

Introduction to T1 Renal Tumours and Prognostic Indicators

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Abbreviations

ARCD	Acquired renal cystic disease
CSS	Cancer-specific survival
ESRD	End-stage renal disease
NSS	Nephron-sparing surgery
OS	Overall survival
PN	Partial nephrectomy
RCC	Renal cell carcinoma
UCS	Urinary collecting system
VHL	von Hippel-Lindau

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Key Messages

1. Kidney cancers represent the 14th most common malignancies with more than 300,000 new cases diagnosed in 2012.
2. In 2012, kidney cancers accounted for 143,000 deaths with a crude rate value of 2% of all cancer deaths.
3. Cigarette smoking, overweight and obesity and arterial hypertension are the most prevalent modifiable risk factors for RCC in both genders.
4. Preoperative variables influencing the decision-making process for T1 renal tumours can be classified as patient-related (age, co-morbidities and performance status) and tumour-related (mode of presentation, clinical tumour size and anatomical/topographic characteristics) factors.
5. The use of nephrometry systems (RENAL or PADUA) to define the anatomical and topographic characteristics of small renal masses should be considered the standard of care for the preoperative evaluation of patients suitable to nephron-sparing surgery.
6. Treatment of cT1N0M0 parenchymal renal tumours should be based on patient-related factors, tumour-related characteristics and surgeon experience.

7. Beyond tumour characterization according to histological subtype, the most important traditional pathological factors dictating the prognosis of patients with RCCs are the pathological size and extent of the primary tumour, nuclear grading, coagulative necrosis, microvascular invasion and sarcomatoid dedifferentiation.
8. Prognosis can be estimated combining clinical and pathological factors in the context of mathematical models. This information can be used to improve the counselling process and to guide the follow-up.

2.1 Epidemiology and Aetiology

Kidney cancers represent the 14th most common malignancies with more than 300,000 new cases diagnosed in 2012. Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney cancers. According to the gender, around 200,000 new cases were observed in men and 100,000 in women. Moreover, there were around 198,000 new cases in more developed regions and 130,000 in less developed regions [1]. Indeed, renal tumours are more frequently detected in Europe, North America and Australia than in India, Japan, Africa and China. The Czech Republic, Lithuania, Latvia, Estonia and Iceland have the highest incidence in Europe. Interestingly, the incidence of kidney cancers is declining in some European countries, namely, Sweden, Poland, Finland and the Netherlands [2]. Furthermore, incidence rates in Europe and the USA increase consistently with age. This trend can be strongly correlated with the parallel use of non-invasive diagnostic testing, such as abdominal ultrasound, for symptoms that are not strictly related to the suspicion of kidney cancer.

In 2012, kidney cancers accounted for 143,000 deaths with a crude rate value of 2% of all cancer deaths. 91,000 deaths were in men (crude rate 2.6%) and 52,000 in women (crude rate 1.5%) [1].

Like incidence trends, overall mortality rates were highest in North America, Australia/New Zealand and Europe and lowest in Africa and Asia [2]. After several years of increasing trends in RCC mortality, it seems that rates are stabilizing or even declining in many Western countries. In Europe, a decrease in mortality was observed in Scandinavian countries, France, Germany, Italy, Austria and the Netherlands, while increased mortality rates are still reported in Ireland and Slovenia [2].

Cigarette smoking, being overweight and obese and arterial hypertension are the most prevalent modifiable risk factors for RCC in both genders. Thus, recommended strategies to prevent kidney cancers should entail programmes for smoking cessation, reducing excess body weight and treatment of uncontrolled arterial blood pressure. Notably, patients with end-stage renal disease (ESRD) or on long-term haemodialysis developing an acquired renal cystic disease (ARCD) present a significant risk to develop RCC. Therefore, these patients should be regularly screened. On the other hand, it is unclear whether renal transplantation in these patients can reduce the risk to develop RCC [3].

