Advances in Urology

Management of Small Renal Masses

Guest Editors: Jose Rubio Briones and F. Algaba

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 606401, 2 pages
doi:10.1155/2008/606401

Editorial

Management of Small Renal Masses

Jose Rubio Briones[1] and F. Algaba[2]

[1] *Urology Department, Valencia Institute of Oncology, C/ Prof. Beltrán Báguena 8, 46009 Valencia, Spain*
[2] *Department of Pathology, Fundación Puigvert, C/Cartagena 340, 08025 Barcelona, Spain*

Correspondence should be addressed to Jose Rubio Briones, jrubio@fivo.org

Received 30 December 2008; Accepted 30 December 2008

When we started to plan this special issue, we were under the thought that we are facing more and more cases of small renal masses in our daily work as urologists and pathologists. This common fact nowadays will probably increase in the near future as radiological studies are more frequently ordered and fortunately we face an increase in longevity, and also as people can get to detect their renal masses before they really arrive to the classic lumbar pain/haematuria/lumbo-abdominal mass symptoms.

First of all, strict definition of small renal mass is lacking; most of the authors consider 4 cm as cut-off, imported from the classical one regarding partial surgery of the kidney and TNM classification; but we all know that these concepts are changing and probably will need to be taken into consideration.

Been sure the increase in detection, we have to precise the different needs of radiological explorations to characterize a small renal mass; is sonography, CT, and MRI necessary for all patients? We are still lacking to differentiate from a standard radiological approach benign and malignant small renal masses. What is the role of percutaneous biopsies in these cases? These (and others) are questions that urologists do not answer uniformly. Economical issues are also important in a public medical system.

When we move to therapeutic aspects, things are even more unresolved. There is an increasing number of small renal masses managed under a strict watchful waiting policy but this is not plausible for all cases. Limits of age and growth rate have been argued again for this approach and most of the times, at least in our country, people are not happy knowing they could harbor a renal cancer been just "observed".

Regarding active treatment, first radical nephrectomy and lastly open partial nephrectomy have been the gold standard approaches. In fact, main guidelines consider the second the treatment of choice for small renal masses nowadays, having shown the same oncological control compared to radical surgery. During the last decade, laparoscopic partial nephrectomy has emerged with comparable oncological results, adding better cosmetical and perioperative recovery data. The main drawback of laparoscopic partial nephrectomy is its difficulty, being just feasible in experienced centers with high volume of patients.

In the last five years, different nonablative techniques have appeared to compete with partial (open or laparoscopic) nephrectomy aiming to achieve same oncological control, testing percutaneous approach, reducing complication rates, and improving recovery, what have been called minimally invasive treatments. As time goes by, these techniques have failed to demonstrate good and reproducible results in any prospective trial for the percutaneous approach, but this and the laparoscopic approach are increasing in number worldwide, mainly radiofrequency and cryotherapy for small renal masses. Follow-up will tell us if they achieve same cancer control, but preliminary results show acceptable results for cryotherapy and are questionable for radiofrequency.

Our aims are to summarize distinct aspects of the management of small renal masses nowadays, focusing on its epidemiology, pathological aspects, prognosis, and mostly the different treatment strategies.

In the first three manuscripts, the authors try to concrete the clinical problem of small renal masses nowadays, focusing on multifocality and other prognostic factors that could guide their management. Two papers more analyze the familial syndromes involved with small renal masses and the possible genetic counselling we should offer the relatives of patients with these tumors.

The next block studies the different radiological aspects of small renal masses, both in the preoperative scenario and then after treatment, where many doubts about local recurrence need to be clarified by radiologists.

There is an interesting and vast review about the physiopathology of renal ischemia, a crucial point in renal partial surgery. The reader will find the limits of it and the research ongoing in such an "unknown" field.

In the therapeutic block, there are two nice reviews about watchful waiting policy analyzing fresh data. Then, open partial nephrectomy will be reviewed and presented with a comparative intent to laparoscopic partial nephrectomy in 3 papers, and reviews on nonablative techniques will be discussed in two papers more.

Finally, two papers analyze the problems that pathologist face in front of these many-times small renal masses.

We hope that this special issue will answer some of the reader doubts about the management of small renal masses, knowing that the next and near future will offer us much more data that can change our actual point of view.

Jose Rubio Briones
F. Algaba

Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 782381, 7 pages
doi:10.1155/2008/782381

Review Article

Epidemiology of Kidney Cancer

D. Pascual[1] and A. Borque[2]

[1] *Department of Urology, San Pedro Hospital, 26006 Logroño, Spain*
[2] *Department of Urology, Miguel Servet University Hospital, 50009 Zaragoza, Spain*

Correspondence should be addressed to A. Borque, aborque@comz.org

Received 24 March 2008; Revised 20 August 2008; Accepted 26 September 2008

Recommended by J. Rubio

Some tumors are known to have a definite cause-effect etiology, but renal cell carcinoma (RCC) is not one of them precisely. With regard to RCC we can only try to identify some clinical and occupational factors as well as substances related to tumorigenesis. Smoking, chemical carcinogens like asbestos or organic solvents are some of these factors that increase the risk of the RCC. Viral infections and radiation therapy have also been described as risk factors. Some drugs can increase the incidence of RCC as well as other neoplasms. Of course, genetics plays an outstanding role in the development of some cases of kidney cancer. Chronic renal failure, hypertension, and dialysis need to be considered as special situations. Diet, obesity, lifestyle, and habits can also increase the risk of RCC. The aim of this review is to summarize the well-defined causes of renal cell carcinoma.

1. INTRODUCTION

Speaking about cancer, one of the most difficult issues is to find a definite and direct cause. There are few tumors with a well-known etiology, but renal cell carcinoma (RCC) is not one of them precisely.

In these cases, we can only try to identify some clinical and occupational factors, or some substances related to carcinogenesis.

Epidemiology is an important tool to answer many questions about cancer origin. Differences in age, gender, and geographic distribution have been reported, and multiple clinical factors related to the development of RCC have been established. Some of them have been thoroughly demonstrated in experimental models and in vitro studies, however not all of them recognized as definite etiologic factors.

2. MATERIAL AND METHODS

A systematic review search strategy was developed to identify publications related to epidemiology of renal cell carcinoma. This search strategy was run in PubMed through the medical subject heading "carcinoma, renal cell" and the subheading of this descriptor "epidemiology." We limited our search strategy to articles published in the previous 5 years, language English or Spanish, and related to humans.

585 articles were found. Abstracts were evaluated and the full text of articles selected was reviewed. Secondary search from the bibliography of selected articles was also considered.

The European cancer registry-based study on survival and care of cancer patients (EUROCARE) and our experience was considered. Last review was on 31 of March 2008.

3. DEMOGRAPHIC ASPECTS OF RENAL CELL CARCINOMA

Among urologic tumors, RCC takes the third place in incidence, following prostate carcinoma and transitional cell carcinoma of bladder.

Representing two percent of the adult malignancies [1], this malignancy takes the tenth and fourteenth place among men and women, respectively, with a man to woman ratio of 3/2 [2]; see Table 1.

The peak incidence occurs in the sixth decade, with 80% of the cases within the 40 to 69-year-old population.

Although the most frequent renal tumor in the childhood is the Wilms tumor, it is important to state that the RCC represents between 2% to 6% of the renal tumors in

Table 1: Epidemiologic features of the RCC.

3rd urologic tumor in incidence	Maximum incidence on 6th decade
2% of adults malignancies	Male/Female ratio: 3/2
85–90% of adult renal parenchymal malignancies	10th male malignancy and 14th female malignancy
2–6% of child renal malignancies	More frequent in afroamerican people
Cancer specific mortality of 40%	More frequent in urban people

Table 2: Geographic distribution of RCC [8].

Incidence	Zones
High	Denmark, New Zealand, Norway, Scotland
Moderate	United States, Australia, Belgium, France, Holland
Low	Spain, Ireland, Italy, Japan, Venezuela, India, China

Table 3: Some etiologic factors of RCC [15].

Etiologic factor	Relative risk (C.I. 95%)
Von Hipple-Lindau disease	100 (not available)
Chronic dialysis	32 (not available)
Obesity	3.6 (2.3–5.7)
Smoking	2.3 (1.1–5.1)
First relative with RCC	1.6 (1.1–2.4)
Hypertension	1.4 (1.2–1.7)
Dry cleaners	1.4 (1.1–1.7)
Diuretics	1.3 (1.07–1.52)
Trichloroethylene	1 (0.7–9.66)
Radiation therapy	1.1 (3.2–8.1)
Phenacetin	1.1 (2.6–6)
Polycystic kidneys	0.8 (2–4.5)
Cadmium exposure	1 (2–3.9)
Arsenic exposure	1.6 (2.3–4.1)
Asbestos exposure	1.1 (1.4–1.8)

children, without differences between sexes [3, 4]. Besides, the incidence of both malignancies is similar in the second decade of life. In these early ages the papillary differentiation seems to be more frequent with higher tendency to present a locally advanced and high-degree disease at the moment of the diagnosis [5], However, when comparing stage by stage with adult tumors, we find a better response to surgical treatment and higher survival rates, even with positive nodal disease.

RCC represents 85 to 90% of renal parenchymal malignancies [6, 7].

Among urologic tumors, it is the worst in cancer specific mortality, since more than 40% of the patients with RCC die of the disease, opposite to the 20% mortality observed in prostate cancer or bladder carcinoma.

In United States 30 000 new cases are diagnosed every year, and approximately 12 000 patients die of this disease, with an incidence of near nine cases per 100 000 inhabitants per year. Afroamericans have 10 to 20% higher incidence, and the reason is not completely understood [9].

Most of the cases of RCC are sporadic and only 4% are familiar. The estimated number of new cases in the European Union during 2006 was 63300, with 26400 deaths of RCC [10]. The estimated survival in 5 years rises to 54% in males and 57% in women [11].

Table 2 shows different incidences of RCC in the world.

Since 1930 incidence of RCC has been increasing, mostly between 1930 and 1980. Within this period the incidence also rose from 0.7 to 4.2 per 100 000 per year in women and from 1.6 to 9.6 in men [12]. Since 1980 a sharp increase has not been observed comparing to other genitourinary tumors or other type of malignancies. Similarly, deaths caused by RCC had been stable.

Variations of incidence within the first period could be explained by an easier diagnosis, as a result of diffusion and routine use of diagnostic tools such as ultrasound or CT scan, and not due to a real increased incidence of RCC.

It is also important to state that RCC is found incidentally in 1.5% of the autopsies [13].

RCC is more frequent in urban populations rather than in rural ones. This observation may be explained by the sanitary conditions and the smoking habit in urban populations. However it has not been related neither to socioeconomic nor to educational status [14].

There are multiple factors related to the development of RCC; see Table 3. Some of them have been demonstrated in experimental models and in vitro studies, however not all of them can be considered as definite etiologic factors.

Herein, we describe these main factors.

3.1. Smoking

Multiple carcinogenic substances have been identified in tobacco and related to a variety of neoplasms at different levels. A high incidence of RCC in smokers has been shown [16], estimated in 2.3 fold risk ratio, directly related with the number of cigarettes and inversely with age of beginning of the habit. Likewise it has been shown that the carcinogen dimetilnitrosamine induces this neoplasm in experimental studies. Some authors reported that smokers' risk for RCC compares to nonsmokers' after the fifth year of nonsmoking, but a meta-analysis made by Hunt showed that only after ten years the risk can be similar in both groups [17], depending on the dose of tobacco inhaled. Another study by McLaughin [18] and Lipworth [19] confirmed tobacco as the most important risk factor for renal cancer, detected in 20% of the cases of RCC.

But smoking is not only important in the genesis of RCC, and prognostic nomograms have also been developed [20]. A multivariate study carried out in "Miguel Servet" University Hospital of Zaragoza, Spain (in press), smoking habit increases 2.84 fold (1.27–6,32) the risk of progression of the disease after surgery [21], similarly to previous studies in other countries.

3.2. Chemical carcinogens

Some radiological contrasts have been associated with an increased incidence of RCC [22]. Although Cycasin (a substance derived from a palm fruit that grows in the island of Guam) induces RCC in animals, a higher incidence of this neoplasm within the island population could not be shown.

Cadmium was demonstrated to have influence on the development of RCC in smokers [23, 24].

(i) *Asbestos*. A significantly elevated mortality rate for kidney cancer has been reported in two cohort studies, on insulation workers [25] and on asbestos products workers [26]. Autopsy surveys and animal studies indicate that asbestos fibers can be deposited in kidney tissue.

(ii) *Organic solvents*. Pesticides, copper sulphate, benzidine, benzene herbicides, and vinyl chloride have been found as risk factors of RCC in prolonged exposure. A dose dependent effect has been seen only for organic solvents and copper sulphate [27, 28].

Recent reviews of cohort studies found little or no evidence of an increased risk for RCC among people exposed to gasoline and petroleum derived products [29, 30].

(iii) *Polycyclic aromatic hydrocarbons*. Workers exposed to high levels of polycyclic aromatic hydrocarbons like coke and coal oven workers, firefighters, asphalt, and tar have been reported to be at increased risk for kidney cancer.

3.3. Radiation

Ionizing radiation appears to increase the RCC risk slightly, especially among patients treated for ankylosing spondylitis and cervical cancer [31]. An increased risk has also been reported for patients receiving radium 224 for bone tuberculosis and ankylosing spondylitis [32].

3.4. Viruses

The immunosuppressant state related to the HIV infection determines that prevalence of RCC in the infected population rises 8.5 times compared to the prevalence of the noninfected ones.

The influence of the polyomavirus SV 40 and of the adenovirus 7 has also been detected in experimental studies.

A clear-cut association was found between herpes-type virus and renal tumors in toads. These findings led to search for evidence of herpes virus proteins in human tumors as well. Although herpes simplex proteins were found in only one study [33, 34], these findings need to be confirmed by further research.

3.5. Diuretics

This type of drugs which inhibits water reabsorption on the renal tubule cells seemed to be responsible for a higher incidence of RCC in patients with chronic intake of diuretics [35, 36]. Even though, it is noteworthy that hydrochlorothiazide and furosemide (both effective at the renal tubule level) induce tubular cell adenomas and adenocarcinomas of the kidney in rats [37]. But Yuan [38] showed in his study that an adequate use of diuretics for treating hypertension eliminates the risk associated with the above mentioned drugs, differentiating the influence of hypertension as a risk factor for RCC rather than diuretics.

3.6. Analgesics

This is a controverted topic. Several studies reported an increased incidence of RCC in patients with chronic intake of analgesics like paracetamol, salicylates, or phenacetin [39, 40], however in other studies this relationship has not been confirmed neither for time of consumption nor for dose of the drug taken [41].

Although a heavy use of drugs containing phenacetin has been clearly demonstrated to increase the risk for transitional cancer of the renal pelvis, the association with RCC is much weaker. On the other hand, an increased risk of RCC associated with aspirin or acetaminophen consumers was observed [42], but others believe that neither acetaminophen nor other analgesics have been convincingly linked with RCC [19].

3.7. Oestrogens (dietilestilbestrol)

Although oestrogens can induce RCC in the animal model, little evidence supports an association of the disease with oestrogens in humans [43] and only weak relation has been reported for the use of oestrogens after menopause and for oral contraceptives [44].

3.8. Inheritance

Most of the cases of RCC are sporadic; however there are some defined types of RCC with a hereditary pattern [45].

(1) Von Hippel-Lindau (VHL) disease

The VHL disease is inherited through an autosomal dominant trait. The syndrome is caused by germline mutations of the VHL tumor suppressor gene, located on chromosome 3p25-26; these mutations can virtually always be identified [46]. The VHL protein takes part in cell cycle regulation and angiogenesis [47]. Patients develop capillary haemangioblastomas of the central nervous system and retina, clear cell carcinoma, phaeochromocytoma, pancreatic, and inner ear tumors.

The clinical diagnostic criteria of VHL disease consist of

(i) presence of capillary haemangioblastoma in the central nervous system or retina,

(ii) presence of one of the typical VHL associated extraneural tumors, within pertinent family history.

Fourty to sixty percent of the patients with VHL disease present an RCC. Although they are usually low-grade tumors, the progress rate to metastasis is around 30% [48].

Renal lesions in carriers of VHL germline mutations are either cysts or clear cell RCC. They are typically multifocal and bilateral.

(2) Hereditary papillary renal carcinoma

This type of renal carcinoma is an inherited tumor syndrome with autosomal dominant trait and of late onset, with multiple and bilateral papillary renal cell carcinomas type 1. The disease is caused by activating mutations of the MET oncogene which maps the chromosome 7q31.

(3) Hereditary leiomyomatosis and renal cell carcinoma

This is an autosomal dominant tumor syndrome with germline mutations in the FH gene (chromosome lq42.3–q43), These patients have the tendency to acquire benign leiomyomas of the skin and the uterus, and occasionally papillary renal cell carcinoma type 2 and uterine leiomyosarcomas.

(4) Birt-Hogg-Dube syndrome

This syndrome is characterized by benign skin tumors, specifically fibrofolliculomas, trichodiscomas, and acrochordons. Multiple renal tumors and spontaneous pneumothoraces are also frequent. We can find chromophobe RCC, typical RCC, hybrid oncocytoma, papillary RCC, or oncocytic tumors.

The Birt-Hogg-Dube gene maps the chromosome 17p11.2 and encodes the protein called folliculin. This gene is also involved in sporadic RCC [49].

(5) Familiar clear cell renal cell carcinoma

These families present a hereditary form of multiple, bilateral clear cell RCC but without any clinical evidence of suffering the von Hippel-Lindau disease.

This hereditary cancer is characterized to present translocations affecting the chromosome 3. Translocations have been described among the chromosome 3 and the chromosomes 8 [50], 6 [51, 52], 2 [53, 54], 1 [55], and 4 [48].

3.9. Acquired cystic disease/chronic dialysis

Approximately the 35 to 47% of the patients on dialysis and specially those with a very long history present acquired cystic disease. Some patients with this disease develop a papillary hyperplasia in the epithelium of the cysts that would be the origin of the RCC [56, 57].

Approximately the 5 to 9% of the patients with acquired cystic disease will develop an RCC [58], showing a higher incidence than the general population. As such, we suggest a close follow-up in the kidney-transplant population, and therefore the immune-suppressed individuals who are on dialysis for a long time, due to a high risk of developing RCC.

3.10. Diet and obesity

Hypercaloric diet and obesity seem to be associated with a higher risk for suffering of RCC. Obesity accounts for about 30% of renal cancers [19].

Some studies relate a higher incidence of RCC with high body mass index. The relative risk was found to be 3.3 in males and 2.3 in females [59].

The mechanism of obesity to cause kidney cancer is not clear. Hormonal changes such as increased levels of endogenous oestrogens in the obese may be the mechanism through which oestrogens induce renal cancer as observed in animal models. However, there is scant epidemiologic evidence supporting hormonal carcinogenesis regarding RCC. Obesity may also predispose to arterionephrosclerosis, which may render the renal tubules more susceptible to carcinogens. Elevated cholesterol levels associated with obesity might also play a role, as suggested by animal studies showing that cholesterol-lowering drugs provide some protection against RCC. Cholesterol and other lipids may favour tumor development by an inhibitory effect on immune cells.

Low vitamin D level, which is usually present in obese patients, may predispose to acquire RCC. This vitamin is known to have inhibitory effects on the growth of RCC cell lines in vitro [60].

Finally, Lipworth [19] reported that the only consistent protective factor is consumption of fruit and vegetables.

3.11. Coffee, alcohol, and other beverages

Case-control studies have not confirmed the suggested relationship between kidney cancer and consumption of coffee, when adjusting the smoking variable. Although two studies have suggested a positive association, a two-fold increased risk in both sexes was associated with the use of decaffeinated coffee. In another study, an increased risk of RCC was found only among women with regular coffee intake [61]. No dose-dependent risk was reported in either study.

On the other hand, a significant lower risk was reported in Norway among consumers of seven or more cups of coffee compared to those who drink two or fewer cups daily, representing a relative risk of 0.25 [62]. Review studies indicate that coffee consumption does not increase RCC risk.

Few studies have shown an increased risk of RCC among tea women consumers [63]. Another study has found a dose-response relationship between tea consumption and kidney cancer mortality [64]. The etiologic significance of these findings in direct relationship with tea tannins is not clear [65].

The association between alcoholism and kidney cancer mortality has not been demonstrated by well-deisgned studies [66]. In fact, a recent case-control study found a statistically significant inverse association between alcohol consumption and RCC risk [67]. No increase in mortality from kidney cancer has been reported either within alcoholic patients or brewery workers [68].

3.12. Physical activity

A moderate recreational activity reduces the risk of renal cancer both in men and women. The mechanism is not clear, but there is no doubt that energy expenditure is one of the major determinants for obesity, which is a strong risk factor for RCC.

3.13. Hypertension

Hypertension seems to be significant for the development of kidney cancer. The strength of this relationship is reduced with the use of diuretics and other antihypertensive drugs, regardless of some of these drugs have been associated with RCC risk. The main problem consists to identify whether the increased risk is due to hypertension or antihypertensive medications.

Despite the mechanism for hypertension to cause renal cancer is not completely understood [69] it seems that metabolic and/or functional changes in the renal tubular cells produce carcinogenesis. Wide case-control studies have only found a slight relation between RCC and hypertension [70]. Further studies are needed.

3.14. Alterations in development of the kidney

The anomalous development of the kidneys may act as a teratogenic factor.

In horseshoe kidneys, the area of the isthmus is prone to develop tumors [71], due to an anomalous migration of the cells toward this area. However, although the most frequent tumor developed in this malformation is the RCC, the incidence remains identical to that of the general population, without differences in evolution or prognosis [72].

In conclusion we can affirm that respect RCC, like in other malignant diseases, ethiology, and risk factors are not completely understood. There is some evidence that certain situations, drugs, habits, or genetics are related to the development of renal cancer, but several studies found controversial results and different degrees of evidence.

Smoking and obesity seem to be the most important independent risk factors in the genesis of RCC, reported by different authors.

Chromosomal mutations were clearly identified in the context of well-defined hereditary diseases.

The adequate use of diuretics and analgesics may be recognized as protective factors not only for RCC but for other diseases as well.

General healthy habits like limiting alcohol and coffee intake, decreasing the number of cigarettes, lowering fat consumption, keeping a suitable weight, and practicing regular exercise may reduce the risk and indicence of RCC.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 310694, 6 pages
doi:10.1155/2008/310694

Review Article

Small Renal Masses: Incidental Diagnosis, Clinical Symptoms, and Prognostic Factors

F. M. Sánchez-Martín,[1] F. Millán-Rodríguez,[1] G. Urdaneta-Pignalosa,[1] J. Rubio-Briones,[2] and H. Villavicencio-Mavrich[1]

[1] *Servicio de Urología, Fundació Puigvert, C/Cartagena 340, 08025 Barcelona, Spain*
[2] *Servicio de Urología, Instituto Valenciano de Oncología, C/Beltrán Báguena 8, 46009 Valencia, Spain*

Correspondence should be addressed to F. M. Sánchez-Martín, fsanchez@fundacio-puigvert.es

Received 13 May 2008; Revised 26 September 2008; Accepted 18 November 2008

Recommended by Maxwell V. Meng

Introduction. The small renal masses (SRMs) have increased over the past two decades due to more liberal use of imaging techniques. SRMs have allowed discussions regarding their prognostic, diagnosis, and therapeutic approach. *Materials and methods.* Clinical presentation, incidental diagnosis, and prognosis factors of SRMs are discussed in this review. *Results.* SRMs are defined as lesions less than 4 cm in diameter. SRM could be benign, and most malignant SMRs are low stage and low grade. Clinical symptoms like hematuria are very rare, being diagnosed by chance (incidental) in most cases. Size, stage, and grade are still the most consistent prognosis factors in (RCC). An enhanced contrast SRM that grows during active surveillance is clearly malignant, and its aggressive potential increases in those greater than 3 cm. Clear cell carcinoma is the most frequent cellular type of malign SRM. *Conclusions.* Only some SRMs are benign. The great majority of malign SRMs have good prognosis (low stage and grade, no metastasis) with open or laparoscopic surgical treatment (nephron sparing techniques). Active surveillance is an accepted attitude in selected cases.

1. INTRODUCTION

The incidence of renal cell carcinoma (RCC) has increased over the past two decades reflecting earlier diagnosis at an earlier stage, largely due to more liberal use of radiological imaging techniques [1], introducing concepts as "incidental" or "small renal masses" (SRMs). SRM could be defined as those renal masses lower than 4 cm in diameter [2–4], accounting for 48–66% of RCC diagnosis [5]. Actually, 79–84% of SRM are detected before genitourinary symptoms are present [6–8] (size is smaller than symptomatic cancer classifying it as local stage with a better prognosis) [9]. Although mean tumor size has decreased in the last years, several studies indicate that this variable is one of the most important prognosis factors for RCC, and it has also contributed to the last modifications of RCC staging and treatment [10, 11].

Years ago, when most RCC were symptomatic, hematuria was the main symptom, so asymptomatic tumors were diagnosed later or not diagnosed. Before widespread use of imaging techniques, 67–74% of RCC remained undetected until death (autopsies), and only 8.9–20.0% of these undiagnosed RCC were responsible for the patient's death [5]. These data support the fact that some RCC have a favorable evolution and support active surveillance in select cases. Natural history of SRM has not been historically well established because most masses were surgically removed soon after diagnosis.

2. DEFINITIONS AND GENERAL CONCEPTS

A renal mass discovered by routine ultrasound, CT or MR indicated for other pathology, could be named incidental. A significant number of SRMs are incidentally diagnosed [2, 12]. Renal masses (benign and malign) can be considered incidental if they are diagnosed in the absence of symptoms or signs. "Incidentaloma" or "incidental" masses related to other organs such as adrenal, pituitary, thyroid and parathyroid, as well as the liver are published. Mirilas and Skandalakis questioned the scientific justification for

this neologism and suggested that should be replaced by "incidentally found" [13]. Narrow relation of "incidental" and "small masses" are considered in some papers [2, 14–16]. A possible confusion factor may be that tumors classified as "incidental" show symptoms not directly attributable to the renal mass, thus not detected by the urologist [5].

Small renal masses include all solid or complex cystic lesions lower than 4 cm. Among them, different benign tumors are found in a 12.8 to 17.3% of cases [17–19] including oncocytoma in 53%, angiomyolipoma in 22%, atypical cyst in 10%, and different benign lesions as leiomyoma, xanthogranulomatous pyelonephritis, and focal infarction in 13% [17].

Incidental renal tumors have a mean size of 3.7 cm (median 3, range 0.8 to 12) [7]. Nevertheless, tumors greater than 4 cm could be incidental. Incidental diagnosis is performed in the 82.4%, 78.9%, and 56.7% of the 1–4 cm, 4–6 cm and greater than 6 cm renal masses, respectively [5]. If a cut-off should be made, most cases of RCC lower than 7 cm are incidentally discovered, while tumors greater than 7 cm are mainly symptomatic but, as mentioned previously, this cannot be taken as a rule [7].

3. SYMPTOMS

The main symptom of RCC is hematuria (35%–60%) [20–22] but SRMs are often asymptomatic (incidental). Classical manifestations of RCC such as fever or jaundice are extremely rare in front of an SRM. In a study of 349 SRM's, microhematuria was reported in only 8 cases. Prognostic of those RCC diagnosed by hematuria is worse than those incidentally diagnosed [23]. Stage I lesions were observed in 62.1% of patients with incidental RCC renal cell carcinoma and just in 23% with symptomatic RCC [6]. Among the different entities causing the incidental diagnosis of an SRM, many have been considered; evaluation for other malignancy (17.7%), gastrointestinal symptoms including nonspecific abdominal pain (16%), evaluation of medical renal disease (6.6%), hypertension (4%), back pain (5.1%), cirrhosis (1.4%), nephrolithiasis (1.4%), diverticulitis (1.4%), lung lesion (1.1%), increased liver enzymes (1.1%), trauma (0.8%), screening CT (0.8%), urinary tract infection (0.8%), chest pain (0.8%), aortic aneurysm evaluation (0.8%), cough (0.5%), shortness of breath (0.5%), Crohn's disease (0.5%), bronchocele (0.5%), and anemia (0.5%). No differences were found among incidental or symptomatic RCC according to age, sex, and laterality [15].

Laboratory findings have a significant impact on the patients with organ-confined RCC prognosis. Although, neoplasic condition reflects an increased invasive potential, characterized by overexpression of substances involved in cell proliferation as matrix metalloproteinases [24]; however, inflammatory markers like erythrocyte sedimentation rate greater than 30 mm/hour, hemoglobin levels less than 10 gm/dL (female) or 12 gm/dL (male), and increased alkaline phosphatase are negative prognosis elements [22].

Some demographic data may help to presume the matter of SRM: RCC is unusual in young patients; angiomyolipomas and multilocular cystic nephromas are more common in women [25].

4. PROGNOSIS FACTORS

Age is not a significant factor on survival in patients with incidental RCC [26], so it is probably not a prognosis factor for SRM [5]. However, as the patient ages, the SMR stage is higher; so the incidence of SRM finally staged as pT3 tumors in younger than 45 years, 45–75 years, and older than 75 years is 2.3%, 6.9%, and 14.3%, respectively [17]. The probability of developing metastases, with 12 years follow-up, is greater in men [27].

5. BENIGN TUMOR FREQUENCY

Lee et al. published 230 cases of SRM (lower than 4 cm), 88% malignant and 12% benign (oncocytoma) [6]. DeRoche et al. described that SRMs are nonneoplasic entities. Benign neoplasms and low-and high-grade carcinoma accounted for 1.6%, 18.0%, 49.0%, and 31.4%, respectively [8]. The percentage of malignancies increases from 72.1% in masses lower than 2 cm to 93.7% in tumors greater than 7 cm [7].

In conclusion, if the tumor is greater in dimensions, the possibility of being benign is lower; so tumors lower than 1, 2, 3, and 4 cm were benign in 46.3, 22.4, 22, and 19.9%, respectively [18].

6. SIZE AND STAGE

In a study from Schlomer et al., global mean renal tumor size decreased by 32% and pT1 tumors increased from 4% to 22% (1989–1998). For every cm increase in size, the odds ratio of malignancy increased 17–39% [7, 18]. Mean tumor size for benign tumors was 4.2 cm (median 3.3, range 0.2–25) compared to 6.3 cm (median 5.5, range 0.1–24) for malignant tumors. Median clinical diameter was 2.93 cm (range 0.8 to 4.0) in RCC lower than 4 cm. RCC mean size was 4.6 cm (range 0.8–21) and benign masses mean size 2.8 cm (range 0.8–9.5) [5]. Incidental RCC mean size was 3.7 cm (median 3, range 0.8–12) and symptomatic RCC mean size was 6.2 cm [7]. In pathological stage, 51.33% and 27.3% were pT1, 25.6% and 27.3% pT2, 10.9% and 23.8% pT3a, 10.9% and 16.6% pT3b, 1.2% and 2.3% pT3c, and 0% and 2.3% pT4 in incidental and symptomatic RCC, respectively.

Puppo et al. reported 94 patients with resected RCC (size: 1.1–4.5 cm), describing that pathological stage was pT1a in 92.5%, pT1b in 4.2%, and pT3a in 3.1% [28], similar to Pahernik et al. that reports pT1a in 84.5%, pT1b in 8%, and pT3 in 7.5% (organ confined in 92.5%) and ≥pT3 was found in 3.0%, 5.1%, and 12.1% of the patients when analyzed by tumor size 2, 3, and 4 cm, respectively [17]. A total of 25% of SRM doubled in volume within 12 months, 34% reached 4 cm and experienced rapid doubling time [5].

Kunkle et al. found synchronous metastatic disease increased by 22% with each cm increase in tumor size, by 50% for each increase of 2 cm, and doubled for each 3.5 cm increase in primary tumor size [11].

In other manuscript, incidental RCC had lower stages compared to symptomatic RCC [15]. Between T1a and T1b lesions, there was no significant difference in the rate of malignancy and high-grade malignancy regarding incidental or symptomatic presentation. The different percentage of T2 malignant tumors between incidental (90.9%) and symptomatic tumors was neither significant [5]. Understaging for pT3 tumors lower than 3 cm was 7.5% [17]. Cystic component appears in 24.1% of renal masses lower than 4 cm, being 57.1% in Bosniak type III and the rest in Bosniak type IV [5].

Volpe et al. showed no differences between the average growth rate for solid SRM (0.11 cm per year) and cystic masses (0.09 cm per year) [5]. Multifocality was present in 5.3–12% in small RCC [7, 8]. The rate of multifocality was 2.0%, 5.1%, and 7.05% in tumors of 2, 3, and 4 cm, respectively [17].

7. GRADE

Ninety percent of tumors lower than 1 cm were low-grade compared to only 37.9% of tumors ≥7 cm [18]. Grade 3 was found in 7.1%, 9.0%, and 14.0% of the patients in the 2, 3, and 4 cm groups, respectively and just 10.6% of small RCC were grade 3 [17]. Tumor grade increase as tumor size increase from 2 to 4 cm. Grade 1 was 31.3% for 2 cm, 27.4% for 3 cm, and 18.1% for 4 cm tumors; and grade 3 was 7.1% for 2 cm, 9% for 3 cm, and 14% for 4 cm tumors [17]. Urinary tract invasion, reported in some low-grade tumors, is a negative prognostic factor [29]. However, 45% of T2 incidental malignancies were high grade compared to 78.8% of T2 symptomatic malignancies [5]. Tumor grade increased according to size in clear cell, papillary, and chromophobe tumors. In high-grade carcinomas, 65% of the tumors had a 1-year volume doubling time.

8. CELLULAR TYPE

Clear cell is the most frequent cellular type regardless of tumor size [7]. Among SRM, Frank et al. showed that percentage of clear cell cellular type increased according to size: 59.9, 70.2, and 72% in lower than 2, 3, and 4 cm, respectively [18]. Cellular type for small RCC was 78% clear cell carcinoma, 15.3% papillary carcinoma, and 7% chromophobe carcinoma [17].

Volpe et al. showed that papillary RCC incidence is more frequent in 2 cm tumors than in 3 and 4 cm tumors (24%, 13.2%, and 13.5%, resp.) [17]; data not refuted by other authors [5]. Papillary cell type is more frequent than clear cell in tumors lower than 1 cm [18].

9. METASTASES

Metastases at diagnosis were found in 3.0%, 2.6%, and 6.0% of the patients with 2, 3, and 4 cm renal tumors, respectively [17]. Furthermore, lymph node spread was 4.8% and 15%, metastasis was 9.2% and 26%, and local recurrence was 1.2% and 8.3%, among incidental and symptomatic RCC, respectively [15]. With active surveillance, enhancing lesions with zero median growth rates did not progress to metastatic disease, and only 1.4% of patients with 0.31 cm yearly median growth rate progressed to metastatic disease [7]. Chawla et al. showed RCC mean growth rate of 0.40 cm yearly (median 0.35, range 0.42 to 1.6) [30].

Median tumor size for patients presented with pathologically confirmed synchronous metastatic disease was significantly greater than for those presenting with localized disease, 8.0 cm (range 2.2 to 20.0) and 4.5 cm (range 0.3 to 17.5), respectively. Tumors of 3.0 cm or smaller had synchronous metastasis in just 4.5% of the cases [31].

10. SURVIVAL

A total of 548 patients with small RCC were analyzed by Pahernik et al.: 22 (4%) had metastasis, 9 died by cancer in a mean time of 1.9 years (range 0.7 to 3.4) after diagnosis [17]. D'allOglio et al. observed a mean overall survival of 91% in patients with T1a tumors and up to 78.7% survival after 10 years of local treatment [15].

Several groups have developed predictive models to construct prognosis algorithms in order to facilitate follow-up and to indentify progression risk. Raj et al. present a predictive model that includes gender, symptoms, radiological findings, and size as preoperative prognostic factors; in order to establish a chance of being cancer-free 12 years after surgery (Figure 1). In case of SRM, it could not be useful to decide surveillance or active treatment. For example, a woman with a 3 cm incidental malign SRM has a 96% chance of being cancer-free 12 years after surgery. In contrast, a man with a 4 cm symptomatic (local signs) malign SRM and positive TC showing enlarged lymph nodes has 60% chance of being cancer-free 12 years after surgery [27].

Classically, better prognosis has been assigned to incidental diagnosis, papillary or chromophobe pathology, small size, and early stage [32]. Presence of necrosis and vascular invasion is useful in a specific algorithm looked toward clear cell renal tumor [33].

Table 1 resumes the main prognosis factors useful on SRM.

11. TREATMENT AS PROGNOSIS FACTOR

Size is a significant factor in the decision to perform NSS: tumors sized 2 cm (81%), 3 cm (73%), and 4 cm (44%) cm could be treated by means of NSS. This treatment is technically easier in incidental than not incidental RCC (76% versus 24%) [15]. Local excision is a safe treatment for small RCC, even in extreme cases such as living donor kidney with a 5 × 5 mm RCC found on its surface [34]. In patients with RCC lower 4 cm, who underwent partial or radical nephrectomy 14% and 10% died during follow-up (cancer-specific death occurred in 3% in both approaches). Disease specific survival rate at 3 and 5 years is 95 and 97% in partial and radical nephrectomy, respectively [6].

When active surveillance is applied to 2 cm mean size contrast-enhancing renal masses, no differences were reported about age, sex, initial size, and solid versus cystic radiologic appearance. A significant different frequency

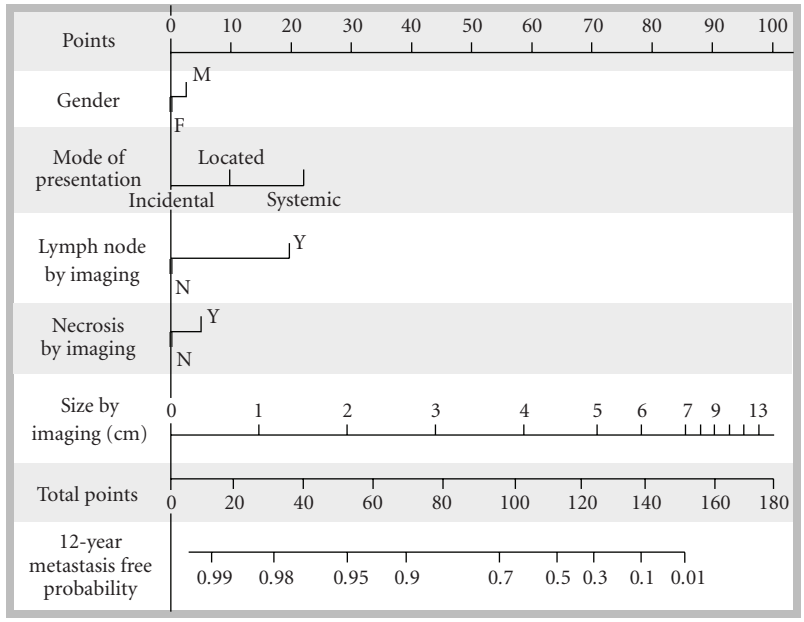

Figure 1: Preoperatory prognosis RCC nomogram [27].

Table 1: Small RCC prognosis factors.

Better prognosis	Worse prognostic
Incidental	Symptoms
Small size <3 cm	Size > 3 cm
T1	T2 and >
Low grade	High grade
No upper tract invasion	Upper tract invasion
No lymph nodes	Necrosis
No necrosis	Lymph nodes
No vascular invasion	Vascular invasion
Negative biological markers	Positive biological markers
Papillary or chromophobe pathology (¿)	Sarcomatoid component
Zero median grown rate	Grown rate > 0.31 cm yearly
Option to NSS	No option to NSS

of surgery was found among tumors with 0 or 0.31 cm mean yearly growth rate of 17% and 51%, respectively [7]. However, 33% of SRM under active surveillance showed zero or negative radiologic growth [7]. The probability to develop metastasis in masses lower than 3 cm managed by active surveillance was only 2% [14]. Prior and during follow-up, renal tumor biopsies are recommended. As a general rule, biopsy may be indicated in masses that have features of oncocytoma in poor surgical candidates. For patients who have a surgical contraindication or reject surgery, alternative ablation techniques can be proposed (cryoablation, radiofrequency) [35].

For Kassouf et al., 20.8% of renal masses showed tumor growth during the surveillance period (mean 31.6 months), but neither of them developed metastasis. Patients receiving surgical treatment after surveillance did not modify their prognostic [16]. Hereditary renal tumors may have a more aggressive natural history, and thus surveillance should be made with caution. Meta-analysis of Kunkle et al. observed no statistical differences in the incidence of SRM progression regardless excision, ablation, or active surveillance [2].

12. CONCLUSIONS

SRMs are those smaller than 4 cm, often incidentally diagnosed. Clinical symptoms, like hematuria, are rare, but confer worse prognosis. Size, stage, and grade are still the most consistent prognostic factors in RCC. It is important to keep in mind that SRM could be benign tumors, mainly oncocytoma. Most malign SMRs are low stage and low grade, without metastatic spread if diameter is below 2-3 cm. Clear cell carcinoma is the most frequent cellular type of malign SRM. Papillary tumors are more frequent when SRM size is less than 1 cm, having a better prognosis. Aggressive potential of small RCC could increase in tumors greater than 3 cm, so it is suggested that the threshold for selecting patients (old age, high-risk, solitary kidney, reject surgery) for a surveillance strategy should be set well below a tumor size of 3 cm. In active surveillance, the size increase of an SRM is a strong indicator of malignancy; helping to decide a surgical treatment.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 518091, 7 pages
doi:10.1155/2008/518091

Research Article

Multifocal Renal Cell Carcinoma: Clinicopathologic Features and Outcomes for Tumors ≤4 cm

Paul L. Crispen,[1] Christine M. Lohse,[2] and Michael L. Blute[1]

[1] *Departments of Urology, Mayo Clinic, Rochester, MN 55905, USA*
[2] *Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA*

Correspondence should be addressed to Michael L. Blute, blute.michael@mayo.edu

Received 27 February 2008; Accepted 20 March 2008

Recommended by José Rubio-Briones

A significant increase in the incidental detection of small renal tumors has been observed with the routine use of cross-sectional abdominal imaging. However, the proportion of small renal tumors associated with multifocal RCC has yet to be established. Here then, we report our experience with the treatment of multifocal RCC in which the primary tumor was ≤4 cm. In our series of 1113 RCC patients, 5.4% (60/1113) had multifocal disease at the time of nephrectomy. Discordant histology was present in 17% (10/60) of patients with multifocal RCC. Nephron sparing surgery was utilized more frequently in patients with solitary tumors. Overall, cancer-specific, and distant metastasis-free survival appeared to be similar between multifocal and solitary tumors. These findings are consistent with previous series which evaluated multifocal RCC with tumors >4 cm. With the known incidence of multifocality RCC, careful inspection of the entire renal unit should be performed when performing nephron sparing surgery.

1. INTRODUCTION

The routine use of cross-sectional abdominal imaging has led to a significant increase in the diagnosis of renal cell carcinoma (RCC) [1, 2]. An estimated 51000 new cases of cancer of the kidney and renal pelvis were diagnosed in 2007, with the vast majority representing RCC [3]. While the preponderance of patients with sporadic RCC will have solitary tumors, 4–20% of patients will have multifocal RCC at the time of diagnosis [4–9]. This is in contrast to patients with hereditary forms of RCC, such as von Hippel-Lindau, Birt-Hogg-Dubé, and hereditary papillary renal carcinoma, who typically have multifocal disease at the time of presentation [10–12]. Whether a patient with multifocal RCC has sporadic or hereditary disease, treatment decisions are based on balancing the preservation of renal function with oncologic efficacy. This is especially true in the case of small (≤4 cm) renal tumors, which are often amenable to nephron sparing surgery (NSS) [13, 14].

Although several previous series have reported on the incidence of multifocality (Table 1), there are limited data on the incidence and outcomes of patients with small (≤4 cm) sporadic multifocal RCC. Here then, we review our experience with the management and outcomes of patients with multifocal sporadic RCC in which the primary tumor size was ≤4 cm.

2. MATERIALS AND METHODS

We studied 1113 patients treated with radical nephrectomy or NSS for sporadic, pNX/pN0, pM0 RCC ≤4.0 cm between 1970 and 2004. Of these, 1053 (94.6%) patients had a solitary, unilateral RCC. The remaining 60 (5.4%) patients had unilateral multifocal RCC. Patients with bilateral disease at time of presentation were excluded from analysis. Clinical and pathologic variables were compared between patients with multifocal and solitary tumors. Clinical variables evaluated included patient age, gender, symptoms at presentation, ECOG performance status, and type of surgery. Pathologic features evaluated included 2002 primary tumor classification, histologic subtype, nuclear grade, presence of histologic necrosis, and sarcomatoid differentiation. Histologic subtype was assigned following the recommendations of the 1997 Union Internationale Contre le Cancer and American Joint Committee on Cancer workshop on the classification of RCC [15]. For the 60 patients with multifocal RCC, pathologic

Table 1: Incidence of multifocal RCC in prior series. ccRCC = clear cell renal cell carcinoma; pRCC = papillary renal cell carcinoma; NA = not available.

Author	Year	Total Patients	Multifocal (%)	Median Tumor Size (cm)	≤4 cm (%)
Richstone	2004	1071	57 (5.3)	5.0	16%
Dimarco	2004	2373	101 (4.3)	4.5 ccRCC 4.0 pRCC	NA
Lang	2004	255	37 (14.5)	NA	12.9%
Junker	2002	372	61 (16.4)	NA	NA
Karayiannis	2002	56	10 (17.8)	7.5	30%
Schlichter	2000	281	48 (17.1)	NA	NA
Baltaci	2000	103	22 (21.4)	7.5	24.1%
Wunderlich	1999	260	36 (13.9)	NA	NA

characteristics of the largest tumor were summarized, with the exception of histologic subtype. All pathologic specimens were reviewed by a single urologic pathologist. Patient followup data are obtained and maintained through our nephrectomy registry. Information on patients who do not follow up at our institution is obtained by a registered nurse via outside medical records, patient/physician correspondence, or death certificates. Fewer than 3% of the patients in the Nephrectomy Registry have been lost to follow up.

Clinical and pathologic features between the multifocal and solitary groups were compared using Wilcoxon rank sum, chi-square, and Fisher's exact tests. Overall, cancer-specific and distant metastases-free survivals were estimated using the Kaplan-Meier method and overall survival was compared between patient groups using the log-rank test. All tests were two-sided and P-values less than .05 were considered statistically significant. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC, USA).

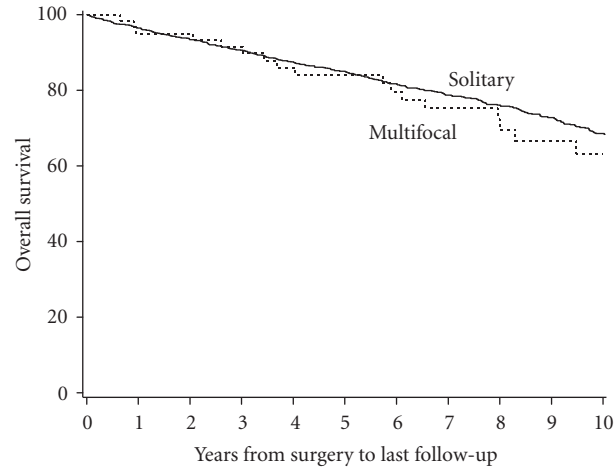

Figure 1: Overall survival in patients with multifocal versus solitary RCC.

3. RESULTS

Multifocal RCC was present in 5.4% (60/1113) of patients with a primary tumor ≤ 4 cm. Clinical and pathologic features between patients with solitary and multifocal RCC tumors ≤ 4.0 cm are summarized in Table 2. Multifocal disease was suspected in only 27% (16/60) of patients based on preoperative imaging. Median age at surgery for the solitary patients was 64 years (mean 62.3; range 22–87) compared with 67.5 years (mean 64.1; range 21–82) for the multifocal patients (P = .147). Median tumor size for the solitary patients was 3.0 cm (mean 2.8; range 0.2–4.0) compared with 2.9 cm (mean 2.8; range 0.4–4.0) for the multifocal patients (P = .631). A comparison of histologic subtype is shown in Table 3. Note that 10/60 (17%) of the patients with multifocal RCC had multiple tumors of different histologic subtypes.

Among the 1053 patients with solitary RCC, 414 died at a median of 7.7 years following surgery (range 1 day to 37.0 years), including 29 who died from RCC at a median of 5.5 years following surgery (range 0.5–21.5). Among the 639 patients who were still alive at last followup, the median duration of followup was 6.8 years (range 2 days to 35.1 years). Forty-four patients experienced distant metastases at a median of 4.0 years following surgery (range 0.2–21.5). Sixteen patients experienced a contralateral recurrence at a median of 2.9 years following surgery (range 0.3–13.8).

Among the 60 patients with multifocal RCC, 23 died at a median of 6.1 years following surgery (range 0.7–14.1), including 4 who died from RCC at 1.0, 3.4, 5.7, and 9.5 years following surgery, respectively. Among the 37 patients who were still alive at last followup, the median duration of followup was 7.6 years (range 0.7–29.3). Three patients experienced distant metastases at 0.8, 0.9 and 6.8 years following surgery, respectively. Eight patients experienced a contralateral recurrence at a median of 5.5 years following surgery (range 0.6–8.1).

Overall survival rates (SE, number still at risk) at 5 and 10 years following surgery were 84.8% (1.2%, 691) and 68.4% (1.7%, 373), respectively, for patients with solitary RCC compared with 84.0% (4.9%, 40) and 63.3% (7.5%, 17), respectively, for patients with multifocal RCC (P = .531; Figure 1). Median overall survival for the two groups was 15.2 and 12.3 years, respectively.

Table 2: Clinical and pathologic features.

Feature	Solitary $N = 1053$ N (%)	Multifocal $N = 60$ N (%)	P-value
Age at Surgery (years)			
<65	554 (52.6)	23 (38.3)	.031
≥65	499 (47.4)	37 (61.7)	
Sex			
Female	339 (32.2)	11 (18.3)	.025
Male	714 (67.8)	49 (81.7)	
Symptoms at presentation			
Absent	582 (55.3)	39 (65.0)	.140
Present	471 (44.7)	21 (35.0)	
Constitutional symptoms at presentation			
Absent	893 (84.8)	49 (81.7)	.512
Present	160 (15.2)	11 (18.3)	
ECOG Performance status ($N = 903$)			
0	749 (88.4)	50 (89.3)	.846
≥1	98 (11.6)	6 (10.7)	
Type of Surgery			
Open radical nephrectomy	532 (50.5)	41 (68.3)	.007
Open nephron-sparing surgery	460 (43.7)	16 (26.7)	
Laparoscopic radical nephrectomy	23 (2.2)	3 (5.0)	
Laparoscopic nephron-sparing surgery	38 (3.6)	0	
2002 Primary tumor classification			
pT1a	1020 (96.9)	59 (98.3)	1.00
pT3a	20 (1.9)	1 (1.7)	
pT3b	11 (1.0)	0	
pT3c	2 (0.2)	0	
RCC Nuclear grade			
1	147 (14.0)	6 (10.0)	.672
2	673 (63.9)	40 (66.7)	
3	221 (21.0)	14 (23.3)	
4	12 (1.1)	0	
Coagulative tumor necrosis			
Absent	921 (87.5)	54 (90.0)	.562
Present	132 (12.5)	6 (10.0)	
Sarcomatoid Differentiation			
Absent	1048 (99.5)	60 (100.0)	1.00
Present	5 (0.5)	0	

Cancer-specific survival rates (SE, number still at risk) at 5 and 10 years following surgery were 98.7% (0.4%, 691) and 96.7% (0.7%, 373), respectively, for patients with solitary RCC compared with 96.2% (2.6%, 40) and 89.0% (5.7%, 17), respectively, for patients with multifocal RCC (Figure 2). Median cancer-specific survival was not attained for either group during the observed duration of followup. Because so few patients with multifocal RCC died from RCC, no statistical comparison of outcome between the two patient groups was performed.

Distant metastases-free survival rates (SE, number still at risk) at 5 and 10 years following surgery were 97.6% (0.5%, 687) and 95.1% (0.9%, 368), respectively, for patients with solitary RCC compared with 96.5% (2.1%, 39) and 93.7% (3.7%, 17), respectively, for patients with multifocal RCC (Figure 3). Median distant metastases-free survival was not attained for either group during the observed duration of followup. Because so few patients with multifocal RCC experienced distant metastases, no statistical comparison of outcome between the two patient groups was performed.

Contralateral recurrence-free survival rates (SE, number still at risk) at 5 and 10 years following surgery were 99.1% (0.3%, 684) and 98.3% (0.5%, 366), respectively, for patients with solitary RCC compared with 94.4% (3.2%, 38) and 79.2% (6.9%, 16), respectively, for patients with multifocal RCC ($P < .001$; Figure 4). Median contralateral

Table 3: RCC histologic subtype.

Patient Group	N (%)
Solitary RCC ($N = 1053$)	
Clear cell	771 (73.2)
Papillary	226 (21.5)
Chromophobe	45 (4.3)
Collecting duct	2 (0.2)
RCC, not otherwise specified	9 (0.9)
Multifocal RCC ($N = 60$)	
Clear cell	26 (43.3)
Papillary	23 (38.3)
Chromophobe	1 (1.7)
Clear cell + papillary	8 (13.3)
Clear cell + chromophobe	1 (1.7)
Papillary + chromophobe	1 (1.7)

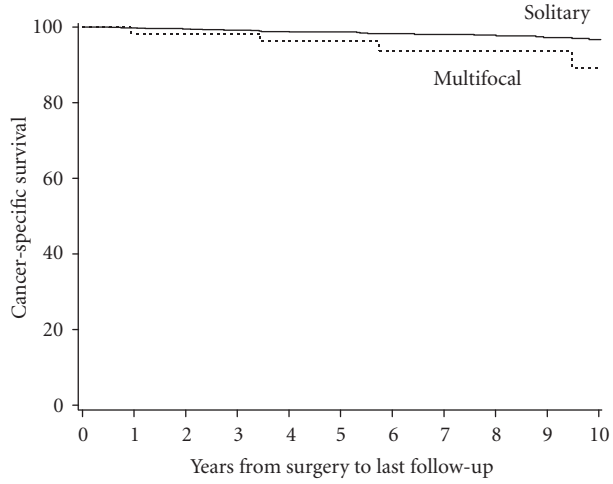

Figure 2: Cancer-specific survival in patients with multifocal versus solitary RCC.

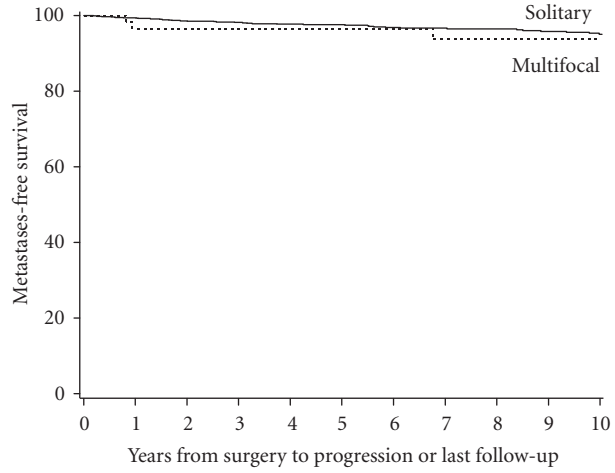

Figure 3: Distant metastasis-free survival in patients with multifocal versus solitary RCC.

