Is imagery distinctive in papillary renal cell carcinoma subtypes?

Quelle place pour l'imagerie dans la différenciation des sous-types du carcinome papillaire du rein?

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RÉSUMÉ

Introdution : La subdivision en deux entités des carcinomes papillaires du rein était initialement établie sur des critères histo-pronostiques. Il est actuellement possible de distinguer les deux sous-types au moyen des données radiologiques et évolutives. Le sous-type 1 s'associe à un profil évolutif favorable par rapport au sous-type 2. L'échographie et particulièrement l'uro-scanner assurent une approche diagnostique assez précise avec des implications thérapeutiques et pronostiques conséquentes. L'objectif de l'étude est de définir les particularités radiologiques permettant de distinguer les deux sous-types des carcinomes papillaires du rein, et d'étudier les facteurs radiologiques prédictifs des récidives locorégionales, de la survie sans métastases et de la survie spécifique.

Methodes : Il s'agit d'une étude monocentrique, rétrospective, menée entre Janvier 2005 et Juin 2017, colligeant 49 cas de carcinomes papillaires du rein. L'étude concernait les patients âgés de plus que 18 ans, chez qui le diagnostic était établi suite à l'examen anatomopathologique de la pièce opératoire (néphrectomie élargie ou chirurgie conservatrice). Les cas dans lesquels le diagnostic était établi par une biopsie rénale étaient exclus.
L'étude comparative des données radiologiques concernait les explorations échographiques et tomodensitométriques, afin de définir l'ensemble des critères permettant de faire la part entre les deux sous-types histologiques. Une analyse univariée et multivariée était effectuée afin de déterminer les facteurs radiologiques ayant une valeur pronostique dans l'évolution des carcinomes papillaires du rein, en termes de survie sans récidives locorégionales et sans métastases.

Resultats : A l'échographie, le sous-type 1 histologique s'associait significativement aux tumeurs homogènes avec des contours réguliers. Les tumeurs étaient globalement spontanément hypodenses et hypo vasculaires dans 97,8% des cas. Le rehaussement était significativement plus hétérogène pour les tumeurs de sous-type 2 (p=0,01). La nécrose intra-tumorale et les adénomégalies étaient significativement associées au sous-type 2 (p=0,0001 et 0,005). Les facteurs prédictifs des récidives locorégionales, de la survie sans métastases et de la survie spécifique des carcinomes papillaires en analyse univariée étaient l'aspect des contours à l'échographie et à l'uro-scanner, le degré de rehaussement et la présence d'adénomégalies. En analyse multivariée, seul l'aspect mal limité tomodensitométrique des contours influait la survie sans récidives et la survie spécifique de l'ensemble des tumeurs papillaires.

Conclusions : Des différences significatives entre les deux sous-types étaient observées en étudiant les données radiologiques. Les contours irréguliers, les adénomégalies et le degré de rehaussement avaient un impact sur la progression des carcinomes papillaires du rein après la chirurgie.

Mots cles : Tumeurs du rein, carcinome papillaire, histologie, tomodensitométrie, chirurgie, pronostic

SUMMARY

Introduction : The subdivision into two entities of papillary renal cell carcinoma (PRCC) was established on histological criteria. It's in fact possible to distinguish the two subtypes by the means of radiological and progressive data. The subtype 1 is associated with the favorable profile. The ultrasound and especially CT urography ensure an accurate diagnostic approach with substantial therapeutic and prognostic involvement.
The aim of the study is to define the radiological features that distinguish the two subtypes of renal papillary carcinoma, and to study the radiological predictive factors of locoregional recurrence, metastases free survival and specific survival.

Methods: It's about a monocentric, retrospective study led between January 2005 and June 2017, gathering 49 cases of operated PRCC. The study concerned patients over the age of 18, who were diagnosed after anatomopathological examination of the operative specimen (enlarged nephrectomy or conservative surgery). Cases in which diagnosis was made by renal biopsy were excluded. The comparative study concerned ultrasound and CT scan data. Univariate and multivariate analysis were performed to determine factors having a prognostic value in terms of locoregional recurrence, metastases-free and specific survival.

