Urooncology / Üroonkoloji Review / Derleme

The importance of benign kidney tumors among small renal masses: diagnosis and treatment algorithms

Küçük boyutlu böbrek kitlelerinde iyi huylu tümörlerin önemi: Tanı ve tedavi algoritmleri

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Abstract

Recently, the detection rate of small renal masses has been increasing due to the radiologic and clinical improvements. These improvements have also led to a significant change in approach to renal masses. Small renal masses are defined as cortical renal masses smaller than 4 cm in diameter. Besides renal cell carcinoma, benign kidney tumors were also frequently detected pathologically among small renal masses. The clinical identification of benign kidney tumors provides efficient treatment approaches and avoiding from overtreatment. In this review, the importance of benign kidney tumors among small renal masses, and diagnosis and treatment policies to these tumors were evaluated.

Key words: Benign tumor; kidney neoplasms.

Özet

Son yıllarda, küçük boyutlu renal kitlelerin tanı oranları radyolojik ve klinik gelişmelere paralel olarak artmıştır. Bu gelişmeler ile beraber renal kitlelere yaklaşımda da anlamlı değişimler olmuştur. Küçük boyutlu renal kitleler, çapı 4 cm'den daha küçük kortikal böbrek kitleleri olarak tanımlanmıştır. Bunlar arasında patolojik olarak renal hücreli karsinom olabileceği gibi iyi huylu tümörlere de sıklıkla rastlanmaktadır. İyi huylu renal tümörlerin klinik olarak tanımlanması, etkin tedavi yönteminin uygulanmasını ve gereksiz tedavilerden kaçınılmasını sağlamaktadır. Bu derlemede, küçük boyutlu renal kitleler arasında iyi huylu tümörlerin önemi ile bu tümörlere yönelik tanı ve tedavi yaklaşımları değerlendirilmiştir.

Anahtar sözcükler: Benin tümör; böbrek kitleleri.

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Incidence of small renal tumors

Understanding the biologic behavior and natural history of small renal masses is crucial in predicting tumor growth and metastatic potential, so as to properly select the methods and optimal timing of intervention.[1] Since the wide-spread introduction of cross-sectional imaging modalities such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI), the detection rate of renal tumors have increased. The majority of these solid renal tumors (SRTs) are actually small SRTs ≤4 cm in diameter.[2,3] Today the majority (>60%) of renal tumors are found incidentally in asymptomatic patients. In their study over a 20-year period, Hollingsworth et al.[4] reported an increase of 285% and 244%, in the incidence of SRT <2 cm and 2-4 cm, respectively. However, the underlying biology of the lesion, benign or malign, was still unknown.[5,6] It is generally believed that most renal tumors are renal cell carcinomas (RCCs). Benign renal tumors are classified into renal cell tumors, metanephric tumors, mesenchymal tumors, and mixed epithelial and mesenchymal tumors. Several benign tumors show characteristic imaging features, like typical angiomyolipomas (AMLs). However, because of overlapping of findings between benign and malignant renal tumors, histological evaluation is required to establish a definitive diagnosis in most cases. Accurate preoperative characterization facilitates optimal patient management. In a study from the Mayo clinic, Frank et al.[7], retrospectively examined 2935 SRTs of all sizes treated over a 25-year period and reported 46.3%, 22.4%, 22.0%,

and 19.9% of renal lesions <1 cm, 2 cm, 3 cm, and 4 cm in size, respectively, to be benign. In a recent report by Remzi et al.[8], SRTs <2 cm, 2-3 cm, and 3-4 cm in size were reported to be benign in 24.6%, 20.4%, and 16.0% of cases, respectively (p=0.66). Thus, tumor size alone was not able to provide adequate information for a treatment decision. The crucial issue before a treatment decision should be the determination of the exact nature of an incidentally discovered mass, because SRTs show heterogeneous pathologic features ranging from totally benign to highly aggressive.