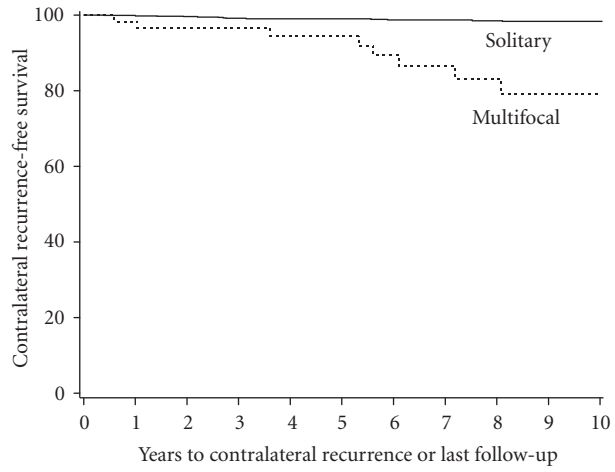

Figure 4: Contralateral recurrence-free survival in patients with multifocal versus solitary RCC.

recurrence-free survival was not attained for either group during the observed duration of followup.

4. DISCUSSION

In the current series of tumors ≤ 4 cm, the rate of multifocal RCC was similar to prior reports. In a review of series published between 1988 to 1999, multifocal disease was noted in 15.2% (179/1,180) of patients, with 9–100% of the primary tumors being ≤ 4 cm in individual reports [13]. Contemporary series have shown a similar rate of multifocal RCC, ranging from 4.3% to 21.4% [4–9, 17, 18]. With the known incidence of multifocal disease, the ability to identify multifocal renal tumors preoperatively is extremely important and has been evaluated by several series. Kletscher et al. noted that preoperative imaging suggested multifocality in only 44% (7/16) of patients prior to nephrectomy [19]. While in the series by Richstone et al. only 33% of multifocal tumors were identified on preoperative imaging, resulting in the discovery of occult multifocal disease in 3.5% of all patients overall at the time of nephrectomy [7]. Another series by Schlichter et al. investigated the ability of ultrasound and computed tomography to identify multifocality. Upon pathologic evaluation 17.1% (48/281) of radical nephrectomy specimens contained multifocal RCC. However, preoperative imaging was only able to identify 23% (11/48) of multifocal tumors. Collectively, these and the current series demonstrate that preoperative imaging is not a sensitive means of identifying multifocal disease preoperatively. Thus complete mobilization and inspection on the entire kidney is warranted when performing NSS to properly evaluate the presence of multifocal disease.

Several associations have been suggested between clinicopathologic features and the presence of multifocal RCC including primary tumor size, histologic subtype, bilateral disease, nodal status, and tumor stage. However, only two series have performed multivariate analysis when evaluating the associations between multifocality and clinicopathologic

Table 4: Cancer-specific survival in patients with multifocal versus solitary RCC. ccRCC = clear cell renal cell carcinoma; pRCC = papillary renal cell carcinoma; NS = not significant.

Author	N multifocal	5 year survival	N solitary	5 year survival	*P*-value
Dimarco et al. [4]	40 (ccRCC)	74.6%	1934 (ccRCC)	69.0%	.47
	29 (pRCC)	100%	237(pRCC)	86.6%	.62
Lang et al. [5]	37	74.0%	218	79.9%	.26
Richstone et al. [7]	51	71.5%*	938	73.2%*	NS
Méjean et al. [16]	28 (pRCC)	96%	30 (pRCC)	100%	.53

* Disease-free survival.

features. Baltaci et al. evaluated 103 cases of RCC and noted the incidence of multifocal RCC to be 21.4% [18]. Univariate and multiple logistic regression analysis demonstrated that primary tumor stage was the only independent predictor of multifocality. In the series by Richstone et al. of 1071 radical nephrectomy specimens, 5.3% of patients were noted to have multifocal RCC [7]. Multivariate analysis of this population revealed significant associations between multifocality with papillary subtype, lymph node metastasis, advanced tumor stage (pT4), and bilateral disease. Interestingly, neither series noted a significant association with tumor size and multifocal RCC. This is important to consider when treating small renal tumors, as size alone has not been shown to predict the presence of multifocal disease.

Discordant pathology between the primary and satellite tumors occurs in up to 6–30% of multifocal tumors [4, 7, 19]. A similar rate of discordant histology between the primary and satellite tumors was noted in the current series at 17%. Although it is obvious that separate events are likely responsible for multifocal RCC with discordant histology, the origin of multifocal RCC with concordant histology is not as apparent. However, the evaluation of genetic markers has provided insight into the origin of multifocal RCC. An initial report by Miyake et al. evaluated the loss of heterozygosity (LOH) using 18 satellite markers in 10 patients with multifocal clear cell RCC (ccRCC) [20]. Identical LOH patterns were noted in 80% (8/10) cases, suggesting that multifocal ccRCC represent intrarenal metastasis. In a second report examining the genetic clonality of multifocal ccRCC by Junker et al. 89% (17/19) cases demonstrated identical LOH patterns [17]. In contrast to ccRCC, multifocal papillary RCC appears to represent independent primary tumors. In a report by Jones et al. LOH was examined in 21 patients with multifocal papillary RCC [21]. The majority, 95% (20/21), of cases demonstrated distinct LOH patterns between tumors suggesting that multifocal papillary tumors do not represent intrarenal metastasis, unlike ccRCC.

Survival outcomes following the treatment of multifocal RCC have been evaluated in several series (Table 4). Dimarco et al. reviewed 2373 patients treated for RCC over 30 years. Multifocal disease was present in 4.3% (101/2373) of all patients. Of the patients with multifocal disease 70% (71/101) had multifocal lesions of the same histologic subtype; these patients were utilized to evaluate survival outcomes. Ipsilateral recurrence rates were similar between multifocal and solitary RCC following radical nephrectomy. Contralateral recurrence was more common in patients with multifocal ccRCC with an increased risk ratio of 2.91; however, this increase did not reach statistical significance ($P = 1.42$). However, in a separate report by Bani-Hani et al. a significant association between the risk of contralateral recurrence and multifocality was demonstrated [22]. The association between contralateral recurrence and multifocality was again noticed in current series which only includes RCC ≤ 4 cm. Cancer-specific survival was similar between patients with multifocal RCC at 1, 5, and 10 years following nephrectomy in patients with clear cell and papillary RCC [23]. Similar findings were noted by Lang et al. in the review of 255 patients undergoing radical nephrectomy [5]. In this series multifocality was present in 14.5% (37/255) of patients undergoing radical nephrectomy for RCC. Multifocality was not associated with metastatic progression, cancer-specific or overall survival in patients treated with radical nephrectomy during median followup of 183 months compared to patients treated for solitary tumors. Additionally, in the report by Richstone et al. no significant difference was noted in 5 year disease-free (71.5% versus 73.2%) and overall (75.2% versus 79.3%) survival when comparing patients with multifocal and solitary RCC [7]. In another study by Méjean et al. focusing on papillary RCC, the presence of multifocal disease was not a significant predictor of overall survival compared to solitary tumors [16]. Collectively these results, with the inclusion of the results from the current series, suggest that cancer specific outcomes are equivalent between patients with multifocal and solitary RCC when treated with radical nephrectomy.

NSS in the management of solitary RCC provides equivalent oncologic efficacy while improving overall survival compared to radical nephrectomy [13, 24, 25]. Although there are limited data on the efficacy of NSS when treating sporadic multifocal RCC, available data suggest that NSS has equivalent oncologic efficacy when treating multifocal disease. An initial report from the Mayo Clinic by Blute et al. reviewed 16 cases of multifocal tumors treated with NSS [23]. 6/16 (38%) of these patients had a solitary kidney at the time of presentation. Local recurrence was noted in 2/16 patients at 1.7 and 2.8 years following NSS. Recurrent disease was treated with repeat NSS in one patient and systemic therapy in the other. Cancer specific survival was 100% at 5 years, however 2/16 patients died of RCC at 6 and 11 years postoperatively. Because of the small number of patients treated, survival outcome comparisons were not made between patients treated with NSS and radical nephrectomy.

Additionally, when considering disease recurrence in patients undergoing NSS for multifocal disease, it can be difficult discriminating recurrent and persistent disease. Local treatment failures in patients previously treated for multifocal RCC does not automatically indicate radical nephrectomy of the renal remnant. Two recent series have reported the feasibility and outcomes of salvage partial nephrectomy in patients with local recurrence following a previous partial nephrectomy [26, 27]. Bratslavsky et al. reported on 11 patients undergoing salvage partial nephrectomies for von Hippel-Lindau disease [27]. Three renal remnants were lost while attempting to preserve renal function, and 46% of cases were associated with major postoperative complications. It should be noted that salvage partial nephrectomy in this series was defined as at least the third partial nephrectomy on the renal remnant. A second series by Magera et al. reported outcomes following salvage partial nephrectomy in 18 patients (8 solitary kidneys, 7 patients with von Hippel-Lindau disease) [26]. Postoperative complications were noted in 28% of patients. Although there was no reported loss of a renal remnant in this series, chronic renal insufficiency (serum creatinine > 2.0 mg/dl) was noted in one patient and chronic renal failure (serum creatine > 2.5 mg/dl) in two others. Obviously, salvage partial nephrectomy was performed for absolute indications in all cases in an attempt to preserve renal function and avoid long-term hemodialysis.

Additional data from series evaluating the efficacy of NSS for multifocal RCC in patients with von Hippel-Lindau disease have demonstrated the significant impact of tumor size on future disease progression. In the series by Duffey et al., NSS was utilized in 97% of patients with tumors ≤3 cm compared to 69% in patients with tumors >3 cm [14]. Progression to metastatic disease was noted in 27% of patients treated for tumors >3 cm (mean followup 73 months); however, no patients treated for tumors ≤3 cm demonstrated disease progression (mean followup 58 months). Although these data suggest that small multifocal RCCs can be treated with NSS, with a low rate of progression to metastatic disease, direct comparisons between the natural history of sporadic and hereditary multifocal RCC should be made with caution.

5. CONCLUSIONS

In the current series multifocal RCC was present in 5.4% of patients with tumors ≤4 cm. Multifocal RCC presents several challenges in terms of diagnosis and treatment. Although multifocal disease is present in only a small proportion of patients with RCC, recognition of multifocality is important to ensure appropriate treatment. As preoperative imaging is an imperfect means of establishing the presence of multifocal disease, careful intraoperative inspection of the entire renal unit should be performed routinely during NSS. Based on the current and other available series, the presence of multifocal disease does not portend a worse prognosis compared to solitary RCC. Additional evaluation of the role of NSS in patients with multifocal sporadic RCC, especially among those with tumors ≤4 cm, is warranted.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 413505, 7 pages
doi:10.1155/2008/413505

Review Article

Familial Syndromes Coupling with Small Renal Masses

Jorge Hidalgo and Gilberto Chéchile

Department of Urology, Instituto Medico Tecnológico, Barcelona 08024, Spain

Correspondence should be addressed to Jorge Hidalgo, hidarro@hotmail.com

Received 27 March 2008; Accepted 2 July 2008

Recommended by J. Rubio

During the past two decades, several new hereditary renal cancers have been discovered but are not yet widely known. Hereditary renal cancer syndromes can lead to multiple bilateral kidney tumors that occur at a younger age than that at which the nonhereditary renal cancers occur. The aim of our work is to review the features of hereditary renal cancers, the basic principles of genetic relevant to these syndromes, and the various histopathologic features of renal cancer. In addition, we will describe the known familial syndromes associated with small renal masses.

1. INTRODUCTION

The incidence of renal cell carcinoma is increasing. This disease affects approximately 150 000 people annually worldwide, causing nearly 78000 deaths [1]. Of these cases, approximately 4% are thought to be associated with autosomal dominant hereditary cancer syndromes [2].

Hereditary renal cancer differs from sporadic renal cancer in several important respects. A hallmark of hereditary renal cancer is that it is often multiple and bilateral.

These distinct forms of inherited epithelial kidney cancer include von Hippel-Lindau disease (VHC), hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dubé syndrome (BHD), hereditary leiomyomatosis renal cell carcinoma (HLRCC) and renal carcinoma associated with hereditary paraganglioma [2]. The genes for each of these disorders have been identified by positional cloning including the VHL gene, the MET proto-oncogene, the BHD gene, the FH gene, and the SDHB gene [2]. Recently, familial renal carcinoma (FRC) has been described. Families with multiple members with renal carcinoma who do not have one of the known inherited forms of renal carcinoma are considered to have FRC. FRC is currently a diagnosis of exclusion [3].

A small percentage of renal cell carcinomas (RCCs), which are subclassified by histology into clear cell (75% of cases), papillary (10–15%), and chromophobe (5%) RCCs, and renal oncocytoma (3%–5%), are due to inherited cancer syndromes [4]. Each inherited cancer syndrome, such as VHL, HPRC and hereditary leiomyomatosis and renal cell carcinoma (HLRCC), is characterized by the development of specific histologic types of renal cancer [2]. For example, affected members of families with VHL syndrome frequently develop clear cell RCCs, whereas patients with HPRC are predisposed to develop type-1 papillary renal carcinomas [5]. Patients with HLRCC, by contrast, develop aggressive papillary type-2 renal carcinomas [6] (see Table 1).

The widespread use of body imaging in recent years has led to a significant increase in the incidence of renal cell carcinoma (RCC). A distinction between benign and malignant small renal masses cannot be made based on radiographic data alone and percutaneous renal mass biopsy is still controversial [7]. Clinicians therefore, when confronted with small renal masses, must carefully weight the risks and benefits of surgical removal [8].

Herein, we will review the features of hereditary renal cancers, the basic principles of genetic relevant to these syndromes, and the various histopathologic features of renal cancer. In addition, we will describe the known familial syndromes associated with small renal masses.

2. VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome that affects multiple organ systems. Extrarenal manifestations of VHL include central nervous system hemangioblastomas, endolymphatic sac tumors, retinal angiomas, pheocromocytomas, and pancreatic cysts and tumors [9].

Table 1: Characteristics of autosomal dominant (AD) forms of kidney cancer (adapted from Zbar et al. [3]).

Disease	Gene	Renal Tumor histology
VHL	VHL	Clear cell Ca
HPRC	MET	Papillary type 1
HLRCC	FH	Renal cell Ca, HLRC type
BHD	BHD	Chromophobe/hybrid oncocytic neoplasm/clear cell Ca

Renal cancer occurs in 25–45% of patients with VHL; if cystic lesions are included in this estimate, the incidence increases to over 60% [10]. As renal tumors in VHL tend to be multifocal and bilateral and unaffected renal tissue is at risk for developing additional tumors [11], management of these patients is a challenge. The primary goal of managing patients with VHL is prevention of metastatic disease [9]. However, the capacity for CT to detect solid renal masses at an earlier stage increases the importance of secondary goals, such as preservation of renal function and maximization of quality of life, by minimizing the number of surgical procedures that patients must undergo [10].

In VHL, patients inherit a germline mutation of the VHL gene on chromosome 3p25 [12]. The VHL gene encodes pVHL, which is part of a complex (including elongin B/C and CUL2) that targets the α-subunit of hypoxia-inducible factors 1 and 2 (HIF1α and HIF2α) for ubiquitin-mediated proteasomal degradation. If the second copy of the VHL gene in a patient is inactivated, HIF1α and HIF2α accumulate. This leads to an increased transcription of genes that encode downstream substrates of HIF1α and HIF2α, such as vascular endothelial growth factor, platelet-derived growth factor and transforming growth factor-α (TGF-α). These molecules are thought to be important in VHL tumorigenesis [13].

In the pre-CT era, strategies for managing VHL renal tumors were often limited to watchful waiting or bilateral nephrectomy with renal replacement therapy (dyalisis or renal transplantation). The high historical rate of metastasis (13–42%) [14], despite the generally low grade of VHL renal tumors, makes watchful waiting an unappealing strategy. Some researchers have advocated bilateral nephrectomy as a means of removing all renal tissue at risk for tumor development [15].

Performing bilateral nephrectomy necessitates renal replacement therapy. Goldfarb et al. compared 32 patients with VHL who underwent bilateral nephrectomy and subsequent renal transplantation with a matched cohort of renal transplant recipients without VHL [16].

No significant differences in graft survival or renal function were observed between the two groups. Five deaths ocurred in both groups; three in the VHL group were due to metastatic disease. Five-year survival was 65%. The authors concluded that renal transplantation was an effective form of renal replacement therapy for VHL patients with limited risk of cancer recurrence [16].

Nephron-sparing surgery (NSS) has the potential to preserve renal function while maintaining oncology efficacy for appropiately selected patients. Favorable results were achieved in several cohorts of VHL patients undergoing NSS [9].

Factors associated with successful NSS outcomes were small tumor size and low tumor grade; larger tumors (>5 cm) had higher local recurrence and metastatic rates [17].

Even though many VHL patients are young and otherwise healthy, the morbidity of hemodialysis and immunosuppression is significant; five-year survival rates for a cohort of patients demographically similar to VHL patients were 71% on hemodialysis and 86% following renal transplantation [9].

Although salvage partial nephrectomy carries a high rate of perioperative morbidity. However, more than three-quarters of operated kidneys can be preserved with only modest decreases in renal function. These patients are able to avoid or postpone the associated morbidity of dialysis, including some patients with solitary kidney. Oncological outcomes are encouraging at intermediate followup with no evidence of detectable metastatic disease [18].

Undergoing frequent surgeries for small renal masses is not an appealing prospect for VHL patients; an observational strategy in combination with NSS is more attractive.

A cohort of patients with VHL and renal masses were observed until the largest tumor in a renal unit was 3 cm in diameter, at which time surgery was recommended. The pattern of recurrence, bilaterality, and number of tumors were not taken into consideration [14]. The rate of metastases increases with increasing tumor size (Table 2).

The 3 cm threshold is not an absolute threshold demarcating development of metastatic disease; rather it is a point at which the risk of metastasis with the potential morbidities of multiple procedures are balanced [9].

Because of the high rate of recurrence of renal tumors in VHL and the difficulties associated with repeated renal surgery, ablative technologies such as cryoablation and radiofrequency ablation (RFA) have been valid alternatives. Ablative procedures have been performed both laparoscopically and percutaneously [9].

The potential role of the heat-shock protein 90 inhibitor 17-allylamino-17-desmethoxy-geldanamycin in VHC is currently being evaluated in patients with small (2-3 cm) presurgical renal lesion. Inhibition of heat shock protein 90, a molecular chaperone of HIF, facilitates proteasomal degradation of HIF [9]. These approaches, which target the abnormal molecular pathways involved in VHL tumorigenesis, represent a potential future approach to treatment of patients with both sporadic and VHL-associated clear-cell kidney cancer.

NSS-bases approaches to management of VHL-associated renal tumors, using a 3 cm tumor size threshold for recommendation of surgery, can provide good cancer control while preserving renal function and minimizing

Table 2: Comparision of tumor size and metastaes (adapted from Duffey et al. [19]).

Tumor Size (cm)	Number of metastases	Number of patients	Percentage of patients with metastases
≤3.0	0	108	0
3.1–4.1	1	27	4
4.1–5.5	4	19	21
5.6–10.0	10	20	50
≥10.1	5	7	71

interventions. This type of strategy mandates diligent screening and followup. More experience with minimally invasive techniques is needed before their role in treatment of VHL renal tumors can be defined. Medical therapy with new molecular-targeted agents is a promising potential development in the management of VHL renal tumors [9].

3. HEREDITARY PAPILLARY RENAL CARCINOMA

Papillary renal carcinoma (PRC) comprises 10% to 15% of kidney epithelial tumors and it is histologically subdivided into types 1 and 2 [20]. Hereditary papillary renal carcinoma (HPRC) is an uncommon form of inherited kidney cancer characterized by the predisposition to develop bilateral, multifocal renal tumors with type-1 papillary architecture [21]. Tumors show frequent trisomy of chromosome 7 and they appear to arise from independent clonal events. HPRC is associated with a mutation of the A *MET* proto-oncogene at 7q31.3. The gene was originally described in 1984 but was not linked with papillary renal cancer until 1997 [5]. This gene codes for a transmembrane receptor tyrosine kinase. Mutations lead to activation of the MET protein, which is also the receptor for hepatocyte growth factor. The tumors produced in hereditary papillary renal cancer are well differentiated type-1 papillary renal cancers [22].

Hereditary papillary renal tumors are generally hypovascular and enhance only 10–30 HU after intravenous administration of contrast material. This mirrors the experience with sporadic papillary renal cancers, which are also typically hypovascular. Papillary renal cancers can be mistaken for cysts, and one must be careful to obtain accurate attenuation measurements before and after contrast enhancement. Ultrasonography can be particularly misleading with this disorder, because small tumors are often isoechoic [22].

Patients in HPRC have previously been reported to have renal cancer on average in the sixth decade of life [21], later than other inherited renal cancer syndromes such as VHL disease, which often develops in patients in the third and fourth decades of life. Schmidt and colleagues reported on 3 families with HPRC in which, individuals in HPRC are at risk for bilateral, multifocal kidney cancer earlier in life (second decade) [23]. In addition, this report emphasizes that HPRC can be a lethal disease since a number of affected individuals in these families died of metastatic kidney cancer. Type-1 papillary renal carcinoma in patients with HPRC is a malignant tumor that can be lethal if it is not detected and treated early [23].

4. BIRT-HOGG-DUBÉ SYNDROME

Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant cancer syndrome characterized by the development of small dome-shaped papules on the face, neck, and upper trunk (fibrofolliculomas). In addition to these benign hair follicle tumors, BHD confers and increases the risk of renal neoplasia and spontaneous pneumothorax. The gene has been mapped to chromosome 17p11.2 and recently identified, expressing a novel protein called folliculin [24].

Recently, individuals with BHD syndrome were found to have a seven-fold higher risk over the general population of developing kidney neoplasms [25].

Unlike renal tumors in patients with other inherited kidney cancer syndromes, renal tumors from BHD patients exhibit a spectrum of histologic types, including chromophobe (34%), oncocytoma (5%), clear cell (9%), papillary (2%), and an oncocytic hybrid (50%) with features of chromophobe RCC and renal oncocytoma [26]. Germline mutations have been identified in a novel gene, BHD in affected family members [27]. BHD encodes a protein, folliculin, which is named for the hallmark dermatologic lesions found in BHD patients. All germline mutations identified to date are frameshift or nonsense mutations that are predicted to truncate folliculin, including insertions or deletions of a tract of eight cytosines (C8) in exon 11 [27].

Pavlovich et al. [26] reported 130 solid renal tumors resected from 30 patients with BHD in 19 different families. Preoperative CT demonstrated a mean of 5.3 tumors per patient (range 1–28 tumors), the largest tumors averaging 5.7 cm in diameter (±3.4 cm, range 1.2–15 cm). Multiple and bilateral tumors were noted at an early age (mean 50.7 years). The resected tumors consisted predominantly of chromophobe renal cell carcinomas (34%) or of hybrid oncocytic neoplasms that had areas reminiscent of chromophobe renal cell carcinoma and oncocytoma (50%). Twelve clear cell (conventional) renal carcinomas (9%) were diagnosed. The tumors were on average larger (4.7 ± 4.2 cm) than the chromophobe (3.0 ± 2.5 cm) and hybrid tumors (2.2 ± 2.4 cm). Microscopic oncocytosis was found in the renal parenchyma of most patients, including the parenchyma of five patients with evidence of clear cell renal cell carcinoma. These findings suggest that microscopic oncocytic lesions may be precursors of hybrid oncocytic tumors, chromophobe renal cell carcinomas, and perhaps clear cell renal cell carcinomas in patients with BHD syndrome.

The malignant nature of BHD associated renal tumors has not been previously established. BHD associated kidney

cancer has the potential to be a lethal disease based on family histories of death from metastatic RCC in several patients with BHD. Pavlovich and colleagues [28] suggest that BHD-associated chromophobe and hybrid oncocytic RCC may be of lesser malignant potential than BHD associated clear cell RCC but these lesions cannot be considered completely benign based on their cytomorphology and the known occasionally malignant behavior of chromophobe tumors. In families in which multiple members are found to have chromophobe or hybrid oncocytic renal carcinomas, BHD should be considered. Efforts are currently underway to determine why some BHD families have kidney cancer and others do not [28].

Urological surgeons who treat patients with BHD should keep in mind the potential for perioperative pneumothorax in these patients. A high percent of patients with BHD is affected with pulmonary cysts (almost 90%) and more than 20% have a history of spontaneous pneumothorax.

To address the mutation status of the BHD gene in tumors from Birt-Hogg-Dubé patients, Vocke and colleagues [29] analized a panel of 77 renal tumors by direct DNA sequence analysis. Tumor samples, as well as matched normal samples, were obtained from 12 affected members of BHD families after renal surgery. BHD patients were often found to have bilateral, multifocal tumors and underwent staged bilateral partial nephrectomies, providing tumor samples for the study. The entire coding region of BHD (exons 4–14) was sequenced in each tumor sample, following polymerase chain reaction (PCR) amplification. Their data showed that the tumors from a given BHD patient have different second hits. These observations strongly suggest that multiple renal tumors from some BHD patients are independent, clonal events, each arising from a separate and unique second mutation in the BHD gene. However, some tumors with mixed histologies shared a common somatic mutation in the distinct histologic regions within each tumor. This finding suggests that in some cases, a somatic second hit precedes histologic diversification within a single tumor. The molecular mechanism that drives these events is unknown. These results document the high frequency and wide spectrum of second mutations, which strongly support a tumor suppressor role of BHD. Inactivation of both copies of BHD ocurred in several histologic types of renal tumors, suggesting that BHD may act at an early stage of renal oncogenesis. Further understanding of the mechanism of BHD-induced tumorigenesis awaits functional studies of the follicullin protein [29].

In addition, BHD is an autosomal dominant hereditary cancer syndrome, in which affected individuals are at risk for cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and kidney tumors. Almost 30% of affected patients with BHD examined had solid renal tumors. Because of the spectrum of renal tumor histologies found in patients with BHD, their variable natural history, and the risk of recurrent renal tumors in such patients, it is important for urologists to be aware of this syndrome. The current management approach for BHD associated renal tumors is to perform nephron sparing surgery when possible [28].

5. HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER

A hereditary form of kidney cancer referred to as hereditary leiomyomatosis and renal cell cancer (HLRCC) has been identified, in which affected family members have cutaneous leiomyomas, uterine fibroids, and/or kidney cancers [6]. The renal malignancies that develop in HLRCC families are often metastatic at presentation and are a significant cause of mortality in these families. Analysis of families with this disorder has identified the responsible gene locus as FH [30]. This gene encodes fumarate hydratase (FH), an enzyme that is part of the mitochondrial Krebs or tricarboxylic acid (TCA) cycle, located at 1q42.2-42.3. The gene is inherited in an autosomal dominant manner. The mechanism by which alterations in FH lead to HLRCC remains to be determined, but it apparently involves increased cellular dependence on glycolysis.

The reason why *FH* alterations are associated with tumor formation in HLRCC families is not entirely clear at this time. It seems intuitively that a cell that lacks functional FH (and hence has a defective TCA cycle) would be at a metabolic disadvantage, particularly with regard to the efficiency of nutrient catabolism. HLRCC is not, however, the only hereditary cancer syndrome associated with a defective enzyme of the Krebs cycle. Germline mutations in the succinate dehydrogenase complex have been identified that predispose to the development of hereditary paragangliomas. Succinate dehydrogenase catalyzes the conversion of succinate to fumarate—the step in the TCA cycle that immediately precedes the reaction catalyzed by FH. Mutations in subunits B, C, and D of the succinate dehydrogenase complex have all been linked to hereditary paraganglioma.

The extrarenal manifestations of HLRCC were described previously [6]. The most frequent manifestation is uterine leiomyomas in affected females (75% to 98%). More than 90% of the women underwent myomectomy or hysterectomy and approximately half had undergone hysterectomy by age of 30 years. Cutaneous leiomyomas are firm, skin-colored to light brown or red papules. They may be segmental and multifocal, and are mainly found on the trunk and extremities. They may be painful. Mean age at onset of cutaneous manifestations is 25 years (range 10 to 47) [31]. The incidence is 36% to 85%.

There are several unique aspects to HLRCC-associated renal tumors that differentiate them from other inherited forms of kidney cancer. Whereas tumors in VHL, HPRC, and BHD twins are often multifocal and involve the 2 kidneys [2], renal tumors in patients with HLRCC may be solitary.

Toro et al. [31] reported 19 patients with hereditary leiomyomatosis and renal cell cancer associated renal tumors. Individual considered affected by HLRCC had greater than 10 skin lesions clinically compatible with leiomyoma and a minimum of 1 lesion histologically confirmed as leiomyoma or tested positive for a germline FH mutation. Patients underwent precontrast and postcontrast CT of the chest, abdomen, and pelvis after informed consent was provided. Renal lesions were considered indeterminate if they were too small (less than 1 cm in diameter) to be

accurately classified as solid or cystic. Only lesions 1 cm or greater and enhancing more than 20 HU that were predominantly solid were considered renal tumors.

For HLRCC they did not adhere to the strategy of expectant management for tumors less than 3 cm, as we previously described for other hereditary kidney cancer syndromes, such as VHL, HPRC, or BHD [2, 19, 28].

HLRCC-associated renal tumors appear to represent a significantly more aggressive type of renal cancer than that in patients with VHL, HPRC, or BHD. Even small HLRCC renal tumors are associated with nodal and metastatic disease. In the reported study [32], they often treat patients with VHL, HPRC, and BHD and small (less than 3 cm) tumors expectantly, recommending surgery in many when the largest lesion reached 3 cm. To their knowledge no patients with VHL, HPRC, or BHD who presented with tumors less than 3 cm have had metastatic disease using this clinical management approach [14, 19]. Because of the aggressive nature of the renal cancer in HLRCC in the current study [32] and the potential for small tumors to metastasize, the data suggest that small lesions prospectively identified in patients at risk for HLRCC should not be managed by an expectant, nonsurgical strategy. Experience with nephron sparing surgery in the setting of HLRCC is limited to date and no formal recommendations regarding the most efficacious surgical approach (radical versus partial nephrectomy) for clinically localized renal tumors can be made at this time, nephron-sparing surgery could be potentially as curative as radical nephrectomy as has been demonstrated in nonhereditary forms of RCC.

A family history of renal tumors, especially causing death at a young age, early hysterectomy in women due to symptomatic fibroids, cutaneous leiomyomas, and importantly small tumors with a lymph node or metastatic disease burden out of proportion to tumor size should alert clinicians to the possibility of HLRCC. Renal tumors found in this syndrome, which are frequently described as papillary type II or collecting duct histology, appear to be significantly more aggressive than other forms of hereditary renal cancer. Because of limited experience with screening and treating these patients, optimal management strategies remain to be defined. However, the early experience with HLRCC-associated renal carcinoma suggests that extreme caution is warranted. Observational strategies that are suitable for select patients with small renal masses associated with other hereditary renal cancer syndromes are not appropriate for patients with HLRCC. HLRCC-associated kidney cancer is markedly different from kidney cancer associated with other hereditary cancer syndromes, such as VHL, HPRC, and BHD. These patients should be evaluated and treated cautiously [32].

6. RENAL CARCINOMA ASSOCIATED WITH HEREDITARY PARAGANGLIOMA

Germline mutations of the genes encoding succinate dehydrogenase subunits B (SDHB) and D (SDHD) predispose to paraganglioma syndromes type-4 (PGL-4) and type-1 (PGL-1), respectively. In both syndromes, pheochromocytomas as well as head and neck paragangliomas occur; however, details for individual risks and other clinical characteristics are unknown.

Table 3: Clinical and pathological subtypes of familial renal carcinoma (adapted from Zbar et al. [3]).

(1) Single clear cell renal carcinomas
(2) Bilateral multiple clear cell renal carcinomas, without VHL
(3) Single clear cell renal carcinomas and renal oncocytomas*
(4) Single clear cell renal carcinomas and papillary renal carcinomas**
(5) Single and multiple renal oncocytomas without the other clinical features of BHD syndrome
(6) Single or multiple bilaterally renal carcinomas but not HPRC or HLRCC
(7) Other
*Families with some members affected with single clear cell renal carcinomas and other members affected with single renal oncocytomas
**Families with one member affected with single clear cell renal carcinoma and another member affected with single clear cell renal carcinoma and another member affected with papillary renal carcinoma

The paraganglioma syndromes have been relatively newly delineated as unique entities. Although paraganglioma has been clinically recognized for more than 40 years, only in the last 4 years they have been classified based on molecular genetics: SDHD mutations predispose to PGL-1, mutations in an unidentified gene on chromosome 11 to PGL-2, SDHC mutations to PGL-3, and SDHB mutations to PGL-4. In Neumann et al. report [33], consistent with the apparently aggressive nature of SDHB dysfunction, 5 mutation carriers in their study were also found to have extra paraganglial malignancies (e.g., renal cell carcinoma and thyroid papillary carcinoma). Kidney carcinomas are considered oncocytic tumors (replete with mitochondria) and thus, the involvement of a mitochondrial complex II gene in kidney carcinogenesis may be explained. The apparently more aggressive nature of the tumors in SDHB mutation carriers may be postulated to be a consequence of the prevention of assembly of the catalytic complex that normally comprises SDHA and SDHB, thus leaving only complexes of the structural SDHC and SDHD moieties.

Mutations in other genes can be causes of hereditary renal carcinoma. These genes include hepatocyte nuclear factor 1 α and 1 β, the tuberous sclerosis genes and and SDHB [33].

7. FAMILIAL RENAL CARCINOMA

There are several interrelated questions when approaching the family with multiple members with renal carcinoma. The first issue is determining whether the family is affected with one of the known inherited forms of renal carcinoma. The diagnosis of one of the known inherited forms of renal

Table 4: FRC versus autosomal dominant (AD) forms of kidney cancer (adapted from Zbar et al. [3]).

Disease	Inheritance mode	Age at onset	Tumor multiciplicity	Histology
FRC	Complex	Late	Single	varied
VHL	AD	Adolescence	Bilat, multiple	Clear cell
HPRC	AD	40–49 years	Bilat, multiple	Papillary type 1
BHD	AD	30–39 years	Bilat, multiple	Chromophobe/hybrid oncocytic
HLRCC	AD	10–20 years	Single or multiple	Renal cell Ca, HLRCC type

carcinoma is based on clinical evaluation and DNA testing. Families with 2 or more members with renal carcinoma who do not have one of the known inherited forms of renal carcinoma are considered to have FRC. Recently, Zbar et al. [3], reported a study in which familial renal carcinoma (FRC) was described and provisionally clasified (Table 3). They evaluated 141 at risk asymptomatic relatives of affected individuals from 50 families with 2 or more members with renal carcinoma. Histology slides of renal tumors from affected family members were reviewed and were not found to be VHL, BHD, HLRCC, or HPRC. At risk, members from renal carcinoma families were screened for occult renal neoplasms by renal ultrasound and computerized tomography. DNA from selected families was tested for germline mutations of known renal carcinoma genes when clinically indicated and constitutional cytogenetic analysis was performed to search for germline chromosome alterations. This collection of renal carcinoma families represents a well-studied population from which families with the 4 well-known causes of inherited renal carcinoma were removed from the study.

Findings suggested that, when confronted with a family with FRC, careful analysis should be performed of the family to search for known causes of inherited renal carcinoma (Table 4). The manifestations of hereditary leiomyoma renal carcinoma may be particularly difficult to identify. The most likely cause of aggressive, early onset FRC was hereditary leiomyoma renal cell carcinoma. In general, bilateral multiple renal carcinomas in more than 1 family member are highly suggestive of an autosomal dominant form of renal carcinoma. If there is a suggestion of hereditary renal cancer, appropriate biopsies and scans should be performed and DNA mutation studies should be performed to confirm the diagnosis.

8. CONCLUSIONS

Small renal masses in the case of renal cancer syndromes must be studied from a particular point of view because hereditary renal cancers can lead to multiple and/or bilateral kidney tumors. The primary goal of managing patients with familial renal syndromes is prevention of metastatic disease. Nephron sparing surgery has the potential to preserve renal function while maintaining oncology efficacy for selected patients. In some syndromes, it is appropiate to develop a watchful waiting attitude, 3 cm size tumor seems to be the threshold for renal surgery. Due to the aggressive form of renal carcinoma in the case HLRCC, initial surgical approach is recommended.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 720840, 12 pages
doi:10.1155/2008/720840

Review Article

Genetic Counseling in Renal Masses

José Antonio López-Guerrero,[1] Zaida García-Casado,[1] Antonio Fernández-Serra,[1] and José Rubio-Briones[2]

[1] *Laboratory of Molecular Biology, Fundación Instituto Valenciano de Oncología, C/Prof. Beltrán Báguena 8, 46009 Valencia, Spain*
[2] *Service of Urology, Fundación Instituto Valenciano de Oncología, C/Prof. Beltrán Báguena 8, 46009 Valencia, Spain*

Correspondence should be addressed to José Antonio López-Guerrero, jalopez@fivo.org

Received 29 March 2008; Accepted 9 September 2008

Recommended by F. Algaba

All urologists have faced patients suffering a renal cancer asking for the occurrence of the disease in their offspring and very often the answer to this question has not been well founded from the scientific point of view, and only in few cases a familial segregation tree is performed. The grate shift seen in the detection of small renal masses and renal cancer in the last decades will prompt us to know the indications for familial studies, which and when are necessary, and probably to refer those patients with a suspected familial syndrome to specialized oncological centers where the appropriate molecular and familial studies could be done. Use of molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and would reduce costly screening procedures in at-risk members who have not inherited disease-causing mutations. This review will focus on the molecular bases of familial syndromes associated with small renal masses and the indications of familial studies in at-risk family members.

1. INTRODUCTION

Renal cell carcinoma (RCC) affects approximately 150 000 people worldwide each year, causing close to 78 000 deaths annually, and its incidence seems to be rising [1]. This rising trend is partially due to the growing use of new and improved noninvasive abdominal imaging modalities, such as ultrasonography, CT, and MRI [2, 3]. In more recent years, 48–66% of RCCs have been detected incidentally as small renal masses in asymptomatic patients, whereas historically most cases were diagnosed following investigations for flank pain or hematuria [4]. RCC is not a single entity, but rather comprises the class of tumors of renal epithelial origin. Broad histological and molecular studies have resulted in a consensus classification of different RCC subtypes (Table 1) [5].

Most cases of RCC are thought to be sporadic whereas there has been estimated that hereditary RCC syndromes are estimated at 1–4% but have major clinical and scientific implications [6, 7]. First, the identification of predisposing gene offers the possibility of genetic testing: surveillance of mutation carriers results in early diagnosis and treatment. Secondly, the involvement of the same genes is demonstrated in a number of sporadic RCCs, providing insight into the various mechanisms of renal tumorigenesis [8]. To date, 10 familial syndromes associated with one or more of the various histological subtypes of RCC have been described, all of them inherited with an autosomal dominant trait, that means that carrier individuals of a mutant allele have a 50% chance of passing the mutant gene to the offspring and therefore the associated disorder (Table 2) [9]. The diverse nature of these predisposing genes implicates different mechanisms and biological pathways in RCC tumorigenesis. Hence, identification of mutations responsible for these syndromes in healthy carriers constitutes a challenge in the clinical management of these individuals.

There are no generally accepted screening guidelines for hereditary RCC syndromes; however, some recommendations can be made. A hereditary predisposition to renal cancer should be suspected whenever an individual who is diagnosed with renal cancer has a close relative also diagnosed with the disease, and/or when an individual presents with multifocal renal tumors or a history of previous renal tumor. Family history should be obtained and a pedigree created, paying specific attention to relatives with a known history of cancer. Whenever possible (when a gene-causing disease is identifiable), a germline genetic testing should be performed on the proband. In addition, and as

Table 1: Classification of renal epithelial tumors.

Histological type	Frequency	Cell of origin	Behavior	Gene involved	Chromosomal abnormalities
Conventional (clear-cell) renal-cell carcinoma	75%	Proximal renal tubule	Malignant	*VHL, BHD*	−3p, +5q, −Y, −8p, −9p, −14q; t(3;5)(p;q)
Papillary renal-cell carcinoma	10–15%	Proximal renal tubule	Malignant	*MET, FH, HRPT2*	+7, +17, −Y, +12, +16, +20; t(X;1)(p11.2;q21.2), t(X;17)(p11.2;q25.3)
Chromophobe renal carcinoma	5%	Intercalated cell of renal collecting duct	Rarely malignant	*BHD*	−1, −2, −6, −10, −13, −17, −21
Oncocytoma	5%	Intercalated cell of renal collecting duct	Benign	*BHD*	−1, −Y; t(5;11)(q35;q13), t(9;11)(p23;q13)
Collecting-duct carcinoma	2%	Renal collecting duct	Aggressively malignant	*FH*	−1p32, −6p, −8p, −21q

BHD, Birt-Hogg-Dubé (encoding folliculin); *FH*, fumarate hydratase; *HRTP2*, hyperparathyroidism 2; *VHL*, von Hippel-Lindau.

Table 2: Hereditary renal cell carcinoma (RCC) syndromes and histological subtypes.

Renal tumors	Manifestation	Disease	Gene
Clear cell RCC			
	Bilateral and multiple	Von Hippel-Lindau	*VHL*, 3p25-26
	Bilateral and multiple	Chromosome 3 translocations	Unknown, *VHL*?
		Hereditary paraganglioma	*SDHB*, 1p36
	Angiomyolipomas	Tuberous sclerosis	*TSC1*, 9q34 *TSC2*, 16q13
Papillary RCC	Solid, bilateral and multiple (type 1)	Hereditary papillary RCC	*MET*, 7q31
	Unilateral solitary, aggressive (type 2)	Hereditary leiomyomatosis	FH, 1q42-43
	Hamartomas, Wilm's tumor	Hyperparathyroidism-jaw tumor	*HRPT2*, 1q25-32
	Oncocytoma	Familial papillary thyroid cancer	?, 1q21
Chromophobe RCC	Oncocytic-chromophobe	Birt-Hogg-Dubé	*BHD*, 17p11.2

a general rule, molecular genetic testing of at-risk family members is appropriate in order to identify the need for continued, lifelong, clinical surveillance. Interpretation of the result is most accurate when a disease-causing mutation has been identified in an affected family member. Those who have a disease-causing mutation require lifelong regular surveillance. Meanwhile, family members who have not inherited the mutation and their offspring have risks similar to the general population [10].

In this case, and generally speaking within a genetic testing context, the presence or absence of a mutation in a predisposing gene or the type of mutation determines the clinical actuation in cases of hereditary syndromes of cancer. In this sense, and following the American College of Medical Genetics (ACMG) recommendations, we can describe the following situations [10]:

Situation 1.

When the mutation is present:

(i) the pathogenic sequence alteration is reported in the literature;

(ii) sequence alteration is predicted to be pathogenic but not reported in the literature;

(iii) sequence variation of unknown clinical significance;

(iv) sequence alteration is predicted to be benign but not reported in the literature;

(v) a benign sequence alteration is reported in the literature.

Situation 2.

Possibilities if a sequence alteration is not detected:

(i) patient does not have a mutation in the tested gene (e.g., a sequence alteration exists in another gene at another locus);

(ii) patient has a sequence alteration that cannot be detected by sequence analysis (e.g., a large deletion, a splice site deletion);

(iii) patient has a sequence alteration in a region of the gene (e.g., an intron or regulatory region) not covered by the laboratory's test.

Herein we review the four most frequent syndromes (von Hippel-Lindau, Hereditary papillary RCC, Hereditary leiomyomatosis RCC, and Birt-Hogg-Dubé), the molecular biology of the associated genes, and the clinical consequences of a genetic counseling.

Table 3: Hereditary patterns and risks of renal cell carcinoma (RCC) associated syndromes.

Syndrome	Hereditary pattern	Risk of developing an RCC of the affected individuals
Von Hippel-Lindau	Autosomal dominant	75%
Papillary RCC	Autosomal dominant	20%
Leiomyomatosis RCC	Autosomal dominant	10–16%
Birt-Hogg-Dubé	Autosomal dominant	15–29%

2. VON HIPPEL-LINDAU (VHL) DISEASE

2.1. Clinical manifestation and molecular biology

VHL (OMIM: 193300) is the main cause of inherited RCC [11]. This syndrome includes central nervous system (CNS) and retinal hemangioblastomas, clear cell RCC and renal cysts, pheochromocytomas, neuroendocrine pancreatic tumors and pancreatic cysts, and endolymphatic sac tumors [12]. VHL occurs at a prevalence of about 1/36 000 and VHL-associated tumors with relatively high penetrance (80–90%) develop in the second to fourth decades of life. RCC affects up to 75% of patients by the age of 60 years. RCC is predominantly multiple and bilateral and occurs at a mean age of 39 years [11, 12] (Table 3).

Genetically, VHL is caused by germline mutations in the *VHL* tumor suppressor gene located on 3p25-26 accompanied by inactivation of the wild-type copy of the *VHL* gene in a susceptible cell through loss of heterozygosity (LOH), promoter hypermethylation, or somatic mutation [6].

VHL disease tumor suppressor protein (pVHL) has been implicated in a variety of functions including transcriptional regulation, posttranscriptional gene expression, protein folding, extracellular matrix formation, and ubiquitinylation [13]. The role of pVHL in the regulation of hypoxia-inducible genes through the targeted ubiquitinylation and degradation of hypoxia-inducible factor-1α (HIF1α) has been elucidated, leading to a model of how disruption of the *VHL* gene results in RCC and the production of highly vascularized tumors.

Under normoxic conditions, HIF1α is hydroxilated (−OH) on two conserved praline residues by a member of the EGLN family of prolyl hydroxylase enzymes. This hydroxylation provides a substrate-recognition site for the pVHL-E3 ubiquitin ligase complex, which contains elongins C and B, cullin-2 (CUL2), and RBX1. Polyubiquitylation of HIF1α by the VHL complex leads to its proteasomal degradation by the 26S proteasome [6] (Figure 1).

However, under hypoxic conditions, HIF1α is not hydroxylated, pVHL does not bind, and HIF1α subunits accumulate. HIF1α forms heterodimers with HIF1β and activates transcription of a variety of hypoxia-inducible genes (i.e., VEGF, EPO, TGFα, PDGFβ). Likewise, when pVHL is absent or mutated, HIF1α subunits accumulate, resulting in cell proliferation and the neovascularization of tumors characteristic of VHL disease [13].

Mutations in the *VHL* gene either prevent its expression (i.e., deletions, and frameshifts, nonsense mutations, splice site mutations) or lead to the expression of an abnormal protein (i.e., missense mutations), and interesting genotype-phenotype correlations are emerging for VHL disease that relate to the development of RCC [14]. A group of *VHL* mutations termed type 1, comprising mostly deletions and premature-termination mutations that cause total loss of pVHL function, predispose to the entire spectrum of VHL-syndrome except pheocromocytomas [15]. By contrast, type 2 mutations, which are mostly missense changes that reduce pVHL activity, predispose to the entire VHL spectrum, including pheochromocytomas with or without RCC, called type 2B and type 2A, respectively [6]. Several studies have revealed that type 1 and type 2B mutations, which predispose to RCC, show complete loss of HIF1α ubiquitylation and regulation, whereas type 2A mutations result in an incomplete defect in HIF regulation [16]. However, type 2A mutations have been shown to disrupt binding of pVHL to microtubules and abrogate the associated microtubule-stabilizing function of pVHL,

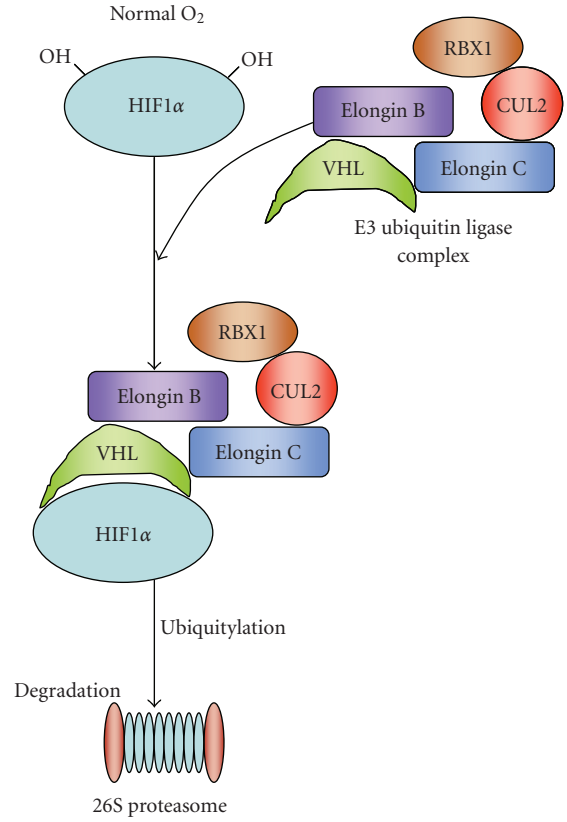


Figure 1: VHL complex interaction with HIFα under normal O_2 levels. Its normal function leads to HIFα degradation (see text for details).

implicating defective cytoskeleton organization in this VHL phenotype [17]. A third VHL-syndrome subclass (type 2C) predisposes almost exclusively to pheochromocytomas [9]. Type 2C mutations produce pVHL that regulates HIF but is defective in fibronectin assembly, indicating a possible link between fibronectin-matrix assembly and pheochromocytoma development [17]. Another class of *VHL* point mutations inactivates pVHL function by disrupting proper protein folding mediated by chaperonin TriC/CCT [18]. More recently, two independent groups reported a reduced risk for RCC in individuals with a complete deletion of the *VHL* gene. This group of individuals would define a new VHL phenotype characterized by a low risk for both RCC and pheochromocytoma [19, 20].

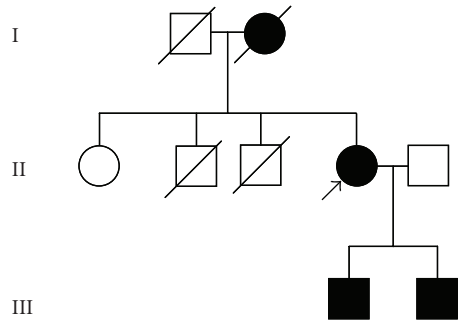


Figure 2: Pedigree showing affected members with VHL. *Open symbols*, unaffected subjects; *solid symbols*, affected subjects; *symbols with slashes*, deceased members; and *arrow*, proband.

2.2. Molecular genetic testing

The molecular genetic testing of *VHL* is mainly performed by sequence analysis of all three exons which detects point mutations and small deletions or insertions and that represents the 72% of *VHL* mutations, and deletion analysis (by means of Southern Blot, MLPA, quantitative PCR, etc.) for detecting partial or complete gene deletions, which account for approximately 28% of all *VHL* mutations [21, 22].

Over 300 different *VHL* germline mutations have been identified [6, 11]. The mutations occur in all three exons, with only a handful of mutations found in four or more families (i.e., delPhe76, Asn78Ser, Arg161X, Arg167Gln, Arg167Trp, Leu178Pro). Codon 167 is a *hot spot* mutation. A database of mutations in the *VHL* gene is maintained on the human gene mutation database website http://www.hgmd.cf.ac.uk/ac/index.php.

Molecular genetic testing is indicated in all individuals known to have or suspected of having VHL syndrome [23]. Since the detection rate for *VHL* gene mutations is nearly 100%, molecular testing may also be used to evaluate individuals with a single VHL-associated tumor and a negative family history of the disease. In addition, for individuals with manifestations of VHL syndrome who do not meet strict diagnostic criteria and who do not have a detectable *VHL* germline mutation, somatic mosaicism for a de novo *VHL* disease-causing mutation should be considered. In some instances, molecular genetic testing of the offspring of such individuals reveals a *VHL* mutation [24].

The level of mutation detection obtained by molecular genetic testing of the *VHL* makes it possible to effectively rule out VHL syndrome with a high degree of certainty in individuals with isolated hemangioblastoma, retinal angioma, or clear cell RCC, who have no detectable *VHL* disease-causing germline mutation; somatic mosaicism for a *VHL* gene mutation still needs to be considered in such individuals. A younger individual, especially one with multiple lesions, is more likely to have a germline *VHL* mutation than an older individual with a single lesion [25].

Since pheochromocytoma is part of the VHL syndrome spectrum and may occur as the exclusive manifestation of VHL syndrome (type 2C), individuals with a family history of these tumors, or those in whom the disease is bilateral or multifocal, should be offered molecular genetic testing for *VHL* germline mutations [26]. Germline *VHL* mutations are rare in simplex cases of unilateral pheochromocytoma (i.e., an affected individual with no family history of VHL syndrome), unless the individual is younger than age 20 years. Exceptions are those individuals with a family history that is more consistent with familial paragangliomas of the head and neck, which are caused by mutations in various subunits of the gene encoding succinic dehydrogenase *(SDH)* [27, 28], or those individuals who have features of other heritable diseases associated with pheochromocytoma such as multiple endocrine neoplasia type 2A or 2B or neurofibromatosis type 1 [25].

Use of molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation [29]. In addition, the American Society of Clinical Oncologists (ASCO) identifies VHL syndrome as a Group 1 disorder, that is, a hereditary syndrome for which genetic testing is considered part of the standard management for at-risk family members [30]. Early recognition of manifestations of VHL syndrome may allow for timely intervention and improved outcome; thus, clinical surveillance of asymptomatic at-risk individuals, including children, for early manifestations of VHL syndrome is appropriate.

2.3. Genetic counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions.

As mentioned above, VHL syndrome is inherited in an autosomal dominant manner, and we call proband (or index case) to the affected individual through whom a family with a genetic disorder is ascertained. It has been reported that about 80% of individuals diagnosed with VHL syndrome have an affected parent whereas de novo mutations of the *VHL* gene are estimated to occur in about 20% of probands. Recommendations for the evaluation of parents of a proband

with an apparent de novo mutation include molecular genetic testing if the *VHL* disease-causing mutation in the proband is known. If the disease-causing *VHL* mutation in the proband is not known, ophthalmologic screening and abdominal ultrasound evaluation, at a minimum, should be offered to both parents [31].

In the case of the sibs of a proband, the risk of VHL syndrome to sibs depends upon the genetic status of the parents: if a parent of a proband is clinically affected or has a disease-causing VHL mutation, the sibs of the proband are at 50% risk of inheriting the altered gene; and if neither parent has the disease-causing VHL mutation identified in the proband, the sibs have a small risk of VHL syndrome because of the possibility of germline mosaicism in one parent (at present the incidence of mosaicism is not known) [24].

Each offspring of an affected individual has a 50% risk of inheriting the mutant *VHL* gene; but the degree of clinical severity is not predictable (Figure 2), whereas the risk to other family members depends upon their biological relationship to the affected family member and can be determined by pedigree analysis and/or molecular genetic testing.

Molecular genetic testing of at-risk family members is appropriate in order to determine the need for continued clinical surveillance. Interpretation of molecular genetic test results is most accurate when a disease-causing germline mutation has been identified in an affected family member. Those who have the disease-causing mutation require regular surveillance, whereas family members who have not inherited the disease-causing mutation and their offspring need have no future concern [31].

Because early detection of at-risk individuals affects medical management, testing of asymptomatic individuals during childhood is beneficial [30]. As ophthalmologic screening for those at risk for VHL syndrome begins as early as possible, certainly before age five years, molecular genetic testing may be considered in young children. Molecular genetic testing may be performed earlier if the results would alter the medical management of the child.

The use of molecular genetic testing for determining the genetic status of presumably at-risk relatives when a family member with a clinical diagnosis of VHL syndrome is not available for testing is less straightforward. Such test results need to be interpreted with caution. A positive test result signals the presence of a VHL disease-causing mutation in the at-risk family member and indicates that the same molecular genetic testing method can be used to assess the genetic status of other at-risk family members. However, a negative test for a VHL gene mutation under such circumstances suggests one of the following possibilities:

(i) the at-risk family member has not inherited a *VHL* disease-causing mutation;

(ii) the familial *VHL* mutation may not be detectable by the assays used; or

(iii) the diagnosis of VHL syndrome in the affected family member is questionable.

