Editorial

Improving the diagnosis of renal masses: can we approach the histological diagnosis to the image?

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Current trends in all surgical pathologies in general, and oncology in particular, is to perform a preoperative diagnosis as accurate as possible, in order to help to achieve an appropriate treatment using clinical and pathological factors.

Regarding renal cell cancer (RCC), the incidentally detection has increased in recent years because of a greater accessibility and improvement in the diagnostic imaging techniques. All this allows detecting asymptomatic small renal masses, which improve the prognosis and facilitate the treatment of this pathology since it involves smaller tumors and more favourable stages (1).

TNM stage system (2,3) remains the "gold standard" in clinical and prognostic classification of the RCC. Prognostic value is known and has been endorsed in different studies (4) and is considered one of the most reliable and robust predictors of oncological outcomes after nephrectomy. It also facilitates the identification of patients at risk of recurrence and progression who have undergone to adjuvance, depending on their staging.

Computed tomography (CT) remains the radiological technique of choice in the diagnosis of RCC. Clinical stage (cTNM) and tumor size are perhaps the most important preoperative criteria to consider before performing surgery. However, it would be very useful to have more pathological data that allow us to individualize surgical treatment and raise the need for adjuvant treatment.

In addition to the histological subtype, the other classic prognostic factor in RCC is Fuhrman's nuclear grade (5), which classifies the different morphological characteristics of the tumor cell nuclei related to prognosis, as an independent factor. This classification, which is still subjective, has its controversies (6). It establishes four grades, which makes it tedious for the pathologist, so usually grades 1 and 2 are classified as low-grade tumours and grades 3 and 4 as high-grade tumours, with a worse prognosis. Furthermore, it is not entirely useful in the gradation of non-clear cell RCC (7). Prognostic value of the Fuhrman's nuclear grade is recognized and, therefore, it has raised the need to develop predictive models of nuclear grade by imaging techniques since, although it has improved, percutaneous biopsy is insufficient for nuclear grade diagnosis and remains still for cases when we propose conservative treatments or in cases which diagnostic imaging is indeterminate and offers doubts about the malignancy (8,9). Therefore, developing methods that improve preoperative diagnosis will lead to more appropriate treatment and even, in selected cases, propose non-aggressive options, such as active surveillance for small renal masses.

RENAL score (radius, exophytic properties, nears, anterior-posterior, location) is an example of the first attempts to establish a prediction of aggressiveness of renal tumors with non-invasive methods (10).

Classic criteria for differentiating high-grade renal masses is based on the high correlation between tumor size and nuclear grade and, likewise, a positive correlation between delayed enhancement of the peritumoral cortex in clear cell

RCC (11). In chromophobe RCC tumors, nuclear grade is associated with tumor heterogeneity in unenhanced CT (12). However, not all solid renal masses are malignant, and up to 20% of less than 4 cm solid renal masses are benign (13). This aspect must be highlighted in cases of fat-poor angiomyolipomas, with attenuation values which are very similar to clear cell RCC. Another important point would be the ability to differentiate oncocytomas from other RCC, since their clinical behavior is usually benign (14).

Different methods have been designed in order to obtain radiological information over the histological subtype and to be able to find specific characteristics of the clear cell RCC versus non-clear cell RCC (15), and on the other hand, imaging features for nuclear grade. In addition to the classic findings such as tumor size (easily measurable by CT), there are other aspects to be considered such as the presence of intratumoral necrosis, whose presence in the CT is a predictor of aggressiveness, regardless of its size, so, the greater presence of necrosis, the higher probability of high-grade tumors (16).

Based on enhancement patterns and tumor attenuation, it is possible to find a correlation with histological grade. In small clear cell RCC (<4 cm), attenuation values under 30 HU on unenhanced CT and homogeneous or relatively homogeneous enhancement can predict low grade tumors (16).

A relationship between a low enhancement and a high-grade clear cell RCC is justified by the fact that the presence of necrosis, edema and intratumoral hemorrhage are, in themselves, high histological grade predictors and that are associated with low enhancement in those areas. Thus, high-grade tumors would have less contrast uptake and more irregularly. This does not occur in low aggressiveness tumors because the vascularization is more homogeneous. Then, an irregular appearance of the tumor margins and a relative enhancement >0.65 are associated with high nuclear grades and more aggressiveness. However, one of the limitations of the predictive analysis by CT of the nuclear grade of a clear cell RCC are the areas that we use as a reference when comparing with enhancing renal masses. They are usually compared with areas of non-tumoral renal cortex but it has been found that in the corticomedullary phase of a CT, the relative enhancement seems to be more effective than in nephrographic phases to predict the nuclear grade. Perhaps it would be more appropriate to use the values obtained from the renal artery or aorta as a reference (17).

In order to try to obviate all these problems, models based on CT tumor texture analysis are currently being developed to make a prediction of the nuclear grade in clear cell RCC, with promising results (18,19). These studies show certain limitations, since prospective studies are required and the same method is not able to distinguish benign of malignant renal tumors. Although clear cell RCC are the most frequent, there are other histological subtypes with an important malignant potential that should be taken into account in differential diagnosis, as well as sarcomatoid differentiation with a very poor prognosis.

Other imaging techniques have also been used, so as to obtain a precision diagnosis before the histological confirmation, such as magnetic resonance imaging (MRI), allowing good results in the diagnosis of malignance of solid masses (20), and also for low or high grade (21) with a sensitivity and specificity similar to those offered by CT or even higher.

Currently, we have different radiological modalities for the kidney cancer diagnosis and these offer a lot of options, so there are studies with the same objectives (differentiate high and low nuclear grade) using the positron emission tomography-computerized tomography (PET-CT) (22). This technique is not adequate to differentiate the different histological subtypes although the correlation is good for clear cell RCC and not for chromophobe RCC.

All the aforementioned aspects are subjective evaluations and have limitations. Nephrectomy remains the treatment of choice in patients with RCC, and the histopathologic analysis of the tumor is needed for final diagnosis. The utility to know the Fuhrman grade before surgery is limited, only to small masses and in patients whose conditions require active surveillance.

These techniques require learning by the radiologist to minimize subjectivity; they must show reproducibility and can be adopted in the usual hospital environment. Further prospective studies are needed, which determine the diagnostic power of these techniques and the practical usefulness in a more adequate way.

As it is known, renal cancer is a heterogeneous tumor from the genetic point of view. So, there are no specific genetic determinations, apart from the known alterations in *VHL* gene. However, determination of genetic sequences in plasma with high molecular sensitivity techniques is currently under development in RCC (and already established in other types of tumors). The term "liquid biopsy" is a non-invasive technique and it can, through the circulating nucleic acids analysis of in plasma, improve the

accuracy on the nuclear grade diagnosis in renal tumors (23).

In conclusion, the immediate future in preoperative diagnosis of renal masses leads us to a clinical, radiological and molecular management, which will allow to establish individualized prognosis and targeted and personalized treatments.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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