Numerous studies have tested the potential role of nutrition and diet as risk factors for RCC. Conflicting or inconclusive data have been reported for proteins and fats, vitamins, fruits and vegetables, meat and fish, alcohol, coffee and other beverages. Currently no dietary recommendations can be given. Moreover, epidemiological studies have demonstrated that kidney cancer should not be considered to be a typical occupation-related tumour. Nevertheless, current guidelines recommend decreasing or preventing exposure to occupational carcinogens like asbestos, polycyclic aromatic hydrocarbons, dry-cleaning solvents and cadmium [2].

Genetic factors are implicated in the development of the 2–3% of familial RCC syndromes, such as von Hippel-Lindau syndrome, hereditary papillary RCC syndrome, familial leiomyomatosis and RCC syndrome and Birt-Hogg-Dubé syndrome. All these syndromes are transmitted in an autosomal-dominant manner. Germline mutations in the von Hippel-Lindau (VHL) gene are

the most common alterations, and active screening in these patients might be considered to detect RCC at an early enough stage to permit nephron-sparing surgery (NSS).

Despite advances in imaging techniques and the increase in incidentally detected renal tumours with abdominal ultrasound performed for unrelated complaints, about 20–30% of all patients are still diagnosed with metastatic disease. Moreover, 20–30% of patients undergoing surgical treatments for organ-confined disease will have a local relapse or develop distant metastases [2]. This chapter focuses on non-metastatic RCC confined to the parenchyma and ≤ 7 cm in largest size, i.e. clinically T1N0M0. The 2009 TNM staging system classifies organ-confined renal tumours according to the 7-cm size cut-off. Specifically, masses ≤ 7 cm are classified as T1 and larger tumours as T2. Moreover, the latest version of TNM classification confirms the classical stratification of T1 tumours in two different subgroups (T1a and T1b) according to the 4-cm size cut-off. Notably, the system introduces a further stratification of T2 tumours in two categories (T2a and T2b), according to the 10-cm size cut-off [4].

Several clinical factors play a relevant role in the decision-making process for surgical treatment planning of T1N0M0 RCC. Similarly, certain pathological features warrant tailored post-operative management plan and, in the future, will determine selection for targeted adjuvant therapy. Moreover, both clinical and pathological factors are key to predicting the prognosis of patients who are candidates for surgical treatment. To improve their accuracy, prognostic variables have been combined to generate mathematical models, such as algorithms and nomograms [4].

2.2 Clinical Factors

Preoperative variables influencing the decision-making process for T1 renal tumours can be classified in patient-related (age, co-morbidities and performance status) and tumour-related (mode of presentation, clinical tumour size and anatomical/topographic characteristics) factors.

Few data are available about the potential impact of age on renal tumour characteristics and prognosis. A multi-institutional study showed that patients aged ≤ 40 years were more likely to have papillary or chromophobe RCC and less likely to have clear cell RCC. Interestingly, the authors have observed that age was an independent predictor of cancer-specific survival (CSS), with older patients having significantly worse survival [5]. Notably, Sun et al. recently published a SEER database analysis showing that in patients aged ≥ 75 years, 2- and 5-year overall survival (OS) is comparable after radical nephrectomy or partial nephrectomy (PN). According to this study, the indication for elective PN in patients aged ≥ 75 years should be carefully discussed during pretreatment counselling [7]. Similar considerations can be made considering the co-morbidity profile of patients with T1 tumours suitable for NSS. Indeed, in the SEER registry analysis, patients with >2 baseline co-morbidities showed a comparable 2- and 5-year OS after PN or radical nephrectomy [7]. Therefore, patient co-morbidities must be taken into account as a selection criterion for NSS. Performance status was an independent predictor of CSS [7], but its prognostic role seems to be more relevant in patients with locally advanced or metastatic tumours [8].

