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Review

Introduction to small renal tumours and prognostic indicators

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HIGHLIGHTS

- The changes in the definition of small renal tumours over the years were reviewed.
- The preoperative patient characteristics were described.
- The anatomical and topographic characteristics of patients with these tumours were studied.

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ABSTRACT

Over the past years, the widespread use of radiological imaging for evaluating abdominal symptoms unrelated to kidney cancer has been linked to a significant increase in the percentage of renal tumours incidentally detected at an asymptomatic stage. The definition of 'small' renal tumours has changed over the years. Presently, according to dimensional criteria, surgical indications and prognostic impact, small renal tumours are defined as masses ≤4 cm in size. Classical preoperative variables that influence the decision-making process in the management of T1a renal tumours can be classified as patient-related and tumour-related factors. Age is an independent predictor of cancer-specific survival (CSS), with older patients exhibiting significantly worse survival. An accurate classification of the anatomical and topographical characteristics of small renal masses based on available nephrometry systems is necessary for standard preoperative evaluation of patients eligible for partial nephrectomy (PN). Renal tumour biopsies (RTBs) can be indicated in patients eligible for active surveillance or ablative treatments, those with other primary tumours, those with prior renal lesions and/or those with multiple synchronous tumours, showing a median diagnostic rate of 92%. Small renal tumours typically have a good prognosis. Patient age, mode of presentation, nuclear grading, coagulative necrosis and histologic subtype can influence the prognosis of this subgroup of RCC.

1. Epidemiology

Kidney cancers are the 14th most common malignancies; more than 300,000 new cases were diagnosed in 2012. Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney cancers. With respect to gender, around 200,000 new cases were reported in men and 100,000 in women in 2012. Moreover, around 198,000 new cases were reported in more developed regions and around 130,000 in less developed regions [1]. In 2012, kidney cancers accounted for 143,000 deaths, with a crude rate value of 2% of all cancer deaths. A total of 91,000 (crude rate 2.6%) were recorded among men and 52,000 (crude rate 1.5%) among women [1,2].

2. Definition of small renal tumours

The term 'small' renal tumours was first used in the 1974 version of the TNM staging system to identify tumours without kidney enlargement leading to limited caliceal distortion or deformity [3]. This definition changed in the following TNM editions, introducing a dimensional criterion. In the 1987 version of the TNM classification, small renal tumours (T1) were defined as lesions ≤2.5 cm in

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size [4]. Conversely, in the 1997 TNM version, the cut-off value to distinguish T1 and T2 tumours was increased to 7 cm [5]. This cut-off was also confirmed in the more recent TNM classifications. However, from the 2002 version onwards, T1 tumours have been subdivided into two categories (T1a and T1b) according to the breakpoint value of 4 cm [6,7]. Indeed, T1a tumours are the ideal candidate for partial nephrectomy (PN) from an oncological viewpoint, as recommended in the most important international guidelines [8,9]. Therefore, according to dimensional criteria, surgical indications and prognostic impact, small renal tumours are defined as masses ≤4 cm in size.

In the past few decades, the widespread use of ultrasound examination and computer tomography (CT) scanning for evaluating abdominal symptoms not strictly related to suspected kidney cancer has been associated with a significantly increased incidence of asymptomatic, small renal tumours, potentially suitable for PN [10]. Interestingly, unpublished data for the Department of Urology of Padua have shown that the percentage of incidentally detected tumours increased from 22% between 1981 and 1985 to 72% between 2006 and 2007. Specifically, more than 50% of cases were ≤4 cm in size at presentation. Notably, at the final pathological examination, a significant percentage of solid, small renal tumours are benign. In details, benign masses were detected at the final histologic examination in 46% of tumours ≤1 cm in size, 22% of those between 2 and 3 cm in size and in 20% of those measuring 4 cm [11,12].

The management of small renal tumours should be based on an initial careful decision-making process that relies on several preoperative parameters. Moreover, pathological variables must be considered to confirm the clinical diagnosis and to tailor the most appropriate post-operative follow-up procedure. Prognostic information is usually based on a combination of both clinical and pathological variables. In this scenario, some mathematical models have been proposed to combine both clinical and pathological variables and to simplify the counselling process [13].