In this situation, the presumably at-risk family member has a small, but finite, residual risk of having inherited a disease-causing allele (i.e., VHL syndrome or other hereditary disorder). In counseling such individuals, careful consideration should be given to the strength of the clinical diagnosis of VHL syndrome in the affected family member, the relationship of the at-risk individual to the affected family member, the perceived risk of an undetected *VHL* (or other) gene mutation, and the potential need for some form of continued clinical surveillance [31].

It is recommended that physicians ordering *VHL* molecular genetic testing and individuals considering undergoing testing understand the risks, benefits, and limitations of the testing prior to sending a sample to a laboratory. In fact, in some countries the individuals must give and sign an informed consent before the genetic analysis.

When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a de novo mutation. However, possible nonmedical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be carefully explored.

3. HEREDITARY PAPILLARY RCC

3.1. Clinical manifestation and molecular biology

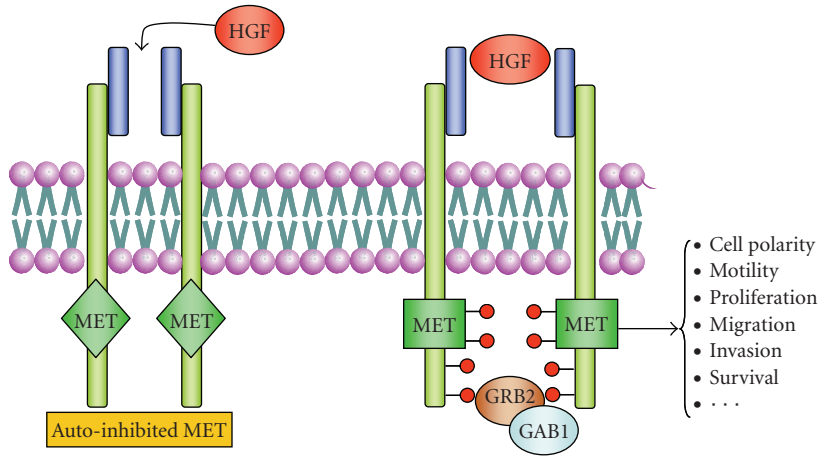
Hereditary papillary RCC (HPRCC) (OMIM 605074) is characterized by the development of multifocal, bilateral papillary type-1 RCCs (low-grade tumors with basophilic cells and a favorable prognosis) occurring at a late age in ~20% of gene carriers and a male/female ratio of 2:1 among affected members [6, 32] (Table 3). The pattern of inheritance is consistent with autosomal dominant transmission with reduced penetrance. Metastasis is less frequent, and age-dependent penetrance in mutation carriers seems to be reduced relative to penetrance in VHL syndrome [6].

HPRCC is mainly caused by activating germline mutations in the tyrosine kinase domain of the *MET* proto-oncogene. *MET* is located in 7q31 and codifies a tyrosine kinase receptor that is normally activated by hepatocyte growth factor (HGF) [33] (Table 2). The MET–HGF signalling pathway is important for cell proliferation, epithelial–mesenchymal transitions, branching morphogenesis, differentiation and regulation of cell migration in many tissues. Most of the germline mutations occur within the MET activation loop or in the ATP-binding pocket and cause ligand-independent MET activation (Figure 3) [34].

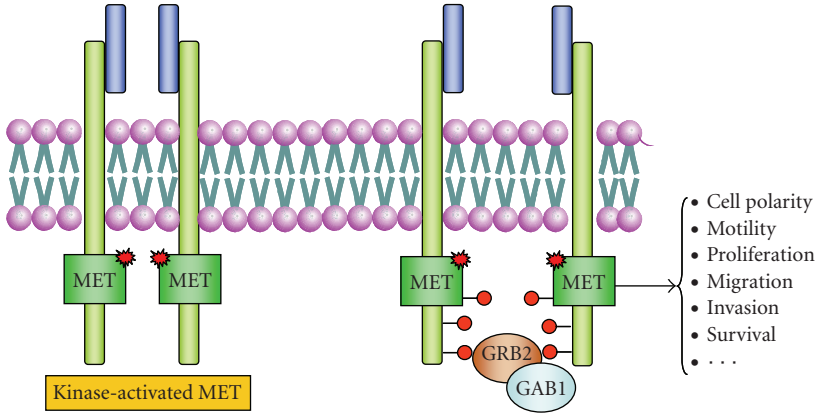
Tumors from patients with papillary RCC and germline mutations of *MET* commonly show trisomy of chromosome 7 when analyzed by cytogenetic studies and comparative genomic hybridization (CGH) providing the second activating event in the renal cells [9].

3.2. Molecular genetic testing

The molecular genetic testing of *MET* is mainly performed by sequence analysis of exons 16 to 19. All reported



(a) Normal cell



(b) HPRCC cell with *Met* mutation

Figure 3: Activating mutations in MET in HPRCC. (a) In normal cells, hepatocyte growth factor (HGF) binds to MET receptor to induce MET dimerization and release autoinhibition. This permits, through several phosphorilation steps, the activation of second-messenger molecules (such as GRB2, GAB1, or PI3K) leading to morphogenic, motogenic, and mitogenic programmes. (b) Renal cells from patients with HPRCC can harbour germline mutations in the tyrosine kinase domain of MET. These mutations release the autoinhibition by the MET carboxyl terminus, allowing the transition of the receptor to the active kinase form in absence of ligand stimulation.

alterations consist in point mutations. Ten known mutations are clustered in exons 16–19 of the tyrosine kinase domain and all are missense mutations which change the amino acid (V1110I, H1112R, H1112Y, M1149T, V1206L, V1238I, D1246N, Y1248C, Y1248D, M1268T). Mutations at four codons (V1110, D1246, Y1248, M1268) are homologous to sites of disease-associated activating mutations in other RTKs (RET, c-kit, c-erbB). Two unrelated North American families have been identified with the H1112R mutation and shared flanking genotyping data, suggesting a founder effect. Other mutations with only weak transforming potential (Y1248C, L1213V) confer anchorage-independent growth and an invasive phenotype in transfected cells.

Molecular genetic testing for a germline *MET* mutation is indicated in all individuals known to have or suspected of having HPRCC.

3.3. Genetic counseling

There are no specific screening guidelines for families suspected of having HPRCC. Individuals in these families are encouraged to talk with their doctor about screening options for kidney cancer, including ultrasound, and CT scan. Some clinicians suggest that individuals who have HPRCC, or a family history that suggests HPRCC, should have yearly screening beginning at age 30.

4. HEREDITARY LEIOMYOMATOSIS RCC

4.1. Clinical manifestation and molecular biology

Hereditary leiomyomatosis renal cell cancer (HLRCC) (OMIM 605839) predisposes to multiple cutaneous and

uterine leiomyomas and solitary papillary type 2 RCCs [6, 35] (Table 2).

The majority of individuals (76%) present with a single or multiple cutaneous leiomyoma. These lesions appear as skin-colored to light brown papules or nodules distributed over the trunk and extremities, and occasionally on the face. Forty percent of individuals with HLRCC have mild cutaneous manifestations with five or fewer lesions [36]. Histologically, proliferation of interlacing bundles of smooth muscle fibers with centrally located long blunt-edged nuclei is observed.

Practically all females with HLRCC develop uterine leiomyomas [36–38]. However, whether all women with HLRCC have a higher risk of developing uterine leiomyosarcomas is unclear. In the original description of HLRCC, it was reported that 15% of women with uterine leiomyomas also had uterine leiomyosarcoma [39].

Most renal tumors are unilateral and solitary. Approximately 10%–16% of individuals with HLRCC who present with multiple cutaneous leiomyomas had renal tumors at the time that renal imaging was performed [37, 38]. Most tumors are classified as "type 2" papillary renal cancer, which display distinct papillary architecture and characteristic histopathology (high-grade tumors with large eosinophilic cells, an aggressive course, and a bad prognosis) [38] (Table 3). The median age at detection of renal tumors is 44 years, and, in contrast to other hereditary renal cancer syndromes, renal cancers associated with HLRCC are aggressive [38].

The disease is caused by germline mutations in the tumor suppressor gene *FH* located in 1q42-43 that encodes the mitochondrial Krebs cycle enzyme fumarate hydratase (EC 4.2.1.2.) [35]. *FH* consists of ten exons encompassing 22.15 kb of DNA and is highly conserved across species. The active form of the enzyme is a homotetramer and catalyzes the conversion of fumarate to L-malate. In mammals, there are two fumarase isoforms (mitochondrial and cytosolic) that are synthesized from the same mRNA. After initial synthesis, the FH proteins are partially imported and processed at the mitochondrial outer membrane [6].

Activity of FH enzyme can be measured in cultured skin fibroblasts or lymphoblastoid cells to confirm the diagnosis. Reduced activity ($\leq$60%) of FH enzyme was found in all affected individuals with the diagnosis of HLRCC [40, 41].

The overall risk for renal tumor development is unclear and the mechanism of *FH*-mutation-driven tumorigenesis remains unknown so far [6]. It is plausible that intracellular fumarate accumulation as a result of *FH* inactivation causes decreased HIF degradation and overexpression of genes more downstream in the HIF pathway [42].

4.2. Molecular genetic testing

FH is the only gene known to be associated with HLRCC. Between 80% and 100% of individuals with HLRCC have identifiable sequence variants in *FH* [36–38]. The spectrum of mutations includes missense, insertion/deletion, and nonsense mutations that are predicted to truncate the protein, or substitute or delete highly conserved aminoacids, along with several whole-gene deletion. About 40 different *FH* mutations have been identified and are distributed throughout the entire gene without genotype-phenotype correlation [40]. Several of the mutations occur in many families, which could reflect a founder effect; notably, the Arg190His mutation, which is the most frequent mutation (33%) in a North American family study, and the Arg58X and Asn64Thr mutations in studies by the European-based Multiple Leiomyoma Consortium [6].

Molecular genetic testing for a germline *FH* mutation is indicated in all individuals known to have or suspected of having HLRCC, including individuals with the following:

(i) multiple cutaneous leiomyomas (with at least one histologically-confirmed leiomyoma) without a family history of HLRCC;

(ii) a single cutaneous leiomyoma with family history of HLRCC;

(iii) one or more tubulo-papillary, collecting-duct, or papillary type 2 renal tumors with or without a family history of HLRCC.

Measurement of FH enzyme activity can be useful in the diagnosis of HLRCC in cases with atypical presentation and undetectable *FH* mutations [40, 41].

No correlation is observed between *FH* mutations and the occurrence of cutaneous lesions, uterine fibroids, or renal cancer of HLRCC [36]. To date, six women with a germline mutation in *FH* have been reported with uterine leiomyosarcoma [43, 44]. It seems that *FH* mutation-positive families are in general not highly predisposed to uterine cancer, but a few individuals and families seem to be at high risk.

4.3. Genetic counseling

HLRCC is inherited in an autosomal dominant manner. Some individuals diagnosed with HLRCC have an affected parent and some have HLRCC as the result of a de novo gene mutation. In this case, the proportion of cases caused by de novo mutations is unknown as subtle manifestation in parents has not been evaluated and genetic testing data are insufficient. Recommendations for evaluation of parents of a proband with a suspected de novo mutation include molecular genetic testing if the *FH* disease-causing mutation in the proband has been identified. However, it is important to note that although some individuals diagnosed with HLRCC have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

In the case of the siblings of a proband, the risk depends upon the genetic status of the proband's parents. If a parent of a proband is clinically affected or has a disease-causing mutation, each sibling of the proband is at a 50% risk of inheriting the mutation. If the disease-causing mutation cannot be detected in the DNA of either parent, the risk to siblings is low, but greater than that of the general population because the possibility of germline mosaicism exists [38].

The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

It is not possible to predict whether symptoms will occur, or if they do, what the age of onset, severity, and type of symptoms, or rate of disease progression will be in individuals who have a disease-causing mutation.

When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a de novo mutation. However, possible nonmedical explanations including alternate paternity or undisclosed adoption could also be explored.

There is no consensus on clinical surveillance for HLRCC individuals so far but the following provisional recommendations have been accepted until a consensus conference is conducted [31].

Individuals with the clinical diagnosis of HLRCC, individuals with heterozygous mutations in FH without clinical manifestations, and at-risk family members who have not undergone molecular genetic testing should have the following regular surveillance by physicians familiar with the clinical manifestations of HLRCC.

(i) *Skin.* Full skin examination is recommended annually to every two years to assess the extent of disease and to evaluate for changes suggestive of leiomyosarcoma.

(ii) *Uterus.* Annual gynecologic consultation is recommended to assess severity of uterine fibroids and to evaluate for changes suggestive of leiomyosarcoma.

(iii) *Kidneys.* If both the initial (baseline) and the first annual follow-up abdominal CT scan with contrast are normal, this evaluation should be repeated every two years.

Any suspicious renal lesion (indeterminate lesion, questionable or complex cysts) at a previous examination should be followed with a CT scan with and without contrast. PET-CT may be added to identify metabolically active lesions suggesting possible malignant growth. It must be taken into consideration that ultrasound examination alone is never sufficient.

Renal tumors should be evaluated by a urologic oncology surgeon familiar with the renal cancer of HLRCC.

5. BIRT-HOGG-DUBÉ SYNDROME

5.1. Clinical manifestation and molecular biology

Birt-Hogg-Dubé (BHD) syndrome (OMIM 135150) is a genodermatosis that predisposes individuals to benign cutaneous lesions of the face and neck, spontaneous recurrent pneumothorax and/or lung cysts, and renal tumors [6, 7]. Approximately 15–29% of individuals with BHD syndrome have renal tumors [45, 46] (Table 3). The renal tumors are usually bilateral and multifocal. Tumor types include renal oncocytoma, chromophobe RCC, oncocytic hybrid tumor, and a minority of clear cell RCC [47]. The most common tumors are a hybrid of oncocytoma and chromophobe histologic cell types, so-called oncocytic hybrid tumor (67%), chromophobe RCC (23%), and renal oncocytoma (3%). Only renal oncocytoma is considered a benign tumor [48]. Other types of renal tumors reported in lower frequency include clear cell RCC and papillary renal carcinoma. Most renal tumors are slow-growing. Median age of diagnosis is 48 years with range from 31 to 71 years [46].

The disease is caused by germline mutations in the *BHD (FLCN)* gene on chromosome 17p11.2 [49]. *BHD* encodes folliculin, a new protein with unknown function but it is highly expressed in a variety of tissues including skin and skin appendages, type 1 pneumocytes, and distal nephrons of the kidney [50]. Recent studies suggest that folliculin might be involved in energy and/or nutrient sensing through the AMPK and mTOR signaling pathways [51].

BHD somatic mutations are very rare in sporadic RCC but hypermethylations are encountered in ~30% of all RCC histological types [52]. Germline mutations in *BHD*, plus somatic mutations and loss of heterozygosity in tumor tissue, suggest that loss of function of the folliculin protein is the basis of tumor formation in BHD syndrome [53].

5.2. Molecular genetic testing

BHD is the only gene known to be associated with BHD syndrome. Various mutations have been identified in families with BHD syndrome. All mutations predict protein truncation. The most common mutation is cytosine insertion or deletion, which occurs in a polycytosine tract in exon 11, suggesting the presence of a hypermutable hot spot [46, 47]. Fifty-three percent of families with BHD syndrome have been found to have an insertion or deletion in the polycytosine tract in exon 11 (mutational hot spot) [46]. Sequence analysis of all coding exons (exon 4–14) increases the mutation detection in probands to 84% [46].

Molecular genetic testing is indicated in all individuals known to have or suspected of having BHD syndrome including individuals with the following.

(1) Five or more facial or truncal papules with at least one histologically confirmed fibrofolliculoma [54] with or without family history of BHD.

(2) A family history of BHD syndrome with a single fibrofolliculoma or a single renal tumor or history of spontaneous pneumothorax.

(3) Multiple and bilateral chromophobe, oncocytic, and/or oncocytic hydrid renal tumors.

(4) A single oncocytic, chromophobe, or oncocytic-hydrid tumor and a family history of renal cancer with any of the above renal cell tumor types.

(5) A family history of autosomal dominant primary spontaneous pneumothorax without a history of chronic obstructive pulmonary disease.

Mutations in *BHD* were found in families with dominantly inherited spontaneous pneumothorax. Pulmonary

involvement appears to be the only manifestation; penetrance is 100% [55, 56].

Acquired mutations in *BHD* have been identified in sporadic clear cell renal cell carcinoma [52, 57] and colon cancer [58, 59] without other associated tumors characteristic of the heritable disease.

No correlation is observed between type of *BHD* mutation and pulmonary and cutaneous manifestations. However, individuals who have a deletion in the polycytosine tract of exon 11 may have a lower risk of developing renal cancers than individuals with other mutations [46].

5.3. Genetic counseling

BHD syndrome is inherited in an autosomal dominant manner. Some individuals with BHD syndrome have an affected parent and some have BHD syndrome as a result of a de novo gene mutation. The proportion of cases caused by de novo mutations is unknown as a sufficient number of parents have not been evaluated for subtle manifestations, nor are there sufficient data on clinically unaffected parents who have been evaluated by molecular genetic testing. Recommendations for the evaluation of parents of a proband with a suspected de novo mutation include molecular genetic testing if the disease-causing mutation in the *BHD* gene in the proband is identified. But, although some individuals diagnosed with BHD syndrome have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

The risk to the siblings of the proband depends upon the genetic status of the proband's parents. If a parent of a proband is clinically affected or has a disease-causing mutation, the sibs of the proband are at a 50% risk of inheriting the mutation. If neither parent has the disease-causing mutation identified in the proband, the risk to sibs is low, but greater than that of the general population because the possibility of germline mosaicism exists.

When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a de novo mutation. However, other possible nonmedical explanations could also be explored.

There is no consensus on clinical surveillance; therefore, these recommendations are provisional until a consensus conference is conducted.

Individuals with known BHD syndrome, individuals known to have disease-causing mutations in *BHD* without clinical manifestation, and at-risk family members who have not undergone genetic testing should have regular monitoring by physicians familiar with the spectrum of BHD syndrome. In particular, surveillance for and monitoring of renal tumors include the following:

(i) if normal at baseline, abdominal/pelvic CT scan with contrast every two years;

(ii) if any suspicious lesion (indeterminate lesion, questionable or complex cysts) at previous examination, annual abdominal/pelvic CT scan with contrast alternating every other year with MRI to reduce lifetime exposure to radiation;

(iii) evaluation of renal tumors by a urologic surgeon;

(iv) monitoring of tumors less than three centimeters in diameter by periodic imaging; they may not require surgical intervention while this small.

6. FUTURE TRENDS

The identification of genes responsible for inherited RCC has resulted in a better understanding of renal tumorigenesis including sporadic RCC and is paving the way for new therapeutic approaches [6, 7]. For VHL, recent and ongoing insights into the functions of the VHL gene, especially the HIF-ubiquitylation pathway, provide an attractive molecular basis for the development of specific inhibitors of HIF and/or its downstream targets [13]. Preliminary studies with the VEGF receptor inhibitor SU5416 showed that at least a third of patients with advanced VHL disease improved their clinical status giving promising expectations [60]. In same directions, new protein kinase receptor inhibitors are emerging [9]. In HPRCC, MET inhibitors gave encouraging results in in vitro studies, but clinical trials have started very recently and although data on the antitumor activity of the anti-MET compounds are not yet available, these studies have shown that MET inhibition results in low-grade toxicity, in agreement with the preclinical analyses performed in animal models [61, 62].

Recent studies suggest that HIF overexpression is involved in HLRCC tumorigenesis [42, 63]. Therefore, future target therapies for HLRCC-associated tumors may include, for example, anti-HIF therapies such as R59949 that regulate prolyl hydroxylase activity, thus preventing HIF accumulation.

The study of families with increased rates of cancer will continue to yield more insight into the factors that increase cancer risk. Genetic predisposition in the form of mutations and polymorphisms will increasingly be catalogued and DNA-level genetic profiling of high-risk families and individuals will become commonplace. The increase in availability of genetic testing and counseling for high-risk families should prove both helpful and cost-effective, as genetically unaffected family members reassured regarding their health status and removed from lifelong follow-up screening programmes.

Finally, we also should keep in mind, although not deeply discussed in this review, the psychological and ethical implications of the genetic counseling [64–66], not only from the strictly clinical point of view, but also regarding the management of personal genetic information that could have an impact on the individual and their relatives from certain health insurance companies.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 415848, 16 pages
doi:10.1155/2008/415848

Review Article

Radiologic Evaluation of Small Renal Masses (I): Pretreatment Management

A. Marhuenda,[1] M. I. Martín,[1] C. Deltoro,[1] J. Santos,[1] and Jose Rubio Briones[2]

[1] *Departamento de Radiología, Instituto Valenciano de Oncología, C/Profesor Beltrán Báguena 8, 46009 Valencia, Spain*
[2] *Departamento de Urología, Instituto Valenciano de Oncología, C/Profesor Beltrán Báguena 8, 46009 Valencia, Spain*

Correspondence should be addressed to A. Marhuenda, amarflu@gmail.com

Received 9 April 2008; Accepted 11 December 2008

Recommended by F. Algaba

When characterizing a small renal mass (SRM), the main question to be answered is whether the mass represents a surgical or nonsurgical lesion or, in some cases, if followup studies are a reasonable option. Is this a task for a urologist or a radiologist? It is obvious that in the increasing clinical scenario where this decision has to be made, both specialists ought to work together. This paper will focus on the principles, indications, and limitations of ultrasound, CT, and MRI to characterize an SRM in 2008 with a detailed review of relevant literature. Special emphasis has been placed on aspects regarding the bidirectional information between radiologists and urologists needed to achieve the best radiological approach to an SRM.

1. INTRODUCTION

Over the last 3 decades, there has been a rising trend to define small renal masses (SRMs) as masses below 4 cm in diameter [1], making it the major reason for the 126% increase in incidence of renal cell carcinoma (RCC) in the United States. The reason for that is well known; the increasing number of imaging examinations performed for unrelated indications with many renal neoplasms of small size and early stage incidentally detected. Faced with this situation, urologists do not only suggest surgery as 30 years ago, but also offer different options to deal with the problem. Most of their decisions are based on radiological characterization of the SRM, as biopsies of these masses have not been completely accepted by the international urological community.

So, evidently urologists have to ask their colleagues in the Radiology Department to improve their explorations expecting more and more extensive radiological reports analyzing not just the presence of the mass. The SMR analysis must be carried out by both a radiologist and an urologist, as bidirectional information is extremely important to define the most probable nature of the mass.

The accurate diagnosis of a renal mass depends on many factors, including the clinical history; so there is some clinical information that urologists have to report to their radiologists:

(i) presence of a familial syndrome,

(ii) presence of a urological tract infectious disease previous or concomitant to the diagnoses of the SRM,

(iii) presence of previous stone disease and related treatments,

(iv) presence of previous renal trauma,

(v) presence of kidney disease and renal insufficiency.

A high-quality imaging examination, under the control of a radiologist, is essential. The most accurate diagnosis of a renal mass is then made according to the nature of the imaging findings, the experience of the radiologist, and the quality of the examination, as well as the exclusion of conditions that can mimic a renal neoplasm. There are some key points that, due to their therapeutic decision-making importance, radiologists need to provide in their reports:

(i) signs suspecting fat involvement in an SRM,

(ii) metabolic behavior during the different phases of CT and MRI after contrast administration, allowing to characterize benign SRM,

(iii) the need (or not) to complete studies with different techniques,

(iv) accurate and standard (for followup in case of watchful waiting policy) measurement of 3 diameters of the SRM,

(v) signs of active tumoral tissue after conservative treatments which do not remove the SRM,

(vi) differential diagnosis of residual tumour with complications after partial nephrectomies and foreign bodies used to achieve haemostasis.

Having established the collaboration between urologist and radiologist for this review paper, the aim of the two complementary chapters submitted for the SRM diagnoses and characterization is to give some light on the new challenges which face radiologists nowadays, extremely important for the SRM management.

2. OBJECTIVES

Renal cell carcinoma and oncocytoma are indistinguishable from each other at imaging. Many other renal lesions must be considered, such as angiomyolipoma (AML), lymphoma, metastatic disease, renal anomalies, and other pseudotumors that can mimic renal cell carcinoma. Although it is possible to make this differentiation by using the imaging findings alone, the clinical history can often be very important in making the correct diagnosis. In fact, before making a diagnosis of renal cell carcinoma, one should be certain that none of these possible mimickers of renal cell carcinoma are potentially present.

Staging by TNM system can be considered a prognostic classification, and there is evidence that the smaller the size, the better the prognosis [2, 3] . The increasing incidence of renal mass manifestations of tumours that are confined to the renal capsule and relatively small in size has stimulated a growing trend toward nephron-sparing surgical techniques, as current data show survival rates comparable to those associated with radical nephrectomy.

Imaging findings that can affect the decision to perform partial nephrectomy included tumor size in three planes: tumor location within the kidney; presence of a pseudocapsule (a thin band of fibrous tissue and compressed renal parenchyma surrounding the lesion); tumor invasion of the renal sinus fat, collecting system, renal vein, or perinephric fat; presence of lymphadenopathy; morphologic and physiologic status of the contralateral kidney. All these aspects are evaluated by means of different imaging techniques.

The increased implementation of kidney-sparing surgery for renal cell carcinoma may create an important role for diagnostic imaging in the discovery of small synchronous carcinomas. Radiologist should be aware of the possibility of tumor multifocality or of adrenal metastases from a high-grade small renal tumor as well as of the association of RCC with lymphoma [4].

The challenge is to detect and delineate all lesions to ensure complete surgical excision while preserving the maximal amount of functioning parenchyma. For patients who are not surgical candidates, imaging staging, along with the other factors, can provide prognostic information.

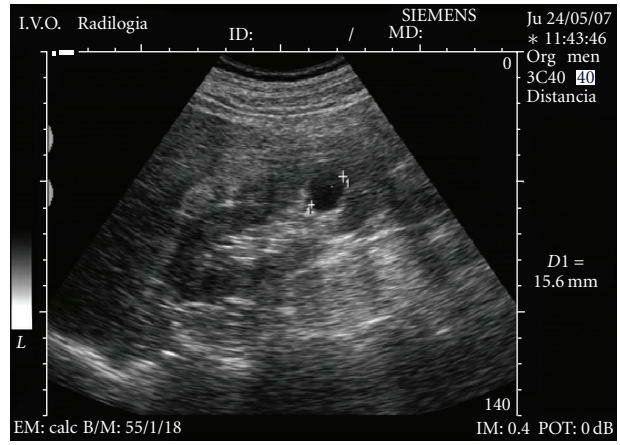


Figure 1: Simple cyst as anechoic lesion with a sharply defined back wall and enhancement of through sound transmission.

3. ULTRASOUND

The fact that renal neoplasms have been detected earlier and with increased frequency is well documented in the literature [5, 6]. This is probably due to two major factors. One factor is that there has been a considerable increase in the number of people who undergo kidney imaging in the general population because of the widespread use of ultrasound (US). The other reason is that this imaging technique is able to depict lesions of the kidneys that could be missed with urography [7]. This increased detection of renal neoplasms also results in the increased detection of benign lesions and nonneoplastic masses, particularly renal cysts. Therefore, the differentiation between a neoplastic and a nonneoplastic lesion is a common dilemma.

To differentiate benign from malignant SRM can prove even more problematic because the findings can also become smaller, hence requiring more detailed and more sensitive imaging studies.

Ultrasound plays an important role in the detection and evaluation of these SRMs. While this technique may not be as sensitive as contrast-enhanced CT or MR for revealing SRM, US has been the initial technique in the discovery of a large number of these incidentally discovered tumors when the kidney is studied in the course of abdominal imaging. Sonography is very accurate in distinguishing liquid from solid tissue. Therefore, its major use in these small lesions is to help differentiate small cysts (see Figure 1) from small solid tumors [8]. Maintaining rigid criteria is necessary to maintain the high accuracy possible with this technique.

In the general population, renal cysts are the most common space-occupying lesions in the kidney. With this technique, 80% of detected renal masses are characterized as simple cysts [9] thus ending their diagnostic evaluation. The remaining 20% of renal masses require further study with CT or MR imaging [10]. Any mass detected that does not meet the strict sonographic criteria for a simple cyst should be further evaluated with CT or MR imaging of the kidneys.

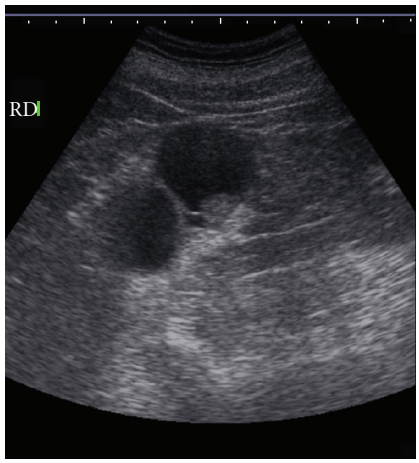


Figure 2: A cyst with nodular thickening of the wall and internal septa.

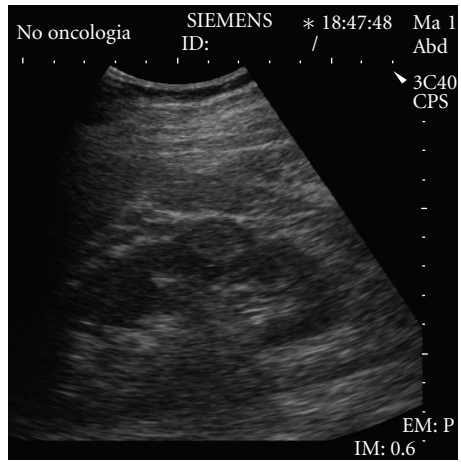


Figure 3: Well-defined hyperechoic small renal mass. Pathologic analysis of the surgical specimen revealed a renal cell carcinoma.

However, one or two thin septations may also be visible sonographically in simple renal cysts [11]. Because these findings are diagnostic, no further imaging or followup is needed in the evaluation of these lesions. However, other atypical features sonographically detected calcifications; more than two septations, septal thickening or nodularity, and the presence of solid components indicate that sonography alone will not be adequate for complete evaluation of these renal masses (see Figure 2). The addition of Doppler sonography, color Doppler sonography, power Doppler sonography [12, 13], and sonographic contrast agents may further improve the detection and characterization of renal masses. However, none of these techniques preclude the need for CT or MR imaging of renal masses that do not meet the sonographic criteria for diagnosis of a simple cyst.

In the study of solid renal masses, the role for US has been mainly centred on the differentiation of RCC and AML, which are the most common malignant and benign solid renal tumors, respectively [14–17]. When a solid mass is diagnosed, RCC or AML should be initially considered because of the high frequency of their occurrence. At US, most AML lesions are markedly hyperechoic relative to renal parenchyma. They may appear less echogenic depending on the relative proportion of fat, smooth muscle, vascular components, and haemorrhage in the lesion [18, 19]. RCC displays a broad range of echogenicities. Although often thought of as hypoechoic or isoechoic, recent studies have shown that most RCC are hyperechoic relative to renal parenchyma and that up to 12% simulate AML [14–17]. Forman et al. [14] have shown that one third of small RCC are as echogenic as a "classical" AML. An echotexture equal to that of renal sinus fat seen in a small renal mass is, therefore, no longer considered adequate to exclude the diagnosis of malignancy (see Figure 3).

Other ultrasound signs have been used to differentiate between hyperechoic RCC and AMLs. The presence of an anechoic rim and/or an intratumoral cyst is only seen in RCC (see Figure 4). The presence of acoustic shadow is specific of AML. However, the detectability of these findings varies

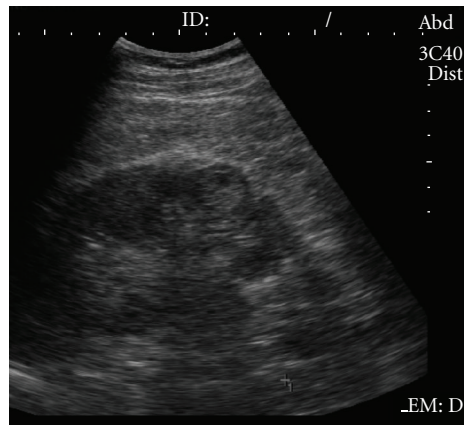


Figure 4: Well-defined hyperechoic small renal mass with hypoechoic rim and intratumoral cystic area, confirmed with pathologic analysis as renal cell carcinoma.

[15, 16], their diagnostic value has not been established, and the presence of these features is not sufficient to differentiate RCC from the other solid renal masses that are incidentally detected on gray-scale US. On the power Doppler US, the analysis of the vascular distribution has not increased the diagnostic accuracy for small renal tumors [12]. Contrast-enhanced Doppler US can increase the detection of intratumoral vascularity compared to color/power Doppler US [20]. However, their signal intensity has not been found to be sufficiently intense for tumor characterization. Recently, the development of contrast-enhanced harmonic US imaging has provided a better assessment of the diagnostic accuracy of RCC as compared with gray-scale US by allowing better visualization of the intratumoral anechoic areas and the pseudocapsule than can the gray-scale US [21], but there still exists an overlapping of signs of RCC and the other solid renal masses, making it necessary to use CT or MR imaging in the study of small renal masses.

4. CT

Helical CT is generally accepted as the critical imaging test for the classification of renal masses. Radiation exposure is the greatest disadvantage of this technique. MRI is comparable to helical CT for detection, diagnosis, and staging of renal masses. However, CT has the advantages of widespread availability, shorter examination time, and lower cost in comparison with MRI.

A detailed analysis of a variety of CT features is required, including the size, location, appearance on unenhanced scan, the presence and location of calcifications, the presence and size of a cyst wall or septations, and the amount and pattern of contrast enhancement [7, 22, 23].

4.1. CT technique

Single detector and especially multidetector spiral (MDCT) have refined the diagnostic evaluation of renal pathologic conditions. Compared with single-detector helical CT, MDCT allows the kidneys to be scanned with a collimation of less than 5 mm during a single breath hold [24]. From a single data set obtained with thin collimation, both thin and thick sections can be reconstructed and no additional radiation exposure is required to obtain the thin sections. This dataset is manipulated by using a workstation to produce volume-rendered and three-dimensional (3D) images when necessary. The 3DCT images can be viewed in multiple planes and orientations to define the lesion.

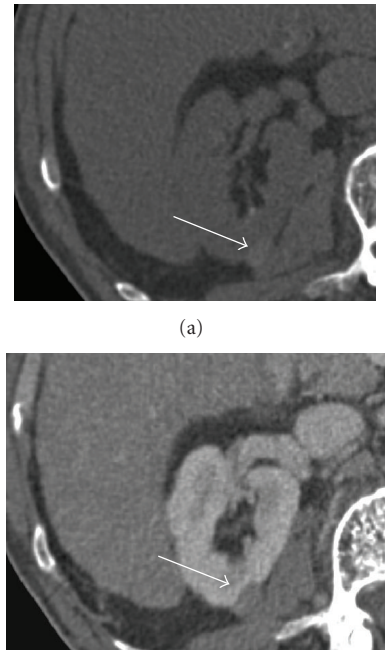
A triphasic imaging protocol consists of an unenhanced phase through the kidneys, an arterial or corticomedullary phase through the liver and kidneys (between 25 and 70 seconds after the start of injection of contrast), and a portal venous or nephrographic phase of the entire abdomen (between 80 and 180 seconds). Excretory phase (>180 seconds) is occasionally helpful.

An initial series of unenhanced scans provides a baseline from which to measure the enhancement within the lesion.

The corticomedullary phase is useful to perform 3D reconstructions and to depict the renal vasculature. Furthermore, this phase is considered essential for staging.

The nephrographic phase provides greater lesion detection and improved lesion characterization of renal masses than corticomedullary phase [25, 26]. However, a case of renal cell carcinoma visible only during the corticomedullary phase has been shown in the literature [27]. The excretory phase is occasionally helpful to better delineate the relationship of a centrally located mass within the collecting system. Delayed scanning (15 minutes) can also be used in lieu of unenhanced scanning to characterize an incidental renal lesion detected on a routine contrast-enhanced CT scan [28].

At present, there is no worldwide agreement upon the specific number that can be used as definitive and unequivocal evidence of enhancement within a renal mass, and it has been proposed by many authors that the previously used threshold of 10 HU should be increased to 20 HU (a currently accepted criterion) (see Figure 5). Some authors think that a renal mass that enhances 10–20 HU is indeterminate and needs further evaluation [29].



(a)

(b)

Figure 5: Hemorrhagic cyst. (a) Unenhanced CT scan shows a hyperattenuating small renal mass (62 H) (arrow). (b) Contrast-enhanced CT scan during the nephrographic phase reveals light enhancing (attenuation value increased 9 H:71 H) (arrow).

4.2. Imaging of specific small renal masses

4.2.1. Cysts

Most small renal masses incidentally discovered on CT are simple cortical cysts that need no further evaluation. The Bosniak classification system is used to asses the likelihood of malignancy in cystic renal masses on the basis of lesion complexity in CT imaging [30, 31]. Application of the Bosniak classification can be difficult in the case of an indeterminate renal lesion, especially if it is small. Bosniak admits that distinction between category II (not requiring surgery) and category III (requiring surgery) can be very difficult [32].

4.2.2. Angiomyolipoma

It is typically a solid lesion that exhibits fat density on CT scans (−10 to −100 HU) (see Figure 6). However, in some cases, it may contain very small quantities of fat that can be overlooked. Angiomyolipomas rarely contain calcification, and, therefore, a diagnosis of angiomyolipoma should not be made if a lesion contains fat and calcium [33, 34]. There have been few case reports of fat from RCC that also contain calcification. In such cases, a renal cell carcinoma must be considered the most likely diagnosis.

4.2.3. Oncocytoma

It is usually a hypodense mass, homogeneous, with smooth contours and a tendency to enhance avidly (see Figure 7).

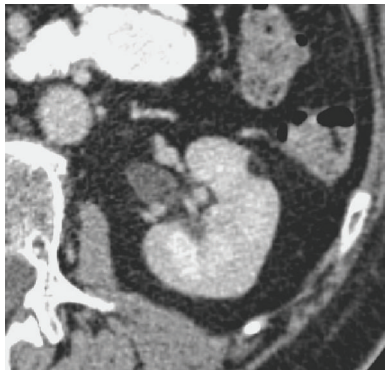


Figure 6: Angiomyolipoma. Contrast-enhanced CT shows a small homogeneous fat-containing mass.

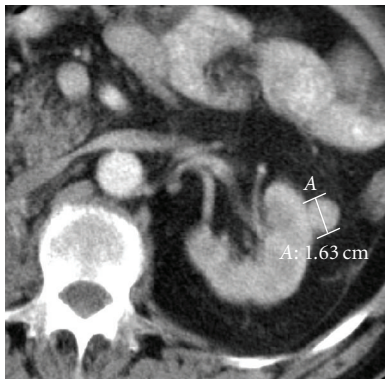
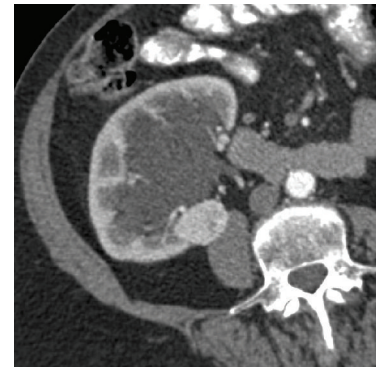


Figure 7: Oncocytoma. Small mass isoattenuated to renal parenchyma after contrast.



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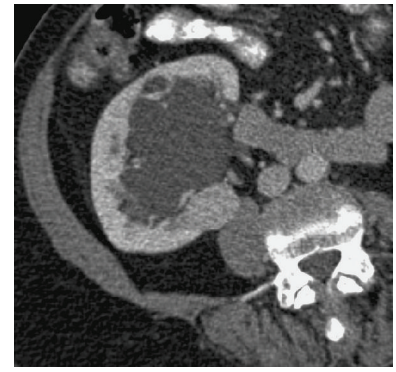


(b)

Figure 8: Small hyper vascular renal cell carcinoma. (a) Contrast-enhanced CT shows small renal mass that enhances early in corticomedullary phase. (b) Rapid washout in nephrographic phase.

Until now, an oncocytoma was suggested on postcontrast CT by the presence of a central hypoenhancing scar. Because of its lack of specificity, patient management has been unaffected by the presence of this finding. Renal cell carcinoma and oncocytoma are indistinguishable from each other at imaging.

4.2.4. Renal cell carcinoma

The imaging characteristics of RCC are extremely varied, with masses ranging from cystic to solid, from homogeneous to heterogeneous and necrotic, from small to large, and from localized to extensive. The typical CT appearance of small RCC is a homogeneously isodense/hypodense mass, noncalcified, with an attenuation value of 20 HU or more, that enhance avidly and early with contrast medium (see Figure 8) [23]. The early-stage contrast enhancement is believed to be caused by tumor angiogenesis. However, a small proportion of RCC are hypovascular, and the amount of enhancement may be minimal. Small RCC with a predominantly cystic growth pattern, necrosis, or calcifications (peripheral curvilinear or punctate central) are uncommon. Areas of fat attenuation can be present within renal cell carcinomas, but are uncommon in small tumors.

Furthermore, a small RCC can be hyperattenuating. If the lesion is depicted only on enhanced CT, delayed scanning can also be used. Macari and Bosniak [28] have suggested that measurement of the washout of contrast material from at least 15 minutes allows differentiation between hyperdense cyst and renal neoplasms. The washout of 15 HU or more indicates that, excluding vascular abnormality, the mass is solid. A lack of washout indicates that the mass is probably a hyperattenuating cyst.

On the other hand, renal cortical tumors are family neoplasms with distinct cytogenetic and molecular characteristics and varying malignant potential. In the 1997 Heidelberg classification, renal cell carcinoma was subdivided in subtypes [35]. It has been suggested that certain imaging features may be associated with different subtypes of solid renal cortical tumors [36, 37]. The most consistent finding in these studies was that the degree of enhancement was the most valuable parameter for differentiation of RCC subtypes, as clear cell RCC enhance to a greater degree than other subtypes, especially papillary RCC. Clear cell RCC is also strongly associated with a mixed enhancement pattern of both enhancing soft-tissue components and low-attenuation areas (necrotic or cystic changes). When homogeneous or peripheral enhancement is present, clear cell RCC is a less likely diagnosis, and other cell types should be considered.

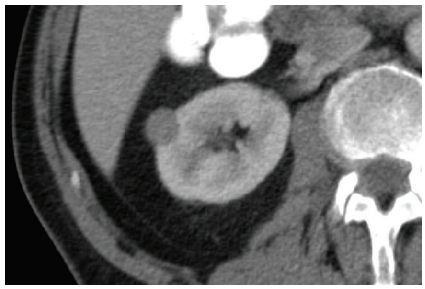


Figure 9: Papillary renal cell carcinoma. Contrast-enhanced CT shows small homogeneous mass that is mild and less enhanced than renal parenchyma does.

Notably, a majority of papillary tumours were either homogeneous or peripheral enhancement (see Figure 9). The presence to neovascularity was mildly associated with more aggressive tumor. The clear cell RCC (and oncocytomas) enhanced avidly during the parenchymal phase; the chromophobe RCC (and lipid poor angiomyolipoma) enhanced moderately and papillary RCC enhance mildly.

4.2.5. Non-Hodgkin's lymphoma

Lymphoma can have a variable appearance and may on occasion resemble renal cell carcinoma. Most frequently, it manifests as bilateral solid renal masses, and in a patient with systemic lymphoma, the proper diagnosis is not difficult. Characteristically, lymphoma often infiltrates into the kidney via the renal sinus or surrounds the kidney. In a patient with known systemic lymphoma to whom a renal mass with imaging is detected, systemic treatment for lymphoma should be instituted. If the patient's systemic disease responds, and the renal mass does not respond, biopsy of the mass is indicated. However, lymphoma may rarely manifest as a solitary renal mass or a homogeneous infiltrating renal mass. In this case, biopsy of the mass is indicated previous to systemic therapy.

4.2.6. Metastases

Metastatic disease to the kidney typically manifests as multiple bilateral renal masses, often associated with metastatic disease to other organs. They are often poorly defined and infiltrate the renal parenchyma. With the appropriate clinical history, the diagnosis is straightforward. However, in a patient with a solitary renal mass (especially an infiltrating mass) and history of previous malignancy, percutaneous renal biopsy is indicated for a definitive diagnosis.

4.2.7. Benign mesenchymal tumors

Included leiomyomas, lipomas, fibromas, and mixed mesenchymal nodules. They are usually small (< 1 cm) lesions, found in autopsies.

4.2.8. Pseudotumors

They include congenital anomalies (prominent renal columns of Bertin, renal dimorphisms, and dromedary humps) and acquired pseudotumors (hypertrophied normal renal parenchyma). This condition enhances identically to the normal renal parenchyma. In these situations it proves appropriate to scan during the corticomedullary and nephrographic phase.

4.2.9. Renal mass mimickers

These include inflammatory masses (including focal pyelonephritis, renal abscess) and hematoma. A careful evaluation with high-quality CT or MR examination combined with the clinical context of the case and a familiarity with this group of "lesions" should reveal its true nature. Most hematomas are perinephric and are surrounded by fat stranding. They may occasionally have a masslike appearance, and some may not be discovered until long time after the traumatism. Chronic hematomas can have calcifications and do not enhance.

4.3. Diagnosis and management of renal call carcinoma with MD-CT

CT remains the most widely available and single most effective modality for staging renal call carcinoma [38, 39]. 3DCT combined with CT angiography has the potential to provide all the critical information needed to plan the surgical procedure. 3DCT images can be viewed in multiples planes and orientations to define the tumor and its relationship to the renal surface, the collecting system, and adjacent organs. A 3DCT angiogram can be created to delineate the renal arterial and venous anatomy.

The anatomic extent of the tumor at the time of diagnosis is the single most important factor in determining prognosis (see Table 1) [38].

Most urological surgeons continue to refer to Robson's classification, which is essentially a surgical staging approach. This system includes the important staging variables that have survived scrutiny over the years. Confinement within the renal capsule, penetration into the perirenal fat, invasion into the renal vein, and lymph node metastases are all important in determining the prognosis.

Under and overstating of perinephric invasion are the most common staging errors at CT [40]. The most specific finding of stage T3a, the presence of an enhanced nodule in the perinephric space, is highly specific but also low sensitive. The differentiation between stage T2 and T3a tumors is very problematic.

If tumoral spread within the IVC is identified, precise delineation of the superior extent of the thrombus is essential for the surgeon to plan the optimal surgical strategy for thrombectomy and minimize the risk of embolism. The level of involvement of the IVC dictates the surgical approach. Involvement of the IVC is best shown during corticomedullary phase. Because of its multiplanar capability, magnetic resonance imaging is the preferred modality to image. However, the three-dimensional CT with sagittal and coronal reconstructions is also effective in depicting the superior extent of inferior vena cava thrombus (see Figure 10), with the advantages of widespread availability,

Table 1: Staging system for renal carcinoma and CT criteria.

Tumour position	Robson	TNM	CT findings
Confined within renal capsule	**I**		Soft-tissue mass enhances less than normal renal parenchyma; central necrosis in large RCC.
Small (<7 cm)		**T1**	
Large (≥7 cm)		**T2**	
Spread to perinephric fat	**II**	**T3a**	Perinephric stranding; Perinephric collateral vessels; Soft-tissue mass in perinephric space
Venous thrombus	**III A**		
Renal vein only		**T3b**	Low-attenuation filling defect vein;
IVC infradiaphragmatic		**T3c**	Direct continuity of thrombus with primary mass;
IVC supradiaphragmatic		**T4b**	Enhanced thrombus
Regional lymph node metastases	**III B**	**N1-N3**	Lymph nodes 1 cm in diameter or larger
Direct invasion of adjacent organs	**IV A**	**T4a**	Obliteration of normal soft-tissues planes between tumor and adjacent organs
Distant metastases		**M1**	Metastases enhance with IV contrast material; Hepatic metastases best in arterial phase

IV: intravenous, IVC: inferior vena cava.

shorter examination time, and lower cost in comparison with MR [40].

5. MR

5.1. Indications

Although ultrasound and CT are often combined to reveal and characterize most renal lesions, MR is sometimes required when indeterminate lesions are found [41], or when a hyperattenuating renal mass is observed on CT [42]. Furthermore, some renal masses are incidentally discovered when MR imaging is performed to answer questions other than urology ones.

On the other hand, MR imaging has been considered the most accurate method for those patients with contraindications to iodinated contrast administration such as in patients with renal failure and those with an allergy to iodinated contrast material [43].

Recently, nephrogenic systemic fibrosis was linked to gadolinium contrast agent exposure in patients with renal failure; therefore its use should be reserved for neurological and vascular cases where the quality of information gained was sufficient to justify the risk of potential devastating adverse effects [44]. Nevertheless, the better contrast resolution of MR imaging, as opposed to CT, is an undoubtful advantage in those patients for performing an MR exploration, even though no contrast is provided.

MR imaging has been considered useful not only in characterization but also in evaluation of most cystic renal masses with the Bosniak classification system [45]. In addition, MR imaging can potentially improve staging and preoperative studying of a renal mass [41, 46–51] as well as tumor multifocality, collecting system invasion, and venous invasion [52]. Moreover, MRI is capable of showing the patency of a blood vessel without the use of intravenous contrast medium.

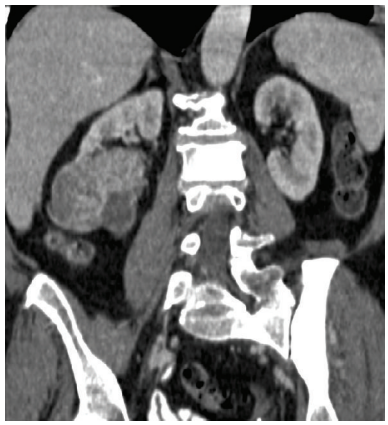
The accuracy in detection and characterization of SRM carries great significance when nephron sparing surgery is being considered for a renal cell carcinoma because synchronous lesions measuring 1–15 mm have been reported to a frequency as high as 19.7% [53].

5.2. Basic technical examination

A proper technical examination is needed for studying a renal mass which is indeterminate after US and CT techniques. Owing to intrinsic proprieties of magnetic resonance examination, high-quality renal MR imaging is dependent on multiple factors, includingpatient cooperation in holding breath. In patients referred for evaluation of a renal mass, examinations are currently performed with a torso phased-array coil, preferably during a more reproducibility end-expiratory breath hold [29, 54].

Different protocols can be used by different institutions depending on their technical requirements. Essentially, the common aspects are shown as follows. Prior to contrast administration, sequences are used to obtain images weighted on T1 and T2, in and out of phase T1, and a precontrast 3D weighted T1 with fat saturation can be acquired in different planes, basically on axial plane but also coronal or sagittal can be employed to best depict the mass, especially for such lesions located in renal poles. This approach is most important when evaluating a patient with a solitary kidney that contains a renal neoplasm that is amenable to partial nephrectomy.

These sequences provide us with morphologic information about the renal parenchyma and a renal mass (location, size, and signal intensity), parenchymal structures and adjacent organs, vascular structures and lymphadenopathies,



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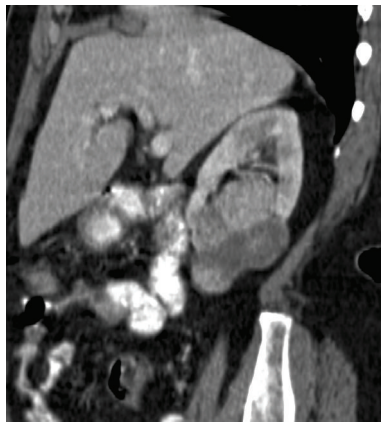


(b)

Figure 10: Renal cell carcinoma. (a) Three-dimensional CT with coronal reconstruction, (b) sagittal oblique reconstruction.

and are designed to improve visualization of tisular intrinsic characteristics (fluid, haemorrhage, fat, fibrosis), except for detecting calcification.

Use of gadolinium as a contrast agent has been described as a higher detection and characterization of SRM with MR imaging to a higher level than does contrast CT [55, 56]. After contrast administration, MR angiography, MR venography, and MR urography are performed by using an oblique coronal breath-hold 3D fat-suppressed dynamically acquired T1-weighted spoiled sequence. The imaging delay for MR angiography is based ona bolus test with a power injector. MR venography and MR urography are performed at approximately 30 seconds and 5 minutes after MR angiography, respectively. The postcontrast acquisition is performed between MR venography and MR urography. For the characterization of renal masses and to determine the presenceor absence of enhancement, most authors recommend an imaging delay of 3–5 minutes [29].

These sequences are used to increase conspicuity of a renal mass, and to depict the renal arteries and veins, for the evaluation of the extent of the tumor in the perinephric fat and the relationship of a renal tumor to the hilar vessels and collecting system, which is helpful to the urologist in surgical planning [49].

5.3. Important features to recognize on MR imaging

5.3.1. Signal intensity

Most renal masses are hypointense on T1 and hyperintense on T2-weighted images, reflecting their water content (fluid, oedema, etc.). Haemorrhage or infection causes different and heterogeneous signal intensities both on T1 and T2, depending on the age of the bleed or the protein concentration, making difficult the characterization of lesions.

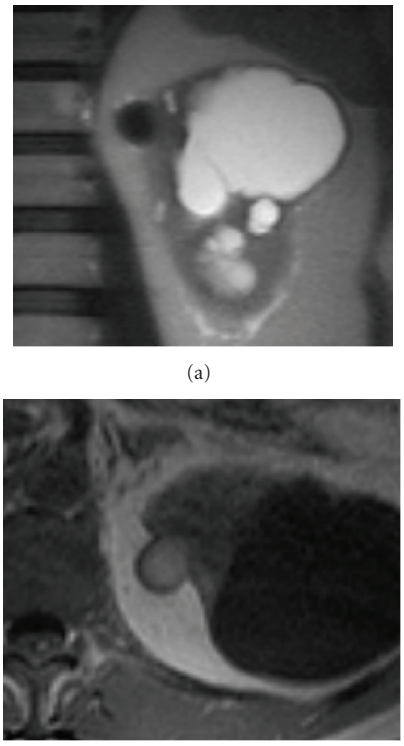
In some cases, T1 hyperintensity and T2 hypointensity renal lesions are noticed (see Figure 11), and most of them are also hyperattenuating renal masses on unenhanced CT. These are either benign or malignant masses and include blood breakdown products or proteinaceous cysts, haematomas and vascular malformations, and oncocytomas or angiomyolipomas with minimal fat, but also some malignant lesions such as RCC and lymphomas. Shinmoto et al. [57] reported that papillary RCC is associated with T2-hypointense appearance as well as hemosiderin deposition, haemorrhage, and necrosis. When a solid hyperattenuated renal mass is seen on unenhanced CT, an MR must be performed to characterize the lesion looking for signal loss on T2-weighted images owing to blood products, iron deposits, hypercellularity, and proteinaceous content. MR is helpful to recognize lesions that are otherwise impossible to differentiate by CT alone, such as AML with minimal fat and clear cell renal cell carcinomas. However, differentiation between AML with minimal fat and papillary RCC is often not always possible by MR, and a percutaneous biopsy may be useful [42]. When a cystic mass is evaluated, MR may show additional thickness of the septa and wall on T2-weighted images than on CT [29].

5.3.2. Presence of fatty tissue

AMLs are the only solid renal tumors that can be positively characterized using MR by demonstrating macroscopic fat in the lesion, and this fact is basically useful in patients with tuberous sclerosis, since they develop AML and an increasing risk of renal cell carcinomas [49] (see Figure 12).