Considering preoperative tumour-related variables, mode of presentation was extensively evaluated, and its independent predictive role was demonstrated in multi-institutional series [8]. According to the Patard classification, tumours diagnosed during abdominal imaging for signs and symptoms unrelated to RCC are classified as incidental (S1). Conversely, flank pain, haematuria and flank mass are considered as local symptoms (S2). Systemic symptoms suggesting advanced stage disease (weight loss, fever and para-neoplastic syndromes) are defined as S3 cases [9]. Notably, asymptomatic patients have more favourable CSS rates in comparison with patients with local symptoms. Therefore, this parameter might be considered a further criterion in the decision-making process for management of T1 tumours. Haematuria is considered by some authors as a relative contraindication for PN because this sign may indicate upper collecting

system involvement. Notably, urinary collecting system (UCS) involvement is still not included in the current TNM staging system. However, Verhoest et al. in 2009 demonstrated in a large series of patients the independent role of UCS invasion to predict the cancer-specific survival of both patients with pT1 and pT2 tumours [10].

Clinical tumour size is traditionally recognized as an important prognostic factor, and it has been used as the main criterion to select patients suitable for NSS. Considering T1 tumours, international guidelines recommend NSS as standard of care for T1a tumours and strongly support expanding indications also for T1b tumours whenever technically feasible.

However, rather than size alone, it is the anatomical and topographic characteristics of T1 renal tumours as well as surgeon experience that represent the main factors influencing the technical feasibility of NSS. In 2009, two nephrometry systems, the RENAL nephrometry and PADUA classification, were proposed to classify parenchymal renal tumours according to their anatomical and topographic characteristics with the aim to predict the surgical complexity, thereby refining selection criteria for, and improving the main outcomes of, PN [11, 12]. Figure 2.1 shows the variables included in PADUA classification and the different scores applied for each anatomical situation.

Table 2.1 describes the parameters included in the RENAL and PADUA classifications. Besides a different criterion used to define longitudinal polar location (Fig. 2.2), the PADUA system includes rim location and considers involvement of urinary collecting system and of renal sinus separately (Table 2.1). In 2010, Simmons et al. described the centrality index (c-index) system, which gives a single score based entirely on tumour size and tumour depth variables. This system does not communicate data on geographic location, but provides information about the proximity of the tumour to the kidney centre [13]. Probably, the complexity to calculate this score was responsible of a more limited application of this system compared to PADUA and RENAL nephrometry scores.

Neither nephrometry systems consider the status of perirenal fat tissue as a further potential factor influencing the complexity of a PN. The presence of adherent perinephric fat is known to make tumour exposure and excision more difficult, requiring subcapsular renal dissection and hence increasing the risk of complications. In 2014, an additional scoring system, called the Mayo Adhesive Probability, has been proposed by Davidiuk et al. [14]. Based on a series of 100 patients undergoing robot-assisted PN, the authors built a scoring algorithm predicting the presence of adherent perinephric fat. The risk score was created using two image-derived variables, i.e. posterior perinephric fat thickness and stranding, which were most highly predictive at multivariable analysis. This system requires external validation on a large-scale basis before entering clinical practice. Similarly, Zheng et al. tested the role of perinephric fat density measured during preoperative CT scan to predict intraoperative fat dissection difficulty. They reported that this parameter is a strong indicator of so-called sticky fat and can anticipate more difficult PN cases [15].

Several studies demonstrated that RENAL and PADUA systems are able to predict perioperative outcomes such as ischaemia time, blood loss and intra- and post-operative complications regardless of the approach used to perform NSS [16]. Therefore, both systems are widely used in clinical practice. However, few studies compared the PADUA and RENAL systems. In 2011, Hew et al. tested the PADUA and RENAL systems in a series of 134 patients undergoing PN. Both systems predicted complications at univariable analysis. At multivariable analyses, PADUA score ≥ 10 (OR 3.98, $p = 0.01$), RENAL score ≥ 9 (OR 4.21, $p = 0.02$), tumour size (OR 1.35, $p = 0.02$) and age (OR 1.04, $p = 0.04$) were independent predictors of complications. Moreover, both scores resulted able to predict ischaemia time. Interestingly, both systems showed a substantial reproducibility with an interclass correlation coefficient of 0.73 for PADUA and 0.70 for RENAL score [16]. In 2012, Bylund et al. evaluated the association of tumour

