions.

Our retrospective study of 1082 small renal masses, less than 1 cm in size, established the fate of these lesions on a second and sometimes third 3 or 4 phase MDCT. This study revealed most importantly that 604/1082 (55.8%) renal masses disappeared, while another 231 decreased in size in the interval of 4 to 36 months between the first and second CT. Partial volume averaging and the disparity of resolution between 2 phase and 4 phase studies may have caused false negatives (i.e., a lesion observed on the initial 4 phase study may not be apparent on a follow-up 2 phase CT). Tever, this scenario affected only 6% of patients.

Four hundred and ninety-six patients in whom the lesions either disappeared or substantially decreased in size had been treated with antibiotics for gastrointestinal, biliary or pancreatic infections (Table-3). This fact raises the question whether a co-existent urinary infection causing the mass lesions might have responded to these non-urinary tract antibiotics. The prevalence of RMN lesions (N = 62) suggests that many of the smaller disappearing lesions may likewise have been of RMN or inflammatory etiology (Tables 2 and 3).

The incidence of neoplasms is the most significant finding of our targeted follow-up CTs of lesions with increased or stationary size. Two renal cell carcinomas and 2 metastatic carcinomas, all with growth rates indicative of histologically aggressive behavior, were identified (Tables 2 and 3). Despite the rapid growth rate, the delay in surgical resection is not likely to have adversely influenced survival. Two patients with AML and 1 with a benign fibroma were also identified on targeted MDCTs (Table-2). Though benign in nature, their rate of growth, partly caused by hemorrhage into the AML, warranted resection.

The diagnosis of all 53 inflammatory lesions made possible early and definitive treatment by drainage and/or GU specific antibiotics, preventing propagation of the process and loss of parenchyma (Table-2).

The pertinent question of whether the incidental discovery of a small renal mass warrants follow-up by imaging, is to some degree answered by our data (2).

Neither the incidence of malignant neoplasms (< 0.4%) nor of inflammatory entities (5%) or of renal medullary necrosis (6%) seems to justify follow-up CTs. A delay in identification and hence surgical (or ablative) intervention of renal masses up to 3.5 cm in size is not likely to adversely influence recurrence-free survival. Inflammatory lesions, by nature of their pathophysiology, tend to become symptomatic early. The predominance of medullary lesions and their greater probability of spontaneous disappearance (73% for medullary lesions versus 22% for cortical lesions, p = 0.0001) favor an inflammatory etiology in masses prone to resolve. To avoid unnecessary radiation exposure to these patients, follow-up by imaging studies should be reserved for lesions exhibiting aggressive characteristics.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In the United States, the frequency of CT scans has increased up to three fold during the last decade without an equal increase in the prevalence of life-threatening conditions (1). It seems the excessive use of medical imaging increases health care costs and exposure to ionizing radiation without yielding significant benefits to all patients.

As a natural consequence of this "over-diagnostics" a high number of pathological findings are detected leading to the question for the need for therapy in these cases.

In case of RCC the detection of smaller renal masses, i.e., earlier tumor stages, leads to a change in the management of localized disease:

radical nephrectomy is not the standard therapy anymore but nephron sparing treatment is a common option with significant benefits regarding kidney function and patients outcome (2,3).

But, does that mean: the smaller detected the better treated? Obviously not. In a retrospective analysis of 1082 renal lesions the current study shows the doubtful benefit of an excessive use of diagnostic tools. Even in the age of high-resolution imaging, the characterization of very small renal lesions remains difficult and not reliable - in the study almost 60% of the lesions disappeared during follow-up: in 70% of the patients who received antibiotics only but in 90% of the untreated patients. Malignancies have been found in 0.4% only.

This analysis shows in an impressive way the limits of a worthy and reliable diagnostic instrument. Therefore, the major goal must still be the reasonable interpretation of the data in order to develop strategies for patient care and avoid insufficient therapy as well as overtreatment. This still remains the mission of the Urologist who needs to evaluate "pathological" findings critical to counsel his patients properly.

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EDITORIAL COMMENT

This is an interesting study in an impressive casuistic of small renal masses (SMR) < 1.0 cm, showing the clinic and radiologic outcomes of theses lesions. It's an original contribution to the scientific literature and to the clinical practice; these informations should be considered before clinic decisions for this prevalent situation nowadays.

Despite the retrospective nature and the long duration of the study in several institutions and with different CT equipments, the study has the merit to show the situation as it occurs in real life, during 12 years, in multiple academic institutions.

With the information provided, we must be sure not to offer intensive follow-up protocols for this kind of SMRs. Accordingly, the patients will be less frequently exposed to the pre-exam anxiety, and costs, radiation and radiologic contrast side effects of repeated CTs.

In the future, a prospective study with modern high resolution helicoidally CT equipments could be done.

For a specific subgroup of patients, with hereditary or familial renal cell carcinoma syndromes, the fate of their little SMRs probably will be different, since those individuals have thousands of microscopic malignant lesions in each kidney, although in these cases the clinical decision will be not changed; usually the surgical or ablative procedures are not offered until their lesions reaches 3.0 cm.

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