Results: On the ultrasound, the subtype 1 tumors were significantly homogenous with regular contours. Tumors were globally spontaneously hypodense and hypo vascular in 97,8% of cases. Enhancement was significantly more heterogonous for subtype 2 (p=0,01). Intratumoral necrosis and adenomegalies were associated with subtype 2 (p=0,0001 and 0,005). The predictive factors of locoregional recurrence, metastases-free survival and specific survival in univariate analysis were the contours' aspect, moderate enhancement and the presence of adenomegalies. On multivariate analysis, only the irregular contours were retained for locoregional recurrence-free survival and specific survival.

Conclusions: Significant differences between the PRCC subtypes were observed when studying the radiological data. Irregular contours, adenomegalies and enhancement degree seemed to predict the progression of PRCC after curative surgery.

Key Words: Kidney tumors, papillary carcinoma, histology, ultrasonography, tomography; prognosis.

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INTRODUCTION

The generalization of explorations and the improvement of the imaging means precision explain largely the increase in the number of the diagnosed renal tumors.

Ultrasound took its place as first-line exploration guiding the etiological diagnosis of kidney masses. The CT urography offers, by its different times, the possibility of differentiating between the clear-cell carcinoma and the other renal tumors, whose papillary carcinoma of the kidney, by studying specifically enhancement kinetics.

METHODS

The study of radiological data concerned ultrasound and CT scan explorations.

The ultrasound data collected concerned the echogenicity degree, heterogeneity as well as contours regularity. The CT sequence included in all cases a time without injection, a cortical phase, a tubular phase and an excretory phase.

The first evaluated criterion was the size of the tumor as well as its site and its focal or multiple characters. We also studied the endophytic or exophytic characters, the solid or cystic nature of the tumor, the contours aspect, the spontaneous density, the homogeneity, the degree and homogeneity of enhancement. Enhancement was judged to be weak if it was lower than 20 unities Hounsfield (UH), moderated between 20 and 40 UH and important to more than 40 UH. The presence of calcification as well as their site (central or peripheral) was noted. The other data compared between the two groups were the intratumoral necrosis, the presence of fat into the tumor, and the presence of adenomegalies (defined by the presence of adenopathy whose minor axis exceeded 10mm).

The comparisons of averages were performed by the means of Student's-t test. The comparisons of percentages were performed by the means of Chi-Square test, and in case of the latter non-validity by Fisher's exact test. The significance level was fixed at 0, 05. The survival curves were established according to the Kaplan-Meier estimator. The study of survival prognostic factors was performed in univariate analysis by the means of the log Rank test. The significance level was fixed at 0, 05. The multivariate analysis was conducted in Cox regression according to the step-by-step «top-down» approach. The multivariate analysis allowed calculating the adjusted relative risks, measuring the proper role of each factor.

RESULTS

Our study included 49 patients divided into two groups. The first group of subtype 1 was made of 23 patients (47%). The second group, of subtype 2 was made of 26 patients (53%). The mean age of patients was 57, 8 (18-88) years. 38 were men (78%) and 11 were women (22%). The sex ratio was of 3, 4. Among the 23 patients of the first group, the tumor was located on the right kidney in 14 cases (60, 9) and on the left kidney in 8 cases (34, 8%). Only one patient presented a bilateral tumor (4, 3%).

For the 26 patients of the second group, the tumor was located on the right in 18 observations (69%) and on the left in 8 others (30, 8%). No case of bilaterality was observed. The discovery was accidental at the imaging in 13 cases (27%). Among these 13 cases, 6 were classified in the first group (26%) and 7 in the second group (27%). The clinical features are detailed in Table 1.

Table 1. Clinical features.