Opposed phase images and spectral fat suppression are useful in differentiating fat from haemorrhage containing carcinomas causing high signal intensity on T1. Furthermore, in phase gradient echo images are often helpful because the fatty portions of AML will be hyperintense and renal clear cell carcinomas usually will not, although renal cell carcinomas incidentally may be hyperintense on T1; in these cases spectral fat suppression images should be used to prove the presence of macroscopic fat in the AML [49].

Some renal lesions may contain very small amount of fat, the so called "minimal fat AML," with microscopic fat and without demonstrable macroscopic fat (angiomyomas), and it is not possible to differentiate from a renal neoplasm. Fat suppression techniques generally are not helpful for detecting fat in AML with minimal fat, because such masses



(a)

(b)

Figure 11: (a) Coronal haste T2 and (b) axial precontrast T1: small lesion on medial aspect of the upper pole of the left kidney shows a low signal intensity on T1 and hyperintensity on T1, revealing blood breakdown products consistent with haemorrhagic cyst.

contain little or no fat and often appear as isointense to the renal parenchyma. Chemical shift imaging may be used to determinate a small amount of fat within a mass, and can be used to differentiate AML with minimal fat from other renal neoplasms, with a high sensitivity and specificity [58].

However, a renal mass that is suppressed focally or diffusely on opposed-phase sequences and that does not exhibit fat suppression should arouse suspicion about the possible presence of clear renal cell carcinoma due to intracellular lipid [42]. Obviously, this differentiation cannot be made only with this unique technique and information of other sequences, such as signal intensity on T2 and dynamic gadolinium enhancement, and proper followup should therefore take place. Kim et al. [58] suggested followup with CT or MR imaging for two years after detection for such lesions.

The presence of fat in clear cell carcinoma has been used to differentiate subtypes of renal cell carcinoma because this fact does not occur in oncocytoma and transitional cell carcinoma [49], but if the tumor does not show signal loss, it can still be a clear cell carcinoma.

5.3.3. Presence of pseudocapsule

This is a pathologic feature composed of fibrous tissue and compressed renal parenchyma, seen frequently in the early stages of a SRM. Although not specific (also seen in some oncocytomas), it has been related to renal cell carcinomas usually small and of low histologic grade, slow growing, and less likely to metastasize [15]. Their presence is an indicator of prognostic value [59]. This condition allows renal parenchyma-sparing surgery, especially if simple enucleation is considered in patients with multiple tumors, Von Hippel-Lindau disease or familial tendency for RCC.

At MR, a pseudocapsule was seen as a hypointense thin rim surrounding the tumor on both T1- and T2-weighted images and is more difficult to detect in hypointense tumors [60, 61]. With postcontrast images, late enhancement of the pseudocapsule resulted in poor contrast relative to the surrounding tissue, lessening its own visualization in this sequence (see Figure 13). Some reports [61, 62] noticed that the presence of a pseudocapsule offers an additional value for local staging. On that series, T2-weighted imaging was the most sensitive technique for visualization of the pseudocapsule (sensitivity: 68%; specificity: 91%), and is corroborated by other authors [15, 63, 64]. For this reasons, MR shows a moderate to high sensitivity in depicting the pseudocapsule than CT [49]. In some large tumors, although tumor invasion was seen, a residual pseudocapsule was found in some areas.

5.3.4. Involvement of perinephric fat

This is a key point in treatment planning in modifying the surgical approach from conservative to radical nephrectomy (Robson's stage I versus stage II). If partial nephrectomy is considered, it is essential to know preoperatively if the perinephric fat is invaded or not by the tumor. Although MRI appears slightly more sensitive than CT, it is not specific in distinguishing between these two stages.

The presence of an intact pseudocapsule is an indirect sign of lack of perinephric fat invasion [61]. The overall sensitivity of CT in detecting pseudocapsule is very low [62, 63, 65, 66], and MR had a pertinent accuracy for evaluating possible involvement of perinephric fat using the aspect of the pseudocapsule as an additional feature [61].

Perirenal fat invasion diagnosis was made when there was loss of capsular integrity indicated by interruption of the low signal intensity line around the kidney on T1- and T2-

weighted images and thick (>0.5 mm) perinephric stranding. Thin perinephric stranding and collateral vessel formation alone were not considered features of perinephric fat invasion. This causes under- and overstaging on CT and MR and lacks good specificity [67]. It also may be caused by edema, vascular engorgement, and/or inflammation [65]. The only highly specific finding was the presence of an enhancing nodule or soft-tissue mass in the perinephric space but this sign had only 46% sensitivity [38].

5.3.5. Enhancement

Different patterns of enhancement have been observed, predominantly peripheral, heterogeneous, and homogeneous. The dynamic evaluation appears to be useful in the detection

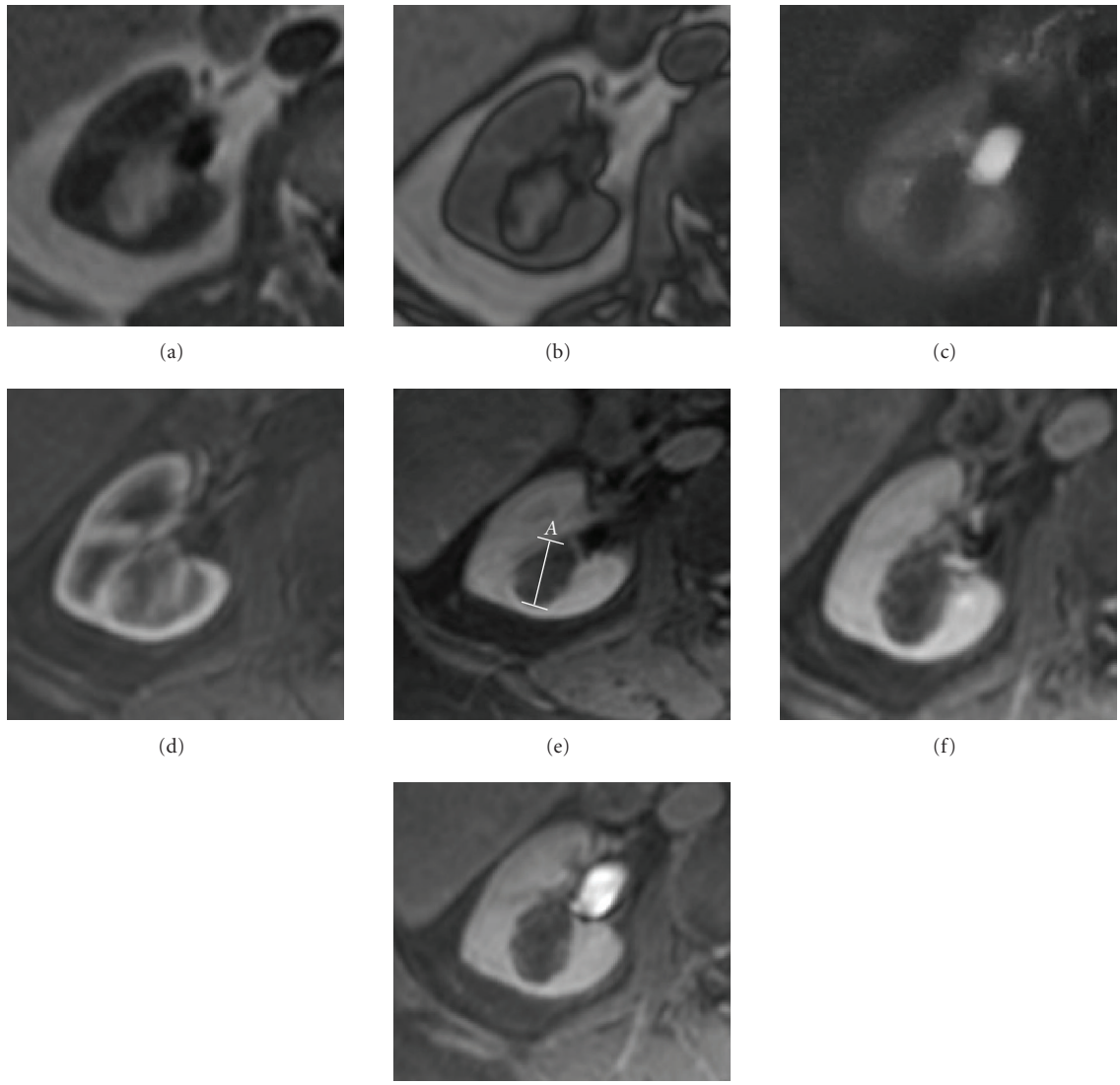


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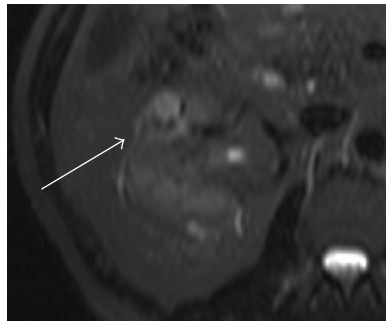
Figure 12: (a) Axial T1 in phase, (b) axial T1 out of phase, (c) axial haste T2 with fat saturation, and ((d–g) axial dynamic postcontrast T1 (d), arterial; (e), venous; (f), nephrographic, and (g), excretory phase): right yuxtahilar renal lesion seen as a T1 hyperintense mass that shows gross fat suppression on T2 revealing macroscopic fat and also probably small foci of peripheral fat as there is a small amount of signal loss on out of phase sequence. On dynamic postcontrast images the mass shows a transitional highly peripheral enhancement in the non-fat components with poor enhancement on the remaining postcontrast study. An angiomyolipoma was found at surgery.

and characterization of simple renal cysts and solid neoplasms [68].

The presence or absence of enhancement within a renal mass is the most important factor in its proper characterization. When a predominant part of a renal mass enhances, the mass is considered solid and likely neoplastic. Otherwise, it is important to be aware of the possibility of pseudoenhancement and to know when to suspect it. All solid lesions demonstrated gadolinium enhancement, not only RCC and invasive transitional cell carcinomas but also oncocytomas and AML (see Figures 12 and 14). Although enhancement is sufficient for predicting malignancy, nonenhancement is not sufficient to exclude malignancy, and again the integration of T2 appearance is useful in improving the differentiation between benign from malignant renal lesions [41].

Hypervascular RCC can be easily differentiated on dynamic contrast-enhanced MR. Hypovascular RCC, AML, and complicated cysts enhanced significantly less than cortical and medullary tissue did (see Figure 15). Furthermore, papillary RCC is typically hypovascular and shows mild contrast enhancement, whereas AML with minimal fat is generally hypervascular and shows marked enhancement, but occasionally the degree of enhancement varies, making this differentiation difficult [42]. Also hypovascular RCC from the first minute after gadolinium injection showed significantly greater enhancement than complicated cyst [69].



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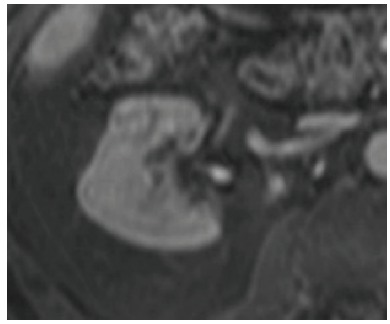

(b)

Figure 13: (a) Axial stir and (b) axial postcontrast T1. A pseudocapsule is seen as a hypointense rim surrounding the tumor on T2 and is better delineated than on postcontrast T1 owing to the late contrast enhancement of the pseudocapsule.

Thus, areas with haemorrhage or infection products do not enhance but their signal intensity remains higher than that of simple cyst, making quantitative ROI measurements in these lesions essential [70] for correct characterization. This can be made by quantitative and qualitative methods. Ho et al. [71] concluded that above 15% was the optimal percentage of enhancement threshold for distinguishing cysts from malignancies. Although usually quantitative and qualitative methods are sensitive in the detection of enhancement, in hyperintense lesions on unenhanced T1, qualitative assessment based on image subtraction should be performed to avoid false negative quantitative results [54].

When a cystic mass is evaluated, MR imaging may demonstrate definitive enhancement that shows only equivocal enhancement on CT. In a cystic lesion with only a small solid component, subtraction images may again be used to better assess the presence of enhancement [49]. Furthermore, even if detecting a calcification is a limitation on MR imaging, it is however an advantage to determine whether enhancement is present in a heavily calcified cyst on CT given that it could be better appreciated [45]. The combination of mural irregularity and intense mural enhancement is a strong predictor of malignancy in renal cystic lesions (see Figure 16). However, the appearance of benign and malignant lesions may overlap [72, 73].

5.3.6. Other

Invasion of Gerota's fascia was diagnosed when continuity of the low signal intensity line around the perinephric fat on T1-weighted images was disrupted by tumor. Imaging of the ipsilateral adrenal gland and venous spread of tumors are out of the scope of this chapter, thus the clinical setting of small renal tumors is not found incidentally, as it is the case in the low probability of nodal metastases in this stage of disease.

On the other hand, advanced imaging techniques led to improve the global accuracy for MDCT to adequately stage these clinical aspects [38]. Hricak et al. [60] reported accuracy rates for detecting adjacent organ invasion with MRI, although, in their series, overstaging was caused by the presence of abnormal signal, indistinct interface, and absence of a free fat plane between the tumor and the adjacent organ.

5.4. Interpretation of images and surgical criteria

When characterizing a renal mass, the major question to be answeredis whether the mass represents a surgical or nonsurgical lesion or, in some cases, if followup studies are necessary.

Magnetic resonance imaging allows an accurate differentiation between solid and cystic masses, as a first approximation, but angiomyolipomas are the only solid renal tumors that can be positively characterized using MR. Nevertheless, Prasad et al. [74] reported that small renal medullary tumors may be differentiated from the more common renal adenocarcinomas by their central location and certain demographic characteristics. Furthermore, some authors recently [75] analyzed the correlation between MR image features and histopathological findings, giving value to subvoxel fat on chemical shift imaging as a good correlation to clear cell type with a high specificity. These authors reported that small size, peripheral location, low intratumoral signal intensity on T2, and low level enhancement were also associated with low-grade papillary carcinomas.

Detection of macroscopic *fat* is the key for diagnosing AML in the proper clinical setting, and it is decisive because AML does not need to be surgically removed. The diagnosis is made by demonstrating fat within a solid renal mass. One pitfall of fat containing renal masses is the presence of a renal cell carcinoma involving the perinephritic fat. This differentiation is easily made if there is some calcification on CT, as do some RCC [29]. However, calcium is not always present in renal cell carcinoma [76].

The observation of a *pseudocapsule* surrounding a renal cell carcinoma is a sign of lack of perinephric fat invasion, and therefore it is more likely to predict that the tumor can be removed by nephron sparing, so partial nephrectomy or simple enucleation may be indicated when a pseudocapsule is detected [49, 62].

The presence of *haemorrhagic* products may obscure enhancement on dynamic postcontrast T1 images, and it may also contribute to heterogeneity on T2 images. Thus, in the setting of a T2 heterogeneous nonenhancing mass, careful followup after an antibiotic trial may be a prudent recommendation to avoid nephrectomy of renal abscess and

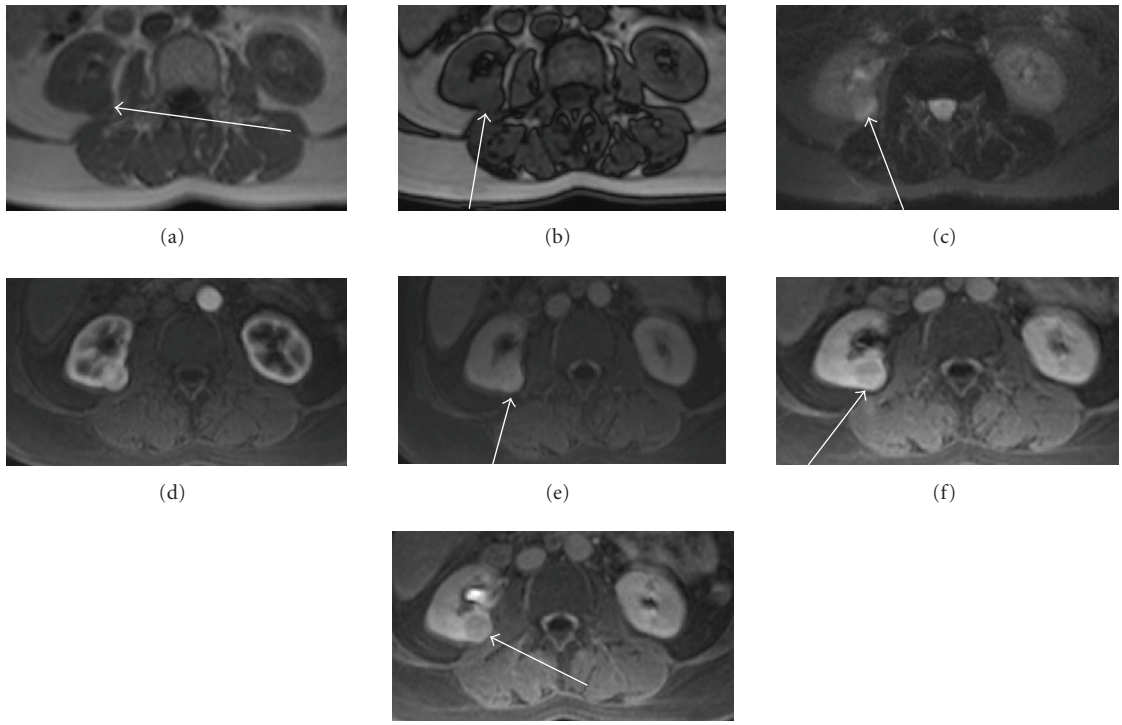

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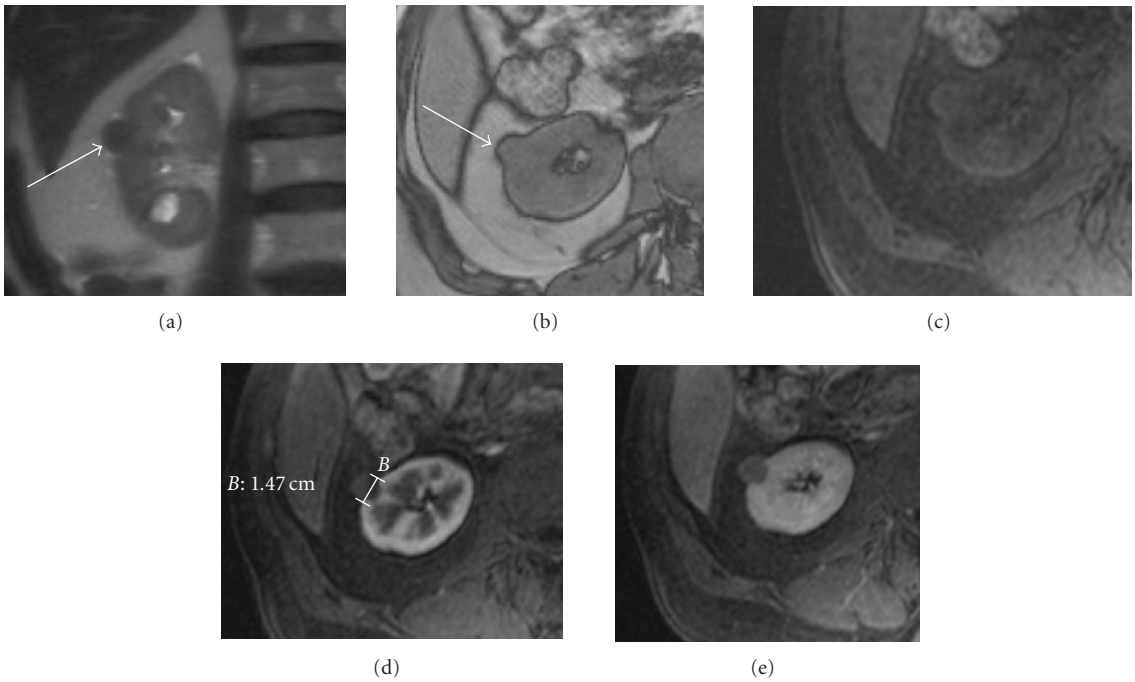
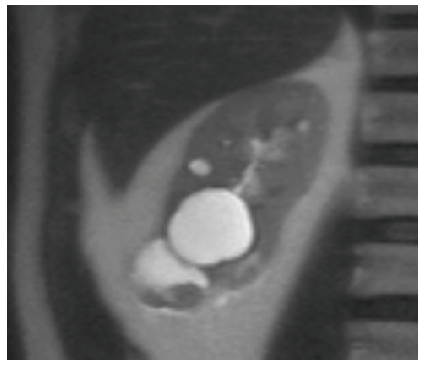
Figure 14: (a) Axial T1 in phase, (b) axial T1 out of phase, (c) axial stir, and (d–g) axial dynamic postcontrast T1 ((d) arterial; (e) venous; (f) nephrographic, and (g) excretory phase). A nonfatty mass hyperintense on T2 and highly vascular on corticomedullary and nephrographic phase with late mild washout as is shown on this clear renal cell carcinoma.



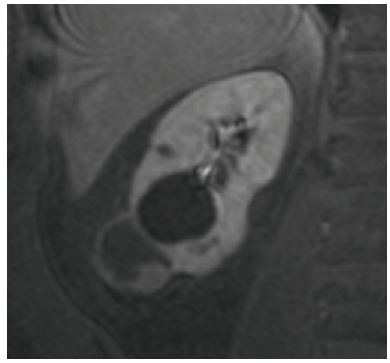
(a) (b) (c)

(d) (e)

Figure 15: (a) Cor haste T2, (b) out of phase axial T1, (c) axial precontrast T1 with fat suppression, (d) early postcontrast axial T1 with fat saturation, and (e) axial postcontrast T1 with fat suppression. Small renal lesion on the lateral aspect of the upper pole of the right kidney shows a solid mass hypointense on T2 that does not present a loss of signal out of phase sequence and only a small enhancement on postcontrast sequences, consistent with a papillary renal carcinoma.



(a)



(b)

Figure 16: (a) Coronal haste T2 and (b) late postcontrast coronal T1 with fat saturation. Cystic lesion with an enhancing nodule on the caudal aspect of the kidney. Renal cell carcinoma was found at surgery.

to avoid misdiagnosis of a hemorrhagic renal cell carcinoma [41]. Furthermore, a common occurrence of haemorrhage is described in patients with renal cancer and/or in patients with renal insufficiency, and caution should be exercised when evaluating haemorrhagic cystic lesions in these patients [77].

The most importantcriterion used in differentiating surgical fromnonsurgical renalmasses is the determination of *enhancement* [29]. Despite that, the lack of enhancement of a renal lesion, particularly if small (<1 cm), is not considered a sufficient criterion for excluding malignancy, as the haemorrhagic lesions occur, and in this setting, T2-weighted images must be considered. Moreover, it is important to combine the degree of enhancement with the morphologic features of the lesion, such as homogeneity, wall thickening, and presence of calcifications.

When a *cystic* mass is evaluated, a surgical cyst can be suspected only if enhancement is present. Calcification in a cystic renal mass is not as important in diagnosis as the presence of associated enhancing soft-tissue elements [78]. MR imaging may depict additional septa, thickening of the wall and/or septa, or enhancement, which may lead to an upgraded Bosniak cyst classification and can affect case management [31, 49].

5.5. Limitations

As with all imaging techniques, it is extremely difficult with MR to determine whether malignant tissue extends to adjacent normal tissue when strictly regular margins are found because microscopic local invasion could have occurred [61, 64]. Staging errors were made because of limitations of the imaging technique: inability to detect microscopic invasion of the perinephric fat, difficulty in differentiating inflammatory changes from tumor infiltration, and insensitivity in differentiating small collateral blood vessels from tumor extension in the lymphatics [67].

There are also limitations to the detection of a pseudocapsule by MR, mainly with hypointense tumors because its detection may be less accurate on T2-weighted owing to the lack of delineation of the surrounding rim, as is the case of some papillary tumors. With SRM, partial volume averaging may obscure its visualization, thus evaluation in three planes, and coronal, sagittal, or oblique views are required to avoid this phenomenon on the upper and lower part of the tumor [61]. Furthermore, given that the pseudocapsule was also found in oncocytomas, it is not useful for differentiating RCC from this benign solid tumor, and it cannot be used to predict the nature of the lesion. But it can offer an additional value to the performance of preoperative MR to stage renal tumors, aiding to make decisions about the most appropriate surgical technique to employ.

Concerning nodal staging, MR has the same limitations as CT according to the nodal size over 1 cm in short-axis diameter, being this an additional indication for the future use of new iron oxide-based contrast agents on MR to improve specificity and accuracy in nodal staging [49, 79].

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 918050, 8 pages
doi:10.1155/2008/918050

Review Article

Radiologic Evaluation of Small Renal Masses (II): Posttreatment Management

J. Santos, C. Deltoro, M. I. Martín, and A. Marhuenda

Departamento de Radiología, Instituto Valenciano de Oncología, C/ Profesor Beltrán Báguena 8, 46009 Valencia, Spain

Correspondence should be addressed to J. Santos, jsantosc63@gmail.com

Received 9 April 2008; Accepted 5 August 2008

Recommended by J. Rubio

The increase in the detection of small renal masses (SRMs) and their best knowledge leads to a change in the therapeutic management of these lesions. The use of a less aggressive surgical technique or even an expectant attitude is the current tendency, in order to preserve as much renal function as possible. Imaging techniques are essential in the followup of these lesions. It allows us to know the postsurgical changes and possible complications due to treatment and the presence of local recurrence and metastases. Furthermore, a close radiological followup of SRM related to ablative treatments is mandatory. The purpose of this article is to reveal the imaging features of complications due to surgical or ablative treatments, local recurrence and metastasis, as well as their followup.

1. IMAGING FOLLOWUP OF SRM

Several authors have reported that small incidentally detected tumors are associated with better survival outcomes. The 5-year disease-free survival rate for incidental renal tumors of <4 cm treated with radical or partial nephrectomy is 95%–100%. There is a clear increased rate of metastases in patients found to have renal cell carcinoma (RCC) >3 cm in maximum dimension at autopsy compared to those with RCCs of < or =3 cm [1, 2].

Silverman et al. [3] have established the indications for percutaneous biopsy of renal masses in patients with a renal mass and known extrarenal primary malignancy, imaging findings that suggest unresectable renal cancer, surgical comorbidity, those that may have been caused by an infection. Emerging indications are patients with a small (<3 cm) hyperattenuating, homogeneusly enhancing renal mass, those with a renal mass considered for percutaneus ablation and patients with an indeterminate cystic renal mass.

After surgical treatment, radical nephrectomy (RN) or partial nephrectomy (PN), about 20%–30% of patients with localized renal tumors relapse [4]. The recurrences occur three years after surgery, with a median time to relapse being 1 to 2 years. In multifocal renal cortical tumors, local recurrences rates following elective partial nephectomy are from 0% to 10% with a risk of local recurrence for tumors of 4 cm or less [5]. However, late tumor recurrences can occur many years after treatment. The lung is the most vulnerable site for distant recurrence (50%–60% of patients) [6]. Other sites of recurrence are bone, surgical site, brain, liver, and the contralateral kidney.

There are multiple prognostic factors to predict recurrence after surgery. A postoperative prognostic nomogram has been published predicting recurrence for patients with conventional clear cell renal cell carcinoma [7], and it can be useful for patient counselling, clinical trial, and effective patient followup strategies.

Greatest tumor diameter, T stage, stage group, and nuclear grade are important factors in determining the likelihood of recurrence. At the present time, active surveillance of small renal masses is an experimental approach, but represents an attractive option for elderly patients and those with significant comorbidity.

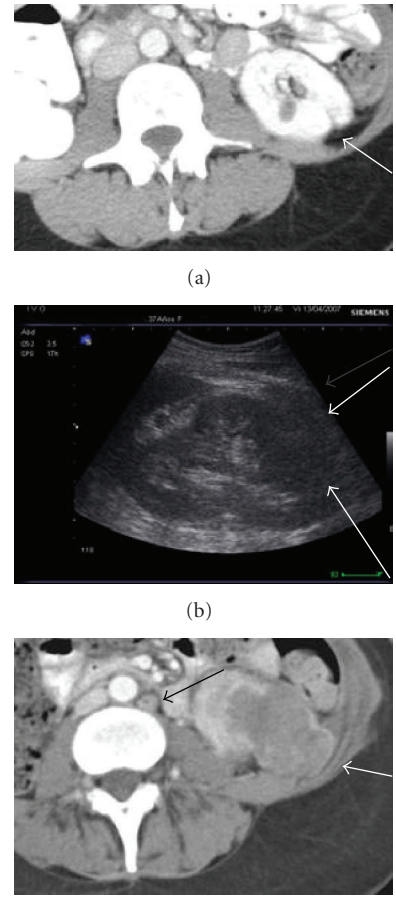
Bilateral multifocal renal tumors are present in approximately 5% of patients with sporadic renal tumors [8]. Conventional clear cell carcinoma is the most common histologic subtype, followed by papillary carcinoma [5]. Most of them can be synchronous but asynchronous lesions may occur many years after the initial nephrectomy, and that is why a long-term followup. must be maintained.

In imaging followup evaluation of kidney cancer, CT is the modality of choice for detection of local recurrence and distant metastases. In patients with compromised renal function or with contraindications to iodinated contrast, gadolinium-enhanced MR imaging of the abdomen and pelvis may be used. Also a chest radiograph or chest CT study can be performed for surveillance of pulmonary metastasis.

Renal cysts are common benign lesions and are often an incidental finding during abdominal CT, (see the appendix) [9]. If they are of fluid attenuation, lack internal architecture, have thin walls, and show no evidence of enhancement after IV contrast administration, they can be easily dismissed as benign. However, the appearance of moderately complex or mild renal cyst varies and can cause difficulties in diagnosis and management. The Bosniak classification or renal cysts has proven to be a useful tool in helping to evaluate these lesions and decide clinical management [10]. In 1993, Bosniak revised the original classification system [11] to include a subset of category II lesions, category IIF lesions ("F" for followup).

CT studies are an effective way of managing patients with moderately complex cystic lesions of the kidney (Bosniak category IIF) because the absence of change supports benignity and progression indicates neoplasm. Alternatively, MRI may prove helpful in the characterization of these lesions and may possibly avoid the need for followup examinations in these cases [12]. In these lesions considered to be category IIF, the followup examinations are necessary to prove stability and, therefore, benignity. The first followup examination is recommended 6 months after the initial examination. If the lesion is unchanged, additional followup examinations should be performed at yearly intervals for at least 5 years, although the optimal followup period has not been determined. However, in younger patients, a longer followup period may be necessary.

45% of the patients with von Hippel-Lindau disease will have a renal adenocarcinoma, often (80%) multifocal or bilateral. Treatment must be as conservative as possible because of the multifocality and its usual low grade. The risk of recidive is very high: 30% at 5 years, 80% at 10 years, therefore, they must be followed up strictly and regularly (Figure 1) [13].



(a)

(b)

(c)

Figure 1: 37-year old woman with von Hipple Lindau disease. Radical right nefrectomy and partial tumorectomy in left kidney. (a) Axial contrast-enhanced CT scan shows scar in the lower pole in the left kidney (*arrow*), without any mass. Note the absence of right kidney. (b) One year later sagittal US scan with a large mass less echogenic than renal sinus fat, involving the lower pole parenchyma (arrows). (c) Axial contrast-enhanced CT (nephrographic phase) scan obtained at the same time shows the mass that has grown with perinephric extension (white arrow). It was a renal adenocarcinoma. Note of the presence of paraaorthic lymph node (black arrow).

2. IMAGING OF COMPLICATIONS OF PARTIAL NEPHRECTOMY

The standard treatment for renal cell carcinoma was, for many years, radical nephrectomy, but over the past 10 years, there has been a trend toward the use of nephron-sparing surgery to treat renal cell carcinoma. The results of numerous studies have demonstrated equivalent cancer survival rates for patients who underwent radical nephrectomy and those who underwent partial nephrectomy for small renal neoplasms [14–16].

The procedure can be performed by using open or laparoscopic techniques. However, partial nephrectomy with laparoscopic techniques is a more complex operation than the traditional radical nephrectomy and higher complication rates have been reported [17].

It is important to know normal findings and imaging features of postsurgical complications after partial nephrectomy, for appropriate postoperative management.

2.1. Postoperative appearance

The appearance of the postoperative kidney depends on the size and location of the resected tumor. After partial nephrectomy for a small peripheral tumor, a wedge-shaped defect in the renal parenchyma is typically visible at CT and MR imaging. The postoperative kidney usually has a more posterior location and abuts to the posterior abdominal wall (Figure 2). Perinephric fat maybe packed into the surgical bed to help achieve haemostasis. This material may be mistaken for a fatty mass such as an AML.

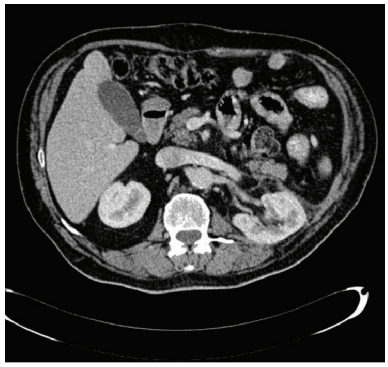


Figure 2: Postoperative findings after laparoscopic left partial nephrectomy, image shows a posterior location of the left kidney, which abuts the posterior abdominal wall.

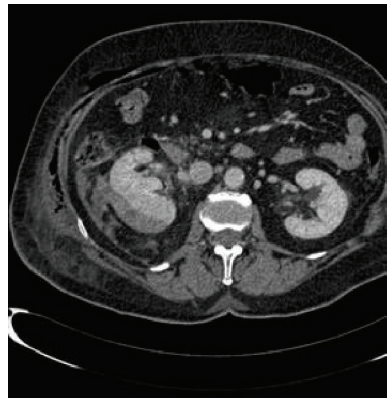


Figure 3: Hematoma after open right partial nephrectomy. Mass with attenuation of 60HU that extends from postoperative bed to the perinephric space.

To help control intraoperative bleeding, biologically absorbable haemostatic agents also may be used. Such materials may contain bubbles or air pockets that may resemble a focal abscess. The possible presence of a haemostatic agent should be considered if a linear arrangement of air bubbles is noted or if air bubbles maintain the same position on subsequent images. In most cases, the air in a haemostatic agent is rapidly reabsorbed during the first postsurgical week. However, in some cases, air bubbles can be identified on images even 1 month after surgery. The presence of an abscess should be suspected if a localized fluid collection that has an enhanced rim and contains gas bubbles or a gas-fluid level is seen. In addition, decreased intensity of the nephrogram because of edema in the surrounding renal parenchyma supports the diagnosis of an abscess. Of course it is necessary to consider the imaging findings in combination with the patient's clinical history and symptoms [18–20].

The biologically absorbable haemostatic agents may also mimic a pseudotumor that can lead to confusion. Several cases have been reported on literature after nephron-sparing surgery using gelatine bio absorbable sponge. They were seen as solid masses, with regular borders and enhancement after injection of intravenous contrast agent, due to the presence on granulomatous tissue surrounding the haemostatic material. In all the cases there was a complete resolution of such lesions in an average time of thirteen months [21, 22].

2.2. Complications

Complications seen on partial nephrectomy can be divided into vascular complications, complications in the collecting system, infection, recurrent tumor and complications due to technical factors [20].

2.2.1. Vascular complications

During partial nephrectomy, the renal hiliar vessels must be temporarily clamped to ensure a bloodless surgical field; however, clamping may injure the arterial intima and lead to thrombosis. If that complication is not recognized at the time of surgery or in the immediate postoperative period, renal infarction and atrophy will occur. Complications related to injury of the intrarenal arteries in the surgical bed may also occur. A hematoma may result if the suturing of transected blood vessels is inadequate (Figure 3). A pseudoaneurysm may result from injury to an intrarenal artery at the surgical site or to the main renal artery or one of its major branches [23–25].

2.2.2. Complications in the collecting system

When calyceal entry is necessary, it would have to be repaired in order to avoid urinary leakage. If the repair is not watertight, a urine leak may occur into the surgical bed. Such leakage may have the appearance of a simple fluid collection in the perirenal space [26], or it may have a more heterogeneous appearance if it contains blood products. This complication can be diagnosed on the basis of contrast-enhanced CT and MR images acquired during the excretory phase, with the observation of contrast material leakage from the collecting system into the surgical bed. In most cases, the fluid collection resolves either spontaneously or after placement of a ureteral stent or nephrostomy catheter. Less commonly, urinary leakage persists and an urinoma forms [20].

2.2.3. Infection

A fluid collection in the surgical bed may become infected, and an abscess may develop. With imaging techniques alone, it may be difficult to differentiate an infected fluid collection from an uninfected one. Moreover, as mentioned before, the presence of air bubbles in a bioabsorbable haemostatic agent may further complicate the interpretation of imaging studies. However, patients with a postoperative abscess are likely to manifest clinical symptoms and signs suggestive of infection; in such cases, a needle aspiration is performed for laboratory analysis, followed by drainage if necessary. In addition, patients who have undergone a partial nephrectomy may present with symptoms of pyelonephritis, which may appear

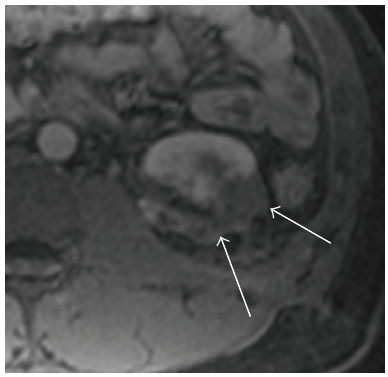


Figure 4: Fibrosis. Axial post contrast T1 with fat saturation shows a hipointense lesion on the lateral aspect of the left kidney that does not enhance with gadolinium, revealing post surgical changes.

as a striated or heterogeneous nephrogram and may be difficult to differentiate from renal infarction on images alone [20].

2.2.4. Complications due to technical factors

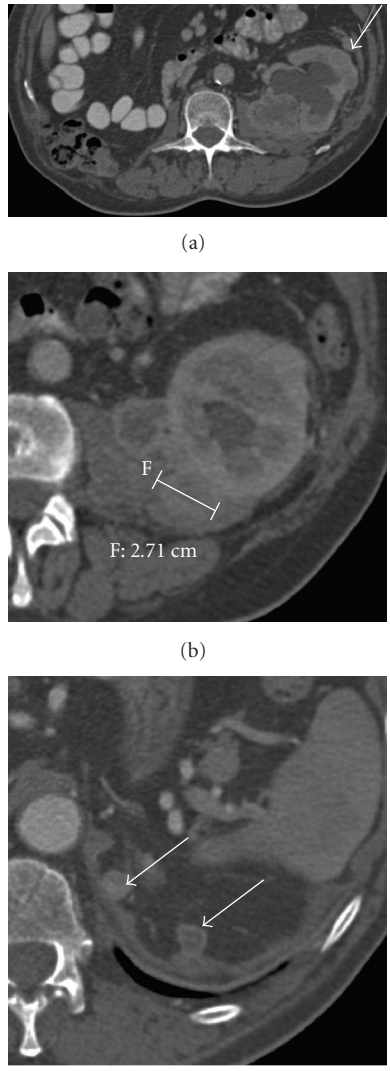
During partial nephrectomy, the liver or spleen may be inadvertently lacerated or contused by surgical instruments used to keep adjacent organs away from the surgical field. Such injuries may be detected with CT and MR imaging. In addition, hernias may occur at the incision site and may contain portions of the bowel or other abdominal organs [26].

3. IMAGING OF LOCAL RECURRENCE

The most important risk factor for recurrence is the surgical stage of renal cell carcinoma at the time of diagnosis, being for large tumors a bigger incidence than for small ones. However, size is not of prognostic value if capsule is not invaded (13). Patients with positive nodes at surgery relapse sooner, and factors like a high Fuhrman grade on histopathology, and collecting duct carcinoma spindled (sarcomatoid) tumor architecture also adversely influence prognosis [27]. Recurrence must be differentiated from postsurgical fibrosis (Figure 4) and multifocality within the kidney, probably more often seen since small renal tumors are managed with conservative surgical techniques (Figure 5) [13].

The possibility of local recurrence in the remaining kidney is the main limitation of nephron-sparing surgery in patients with renal-cell carcinoma. Local recurrence occurs in about 5% of patients, and has been related to cancer multifocality, incomplete resection of the primary tumor, positive surgical margins, or regional lymph node metastasis. Some authors reported that the type of surgical intervention (enucleation, enucleoresection and resection) does not affect the frequency of tumor local recurrence [28].

Recurrence usually occurs within the first five years after surgery, but late recurrence has been related to renal cancer and long-term followup after a nephrectomy is



(a)

(b)

(c)

Figure 5: Local recurrence. (a) Axial contrast enhanced CT scan showing the postsurgical changes on the right lumbar fosse with removal of the kidney and migration of the right colon to the nephrectomy fosse. Note the second small renal lesion on the anterior pole of the left kidney, probably due to multifocality that was not advertised on the previous studies of the patient (arrow). (b) A soft tissue mass on the medial aspect of the left kidney at the site of the previous enucleation resection with enhancing nodules around the kidney and adjacent to the psoas. (c) Enhanced nodules adjacent to the diaphragm muscle (arrows).

mandatory for patients with perinephric invasion of a renal cell carcinoma due to the risk of renal fosse recurrence [29]. Followup of these patients is usually made by CT but also MRI for selected cases, as mentioned in the previous article and, in both techniques, arterial phase scanning is essential for maximizing lesion conspicuity, followed by a portal venous phase. Owing to the increased risk of these patients for additional renal primary carcinomas, the renal fosse and remaining kidney must be carefully evaluated looking for a recurrence.

3.1. Local recurrence in renal fosse after nefrectomy

Recurrent cancer after nephron-sparing surgery can be suggested when an enhancing nodule develops in the wedge-shaped partial nephrectomy defect. After radical nephrectomy at imaging, retroperitoneal anatomy is significantly altered after surgical removal of the kidney. Small bowel, spleen, pancreas, and colon may migrate into the nephrectomy fosse [30] (Figure 5(a)).

At partial nephrectomy if an adequate margin is not obtained and surgical excision is incomplete, the growth of any remaining neoplastic cells at the resection site over time may result in tumor recurrence in the surgical bed. Even if a tumor is completely excised, it may recur if tumor cells are spilled into the surgical field at the time of resection.

Alternatively, in a patient with multiple foci of disease, an apparent tumor recurrence may actually be an additional preexistent renal cell carcinoma that either was not depicted at preoperative imaging studies or was not identified intraoperatively [23]. The surgical field of view during laparoscopic partial nephrectomy is limited, and the surgeon can see only a small portion of the kidney. This limitation may lead to a failure to identify a specific small renal tumor if there is more than one small lesion in the vicinity. Unless previous imaging studies are carefully reviewed, the latter then might be misidentified as a recurrent lesion.

The radiologic presentation of a recurrent renal carcinoma after surgery appears as an enhancingmass in the surgical site. The recurrence often involves the quadratus lumborum and psoas muscles andcan displace or invade nearby structures, even the spine. The cephalic extent may reach the adrenal bed or may involve the ipsilateral adrenal gland if the latter was spared at the time of nephrectomy [31].

Moreover, as mentioned earlier, bioabsorbable haemostatic agents may be seen as pseudotumor, so, a close followup examination is required to see the evolution.

3.2. Local recurrence and residual disease after thermal ablation

Early detection of a recurrence following initial treatment is mandatory for any surveillance protocol, and it is essential to review the preablation and ablation images for a good interpretation of followup images. Imaging must be carefully evaluated to determine the initial tumor size, tumor location, and electrode placement in an effort to predictare as that are likely to demonstrate recurrence. Eccentric electrodeplacement within a mass is likely to result in residual disease at the tumor margin farthest from the ablation device tip. Occasionally, a new tumor focus may develop.

As with local recurrence, residual tumor is suggested when enhancing nodules or crescents areas noted in the vicinity of the treated tumor on contrast enhanced CT or MR images. Furthermore, gadolinium-enhanced fat-suppressed T1-weighted subtraction MR images are helpful in demonstrating subtle areas of enhancement by eliminating the high signal intensity often present within the tumor on unsubtracted images. Because the ablation zone following RF ablation typically has low signal intensity on T2-weighted MR images, a new or enlarging focus of hyperintensity on these images may also be a sign of viable tumor.

Ablated tumors remain stable in size or involute over time on followup images. Therefore, an increase in tumor size after the acute postablation changes have resolved should raise concern for tumor recurrence, as well as within the renal vein and inferior vena cava, even in the electrode insertion site [30].

4. FOLLOWUP IMAGING AFTER RADIOFREQUENCY ABLATION OF SRM

There has been a clear increase in the incidence of RCC during the past 10 years, as a result of an increased rate of incidental detection of renal neoplasm. It has been reported that radiofrequency ablation can completely destroy renal cancers, while transmitting minimal collateral damage to surrounding renal parenchyma [32].

Radiofrequency ablation is a safe effective treatment for small renal-cell carcinoma (RCC) in selected patients who are not good operative candidates. Small size and noncentral location are favorable tumor characteristics (large tumors can sometimes be successfully treated but could result in an increased risk of residual RCC). After ablation, computed tomography or magnetic resonance imaging is used to confirm complete eradication or the presence of residual unablated tumor. When the appearance of the ablated tumor deviates from expected findings, percutaneous biopsy is necessary to further evaluate the ablation zone [33].

4.1. Imaging followup

All patients must undergo contrast-enhanced imaging (MRI or CT) before radiofrequency ablation as a baseline comparison for subsequent imaging after ablation (initial tumor control).

4.1.1. CT imaging

CT scan of the kidney must be obtained immediately after the ablation session to assess tumor destruction. Normal tissue shows enhancement, with no enhancement in treated area, which encompasses tumor. Small gas bubbles are seen in area of treatment, this is an expected finding resulting from tissue boiling during ablation [34]. After ablation an initial CT scan, imaging followup without and with contrast agent must be performed after 1 month, 3 months, and 6 months and subsequent followup will depend on the clinical condition of the patient and the comorbid conditions, generally at 6 to 12 month interval. Enhancement of any portion of the tumor must be considered residual viable tumor, and the absence of enhancement as no evidence of disease (complete necrosis and thus completely ablated tumor). Images must also be reviewed for the presence of any new metastatic disease or new renal cell carcinomas [34, 35].

4.1.2. MR imaging

A considerable number of patients of eligible patients cannot receive contrast agents that contain iodine because of preexisting impaired renal function or severe contrast material allergies. These patients are usually referred for contrast enhanced magnetic resonance (MR) imaging of the kidney. As in CT imaging, followup MR imaging must be performed in all patients immediately after the completion of the RF ablation. At T2-weighted fast SE images performed, the ablation zone, in all cases appear as a round or ovoid hypointense region that replaces the intermediate or high signal intensity tumor seen on the preablation image. The hypointense thermal ablation zone is surrounded by a bright rim with a well-defined outer border. Thin rim enhancement is noted in all contrast-enhanced MR images [36].

Followup MR imaging must be performed every 3 months during the first year after ablation and every 6 months thereafter.

Tumor recurrence is defined as the appearance of hyperintense soft-tissue signal within the ablation zone or along its margin on T2-weighted or STIR MR images or as areas of abnormal contrast enhancement within the treated region on the postcontrast images [37].

5. FOLLOWUP CRYOSURGYCAL ABLATION OF SRM

Concomitantly with the change in presentation of renal masses there is a paradigm shift in the management of localized small renal lesions. Minimally invasive options such as cryoablation have emerged as an alternative surgical option for selected patients. The potential complications of nephron-sparing kidney surgery make renal cryoablation an appealing option in high-risk surgical populations.

Cryoablation requires real-time monitoring of the ice ball by ultrasound, CT, or magnetic resonance imaging (MRI), to ensure that the tumour is completely frozen and to minimize injury to the surrounding healthy tissue. However, it is preferable to use the MR imaging guidance to monitor in real time so that the entire circumference of the treatment effects can be viewed during the procedure.

The MR imaging protocol is limited to the abdomen and included: transverse T2-weighted, transverse T1-weighted sequences, and transverse fat-suppressed T1-weighted sequences before and four phases after the intravenous administration of contrast medium.

The purpose of the cryotherapy is not the excision of the tumor, but their necrosis "in situ." The effects of renal cryoabation on the kidney have been studied in animal models [38].

The acute histologic changes are rapid coagulation necrosis and a sharp zone of transition within the normal kidney. A peripheral zone of incomplete necrosis surrounds the area of necrosis. Over time, resorption of cellular debris and fibrosis lead to shrinkage of the cryolesion.

Given that the renal lesions are treated "in situ," a rigourous followup is required, usually with MR. Data form long-term followup examinations are crucial to asses the usefulness of cryotherapy and detecting tumor recurrence.

MR imaging and the same protocol used prior to the treatment are performed also at 24–48 hours after treatment, for assessment of complications (bleeding or urinoma).

Remer and coworkers [39] reported several characteristic findings in serial MR scans performed on the first day, 1 month, 3 months, 6 months, and 12 months after renal cryoablation. MR images are also compared with the pretreatment MR images, to determine the amount of cryonecrosis, defined as tissue that no longer appeared to be enhanced by intravenous contrast material.

The signal intensities of cryolesions on T1-and T2-weighted images were somewhat variable. Lesions were generally isointense on T1-weighted images and iso-or hypointense on T2. The borders of cryolesions were well depicted on T2-weighted images because of the relative hypointensity of the lesion compared with normal renal parenchyma.

In patients without evidence of tumor recurrence, all cryolesions showed a dramatic progressive decrease in size over time (63% and 94% at 1 month and 1 year, resp.). Some cryolesions had a peripheral hypervascularized rim on T1-weighted gadolinium enhanced images. This was seen in up to 50% of lesions imaged within the first 3 months after ablation, but was present in just 10% of lesions at 12 months. Initial rim enhancement has been reported in liver ablation cases and has been attributed to the inflammatory response.

Any increase in size of a cryolesion should be viewed with suspicion.

Although MR is the most studied method of monitoring cryolesions, CT has also been evaluated [40]. The cryolesions on followup CT showed no evidence of enhancement and the tumor demonstrate stable size or decease in size.

APPENDIX

THE BOSNIAK RENAL CYST CLASSIFICATION SYSTEM

Category I

A benign simple cyst with a hairline-thin wall that does not contain septa, calcifications, or solid components: it measures water density and does not enhance with contrast material.

Category II

A benign cyst that may contain a few hairline-thin septa: fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuation lesions (<3 cm) that are sharply marginated and do not enhance are included in this group.

Category IIF

These cysts may contain an increased number of hairline-thin septa. Minimal enhancement of a hairline-thin smooth septum or wall can be seen, and there may be minimal thickening of the septa or wall. The cyst may contain calcification that may be thick and nodular, but no contrast

enhancement is present. There are no enhancing soft-tissue components. Totally intrarenal nonenhancing high-attenuation renal lesions that are 3 cm or larger are also included in this category. These lesions are generally well marginated.

Category III

These lesions are indeterminate cystic masses that have thickened irregular walls or septa in which enhancement can be seen.

Category IV

These lesions are clearly malignant cystic masses that not only have all the characteristics of category III lesions, but also contain enhancing soft-tissue components adjacent to but independent of the wall or septa.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 102461, 10 pages
doi:10.1155/2008/102461

Review Article

Importance and Limits of Ischemia in Renal Partial Surgery: Experimental and Clinical Research

Fernando P. Secin

Urology Section, CEMIC University Hospital, Buenos Aires C1431FWO, Argentina

Correspondence should be addressed to Fernando P. Secin, secinf@mskcc.org

Received 29 February 2008; Accepted 18 June 2008

Recommended by J. Rubio

Introduction. The objective is to determine the clinical and experimental evidences of the renal responses to warm and cold ischemia, kidney tolerability, and available practical techniques of protecting the kidney during nephron-sparing surgery. *Materials and methods*. Review of the English and non-English literature using MEDLINE, MD Consult, and urology textbooks. *Results and discussion*. There are three main mechanisms of ischemic renal injury, including persistent vasoconstriction with an abnormal endothelial cell compensatory response, tubular obstruction with backflow of urine, and reperfusion injury. Controversy persists on the maximal kidney tolerability to warm ischemia (WI), which can be influenced by surgical technique, patient age, presence of collateral vascularization, indemnity of the arterial bed, and so forth. *Conclusions*. When WI time is expected to exceed from 20 to 30 minutes, especially in patients whose baseline medical characteristics put them at potentially higher, though unproven, risks of ischemic damage, local renal hypothermia should be used.

1. INTRODUCTION

Nephron-sparing surgery in the oncologic setting entails complete local resection of a renal tumor while leaving the largest possible amount of normal functioning parenchyma in the involved kidney. Different surgical techniques can be employed for performing partial nephrectomy, but all of them require adherence to basic principles of early vascular control, avoidance of ischemic renal damage with complete tumor excision with free margins, precise closure of the collecting system, careful hemostasis, and closure with or without tamponading of the renal defect with adjacent fat, fascia, or any available artificial sealant [1, 2].

Observance of all these principles is extremely important, however, prevention of ischemic renal damage is a key to the final success of the procedure. Ischemia is the leading cause of postoperative acute and chronic renal failure in patients undergoing nephron sparing surgery, for which no specific medical treatment modality has been established to date.

By the same token, surgeons need to apply transitory occlusion of the renal artery as it not only diminishes intraoperative parenchymal bleeding but also improves visualization and facilitates access to intrarenal structures by causing the kidney to contract and by reducing renal tissue fullness. Surgeons performing this approach require an understanding of renal responses to warm ischemia (WI) and available methods of protecting the kidney when the period of arterial occlusion exceeds normal parenchyma tolerability [3].

In order to decrease the exposure of the spared parenchyma to ischemia, the surgeon should have a complete preoperative and intraoperative assessment of the relationship of the tumor and its vascular supply to the collecting system and adjacent normal renal parenchyma [4–6].

There is no question that the less the better, whenever the philosophy to preserve as much functioning renal tissue as possible is followed. This manuscript seeks to determine the clinical and experimental evidences of the renal responses to warm and cold ischemia, kidney tolerability, and available practical techniques of protecting the kidney when the period of arterial occlusion surpasses that which may be safely tolerated during renal nephron sparing surgery.

2. MATERIAL AND METHODS

Biomedical and related databases were queried including MEDLINE, MD Consult, and urology textbooks. Manuscripts and library archives were retrieved from the

Nathan Cummings Center, Memorial Sloan-Kettering Cancer Center, NY, USA.

A Medline search in combination with additional references of non-Medline-indexed journals included the following key words: "nephron-sparing surgery," "partial nephrectomy," "warm ischemia and kidney," and "ischemia time and kidney," as well as links to related articles. Non-English articles and letters to editors were reviewed as well. These references formed the basis of the article. Following selection and deletion based on relevance of the subject and importance of the studies, a library of 115 references remained.

3. RESULTS AND DISCUSSION

3.1. Intraoperative renal ischemia: pathophysiology of injury

In recent years, there have been significant insights into the pathophysiologic process of renal ischemia [7, 8]. Ischemic insult to the kidney often results in damage to cells of nephron and renal vasculature. Cells are lost through the processes of necrosis and apoptosis, inevitably leading to renal failure. Renal failure is characterized by a decline in glomerular filtration rate, retention of nitrogenous waste products, perturbation of extra cellular fluid volume, and electrolyte and acid-base homeostasis. Renal failure is only diagnosed when these pathophysiologic perturbations are advanced enough to manifest biochemical abnormalities in the blood. The pathophysiologic response to cell death dictates the prevailing level of renal functional impairment [9]. Therefore, a clear understanding of the extent of post ischemic kidney damage and associated inflammation is needed to prevent this hitherto intractable condition, which will ultimately impact on overall survival [10].