3. Preoperative parameters

Classical preoperative variables that influence the decision-making process in the management of T1a renal tumours can be classified as patient-related (i.e., age, co-morbidity profile, performance status and laboratory parameters) and tumour-related (i.e. mode of presentation, clinical tumour size and anatomical/topographic characteristics) factors. Moreover, over the past years, several urologists have proposed the use of renal tumour biopsy (RTB) for a more accurate histologic definition of small renal tumours and for a more appropriate treatment strategy.

3.1. Patient-related factors

Limited data are available on the potential impact of age on the characteristics and prognosis of renal tumours. According to a multi-institutional study, patients aged ≤40 years were more likely to have papillary or chromophobe RCC and less likely to have clear cell RCC. Interestingly, the authors observed that age was an independent predictor of cancer-specific survival (CSS), with older patients exhibiting significantly worse survival [14]. Notably, Sun et al. recently published a Surveillance, Epidemiology, and End Results (SEER) database analysis; they found that the 2- and 5-year other-cause mortality (OCM) of patients aged ≥75 years was comparable after radical nephrectomy (RN) and PN. According to this study, the indication for elective PN in patients aged ≥75 years should be carefully discussed during pretreatment counselling [15]. Similar considerations should be made for the co-morbidity profile of patients with T1a tumours eligible for PN. Indeed, in the SEER registry analysis, patients with ≥2 baseline co-morbidities showed a comparable OCM rate 2 and 5 years after PN and RN [15]. Therefore, patient co-morbidities must definitely be considered as a selection criterion for PN. Performance status was an independent predictor of CSS [15], although its prognostic role is more relevant in patients with locally advanced or metastatic tumours than in confined small renal masses [16]. In patients with small renal masses, CSS does not appear to be influenced by performance status. The erythrocyte sedimentation rate (ESR), platelet count, serum calcium and haemoglobin levels and serum lactate dehydrogenase (LDH) levels can predict CSS in patients with localized disease. However, in patients with small renal tumours eligible for PN, laboratory tests evaluating renal function, such as serum creatinine levels and estimated glomerular filtration rate (eGFR), must be carefully considered before surgery. An eGFR below 60 mL/min can be considered a predictor of renal failure, and PN is highly recommended if technically feasible. Indeed, many studies recently showed that preoperative eGFR and/or serum creatinine levels to be independent predictors of impairment of renal function in patients undergoing PN for small renal tumours [17–19].

3.2. Tumour-related factors

Considering preoperative tumour-related variables, the mode of presentation has been extensively evaluated, and its independent predictive role has been demonstrated in multi-institutional series [16]. According to Patard's classification [20], tumours detected during abdominal imaging for signs and symptoms unrelated to RCC are classified as incidental (S1). Conversely, flank pain, haematuria and flank mass are considered local symptoms (S2). Systemic symptoms suggesting advanced stage disease (weight loss, fever and paraneoplastic syndromes) are defined as S3 cases. Small renal tumours are typically asymptomatic or, less frequently, associated with local symptoms such as haematuria or flank pain. Notably, asymptomatic patients have more favourable CSS rates than patients with local symptoms do. Therefore, this parameter should be another criterion in the decision-making process for the management of T1a tumours. Indeed, some authors considered haematuria as a relative contraindication for PN because this symptom could reflect the involvement of the upper collecting system. Notably, the involvement of the urinary collecting system (UCS) can represent an independent predictor of CSS in both patients with pT1 and those with pT2 tumours [21].

Traditionally, clinical tumour size has been considered an important prognostic factor, and it has been used as the main criterion to select patients eligible for PN. International guidelines recommend PN as the standard of care for T1a tumours; they also strongly support expanding indications for T1b tumours whenever technically feasible [8,9].

However, not only size but also anatomical and topographic characteristics of T1 renal tumours as well as surgeon experience are the main factors influencing the technical feasibility of PN. In 2009, two nephrometry systems, the RENAL nephrometry and PADUA classification, were proposed to classify parenchymal renal tumours based on their anatomical and topographic characteristics (Fig. 1) with the aim of predicting surgical complexity. These systems refined the selection criteria and the main outcomes of PN [22,23]. Fig. 1 presents the features included in the PADUA classification and scores given for each anatomical situation. PADUA scores of 6 and 7 indicate a low risk, 8 and 9 indicate an intermediate risk and higher than or equal to 10 a high risk of renal mass.

Table 1 summarizes the parameters included in the RENAL and PADUA classifications. Fig. 2 presents the definition of polar lines according to the PADUA and RENAL nephrometry systems. In 2010, Simmons et al. proposed the centrality index (c-index) system,