	Subtype 1 *(n= 23)*	Subtype 2 *(n= 26)*
Age *(mean)*	*55*	*60,3*
Sex		
Male	*17 (74%)*	*21 (81%)*
Female	*6 (26%)*	*5 (19%)*
Sex Ratio	*2,8*	*4,2*
Tumor's location		
Right kidney	*14 (61%)*	*18 (69%)*
Left kidney	*8 (35%)*	*8 (31%)*
Bilateral	*1 (4%)*	
Revealant Circumstances		
Fortuitous revealanc	*6 (26%)*	*7 (27%)*
Symptomatic tumor	*17 (74%)*	*19 (73%)*

Ultrasound appearances, performed in all the cases, allow the detection of some significant differences between the two groups (Table 2). If the difference regarding echogenicity hadn't any statistical significance, the histological subtype 1 tumors were more homogenous with regular contours in comparison with subtype 2 tumors (Figure 1).

Among the 23 first group patients having presented at the histology a subtype 1 of papillary carcinoma, 21 patients were explored by CT urography preoperatively. The two remaining patients, hemodialyzed in the long term, had Uro-MRI prior to surgery. Imagery data related to these two patients weren't taken into consideration in our study. The 26 patients constituting the second group were all explored by CT urography.

Table 2. Ultrasound charactersitics.

		Subtype 1 *(n=23)*	Subtype 2 *(n=26)*	« p » value
Echogenicity	Hypo-echoic	19 *(83%)*	19 *(73%)*	*0,29*
	Iso-echoic	1 *(4%)*	0	
	Hyper-echoic	3 *(13%)*	7 *(27%)*	
Homogeneity degree				
	Homogeneous	17 *(74%)*	6 *(23%)*	*0,001*
	Heterogeneous	6 *(26%)*	20 *(77%)*	
Contours regularity				
	Regular	23 *(100%)*	13 *(50%)*	*< 0,0001*
	Irregular	0	13 *(50%)*	

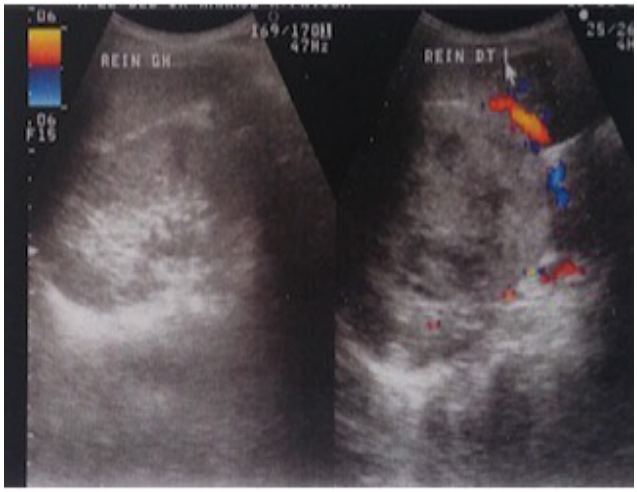

Figure 1. Subtype 2 of a papillary carcinoma in 68 years old woman. US shows a 10 centimeters hypoechoic and heterogeneous mass. In doppler, the tumor appears to be hypo-vascularized. The contours are focally irregular.

By analyzing tomodensitometric data, we concluded to a statistically significant difference for the criteria concerning the size of the tumor, the appearance of contours, homogeneity, enhancement type, intratumoral necrosis and the presence of adenopathies (Table 3).

The mean size of tumors on the scanner of the subtype 1 diagnosed tumors at histology was of 46, 8 mm [7-160 mm]. Type 2 classified tumors had a mean size of 76, 3 mm [20-230 mm]. The difference was statistically significant, and the value of «p» was 0,03. The histological subtype 1 tumors were well limited, homogenous in a spontaneous density and after the injection of contrast medium (Figure 2). The histological subtype 2 tumors were, most often, site of intratumoral necrosis and associated with adenomegalies (Figure 3). The differences observed for the nature of tumors, their spontaneous density, the degree of enhancement and the presence of calcification had no statistical significance.

Table 3. Computed tomography characteristics of the two subtypes of papillary renal cells carcinoma.