For understanding and didactic purposes, three interrelated main mechanisms through which ischemia damages the kidney are herein described based on a recent review by Abuelo [7]. One mechanism is merely vascular, caused by persistent vasoconstriction and an abnormal response of endothelial cells to compensatory means. The second is obstructive, where soughed tubular epithelial cells and brush-border-membrane debris form casts that obstruct tubules, and glomerular filtrate leaks from the tubular lumen across denuded tubular walls into capillaries and the circulation (back-leak) causing a reduction in the "effective" GFR, where the latter is defined as the rate at which filtrate is delivered into final urine. The third has to do with reperfusion injury after blood flow is restored [7, 11].

3.1.1. Vascular mechanism

Both animal and human studies have found that a multi-inflammatory response is involved in ischemia/reperfusion injury of the kidney [12]. The inflammatory reaction incurred after an ischemic insult precipitates more damage to the tissue and impedes intrarenal blood flow caused by vasoconstriction and vascular congestion, leading to a vicious cycle [13].

This damage mainly takes place in endothelial cells of the peritubular capillaries, especially in the outer medulla, which is marginally oxygenated under normal circumstances. This oxidant injury, together with a shift in the balance of vasoactive substances toward vasoconstrictors such as endothelin, results in vasoconstriction, congestion, hypoperfusion, and expression of adhesion molecules. The expression of adhesion molecules, in turn, initiates leukocyte infiltration, augmented by proinflammatory and chemotactic cytokines generated by ischemic tubular cells [7].

Inciting stimuli induce kidney macrophages and probably renal parenchymal cells to release inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1). TNF-α and IL-1 promote renal parenchymal damage by directly inducing apoptosis in epithelial cells, recruitment of neutrophils that release reactive oxygen metabolites and proteases, and up regulating adhesion receptors on endothelial cells and leukocytes [14, 15]. These cytokines also stimulate renal cortical epithelial cells to release the chemoattractant interleukin-8 [16, 17]. The arrival of additional leukocytes obstructs the microcirculation and releases more cytotoxic cytokines, reactive oxygen species, and proteolytic enzymes, which damage the tubular cells [7].

Endothelial injury results in cell swelling and enhanced expression of cell adhesion molecules. This, together with leukocyte activation, leads to enhanced leukocyte-endothelial cell interactions, which can promote injury and swelling of the endothelial cell. Endothelial swelling contributes to the production of local factors promoting vasoconstriction and adds to the effects of vasoconstriction and tubule cell metabolism by physically impeding blood flow, perpetuating that vicious cycle [18].

Heterogeneity of intrarenal blood flow contributes to the pathophysiology of ischemic renal failure. An imbalance between the vasodilator nitric oxide and the vasoconstrictor endothelin impairs medullary blood flow, especially in the outer medulla, where tubules have high oxygen requirements, resulting in cellular injury due to a mismatch between oxygen delivery and demand. Endothelial activation and injury together with increased leukocyte-endothelial cell interactions and activation of coagulation pathways may have a greater effect on outer medullary ischemia than arteriolar vasoconstriction, as there can be markedly impaired oxygen delivery to the outer medulla despite adequate renal blood flow [18].

The arteriolar response to vasoactive substances can also be altered during endothelial injury. The basal tone of arterioles is increased in post ischemic kidneys as well as their reactivity to vasoconstrictive agents. These arterioles also have decreased vasodilatory responses compared with arterioles from normal kidneys. Alterations in local levels of vasoconstrictors (angiotensin II, thromboxane A_2, leukotrienes, adenosine, endothelin-1) have been implicated in abnormal vascular tone [19]. Angiotensin II seems to play a key role by activating endothelin B or prostaglandin H_2-thromboxane A_2 receptors. Systemic endothelin-1 levels increase with ischemia, and administration of antiendothelin antibodies or endothelin receptor antagonists has been reported to protect against ischemia-reperfusion injury [20]. Saralasin, an angiotensin II receptor antagonist, could

also attenuate angiotensin II vasoconstricting effect [21]. Nitric oxide, an endothelial-derived relaxing factor, plays a theoretical protective role against ischemic renal injury, by means of its vasodilatory effect and by decreasing endothelin expression and secretion in the vascular endothelium. Of interest, endothelial nitric oxide synthase is inhibited during endothelial injury [22]. A combination therapy consisting of 5-aminoimidazole-4-carboxamide-1-beta-D-ribonucleoside (AICAR) and N-acetyl cysteine (NAC), drugs that inhibit the induction of proinflammatory cytokines and nitric oxide synthase, and block tumor necrosis factor-alpha induced apoptotic cell death, has shown to attenuate ischemia-reperfusion injury in a canine model of autologous renal transplantation [23]. Early studies showed no conclusive evidence that vasodilators (such as diltiazem or dopamine) or other compounds have any clinical utility in either preventing or treating ischemic renal failure in humans thus far [24–26]. More recently, however, the highly selective dopamine type 1 agonist fenoldopam mesylate [27] and the antianginal medication trimetazidine [28] appeared to aid in restoring renal function to baseline values in patients with prolonged WI time. Further research is needed.

3.1.2. Obstructive mechanism

Normally, the cells are bathed in an extra cellular solution high in sodium and low in potassium. This ratio is maintained by a sodium pump (Na^+-K + ATPase pump) which uses much of the adenosine triphosphate (ATP) energy derived from oxidative phosphorylation. ATP is required for the cellular sodium pump to maintain a high intracellular concentration of potassium and a low concentration of sodium. The sodium pump effectively makes Na^+ an impermeant outside the cell that counteracts the colloidal osmotic pressure derived from intracellular proteins and other anions [29].

The ischemic insult causes a failure of oxidative phosphorylation and ATP depletion, leading to malfunctioning of the sodium pump. When the sodium pump is impaired, sodium chloride and water passively diffuse into the cells, resulting in cellular swelling and the "no-reflow" phenomenon after renal reperfusion. Cellular potassium and magnesium are lost, calcium is gained, anaerobic glycolysis and acidosis occur, and lysosomal enzymes are activated. This results in cell death. During reperfusion, hypoxanthine, a product of ATP degradation, is oxidized to xanthine with the formation of free radicals that cause further cell damage [29]. (See later.)

As mentioned, the mechanism whereby ischemia and oxygen depletion injure tubular cells starts with ATP depletion, which activates a number of critical alterations in metabolism, causing cytoskeletal disruption and loss of those properties that normally render the tubule cell monolayer impermeable to certain components of filtrate. Cytoskeletal disruption causes not only loss of brush-border microvilli and cell junctions but also mislocation of integrins and the sodium pump from the basal surface to the apical surface.

In addition, impaired sodium reabsorption by injured tubular epithelial cells increases the sodium concentration in the tubular lumen. The increased intratubular sodium concentration polymerizes Tamm-Horsfall protein, which is normally secreted by the loop of Henle, forming a gel and contributing to cast formation. As a result, brush-border membranes and cells slough obstruct tubules downstream. As mentioned before, these debris form casts that obstruct tubules, and glomerular filtrate leaks from the tubular lumen across denuded tubular walls into capillaries and the circulation (back-leak) causing a reduction in the "effective" GFR. ATP depletion also activates harmful proteases and phospholipases, which, with reperfusion, cause oxidant injury to tubular cells, the so-called reperfusion injury [7].

3.1.3. Reperfusion injury

WI insult followed by restoration of blood flow to the ischemic tissue frequently results in a secondary reperfusion injury. Despite WI causing significant renal dysfunction, reperfusion injury has been shown to be as damaging or even more detrimental than renal ischemia itself, producing an inflammatory response that worsens local kidney damage and leads to a systemic insult [30, 31].

The reperfusion injury can be mediated by several mechanisms including the generation of reactive oxygen species, cellular derangement, microvessel congestion and compression, polimorphonuclear (PMN)-mediated damage, and hypercoagulation. Reperfusion with the resulting reintroduction of molecular oxygen of constricted microvessels leads to congestion and red cell trapping. This vascular effect can reduce renal blood flow by as much as 50% [32].

During the reperfusion period, superoxide production in the kidney is markedly enhanced by the transformation of xanthine dehydrogenase to xanthine oxidase and the increase in free electrons in mitochondria, prostaglandin H, and lipoxygenase with the coexistence of NAD(P)H and infiltrated neutrophils. Superoxide raises the following chain reactions, producing hydroxyl radicals or other reactive oxygen species (ROSs), or interacts with nitric oxide (NO), which is produced by macrophage inducible NO synthase, generating a highly toxic radical peroxynitrite. These ROS and NO derived species consume tissue antioxidants and decrease organ reducing activity [33].

The exact magnitude of reperfusion injury is still unclear. Some authors state that the role of free radicals mediated injury in kidneys may not be as significant as in other organs given the low relative activity of renal xanthine oxidase compared with the high endogenous activity of superoxide dismutase [29].

Notwithstanding, nicaraven (N,N9-propylenebisnicotinamide), a drug that may actively trap free radicals and prevent vascular constriction due to lipid peroxide [34] and edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, MCI-186), a synthetic free radical scavenger, have shown in vitro experiments to protect endothelial cells against ischemic injury in different organs, including ischemically damaged kidneys [35, 36]. Clinical studies are eagerly awaited.

4. FOR HOW LONG CAN THE KIDNEY TOLERATE WARM ISCHEMIA?

Despite several animal studies [37–39] and clinical reports [40, 41] demonstrating kidney tolerance to warm ischemia times beyond 30 minutes, concern still remains regarding the potential for full-renal function recovery after this time period [42]. The stoic 30-minute cutoff has been questioned by some authors [43] on the grounds that kidneys harvested from nonheart beating donors (NHBDs) have shown favorable recovery of renal function in transplanted kidneys that sustained warm ischemia times well over 30 minutes [44–46]. Nishikido et al. [45] found that the risk factors affecting significant *graft loss* were WI time more than 20 minutes, donor age above 50 years, and donor serum creatinine at admission above 1.0 mg/dL. Today, most nonheart beating donor programs currently exclude those donors with a WI time exceeding 40 minutes [45, 47–49].

Although laparoscopic surgeons are gaining further experience and are more ambitious to perform partial nephrectomy for larger and deeper tumors, the 30-minute cutoff still remains the accepted safe limit time beyond which irreversible kidney damage occurs in the absence of renal cooling [50–52].

Although early observations in dog models showed that there may be substantial variation in kidney tolerance up to two or three hours of ischemia [53] there is no doubt that the extent of renal damage after transitory arterial occlusion exclusively depends on the duration of the ischemic insult [25, 54, 55]. The literature also demonstrates that, even within a tolerable period of WI, the longer the WI time the longer it takes for the kidney to recover (or approach) its preoperative function [55]. Notwithstanding, the maximum tolerable limit of renal warm ischemia time that can render complete function recovery remains to be established in humans.

The study by Ward [56] is commonly cited by opinion leaders to state a maximum 30-minute tolerance of the kidney to WI. These authors showed in dogs that warm ischemic intervals of up to 30 minutes can be sustained with eventual full recovery of renal function. However, this study was not strictly designed to establish the most accurate length of time a kidney would be able to sustain reversible damage following ischemic injury. What the authors actually concluded was that no additional protection to ischemia could be gained by cooling below 15 degrees. Thus, they recommended 15 degrees as the optimum temperature for use in clinical renal hypothermia.

Research in rats, pigs, and monkeys has also been conducted by other investigators. Laven et al. [38] found renal resilience to WI beyond the traditionally accepted 30 minutes in a solitary kidney pig model. Prolonged renal WI time increased the incidence of renal dysfunction during the initial 72 hours after the ischemic insult. However, by 2 weeks after the WI insult renal function returned to baseline in the 30, 60, and 90-minute WI groups. However, the same study group found that prolonged WI time of 120 minutes produced significant loss of renal function and mortality [43].

Martin et al. [57] proved potential kidney WI tolerability of up to 35 minutes in a single kidney monkey model.

Haisch et al. [58] studies in dog models suggested that the window of reversible WI injury could be as long as 2 hours after the insult.

The question remains whether findings in animal studies can be extrapolated to humans. One limitation has to do with a reliable method to differentiate between ischemic injury and the loss of renal volume secondary to tumor excision. The ideal method to evaluate residual kidney function in the operated kidney is still undefined. While most authors use serum creatinine assay or 99mtechnetium-labeled mercaptoacetyl triglycine (MAG3) renal scintigraphy with split renal function, others, like Abukora et al. [59] proposed estimation of parenchymal transit time (PTT) as a good indicator of ischemic injury. Transit time is the time that a tracer remains within the kidney or within a part of the kidney. However, the international consensus committee on renal transit time, from the subcommittee of the International Scientific Committee of Radionuclides in Nephrourology, recently concluded that the value of delayed transit remains controversial, and the committee recommended further research [60].

Bhayani et al. [40] evaluated 118 patients, with a single, unilateral, sporadic renal tumor, and normal contralateral kidney, who underwent laparoscopic partial nephrectomy (LPN) to assess the effect of variable durations of WI on long-term renal function. Patients were divided into 3 groups based on WI time: group 1, no renal occlusion ($n = 42$), group 2, WI < 30 minutes ($n = 48$), and group 3, WI > 30 minutes ($n = 28$). At a median followup of 28 months (minimum followup of 6 months) median creatinine had not statistically increased postoperatively and none of the 118 patients progressed to renal insufficiency or required dialysis after LPN. The authors concluded that WI time up to 55 minutes did not significantly influence long-term renal function after LPN. A main limitation of this study has to do with the fact that all patients had a normal contralateral kidney so that 6 months postoperatively creatinine values could have reflected contralateral kidney function.

A similar study has been conducted by Shekarriz et al. [61] on a substantially lower number of patients ($n = 17$); however, the authors assessed kidney function using 99technetium labeled diethylenetetraminepentaacetic acid scan renal scan with differential function 1 month before and 3 months after surgery in all patients. The authors found that all their patients preserved adequate renal function in the affected kidney following temporary hilar clamping of up to 44 minutes. (The mean WI time was 22.5 minutes.)

In line with this author, Kane et al. [62] showed that temporary arterial occlusion did not appear to affect short-term renal function (mean followup: 130 days) in a series of laparoscopic partial nephrectomies (LPNs) with a mean WI of 43 minutes (range: 25–65 minutes).

Desai et al. [50] retrospectively assessed the effect of WI on renal function after LPN for tumor, and evaluated the influence of various risk factors on renal function in 179 patients under WI conditions. No kidney was lost because of ischemic sequelae with clamping of the renal artery and

vein of up to 55 minutes. The mean WI time was 31 minutes. Nonetheless, the authors concluded that advancing age and pre-existing azotaemia increased the risk of renal dysfunction after LPN, especially when the warm ischemia exceeded 30 minutes.

In contrast, Kondo et al. [63] found that patient age did not influence residual function in patients undergoing partial nephrectomy, while tumor size was the only significant factor that inversely correlated with the relative 99technetium labeled dimercaptosuccinic acid (DMSA) uptake.

Porpiglia et al. [52] assessed kidney damage in 18 patients 1 year after LPN with a WI time between 31 and 60 minutes. The authors evaluated the contribution of the operated kidney to the overall renal function by radionuclide scintigraphy with 99mTc-MAG3. They observed that there was an initial significant drop of approximately 11% in the operated kidney's contribution to overall function, followed by a constant and progressive recovery that never reached the preoperative value (42.8% at 1 year versus 48.3% before surgery). The authors stated by logistic regression analysis that the loss of function of the operated kidney depended mostly on the WI time and less importantly on the maximum thickness of resected healthy parenchyma. Unfortunately, the full regression model that included 6 variables to predict an event in only 18 patients is not shown in the manuscript.

Recently, Thompson et al. [42] made a retrospective review of 537 patients with solitary kidneys who underwent open nephron sparing surgery by more than 20 different surgeons from both the Cleveland Clinic, Ohio, USA, and Mayo Clinic, Minn, USA, to evaluate the renal effects of vascular clamping in patients with solitary kidneys. After adjusting for tumor complexity and tumor size, the author found in a subsequent analysis [64] that patients with more than 20 minutes of WI were significantly more likely to have acute renal failure (24% versus 6%, p 0.002) compared to those requiring less than 20 minutes, and this risk remained significant even after adjusting for tumor size (odds ratio 3.4, p 0.025). Additionally, patients with more than 20 minutes of WI were significantly more likely to progress to chronic renal failure (odds ratio 2.9, p 0.008) and were more than 4 times more likely to experience an increase in creatinine postoperatively of greater than 0.5 mg/dL (odds ratio 4.3, p 0.001) compared to those requiring less than 20 minutes of WI. After adjusting for tumor size, the risk of chronic renal failure (odds ratio 2.6, p 0.03) and an increase in creatinine of greater than 0.5 mg/dL (odds ratio 4.6, p 0.002) remained statistically significant if more than 20 minutes of WI were needed. The authors concluded that WI should be restricted to less than 20 minutes when technically feasible, especially in patients with solitary kidneys.

5. WHAT ARE THE FACTORS AFFECTING TOLERANCE TO WARM ISCHEMIA?

It often goes without saying that there may be individual variation to WI tolerance. Baldwin et al. [37] observed that some of the 16 solitary porcine kidneys showed a rapid return to the dark red color, and other animals demonstrated minimal color change during the several minutes following complete hilar clamp removal, despite all of them receiving similar surgical technique and ischemia time. Having acknowledged the potential for individual variation, there may be other multiple factors that can affect tolerance to WI which are herein described.

It has been suggested that patients with solitary kidneys might safely tolerate longer periods of ischemia than patients with both kidneys as the result of development of a collateral vascular supply; [65–67] however, the presence of vascular collateralization secondary to vascular occlusive disease, [68] or yet other clinical entities like hypertension, [69] should warn the surgeon for the possibility of a kidney less resistant to WI injury for the likely presence of panvascular disease and or occult chronic renal insufficiency.

Another factor that can impact ischemic damage is the method employed to achieve vascular control of the kidney. When technically possible, depending on the size and location of the tumor, it is helpful to leave the renal vein patent throughout the operation. This measure has been proven to decrease intraoperative renal ischemia and, by allowing venous backbleeding, facilitates hemostasis by enabling identification of small, transected renal veins [1–3, 5].

Animal studies have shown that functional impairment is least when the renal artery *alone* is occluded. Although some authors found no difference [70] simultaneous occlusion of the renal artery and vein for an equivalent time interval is more damaging because it prevents, as mentioned, retrograde perfusion of the kidney through the renal vein and may also produce venous congestion of the kidney [2, 3, 71–73]. However, this benefit may not be observed in patients undergoing LRP since the pressure of the pneumoperitoneum may cause partial occlusion of the renal vein, thus, negating the advantage of renal artery clamping only [72].

Intermittent clamping of the renal artery with short periods of recirculation may also be more damaging than continuous arterial occlusion, possibly because of the release and trapping of damaging vasoconstrictor agents within the kidney [39, 55, 71, 74–77].

Manual (or instrumental) compression of the kidney parenchyma to control intraoperative hemorrhage (as an alternative to clamping of the pedicle) has the theoretical advantages of avoiding WI of the normal parenchyma while allowing the surgeon to operate in an almost bloodless field, something that could be particularly useful in peripherically located tumors. Although animal studies have shown that the use of renal parenchyma compression may be more deleterious than simple arterial occlusion [71, 76], this technique has been recently "resuscitated" by some authors both in the open kidney surgery [78–82] and in the laparoscopic setting [83].

When the surgeon anticipates a WI time exceeding the "classical" 30 minutes, local renal hypothermia is used to protect against ischemic renal injury. Hypothermia has been the most effective and universally used means of protecting the kidney from the ischemic insult. Hypothermia reduces basal cell metabolism, energy-dependent metabolic activity

of the cortical cells, with a resultant decrease in both the consumption of oxygen and ATP [84–86].

There are multiple ways of achieving hypothermia. Surrounding the fully mobilized kidney with crushed ice (ice slush) is the most frequently used technique because of its ease and simplicity [87, 88]. When using ice slush to reduce kidney temperature, it is recommended to keep the entire kidney covered with ice for 10 to 15 minutes immediately after occluding the renal artery and before commencing the resection of the tumor in order to allow core renal temperature to decrease to approximately 20 degrees centigrade or less [2]. Mannitol, with or without the addition of furosemide, should be administered intravenously 5 to 15 minutes before renal arterial clamping as it increases renal plasma flow, decreases intrarenal vascular resistance and intracellular edema, and promotes an osmotic diuresis when renal circulation is restored [89]. Regular use of heparin to prevent intrarenal vascular thrombosis has not been found to be useful [2, 3, 56].

Other methods than the use of ice slush to achieve renal hypothermia have also being explored, including application of ice-slurry [90, 91], antegrade perfusion of the renal artery either via preoperative renal artery catheterization [92] or via intraoperative renal artery cannulation [93], retrograde perfusion of the collecting system with cold solutions [94, 95] or near-freezing saline irrigation delivered with a standard irrigator aspirator [96] among others, some of them particularly used in the laparoscopic setting. Very few studies compared kidney cooling techniques; [97–100] however, hypothermia by properly applying ice to the renal surface seems to be equivalent to hypothermia by perfusion [98]. Perfusion of the kidney with a cold solution instilled via the renal artery not only may have a theoretic risk of tumor dissemination, but also requires participation of an intervention radiology team to perform preoperative renal artery catheterization, adding complexity and risks of potential complications to the procedure [3]. On the contrary, continuous renal perfusion might have the advantage of providing a more homogeneous and effective hypothermia for a more extended period of time [99, 100]. It is generally accepted, founded on data extrapolated from the kidney stone literature, that adequate hypothermia provides up to 2 to 3 hours of renal protection from circulatory arrest [99, 101–104].

Needless to say, generous preoperative and intraoperative hydration, prevention of intraoperative hypotension, avoidance of unnecessary manipulation or traction on the renal artery as well as the aforementioned administration of mannitol are necessary to keep the kidney adequately perfused before and after the ischemic insult.

Ischemic preconditioning (IP) has emerged as a powerful method of ameliorating ischemia/reperfusion injury not only the myocardium (as initially described) [105] but also to other organs, including kidney. IP is a physiologic phenomenon by which cells develop defense strategies to allow them survive in a hypoxic environment. The original IP hypothesis stated that multiple brief ischemic episodes applied to an organ would actually protect it (originally the myocardium) during a subsequent sustained ischemic insult so that, in effect, ischemia could be exploited to protect that organ (originally the heart) from ischemic injury [105]. The "preconditioned" cells would become more tolerant to ischemia by adjusting its energy balance to a new, lower steady-state equilibrium. Specifically, preconditioned tissues exhibit reduced energy requirements, altered energy metabolism, better electrolyte homeostasis and genetic reorganization, giving rise to the concept of "ischemia tolerance." IP also induces "reperfusion tolerance" with less reactive oxygen species and activated neutrophils released, reduced apoptosis and better microcirculatory perfusion compared to not preconditioned tissue. Systemic reperfusion injury is also diminished by preconditioning [31]. A review by Pasupathy and Homer-Vanniasinkam [31] showed that IP utilizes endogenous mechanisms in skeletal muscle, liver, lung, kidney, intestine, and brain in animal models to convey varying degrees of protection from reperfusion injury. To date, there are few human studies, but some reports suggest that human liver, lung, and skeletal muscle acquire similar protection after IP. IP is ubiquitous but more research is required to fully translate these findings to the clinical arena.

Some authors propose that during laparoscopy, the increase of intra-abdominal pressure due to the pneumoperitoneum may create an IP-like situation that might increase kidney tolerance to subsequent WI and reduce tissue injury [106–110]. For this reason, it might theoretically be possible to increase WI time during LPN, compared to open surgery, something which is still very far from being demonstrated [30, 109–111].

In contrast, other studies expressed some concern about the potential harm of pneumoperitoneum and increased intra-abdominal pressure (IAP) on kidney function. Several experimental animal studies have investigated the effect of pneumoperitoneum on renal function. While some authors demonstrated that increased IAP by insufflation of CO2 gas resulted in decreased renal blood flow that may lead to ischemia and subsequent decreased glomerular filtration rate [112], others denied such effect [37, 113].

Kirsch et al. [112] showed a decrease in urine output and GFR with increasing IAP. A pneumoperitoneum of 15 mmHg for 4 hours resulted in a decrease in renal blood flow to 70% of baseline. Even IAPs of 4 and 10 mmHg resulted in a reduction of the renal circulation of 34% and 41%, respectively. Although, the decreased urinary output during prolonged IAP greater than or equal to 15 mmHg in the animal model was associated with a corresponding decrease in renal vein flow, it did not appear to be associated with any permanent renal derangement nor any transient histological changes [114]. After the release of the pneumoperitoneum or pneumoretroperitoneum, the renal function and urine output return to normal with no long-term sequelae, even in patients with pre-existing renal disease [115].

Lind et al. [113] found that WI time of 20 minutes did not impair graft function and histomorphology during 1 year of followup after renal transplantation in a syngeneic rat model. Most important, WI in combination with pneumoperitoneum did not result in an additive negative effect on long-term graft function.

In addition, Baldwin et al. [37] observed that temporary serum creatinine elevation evident after 60 and 90 minutes of ischemia normalized within 7 days in 16 farm pigs which had been nephrectomized 14 days prior to the laparoscopically applied ischemic insult. No difference from the controls was noted in those pigs receiving 30 minutes of ischemia during the laparoscopic procedure. Of note, insufflation had been maintained for 150 minutes at 15 mmHg in all animals. Those findings suggested that in laparoscopic renal surgery, WI times of up to 90 minutes (and a pneumoperitoneum of up to 150 minutes) might be well tolerated and followed by complete renal recovery. The reader is referred to the excellent review by Dunn and McDougall [115] for further information on the impact of pneumoperitoneum on renal physiology.

6. CONCLUSIONS

The maximal duration of WI allowable before the onset of irreversible renal damage continues to be a topic of debate, irrespective of the surgical approach. In addition, there seems to be variation among patients, possibly related to surgical technique, patient age, presence of collateral vascularization, and indemnity of the arterial bed, among others. Unfortunately, no method exists for predicting preoperatively or intraoperative monitoring for renal injury. Surgeons should exert extreme efforts to keep warm ischemia time as short as possible. When WI time is expected to exceed from 20 to 30 minutes, specially in patients whose baseline medical characteristics put them at potentially higher, though unproven, risks of ischemic damage, the time-tested way around this time limit has been renal hypothermia, regardless of what the time limit may exactly be.

ACKNOWLEDGMENT

The author would like to thank the Nathan Cummings Center, Memorial Sloan-Kettering Cancer Center, New York, for providing all paper references and some of the textbooks.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 196701, 6 pages
doi:10.1155/2008/196701

Review Article

Surveillance for the Management of Small Renal Masses

Mehmet Ozsoy, Tobias Klatte, Matthias Waldert, and Mesut Remzi

Department of Urology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

Correspondence should be addressed to Mesut Remzi, mremzi@gmx.at

Received 16 April 2008; Accepted 8 June 2008

Recommended by J. Rubio

Surveillance is a new management option for small renal masses (SRMs) in aged and infirm patients with short-life expectancy. The current literature on surveillance of SRM contains mostly small, retrospective studies with limited data. Imaging alone is inadequate for suggesting the aggressive potential of SRM for both diagnosis and followup. Current data suggest that a computed tomography (CT) or magnetic resonance imaging (MRI) every 3 months in the 1st year, every 6 months in the next 2 years, and every year thereafter, is appropriate for observation. The authors rather believe in active surveillance with mandatory initial and followup renal tumor biopsies than classical observation. Since not all SRMs are harmless, selection criteria for active surveillance need to be improved. In addition, there is need for larger studies in order to better outline oncological outcome and followup protocols.

1. INTRODUCTION

During the last 20 years, the incidence of renal cell cancer (RCC) has been steadily increasing (2-3%/year) [1]. This rise is mostly due to the increase in detection of incidental small renal masses (SRM $\leq$ 4 cm) by widespread use of cross-sectional imaging techniques such as ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI). Between 1983 and 2002, the detection of SRM showed almost a three-fold increase for tumors <2 cm and 2–4 cm, respectively, whereas the detection rate of 4–7 cm and >7 cm just rose by 50% and 26%, respectively [2]. Nowadays, more than 50% of all renal tumors are SRM [3]. The majority of these tumors are asymptomatic and carry a good prognosis [4]. For open and laparoscopic nephron-sparing surgery (NSS), 5-year cancer-specific survival rates of 96–100% have been reported [5, 6].

The highest incidence of incidentally detected SRM is seen in elderly patients [4], who usually present with a number of comorbidities [7–9]. To manage these patients, a variety of treatment options have evolved in the past several years ranging from radical nephrectomy to observation for SRM. NSS remains the standard of care for small RCC, but minimal-invasive therapies and surveillance evolved as alternative treatment options. Here, we review the literature on surveillance for the management of SRM.

2. ARE SMALL RENAL MASSES ALWAYS MALIGNANT?

Up to 20% of SRM are actually benign [10–12]. Unfortunately, tumor size alone does not appear to be a predictor of benign or malignant tumor biology. Frank et al. retrospectively examined 2935 solid renal tumors at all sizes treated over a 25-year period and reported 46.3%, 22.4%, 22%, and 19.9% of renal lesions lower than 1 cm, 2 cm, 3 cm, and 4 cm to be benign, respectively [12]. In the prospective randomized multicenter EORTC 30904 study, comparing nephron-sparing surgery with nephrectomy in patients with resectable RCC, 11.6% of the 541 surgically removed tumors ($\leq$5 cm) were benign [13] and among the 100 lesions (mean diameter 2.8 cm) on which Gill et al. [14] performed laparoscopic partial nephrectomy 30% were identified as benign. In a recent report by Remzi et al. [11] that reflects the renal tumors of today, renal tumors of $\leq$2 cm, 2-3 cm, 3-4 cm were reported to be benign in 24.6%, 20.4%, and 16.0%, respectively, without any correlation to tumor size ($P = .66$). In another series of 1208 SRM, the frequency of benign lesions in the tumor size ranges 0.1–1.0, 1.1–2.0, and 2.1–3.0 was 15%, 14%, and 14%, respectively. However, the incidence of benign lesions decreased significantly in tumors measuring 3.1–4.0 cm (8%, $P = .001$) [10].

Benign lesions (oncocytomas, low-fat angiomyolipomas) are still difficult to differentiate from RCC's even with

today's advanced imaging modalities. In a recent study by Remzi et al. [3], only 17% of all benign lesions were correctly identified as benign on preoperative CT and 43% of patients who were assessed incorrectly on preoperative CT's underwent unnecessary radical surgery. There are only a few studies pointing out the success of differentiating low-fat AML from RCC with nonroutine special imaging studies [15].

In addition to initial tumor size, growth rate of tumors on surveillance is also not a reliable predictor of histology. In their review, Chawla et al. compared initial tumor size and the observed growth rate between oncocytomas and RCC variants. Of the 76 tumors, 12% were oncocytomas and the remaining 88% were RCC. At first presentation, mean tumor sizes were 2.00 ± 0.99 (median 1.50, ranging from 1 to 3.9) and 2.21 ± 1.5 cm (median 2.0, ranging from 0.20 to 12.0) in oncocytomas and RCC's, respectively, ($P = .59$). The mean growth rate of oncocytomas and RCC variants did not differ statistically (0.05 ± 0.67, median 0.16, ranging from 1.62 to 0.62, and 0.35 ± 0.41 cm yearly, median 0.35, ranging from 0.42 to 1.6, respectively, $P = .15$) [8]. Thus growth rate after opting for surveillance strategy is not an ideal parameter to further initiate surgical treatment [12–14].

3. ARE SMALL RENAL CELL CARCINOMAS HARMLESS?

In their study, Remzi et al. [11] retrospectively analyzed 287 SRMs that were defined to be ≤4 cm by preoperative CT scans and subsequently underwent surgery. About 80% of these lesions were malignant. Tumors were stratified into three groups according to their largest diameter, defined as ≤2 cm, 2.1 to 3.0 cm and 3.1 to 4.0 cm. They were also grouped into two groups of ≤3 cm and 3.1 to 4 cm. There was a significant correlation between tumor size and Fuhrman grade. Two (4.2%), four (5%), and twenty five (25.5%) cases of RCC 2 cm or less, 2.1 to 3 cm, and 3.1 to 4 cm in diameter had Fuhrman grade G3/4, respectively, ($P = .0007$). but there was no statistical difference in Fuhrman grades G3/4 between those ≤2 and 2.1 to 3 cm ($P = .847$), whereas the difference between ≤3 cm and 3.1 to 4 was statistically significant ($P = .0023$). Advanced stage (pT3a or greater) was documented in two (4.2%), 12 (14.9%) and 35 (35.7%) cases for RCC diameter ≤2 cm, 2.1 to 3.0 cm and 3.1 to 4 cm, respectively, ($P = .0023$). At least pT3a stage showed no statistical difference between ≤2 cm and 2.1 to 3 cm group ($P = .172$) whereas the difference between ≤3 cm and 3.1 to 4 cm groups was statistically significant ($P = .0007$). Among the 287 patients, 14 present with distant metastases, 10 of which being among the 119 tumors within the 3.1 to 4 cm group (8.4%) and the remaining four among the 168 tumors of ≤3 cm group (2.4%) ($P = .0045$). This study showed a high-aggressive potential of SRM beyond 3 cm, and thus not all SRM are actually harmless [11].

Klatte et al. [10] investigated 1208 patients with SRM, of whom 88% had RCC. Mean tumor size (±SD) was 2.9 (±0.9) cm. In their study, cancer-specific survival of small nonmetastatic (NX/N0M0) RCC was 96% and 91% after 5 and 10 years, respectively. There was a 7% chance of RCC recurrence post nephrectomy at 5 years. Independent prognostic factors of cancer-specific survival were ECOG performance status, T stage, presence of metastatic disease, and Fuhrman nuclear grade. This study pointed out that there is a small but not insignificant number of patients who recur after curative surgery for SRM.

Measuring tumor diameters by sequential imaging modalities are also not reliable, so when choosing surveillance as an option the cut-off diameter should be set well. As stated above, SRM with a tumor diameter below 3 cm on CT seems to fit better for surveillance than larger tumors. In addition to size, patients with concomitant invasion of the perirenal fat (clinical T3a) on cross-sectional imaging should be excluded from a surveillance protocol, since T3a tumors are at a higher risk of RCC-specific death [10].

In their study, Minardi et al. warn against the possibility of recurrence and death in patients even with low-grade RCC's. They report on 48 patients with pT1a clear cell RCC who underwent NSS. After a median followup of 2 years, 3.9% had died of metastatic RCC. Thus even small lesions can metastasize [16].

4. NEW TREATMENT OPTIONS

Nowadays, NSS is the standard treatment for SRM, which is related to the minimal impairment of renal function and excellent cancer-specific survival rates either in open and laparoscopic NSS of about 96–100% after 5 years [5, 6].

Recently minimal invasive therapy modalities such as radiofrequency ablation (RFA), High-intensity focused ultrasound (HIFU) and cryotherapy emerged as potential treatment options for clinically localized RCC for SRM with promising short-term results [17]. Effective renal cryoablation has been achieved by open and laparoscopic approaches as well as by percutaneous image-guided techniques. Percutaneous RFA has been successfully performed under ultrasound, CT, or MRI guidance [18]. Many studies report excellent cancer-specific survival rates of 90–100% [18, 19], however most of the series do not describe the underlying tumor entity (e.g., benign/malignant), have small number of patients treated and a short followup. Additionally Klingler et al. recently reported that skipping (up to 24%) was a major problem in RFA [20]. It is well known from series of open NSS that the time to recurrence is in mean over 5 years, thus a followup of one or two years, which is reported in most series is insufficient to show oncological safety [5, 21]. In a recent meta-analysis on RFA, cryoablation, and surveillance, the risk of recurrence was 7.45 and 18.23 higher for cryoablation and RFA, compared to NSS. Additionally this meta-analysis showed that NSS, ablation, and surveillance are viable strategies for SRMs based on short-term and intermediate term oncological outcomes [18]. However, a significant selection bias currently exists in the clinical application of these techniques with regard to patient age and tumor size. Although long-term data have demonstrated excellent outcomes for NSS, extended oncological efficacy remains to be established for ablation and surveillance strategies. While current data demonstrate a significantly higher incidence of local tumor progression following cryoablation and RFA,

no significant differences in progression to metastatic RCC were seen regardless of treatment modality [18]. These data suggest an overtreatment bias for SRMs, thus nowadays a new treatment strategy is "surveillance: treatment by initial observation with serial imaging with delayed treatment for progression" gains popularity as a management option for SRMs.

5. ACTIVE SURVEILLANCE IN WHOM, HOW AND WHEN?

5.1. Natural history

The natural history of SRM is not well known due to their early removal after diagnosis in most of the cases. There are only few insights on the natural history of SRMs.

In one of the important studies regarding surveillance Bosniak and colleagues retrospectively examined the followup images of 40 incidentally detected renal masses (<3.5 cm). After an average of 3.8 years, 26 tumors were removed. Of these 26 removed masses, 22 (84.6%) were histologically confirmed as RCC. The overall mean linear growth rate for all tumors was 0.36 cm per year. None of the patients developed metastasis [22].

In one study, 13 patients with SRM who were either too old (median patient age was 69 years) or no candidates for surgery were followed with abdominal imaging for a median of 42 months. The growth rate was highly variable. Most SRM grew at a low rate or not at all [23]. In a subsequent study, 32 renal masses <4 cm (25 solid masses, 7 complex cysts) which were found in 29 patients were managed by surveillance. During a median followup of 27.9 months (range: 5.3–143.0 months) serial abdominal imaging was performed at least three times on each mass. The average growth rate was low and it did not show any statistical difference from zero growth ($P = .09$; 95% confidence interval, −0.005–0.2 cm per year) and was not associated with either initial size ($P = .28$) or mass type ($P = .41$). Seven masses (22%) reached 4 cm in greatest dimension after 12–85 months of followup. Eight masses (25%) doubled their volumes within 12 months. Overall, 11 masses (34%) fulfilled one of these two criteria of rapid growth. Nine tumors were removed surgically after an average of 3.1 years of followup either due to surgeon's concern or patient's anxiety. No progression to metastatic disease was observed [24].

There are a certain number of other retrospective studies investigating the natural history of SRM. Commonly these authors render surveillance as a possible safe option for patients with short-life expectancies or patients who are unfit for surgery. Unfortunately these studies accrued a limited number of patients and had short followup durations [25–29]. In their review, Rendon and Jewett [30] conclude active surveillance as a viable and safe option for the patient with a short-life expectancy or within well-controlled clinical trials. They also point out the necessity of close interval followups using imaging techniques every 3 months for the 1st year, every 6 months for the next 2 years and once every year thereafter.

In a meta-analysis by Chawla et al. [8], 234 SRM under surveillance were included. Mean lesion size at presentation was 2.60 cm (median 2.48, ranging from 1.73 to 4.08). Lesions were observed for a mean followup of 34 months (median 32, ranging from 26 to 39 in all series combined). The mean growth rate was 0.28 cm per year (median 0.28, ranging from 0.09 to 0.86) and only 1% of the patients developed metastatic disease. In 46% of the cases (131 out of 286), a pathological confirmation was available, which showed RCC in 92% (120 of 131). Among RCC, a mean growth rate of 0.40 cm yearly (median 0.35, ranging from 0.42 to 1.6) was observed. Lesion size at presentation did not correlate with growth rate ($P = .46$). Serial radiographic data alone were insufficient to predict the true natural history of SRM and patients concomitant diseases should also be taken into consideration when deciding for active surveillance.

Kouba et al. [31] reported short-term outcomes of patients under surveillance. A total of 43 patients with 46 renal masses underwent planned expectant management of enhancing solid or cystic (Bosniak IV) renal masses. 74% of patients had tumor growth with a mean (median) growth rate of 0.70 (0.35) cm per year during a mean followup of 36 months. There were no significant symptoms, disease progression or cancer-specific death. Four patients (10%) died of other causes. 13 out of 43 patients underwent surgical intervention after a mean delay of 12 months. Initial tumor size showed no significant difference in the intervention and nonintervention group (3.1 cm 2.6 cm, resp., $P = .4504$) and there was also no correlation between growth rate and tumor size. Delayed intervention did not appear to adversely impact pathological outcomes. The authors consider surveillance for SRM as a reasonable option for appropriately selected patients, especially the elderly and those with competing comorbidities.

These data suggest that active surveillance is an option in elderly patients with severe comorbidities or patients, who are not willing to undergo surgery. Excellent patient compliance and close followup with contrast enhanced CT or MRI is mandatory.

5.2. Limitations

Imaging alone is inadequate on defining management in patients with SRMs. Punnen et al. observed inter- and intraobserver variability in measuring tumor diameter (±0.3 cm in diameter). Tumor volume is exponentially related to tumor diameter, and thus inaccuracy of measuring tumor diameters is related to a greater error (inter- and intraobserver variability for tumor volume 2.515 mm^3 and 2.075 mm^3, resp.) [32].

5.3. Role of renal tumor biopsy

There have been serious suspicions in the past about needle-core biopsies of renal masses regarding complications, tumor seeding, and wrong sampling. Due to advances in application techniques and help of imaging guidance, the results of needle biopsies have improved significantly. Fine-needle aspiration (18-gauge or thinner) and core biopsies of renal

masses are now much safer than before and they can even be applied in an outpatient setting with low morbidity rates [33–36].

Today the success rate of obtaining tissue and their pathologic interpretation are excellent [37]. Neuzillet et al. [34] were able to obtain adequate material for histological examination from 96.6% out of 88 patients that underwent Helical-CT-guided percutaneous fine-needle biopsy. 62 patients whose biopsy examinations indicated RCCs were treated surgically (radical or partial nephrectomy). The postoperative evaluation revealed a 92%-sensitivity rate of biopsy in predicting malignancy and tumor subtype. The results also showed no false-positive cases, no track seeding, and no complications.

Schmidbauer et al. [37] published a prospective study on 78 patients with SRMs who underwent 18-gauge core biopsy under computed tomography (CT)-fluoroscopic guidance. In addition, using the same sheath, fine-needle aspiration was taken in 44 patients and analyzed cytologically. The renal masses were subsequently removed surgically and evaluated histologically. The results showed a sensitivity of 93.5% and 90.6%, for core biopsy and fine-needle aspiration for the detection of renal cell carcinoma (RCC), respectively; Fuhrman grade was correctly predicted in 76% and 28% and the correct histologic subtype identified 91% and 86%, respectively. Cytology from fine-needle aspiration revealed a sensitivity of 100% and 75% in detecting malignant and benign lesions, respectively. Two of the SRMs' diagnosed as oncocytomas on core biopsy were revealed to be hybrid tumors with scattered areas of oncocytomas and chromophobe RCC on histological evaluation.

These data suggest that before opting for surveillance a sufficient renal tumor mass biopsy should be performed to further guide followup.

6. WHO AND HOW?

According to many authors, active surveillance is a feasible option especially for elderly and unfit patients. Because active surveillance is a new concept, large studies with appropriate followup are still missing. Which patients should undergo active surveillance? What should be our followup intervals? What is the cut-off tumor diameter? What should be the limit for annual growth? In order to precisely answer these questions, larger numbers of studies are required. In some centers, renal masses below the limit of 3-4 cm in diameter are considered to be at low risk of metastasis [38, 39].

The authors believe that low-grade tumors measuring <3 cm could enter an active surveillance protocol. Prior and during followup, renal tumor biopsies are mandatory. Biopsies should be assessed by the same pathologist to exclude interobserver variations, especially in grading. High-grade tumors, sarcomatoid features, collecting duct, and unclassified RCC have to be excluded because of their known unfavorable outcomes. Additionally, young and/or healthy patients are no good candidates for active surveillance because of lacking long-term data (see Table 1).

For followup, Rendon et al. suggested CT or MRI every 3 months in the 1st year, every 6 months for the next 2 years and every year thereafter [30], however, there are no oncological outcome data that support this approach. Again, repeated biopsies of the mass have to be performed in certain intervals. Tumors that exceed 3 or 4 cm or which double in volume in <12 months need further intervention [7, 10, 11], for example, surgery or ablation.

These short-interval followups may have a negative impact on patient compliance. Another downside of active surveillance is the patient's anxiety. The knowledge of living with a tumor and "not doing anything about it" is also a psychological burden on the patient.

Table 1: Possible inclusion and exclusion criteria for active surveillance of SRM.

Inclusion:
(1) Benign lesion on renal tumor biopsy
(2) Aged and infirm patient
(3) Tumor size <3 cm on cross-sectional imaging
(4) Chromophobe RCC, low-grade, on renal tumor biopsy
(5) Chromophobe-oncocytic hybrid tumor on renal tumor biopsy
(6) Willingness of the patient to undergo regular CT or MRI scans and repeated biopsies (good compliance)
Exclusion:
(1) Young and healthy patient
(2) Sarcomatoid features
(3) Collecting duct or unclassified RCC
(4) Evidence of ≥T3a disease on cross-sectional imaging
(5) High grade
(6) Symptomatic lesions
Unclear:
(1) Low grade clear-cell RCC
(2) Low-grade papillary RCC
(3) Multifocal RCC
(4) Hereditary RCC

7. CONCLUSIONS

Active surveillance is a new management option for the aged and infirm patient with short-life expectancy. The current literature contains mostly small, retrospective studies with limited data. Prior and during followup, renal tumor biopsies are mandatory. Thus, the authors rather believe in active surveillance than in classical observation. Imaging alone is inadequate for suggesting the aggressive potential of SRM for both diagnosis and followup. Current data suggest that a CT or MRI every 3 months in the 1st year, every 6 months in the next 2 years and every year thereafter, is appropriate for observation.

Since not all SRM are harmless, selection criteria for active surveillance need to be improved. In addition, there is need for larger studies in order to better outline oncological outcome and followup protocols.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 705958, 6 pages
doi:10.1155/2008/705958

Review Article

Surveillance as an Option for the Treatment of Small Renal Masses

S. Klaver, S. Joniau, and H. Van Poppel

Department of Urology, University Hospital Gasthuisberg, 3000 Leuven, Belgium

Correspondence should be addressed to S. Klaver, sjoerd.klaver@uzleuven.be

Received 22 April 2008; Accepted 13 July 2008

Recommended by J. Rubio

Objectives. To review the natural history and biological potential of small renal masses in order to evaluate surveillance as a treatment option. *Methods*. Literature search of Medline and additional references from non-Medline-indexed publications concerning surveillance of small renal masses. *Results*. The natural history and biological potential of small renal masses can still not be unambiguously predicted at present. There seems to be no clear correlation between tumour size and presence of benign histology. The majority of small renal masses grow and the majority are cancer, but one cannot safely assume that a lack of growth on serial CT scans is the confirmation of absence of malignancy. Needle core biopsies could be used to help in decision making. They show a high accuracy for histopathological tumour type but are less accurate in evaluating Fuhrman grade. *Conclusions*. At present, surveillance of small renal masses should only be considered in elderly and/or infirm patients with competing health risks, in those with a limited life expectancy, and in those for whom minimal invasive treatment or surgery is not an option. In all other patients, active surveillance should only be considered in the context of a study protocol. Long-term, prospective studies are needed to provide a more accurate assessment of the natural history and metastatic potential of small renal masses.

1. INTRODUCTION

The increased use of modern imaging techniques has lead to an increase in incidentally detected small renal tumours, leading to an increase of asymptomatic small renal masses with no evidence of metastatic disease. The greatest incidence of these tumours occurs in patients older than 70 years in whom multiple comorbidities may increase the risks of surgery [1].

The accepted standard treatment for the last 50 years for clinically localised renal cell carcinoma (RCC) has been radical nephrectomy; however, more recently nephron-sparing surgery has become the gold standard for most small renal masses.

There is an increased interest in minimally invasive therapies nowadays, such as radiofrequency ablation and cryotherapy, with encouraging short-term data. However, long-term outcome data are still awaited. Despite the decreased perioperative morbidity of partial nephrectomy with advances in surgical techniques, especially the laparoscopic approach, some patients may not be candidates for surgery because of medical comorbidities [2–4] or unwillingness to undergo surgical resection.

Previous findings assume that many small renal masses have a slow growth rate and a low metastatic potential. This has raised the question of close monitoring as an alternative to surgery. To be able to implement such strategy, a better understanding of the biological behaviour and natural history of these lesions is important. We reviewed the available data from two prospective studies [5, 6] and several small case series [7–17] describing the short-term outcomes of expectantly followed renal masses to better assess the current role of active surveillance as a therapeutic strategy of these small renal masses.

2. SMALL RENAL MASSES AND THEIR NATURAL HISTORY

Kouba et al. [1] suggested that active surveillance for renal masses is an appropriate option in selected patients, especially those with competing comorbidities, since delayed

intervention after an initial period of surveillance does not appear to adversely impact pathological outcomes. They published the results of a retrospective case series including 43 patients with 46 renal masses (24% of tumours >4 cm) who underwent active surveillance of enhancing solid or cystic Bosniak IV renal masses. A subset of 13 patients who ultimately underwent surgical intervention was also examined. Mean delay to intervention was 12 months. At a 36 months mean follow-up, renal masses grew in 74% of patients with a mean (median) growth rate of 0.70 (0.35) cm per year, no patient died of RCC and none had evidence of metastatic disease. Initial tumour size (3.1 versus 2.6 cm, $p = 0.4504$) was similar in the intervention and nonintervention groups and growth rate did not correlate with initial tumour size.

Volpe et al. [5] reported in their report that only one third of small renal masses grew during surveillance and therefore raising the possibility of a period of initial observation in selected patients, especially in infirm or elderly patients. They prospectively followed 29 patients with 32 small renal masses (<4 cm, 7 lesions were complex cystic masses) for a median of 27.9 months who refused or were deemed unfit for surgical treatment. The median baseline volume was 4.9 cm^3 for the 25 solid masses and 22.8 cm^3 for the 7 cystic masses. The average growth rates for the solid and the cystic masses were comparable (0.11 and 0.09 cm per year, resp.; $P = .41$).

Also Rendon et al. [6], who prospectively followed 13 patients with small renal masses for a median of 42 months, concluded that most small renal masses grow slowly, if at all, and metastases are unlikely to arise before the mass shows rapid growth. Later, in 2006 Rendon and Jewett [18] reviewed the available data on the natural history of small renal masses and considered surveillance a feasible and safe option in patients with a short-life expectancy or within a well-controlled clinical trial. They recommended close imaging follow-up should be performed every 3 months for the 1st year, every 6 months for the next 2 years, and every year thereafter. A cut-off tumour size of 4 cm was considered safe although this has not yet been systematically validated.

Most other published series concerning this matter are small retrospective case series with limited follow-up and pathology data for many patients are missing [7–15]. The individual investigators advise that a period of surveillance can be safely performed in patients who are medically unfit for surgery.

Chawla et al. [16] performed a meta-analysis in which they combined the data from several small observational series and their institutional series, including 234 untreated localised small renal masses with a mean follow-up of 34 months [5–15]. This analysis revealed first of all that the majority of the lesions with a mean size of 2.60 cm have a slow growth rate (mean rate 0.28 cm per year) and rarely metastasise and this in only 1% of cases while under active monitoring. Secondly, the initial tumour size did not predict the overall growth rate ($P = .46$). An absolute safe cut-off for surveillance may therefore not exist since the metastatic potential of observed tumours cannot be predicted. Only 46% of the patients had pathological evaluation however and the pathologically analysis was incomplete in many cases.

3. NATURE OF SMALL RENAL MASSES IN RELATION TO TUMOUR SIZE

3.1. Benign lesions

A significant number of renal masses are actually benign tumours. It remains difficult to differentiate oncocytomas, for instance, from renal cell carcinomas (RCCs) and this even with the most advanced cross-sectional imaging techniques. In a literature review by Chawla et al. [16] including 76 tumours (12% oncocytomas, 88% RCCs), there was no statistical difference in mean initial tumour size (2 versus 2.2 cm) or mean growth rate (0.16 versus 0.35 cm per year) comparing oncocytomas versus RCCs, respectively [16, 17]. Radiographic data alone are yet still unable to predict the exact natural history of small renal masses. A retrospective study by Remzi et al. [19] reported that 81.9% of all small renal masses were RCC and only 17% were correctly defined as benign on preoperative CT.

Although up to 90% of the solid renal masses are RCCs, elderly patients with small renal masses are up to 3.5 times more likely to have benign lesions than RCCs [18]. Recent data suggest that smaller lesions may have an even greater chance of being benign than previously recognised [20–22]. As the tumour size increases, there is a significantly greater probability that the tumour is malignant versus benign, clear cell versus papillary RCC, and high-grade versus low-grade RCC. These results provide a pathological basis for the use of surveillance strategies in the treatment of small renal masses in poor surgical candidates. In the EORTC 30904 study by Van Poppel et al. [21], 11.6% of the 541 surgically removed tumours (≤5 cm) were benign. In another study by Gill et al. [22], 30% of the 100 tumours treated with laparoscopic partial nephrectomy were benign. The tumours had a mean diameter of 2.8 cm.

Schlomer et al. [23] examined the relationship between tumour size and pathological findings in 349 renal masses (Table 1). The percent of malignant tumours increased from 72.1% for those <2 cm in diameter to 93.7% for those >7 cm (odds ratio = 1.39; 95% confidence interval, 1.17–1.65). Lesions ≤4 cm and >7 cm were associated with high-Fuhrman grade (G3/G4) in fewer than 28% and in greater than 63% of the cases, respectively (chi-square test $P < .001$). Small renal tumours are more likely to be benign or to be of lower grade than larger tumours.

It seems to be that small renal masses might be benign and that larger renal masses are RCC. Tumour size alone however does not provide adequate information for deciding on the optimal treatment. Preoperative evaluation should be more refined.

3.2. Small renal tumours: how benign are they?

Remzi et al. [24] reviewed data of 287 small renal masses (≤4 cm) detected by CT and treated surgically with pathological analysis. They found no correlation between tumour size and benign histology. In this analysis, tumours were stratified according to preoperative diameter into three or two groups (Table 2). What they found is that Fuhrman

Table 1: Tumour size versus histology [23].

Tumour size (cm)	No. of benign tumours (%)	No. of RCC (%)
0.0–0.9 ($n = 7$)	1 (14.3)	6 (85.7)
1.0–1.9 ($n = 54$)	16 (29.6)	38 (70.4)
2.0–2.9 ($n = 83$)	19 (22.9)	63 (75.9)
3.0–3.9 ($n = 63$)	11 (17.5)	52 (82.5)
4.0–4.9 ($n = 32$)	3 (9.4)	28 (87.5)
5.0–5.9 ($n = 29$)	2 (6.9)	26 (89.7)
6.0–6.9 ($n = 18$)	0 (0.0)	18 (100.0)
7.0 or greater	4 (6.3)	58 (92.1)
Totals	56 (16.0)	289 (82.8)

grades G3 and G4, higher pathological stage (pT3a or greater), and metastatic disease were seen significantly more frequently in tumours >3 cm in diameter. This difference was however not observed when masses ≤2 cm in diameter were compared with those measuring 2.1–3.0 cm. Taking into account that measuring tumour diameters is difficult and is based on the reliably of sequential imaging, one may speculate that surveillance strategies should be limited to patients with tumours below the diameter of 3 cm.

To analyse which malignant potential small renal masses might have, Gill et al. analyzed their own series. They included tumours with a mean diameter of 2.8 cm. Even though it was assumed that the risk of malignancy was less in smaller tumours, their findings showed that the majority of these tumours were malignant with growth potential [16, 18].

Also, Hsu et al. [25] showed that 38% of the 50 resected RCCs of <3 cm had extracapsular extension (pT3 or pT4) and 28% were Fuhrman grade G3/G4.