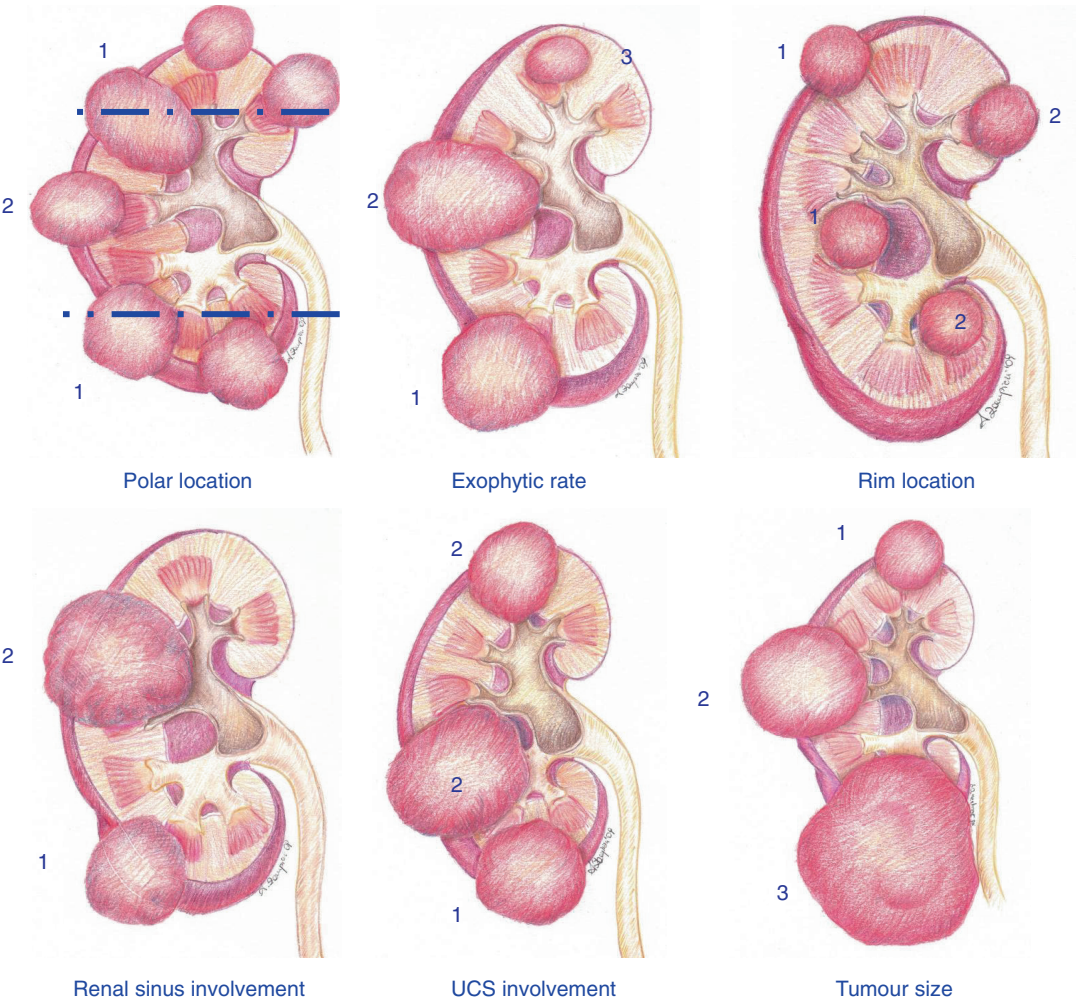


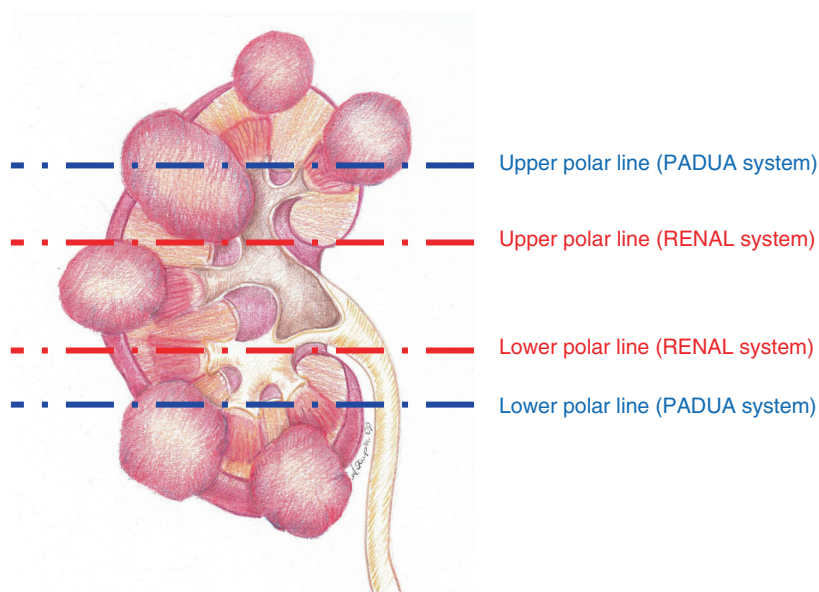
Fig.2.1 Features included in the PADUA classification and scores applied for each anatomical situation

Table 2.1 Differences and parameters included in RENAL nephrometry and PADUA classification

Variables	RENAL	PADUA	Differences
Tumour size	≤4; 4–7; >7 cm	≤4; 4–7; >7 cm	No
Exophytic (%)	≥50%; <50%; endophytic	≥50%; <50%; endophytic	No
Polar location	Renal hilar as landmark	Sinus line as landmark	Yes
Rim location	Not evaluated	Lateral, medial	Yes
Renal sinus involvement	≤4; 4–7; >7 mm	Not involved, involved	Yes
UCS involvement		Not involved, involved	Yes
Face	Anterior/posterior	Anterior/posterior ^a	No/Yes

^aExcluded from the score according to univariable analysis

Fig. 2.2 Definition of polar lines according to PADUA and RENAL nephrometry systems



size, location, RENAL, PADUA and centrality index score with perioperative outcomes and post-operative renal function. Both PADUA and RENAL systems outperformed tumour size and location in the prediction of perioperative outcomes [17]. In 2014, Zhang et al. tested PADUA and RENAL systems in a series of 245 Chinese patients undergoing laparoscopic PN. In this retrospective study, at multivariable analysis both scores were able to predict the percent change in estimated glomerular filtration rate. Moreover, this study confirmed the reproducibility of PADUA and RENAL systems, with concordance values ranging between 0.69 and 0.89 for the various components of the PADUA and between 0.67 and 0.89 for those of the RENAL system [18].

The predictive accuracy of nephrometry systems has been demonstrated not only for PN but also for other minimally invasive treatments of renal tumours, such as cryoablation and radiofrequency ablation. Schmit et al. tested the RENAL system in a series of 751 renal tumours treated with percutaneous ablation (430 cryoablation and 321 radiofrequency ablation) [19]. The RENAL system accurately predicted treatment efficacy and complications. These systems can be applied also to the laparoscopic approach, as shown by Klatte et al. in a cryoablation series using PADUA system [20] and by Chang et al. in a radiofre-

quency ablation series using the RENAL system [21].

Accurate classification of the anatomical and topographic characteristics of small renal masses according to available nephrometry systems must be considered as a standard of care for the preoperative evaluation of patients suitable for NSS.