	Subtype 1 (n=21)	Subtype 2 (n=26)	« p » value
Tumor's size (mean, millimeters)	46,8	76,3	*0,03*
Multifocality			
Unique tumor	16 *(76%)*	23 *(88%)*	*0,33*
Multiple tumor	5 *(24%)*	3 *(12%)*	
Tumor's location in the parenchyma			
Endophytic	8 *(38%)*	6 *(23%)*	*0,82*
Exophytic	13 *(62%)*	20 *(77%)*	
Tumor's nature			
Solid	13 *(62%)*	22 *(84%)*	*0,34*
Cystic : Bosniak 3	3 *(14%)*	2 *(8%)*	
CYstic : Bosniak 4	2 *(10%)*	1 *(4%)*	
Mixed tumors (Solid and cystic components)	3 *(14%)*	1 *(4%)*	
Regularity of tumor's contours			
Regular	21 *(100%)*	16 *(62%)*	*<0,0001*
Irregular	0	10 *(38%)*	
Spontaneous density			
Hypodense	16 *(76%)*	5 *(19%)*	*0,86*
Isodense	3 *(14%)*	18 *(69%)*	
Hyperdense	2 *(10%)*	3 *(12%)*	
Homogeneity degree			
Homogeneous	14 *(67%)*	6 *(23%)*	*0,003*
Heterogeneous	7 *(33%)*	20 *(77%)*	
Degree of enhancement			
Low (< 20 HU)	9 *(43%)*	11 *(42%)*	*0,66*
Moderate (20-40 HU)	12 *(57%)*	14 *(54%)*	
Elevated (> 40 HU)	0	1 *(4%)*	
Homogeneity of enhancement			
Homogeneous	11 *(52%)*	5 *(19%)*	*0,01*
Heterogeneous	10 *(48%)*	21 *(81%)*	
Intra-tumoral calcifications			
Presence	2 *(10%)*	9 *(35%)*	*0,11*
Location : Central	0	2 *(8%)*	
Peripheral	2 *(10%)*	7 *(27%)*	
Intra-tumoral necrosis	3 *(14%)*	18 *(69%)*	*<0,0001*
Intra-tumoral fat	2 *(10%)*	0	*0,21*
Adenomagalies	0	8 *(31%)*	*0,005*

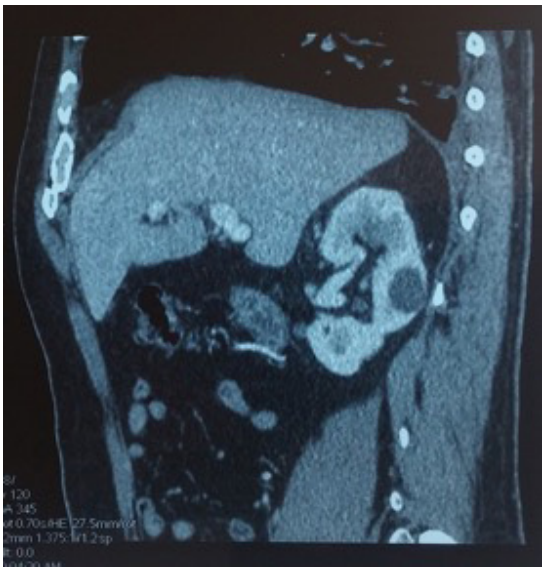

Figure 2. Subtype 1 of a papillary carcinoma in a 53 years old man. Two tissular masses enhancing moderately in contrast, measuring 16 and 20 millimeters. Multiple cysts are observed in the same kidney.

Mean follow-up period was 83 months [7-101 months]. Eleven cases of loco-regional recurrence were documented (24, 5%). The average time of loco-regional recurrence was 21, 6 months [5-96 months]. Four recurrences were of subtype 1, while 7 were of subtype 2. Nine cases of metachronous metastases were diagnosed, two among them were in subtype 1 patients and 7 in subtype 2 patients. The average time of metastases occurrence was 12, 4 [8-18 months]. In the univariate analysis, predictive factors of loco-regional recurrences were the appearance of contours on the ultrasound (p= 0, 01) and CT urography (p= 0, 015), enhancement superior to 20 HU (p=0, 04) and the presence of adenomegalies (p= 0, 029) (Figure 4).