Minardi et al. [26] considered 48 patients with pT1a clear cell RCC. Of the patients treated with nephron-sparing surgery, 3.9% died of metastatic renal cancer at a median follow-up of 2 years, with one patient having Fuhrman grade 2 (G2), one having G3 and two having G4 RCCs.

These findings support resection of even small lesions and support that recurrence and death are possible in patients with small renal tumours even with low-grade RCC. Active monitoring in these patients would have been unsafe.

We can conclude that not all small renal tumours are harmless and that even very small lesions may progress to metastatic disease.

4. GROWTH RATE

4.1. Can the initial tumour size predict its subsequent growth rate?

As stated above, one could not identify a significant correlation between initial tumour size and growth rate in an analysis of 157 tumours from 5 observational series [5, 7–9, 13, 16] ($P = .46$). Therefore, the initial tumour size cannot predict the subsequent growth rate.

4.2. Growth or no growth: what can it predict?

When growth of (small) renal masses is apparent, it becomes more likely that these lesions need treatment because malignant behaviour is suspected. A recent meta-analysis could confirm this. The mean growth rate of pathologically confirmed RCC (92%) was significantly greater than for tumours continued under surveillance (0.40 ± 0.36 versus 0.21 ± 0.40 cm per year, $P = .0001$). Also Kouba et al. [1] showed a higher growth rate in patients undergoing eventual intervention than for tumours continued under surveillance (0.90 versus 0.61 cm per year, resp.; $P = .1486$).

It remains however difficult to predict biological behaviour of small renal masses, even if they do not show growth. We cannot conclude that small renal masses that do not show growth during surveillance are less likely to be cancerous.

Kunkle et al. [17] observed 106 renal masses for at least 1 year and compared clinical, radiographic, and pathological characteristics of the lesions with zero or negative radiographic growth (33%) versus those with positive growth (67%) (median, 0.31 cm per year). Rates of malignancy were similar in both groups (83% and 89%, resp.; $P = .56$). The results suggest that a lack of radiographic growth is not associated with malignant potential or pathological findings.

In other observation series, Kouba et al. [1]. observed a significant difference in growth rates between grades 2 and 3 but not between grades 1 and 2 tumours. Growth rate did not correlate with prognosis [16, 17]. In conclusion, the majority of small renal masses grow and the majority are cancer. One cannot safely assume that a lack of growth on serial CT scanning confirms the absence of malignancy. No clinical or radiological predictors of growth rate are yet identified [17].

4.3. What about age and growth rate?

A meta-analysis of published observation series [5, 6, 11–13, 16] demonstrated an inverse correlation between increasing age and tumour growth rate. Also in the observation study by Kouba et al. [1], patients ≤60 years ($n = 15$) had more rapid growth rate of renal masses compared with those >60 years ($n = 31$) (0.90 versus 0.60, $P = .0570$). Because younger patients have longer life expectancies and most likely fewer comorbidities, these results provide greater support to propose surgery in young patients with renal masses [1].

5. PROGRESSION TO METASTATIC DISEASE

There are no published reports of metastasis occurring in the absence of tumour growth. While all observed lesions do have the potential to metastasise, the risk to do so appears low in the absence of growth. Yet follow-up is however short and we have to take into account the retrospective nature of these studies.

6. ROLE OF BIOPSY

The value of tumour biopsies remains controversial. Some histologically proven RCCs may demonstrate nonaggressive

Table 2: Tumour diameter and aggressiveness [24].

65 tumours: ≤2 cm	103 tumours: 2.1–3.0 cm	119 tumours: 3.1–4.0 cm
73.8% RCC	78.6% RCC	82.4% RCC
24.6% benign	20.4% benign	16.0% benign
168 tumours: ≤3 cm		119 tumours: 3.1–4.0 cm
10.9% pT3a or greater		35.7% pT3a or greater
4.7% G3-G4		25.5% G3-G4
2.4% M+		8.4% M+

behaviour, negative biopsy would not rule out RCC, and a positive biopsy may significantly understage or undergrade the lesion [16, 27, 28]. Preoperative needle biopsies remain inaccurate in 18 to 23% of patients [29, 30]. However, a recent retrospective study of Vasudevan et al. [31] revealed however that a higher than previously anticipated proportion of incidentally detected small renal masses are benign. Given the high sensitivity and specificity of biopsies in their hands, they proposed that there is value in taking a core biopsy of small incidental renal lesions. The investigators concluded that biopsy could avoid unnecessary surgery in one third of the incidental renal masses. When using contemporary biopsy techniques, the risk of tumour seeding or hemorrhage is extremely low [32].

Although the accuracy of fine-needle percutaneous biopsy with CT guidance of small renal masses (<4 cm) evaluated in 88 patients was high for histopathological tumour type (92%), biopsy was less accurate in evaluating Fuhrman grade (70%) [33]. Many benign tumours may be diagnosed with the help of biopsy findings, but more data are still needed to understand the overall accuracy of biopsy for the diagnosis of benign tumours [34].

We currently do not have any reliable molecular marker for separating indolent from aggressive tumours [35]. However a recent pilot study [36] demonstrated that the detection of the MN/CA9 gene can reliably be detected in fine-needle aspiration biopsy and that this gene marker can be helpful in separating malignant from benign renal tumours. It remains to be confirmed that other molecules such as carbonic anhydrase IX and vascular endothelial growth factor could potentially be used in conjunction with usual prognostic parameters for refining prognosis in small renal masses.

7. ACTIVE TREATMENT OPTIONS

In the majority of the patients, nephron-sparing surgery remains the gold standard treatment because it is a safe and effective procedure and because even very small lesions may progress to metastatic disease.

For frail patients who are not fit for open or laparoscopic nephron-sparing surgery, treatment option by minimally invasive techniques, such as radiofrequency ablation and cryoablation under ultrasound or CT guidance, might be a middle way between aggressive treatment and expect monitoring. These newer minimally invasive therapies have become available for the treatment of small renal masses. In patients who have medical comorbidities or a limited life expectancy, radio frequency ablation and cryoablation provides reasonable long-term oncological control and it may have a role in the management of small renal masses [37]. Meticulous long-term follow-up is however required in patients receiving radio frequency ablation.

Cryoablation is less well investigated. Schwart et al. [38] published is Urology in 2006 a retrospective analysis of cryoablation of small peripheral renal masses. They concluded that renal cryotherapy is a viable option for nephron-sparing surgery in small, peripheral renal lesions. The procedure has well-tolerated results, may be considered in patients who are not good candidates for open surgical approaches, in minimal morbidity, and has shown encouraging treatment results. Close post treatment surveillance is essential. Meticulous long-term follow-up is however required before these new ablative treatments can be considered a valuable alternative to surgical extirpation.

Furthermore, whether these treatments provide a benefit over surveillance strategies in older, poor surgical candidates with limited life expectancy needs to be addressed in prospective, randomised, clinical trials.

8. CONCLUSIONS

Approximately 26–33% of observed small renal masses do not show radiographic growth. Therefore, it has been suggested that a short period of active monitoring may be feasible for a very selected patients group.

It has been proposed to delay treatment in these patients when the tumour does not show growth. However, even though tumour growth might be absent or slow, a proportion of these tumours will express significant malignant behaviour, since the natural history and biological potential of small renal masses can still not be unambiguously predicted at present. We therefore believe that the indications for active surveillance with regular radiographic follow-up are limited to elderly and/or infirm patients with competing health risks, to those with limited life expectancy and to poor surgical candidates.

In all other patients, active surveillance can be considered in the context of a study protocol only. It is noteworthy that, because of the increase in life expectancy even in a 70-year-old otherwise healthy patient, some sort of active treatment of small renal masses should be preferred over surveillance [32]. Nephron-sparing surgery remains the gold standard treatment of (small) renal masses. However, minimally invasive techniques like radiofrequency ablation

and cryoablation have emerged. While there is still a need for prospective, randomised, clinical trials with sufficient follow-up, these procedures are considered suitable for patients who have limited life expectancy or are high-risk-surgicalcandidates. These treatment strategies provide reasonable short- and intermediate-term oncological control, however long-term results are unavailable so far.

When facing patients with small bilateral or multiple renal tumours, treatment strategies will not significantly differ compared to patients with small single lesions, since the indications for active surveillance remain limited to elderly and/or infirm patients with competing health risks and those with limited life expectancy.

The value of tumour biopsies remains controversial. Preoperative needle biopsy remains inaccurate in 18 to 23% of patients. Molecular or biochemical markers as well as better imaging techniques are required to select individuals at the highest risk for tumour progression.

To date, there is no a nonstandardised follow-up protocol for surveillance. There is the patients' fear of harbouring a tumour with an uncertain malignant potential. Surveillance requires a high degree of individual compliance by the patient. Even in compliant patients there is a risk that the onset of progression will be missed. When small renal masses have progressed to metastatic disease, there are no effective systemic therapies available. The safety of longer-term surveillance is still questionable. On the basis of current literature, we have no data on the risk and cost of patients on active surveillance.

Finally, the treatment modality of active monitoring should always be combined with close follow-up imaging and should be allowed only when the patient and the urologist accept the calculated risk. Long-term, prospective studies are needed to provide a more accurate assessment of the natural history and metastatic potential of small renal masses in the long term. Until long-term follow-up results including outcome, risk, and cost of patients managed expectantly are available, no definitive guidelines can be established for the surveillance of small renal masses.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 309760, 7 pages
doi:10.1155/2008/309760

Review Article

Open Partial Nephrectomy in the Management of Small Renal Masses

Ziya Kirkali[1] and A. Erdem Canda[2]

[1] *Department of Urology, Faculty of Medicine, Dokuz Eylul University, 35340 Izmir, Turkey*
[2] *1st Urology Clinic, Ankara Ataturk Training and Research Hospital, 06520 Ankara, Turkey*

Correspondence should be addressed to Ziya Kirkali, ziya.kirkali@deu.edu.tr

Received 14 February 2008; Accepted 23 April 2008

Recommended by J. Rubio

Introduction. Most of the kidney masses are being detected incidentally with smaller size due to widespread use of imaging modalities leading to increased RCC incidence worldwide with an earlier stage. This article reviews the role of open partial nephrectomy (PN) in the management of small renal masses. *Material and Methods*. Review of the English literature using MEDLINE has been performed between 1963–2008 on small renal masses, partial nephrectomy, kidney cancer, nephron sparing surgery (NSS), radical nephrectomy, laparoscopy, and surgical management. Special emphasis was given on the indications of NSS, oncological outcomes and comparison with open and laparoscopic PN. *Results*. Overall 68 articles including 31 review papers, 35 human clinical papers, 1 book chapter, and 1 animal research study were selected for the purpose of this article and were reviewed by the authors. *Conclusions*. Currently, open NSS still remains as the gold standard surgical treatment modality in patients with small renal masses.

1. INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of adult solid tumors; and the highest incidence of RCC is detected between 50–70 years of age [1, 2]. Almost 20,000 renal cancer patients are estimated to be detected yearly in the European Union [3]. In the pathogenesis of conventional RCC, mutations leading to inactivation of the von Hippel Lindau (VHL) tumor suppressor gene have been detected in the hereditary and up to 80% of sporadic forms of clear cell RCC. Premalignant lesions in the kidney such as renal intraepithelial neoplasia have been described, which seems to be sharing similar genetical changes with RCC [4, 5]. Independent predictors of survival in patients with RCC are limited. Tumor stage, grade, and patient-performance status are the known prognostic indicators [6].

Currently, most of the kidney masses are being detected incidentally up to 40% with smaller size due to widespread use of imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). This leads to increased RCC incidence worldwide [7] with an earlier stage which can be cured by surgery [8].

This paper reviews the role of open partial nephrectomy (PN) in the management of small renal masses particularly focusing on indications, oncological outcomes and comparison with laparoscopic PN.

2. MATERIALS AND METHODS

Review of the English literature using MEDLINE has been performed between 1963–2008 on small renal masses, partial nephrectomy, kidney cancer, nephron sparing surgery, radical nephrectomy, indications, outcomes, surgical management, and laparoscopy.

Overall 68 articles including 31 review papers, 35 human clinical papers, 1-book chapter, and 1 animal research study were selected for the purpose of this article and were reviewed by the authors.

3. RESULTS AND DISCUSSION

Small renal masses are considered as tumors less than 4 cm in size in the kidney although there is not an established consensus concerning a clear cut-off value for the definition

of a "small renal mass." However, although 4 cm is commonly considered as the size limit for nephron sparing surgery (NSS) in kidney tumors, when technically feasible, partial nephrectomy (PN) should be performed irrespective of tumor size [9].

3.1. Radical nephrectomy versus partial nephrectomy

Radical nephrectomy (RN) was first described by Robson in 1963; it has been the standard for the surgical treatment of kidney cancer [10]. Traditionally, RN can be regarded as the optimal technique with long-term cancer control in kidney cancer [11]. Five-year cancer specific survival for patients with organ-confined disease is over 90% after surgery alone. Since 15–25% of incidentally detected tumours are benign, removing the whole kidney for a small benign lesion is not logical [12]. Current indications of open RN can be summarized as large tumor size which is not suitable for NSS or for laparoscopy, locally advanced diseases, existence of complicated tumor thrombus with vena cava extension, and presence of other concomitant diseases such as renal artery stenosis or single-organ metastases necessitating open surgery [13]. Due to improved technology regarding radiologic imaging modalities and their frequent use, currently most of the kidney tumors are detected incidentally with smaller tumor size and are associated with less lymph node and adrenal gland involvement [14]. Therefore, there is a tendency to perform NSS rather than RN in suitable kidney tumors particularly with recent improvements in surgical techniques.

PN was first performed by Czerny in 1887 [15] and Vermooten described indications of conservative surgery in kidney tumors in 1950 [16]. The goal of NSS is to preserve as much normal renal parenchyma as possible and meticulous cancer control with negative surgical margins and no local recurrence in the follow-up [17]. Multiple studies in the last decade have established the safety and efficacy of PN for selected cases with small renal tumors [11, 18, 19]. Such considerations have led to expanding the indications of PN to include centrally located tumors and larger tumors up to 7 cm [18, 19].

3.2. Indications of open partial nephrectomy

The TNM 1997 classification considers tumor size of 4 cm as cut-off value in order to classify stage T1 tumors as T1a ($\leq$4 cm) and T1b (4–7 cm) [20]. Excellent outcomes regarding tumors less than 4 cm in size treated with NSS have an important impact in this staging. Current indications for open PN are summarized on Table 1. In elective setting when contralateral kidney is normal, NSS should be attempted whenever feasible irrespective of the status of the contralateral kidney.

Table 1: Open partial nephrectomy indications (table adapted from 12).

I. Absolute Indications
a. Tumors in a solitary kidney
b. Bilateral synchronous renal masses
c. Severe renal insufficiency
II. Relative Indications
a. Presence of pre-existing renal disease in the contralateral kidney
1. Nephrolithiasis
2. Recurrent pyelonephritis
3. Mild-moderate renal insufficiency
4. Ureteropelvic junction obstruction
5. Vesicoureteral reflux
b. Presence of diseases predisposing to renal insufficiency
1. Diabetes
2. Hypertension
c. Patients with known multifocal disease or underlying genetic syndromes
1. Papillary RCC
2. Von Hippel-Lindau disease

3.3. Surgical technique and complications

We prefer a flank incision and a lumbar extraperitoneal approach. Kidney is mobilized completely and explored for satellite lesions. If necessary, intraoperative ultrasound can be used. Renal vessels are controlled by using vascular clamps, vascular tape, or by the surgeon's fingers. In difficult cases the artery and the vein are clamped, and ice slush should be applied in order to cool down the kidney. Scalpel, laser, ultrasonic aspirator, water jet, cautery, blunt dissection, or combinations of these can be used to cut the renal parenchyma in order to remove the tumor with surrounding few millimeters of healthy parenchyma and together with the covering perirenal fat. In case of any suspicion in terms of surgical margins, further resection can be performed. Frozen section examination of the tumor bed is usually not helpful. Bleeders are coagulated or sutured and collecting system is closed by absorbable sutures in a water-tight manner if it has been opened. Peroperative hydration and diuresis by mannitol infusion are very helpful. Absorbable sutures for approximation of the renal parenchyma in a "suture of eight" or "Z" sutures fashion are useful. Perirenal fat or omentum can be used in order to close the defect. A drain is placed in the retroperitoneum and wound is closed. Because tumor cells might remain in the residual kidney after resection, enucleation is usually discouraged (Figure 1) [21].

Renal failure, post operative hemorrhage, urine leak, and urinary fistula are the most frequently seen complications after open NSS [21, 22]. Recently, Van Poppel et al. compared the complications of elective open NSS surgery and RN for low-stage, incidentally detected, solitary, small ($\leq$5 cm) RCCs in a prospective study in the presence of a normal contralateral kidney (Table 2). They concluded that NSS can be performed safely in this patient group with slightly higher complication rates than after RN [23].

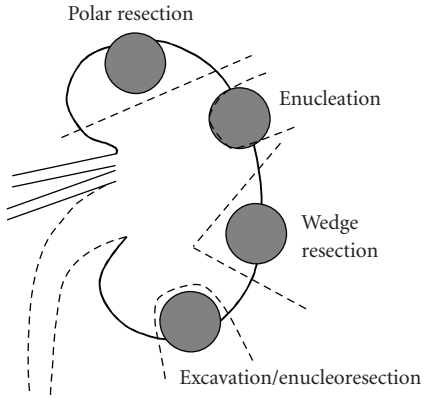

Figure 1: Techniques used in open NSS. NSS: Nephron sparing surgery.

Table 2: Complications of open NSS and RN [23].

	NSS (%), ($n = 268$)	RN (%), ($n = 273$)
Rate of severe haemorrhage	3.1	1.2
Pleural damage	11.5	9.3
Spleen damage	0.4	0.4
Postoperative CT abnormalities	5.8	2.0
Urinary fistula development	4.4	—
Reoperation for complications	4.4	2.4

Perioperative blood loss was slightly higher after RN ($P > .05$).
NSS: Nephron sparing surgery, RN: Radical nephrectomy, CT: Computed tomography.

3.4. Outcomes of open partial nephrectomy

Similar cancer-specific survival rates and oncologic outcomes have been detected in patients with small (<4 cm) renal masses who underwent RN or NSS. Therefore, currently NSS is considered as the treatment of choice in these patients (T1a tumors) [9, 24–29] (Table 3).

Ten-year oncological and functional follow-up data revealed almost 100% survival, especially in patients with renal tumors less than 4 cm in size [34–38] with PN. Therefore, open NSS is currently accepted as the gold standard treatment modality for patients with small, exophytic, easily resectable renal masses [19, 34]. In a series of 435 patients who underwent NSS for a tumor size between 2.6–4.0 cm, local recurrence was detected in 3 patients (0.7%) with a mean follow-up of 31–76 months, which is ten times lower than the rate for NSS performed for an absolute indication [39]. Local recurrence has been reported to be between 0–12% in NSS which is related with multifocal disease or insufficient resection of the tumor [40]. Local recurrence is expected to be more frequent locally advanced disease [41].

Presence of preneoplastic lesions such as renal intraepithelial neoplasia in the residual kidney might be a factor for the occurrence of local recurrence [4]. However, recurrence due to insufficient resection could be prevented by proper surgical technique [42]. Multifocal tumors can be detected both in large- and small-sized tumors [4]. Although there is a possibility of presence of multifocality and premalignant lesions, local recurrence rate is quite low in well selected cases after NSS [43].

3.5. Preoperative kidney biopsy

It has been demonstrated that almost a quarter of all small renal masses (<4 cm) are benign lesions like angiomyolipoma, oncocytoma, or metanephric adenoma. Preoperative diagnosis of these lesions is difficult despite latest advances in imaging techniques [27, 40, 44, 45]. Therefore, performing RN would be unnecessary for these benign lesions. One may possibly think of diagnosing these lesions preoperatively by kidney biopsy. Currently, the role of renal biopsy in diagnosing these lesions is controversial. Although preoperative fine needle aspiration biopsy can be performed for diagnosis, its sensitivity is low, has complication risks such as bleeding and tumor seeding, might give false positive and false negative results, and finally it needs an experienced cytopathologist particularly subspecialized in kidney and RCC [17, 46]. We suggest kidney biopsy particularly in those patients where renal lymphoma or metastatic involvement of the kidney is suspected [47].

3.6. Optimal margins in open NSS and significance of performing tumor bed biopsies

For tumors smaller than 4 cm, the local/ipsilateral renal recurrence rate has been reported to range between 1.5 and 4% in open NSS series [34, 36]. In the past, a 1 cm normal parenchyma was suggested as a safety margin in NSS but controversy exists concerning the optimal margin width [48]. Intraoperative biopsy and frozen-section examination of the tumor bed is suggested in order to rule out residual tumor in the kidney [49]. However, false-positive and false-negative results can be obtained due to freezing artifacts and difficulty in distinguishing cancer cells from normal cells [50] which might also lead to unnecessary resections or even RN [51]. It has been shown that more than 30% of small renal tumors (≤4 cm) did not have an intact pseudocapsule; and cancer cells might be detected beyond the pseudocapsule reaching up to 0–5 mm [52] therefore, an amount of normal kidney tissue surrounding the tumor is suggested to be included with PN in order to prevent incomplete resection [53]. This amount has been recommended to be at least 5 mm in NSS by some authors [52], whereas others suggest a normal tissue safety margin of ≥1 mm to be removed [54]. In conclusion, the margin status rather than size seems to be important in NSS and 1 mm of normal parenchyma around the tumor seems to be enough.

It is known that RCC has a 1–5% recurrence rate in the contralateral kidney particularly in surgical margin positive patients and patients with multifocal tumors which support NSS in this patient group [55, 56]. Several authors suggest intraoperative use of ultrasonography to rule out multifocal disease, and to clearly define tumor extent [57, 58]. Coagulation of the tumor bed in addition to biopsies is recommended when tumor enucleation is performed [59].

Table 3: Selected published series including patients who underwent open NSS or RN for renal masses due to their tumor size (table modified from [14]).

Author	Reference	Year	*N*	Local recurrence (%)	5-year dfs (mos)
Tumor size <4 cm in size*					
Hafez et al.	[26]	1999	310	0.6	96
Lee et al.	[27]	2000	79	0	100
McKiernan et al.	[24]	2002	117	1.2	100
Patard et al.	[18]	2004	314	0.8	98
Tumor size >4 cm in size**					
Hafez et al.	[26]	1999	175	0.8	86
Patard et al.	[18]	2004	65	3.6	94
Leibovich et al.	[28]	2004	91	5.4	98
Becker et al.	[29]	2006	69	5.8	100

Selected series comparing outcomes of patients underwent NSS or RN for renal masses*								
			RN	NSS	RN	NSS	RN	NSS
Patard et al.	[18]	2004	1075	379	99	99	97	98
Lee et al.	[27]	2000	183	79	100	100	96	96
Leibovich et al.	[28]	2004	841	91	98	95	86	98
McKiernan et al.	[24]	2002	173	117	99	96	100	100

* Median follow-up is >25 months for all studies.
** Median follow-up is >47 months for all studies.
N: Number of patients, dfs: disease-free survival, FU: Follow-up, mos: months.

Table 4: Comparison of laparoscopic versus open PN in patients with a solitary renal tumor of 7 cm or less in size (table modified from [30]).

		Laparoscopic PN ($n = 100$)	Open PN ($n = 100$)	*P*
Complications:	Major intraoperative	5%	0%	.02
	Renal/urological	11%	2%	.01
Median surgical time (hours)		3	3.9	<.001
Blood loss (mL)		125	250	<.001
Mean warm ischemia time (minutes)		27.8	7.5	<.001
Median analgesic requirement (morphine sulfate equivalents, mg)		20.2	252.5	<.001
Hospital stay (days)		2	5	<.001
Average convalescence (weeks)		4	6	<.001
Median preoperative serum creatinine (mg/dL)		1.0	1.0	.52
Median postoperative serum creatinine (mg/dL)		1.1	1.2	.65

PN: Partial nephrectomy.

3.7. Open versus laparoscopic partial nephrectomy

In the recent years, laparoscopy has gained popularity and emerged as an alternative to open PN in the treatment of renal masses [58]. Technical advances have enabled laparoscopists to duplicate the techniques used during open PN, including vascular control, hemostasis, and repair of the pelvicalyceal system [58, 60]. Promising postoperative and intermediate-term oncological outcomes have been reported with laparoscopic partial nephrectomy (LPN) [57, 61, 62].

Recently, Lane BR and Gill IS reported their 5-year outcomes in LPN including 58 patients which are comparable to those of open NSS. At a median follow-up of 5.7 years, no distant recurrence and a single local recurrence (2.7%) were detected. Overall and cancer-specific survival was 86% and 100%, respectively, at 5 years [62]. Moinzadeh et al. also reported oncological results in 100 patients with a minimum follow-up of 3 years. Overall survival was 86%, and a cancer-specific survival was 100% [61].

Although LPN seems to be a promising and attractive surgical approach in the management of renal masses, there are still some problems for LPN. Bleeding and hemostasis, prolonged warm ischemia, longer operative time, increased

Table 5: Comparison of selected published series related with LPN. Min: Minutes.

Authors	Crepel et al.	Häcker et al.	Haber et al.
Reference	[31]	[32]	[33]
Center	Mutlicenter study France	Elisabethinen hospital Austria	Cleveland clinic Ohio, USA
Year	2007	2007	2006
Number of patients	91	25	>500
Tumor size (cm)	2.7	2.6	2.9
Route	Transperitoneal retroperitoneal	Transperitoneal	Transperitoneal retroperitoneal
Warm ischemia time (min)	35	29	32
Mean operating time	163 min	212 min	Transperitoneal: 3.5 h Retroperitoneal: 2.9 h
Complication rate (%)	17.6	8	36 and 16
Mean blood loss (mL)	363	177.4	150 versus 100 and 231
Transfusion rate (%)	6.6	4	Not reported
Hospital stay (days)	9.1	8.3	Transperitoneal: 2.9 Retroperitoneal: 2.2

LPN: Laparoscopic partial nephrectomy.

intraoperative and renal/urological major complication rates are considered as current problems associated with LPN. Hemostasis and ischemia time is the most challenging steps in LPN [60]. Bleeding during LPN is an important problem for the surgeon although improved surgical techniques and skills together with the use of new hemostatic sealants such as fibrin glue-coated collagen patch which contains purely human coagulation factor components can be helpful in order to overcome this problem [63–65].

There are several studies investigating the impact of the warm ischemia time on renal functions and as a widely accepted guideline for clinical practice, warm renal ischemia period exceeding 30 minutes is not recommended [66]. Furthermore, it is technically very demanding and time consuming to produce cold ischemia during laparoscopic surgery [66]. Preservation of maximum functional kidney tissue is one of the goals in PN, however, longer warm ischemia times have been reported with LPN [33] compared to open NSS [30, 37].

The operating time seems to be decreased for LPN in the most experienced centers [30] however the learning curve is not short and technical feasibility of an operation does not always necessarily mean that it can be performed in common practice. This is still a major issue when health care costs to society are concerned [12].

Significantly increased major complication rates have been reported with LPN compared to open NSS by experienced authors [30, 37, 67]. However, for peripherally located, small, and exophytic renal masses, we expect these complications to be lower.

The risk of tumor spillage is also a theoretical problem in LPN [60]. However, tumor spillage has been reported at port sites in patients undergoing laparoscopic nephrectomy and nephroureterectomy due to tumor [68].

Decreased analgesic requirement, decreased hospital stay, shortened convalescence, and improved cosmetics are considered as the main advantages of LPN. The length of stay for patients undergoing LPN in large series from Europe [31, 32] is ranging from 6 to 9 days whereas the average length of stay in the United States is between 2 and 4 days [30, 33]. Gill et al. reported their results comparing open versus laparoscopic PN (Table 4) [30]. Characteristics of some selected series of LPN are summarized on Table 5 [31–33].

The follow-up after LPN is shorter compared to open NSS concerning oncologic outcomes. LPN has a long learning curve and requires high-level laparoscopic skills and experience. Long-term data indicate that NSS is safe and oncologically effective in small renal masses <4 cm in size. Until the problems with LPN are overcome, high complication rates are lowered and longer oncological follow-up data are available, open NSS will be the standard treatment for the surgical management of kidney tumors [12].

4. CONCLUSIONS

Due to widespread use of radiologic imaging modalities, most of the kidney tumors are being detected incidentally with smaller size and earlier stage. Similar oncologic outcomes have been detected in patients with small (<4 cm) renal masses who underwent RN or NSS. Currently, NSS is considered as the treatment of choice in patients with kidney tumors when technically feasible irrespective of tumor size. In last few years laparoscopy has gained popularity and emerged as an alternative to open PN particularly in the surgical management of small renal masses. However, complication rates are higher and oncological follow-up data is shorter compared to open PN therefore, NSS still remains as the gold standard surgical treatment modality in patients with small renal masses.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 916463, 9 pages
doi:10.1155/2008/916463

Review Article

Open Partial Nephrectomy in Renal Cancer: A Feasible Gold Standard Technique in All Hospitals

J. M. Cozar and M. Tallada

Department of Urology, Virgen de las Nieves University Hospital, Granada, Spain

Correspondence should be addressed to J. M. Cozar, cozarjm@yahoo.es

Received 25 March 2008; Accepted 31 May 2008

Recommended by J. Rubio

Introduction. Partial nephrectomy (PN) is playing an increasingly important role in localized renal cell carcinoma (RCC) as a true alternative to radical nephrectomy. With the greater experience and expertise of surgical teams, it has become an alternative to radical nephrectomy in young patients when the tumor diameter is 4 cm or less in almost all hospitals since cancer-specific survival outcomes are similar to those obtained with radical nephrectomy. *Materials and Methods*. The authors comment on their own experience and review the literature, reporting current indications and outcomes including complications. The surgical technique of open partial nephrectomy is outlined. *Conclusions*. Nowadays, open PN is the gold standard technique to treat small renal masses, and all nonablative techniques must pass the test of time to be compared to PN. It is not ethical for patients to undergo radical surgery just because the urologists involved do not have adequate experience with PN. Patients should be involved in the final treatment decision and, when appropriate, referred to specialized centers with experience in open or laparoscopic partial nephrectomies.

1. INTRODUCTION

In recent years, the surgical treatment of renal cell carcinoma (RCC) has developed towards conservative surgery of the renal parenchyma and the use of minimally invasive techniques. The emerging conservative technique is open partial nephrectomy (PN), which is no longer an option reserved for patients with a single kidney or bilateral renal tumors; it has become a viable alternative to radical nephrectomy, and is considered the treatment of choice for selected patients with a normal contralateral kidney [1, 2].

The more frequent use of PN in renal cancer treatment derives from a spectacular rise in the incidental diagnosis of renal tumors in patients undergoing abdominal ultrasound or computed tomography (CT) for abdominal diseases. This has markedly increased the detection of smaller, asymptomatic tumors than those observed when Robson proposed radical nephrectomy as the technique of choice more than three decades ago [3]. Incidental tumors have a more favorable prognosis than clinically detected or symptomatic tumors of a similar size and stage [4, 5]. The better health and longer life span of the general population and the availability of radiological imaging techniques for closer screening and follow-up programs are creating a favorable environment for the development of conservative renal surgery. When PN is indicated, the decision to adopt an open or laparoscopic (minimally invasive) approach depends on the benefits and risks to the patient and the experience of the surgical team.

This article is devoted to open PN, providing an update on the indications, disease-free and disease-specific survival outcomes, benefits and risks, limitations and technical aspects of the surgery, intra- and postoperative complications, and post-treatment follow-up protocols. The aim is to describe the main concepts to be considered in the decision-taking algorithm for an open PN in the treatment of RCC [6, 7].

2. INDICATIONS FOR PARTIAL NEPHRECTOMY

Indications can be classified as absolute, relative, or elective (Algorithm 1), always basing the selection on the viability of the technique and an optimal cancer control [8].

2.1. Absolute indications

Absolute indications relate to patientswho would be anatomically or functionally anephric if radical nephrectomy was

(1) Absolute
- (i) Single kidney
- (ii) Bilateral renal tumor
- (iii) Severe renal failure

(2) Relative
- (i) Abnormal contralateral kidney (nephropathy, nephrolithiasis, trauma, etc.)
- (ii) Metabolic disease associated with renal failure
- (iii) Genetic syndrome with tumor multifocality (e.g., VHL syndrome)

(3) Elective
- (i) Tumor <4 cm in young and healthy patients
- (ii) Peripheral tumor
- (iii) Tumor >4 cm (limit at 7 cm?)

Algorithm 1: Indications for partial nephrectomy.

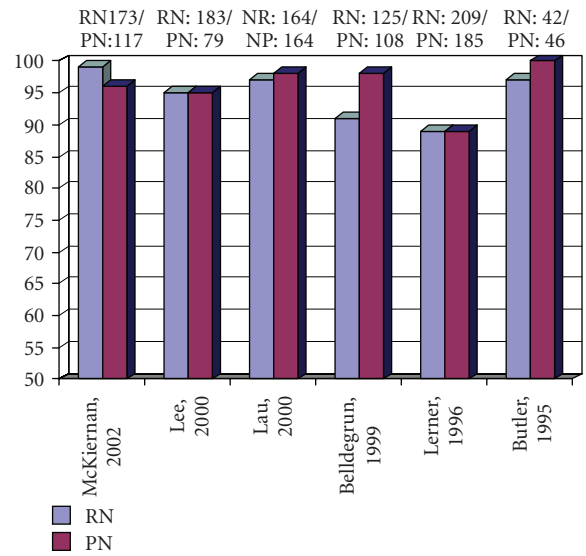

Figure 1: Five-year survival: radical nephrectomy (RN) versus partial nephrectomy (PN).

performed. They include the presence of only one kidney, synchronous bilateral renal cancer, and severe renal failure. It was proposed in the 1950's that these patients undergo conservative tumor excision to preserve maximum renal parenchyma and allow the possibility of renal filtration with no need for dialysis. However, this proposal gained little acceptance among urologists due to the high rate of complications observed after open PN. More recently, there has been a strong resurgence in the use of this technique as an alternative to radical nephrectomy for the above-mentioned types of patients. In the 1990's, various studies reported good survival outcomes and fewer complications with a conservative approach.

2.2. Relative indications

These include conditions that might compromise the future functioning of the contralateral kidney (without tumor), for example, moderate renal failure, nephrolithiasis, recurrent pyelonephritis with parenchymal lesions, vesicoureteral reflux, and congenital or acquired obstruction of the urinary tract, among others. A further relative indication would be the presence of disease with a potentially negative medium-term effect on renal function, for example, diabetes or hypertension. Other factors must be taken into account in these patients, including their current age and age at onset of the disease, estimating the duration of its possible effect on renal function.

2.3. Elective indications

Partial nephrectomy has been proposed for small peripheral renal tumors over the past few years. Being initially controversial, this indication has been supported by wide studies showing similar outcomes to radical surgery in small ($\leq$4 cm) renal tumors (Algorithm 1). The age and general state of the patient are important in the selection of candidates for PN, which is most beneficial for young and healthy patients. Some authors have proposed to widen the indication for a conservative approach to include larger tumors of up to 7 cm. Thus, Fergany et al. at the Cleveland Clinic reported similar five-year disease-free survival rates between patients with tumors <4 cm and those with tumors of 4–7 cm [4].

The greater longevity of the population and the treatment of ever younger patients for incidentally detected tumors have drawn attention to the long-term risks of renal failure or metachronous tumor recurrence posed by PN treatment. Nevertheless, these risks should not outweigh the benefits of this renal parenchyma-preserving surgery.

3. CLINICAL EXPERIENCE: SURVIVAL OUTCOMES

There is now considerable clinical experience in patients with one of the above indications for PN, allowing careful analysis of patient outcomes and evaluation of the prognostic factors that influence results.

Studies of patients with small renal tumors at the Memorial Sloan Kettering Cancer Center of UCLA, Mayo Clinic, and Cleveland Clinic showed no significant differences in five-year survival rates (91–100%) between those treated with open PN and those treated with open radical nephrectomy (Figure 1) [9–14]. Long-term follow-up studies have corroborated these results. Thus, Lau et al. compared between patients treated with open PN (mean tumor size of 3.7 cm) and those treated with radical nephrectomy (mean size of 3.3 cm), and found no significant differences in overall survival, cancer-specific survival, metastasis-free survival, or local recurrence-free survival at 5, 10, or 15 years [11]. These findings validate the oncological efficacy of conservative versus radical renal surgery.

There have been no prospective randomized clinical trials comparing the two techniques. Moreover, global results of the published studies cannot be grouped together because the distribution of indication levels (absolute, relative, or elective) is different in each study population. For this reason,

Table 1: Conservative renal surgery (partial nephrectomy); five-year outcomes in patients with elective indication.

Author, year	N	Disease-specific survival	Local recurrence	Mean tumor size
Morgan, 1990	20	100%	0%	3.1
Selli, 1991	20	90%	0%	3.5
Provet, 1991	19	100%	0%	2.6
Steinbach, 1992	72	94.4%	2.7%	ND
Moll, 1993	98	100%	1%	4
Lerner, 1996	54	92%	5.6%	4
D'Armiento, 1997	19	96%	0%	3.3
Van Poppel, 1998	51	98%	0%	3
Herr, 1999	70	97.5%	1.5%	3
Hafez, 1999	45	100%	0%	4
Barbalias, 1999	41	97.5%	7.3%	3.5
Belldegrun, 1999	63	100%	3.2%	4

outcomes of open PN are reported below in relation to the type of indication.

3.1. Outcomes of partial nephrectomy with absolute indication

In general terms, patient survival rates are lower when the indication for surgery is absolute rather than elective, influenced by the higher age, the more advanced stages, the larger tumor size, and the poorer health status of patients with an absolute indication. Reports from the Cleveland and Mayo Clinics [4, 15] described disease-free survival rates after PN of 81–88% at 5 years and 64–73% at 10 years, being relatively similar to disease-free survival rates described for radical nephrectomy in tumors of the same size and stage. In 2007, Berdjis et al. studied 38 cases of open PN in single kidney carried out between 1993 and 2003 [16]. After a mean follow-up of 41.7 months, they observed local recurrence in four patients (including 3 with distant progression) and metastatic progression in two. Tumor size was significantly larger in patients with metastatic progression versus those without (6.2 cm versus 3.5 cm) and in patients with subsequent renal failure versus those without (5.2 cm versus 3.3 cm).

According to these authors, tumor size is the most significant prognostic factor for disease progression followed by tumor stage (localized versus locally advanced), and larger tumor size is the main prognostic factor for renal failure onset [16].

3.2. Results of partial nephrectomy with elective indication

In the 1990's, numerous reports [5, 10, 11, 17–26] were published on a total of 572 patients with normal contralateral kidney treated by open PN, having tumor sizes ranging from 2 to 4.3 cm (Table 1). A survival rate of 90–100% was achieved in these cases, with a local recurrence rate of 0% in most series [10, 11, 18–20, 22–25, 27], 1% in 2 series [5, 22], 3% in 2 series [12, 21], and 6-7% in 2 series [13, 26]. These outcomes opened up the way for open PN to become an effective alternative to radical nephrectomy although higher rates of intra- and postoperative complications were initially observed.

Published data establish 4 cm as the cut-off tumor size for indication of this surgery, describing a shorter disease-free survival period in patients with larger tumors. Studies report 95% five-year disease-free survival rates in patients with a tumor <4 cm, comparable to the outcomes of radical nephrectomy in tumors of a similar size (Table 1).

3.3. Results of partial nephrectomy in patients with Von Hippel Lindau (VHL) syndrome

The risk of local recurrence is very high in VHL patients because of the multifocal nature of their malignant tumors; consequently their disease-free survival is much lower in comparison to patients with incidental or sporadic renal carcinoma.

Out of nine VHL patients with bilateral renal carcinoma studied by Novick and Campbell, seven had local recurrence and one died from metastatic disease [2]. It is likely that most of these recurrences represented a manifestation of a microscopic residual CCR that was not excised during the NP [2].

Walther et al. [27] reported on 52 VHL patients with renal cancer treated at the National Cancer Institute, finding that no patient with tumors <3 cm developed metastatic disease. They therefore recommend waiting until this type of tumor reaches 3 cm in order to reduce the need for surgery before onset of the multiple recurrences observed during follow-up of these patients.

The effectiveness of PN as a valid alternative for the treatment of this disease was demonstrated by a multicenter study in USA on the results of treating 65 patients with VHL and localized RCC (54 bilateral, 11 unilateral). PN was performed on 49 of these patients, with five-year and ten-year survival rates of 100% and 81%, respectively. These survival outcomes are similar to those obtained with radical nephrectomy, and they support the role of PN in the treatment of this type of patient.

In patients with advanced VHL and large multiple bilateral tumors that require complete excision of both kidneys at first surgery or after various interventions due to the post-PN growth of residual RCCs, renal transplant is

an appropriate option to avoid terminal kidney failure and the need for dialysis, especially in young patients with this genetic syndrome.

4. PROGNOSTIC FACTORS FOR TUMOR RECURRENCE AFTER PARTIAL NEPHRECTOMY

In RCC, prognostic factors for distant recurrence or metastatic progression after radical nephrectomy are known to include the Fuhrman grade, size, and stage, as well as histological type of the tumor, the presence of positive lymph nodes, and ECOG performance status [2, 8]. Some of these factors, described below, are of special interest in selecting candidates for PN.

4.1. *Tumor size >4 cm*

Tumor size was found to be the most significant predictor of the outcome in large series of PN patients [4, 11, 13, 25]. Tumor size independently predicts local recurrence and is the most important criterion for the indication of a PN. The Cleveland Clinic series of 485 PNs, including 9% with elective indications, showed significant differences in five-year and ten-year survival rates between patients with tumors smaller and larger than 4 cm, with a significant correlation between recurrence rate and tumor size. For this reason, Barbalias et al. [25] proposed a subclassification of stage T1 (tumors <7 cm and limited to renal parenchyma) into T1a and T1b for tumor sizes of <4 cm and ≥4 cm, respectively.

Lerner et al. [13] observed a 95% five-year survival rate in PN patients with tumors <3 cm versus an 80% rate in those with tumors >6 cm. They also reported a significantly higher disease-free survival rate in patients with tumors >4 cm after radical versus partial nephrectomy. More recently, various studies [9–14, 23] (Figure 2) demonstrated equivalent cancer control rates between patients with tumors <4 cm and those with tumors of 4–7 cm after electively indicated PN.

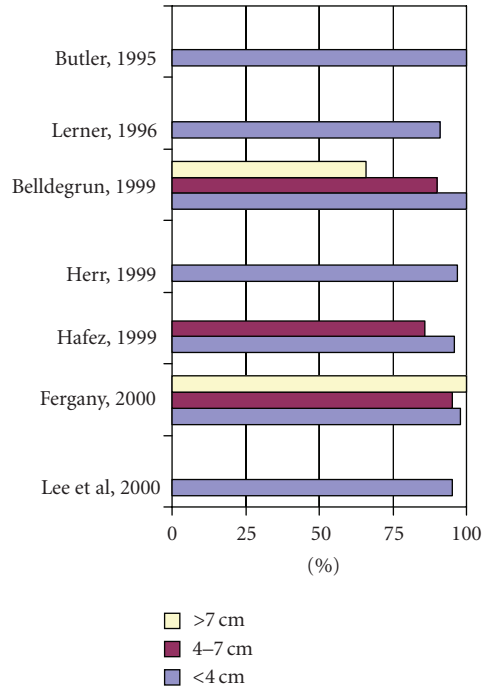

Figure 2: Five-year disease-free survival by tumor size in patients undergoing partial nephrectomy.

4.2. *Localization of tumor*

It was classically thought that centrally localized tumors carried a greater risk of metastasis at the time of disease presentation. It was therefore considered that the risk of recurrence and/or progression would be higher after partial versus radical nephrectomy in central tumors. This idea was challenged by the results of a retrospective study by D'Armiento et al. [23] on tumor localization as an independent risk factor. They found no difference in cancer-free survival or recurrence between peripheral tumors (not extending into the interior of the kidney) and central tumors (infiltrating beyond the renal medulla). These authors concluded that PN is more complex in the case of central tumors, but it is not associated with a worse recurrence or progression prognosis.

4.3. *Multifocality*

The incidence of small renal tumors removed during radical nephrectomy for RCC or in necropsies ranges from 4 to 25% [27, 28]. As a consequence, many urologists have argued against PN as a standard treatment for RCC, even when tumors are small, due to the high risk of multifocality. We need to know the factors that increase the risk of multifocality to allow us to select PN when the risk of multifocality is low and radical nephrectomy when the risk is high.

The main factor signaling an increased risk of multifocality is large tumor size, since 91% of multifocal tumors are associated with primary tumors >5 cm [29]. The second factor is tumor stage (pT2 or higher). Thus, stage pT3a shows a 16.4% incidence of multifocality, with a mean distance between primary and secondary tumors of 26.4 mm [30]. Other factors increasing the risk of multifocality cannot be known before surgery but only after examination of the surgical specimen, including histological factors such as vascular infiltration and papillary or mixed histological variants [27]. Knowledge of factors carrying an elevated risk of multifocality alerts to the need for more rigorous patient follow-up and inspection of the whole defatted kidney to rule out satellite tumors during PN.

With regard to the preoperative detection of multifocal lesions by imaging techniques, only 22.9% of additional tumors subsequently observed in specimens after radical nephrectomy had been detected by ultrasound or CT [31]. Intraoperative ultrasound studies show a higher sensitivity, detecting up to 78% of multifocal tumors, which may be very useful when there are multifocality risk factors and a PN has been proposed to the patient.

4.4. *High Fuhrman nuclear grade and symptomatic clinical presentation*

It was reported that recurrence-free survival after PN was not only significantly improved by smaller tumor size (<4)

but also by low Fuhrman grade and incidental clinical presentation [4]. This finding was confirmed by Licht [32], who observed a significantly worse prognosis after this surgery in symptomatic (83% five-year survival) versus incidental (94% five-year survival) tumors.

Moll et al. [5] and Ghavamian et al. [15] reported that tumor stage and nuclear grade are significantly associated with RCC mortality. These classic prognostic factors are valid for both radical and partial nephrectomies, but a much more rigorous follow-up is required if partial nephrectomy is selected and the pathology study reports grade III disease.

4.5. *Surgical margins*

Conventional PN includes ≥1 cm margin of healthy parenchyma, whereas this margin is not left in tumor enucleation and there is a higher risk of surgical margin involvement. Recent reports have shown similar rates of cancer control between PN and enucleation, provided that surgical margins in enucleation are examined by intraoperative biopsy of the kidney bed.

In a series of 44 patients treated with PN for tumors with a mean size of 3.2 cm and a mean surgical margin of 2.5 mm, 93% had negative surgical margins and showed no local recurrence after after a mean follow-up of 4 years [33]. In the Mayo Clinic series, all partial nephrectomies were carried out with margins ≥3 mm of healthy peritumoral renal tissue, verified by intraoperative biopsy of the kidney bed. Local five-year recurrence-free survival was 97% in a series of 130 patients [34].

It can therefore be proposed that a margin of 1-2 cm is not necessary in PN, for which a few millimeters (3–5 mm) can be adequate as long as the intraoperative biopsy of the kidney bed is negative.

5. SURGICAL TECHNIQUE IN PARTIAL NEPHRECTOMY

Surgical technique in PN has advanced over recent years, offering improved cancer control and anatomical-functional outcomes for the saved kidney.

A flank incision approach is used, opening Gerota's fascia and localizing the kidney and the tumor. A thorough visual inspection is essential for adequate planning of the resection, especially if the tumor is near the hilum. It is controversial whether renal ischemia is required for the resection. This decision depends on the nature of the tumor and the skill of the surgeon. At our center, where there is considerable experience acquired over many years and excellent cancer control and renal preservation outcomes have been obtained, the renal pedicle is identified and released, isolating the main renal artery and vein with vessel-loops.

If the tumor is small and the indication is elective, resection of the tumor then commences, allowing a safety margin of several millimeters of healthy renal parenchyma. If there is no major bleeding as the resection proceeds, total resection of the tumor is completed without recourse to any type of renal ischemia. If there is any doubt about the resection margins after removal of the tumor, an intraoperative biopsy of the bed is performed and we proceed according to the results. Then, hemostasis of the tumor bed is started rapidly with single stitches of 4/0 vicryl at the main bleeding points using spray-coagulation on secondary vessels with an electric scalpel, which takes considerable time. To reduce this time, a technique modification was introduced at our centre one year ago, with the application of a fibrinogen hemostatic patch (Tachosil, Nycomed Pharma, Austria) on the resection surface after suturing the main bleeding vessels. This has shortened the time for intervention and hemostasis to 15–20 minutes, and improved the visual appearance (Figure 3). We also leave the surgical bed open after the resection, without using a mattress stitch to draw the renal parenchyma together for better hemostasis. The resection bed must be carefully inspected, and the opening of the urinary passage (calyx or pelvis) must be avoided or, when necessary, repaired.

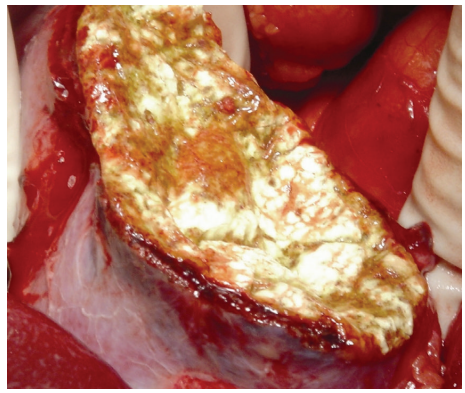

Figure 3: Open partial nephrectomy for renal cell carcinoma of inferior pole satisfactory hemostasis with application of a fibrinogen hemostatic patch (Tachosil, Nycomed Pharma, Austria).

When tumors are large but PN is relatively or absolutely indicated, we prefer to clamp the renal artery to produce ischemia after administering intravenous mannitol, keeping the renal vein patent to minimize the risk of postoperative acute tubular necrosis. It may also be necessary to clamp the renal artery in cases of central tumors that affect major vessels (e.g., arcuate arteries) or in cases of unexpected bleeding that can only be controlled by ischemia. In these cases, it is very useful to have the renal pedicle prepared in advance, allowing ischemia to be produced within a few seconds and minimizing blood loss.

Intraoperative ultrasonography is not a standard procedure in our setting but can greatly assist in the identification of other renal tumors when multifocality is suspected. Some authors use intraoperative ultrasonography to demarcate intrarenal tumors and to avoid damaging large vessels near the resection line or bed.

Once hemostasis has been achieved, a careful examination is required to detect any inadvertent opening of the urinary tract, thereby avoiding postoperative leaks or fistulas. If an opening is identified, it is closed using a resorbable suture. When an opening is suspected but cannot be seen, an intrapelvic injection of methylene blue is required, leading some authors to previously insert a ureteral stent in patients with central-located tumors. Fibrin sealants,

Table 2: Complications after open partial nephrectomy.

Author, year (Hospital)	N	Acute renal failure (%)	Urinary fistula (%)
Ghavamian, 2002 (Mayo Clinic)	63	12.7	3.2
Duque, 1998 (Brigham)	64	15.1	9.1
Polascik, 1995 (Johns Hopkins)	67	1.5	9
Herr, 1994 (Memorial Sloan-KCC)	41	0	0
Campbell, 1994 (Cleveland Clinic)	259	12.7	17.3

as well as being hemostatic agents, can reinforce repair of the collecting system. Gelfoam soaked with thrombin can be placed over the defect and then infiltrated with Hemaseel fibrin sealant to close small defects of the urinary tract at the level of the calyces.

6. COMPLICATIONS OF OPEN PARTIAL NEPHRECTOMY

Open partial nephrectomy is more complex than radical nephrectomy, and many authors place limits on its use citing a higher risk of complications. Several decades ago, reports on open PN described a greater risk of acute renal failure, urinary fistula, and hemorrhage of the surgical bed, among other complications [15, 22, 35, 36].

The lower incidence of complications in the present patient series can be attributed to the greater experience that urologists have gained with this technique and the higher prevalence of incidental small tumors. In 1994, Campbell et al. [35] described complication rates after open PN of 37% for symptomatic tumors and of 22% for incidental tumors Table 2.

More recently, however, open PN and radical nephrectomy have shown a similar complications' rate, overall morbidity rate, hospital stay, blood losses, and frequency of acute renal failure [37, 38]. The risk of acute renal failure after open PN ranges from 0 to 18% according to the series. Campbell et al. [35] reported a 13% incidence of acute renal failure in 259 patients after open PN (for which only 10/259 patients [3.9%] had an elective indication). Risk factors for postoperative acute renal failure were tumor size >7 cm, excision of more than half the renal parenchyma, and ischemia >60 minutes. In patients with PN, the renal parenchymal volume loss correlates best with the renal function loss several months after surgery. Estimates of volume loss may be useful for predicting postoperative renal function when planning PN in patients with a solitary kidney [6, 7, 39].

The risk of urinary fistula after open PN ranges from 1.8 to 21%, and is lower in patients treated for a small incidental tumor with elective indication. Campbell et al. [35] described an increased risk of urinary fistula in tumors >4 cm localized centrally or near the hilum in surgery requiring reconstruction of the excretory tract.

To summarize, complications of open PN appear to have been reduced to levels found with open radical nephrectomy—thanks to the greater experience of surgical teams with this technique. In the medium term, however, at 6–12 months, open PN patients have a significantly lower serum creatinine level compared with laparoscopic radical nephrectomy patients [40]. This information must be explained to patients when they are informed about the short-term and long-term risks of the two approaches.

7. FOLLOW-UP GUIDELINES AFTER OPEN PARTIAL NEPHRECTOMY

Several clinical guidelines have been established for the follow-up of patients after open PN, based on detailed analysis of reported tumor recurrence patterns at specialized centers (e.g., Cleveland Clinic).

Rates of local recurrence and metastatic progression vary as a function of the tumor stage at surgery as follows: T1N0M0: 0% local recurrence and 4.4% distant progression; T2N0M0: 2% and 5.3%, respectively; T3aN0M0: 8.2% and 11.5%, respectively; T3bN0M0: 10.6% and 14.9%, respectively. Postoperative time periods associated with a maximum incidence of local recurrence are between 6 and 24 months for T3 and T2 tumors and after 48 months for T1 tumors. Hence, the follow-up time and protocol are selected according to the pathological stage at the time of the open PN.

Novick and Campbell [2] proposed these follow-up guidelines.

(1) Patients with T1N0M0 tumors have annual anamnesis, physical examination, and serology, with no need for radiology during the first year. No subsequent systematic diagnostic imaging studies are required due to the low risk of recurrence.

(2) Patients with T2N0M0 tumors have annual anamnesis, physical examination, chest X-ray, and abdominal CT scan, with abdominal X-ray every 2 years.

(3) Patients with T3N0M0 tumors have anamnesis, physical examination, chest X-ray, and abdominal CT every 6 months for 3 years and then annually.

In the long term, hyperfiltration can cause renal injury in these patients, especially if there has been >50% loss of nephrons, with proteinuria, focal segmental glomerulosclerosis, and progressive renal failure. Because proteinuria is the first change in this disorder, 24-hour urine proteins should be determined annually in all patients with suspicion of hyperfiltration due to loss of renal parenchyma.

8. WHEN TO PROPOSE OPEN PARTIAL NEPHRECTOMY

Based on the above reported data, clinical studies (Mayo Clinic, Cleveland Clinic, UCLA, etc.), and our own

experience, we can affirm, in common with other authors [1, 2], that open PN is now the gold standard treatment for young and healthy patients with incidentally detected small renal tumors (<4 cm). It also represents an alternative to radical nephrectomy in single-kidney patients or those with bilateral tumors.