Benign renal tumors: incidence, types and classification

It is often impossible to radiologically identify SRTs as benign and definitely differantiate them from RCCs.[9] Only fat-containing AMLs can be distinguished from RCCs with the current imaging modalities. The incidence of benign renal tumors treated surgically ranges was reported as ranging from 6.1% to 16.9%.[10-12] In another report, the incidence was shown in tumors <4 cm as 19.5%.[8] However, 12.8% of the 2.935 tumors studied and 50% of tumors <1 cm was benign in nature, so these results provide a rationale based on the pathology for conservative management of cases that are poor surgical candidates.[7] In EORTC 30904 study, comparing nephron-sparing surgery (NSS) with nephrectomy in patients with resectable RCC, 11.6% of the surgically removed tumors (<5 cm) were benign.[13] In a recent report by Remzi et al.[14], only 17% of all benign lesions were correctly identified as benign at routine preoperative CT scan, but 43% underwent unnecessary radical nephrectomy.Vasudevan et al.[9] reported that 33% of cases considered malignant on radiological features ultimately proved to be benign by renal biopsies and in 47% of patients, radical surgery was avoided in which the benign pathology was proven by biopsies. Additionally, a report of 100 laparoscopic partial nephrectomies for a mean tumor size of 2.9 cm showed that 32% of the surgeries were performed for benign disease, as indicated by the final pathology specimen.[15] The outcomes give us the message that is the general incidence of benign renal tumors has been increasing. Skolarus et al.[16], confirmed that the number of AML decreased (p<0.001), whereas the number of oncocytoma increased with age (p<0.001). This might show the variability in type of benign renal tumor with age.

The 2004 World Health Organization (WHO) classification categorizes benign renal neoplasms on the basis of histogenesis (cell of origin) and histopathology.[17] Renal neoplasms are thus classified into renal cell (oncocytoma, papillary adenoma), metanephric, mesenchymal (AML, hemangioma, lymphangioma, leiomyoma, renomedullary interstitial cell tumor), and mixed epithelial and mesenchymal (mixed epithelial and stromal tumor, cystic nephroma) tumors (Table 1).[17,18]

Oncocytoma and AML were the most frequent two benign lesions of the kidney. Apart from these lesions, there are many kind of benign lesions (leiomyoma, metanephric adenoma, lipoma etc.) which have to be separated from the malign tumors to choose the right treatment policy, conservatively or surgically, if surgically, ablative, partial or radical nephrectomy. However, it seems that the young women might have a higher chance to have a benign tumor. The proportion of benign lesions was significantly higher in women than in men.[19]

Table 1. World Health Organization (WHO) histological classification of benign renal neoplasms

Renal cell tumors	Metanephric tumors	Mesenchymal tumors	Mixed epithelial mesenchymal tumors
Oncocytoma	Metanephric adenoma	Angiomyolipoma	Cystic nephroma
Papillary adenoma	Metanephric adenofibroma	Leiomyoma	Mixed epithelial
	Metanephric stromal tumor	Hemangioma	and stromal tumor
		Lymphangioma	
		Reninoma	
		Fibroma	
		Schwannoma	

Treatment policies for small renal tumors: ablative therapies and surveillance

The aim of management of SRTs is to treat them without the complication and the loss in renal function. It has been clear that NSS or minimal invasive treatment modalities, even watchful waiting have been accepted as an undeniable appropriate interventions for benign SRTs. NSS for RCC <4 cm in diameter provides recurrence-free and long-term survival rates similar to those observed after a radical surgical procedure (level of evidence: 2b).[20] NSS remains the standard of care for small RCC, but energy-ablative techniques and surveillance protocols have evolved as alternative management options.[21] Today, the challenge with the treatment of SRTs is to find a balance between the need for the surgical treatment of aggressive tumors and the observation of less aggressive or harmless tumors.

In the recent reports, it was stressed that conservative, nonsurgical management of SRT in suboptimal surgical candidates has been suitable approach.[22,23] The prognosis of these patients was reported to be good at the short-term period.[22,23] Therefore, the significant portion of the SRTs are benign and they have to be managed with appropriate intervention to preserve the renal function and to avoid from the overtreatment. Preserving renal function is a significant concern in all situations. The preoperative investigations must give accurate information regarding the nature of the renal mass, and then the attempts could be made to manage these lesions conservatively or surgically.