The multivariate analysis concluded that only the irregular tomodensitometric contours of the tumor conditioned the survival without loco-regional recurrence (relative risk: 3,994; Confidence interval 95%: 1,167-13,670; p=0,027).

The factors condition the mestastasis free survival after the univariate analysis were the appearance of contours in tomodensitometry (p=0,049), the presence of adenomegalies

(p= 0, 036), enhancement superior to 20 HU (p= 0, 05) and the presence of calcifications (p= 0; 02) (Figure 5). No studied radiological factor was correlated to survival without metastases in multivariate analysis.

The mean specific survival was 83 months. Predictive factors of specific survival in univariate analysis were the appearance of contours on the ultrasound (p= 0, 07), and tomodensitometry (p= 0, 001), the presence of adenomegalies (p= 0, 005) and enhancement superior to 20 HU (0, 01) (Figure 6). Only the irregular tomodensitometric aspect of the tumor's contours was linked independently to

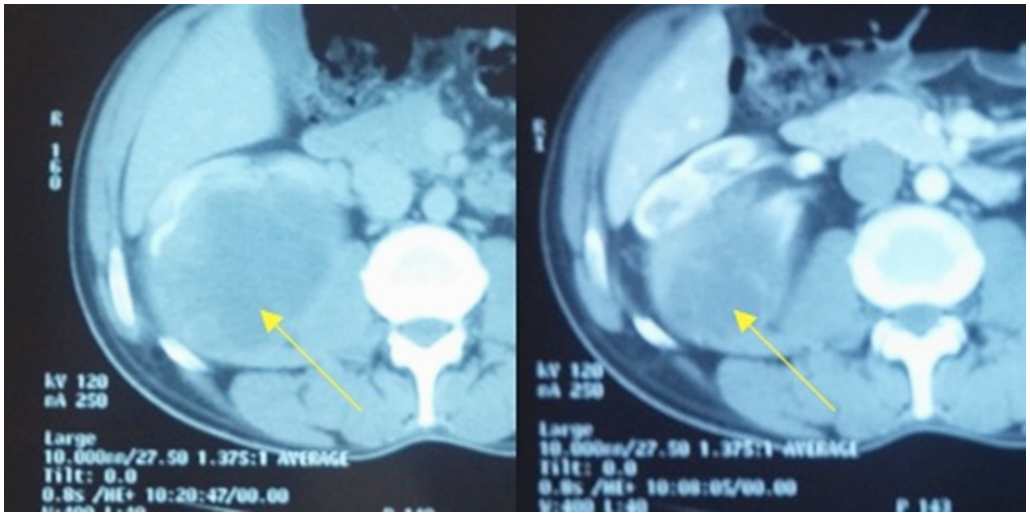

Figure 3. Subtype 2 of a papillary carcinoma in a 61 years old female patient. A 10 centimeters tissular and irregular mass, developped from the right kidney (arrow). The tumor contains calcifications. It's spntaneously hypodense, enhancing heterogeneously in contrast.

the specific survival in the multivariate analysis (Relative Risk: 13,925; Confidence Interval 95%: 1,672-115,961; p=0,015).

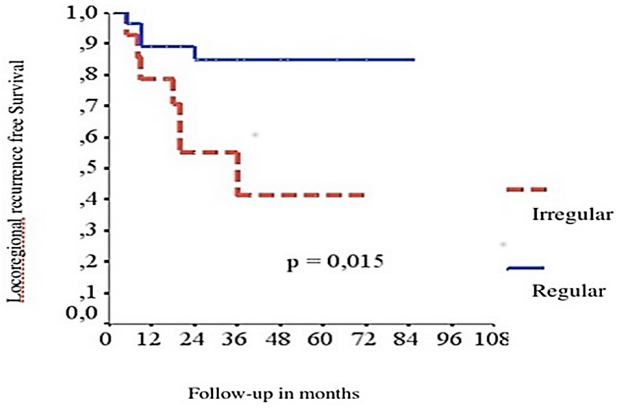

Figure 4. Locoregional recurrence free survival on univariate analysis. The irregular aspect of tumor's contours in CT is a significant predictor.