The presence of renal failure, diseases that predispose towards renal failure, or genetic syndromes associated with multifocality also shows indications for open PN versus radical nephrectomy since, in small tumors, there are no differences in disease-free survival, morbidity, or complication rates between the techniques.

The current standard surgical technique for partial nephrectomy is open partial nephrectomy. Only certain highly specialized centers have gained sufficient experience with laparoscopic PN to minimize its risks and complications [40]. It remains a challenging technique, requiring a longer period of warm renal ischemia, vein closure, and the difficult suturing of open vessels during tumor resection. In fact, the laparoscopic approach has been associated with a higher rate of complications, even in the best hands. Thus, Sharma et al. reported intra- and postoperative complication rates of 5% and 11%, respectively, using laparoscopic PN, compared with 0% and 2%, respectively, using open PN [39].

Although no studies have been published to date on the long-term oncological effectiveness of laparoscopic PN [1], preliminary data indicate that it does not differ from that obtained with the open approach. In 2007, Gill et al. [41] reported three-year cancer-specific survival rates of 99.3% in 771 patients treated with laparoscopic partial nephrectomy and 99.2% in 1028 patients treated with open partial nephrectomy. The same study confirmed a shorter surgery time ($P < .0001$), hospital stay ($P < .0001$), and a lower blood loss ($P < .0001$) with laparoscopic partial nephrectomy versus open partial nephrectomy, while intraoperative complication rates were similar. Disadvantages of laparoscopic versus open partial nephrectomy were the significantly longer ischemia time ($P < .0001$) and the more frequent postoperative complications, especially urological disorders ($P < .0001$).

Importantly, the laparoscopic approach is associated with a reduction in postoperative pain and a shorter recovery period, posing surgeons and patients with a difficult decision between open and laparoscopic partial nephrectomies for a small incidentally detected renal tumor.

Renal laparoscopy will continue to develop, and urologists will gain greater experience with the technique over time. Thus, outcomes published by Gill et al. in 2007 were superior to those obtained by the same author in 2003 [41, 42]. It should be taken into account that the study by Gill et al. comparing laparoscopic nephrectomy with open partial nephrectomy [41, 43] was not a randomized clinical trial. In fact, most of the tumors selected for open partial nephrectomy were >4 cm, and all of them were centrally localized single tumors (size up to 7 cm) with a malignant histology. These cases are technically more challenging and carry a higher oncological risk, representing an important selection bias. There is a need for a randomized clinical trial to be undertaken to assess the risks and benefits of each approach. Nevertheless, there is an evident trend towards a minimally invasive approach to renal tumor treatment, and we can expect laparoscopic PN to develop in the near future to a point where it can replace open PN as a standard treatment for localized renal tumors.

At our center, we have treated 35 patients by conservative surgery of the renal parenchyma over the past 14 years (1993–2007), using open PN in 7 and enucleation in 28, with biopsies of the renal bed when involvement of the surgical margin was suspected. Indications were elective in 16 cases (45.5%), absolute in 11 (31.5%), and relative in 8 (23%). Mean size of tumors was 3.6 cm (range of 1–9 cm), with peripheral localization in 22 patients (63%), mesorenal in 12 (34%), and multifocal (6 tumors) in 1 patient (3%). Applying the technique described above in Section 5, we have had no intraoperative complications. Postoperative complications were renocutaneous fistula (resolved by internal derivation via ureteral catheter) and acute tubular necrosis (renal function recovered after hemodialysis) in the same single-kidney patient. After a median follow-up time of 69 months, we have observed one local recurrence (3%), which was from enucleation and was excised. Three patients died due to other causes and three were lost to the follow-up after moving from the area. All followed-up patients are disease-free and have creatinine levels similar to preoperative values.

Based on this experience, our group considers conservative renal surgery to be an alternative to radical surgery in tumors <4 cm or in larger tumors in single-kidney patients. Our selection of partial nephrectomy or enucleation is based on tumor localization and size. Thus, we prefer enucleation in tumors in mesorenal location because of its lower comorbidity versus PN. Our approach to peripheral tumors depends on their size. We use enucleation for small tumors of 1–3 cm, but we prefer partial nephrectomy for tumors ≥4 cm or when there is any suspicion of positive margins.

9. CONCLUSIONS

Open PN has been shown to be a safe and effective surgical technique in patients with a localized renal tumor, including patients with a normal contralateral kidney. We have gained experience with this technique by applying it to patients with an absolute indication, and we are now increasingly able to recommend it to patients with an elective indication, based on its good oncological outcomes and lower morbidity rates versus radical nephrectomy. Moreover, the preservation of nephrons achieved with open partial nephrectomy reduces the long-term risk of renal failure in these patients. These benefits outweigh any problems caused by the follow-up required for these patients due to fears of local recurrence, which will undoubtedly be more effectively detected at an earlier stage with new three-dimensional imaging techniques.

Nowadays, open PN is the gold standard technique to treat small renal masses, and all nonablative techniques must pass the test of time to be considered equally effective.

It is not ethical for patients to undergo radical surgery just because urologists involved do not have adequate experience with PN or have concerns about their capacity

to manage its possible complications. Patients must be clearly informed about the possibility of laparoscopic PN in specialized centers. Patients should be involved in the final treatment decision and, when appropriate, referred to centers with experience in open or laparoscopic partial nephrectomies.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 507543, 5 pages
doi:10.1155/2008/507543

Clinical Study

Fast Track Open Partial Nephrectomy: Reduced Postoperative Length of Stay with a Goal-Directed Pathway Does Not Compromise Outcome

Bilal Chughtai, Christa Abraham, Daniel Finn, Stuart Rosenberg, Bharat Yarlagadda, and Michael Perrotti

Urology Service, Saint Peter's Cancer Care Center, and Department of Surgery, Albany Medical College, Albany, NY 12208, USA

Correspondence should be addressed to Michael Perrotti, perrotmi@yahoo.com

Received 10 April 2008; Accepted 5 August 2008

Recommended by J. Rubio

Introduction. The aim of this study is to examine the feasibility of reducing postoperative hospital stay following open partial nephrectomy through the implementation of a goal directed clinical management pathway. *Materials and Methods*. A fast track clinical pathway for open partial nephrectomy was introduced in July 2006 at our institution. The pathway has daily goals and targets discharge for all patients on the 3rd postoperative day (POD). Defined goals are (1) ambulation and liquid diet on the evening of the operative day; (2) out of bed (OOB) at least 4 times on POD 1; (3) removal of Foley catheter on the morning of POD 2; (4) removal of Jackson Pratt drain on the afternoon of POD 2; (4) discharge to home on POD 3. Patients and family are instructed in the fast track protocol preoperatively. Demographic data, tumor size, length of stay, and complications were captured in a prospective database, and compared to a control group managed consecutively immediately preceding the institution of the fast track clinical pathway. *Results*. Data on 33 consecutive patients managed on the fast track clinical pathway was compared to that of 25 control patients. Twenty two (61%) out of 36 fast track patients and 4 (16%) out of 25 control patients achieved discharge on POD 3. Overall, fast track patients had a shorter hospital stay than controls (median, 3 versus 4 days; $P = .012$). Age (median, 55 versus 57 years), tumor size (median, 2.5 versus 2.5 cm), readmission within 30 days (5.5% versus 5.1%), and complications (10.2% versus 13.8%) were similar in the fast track patients and control, respectively. *Conclusions*. In the present series, a fast track clinical pathway after open partial nephrectomy reduced the postoperative length of hospital stay and did not appear to increase the postoperative complication rate.

1. INTRODUCTION

Radical nephrectomy has considered the optimal surgical approach to the management of renal cancer [1]. Additional options include observation, cryosurgery, and radiofrequency ablation [2, 3]. Management of the small renal mass requires multiple perspective decision making on the part of the physician [4]. Recently, partial nephrectomy has been shown to have efficacy in the management of select patients with small renal masses (4 cm or less) [5, 6]. Several investigators have reported an expanded use of this approach with success in patients with larger renal neoplasms (7 cm or less). Hospital stay after partial nephrectomy is usually 5–8 days [7]. Factors limiting early discharge are usually pain, stress-induced major organ dysfunction (i.e., ileus, atelectasis), tradition, fatigue, pain, nausea, and morbidity [8, 9]. In other abdominal procedures, including colon resection, lung transplant, and laparoscopic nephrectomy, the introduction of a program comprised of optimized pain relief using nonsteroidal anti-inflammatories for analgesia enforced oral nutrition and mobilization, and revision of traditional care principles has reduced hospital stay from 5–8 days to 220 133 days in some studies [10, 11]. The concept of fast-track (FT) surgery has recently attracted more interest, but has not yet been applied in patients undergoing partial nephrectomy. The purpose of this study was to investigate the postoperative course before and after the introduction of a fast track program in patients undergoing open partial nephrectomies. We sought to determine whether the use of this fast track program might decrease length of hospital stay without sacrificing outcomes.

Table 1: Fast track pathway.

Day	Goal
Preoperative	Patient and family counseling Medication review Preparation instructions
Postoperative day 0 (evening of surgery)	OOB at least once Clear liquids
Postoperative day 1	OOB four times Liquid diet Oral pain medications
Postoperative day 2	OOB ad lib Regular diet Remove Foley catheter at 7 am Flank drain fluid for Cr at 2 pm Remove drain if fluid Cr = serum Cr
Postoperative day 3	Discharge to home

2. MATERIALS AND METHODS

A fast track clinical pathway for open partial nephrectomy was introduced at our institution in July 2006. The pathway has an established management protocol (Table 1). All patients undergoing open partial nephrectomy from July 2006 thus far at our institution were managed by the fast track protocol, and comprise the study cohort. Patients undergoing laparoscopic partial nephrectomy and robotic partial nephrectomy were not included. In the event that the decision was made intraoperatively to perform complete nephrectomy, patients were included on an intention-to-treat basis. Demographic data, tumor size, blood loss, transfusion, final pathology, margin status, length of hospital stay, and complications were captured in a prospective database, and compared to a control group managed consecutively immediately preceding the institution of the fast track clinical pathway. All operations were performed for a renal tumor less than 7 cm in greatest diameter by the same surgical team.

2.1. Preoperative preparation

Patients were admitted to the hospital on the day of surgery and performed all preparation on an outpatient basis. All patients were counseled preoperatively regarding the target goals outlined in Table 1. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) were stopped 10–14 days prior to surgery. Coumadin was stopped 5 days preoperatively and stat protime/partial thromboplastin time obtained on the morning of surgery to confirm acceptable value. All patients received 3 bisacodyl tablets and 1 bottle of magnesium citrate at noon on the day prior to surgery. All patients received erythromycin and neomycin antibiotic per oral (PO), 500 mg (milligram) tab, at 3 pm, 6 pm, and 9 pm on the day prior to surgery. All patients were instructed to eat lightly and orally hydrate on the day prior to surgery.

2.2. Intraoperative

This report is restricted to patients undergoing open partial nephrectomy on an intention to treat basis. General anesthesia, oral gastric tube (removed at case conclusion), and Foley catheter were used in all cases. Compression pneumatic stockings were placed as soon as the patient moved from the stretcher onto the operating table. The retroperitoneal flank approach was used. All patients were positioned with the bean bag, with legs straight, hyper-extended with the kidney rest raised maximally. Before draping, the surgeon marked the posterior axillary line (PAL), the anterior axillary line (AAL), the lateral border of the rectus muscle, and the course of the 10th, 11th, and 12th ribs. Incision was made from the PAL to the AAL in the course of the 11th rib using the cautery on pure cut (setting of 30). The distal tip of the 11th rib was removed in the standard manner. An extra-pleural/extra-peritoneal approach to the kidney was used. The kidney was explored, and vessel loop passed to tag the ureter, renal artery, and renal vein. A double loop was passed around the vein for subsequent occlusion. Patients received mannitol 12.5 gm (gram) IV (intravenous) bolus prior to manipulation of the renal vessels followed by 5 gm/hour continuous infusion for the remainder of the operation. Renal artery was clamped in all cases and the kidney cooled. The renal vein was selectively occluded as required to provide a bloodless operative field. The collecting system was closed with 3–0 monocryl on SH needle in all cases. Renal arteries and venules were oversewn in figure of eight fashions with 3–0 monocryl on SH needle. Prior to the removal of the renal artery clamp, the kidney was reconstructed essentially obliterating the resection defect utilizing 0-Chromic suture on CT needle in horizontal mattress fashion. This resulted in a reniform shape approximation in nearly all cases. The rib bed and skin were infiltrated with 0.25% marcaine (30 ml (milliliters)). The skin wound was closed in a subcuticular (3–0 monocryl). A #7 Jackson-Pratt drain was placed in all cases. In no case was a ureteral stent placed.

Table 2: Outcomes of fast track open partial nephrectomy.

	Conservative group	Fast track group
(N)	25	33
Discharge in <3 days	4	22
Age range	32–74	39–73
Male/female	18/8	22/11
Length of stay		
Range	3–10 days	2–6 days
Median	4 days	3 days
Average	4.4 days	3.3 days
Estimated blood loss		
Range	50–500 cc	50–600 cc
Median	200 cc	200 cc
Average	228 cc	263 cc
Transfusions	3	2
Complications	4	4
Respiratory distress	1	1
Conversion to nephrectomy	2	1
Post operative bleed	0	1
Urine leak	0	1
Tumor size		
Range	1.1–6.8 cm	1.2–6.2 cm
Median	2.5 cm	2.5 cm
Average	2.8 cm	2.9 cm
Pathology		
Clear Cell RCC	17 (68%)	25 (76%)
Papillary RCC	2 (8%)	3 (9%)
Chromophobe RCC	—	3 (9%)
Oncocytoma	3 (12%)	—
AML	1 (4%)	2 (6%)
Other	2 (8%)	—

2.3. Postoperative

On POD 0 (postoperative day), on the evening of surgery, patients received celecoxib 200 mg per oral in the postanesthesia care unit (PACU) with sip when awake, and daily thereafter (Table 1). Morphine sulfate was administered IV at 2 hour intervals as needed. Metoclopramide was administered IV 10 mg every 6 hours. Famotidine was administered 20 mg IV every 12 hours. On the day of surgery, patients ambulated and were encouraged to take liquids by mouth. On POD 1, diet was advanced to tray of clears, and oral pain medication administered (hydrocodone/acetominophen 5–10 mg/500 mg every 4 hours as needed). On day 2, the Foley catheter was removed at 7 am and regular diet initiated. Patients received milk of magnesia 30 cc PO at 8 am and a repeat dose in 4 hours. Jackson-Pratt drain fluid was sent to the laboratory for creatinine measurement and if equal to serum creatinine level, the Jackson-Pratt drain was removed. The patient was assessed and discharged to home on POD 3 if appropriate.

3. RESULTS

A total of 33 patients were managed by fast track and compared to 25 control patients (Table 2). The estimated blood loss, transfusion rate, tumor size, pathology, and complication rate were similar between groups. There was, however, a significant difference in the length of hospital stay observed between groups. Of 25 control patients, 4 (16%) achieved discharge to home in <3 days compared to 22 (67%) of the 33 patients managed in the fast track program. Overall, fast track patients had a shorter hospital stay compared to controls (median, 3 days versus 4 days; $P = .012$). Of the 11 patients in the fast track cohort who were discharged after the third postoperative day, this was due to poor ambulation/inadequate pain control ($n = 5$), abdominal bloating ($n = 3$), multiple co-morbidities ($n = 2$), and respiratory distress postoperatively requiring ICU care ($n = 1$).

Complications are worth noting to determine whether the fast track approach was harmful in any way to the

study cohort. In the control cohort, there was 1 patient with respiratory distress requiring ICU admission, 3 patients received blood transfusion, there were 2 conversions to complete nephrectomy, and 1 positive surgical margin. In the fast track cohort there was 1 patient with respiratory distress requiring ICU admission, 2 patients required blood transfusion, there was one conversion to total nephrectomy, 1 postoperative bleed (gross hematuria) requiring selective arterial embolization, and 1 urine leak requiring percutaneous drainage and ureteral stent placement.

The percentage of patients with malignancy increased in the fast track cohort compared to control (85% versus 76%). This may represent improved preoperative assessment.

4. DISCUSSION

Since 1950 in the United States, there has been a 126% increase in the incidence of renal cancer [7, 8]. Although there has been an increase in all stages of renal cancer including advanced cases (i.e., regional extension, distant metastases), there has been the greatest increase in those discovered incidentally [8, 12]. In the early 1970s, approximately 10% of tumors were detected incidentally compared with 61% in 1988 [8].

Previous studies of other types of major surgery have shown that a combined effort comprising intensive preoperative information, effective postoperative pain relief and enforced mobilization, and early enteral nutrition can accelerate postoperative recovery and decrease hospital stay [11, 13].

Investigators have recently illustrated that in elderly high-risk patients undergoing colonic resection, mean hospital stay could be reduced to 2-3 days [11]. In another group of high risk patients undergoing open aortic surgery, mean hospital length of stay was reduced from a mean of 9 days to 5 days [14–16]. In a study by Harinath et al., a decrease in length of stay was observed from 5 to 4 days for ileal pouch-anal anastomosis [11]. The concept of fast track has also been applied to infants and children [17]. In the urologic literature, after radical prostatectomy, median hospital stay in 252 consecutive patients was reduced to 1 day [13]. Specifically with kidney surgery, postoperative hospital stay after open nephrectomy was reduced to 4 days [18]. With laparoscopy, hospital stay has been reduced to 2 days with an FT rehabilitation program [19].

In this study, with the introduction of a fast-track program, open partial nephrectomy hospital stay was decreased to 3 days, compared to 4 days before implementation of the program. Sixty six per cent of patients achieved a target discharge on day 3 or less. Notably, both groups did have similar characteristics as demonstrated in Table 2. The estimated blood loss, transfusion rate, tumor size, pathology, and complication rate were similar between groups. We suspect that based upon our data the main contributing factors responsible for the decrease in hospital stay was a clear protocol of expectations at each stage of the recovery period. This was accomplished in the present series without an apparent increase in complication rate. Most notably, fast track did not lead to an increase in readmissions.

It is impossible to discern exactly which components of our protocol are "more essential" than others, and this would require selective application in future investigations. In addition, we have no proof from the present investigation that the fast track protocol is advantageous to the patient. The purpose of the present study was to assess the feasibility of such an approach and we conclude that such an approach is feasible. Ultimately, the patients in this study decided their discharge date. Most patients were eager to receive discharge to home as soon as they are medically safe. One patient in the fast track protocol was discharged to home at her request on POD 2. She expressed regret at doing so at her first postoperative visit.

Our readmissions to the hospital were as follows. One (3.0%) patient had returned to hospital for postoperative hemorrhage resulting in gross hematuria. This patient was managed successfully with embolization. One (3.0%) patient had returned to hospital forurinoma. This was managed successfully with indwelling ureteral stent for 6 weeks and transient percutaneous drainage of urinoma. Both patients had complex resections, and it is unlikely that fast track management resulted in return to hospital.

5. CONCLUSIONS

In the present investigation, a fast track clinical pathway after open partial nephrectomy reduced the postoperative length of hospital stay and did not appear to increase the postoperative complication rate.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 479495, 10 pages
doi:10.1155/2008/479495

Review Article

Cryoablation for Small Renal Masses

J. L. Dominguez-Escrig,[1] K. Sahadevan,[2] and P. Johnson[2]

[1] *Department of Urology, Freeman Hospital, Freeman Road, High Heaton, Newcastle Upon Tyne NE7 7DN, UK*
[2] *Department of Urology, Sunderland Royal Hospital, Kayll Road, Sunderland SR4 7TP, UK*

Correspondence should be addressed to J. L. Dominguez-Escrig, jldominguezescrig@hotmail.com

Received 13 March 2008; Accepted 19 May 2008

Recommended by J. Rubio

Advances in imaging techniques (CT and MRI) and widespread use of imaging especially ultrasound scanning have resulted in a dramatic increase in the detection of small renal masses. While open partial nephrectomy is still the reference standard for the management of these small renal masses, its associated morbidity has encouraged clinicians to exploit the advancements in minimally invasive ablative techniques. The last decade has seen the rapid development of laparoscopic partial nephrectomy and novel ablative techniques such as, radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), and cryoablation (CA). In particular, CA for small renal masses has gained popularity as it combines nephron-sparing surgery with a minimally invasive approach. Studies with up to 5-year followup have shown an overall and cancer-specific 5-year survival of 82% and 100%, respectively. This manuscript will focus on the principles and clinical applications of cryoablation of small renal masses, with detailed review of relevant literature.

1. INTRODUCTION

Worldwide, around 208 500 new cases of renal cancer are diagnosed each year, accounting for just under a 2% of all cancers with higher incidence in more developed countries [1–3]. Regardless of its true impact on annual incidence, the widespread use of more sensitive imaging techniques (USS, CT, and MRI) has led to an increase in the number of incidentally detected renal tumors [4–7], with an estimated increased detection of asymptomatic, small renal masses by 60% in recent years [8].

In Europe, the most recent estimates of incidence of renal cancer suggest that there are 63 300 new cases annually in the EU25, accounting for nearly 3% of all cancers [9], with an estimated annual increase in incidence of approximately 2% [2, 10]. In Spain, the estimated incidence and mortality for the year 2002 were 4085 (2778 men, 1307 women) and 1644 (1093 men, 551 women) cases, respectively (FCAECC, La situacion del cancer en España. Ministerio de Sanidad, 2005).

In contrast to a historical incidence of 5% of renal tumours of less than 3 cm in size, current incidence of such tumours ranges between 10% and 40% [11, 12]. Although the natural history and biological behaviour of this "small renal mass" are yet to be understood, the available evidence demonstrates a rather slow growth of these small masses, with an annual size increase not greater of 0.5 cm [13–17]. Furthermore, between 15% and 30% of small renal tumours are confirmed to be benign or to have a low grade and low-malignant potential on pathological examination [18–21].

As a result, urologists now face a subset of early-stage asymptomatic patients with clinical, pathological, and morbid characteristics clearly different from those with a classically presented renal malignancy. The management of this group of patients, while still controversial, has evolved dramatically in recent years. Conservative approach by means of active monitoring or watchful waiting has been advocated by some authors [14, 22–24], and is a feasible option particularly in the elderly and significantly comorbid patient. Surgery, however, is the preferred management option for the younger, healthier patient. In recent years, nephron-sparing surgery (open and laparoscopic partial nephrectomy) has become the standard treatment for small renal masses, with data available from large series confirming similar 5-year cancer-specific survival rates (90%–100%) and a low risk (0%–3%) of local recurrence [25–29]. Although

laparoscopic partial nephrectomy has clear advantages over the open approach, particularly on wound-related morbidity, its technical difficulty has limited its widespread use. Consequently, laparoscopic and percutaneous ablative techniques in renal surgery, such as, radio frequency ablation (RFA), high-intensity focused ultrasound (HIFU), and cryoablation (CA) are being increasingly utilized as they offer parenchymal preservation along with less morbidity. Although long-term oncological data is currently not available, present 5-year followup data is very encouraging. This article will focus on cryoablation (CA) of small renal masses and in particular, on laparoscopic cryoablation (LCA), with an up-to-date review of the available literature and detailed analysis of the largest published series.

2. HISTORICAL BACKGROUND

Cryoablation has been used in medicine since James Arnott, back in 1845–1851, demonstrated that freezing temperatures could be applied to cause tissue destruction [30]. Further interests in this field with improved delivery system and understanding of freeze-thaw sequence were followed by the use of CA in the treatment of prostate cancer only to be abandoned because of local complications [31–34].

At the turn of the last century, driven by the need for minimally invasive techniques and facilitated by rapid technological developments, a renewed interest on cryoablation and its applications in urological oncology re-emerged. Experience with vacuum-insulated liquid nitrogen or argon-cooled probes in other disciplines and technological advantages in intraoperative imaging [35], laparoscopic USS probes in particular, has allowed a safe and efficient targeting of kidney tumours. As a result, renal cryoablation, either percutaneous or laparoscopic, has become a feasible and exciting new minimally invasive surgical option for the treatment of small masses.

3. CRYOBIOLOGY AND PATHOPHYSIOLOGY OF CRYOABLATION

Cryoablation causes tissue destruction by a direct, as well as by a vascular, delayed mechanism [36, 37]. Direct cell damage begins with falling temperatures as structural/functional cell components are stressed and cell metabolism progressively fails. With freezing, ice crystal formation first occurs in the extracellular space, creating a hyperosmotic environment which draws water from the cells and, by a "solution-effect injury," causes cell shrinkage and membrane damage. With further cooling, especially at high cooling rates, ice crystals will form within the cell. This phenomenon, possibly facilitated by cell-to-cell propagation via intercellular channels [38], is almost always lethal to the cell. While some cells will contain ice crystals at temperatures as high as -15°C, certainty of intracellular ice formation requires temperatures below -40°C (homogeneous nucleation) [37, 39]. During thawing, with temperatures above -40°C, ice crystals fuse into larger crystals ("recrystallization") which, together with a transient hypotonic extracellular environment that draws water back into the cell, will result in further damage of the cell membrane and membrane rupture.

Indirectly, hypoxic damage occurs as a result of microvascular stasis. With lowering temperatures, initial vasoconstriction produces a decrease in blood flow, with complete cessation during freezing. During thawing, the circulation returns with transient vasodilatation. Endothelial damage produces increased permeability, oedema, platelet aggregation, and formation of thrombi, resulting in a sustained microvascular occlusion and stagnation [40, 41].

While downregulation of tumour suppressor genes essential to the control of apoptosis has been implicated in most malignancies and proapoptotic factors such as hypothermia, ischaemia, inflammation, elevated calcium levels, immunologic-based mechanisms including macrophage recruitment are associated with freezing injury. Recent studies implicate gene regulated cell death (apoptosis) in cryosurgical outcomes [42, 43].

The histological end result is a confluent coagulative necrosis, as evidenced by the presence of numerous histiocytes, cholesterol crystals, and dystrophic calcification within the cryolesion, with eventual fibrosis and scarring. Features that have been demonstrated in animal models [44, 45] as well as in human renal cryoablated tumours [46, 47].

4. TECHNICAL PRINCIPLES OF CRYOABLATION

Renal cryoablation has been shown to produce predictable and reproducible tissue destruction in animal models [48–53]. Cell damage depends on the cooling rate, the number of freeze-thaw cycles [45], the lowest temperatures achieved as well as the hold time at subzero temperatures [37, 54]. Importantly, while temperature below -19.4°C has been shown to be sufficient for complete destruction of normal renal parenchyma [48], neoplastic cells may require temperatures as low as -50°C to guarantee cell death [37]. Moreover, preclinical models have demonstrated that such low temperatures can only be achieved within a core volume of tissue, limited to 4 to 6 mm inside the edge of the forming ice ball [48, 49]. Thus, most authors will extend the ice ball to 1 cm beyond the tumour margins, incorporating the outer few millimetres or "indeterminate zone" and a margin of normal renal parenchyma, to optimize oncological control [55].

Modern cryoprobes can achieve temperatures as low as -190°C by exploiting the Joule-Thompson effect. Typically, compressed argon gas is allowed to expand through a small orifice, producing temperatures well below those required to ablate normal renal tissue (-19.4°C) [48] and cancer cells (-40°C), as demonstrated on in vivo prostatic [56] and renal cryolesions [45]. Although, the number of cycles is still controversial, early data from in vivo experiments [37] has now been corroborated in cryoablated tumours. With the incorporation of double-freeze cycles, a larger cryolesion can be achieved than with a single cycle. Apart of the number of cycles and in contrast to original experimental observations, it has been demonstrated that rapid thawing, with helium gas at 15°C to 20°C/min, does not infringe on lesion size, while reducing procedural time [45].

5. CLINICAL APPLICATION OF RENAL CRYOABLATION

Following the first experimental renal cryosurgery by Lutzeyer et al. [57, 58], it was not until 1995 that Uchida et al. performed the first reported percutaneous cryoablation in canine kidneys and, later that year, reproduced the technique in 2 patients with advanced renal carcinoma [59]. CA has developed rapidly since and can currently be delivered via open, laparoscopic and percutaneous approaches.

6. OPEN CA

Feasibility of open renal cryotherapy in humans was first reported in 1996 by Delworth et al., at the University of Texas M. D. Anderson Cancer Center, after a successful treatment of two patients with tumours in a solitary kidney, one renal cell carcinoma and one angiomyolipoma [60]. Rukstalis et al. published in 2001 the first report on systematic use of this approach [61]. A total of 29 tumours (22 solid masses and 7 complex cysts) with a median size of 2.2 cm were treated using intraoperative ultrasound monitoring and double-freeze sequences. With a median followup of 16 months, only one patient had a biopsy-confirmed recurrent tumour. Five serious adverse events occurred in 5 patients, with only one event directly related to the procedure. Overall, 91.3% of patients demonstrated a complete radiographic response [61]. In 2002, Khorsandi et al. reported open cryoablation on 17 patients with small renal tumours (median 2 cm; range: 1.1–4.2 cm), using a double freeze-thaw technique to −180°C. Median age was 62 years (range: 35–75 years). With a median followup of 30 months (range: 10–60 months), MRI demonstrated infarction and a reduction of lesion size in 15 of 16 cases. One patient's mass was unchanged at 3 months followup [62].

Whilst open CA offers safe parenchymal preservation, wound morbidity appears to be the drawback of this technique. With only two further reports in the literature [63, 64], practice in recent years has clearly favoured the laparoscopic and percutaneous approaches, with a marked trend towards the former.

7. LAPAROSCOPIC CA (LCA)

Laparoscopic cryoablation (LCA) offers several procedural advantages, namely, a minimally invasive approach, magnification, direct visualization of the tumour and internal manipulation of the cryoprobes and dual (visual and ultrasound) monitoring of the cryolesion [65] as well as allowing extensive pathologic sampling [66]. Surgeon preference and experience are crucial for choosing between transperitoneal and retroperineoscopic approaches. While transperitoneal approach allows a more direct access to anterior tumours, it carries a higher risk of bowel injury. Posteriorly located tumours are more amenable to retroperineoscopy, however, blunt dissection in this approach is associated with an increased risk of bleeding [12].

In our experience at Sunderland Royal Hospital, from September 2005, 17 patients have undergone LCA under a strict departmental protocol. Patient is positioned in lateral position as for nephrectomy. We used one 10 mm port for camera and two working ports (10 and 5 mm). Depending on the position of the tumour, we have used a further 5 mm port to retract the liver. Following adequate pneumoperitoneum, kidney is mobilised in order to access the tumour favourably for the needle insertion and for ultrasound probe positioning. Gerota's fascia and peri-renal fat are carefully dissected to expose the tumour. A standard biopsy of the tumour is then performed. Cryoprobes (17G) are inserted under visual and ultrasound control (Figure 1), at a maximum distance of 1 cm apart from each other. Tumour core temperature and tumour margin temperature are monitored throughout. Our protocol includes 2 Freeze-Thaw cycles: Freezing, during 10 minutes, achieving a core temperature of −70°C and a peripheral temperature of at least −40°C, followed by of 10 minutes of thawing (5 minutes active + 5 minutes passive thawing). The ice-ball is monitored visually by the surgeon and by real-time laparoscopic USS probe (Hitachi) performed by an expert consultant uroradiologist (Figure 2). The ice-ball is extended to a minimum of 5 mm beyond the tumour margins. Following surgery, our preferred imaging modality is pre- and postcontrast CT, which is performed as part of our followup protocol at 3, 6, 12, 18, 24 and yearly thereafter. Renal function is checked at each clinic visit. Since majority of recurrences are found at 3 months and almost all at 1 year, CT or MRI at 3, 6, 12 months and yearly thereafter has been recommended by other authors [67].

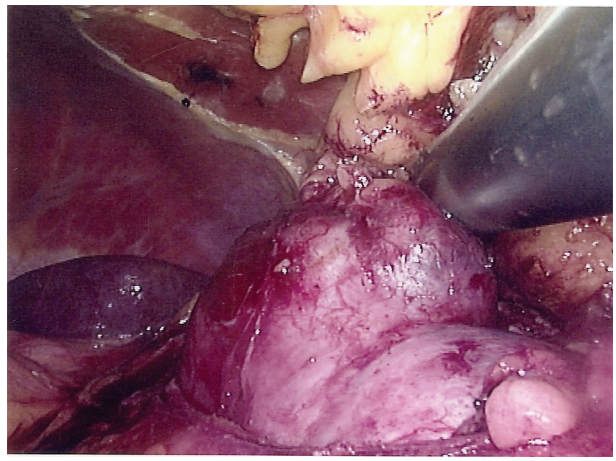

Figure 1: Ultrasound scanning of an exophytic left renal tumour exposed by laparoscopic mobilisation prior to cryoablation.

No treatment failures have been so far observed. Twelve masses (70%) were demonstrated to be a RCC. Histology in one patient revealed urothelial carcinoma necessitating nephroureterectomy. One patient required transfusion and another underwent embolisation of an arterio-venous fistula.

A comprehensive review of the literature reveals promising results. A summary of outcomes for the larger series is summarised in Table 1.

In 2003, Lee et al. reported results of LCA with ultrasound guidance, double-freeze cycle and up to 3-years followup (mean 20.25 months), in 20 patients with small

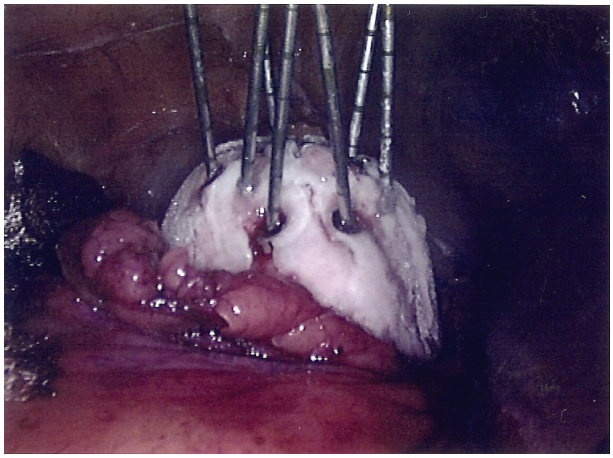

Figure 2: Visualisation of the Ice-ball during thawing, demonstrating arrangement of cryoprobes and temperature monitoring probes.

renal masses (1.4–4.5 cm) and age ranging from 43 to 84 years. Mean operating time was 305.9 minutes and blood loss 92.5 mL (50–200 mL). Biopsies demonstrated renal cell carcinoma (RCC) in 11 cases, none of which had recurred. Overall survival was 100% for this cohort [68].

In the same year, Nadler et al. reported results on 15 patients. Mean age was 68.5 years (range: 49–86 years). Mean tumour size was 2.15 cm (range: 1.2–3.2 cm), and mean estimated blood loss was 67 mL (range: 15–125 mL). RCC was demonstrated in 10 cases. Median radiographic followup (15 months, range 4.9–27 months) revealed stable lesions in all patients. There was 1 treatment failure due to incomplete treatment of the periphery of the lesion. Another patient, with a successfully treated tumour, had a positive followup biopsy due to multifocal papillary renal cell carcinoma and required nephrectomy [69].

Initial data from the Southern Illinois University was published in 2005, a total of 25 patients with an average age of 65 years (range: 32–83 years) and mean tumour size of 2.4 cm (range: 1.5–3.6 cm). Pathology revealed RCC in 72% of cases. With a followup for up to 36 months (range: 6–36 months), no recurrences were reported [70]. Subsequent publication including 84 consecutive patients with an average age of 67 years and a mean tumour size of 2.6 cm (range: 1.2-4.7 cm) of which, 70 procedures were performed laparoscopically. They reported 7 conversions, 2 of them for failures. Intraoperative biopsy yielded a 59% malignancy rate. With a mean followup of 10 months (range: 3–36 months), an abnormal postoperative enhancement occurred in 2 patients, one of which was confirmed to be a RCC [71].

Cestari et al. presented data from a cohort of 70 patients treated with laparoscopic (48 transperitoneal, 28 retroperineoscopic) cryoablation (LCA). Average age was 63.2 years, mean size 2.37 cm (range: 1–6 cm), mean operating time and blood loss were 181.4 minutes and 164.2 mL, respectively. With a followup of up to 36 months, progressive reduction of the cryolesion was demonstrated in all patients on MRI. Only 1 patient required radical nephrectomy for recurrent tumour [72].

In 2005, with 168 cases performed at the Cleveland Clinic Foundation (1997–2005), Hegarty et al. reported, prospectively collected, intermediate-term (3 years) followup data in 56 patients, with a mean tumour size of 2.3 cm, who underwent LCA under a strict MRI imaging and CT-guided biopsy followup protocol, introduced in 1997. Sequential mean cryolesion size on MRI on postoperative 1 day, at 3 and 6 months, and at 1, 2, and 3 years was 3.7, 2.8, 2.3, 1.7, 1.2, and 0.9 cm, representing a 26%, 39%, 56%, 69%, and 75% reduction in cryolesion size at 3 and 6 months and 1, 2, and 3 years, respectively. At 3 years, 17 cryolesions (38%) had completely disappeared on MRI. Postoperative needle biopsy identified locally persistent/recurrent renal tumour in 2 patients. In the 51 patients undergoing cryotherapy for a unilateral, sporadic renal tumour 3-year cancer specific survival was 98%. There was no open conversion. During the 2006 AUA Meeting, this group presented updated results on 60 patients that had each completed 5 years followup (median 72 months). Mean tumour size was 2.3 cm (range 1–4.5 cm). Three patients (6.7%) developed local recurrence. Overall and cancer-specific 5-year survival was 82% and 100%, respectively [73].

Moon et al. published results on 16 patients with small renal masses (mean size 2.6 cm), and their mean operating time was 188 minutes. There was 1 reported conversion, and mean blood loss was 40 mL. Tumour biopsy demonstrated 5 RCC. With a mean followup of 9.6 months, all tumours remained nonenhancing and either stable or smaller than the original lesion [74]. This group has recently reported combined data from its 5-year experience with renal cryoablation on 88 cases, treated by LCA [58] or PCA [20]. Mean tumour size was 2.6 cm. At a mean followup of 19 months, the overall, cancer-specific and recurrence-free survival rates were 88.5%, 100%, and 98.7%, respectively. Four patients required a further treatment due to persistent disease, and one had progression to locally advanced disease [75].

In 2007 Polascik et al. published results from his experience in 26 patients who underwent LCA using third-generation cryotechnology, for 28 renal masses of 3.5 cm or less (median 2 cm). Patients were followed by serial CT or MRI scan, at least every six months after cryoablation. The mean patient age was 64 years (range: 44–79), and the mean followup was 20.9 months. The median tumour size was 2.0 cm (range: 1–3.5 cm). No patient was converted to open surgery. With an overall survival rate of 100%, no evidence of recurrence or progression was found in this cohort [76].

With 47 cases in their series, Beemster et al., from the University of Amsterdam group, have now published data on 26 patients with available followup of 6 months or more. With an average followup of 17.2 months (range: 6–36 months) and a mean tumour size of 2.4 cm (range: 1.3–3.8 cm), only 1 treatment failure has been reported [77].

In agreement with data generated by larger series, preliminary results from smaller series have recently been published [78–81]. Although comprising smaller number of patients and limited followup in some cases, the published

Table 1: Summary of largest reported series on LCA.

	n	Age, years	Follow-up, months	Tumour diameter, cm	% of RCC	Failures/ Recurrences	Operative time, min.	Hospital stay, days	Complications
Lee et al. [68]	**20**	67.9 (43–84)	20.3 (1–40)	2.6 (1.4–4.5)	55%	1/0	305.9	2.6	Atrial fibrilation (1), ECG changes, no MI (1), Pancreatic injury (1), transient raised lipase-amylase (5), Transfusion (1)
Nadler et al. [69]	**15**	68.5 (49–86)	15 (4.9–27)	2.15 (1.2–3.2)	67%	1/1		3.5	Respiratory failure (1), prolonged ileus (1)
Schwartz et al.§ [71]	**70**	67 (32–85)	10 (3–36)	2.6 (1.2–4.7)	59%	1/1		2.2	CVA (1), transfusion (2), renal fracture (1), Transient hydronephrosis (1)
Cestari et al. [72]	**70**	63.2	36 (28–48)	2.37 (1–6)	69%	0/1	181.4	4.5	Haematuria (2), pyrexia (6), bleeding (1), Anaemia (6), Pulmonar oedema (1), PUJ Obstruction
Hegarty et al. [73]	**60**		72	2.3 (1–4.5)		0/3	174.2	2.4	2% transfusion rate. Congestive Heart Failure (1), Splenic haematoma (1), oesophagitis (1), Pleural effusion (1)
Moon et al. [74]	**16**		9.6 (1–28)	2.6 (1.5–3.5)	33%	0/0	188	1.9	Pneumonia (1)
Polascik et al. [76]	**26**	64 (44–79)	20.9 (2–53)	2.5 (1–3.5)		0/0		2 (0–9)*	Transfusion (1), prolonged ileus (1)
Beemster et al. [77]	**26**		17.2 (6–36)	2.4 (1.3–3.8)		1/0			Paraesthesia (1), UTI (1), pneumonia

n: Number of patients.
RCC: Renal cell carcinomas found on histology.
Values expressed as mean unless stated otherwise.
§Total of 84 cases in this series. Only 70 of them were performed laparoscopically.
*Value expressed as median.

series clearly demonstrate the increasing interest and rapid expansion of this novel ablative technique.

8. PERCUTANEOUS CRYOABLATION (PCA)

While technical limitations hampered initial attempts at percutaneous cryoablation in human kidneys [59], the rapid development of argon technology and ultrathin probes, together with CT and open access interventional MRI, allowing real-time monitoring of the ice ball, provided the much needed technical breakthroughs, making this approach safe and reproducible.

In 2001, Shingleton and Sewell [82] reported their initial experience in 20 patients (22 tumours) treated with 2 or 3 mm cryoprobes and interventional MRI. Mean tumour size was 3 cm (range: 1.8–7 cm), and average treatment time was 97 minutes (range: 56–172 minutes). Procedures were performed under general anaesthesia or sedation, and 95% of patients were discharged within 24 hours. With a mean followup of 9.1 months (range: 3–14 months), they reported only one failure, requiring retreatment. The only complication was a superficial wound abscess. Recently, the authors have updated their series including patients with von Hipple-Lindau [83] and with tumour/s in a solitary kidney [84]. With an average followup of 24 months, 9 (15%) cases required retreatment due to incomplete initial ablation. Only 1 patient required transfusion, and there were no reported cancer-related deaths.

Experience on 23 patients (26 tumours) with mean size 2.6 cm (range: 1–4.6 cm) and mean age of 66 years (range: 43–86 years) was reported by Silverman et al., using a 0.5-T open MR imaging system and general anesthesia. Twenty four masses were RCCs, 1 was an urothelial carcinoma and 1 was an angiomyolipoma. With a mean followup of 14 months (range: 4–30 months), 24/26 tumours were successfully ablated, 23 of which required only one treatment session. In 2 cases, a small enhancing nodule located at the margin proved to be recurrent tumours. Two complications

(1 haemorrhage requiring transfusion and 1 abscess drained percutaneously) occurred in a total of 27 cryoablations [85].

In 2006 Gupta et al. published CT-guided PCA on 27 tumours of 5 cm or less (mean size 2.5 cm), using conscious sedation and real-time CT monitoring. With 1 month or more followup imaging available on 16 cases (mean 5.9 months), 15 tumours showed no signs of enhancement. In 1 case, blood transfusion was required for bleeding [86].

The Mayo Clinic experience on 40 cases of PCA with CT monitoring has recently been published [87]. Mean tumour size was 4.2 cm (range: 3.0–7.2 cm) and at least 3 months followup was available in 65% of the cases (mean 9 months; range: 3–22 months). Technical success, defined as extension of the ice ball beyond the tumour margin and absence of postablation enhancement on CT, was reported in 38 (95%) cases, with no tumour recurrence or progression in the cohort. Overall complication rate for this cohort was reported at 8%.

9. FUTURE DIRECTIONS

Initial studies of combination therapy with 5-FU prior to freezing, indicated a temperature-dependent reduction on cell viability in a prostate cancer cell (PC-3) model [88]. Furthermore, molecular analysis using this model has demonstrated a synergistic effect of sublethal concentrations of 5-FU and Cisplatin prior to freezing (-15°C), mediated by a shift in the Bcl-2 to Bax ratio to a prodeath tendency [89]. Similar synergistic response has been reported in a renal cell model, the data suggesting that 5-FU chemotherapy may be more effective when followed by cryosurgery [90]. In the clinical setting, synergistic activity of cryoablation and cyclophosphamide is currently been evaluated on advanced epithelial tumours (NCI. Trial protocol NCT00499733).

Equally, since freezing enhances the radiosentitivity of cells, combination of radiotherapy with cryoablation may potentially confer benefits [65], as already indicated in preclinical models of prostate cancer, where adjuvant radiation and curcumin have demonstrated a synergistic effect with cryoablation [91].

At the time of writing this review, the Cleveland Clinic group have made public the initial results employing Single Port Access Renal Cryoablation (SPARC). A total of 6 patients, with mean tumour size of 2.6 ± 0.4 cm, successfully underwent SPARC, via a transperitoneal or retroperitoneal approach, with no intraoperative complications and no need for conversion, demonstrating the feasibility and safety of this, potentially scarless, procedure [92, 93].

Further development of imaging techniques and cryoprobe technology, clinical evaluation of combination therapy with conventional chemo- and radiotherapy, together with promising novel cryoenhancers, may have major implications on the management of small renal masses in the future

10. CONCLUSIONS

Widespread implementation of USS, CT, and MRI has resulted in an increased detection of early, small renal masses. In the last 20 years, the proportion of incidentally found renal tumours raised from 13% to an estimated 60%, with a substantial parallel decrease in tumour stage, grade, and proportion of metastasis at presentation, in these patients [94]. As a result, urologists are now faced with a new cohort of asymptomatic, healthier patients, with incidentally found small renal masses.

While open partial nephrectomy is still the reference standard [95], its associated morbidity has encouraged researchers and practicing clinicians towards less radical approaches, thus the rapid development of laparoscopic partial nephrectomy and novel ablative techniques such as radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), and cryoablation (CA). Among ablative techniques, cryotherapy, and in particular laparoscopic cryoablation, is the most extensively studied and the one with more rapid expansion in clinical practice.

Cryosurgery offers the clear advantage of combining a nephron-sparing surgery together with a minimally invasive approach. Anaesthetic requirements, postoperative analgesia, and hospital stay are significantly reduced, with a much rapid return to normal activity and work.

In the early days of development and clinical implementation of cryoablation, concerns were raised regarding safety of the procedure, the lack of followup, and oncological outcome [96].

Regarding the safety of the procedure, published studies up to this day have shown minimal procedure-specific morbidity, with complication rates comparable or better than current available minimally invasive procedures. Reports from the largest series have demonstrated to be a less morbid procedure than laparoscopic partial nephrectomy, with a comparable 5-year oncological safety [97].

Among the novel ablative techniques, radio frequency ablation (RFA) is the procedures with more emerging clinical data. Although the procedure-specific morbidity, mostly based on small and nonstandardised series, appears to be low, serious issues have been raised regarding the RFA cell-killing potential and its higher risk of local disease recurrence, as demonstrated en several clinical studies [98–102].

When compared to RFA, available data from preclinical [52] and several clinical studies confer to cryoablation an advantageous oncological safety profile. The Cleveland Clinic group have recently published results from their RFA and LCA series, highlighting the issue of residual disease and demonstrating a clear advantage in the LCA cohort. With 109 renal lesions (88 patients) treated with RFA and 192 lesions (176 patients) treated with LCA, radiographic (CT or MRI) success at 6 months was 85% and 90% for RFA and LCA, respectively. More importantly, when lesions were later biopsied at 6 months, the success in the RFA cohort decreased to 64.8%, while LCA success remained high at 93.8%. Six of 13 patients (46.2%) with a 6-month positive biopsy after radio frequency ablation demonstrated no enhancement on posttreatment MRI or CT, while in the LCA group, all positive biopsies revealed posttreatment enhancement on imaging just before biopsy. The authors recommend postradio frequency ablation followup biopsy

due to the significant risk of residual renal cell cancer without radiographic evidence [103].

Supporting these findings, a recent meta-analysis of available data demonstrates a higher risk of local disease recurrence in tumours treated with RFA, when compared to those managed by cryoablation [104].

While long-term followup is still awaited, encouraging results have been reported in series with up to 5-year followup, with cancer-specific survival rates ranging from 98 to 100% [68, 70, 72, 73, 76, 105] with LCA and 97% with PCA [7]. This is comparable to 5-year cancer-specific survival rate of 92%, reported with partial nephrectomy [95, 97, 106].

While clinical application and indications of cryoablation of small renal masses are still not clearly defined, it is recommended by available clinical evidence, that CA should be reserved for small (<3 cm) solid-enhancing renal masses in older patients with high operative risk. Young age, tumour size >4 cm, hilar tumours, intrarenal tumours, and cystic lesions can be regarded as relative contraindication, whilst irreversible coagulopathy is widely accepted as an absolute contraindication [107].

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 197324, 3 pages
doi:10.1155/2008/197324

Review Article

Cryoablation of Small Renal Tumors in Patients with Solitary Kidneys: Initial Experience

Ravi Munver,[1, 2, 3, 4] Grant I. S. Disick,[1] Salvatore A. Lombardo,[1, 4] Vladislav G. Bargman,[1, 4] and Ihor S. Sawczuk[1, 2, 3, 5]

[1] *Department of Urology, Hackensack University Medical Center, 360 Essex Street, Suite 403, Hackensack, NJ 07601, USA*
[2] *Department of Urology, Touro University College of Medicine, 360 Essex Street, Suite 403, Hackensack, NJ 07601, USA*
[3] *The John Theurer Cancer Center at Hackensack University Medical Center, 20 Prospect Avenue, Hackensack, NJ 07601, USA*
[4] *Division of Urology, Department of Surgery, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, USA*
[5] *Department of Urology, College of Physicians and Surgeons, Columbia University, 161 Fort Washington Avenue, New York, NY 10032, USA*

Correspondence should be addressed to Ravi Munver, rmunver@humed.com

Received 1 May 2008; Accepted 28 August 2008

Recommended by J. Rubio

Introduction. The purpose of this study was to evaluate the role of renal cryoablation in patients with solitary kidneys with the goals of tumor destruction and maximal renal parenchymal preservation. *Methods*. Eleven patients with single tumors were treated with cryoablation, of which 10 patients had solitary kidneys and 1 had a nonfunctioning contralateral kidney. All procedures were performed via an open extraperitoneal approach; ten tumors were treated with in-situ cryoablation and 1 tumor was treated with cryo-assisted partial nephrectomy. *Results*. Cryoablation was successfully performed without any preoperative complications. Mean patient age was 62.4 years (range 49–79), tumor location included: 6 (upper pole), 2 (mid-kidney), 3 (lower pole). The mean and median tumor size was 2.6 cm and 2.8 cm (range 1.2–4.3 cm), mean operative time 205 minutes (range 180–270 minutes), blood loss 98.5 ml (range 40–250 ml), and hospitalization 4.6 days (range 3–8 days). Creatinine values included: preoperative 1.43 mg/dL (range 1.2–1.9), postoperative 1.67 mg/dL (range 1.5–2.5), and nadir 1.57 mg/dL (range 1.3–2.1). All patients were followed postoperatively with magnetic resonance imaging for surveillance. At a median follow-up of 43 months, 9 patients had no evidence of recurrence, 1 patient has an enhancing indeterminate area, and 1 patient was lost to follow-up. *Conclusion*. Intermediate-term results suggest that renal cryoablation offers a feasible alternative for patients that require a maximal nephron-sparing effort with preservation of renal function and minimal risk of tumor recurrence.

1. INTRODUCTION

Nephron-sparing surgery (NSS) entails complete resection or destruction of a renal tumor while maximizing preservation of normal parenchymal tissue. Improvements in surgical techniques have gradually led to more widespread utilization of partial nephrectomy with acceptable postoperative morbidity and equivalent oncologic efficacy as compared to radical nephrectomy. Cryoablation is an alternative to partial nephrectomy for the treatment of renal tumors and it employs the concept of nephron-sparing surgery [1, 2].

The purpose of this study was to evaluate cryoablation as an NSS technique for the treatment of small renal masses in patients with solitary kidneys. We reviewed the application, effect on renal function, and intermediate outcomes of cryoablation in this subset of patients that require maximal renal parenchyma preservation while fulfilling the goal of tumor destruction.

2. MATERIALS AND METHODS

Between August 2000 and November 2004, 11 patients (9 male, 2 female) were treated with renal cryoablation for suspicious renal lesions. All patients had a single renal mass suspicious for malignancy based on radiologic imaging studies. Ten patients had a solitary kidney and 1 had a non-functioning contralateral kidney. Cryoablation was selected

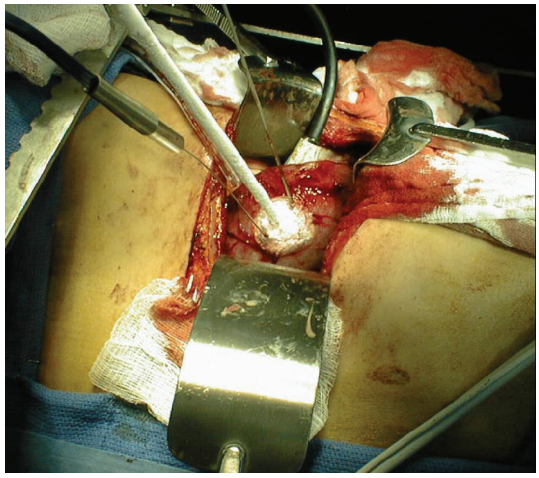

Figure 1: Open renal cryoablation. Cryoprobe with 2 temperature probes are seen.

in order to offer patients a nephron-sparing procedure in cases that, due to tumor location, were not ammenable to partial nephrectomy. Patients did not receive preoperative biopsy of the renal mass lesion due to the associated risk of bleeding and renal injury in patients with solitary kidneys. Ten tumors were treated with insitu cryoablation and 1 tumor was treated with cryoassisted partial nephrectomy.

An extraperitoneal flank incision was made between the 10th and 11th ribs allowing exposure of the kidney and renal tumor. Intraoperative high-resolution renal ultrasonography with a 7.5 MHz transducer was used to establish and confirm tumor size, depth of invasion, and proximity to the renal hilar vessels and the collecting system. The renal hilar vessels were isolated but not occluded in all cases. Each tumor was biopsied with a 14gauge Tru-Cut needle prior to initiation of cyroablation.

Cryoablation was performed using the Cryocare surgical system (Endocare Inc., Irvine, Calif, USA). Under ultrasound guidance, 1 or 2 cryoprobes were placed directly into the identified lesion, and temperature sensor probes were placed at the periphery of each mass to provide intraoperative monitoring of adjacent renal parenchymal temperatures. In each case, the tumor margins were localized with intraoperative ultrasound, allowing for precise placement of the cryoprobes. After cryoprobe placement, the tumor was treated with 2 freeze cycles (-40C° for 10–15 minutes/cycle) (see Figure 1). Each freeze cycle was followed by an active thaw process. In the case of the partial nephrectomy, the tumor was excised with a scalpel by tracing the edge of the ice ball.

Perioperative data were evaluated including tumor size, operative time, estimated blood loss, length of hospital stay, and preoperative and postoperative creatinine.