Alternative treatments like ablative therapies and active surveillance are recently introduced in the armamentarium of treatment for SRTs. Indications for minimally invasive techniques, including radiofrequency ablation, are small, incidentally found, renal cortical lesions in elderly patients, in patients with genetic predisposition to multiple tumors, or in patients with a solitary kidney, or bilateral tumors (level of evidence: 2b).[20] In a recent review by Özsoy et al.[24] it has been suggested that active surveillance is an option in elderly patients with severe co-morbidities or in patients who are not willing to undergo surgery. In this manner, excellent patient compliance and close follow-up with contrast enhanced CT or MRI is mandatory. Additionally, the authors believe that low-grade tumors measuring <3 cm could enter an active surveillance protocol. Prior to and during follow-up, renal tumor biopsies are recommended. Benign lesion on renal tumor biopsy is an inclusion criteria for active surveillance.[24]

Overtreatment of benign renal tumors: review of the literature for oncocytoma and angiomyolipoma

The data on the overtreatment of benign renal tumors has been limited in the literature. Although many articles have been published to focus on the diagnosis and policy regarding the treatment of benign renal tumors, there is still high rate overtreated kidney tumors, up to 50% treated with nephrectomy. That is the reason why the preoperative period has an overwhelming role for the management these small benign lesions. But, SRTs cannot be diagnosed confidently with either imaging techniques alone or percutaneous biopsy.[25-29]

Oncocytomas

Renal oncocytoma is benign lesions, differentiating from type A intercalated cells of the renal collecting tubule. It represents 5% of tumors of the kidney and 10% of renal tumors <3 cm.[30] Oncocytoma is histologically composed of nests and acini of large polygonal cells with mitochondria-rich eosinophilic cytoplasm.[17] It typically appears as solitary, well-demarcated, uncapsulated, and fairly homogeneous renal cortical tumor. Oncocytotic cells are found in numerous RCCs, such as chromophobe RCC, the granular cell variant of RCC, and the eosinophilic variant of papillary type RCC (type 2). Liu et al.[31] reported that all oncocytomas were vimentin negative, whereas granular cell RCC and eosinophilic papillary RCC were vimentin positive. Chromophobe RCCs are also vimentin negative, but they can be differentiated from oncocytomas by Hale's colloid-ferrous staining. C-kit and CK7 are also able to reveal hybrid RCCs, as shown in the study by Liu et al.[31] Most often, the diagnosis of renal oncocytoma is made after surgical removal of the tumor. If not operated, the natural evaluation of renal oncocytoma is not clearly known.[32] Renal oncocytoma is often asymptomatic and diagnosed at autopsy or incidentally, mostly in patients who are being examined with abdominal US or CT for other health problems.[33-35] If renal oncocytoma could be detected before the management

of the renal mass, the treatment modality can be explained to the patients. Therefore, lots of articles have been published in the literature about the preoperative biopsy and full radiologic evaluation of renal mass. Distinguishing oncocytoma from RCC can be difficult, especially from chromophobe RCC that shares similar histologic features and the granular cell type of clear-cell RCC.[36-37] The coexisting finding of RCC and oncocytoma (hybrid-RCC) is interesting, and incidence of this phenomenon has been reported in up to 32% of cases.[38] In a recent paper by Waldert et al.[39] hybrid RCCs were found more common than expected. The survival rate was 100% for both hybrid RCCs and oncocytomas after surgical treatment. The authors also concluded that hybrid RCCs might be candidates for active surveillance, and surgery may be unnecessary. Chao et al.[40] stressed the importance of distinguishing oncocytoma from RCC with the gross, microscopic, immunohistochemical, ultrastructural and radiologic findings, and genetic abnormalities. The standard treatment for oncocytoma is surgical extirpation. NSS is conceivable even for tumors >4 cm in diameter, in contrast to RCC. Treatment modality for the histologically benign oncocytoma is conservative surgery, even for large tumors.[32] However, renal oncocytoma could be an indication for radiofrequency or cryotherapy. The aim of these treatments would be to prevent unnecessary surgery and protect the viable kidney tissue. Oncocytomas can still be associated with significant morbidity. Dechet et al.[33] noted tumor-related constitutional symptoms in 15% and gross hematuria in 12% of patients in a series of 138 oncocytomas. Only two series are available on the evolution of oncocytomas that were not surgically treated.[41,32] In a series reported in 1991, oncocytoma was diagnosed radiologically, with no histologic evaluation; which is clearly inadequate. Twelve patients with suspected oncocytomas were followed for a mean of 7 years, and none of the tumors increased in size. So the investigators concluded that oncocytomas are benign tumors with no further evolution when the final size is reached.[41] In contrast, Neuzillet et al.[32] reported 15 patients with histologically proven oncocytomas that showed an increase in size. Six of their 15 patients needed surgery. These patients were significantly younger, and one patient was found to have chromophobe RCC at final histology.