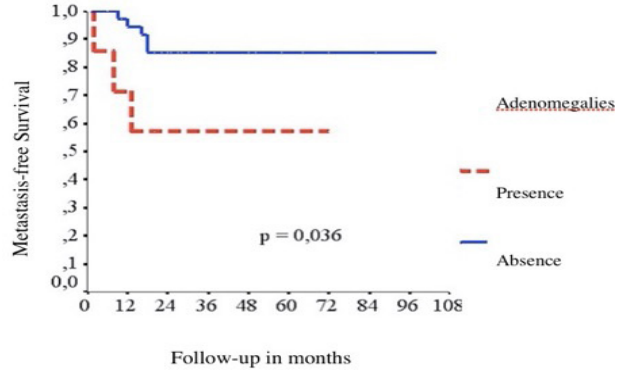

Figure 5. Metastasis-fre survival on univariate analysis. The presence of adenomegalies has a significant impact.

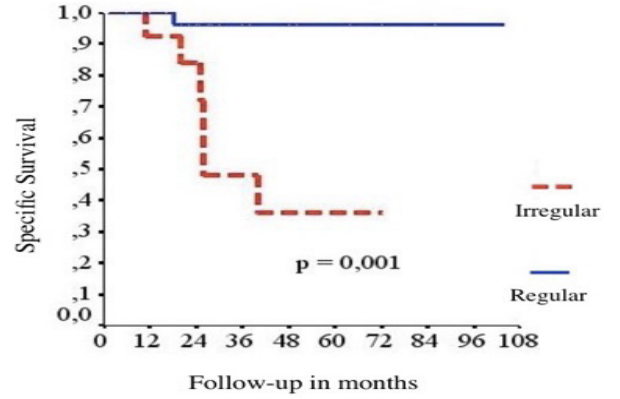

Figure 6. Specific survival on univariate analysis. Specific survival decreases significantly when tumoral limits are irregular in CT.

DISCUSSION

We led a comparative study of radiological data, and their implication in prognostic profiles of both histological subtypes of 49 renal papillary carcinomas operated between January 2005 and December 2015.

Histological subtype 1 showed a significantly more homogeneous appearance with regular ultrasound contours, compared to subtype 2.

Subtype 1 tumors were more homogeneous in spontaneous density and on contrast.

Regular tumor contours were also significantly associated to subtype 1.

Subtype 2 tumors showed more intratumoral necrosis and loco-regional ganglionic areas invasion.

Subtype 2 tumors were larger and associated to higher tumor stage and Fuhrman nuclear grade.

Necrosis and calcification were more marked for subtype 2. Overall survival and recurrence-free survival analysis retained, as radiological prognostic factors for papillary carcinomas: the contours aspect on ultrasound and computed tomography, the ganglionic involvement and the enhancement degree.

Papillary carcinomas are the second histological type of renal cells carcinomas representing 10 to 15% of the kidney's tumors [1]. Heterogeneity within papillary carcinomas was originally mentioned in the eighties. The actual subdivision, into two distinct entities was established on the basis of histological and prognostic criteria in the end of the nineties [2]. Since the first angiographic description of papillary carcinomas of the kidney by Mancilla-Jimenez [3], imaging acquired a primordial place in the management of suspect renal masses. Indeed, ultrasound and especially scannographic appearance of the tumor allows not only discerning the two subtypes of papillary carcinomas, but also predicting the tumor prognosis. Ultrasound, of common practice, allows detecting renal masses, describe their nature, their contours, but is not enough alone to ensure a diagnostic orientation [4]. The suspect tumors in the ultrasound should then be explored by CT urography [5].

Ultrasound appearance of papillary carcinomas of the kidney, like the renal cells carcinomas, is not unequivocal. It may concern a tumor hypo, iso or hyperechoic [4,6]. Hypo-echogenicity is most frequently reported, probably due to the reduced vascularization of papillary carcinomas and to the range of areas of necrosis and hemorrhage [4,7].