3. RESULTS

Eleven patients were treated with cryoablation for 5 right renal tumors and 6 left renal tumors. The mean patient age was 62.4 years (range 49–79 years). Tumors were located in the upper pole ($n = 6$), mid-kidney ($n = 2$), and lower pole ($n = 3$) with a mean and median tumor size of 2.6 cm and 2.8 cm, respectively (range 1.2–4.3 cm). The mean operative time was 205 minutes (range 180–270 minutes), blood loss 98.5 mL (range 40–250 mL), and hospitalization 4.6 days (range 3–8 days). The procedure was successfully completed in all patients without any major intraoperative or postoperative complications.

Biopsies of the 11 lesions confirmed renal cell carcinoma ($n = 7$), oncocytoma ($n = 2$), and angiomyolipoma ($n = 1$), with one biopsy specimen that was indeterminate. The patient that underwent cryoassisted partial nephrectomy had negative margins.

The mean preoperative creatinine was 1.43 mg/dL (range 1.2–1.9) and postoperative creatinine was 1.67 mg/dL (range 1.5–2.5). The nadir creatinine was 1.57 mg/dL (range 1.3–2.1). All patients were followed postoperatively with magnetic resonance imaging (MRI) at 3–6 month intervals. Imaging these patients within the first 3 months was not performed due to our prior experience with inflammatory responses in the treated area that can lead to misinterpretation. At a median follow-up of 43 months (4–59 months), 9 patients had no evidence of recurrence, 1 patient had an indeterminate area, and 1 patient was lost to follow-up after 4 months.

4. DISCUSSION

Cryoablation is a minimally invasive technique that has emerged as an option for small renal masses with reduced morbidity compared to partial nephrectomy. This technology provides a nephron-sparing alternative that is curative by destruction rather than excision of the renal mass [3].

Tissue destruction from cryoablative therapy occurs from sequential freezing and thawing of tissues. Cellular destruction from the freeze process results from complex direct and indirect physiologic mechanisms, including direct physical disruption of the cellular membranes, proteins, and intracellular organelles from ice crystals. In addition, there are indirect effects such as microvascular thrombosis, osmotic dehydration, and cellular anoxia during the freeze process, which may also extend beyond the physical ice ball. The initial histologic change noted after a cryoablative procedure is coagulative necrosis. Subsequently, chronic fibrosis with collagen deposition results [2].

Early animal studies by Nakada et al. utilizing and in vivo rabbit renal cell cancer tumor model demonstrated that thermosensor-monitored renal cryosurgery produces similar outcomes to nephrectomy in terms of preventing metastatic disease [4]. Rodriguez et al. published preliminary results of series of seven patients undergoing renal cryoablation [5]. The estimated blood loss averaged 111 mL and there were no perioperative complications. Six of the 7 patients had a minimum of one follow-up computed tomography scan (mean follow-up of 14.2 months) and each of these studies demonstrated partial resolution of the lesion.

Rukstalis et al. reviewed a cohort of 29 patients that were treated with open renal cryoablation since 1996 [6]. The median preoperative renal mass size was 2.2 cm, of which 22 were solid renal masses and 7 were complex renal lesions.

Five major adverse events occurred of which only one event was directly related to the procedure. At median follow-up of 16 months, 1 patient experienced a biopsy-proven local recurrence, and 91.3% of patients had a complete radiographic response with only a residual scar or small nonenhancing cyst. The authors concluded that open renal cryoablation appeared safe for the destruction of solid or complex renal masses, although rigorous radiographic, and clinical follow-up was required.

Chen et al. reported their experience with laparoscopic cryoablation of renal masses in 35 patients that underwent successful therapy with minimal postoperative complications [7]. In their series, the mean operative time was 3 hours and mean estimated blood loss was 85 mL. At 11 months of follow-up, there were no local or port site tumor recurrences. In a similar study by Gill et al., 32 patients underwent laparoscopic renal cryoablation. In this study, there were no local tumor recurrences in this group of patients [8].

Cryoablation is becoming an increasingly popular minimally invasive technique for treating renal cell carcinoma and has been shown to effectively treat renal and adrenal masses [8, 9]. This technique appears to be safe and efficacious, with recurrence rate reported as low as 6.7%, and a 5year cancer-specific survival rate of 100% for RCC [10–12].

Patients with solitary kidneys or impaired renal function may benefit from renal cryoablation as compared to partial nephrectomy for several reasons. Cryoablation may be associated with a lower risk for bleeding and may obviate the need for hilar occlusion, thus preventing the detrimental effects related to controlled ischemia. Our patients that were considered to be appropriate candidates for cryoablation did not require hilar occlusion of their solitary renal unit. While partial nephrectomy can be selectively performed without warm ischemia, the patients in our series had tumor characteristics that were not optimal for this procedure without hilar occlusion.

In our early experience with cryoablation for patients with solitary kidneys, each patient underwent an open procedure in order to minimize inadvertent injury and confirm adequate placement of the cryoprobes. Since our initial experience, we have continued our efforts to further decrease morbidity by transitioning to a laparoscopic approach for suitable tumors in this cohort of patients.

Intraoperative ultrasound was essential in delineating the intrarenal anatomy and the dimensions of the tumor [13]. Moreover, ultrasonography allows visualization of the ice ball to confirm adequate treatment of the entire lesion. In the patient that underwent cryoassisted partial nephrectomy, the tumor was excised following the freeze cycle with the intention of minimizing blood loss, as hilar occlusion was not employed. Utilization of the edge of the ice ball served as a guide for resection and facilitated complete excision of the mass with minimal blood loss.

Renal cryoablation has been reported to target kidney tumors in a precise, safe, and reproducible manner. This technology offers the ability to treat renal tumors in patients that require a maximal parenchymal sparing procedure, such as patients with solitary kidneys. Renal cryoablation allows the accurate and safe application of this surgical modality for the treatment of renal tumors with emphasis on parenchymal sparing. Additionally, the need for hilar occlusion of a solitary renal unit is completely obviated. Our intermediate follow-up data is promising in terms of both cancer control and preservation of renal function. We do not routinely perform renal biopsies following cryoablation due to the associated risks of bleeding and renal injury in patients with solitary kidneys. Instead, this practice can be reserved for patients with a suspicious enhancing area on follow-up surveillance imaging studies. If a positive biopsy is obtained in this instance, the options for surveillance, repeat cryoablation, or nephrectomy may be considered. Our results are consistent with other reports in the literature and demonstrate that renal cryoablation is a feasible technique for the management of small renal masses in patients with solitary kidneys. Additionally, combined with a laparoscopic approach, cryoablation is an attractive minimally invasive treatment option in such patients.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 809845, 5 pages
doi:10.1155/2008/809845

Review Article

High-Intensity Focused Ultrasound in Small Renal Masses

Jose Rubio Briones, Argimiro Collado Serra, Alvaro Gómez-Ferrer Lozano, Juan Casanova Ramón-Borja, Inmaculada Iborra Juan, and Eduardo Solsona Narbón

Servicio de Urología, Instituto Valenciano de Oncología, C/Beltrán Báguena 8, 46009 Valencia, Spain

Correspondence should be addressed to Jose Rubio Briones, jrubio@fivo.org

Received 26 March 2008; Revised 6 October 2008; Accepted 4 November 2008

Recommended by F. Algaba

High-intensity focused ultrasound (HIFU) competes with radiofrequency and cryotherapy for the treatment of small renal masses as a third option among ablative approaches. As an emerging technique, its possible percutaneous or laparoscopic application, low discomfort to the patient and the absence of complications make this technology attractive for the management of small renal masses. This manuscript will focus on the principles, basic research and clinical applications of HIFU in small renal masses, reviewing the present literature. Therapeutic results are controversial and from an clinical view, HIFU must be considered a technique under investigation at present time. Further research is needed to settle its real indications in the management of small renal masses; maybe technical improvements will certainly facilitate its use in the management of small renal masses in the near future.

1. INTRODUCTION

We are facing a rapid increase of incidentally detected small renal masses (SRMs) nowadays [1, 2], prompting us to face many different clinical scenarios and probably minimally invasive ablative techniques will find their role in those unfit patients who are not operable and do not accept a partial nephrectomy or a watchful waiting policy [3] in case of a possible renal cell carcinoma (RCC) diagnosed probably incidentally [4].

High-intensity focused ultrasound (HIFU) induces thermal damage to the targeted tissue without the need of the insertion of a probe into the tissue, thus being the most real "minimally invasive" proposed technique among the ablative treatments for small renal masses (SRMs).

This manuscript will focus on the principles, basic research, and clinical applications of HIFU in small renal masses, reviewing the present literature and analyzing HIFU as a possible treatment for SRM, recognizing no experience in its use for any renal masses by our group.

2. MATERIAL AND METHODS

We reviewed PubMed with no limit on time, searching for papers in English or Spanish, using HIFU and renal or HIFU and kidney as key words. We included the literature published on HIFU both in the experimental and clinical settings.

3. PRINCIPLES AND TECHNIQUE

The principle of HIFU resembles the one for ultrasound (US), but a higher intensity is used. Ultrasound is progressively absorbed by the tissue and its mechanical energy converted to heat. At a high and focused strategy, the generated heat denatures proteins and produces coagulative necrosis, objectives obtained when temperature reaches 65°C in renal lesions [5]. The induction of thermal necrosis will depend on several factors: the applied power, the US frequency, transducer characteristics (shape, type, size, and number of probes), exposure time, spatial distribution of the field, absorption properties of the tissue, attenuation in the intervening tissue, acoustic reflection and refraction, and finally the perfusion rate in the targeted tissue. Different necrosis rates were shown (volume of ablated tissue per 1 second isonication) for different organs, and for example, the kidney has a lower necrosis rate than the liver [6].

As a technique under development, there are no standard recommendations for its application and this is a point under vast research. Initially, extracorporeal HIFU generators used

multiple piezoelectric elements located in a concave disk, generating intensities of >10000 W/cm^2 which were derived in cavitation lesions, limitating its use in humans [7]. Nowadays, HIFU systems use single transducers, focused by acoustic lenses or by being concave. As the focal lengths are smaller, frequencies of 3-4 MHz can be achieved, producing smaller but better defined lesions. Modern HIFU devices obtain focal depths of 10–16 cm; the focal zones are cigar shaped and the volume ablated depends on power intensity, duration of application, and location of pulses. All this equipment is accompanied by US regular probes trying to control the effectiveness of the HIFU application; interestingly, as power intensity increases (5–20 kW/cm^2), a cavitation phenomenon appears which permits a target point to monitor HIFU effects [8]. An excellent summary on physical principles and devices of HIFU [9] has recently been published.

In the extracorporeal approach, frequencies of 1–1.8 MHz are used in an attempt to increase penetration; in this range, renal thermal lesions were observed in animal models [10, 11]. In the clinical setting, two systems for extracorporeal HIFU have been tested. First, from Storz Medical (Storz; Schaffhausen, Switzerland), we use a 1 MHz piezo element focused at a depth of 100 mm with a parabolic reflector of 10 cm aperture. An integrated 3.5 MHz B-mode US transducer permits inline imaging of the area to treat. The US beam is coupled into the body by a flexible polyurethane cushion filled with degassed water at 16°C, witch permits the variation of the skin-focal spot distance altering its filling [12]. The second HIFU therapeutic system was designed by Chonqing Haifu CO. Ltd (Chonqing, China); it is composed by a patient table, an operating console, and a treatment unit, situated under the table within a basin filled with degassed water to couple with US delivered to the patient, who lies over the water bath. Exchangeable ellipsoidal transducers of 12 or 15 cm diameter are installed in the water bath around a central 3.5 MHz diagnostic transducer. This system permits frequencies of 0.5, 1.2, and 1.5 MHz and focal lengths of 100–160 mm depending on the transducer used. Following the treatment protocol and by exposing the targeted areas up to six times, the authors achieve an estimated site intensity of up to 20000 W/cm^2, enough to create cavitation and even bubble formation on real-time diagnostic imaging, which authors propose as successful tissue ablation marker [13].

Due to the problems with extracorporeal HIFU applications that we will further comment on, the equipment moved into the laparoscopic field. In porcine models, it was modified with acceptable partial kidney ablation with no damage to surrounding not targeted tissues [14]. In phase I study, this approach was attempted in the human setting, using conventional lap isolation of the SRM through four 12 mm access ports; authors used intraoperative renal power Doppler US with a 10 Hz laparoscopic US probe (BK Medical, Denmark) to locate the SRM. They then changed one of the ports to an 18 mm port (Ethicon; San Angelo, Tx, USA) to introduce the laparoscopic HIFU system (Sonatherm, Misonix Inc., Fiarmigdale, NY, USA), which is composed by a treatment console, an articulated probe arm, a pomp unit, and the laparoscopic probe (covered with a system which permits cooling with gas-free cold water) [15]. HIFU energy is delivered by a truncated spherical shell 4 MHz transducer with a 30 × 13 mm aperture and a 35 mm focal length. One of the best improvements of this approach, compared to the percutaneous one, is that the probe works in direct contact with the SRM and real-time imaging, based on qualitative assess on hyperechoic changes resulting from boiling and cavitation events, permitting direct control of the procedure with the 12 mm transducer aligned confocally with the HIFU transducer. The procedure was calibrated resembling the results obtained in animal models research to ablate tissue at an average rate of 0.6 cm^3/min at typical power level between 30–38 W [14, 16].

4. RESULTS

We found 42 manuscripts using HIFU and renal/kidney as key words. HIFU has been extensively used in other organs, targeted to malignant and nonmalignant tissues: brain, breast, eye, prostate, bladder, uterus, liver, and so forth, showing no increase in cell dissemination [17–20]. An attractive indication for tumour in a solitary testis has been recently published with acceptable results [21].

4.1. Pathological assessment

The thermal damage produced by HIFU causes progressive tissue changes depending on the time when the pathological study is done. Immediately after its application in a porcine model, the tissue demonstrated intense congestion, hyperaemia, and alterations of the micropapillaries, and electron microscopy showed alterations of the mitochondria, ribosomes, and lysozymes. At day 2, necrosis starts to be seen within an intense area of hyperaemia and congestion which results in complete necrosis at day 7. Finally, at day 90, a complete fibrosis of the targeted area is observed [22]. On healthy human kidney, haemorrhages were seen in 15 out of 19 cases and microscopically, it was shown that they were caused by fibre ruptures in the wall of small vessels [23]. In papers where SRMs have been excised after HIFU application, "severe thermal tissue damage" has been defined as intravascular disruption of erythrocyte membranes, vacuolisation of tumour and arterial smooth muscle cells, pycnosis and elongation of tumour cell nuclei, rupture of tumour cell membranes, and cell detachment, changes which correspond to complete tissue necrosis if the time elapsed from HIFU application and specimen removal is longer [24]. Negative NADH staining in snap-frozen tissue obtained before tissue fixation with formaldehyde after HIFU treatment also reaffirms irreversible heat damage [15, 24].

4.2. Results in the percutaneous approach

Linke et al. were the first to treat a kidney of a rabbit using extracorporeal HIFU [25]. When applied percutaneously in a rabbit model, it was clearly showed that only 2 out of 9 tumours showed well-demarcated effects of ablation [26]. Watkin et al. treated 18-pig kidneys with acute damage

detected in 67% [11]. In a canine model, HIFU application with 400 W power and 4-second pulse duration and a calculated site intensity of 1430 W/h obtained coagulative necrosis of variable degree in the targeted area [12]. Recently, the use of microbubbles injected before percutaneous HIFU isonication of goat kidneys showed better necrosis rates than direct HIFU application [13].

In humans, phase II study using the Storz system was conducted by the University of Vienna. Sixteen renal tumours were treated with HIFU, two with curative intent and 14 were subsequently removed. Examination of the specimens showed poor results in terms of therapeutic effect, as necrosis was found only in 9 out of 14 cases, all of which had been exposed to the highest site intensities, and the histologically damaged tissue only composed 15–35% of the targeted tissue [27]. In another phase II study, Häcker et al. treated 19 patients with RCC before nephrectomy, focusing HIFU to healthy renal tissue; after immediate removal of the kidney, they observed variable but limited pathological signs of thermal damage, as for example haemorrhages, just in 15 out of 19 specimens, but these effects could not be correlated to the energy administered and lesion size did never reach the targeted volume [23].

When using the Chongqing system, Wu et al. applied percutaneous HIFU with a palliative intent in 13 advanced RCC, having shown clinical improvement (less pain and disappearance of haematuria) in most of the treated patients, although treatment was considered incomplete in 10 patients [18]. Similar disappointing results were published from UK, where 8 patients were treated with a similar system and only 4 out of 6 kidneys showed radiological evidence of treatment effect on MRI 12 days after HIFU application and just 1 out of 4 removed kidneys showed histological confirmed ablation [17]. This group is currently undergoing a prospective, nonrandomized clinical trial of percutaneous HIFU in the treatment of SRM, looking at histological outcome in resected tumours in one arm and following the ablated tumours with contrast enhanced MRI in the other arm [28].

4.3. Results in the laparoscopic approach

In a recently published clinical phase I study, the laparoscopic HIFU approach previously described was applied to 10 patients with solitary renal masses. Two of them had 9 cm tumours and HIFU was applied just as marker lesion before radical laparoscopic nephrectomy; the rest had SRM with a median size of 22 mm and were treated with a "curative intent" applying HIFU to the entire tumour with a margin of 2-3 mm of surrounding parenchyma. Seven of these tumours were operated afterwards by means of a laparoscopic partial nephrectomy and one was left in situ in a patient with high comorbidities. In the SRM subgroup, a median HIFU exposure time of 19 minutes (range 8–42) was used. The first two patients showed, in the subsequent pathological examination, just a 2-3 mm of vital tissue adjacent to where the HIFU probe was approximated with the rest of the tumour with thermal necrosis; the authors explained this phenomenon to an excessive cooling of the probe, and changing this parameter, they did not observe it again in the remaining cases, although a patient showed a 20% central area with no thermal effects, showing complete thermal necrosis in the 4 remaining removed cases (57%). The nonexcised tumour was successfully treated attending to real-time US data, examination of core biopsies showing thermal necrosis, and follow-up CT scans up to 6 months showing no constraint enhancement and shrinking of the lesion [15].

4.4. Complications

There have been just two severe complications due to HIFU application in the abdominal cavity in humans: a superior mesenteric artery infarction and a perforation of the terminal ileum, but both were after treatment of recurrent or metastatic colon carcinoma [29]. When focused to kidneys, no serious side effects have been shown [27]; just 2 patients had grade III skin lesions [28], but the most common type of skin toxicity is less than 1cm blister or track at the treatment site [17]. Changes in laboratory tests are also nonsignificant [17, 18].

5. DISCUSSION

Technology has improved the initial problems of the first HIFU intents to treat kidneys with devices derived from piezoelectric lithotripters [22] which could not focus the targeted lesion; the development of a new HIFU source (Storz UTT System, Storz Medical AG, Kreuzlingen, Switzerland) with a smaller (10 cm) diameter for flexible extracorporeal application permitted the authors to focus precisely on the targeted area in an ex vivo scenario with perfused kidneys, adjusting the pulse duration and the power of the generator to the lesion size [30].

One of the major problems with HIFU is that from an extracorporeal application, there are several factors that interfere between the power emitted by the ultrasound probe and the energy arriving to the targeted area: focal length, type, and characteristics of the tissue to be crossed through variable vascularization of the kidney and its mobility as well as the limitation proximity of air (gut) or bone (ribs) because of reverberation, acoustic shadowing, and refraction [31], the last with burning power with potential damage to close organs.

Another drawback of percutaneous HIFU application is the absence of a reliable radiologic method controlling the effects of HIFU in real time. Research is being done to find more fixed devices coupled with respiratory movements trying to save absorption of ultrasound energy from nontargeted tissues like ribs, fat, or muscles; MRI is being more extensively proposed as a guide to the treatment compared with regular ultrasound due to its information regarding temperature changes in the treated tissue within seconds after application [31]. Unfortunately, movement of the kidney also affects the accuracy of MRI thermometry [32]. Mobility has been partly corrected using multichannel focused US systems, trying to combine motion tracking and feedback electronic steering of the HIFU beam [33] and multiprobe systems of small-aperture confocal HIFU

transducers that also theoretically permit more flexible targeting [34, 35].

All these reasons could explain the poor results in the clinical setting, mostly when histopathological assessment of thermal necrosis on the targeted tissue has been studied. The limited clinical experience with the extracorporeal approach and its poor results make this approach not suitable to treat renal cancer in humans, and it has to be considered a technique under experimental research [12].

Although percutaneous approach would be the ideal and real "no invasive," laparoscopic approach facilitates resolutions of many of the problems facing the percutaneous approach. The use of the 18 mm laparoscopic HIFU transducer, applicable to conventional lap armamentarium and controlled by US, as shown by Klingler et al. in phase I study, indicated just for peripheral tumours not larger than 3.5 cm in size [15], opens a window to clinical research with this method as it really does not clamp the kidney or puncture it as other ablative techniques. Although the protocol is under evolution, the authors have shown safe and promising results with at least better thermal necrosis results than those obtained with the percutaneous approach, but it has to be kept in mind that laparoscopy itself is not complication-free as it needs general anaesthesia, pneumoperitoneum, and tumour isolation, so this approach will have to be compared in randomized trials with other nonablative techniques and also with watchful waiting policies in front of SRM in elderly or unfit patients, the subgroup of patients where it makes sense to avoid open or laparoscopic partial nephrectomy for an SRM.

The follow-up of SRM treated with HIFU is generally performed by contrast-enhanced CT and MRI, but other methods such as PET and microbubble contrast-enhanced ultrasound are under evaluation [36]. Microbubbles increased the ablation efficiency and the visibility of tissue destruction attending to the appearance of hyperechoic regions within the targeted tissue [6]. As with the rest of the nonablative techniques, definitive follow-up protocols are missing [37], and the role of the biopsy in contrast-enhanced lesions has to be investigated [38].

One of the advantages of HIFU applications is that treatments could be repeated, but the need to do it under general anaesthesia results in a limitation of this strategy.

Vast research is needed to establish standards of pulse and power levels which ascertain tissue death, as well as the number and types of probes utilized, as in ex vivo porcine experiments, at identical power levels, lesions induced by multiple probes were larger than those induced by single probe [34]. Another nonresolved issue is the final extent of the coagulative thermal-induced necrosis with time. Finally, extracorporeal or laparoscopic approach will have to define their advantages.

Thus, to establish the clinical usefulness of HIFU to treat SRM, long-term follow-up studies are needed taking into account recurrence-free survival data, quality of life parameters, complications and cost analysis, and all these data compared in clinical trials with open or laparoscopic partial nephrectomy as gold standard techniques [39], cryotherapy and radiofrequency as minimally invasive more developed techniques [40], and watchful waiting policy [3] as options to manage small renal masses.

6. CONCLUSIONS

HIFU is a promising approach to treat SRM because it is probably the most minimally invasive among the proposed techniques. Nevertheless, the number of treated patients is very small, and its results with the percutaneous approach make it not applicable to the humans with a curative intent. Laparoscopic approach makes it a loose part of its "minimally invasive" principles, but preliminary data show better thermal necrosis results and better US real-time control of the treatment. For the moment, we think that HIFU has to be considered as an investigational technique. Technical improvements could certainly facilitate its use in the management of SRM in the near future.

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Hindawi Publishing Corporation
Advances in Urology
Volume 2008, Article ID 974848, 4 pages
doi:10.1155/2008/974848

Review Article

Renal Adenomas: Pathological Differential Diagnosis with Malignant Tumors

F. Algaba

Pathology section, Fundació Puigvert, Universitat Autónoma de Barcelona (UAB), 08025 Barcelona, Spain

Correspondence should be addressed to F. Algaba, falgaba@fundacio-puivert.es

Received 28 May 2008; Accepted 28 August 2008

Recommended by J. Rubio

The renal adenomas can be confused by imaging diagnosis with malignant renal tumors, but there are also real biological dilemmas to determine their behavior. The consensus decisions are the following. (1) The adenoma of clear cells is not accepted, instead it is considered that all the clear-cell tumors are carcinomas, with greater or lesser aggressiveness. (2) Among the papillary neoplasms the WHO 2004 renal cell tumors classification are considered as papillary adenomas tumors with a maximum diameter of 5 mm and may represent a continuum biological process to papillary renal cell carcinoma. The papillary adenomas associated with End-kidney and/or acquired cystic disease may have a different pathogenesis. (3) To consider a tumor as an oncocytoma the size is not important, only the cytological features, microscopic, ultrastructural, and immunohistochemically can help, but some chromosomal observations introduce some questions about its relation with the chromophobe renal cell carcinoma. (4) Finally, the metanephric adenoma, a tumor with some morphological similarity with the nephroblastoma must be considered in the renal adenomas diagnosis.

1. INTRODUCTION

Before sonographic studies, 85% to 90% of renal masses were malignant, with the majority being renal-cell carcinoma. However, with the increasing frequency of incidentally discovered renal masses, only 70% to 85% of lesions are found to be malignant [1].

When we take on the subject of benign neoplasias of the kidney, we must make two large groups, the benign mesenchymal neoplasias and the benign epithelial neoplasias or adenomas.

The benign mesenchymal tumors, with the exception of the angiomyolypoma, are usually subclinical and rarely give the pathologist diagnostic problems, although they can be confused with malignant neoplasias for imaging diagnosis [2].

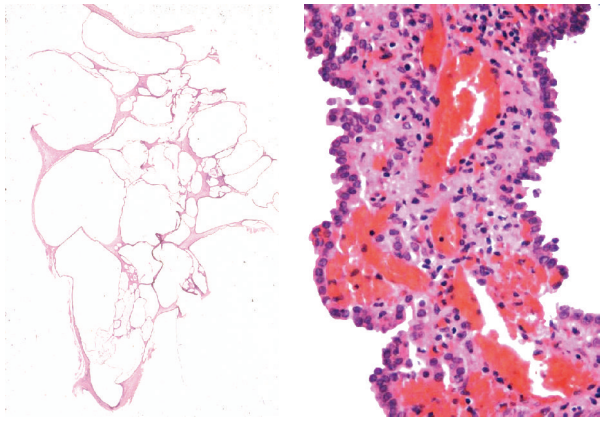
The adenomas are a true clinical-pathological dilemma, not only because they can be confused by imaging diagnosis, but because there are biological dilemmas to determine and therefore different questions emerge: firstly, do the renal adenomas really exist?, and secondly, in case they do exist, are they precursor lesions of renal carcinomas?, and if they were, do we have the possibility of differentiating the benign neoplasias from the malignant ones?

The current classifications of renal carcinomas have managed to integrate the genetic and molecular findings with the cytological characteristics [3]. This conjunction has made it possible to correlate the histological subtypes with the prognostic and therapeutic ones. For this reason, we can approach the renal adenomas according they are of clear cells, of eosinophilic cells (oncocytes), with papillary growth, or have a metanephric blastema appearance.

2. RESULTS

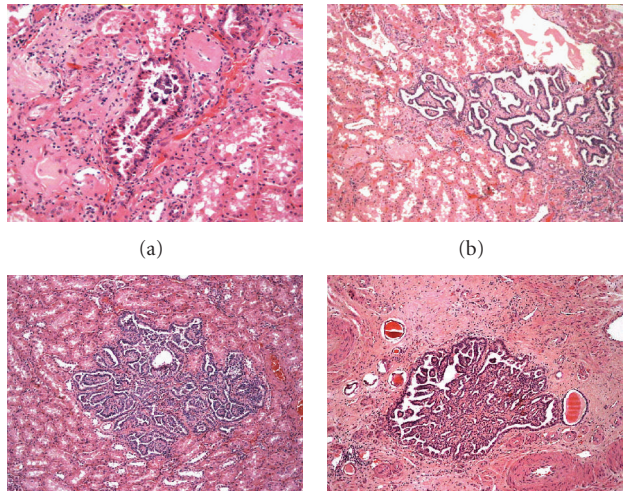
2.1. Adenomas with clear cells?

The most frequent renal neoplasia of the adult is the clear cell renal cell carcinoma. When the pieces from the nephrectomy are studied with this type of carcinoma, around 10% of the cases are multifocal and small tumor nodes with clear cells can be found. This same finding can be made more frequently in kidneys of patients with von Hipel-Lindau disease. These nodes could have been considered adenomas of clear cells, but since Bell's descriptions [4] it is well known



(a) (b)

Figure 1: Cystic nephroma: cystic neoplasm with fibrous stroma an flat epithelium covering the wall.



(a) (b) (c) (d)

Figure 2: Papillary adenomas: different types of basophilic cell adenomas.

that some of the small clear-cell tumors have metastasis capacity and therefore currently the existence of an adenoma of clear cells is not accepted, instead it is considered that all the clear-cell tumors are carcinomas, with greater or lesser aggressiveness.

Having established this axiomatic attitude, there is no problem of differential diagnosis; however, from the morphological point of view, the *cystic nephroma* (Figure 1), formed by multiple separate cysts (which are also known as multilocular cyst) covered by epithelium without nuclear atypia, monolayer, with eosinophilic cytoplasma, can occasionally be covered by cells of clear cytoplasma, without nuclear atypia. In this case, clear cells must not be found in the walls and the intercystic stroma. The cystic nephroma does not have any relation to the multilocular clear cell carcinoma (despite certain similarity with it) [5]. Currently, it is being related to other benign neoplasias such as the mixed epithelial and stromal tumor of the kidney, all of them are much more frequent in women and with estrogen and progesterone receptors in the stromal component [6].

2.2. Papillary adenomas

In about 35% of the cases the renal carcinomas with a papillary pattern have multiple lesions of diverse sizes (from millimeters to centimeters), especially those associated with family syndromes. This fact again poses the existence of adenomas and their possible relation with carcinomas.

The small papillary tumors are characterized by a growth of cells with scant cytoplasma (chromophilic cells), occasionally somewhat eosinophilic, with tubular-papillary patterns, well delimited and not encapsulated (Figure 2). In chromosomal studies, trisomies in chromosomes 7 and 17 were confirmed in the small tumors. Additionally, other chromosomes presented tri-tetrasomies when the in size of the tumor increase. From these findings it was considered that there is a series of small benign lesions and that the increase in size is associated with greater amount of chromosomal alterations and therefore the possible transformation in papillary carcinomas. For this reason, the WHO 2004 renal cell tumors classification considered tumors with a maximum diameter of 5 mm as papillary adenomas [3]. In a practical manner, many pathologists consider that the tumors over 5 mm and up to 10 mm are of low aggressiveness [7].

It should be underscored that although the majority of the papillary adenomas are associated with papillary renal cell carcinoma (47%), they can also be found associated with other variants (16% with clear cell RCC, 8% with chromophobe RCC and 2.5% with oncocytoma) [8].

It should be highlighted that 5% of the papillary adenomas are found in sclerosed kidneys (end-kidneys) and 18% in patients with acquired cystic disease (with or without dialysis). Their morphological characteristics are identical to those associated with carcinomas but curiously they differ from the latter by not expressing alpha-methylacyl-CoA racemase (AMACR) [8].

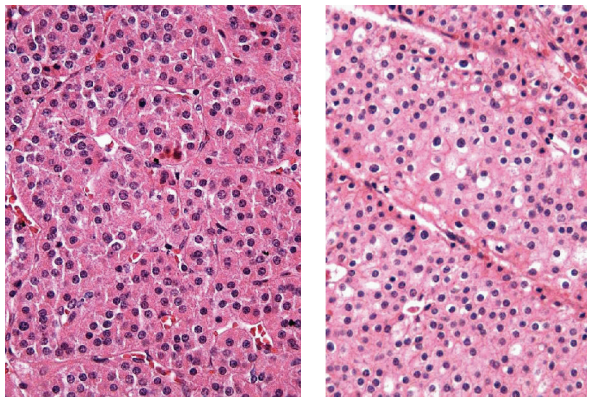
In conclusion, papillary adenoma and papillary renal cell carcinoma may represent a continuum of the same biological process. Unfortunately, it is not possible to define an unequivocally benign papillary renal adenoma, for this reason the WHO used the size (arbitrarily) as a marker.

The papillary adenomas associated with end-kidney and/or acquired cystic disease may have a different pathogenesis.

2.3. Oncocytoma

The clinically most important renal cortical adenoma is the oncocytoma, since despite the fact that it is not usually associated with the carcinoma, in the imaging diagnosis it is usually considered as renal cell carcinoma.

The cytological characteristics of the oncocytoma are defined by the oncocytic cells (tumor cells arranged in nests, cords, or tubules, with eosinophilic cytoplasm and no mitosis). They are usually solid, homogeneous, with



(a) (b)

Figure 3: (a) Oncocitomas, (b) eosinophilic chromophobe renal cell carcinoma variant. Notice the similar aspect that both lesions can present.

occasional sclerosed central areas, which can also present in other tumors, and are of a diameter from millimeters up to 12–15 or more centimeters. Therefore, in this tumor type, the criterion of size does not exist [9].

The problem originates in the cytological characteristics that at times are difficult to distinguish from other neoplasias of eosinophilic cells, such as the clear-cell renal carcinomas eosinophilic variant and especially the chromophobe eosinophilic carcinomas (Figure 3).

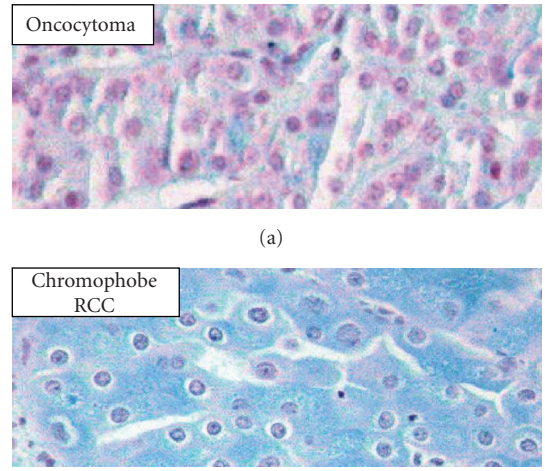
To distinguish them, the electronic microscope, histochemistry (colloidal iron), and immunohistochemistry can help (Figure 4).

It is interesting to point out that the chromosomal studies have demonstrated different types of alterations, and therefore while some tumors do not have any chromosomal alteration, others show translocation 11q13 and (−) 1p, 14q, Y [10]. The latter chromosomal alteration is similar to that of the chromophobe carcinomas (−1p, Y), which together with the finding of hybrid carcinomas (oncocytoma + chromophobe renal cell carcinoma) especially in the Birt-Hogg-Dubé syndrome [11] it has suggested that certain cases of oncocytomas could evolve into chromophobe renal cell carcinoma.

2.4. *Metanephric adenoma*

A relatively short time ago a tumor was introduced among the renal adenomas that was comprised by small cells with scant cytoplasma, uniform, without mitosis, embryonic-appearing, distributed in small round acini with a phenotype similar to the nephroblastoma (Figure 5). They represent 1% of localized tumors of less than 7 cm. The mean age is 41 years (from 5 to 83 years). Fifty percent are incidental and 10% have a polycythemia. Immunohistochemistry, the WT1, CD 56, and CD 57 are positive and the AMACR is negative [12].

From the genetic point of view, it is characterized by allelic loss in 2p13 (56% of the cases) and is differentiated from the nephroblastoma (with alterations 11p13) and from the papillary carcinoma (+7, +17) [13].



(a)

(b)

Figure 4: Colloidal iron to distinguish oncocytoma (negative) and chromophobe renal cell carcinoma (positive).

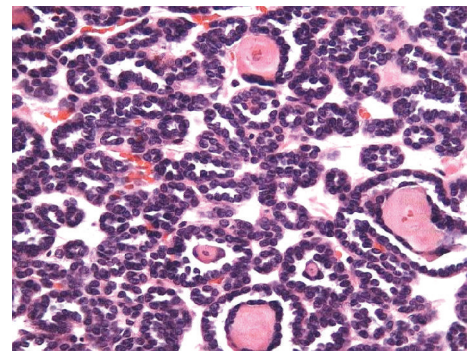


Figure 5: Metanephric adenoma. microacinar structures of basophilic cells with a nephroblastic appearance.

To distinguish the metanephric adenoma from the nephroblastoma, strict diagnostic criteria have been used, and only accepting the tumors without mitosis and nucleoli as metanephric adenoma.

3. CONCLUSIONS

We see that the criteria used to consider renal neoplasia as adenoma vary a great deal according to the cellular type (never in the neoformations of clear cells, only in small neoplasias of papillary pattern, and any size if we are sure that they are oncocytic or metanephric cells). Therefore, it is fundamental to establish the cellular type, and this determination is usually done with the usual pathological anatomical methods with the help of the immunohistochemical markers to which occasionally molecular methods can be added.

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Advances in Urology
Volume 2008, Article ID 758073, 7 pages
doi:10.1155/2008/758073

Review Article

Histological Characterisation of Small Renal Masses and Incidence of Silent Renal Masses

Sergio Almenar Medina and Ana Calatrava Fons

Department of Pathology, Instituto Valenciano de Oncología, 46009 Valencia, Spain

Correspondence should be addressed to Ana Calatrava Fons, an.calatravaf@comv.es

Received 28 May 2008; Revised 8 September 2008; Accepted 30 September 2008

Recommended by J. Rubio

With the introduction of sonographic and CT examinations, the number of small renal masses detected has increased. Benign neoplastic lesions are usually smaller than 4 cm in size, whilst the most common types of renal cell carcinomas have a mean size greater than that, but we must not forget that a significant number of small masses are renal cell carcinomas; even though the rate of benign cases increases as the diameter of the lesions decreases, therefore, size itself cannot be used to rule out a diagnostic of malignancy and often image characteristics are not enough to predict the nature of the lesion with certainty. In this case, histological confirmation must be recommended. Ideally, the histological study must be conducted on the surgical specimen, even though biopsy can be an option in selected cases.

1. INTRODUCTION

Since the beginning of the eighties, with the introduction of sonographic and CT examinations, the number of small renal masses detected is greater than it was previously, when they were discovered by clinical methods [1]. According to a study conducted by The New York University Medical Center, the number of renal masses smaller than 3 cm which were detected in a period of 5 years during the eighties was five times greater than that found in a similar period during the seventies [2] due to, according to Bosniak, the increase in the number of abdominal image studies carried out and to the systematic inclusion of kidneys in these studies. In the Wunderlich series [3], the percentage of tumours of less than 4 cm increased from 28% in 1985 to 61% in 1995.

These lesions can be sporadic or associated to hereditary syndromes, chronic renal failure, or renal transplantation. In the first case, they can be detected during the course of abdominal studies due to renal symptoms or other causes. In the second case, they are detected during the illnesses' follow-up or as a consequence of specific screening programmes.

In every case, masses can be solitary or multiple and may be solid, cystic, or solid-cystic. Depending on their cystic component in images, they can be classified into four categories. Lesions belonging to Bosniak I y II are benign, whereas 59% of Bosniak III and 100% of Bosniak IV are malignant [4].

2. CYSTIC RENAL LESIONS

Renal cysts are frequent lesions of variable size, which appear associated to different clinical situations. Histologically, they are lined by a single layer of cells which may be cubical in the beginning but become more or less flattened as the cyst increases in size. However, sometimes this epithelium may develop hyperplastic lesions, giving way to the big discussion that exists about possible malignant transformation.

Simple renal cysts, whether solitary or multiple, are very variable in size but are frequently smaller than 4 cm. Usually, they are autopsy incidental findings and have no clinical relevance.

In polycystic kidney disease (dominant or recessive), cysts have a cuboidal or flattened lining which may proliferate to form papillary structures inside.

In acquired renal cystic disease, which is associated to dialysis, the majority of the cysts measure between 0.5 and 2 cm, but may develop renal cell carcinomas mainly of papillary type. The risk of developing a carcinoma in patients

which are undergoing dialysis is greater in those who have developed acquired renal cystic disease [5].

3. SOLID AND COMPLEX RENAL MASSES

Solid and complex renal masses are mainly of neoplastic origin but some inflammatory lesions may also have equivocal sonographic images, as it may be seen in Lebret's series, where 22 out of 106 studied lesions turned out to be inflammatory tissues, abscesses, or granulomatous pyelonephritis [6]. On the other hand, most renal cell carcinomas are solid, but 40% of them have a cystic component [7].

Some of the benign neoplastic lesions are usually smaller than 4 cm in size, but we must not forget that, to reach its final size, every lesion must go through this initial stage. Therefore, size itself is not a criterion which can be used to rule out a diagnostic of malignancy.

The most frequently detected benign neoplasms are oncocytomas and angiomyolipomas.

Papillary adenomas are tumours with papillary or tubular architecture of low nuclear grade and 5 mm in diameter or smaller [8]. These are the most common neoplasms of the epithelium of the renal tubules and have been found in 40% of autopsies of patients older than 70 years. Most papillary adenomas are silent, solitary, and occur just below the renal capsule. Histologically, they have tubular, papillary, or tubulopapillary architectures corresponding closely to types 1 and 2 of papillary renal cell carcinoma. Loss of the Y chromosome and a combined trisomy of chromosomes 7 and 17 are the first genetic alterations we can find in papillary tumours and the sole karyotype change in papillary tumours from 2 mm to 5 mm in diameter, all with nuclear grade 1. However, it is not possible to distinguish adenomas and carcinomas by genetic changes, because many carcinomas show only a few genetic alterations [9]. Therefore, the difference between low-grade papillary renal cell carcinoma and adenoma depends mainly on size [8].

Metanephric adenoma is another solid, less frequent, typically benign renal tumour, which ranges widely in size. Jones et al. have reported 7 incidental cases, all of them are less than 1 cm, although symptomatic cases are usually larger than 3 cm [10].

The most common types of renal cell carcinomas have a mean size which is greater than 4 cm, but some unusual types have a mean size of less than 4 cm. According to Nassir, the mean size of multilocular cystic renal cell carcinoma is 3.4 cm [11] and the acquired cystic disease-associated RCC usually has a mean size of around 3 cm and shows peculiar morphological and immunohistochemical features [12, 13]. Normally, they have a microcystic architecture and Fuhrman grade 3. They also describe another group which they refer to as "clear-cell papillary RCC of the end-stage kidneys."

Papillary renal tumours with oncocytic cells of the adult have, according to Lefevre, a mean size of 3.3 cm, they are intrarenal, with sharp edges and all, except one, have Fuhrman grade 2 [14].

Carcinomas belonging to the hybrid oncocytic tumour variety (which frequently occur in the Birt-Hogg-Dubé syndrome) are usually of a small size and their behaviour is between the oncocytoma and the well-differentiated chromophobe renal cell carcinoma [15].

Finally, 10 out of the 13 tubulocystic renal cell carcinomas described by Yang et al. [16] measured less than 3 cm.

4. RELATIONSHIP BETWEEN TUMOURAL SIZE AND HISTOLOGICAL TYPE

One of the main problems when it comes to analysing this relationship is that most of the small renal tumour series are based on clinical and radiological data but histological confirmation lacks [27], especially when lesions are diagnosed incidentally, because the biopsy is not indicated as a routine method [19, 22, 28]. Moreover, the series which includes a histological study uses different criteria to indicate surgery or biopsy, different cutoff points for small masses, and even different pathologic classifications, which make it even more complicated to draw general conclusions (Table 1) [5, 6, 17–25].

Nevertheless, it is clear that a significant number of small solid and complex masses are renal cell carcinomas and they are, according to some authors, more frequent than benign lesions [23, 26], even though the rate of benign cases increases as the diameter of the lesions decreases.

In these cases, it is not possible to predict the behaviour that the lesions will have later neither by their image characteristics [29] nor by their growing speed throughout a short period of time, due to the fact that this speed is not related to the tumoural volume or to the histological grade at a given time [18, 30]. This speed may vary throughout time for a same tumour [31] and can be temporarily zero, even though it is a carcinoma [22]. According to Kunkle, there are no any significant differences between tumours with growth zero during a period of one year and those which have positive growth during the same period at the time of the diagnosis. In both cases, the mean size is of 2 cm and 80% of the lesions of growth zero happened to be carcinomas [17].

According to a recent study by Tabibi [32], amongst renal cell carcinomas, there is no significant relationship between size and histological subtype, even though it is true that, in long series, the size of tumours of the same type tends to gather around a certain value. The usual histological subtypes of renal cell carcinoma have a mean size of more than 4 cm [33] and the same happens with translocation Xp11 renal cell carcinomas [34] and with translocation t(6;11)(p21;q12) [35], where the mean diameter is 6.8 cm and 6.28 cm, respectively. When carcinomas are analysed according to size, it can be observed that when the mean tumoural diameter increases, the ratio of papillary carcinomas decreases and that of chromophobe carcinomas increases (Table 2) [20, 23, 26].

5. RELATIONSHIP BETWEEN SIZE AND AGGRESSIVENESS OF RENAL CELL CARCINOMAS

It cannot be categorically assured that the size of a tumour is directly related to its histological grade and its clinical aggressiveness. For example, low-grade tubular-mucinous

Table 1: Small renal masses with histological confirmation. *N*: total number of cases; *n*: number of cases; RCC: renal cell carcinoma; OM: other malignant tumors; Onc: oncocytoma; AML: angiomyolipoma; AP: papillary adenoma; OB: other benign lesions.

	Size	*N*	RCC		OM		Onc		AML		AP		OB	
			n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Kunkle, 2007 [17]	Median 2 cm	42	37	88.1	0	0.0	4	9.5	0	0.0	0	0.0	1	2.4
Lebret, 2007 [6]	Median 3 cm	135	55	40.7	13	9.6	15	11.1	4	2.9	0	0.0	48	35.6
Chawla, 2006 [18]	Most < 4 cm	21	17	80.9	0	0.0	4	19.1	0	0.0	0	0.0	0	0.0
Vasudevan, 2006 [19]	All < 5 cm	70	41	58.6	6	8.6	14	20.0	9	12.9	0	0.0	0	0.0
Neuzillet, 2005 [5]	Mean 3.7 cm	15	12	80.0	0	0.0	1	6.7	0	0.0	1	6.7	1	6.7
Mindrup, 2005 [20]	Mean 1.7 cm	73	28	38.6	2	2.7	1	1.4	4	5.5	22	30.1	16	21.9
Volpe, 2004 [21]	All < 4 cm	9	8	88.9	0	0.0	1	11.1	0	0.0	0	0.0	0	0.0
Wehle, 2004 [22]	All < 4 cm	5	4	80.0	0	0.0	1	20.0	0	0.0	0	0.0	0	0.0
Frank, 2003 [23]	All < 4 cm	2935	2559	87.2	0	0.0	274	9.3	67	2.3	16	0.5	19	0.7
Bosniak, 1995 [24]	All < 3.5 cm	26	22	84.6	0	0.0	4	15.4	0	0.0	0	0.0	0	0.0
Silverman, 1994 [25]	All < 3 cm	35	27	77.1	2	5.7	0	0.0	1	2.9	0	0.0	5	14.3

Table 2: Distribution of histological subtypes of renal cell carcinoma depending on size. RCC: renal cell carcinoma; *N*: total number of RCC; *n*: number of each subtype; RCCcc: clear cell RCC; RCCp: papillar RCC; RCCchr: chromophobe RCC.

	RCC	RCCcc		RCCp		RCCchr	
	N	*n*	%	*N*	%	*n*	%
Schlomer, 2006 [26]							
0-1 cm	6	5	83,3	0	0,0	1	16,7
1-2 cm	38	25	65,8	10	26,3	3	7,9
2-3 cm	63	49	77,8	12	19,0	2	3,2
3-4 cm	52	43	82,3	9	17,3	0	0,0
4-5 cm	28	22	78,6	4	14,3	1	3,6
> 5 cm	102	81	84,4	11	11,5	4	4,1
Mindrup, 2005 [20]							
Media 1, 7 cm	28	7	35,0	11	68,8	0	0,0
Media 4, 7 cm	40	13	65,0	5	31,2	3	100,0
Frank, 2003 [23]							
0-1 cm			25,6		74,4		0,0
1-2 cm			59,9		38,6		1,5
2-3 cm			70,2		26,0		3,8
3-4 cm			80,2		24,5		3,8

renal neoplasia (also known as mucinous tubular and spindle cell carcinoma) is a neoplasia with a low grade of aggressiveness and, nevertheless, usually has a mean diameter which is larger than 4 cm [12, 41, 42]. In addition, chromophobe carcinomas are usually larger but less aggressive than clear cell renal cell carcinomas [33]. In the same way, among small renal cell carcinomas, the clear cell subtype is much more frequent than chromophobe carcinoma (Table 3) [5, 6, 17–20, 23, 25, 26, 31, 36–38].

Amongst small size tumours, there is a higher rate of low-grade lesions and this percentage tends to decrease as the tumoural size increases (Table 4) [23, 26, 39], but we must not forget that among carcinomas which are smaller than 4 cm, there is a significant ratio, between 6% and 50%, of high-grade tumours (Table 5) [5, 6, 18, 20, 21, 23, 25, 39, 40].

In Schlomer's series [26], 16.7% of the tumours which are smaller than 1 cm are high-grade tumours and 38% of the 50 carcinomas with a size equal to or less than 3 cm included in Hsu's series [39] extend beyond the renal capsule.

This last series also shows that there is no significant difference in grade or stage between tumours of less than 3 cm and those of 3 to 5 cm, but these differences do exist between tumours of less than 5 cm and those which are greater. In the results reported by Tabibi [32], extracapsular spread is rare in tumours of less than 4 cm, but he does not find statistically significant differences in grade when the cutoff point is established at 4 cm. Schlomer and Miyagawa's results [26, 43] point towards this same direction. This is why some authors question that the cutoff point is established at 4 and not at 5 cm [39, 43].

Table 3: Percentage of histological subtypes of renal cell carcinoma in small renal masses. RCCcc: clear cell renal cell carcinoma; RCCp: papillary renal cell carcinoma; RCCchr: chromophobe renal cell carcinoma; RCCo: other variants of renal cell carcinoma.

	Size	RCCcc		RCCp		RCCchr		RCCo	
		n	%	*N*	%	*n*	%	*n*	%
Kunkle, 2007 [17]	Median 2 cm	24	64,9	12	32,4	0	0,0	1	2,7
Lebret, 2007 [6]	Median 3 cm	41	74,5	10	18,2	4	7,3	0	0,0
Chawla, 2006 [18]	Most < 4 cm	9	52,9	7	41,2	0	0,0	1	5,9
Pankhurst, 2006 [36]	21 of them < 1 mm	2	8,0	22	88,0	0	0,0	1	4,0
Schlomer, 2006 [26]	Only < 4 cm	122	76,7	31	19,5	6	3,8	0	0,0
Vasudevan, 2006 [19]	All < 5 cm	32	78,0	4	9,8	5	12,2	0	0,0
Neuzillet, 2005 [5]	Mean 37 mm	7	58,3	3	25,0	2	16,7	0	0,0
Mindrup, 2005 [20]	Mean 17 mm	7	25,0	11	39,3	0	0,0	10	35,7
Kato, 2004 [31]	All < 4 cm	15	83,3	3	16,7	0	0,0	0	0,0
Frank, 2003 [23]	All < 4 cm	1970	77,0	436	17,0	125	4,9	28	1,1
Shishikura,1996 [37]	All < 2, 5 cm	84	86,6	3	3,1	0	0,0	10	10,3
Silverman, 1994 [25]	All < 3 cm	17	63,0	3	11,1	3	11,1	4	14,8
Yamashita, 1992 [38]	All < 3 cm	26	72,2	0	0,0	7	19,4	3	8,3

Table 4: Percentage of low-grade and high-grade carcinomas depending on size. LG: low grade; HG: high grade.

	Schlomer, 2006 [26]		Hsu, 2004 [39]		Frank, 2003 [23]	
	LG %	HG %	LG %	HG %	LG %	HG %
0-1 cm	83,3	16,7	—	—	90,9	9,1
1-2 cm	94,7	5,3	—	—	88,6	11,4
2-3/< 3 cm	71,4	28,6	72,0	28,0	93,6	6,5
3-4 cm	71,1	28,9	—	—	81,3	18,7
4-5/3–5 cm	67,9	32,1	67,8	32,2	77,6	22,4
5-6 cm	53,8	46,2	—	—	69,3	30,7
6-7/> 5 cm	44,4	55,6	40,4	59,6	60,9	39,1
> 7 cm	36,2	63,8	—	—	37,9	62,1

6. INCIDENTAL RENAL TUMOURS

Most of the incidentally diagnosed lesions are benign. In a classical series which studied 205 incidental lesions of less than 1 cm found in autopsies, the most common was medullary fibrous nodules (159), followed by cortical adenoma (49), leiomyoma (12), lipoma (7), and myolipoma (13) [44].

Renal carcinomas which are incidentally diagnosed represent between 15 and 60% of the total number of carcinomas, depending on the series.

A lot of them are smaller than 4 cm [28]. Generally speaking, carcinomas discovered incidentally are smaller than those which are symptomatic [45, 46]. Their mean diameter is 5.7 cm in contrast with the 8.7 cm in symptomatic cases. Moreover, the mean size has reduced notably thanks to image techniques. The mean diameter of renal tumours incidentally found in autopsies at the University of Iowa decreased from 4.63 cm in the fifties to 1.65 cm in the nineties [20]. They are also associated with a lower stage and a lower nuclear grade [47], as well as with the increasing age of patients [48].

Therefore, it would be reasonable to consider incidental carcinomas as a group with its own clinical and pathological significance, even though we cannot establish at present whether they are discovered incidentally because they still small or because they have their own particular biological characteristics which make them behave in a less-aggressive way.

On the other hand, the presence of certain syndromes may influence the size that some tumours reach, as it happens to angiomyolipomas which have a greater mean diameter in the context of tuberous sclerosis than when they appear sporadically [49].

7. CONCLUSIONS

A significant rate of small renal masses, discovered either symptomatic or incidentally, are carcinomas. Moreover, up to 50% of carcinomas measuring less than 4 cm are high-grade lesions and some of them extend beyond the renal capsule despite the fact that they have got such a small diameter. Therefore, when a small renal mass is detected, the

Table 5: Distribution of Fuhrman grades in renal cell carcinomas. F1, F2, F3, F4: Furhman grades.

	Size	RCC	F1+F2		F3+F4	
		n	*n*	%	*n*	%
Lebret, 2007 [6]	Median 3 cm	57	51	89,5	6	10,5
Chawla, 2006 [18]	Most < 4 cm	17	16	94,1	1	5,9
Neuzillet, 2005 [5]	Mean 37 mm	12	6	50,0	6	50,0
Mindrup, 2005 [20]	Only < 4 cm	159	123	77,4	36	22,6
Peces, 2004 [40]	Only < 4 cm	12	11	91,7	1	8,3
Hsu, 2004 [39]	Only < 3 cm	50	36	72,0	14	28,0
Volpe, 2004 [21]	All < 4 cm	8	4	50,0	4	50,0
Frank, 2003 [23]	Only < 4 cm	480	420	87,5	60	12,5
Silverman, 1994 [25]	All < 3 cm	27	24	88,9	3	11,1

size itself is not a reliable feature to rule out a diagnostic of malignancy. Unfortunately, there are many times when image characteristics or speed of growth along a period of several months are not enough to predict the nature of the lesion with certainty. In these cases, histological confirmation must be recommended.

Most of the times, the histological study is conducted on the surgical specimen, though biopsy can be considered a good option if surgery represents a high risk for the patient. The problem is that the smaller a mass is, the more difficult it is to get the right sample; but the bigger it is, the less representative the whole of the lesion is. That is why there is no general agreement about biopsy indications at the moment. On the other hand, surgical resection in the early stage of the tumour is still the best treatment option for renal cell cancer, and small masses are good candidates for conservative techniques. From this point of view, surgery implies a double benefit because it is a good therapeutic choice and provides the most accurate diagnosis.

Risks and benefits must be evaluated in every single case taking into account the particular clinical situation of the patient as well as the available technical means and the expertise of the medical team involved.

ACKNOWLEDGMENT

The authors would like to thank Miss Ana Molina for her assistance in the translation.

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