Angiomyolipomas

Another benign renal lesion which could be confused with RCC is AML. AML contains fat cells, smooth muscle cells, and blood vessels in various proportions. In general, it is uncommon and usually occurs in individuals without tuberosclerosis complex. AML can usually be diagnosed with near certainty due to its unique US and CT appearance. It is the most hyperechoic renal neoplasm, due to a combination of factors, including high fat content, multiple tissue interfaces, and extensive vascular tissue.[42] Unfortunately, 8% to 47% of small RCCs are also hyperechoic[43,44], and so this feature is not pathognomonic. However, AMLs which contain relatively increased tissue of smooth muscle or have intratumoral hemorrhage do not have a highly hyperechoic appearance. The benign nature of AML supports NSS or ablative therapies when possible. The main aim of the surgery of AMLs is to preserve the renal function and to exclude coexistent RCC and the other malignant pathology in kidney. RCC develops in 1% to 3% of the patients with tuberosclerosis complex,[45-47] a rate that is clearly higher than the rate in the general population, although some tumors historically diagnosed as RCCs in this group may actually have been epithelioid AML.[48] Epitheloid AMLs which typically do not show macroscopic fat and appear as soft-tissue masses, is potentially malignant and may exhibit aggressive biology, including recurrence, metastasis, and death.[18] Recent studies indicate that in contrast to RCCs, AMLs with minimal fat show uniform, prolonged contrast enhancement and a higher signal intensity index on double-echo, chemical shift FLASH MRI.[49]

The detection of incidental kidney tumors: the role of biopsy

Percutaneous renal biopsy or fine needle aspiration has a limited role in the evaluation of renal tumors, because of high accuracy of imaging techniques, and false-negativity and potential complications of biopsy. Biopsy was reserved for renal metastasis, abscess, lymphoma or unresectable tumors. Recently Remzi and Marberger[50] evaluated the role of renal tumor biopsies for SRTs. Recommended uses for renal tumor biopsies in SRT in this study are (1) to differentiate benign from malignant SRTs, (2) prior to or during

ablative therapies, and (3) during follow-up after ablative therapies, especially after radiofrequency ablation, for defining treatment success or failure. A recent study showed an accuracy rate of 96% to distinguish between benign and malign lesions with a failure rate of only 3%.[51] The American Urological Association guidelines state that given the significant heterogeneity in the biological aggressiveness of SRTs and the wide range of treatment options now available, renal tumor biopsies is now being used increasingly for patient counselling and clinical decision making.[52]

Conclusion

Parallel to the increase in incidence of renal masses, benign tumors are detected more frequently. SRTs should be evaluated in a detail to avoid overtreatment, especially in benign tumors. About 20% of SRTs are actually benign. Differentiating benign from malign renal tumors is often impossible by imaging alone, thus renal tumor biopsy might be helpful. More advanced diagnostic work-up in SRTs is advisable especially for offering different treatment modalities such as surveillance, ablative therapies, and NSS.

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