Literature data diverge also on the variable character, homogenous or heterogonous, of the papillary carcinomas of the kidney. Combes et al., studying the differences between the histological types 1 and 2 of 58 cases of papillary carcinomas of the kidney, often a tendency of the papillary carcinomas to have a homogenous, iso or hypoechoic, without significant correlation with histological data [8]. The major ultrasound interests remain the screening in the population at risk, especially in the long-term dialysis patients.

Referring to our results, the hypoechoic appearance was prevailing in the subtype 1. On the other hand, hypo-echogenicity wasn't observed in any of the subtype 2 tumors in our study. Homogenous tumors with regular contours were significantly more observed in the subtype 1 group.

At the present time, an increasing interest is vested in contrast-enhanced ultrasound [7,10]. The usefulness of this technique lies in the fact that papillary carcinomas are generally hypovasculaire tumors, whose cortico-medullary phase enhancement can mime those of the

benign tumors [7]. Ultrasonic contrast ultrasound, able to detect intratumoral microvasculature, ensures a better exploration than scanner [7].

Xue et al., in a series comparing 48 patients presenting 49 papillary carcinoma lesions to 153 patients presenting clear cell adenocarcinoma of kidney, find that papillary carcinomas present a homogenous enhancement, even more important since the size of the tumor exceeds 3 cm [9].

If the description of papillary carcinomas, as an entity being part of the renal cells carcinomas was subject to many studies, the comparison of the two histological subtypes from a scannographic point of view wasn't sufficiently treated in literature [11,12]. The widest published study treating scannographic aspect of both papillary renal cell carcinoma subtypes, was led retrospectively by Bindayi et al [13]. There weren't distinctive elements predicting the histological subtype. Authors proposed renal biopsy before conservative surgery once a papillary carcinoma is suspected.

The appearance of papillary carcinomas as well as the kinetics of enhancement depends essentially of the vascularization of tumor. The intratumoral microvasculature is an overriding criterion explaining a significant portion of the differences observed in the Uro-scanner between clear cell Adenocarcinoma of kidney and papillary carcinomas of the kidney. This parameter is expressed in microvessels density [11,14]. Jinzaki et al. studied this density in kidney cells carcinomas microvessels. It was concluded that, like most of the histological types of renal tumors, it's less important in papillary carcinomas in comparison to clear cells carcinomas [12]. The widest series in literature is that of Egbert et al., published in 2013. The key point of this study is the elimination of histological twofold component papillary carcinomas histological forms, those containing clear cells contingent, and the atypical subtypes 1 and 2 forms by their Fuhrman nuclear grade (High-grade type 1 and low-grade type 2). The restriction of comparison groups allowed avoiding all kinds of results overlap due to atypical histologically. Thus, in comparing 43 type 1 papillary carcinomas to 13 other type 2 carcinomas, this work concluded that type 2 are larger (average size of 6 cm for type 2, against 3, 5 for type 1), contain more calcifications, with more frequent irregular limits [11].

In our study, and just like for ultrasound, subtype 1 tumors were more homogenous with more regular contours than those of subtype 2. Such homogeneity was more marked in spontaneous density and after the injection of contrast medium. Subtype 2 tumors showed significantly more images of necrosis in the scanner and were more associated with suspect adenopathy. We didn't conclude to a significant difference concerning enhancement kinetics of the two subtypes.

The observed differences to imaging between the two subtypes, and the best prognosis of subtype 1 in terms of survival without recurrence and specific survival, highlighting the impact of imaging in predicting the evolutionary course of papillary carcinomas of the kidney. The low enhancement was a prognostic factor in Combes and al. series [8]. In our series, the irregular tumor's contours was the most influential prognostic factor in terms of locoregional recurrence and specific survival. Tomodensitometric and preoperative interpretation can predict the tumor evolutionary potential, and guide the attitude namely for multifocal or bilateral tumors [15].

CONCLUSIONS

A set of radiological, ultrasound and scannographic criteria allow distinguishing the two histological subtypes of papillary carcinomas of the kidney. The subtype 2 tumors were larger, bad limited, with heterogonous enhancement with frequent presence of intratumoral necrosis and adenomegalies. These differences to imagery have a

place in the therapeutic attitude as well as a prognostic value.

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