2.3 Pathological Factors

Renal tumours represent a group of entities with different cytogenetic, morphological and clinical characteristics. Moreover, approximately 20% of small renal masses are benign. In particular, papillary adenomas, pure oncocytomas and angiomyolipomas (except for a rare epithelioid variant) do not possess metastatic potential. In the context of malignant tumours, clear cell RCC represents the most common histological subtype, accounting for about 75% of all cases. The most frequent non-clear cell RCC subtypes are papillary (15%), chromophobe (5%) and Bellini duct (<1%) tumours. However, the progress in the knowledge of molecular and cytogenetic characteristics of renal cancers in the last decade has allowed pathologists to describe new subtypes, recently listed in the International Society of Urological Pathology (ISUP) Vancouver Modification of

Table 2.2 International Society of Urological Pathology (ISUP) Vancouver Modification of WHO (2004) Histologic Classification of Kidney Tumours

<i>Renal cell tumours</i>
Papillary adenoma
Oncocytoma
Clear cell RCC
Multilocular cystic clear cell of low malignant potential
Papillary RCC (types 1 and 2)
Chromophobe RCC
Hybrid oncocytic chromophobe tumour
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
MiT family translocation RCC [Xp11, t(6;11)]
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Clear cell tubulopapillary RCC
Hereditary leiomyomatosis RCC
RCC, unclassified

WHO (2004) Histologic Classification of Kidney Tumours [22] (Table 2.2).

The new renal cell tumours proposed by the ISUP in Vancouver were tubulocystic renal cell carcinoma, renal cell carcinoma associated with acquired cystic kidney disease, clear cell (tubulo) papillary renal cell carcinoma, t(6;11) translocation renal cell carcinoma with consequent redenomination of the entire group of tumours with translocation as “MiT family translocation renal cell carcinoma” and, finally, renal cell carcinoma associated with leiomyomatosis and renal cell cancer. Of note, clear cell (tubulo) papillary renal cell carcinoma, a neoplasm originally described in the setting of end-stage kidneys and subsequently recognized in otherwise normal renal parenchyma, has been demonstrated to represent up to 4% of all renal tumours. This entity, along with tubulocystic renal cell carcinoma, renal cell carcinoma associated with acquired cystic kidney and renal cell carcinoma with t(6;11) translocation, shows an indolent behaviour in the majority of cases; none of the clear cell (tubulo) papillary renal cell carcinomas described so far has recurred. On the other hand, renal cell carcinoma associated with hereditary leiomyomatosis and renal cancer syndrome, a tumour characterized

by a germline mutation in the gene coding for the enzyme fumarate hydratase, shows aggressive behaviour. Moreover, during the consensus conference, the following neoplasms were included in the group of emerging entities: thyroid-like follicular renal cell carcinoma, renal cell carcinoma associated with succinate dehydrogenase B mutation and renal cell carcinoma with ALK translocation. New concepts regarding recognized tumour entities were also proposed during the conference, including a multicystic variant of renal cell carcinoma, papillary renal cell carcinoma, chromophobe renal cell carcinoma and hybrid oncocytic tumours, collecting duct carcinoma, medullary renal cell carcinoma, mucinous and spindle cell renal cell carcinoma, angiomyolipoma as well as the epithelioid variant, cystic nephroma, mixed epithelial and stromal tumour and primary synovial sarcoma of the kidney.

While clear cell and papillary subtypes appear to stem from the epithelial cells of proximal tubule, oncocytomas and chromophobe subtypes arise from the distal tubule. Collecting duct and medullary RCCs arise from the collecting ducts of Bellini and renal medulla, respectively. Table 2.3 summarizes macroscopic, histological and cytogenetic characteristics of the main RCC subtypes [23].

Although the prognostic role of the main histological subtypes remains debated, the literature shows that papillary and chromophobe RCC have lower pathological stages and nuclear grades, as well as a lower risk of metastasis, compared to clear cell RCC. Consequently, patients with clear cell RCC have significantly lower CSS rates compared to those with either papillary or chromophobe subtypes, whereas the outcomes of papillary or chromophobe cancers are similar. Five-year CSS probabilities range from 43 to 83% for clear cell RCC, from 61 to 90% for papillary RCC and from 80 to 100% for chromophobe RCC [4]. Conversely, collecting duct and renal medullary carcinoma are commonly diagnosed at an advanced stage and have a poor prognosis after surgery. A recent multi-institutional study estimated a 5-year CSS of only 40.3% in a series of 95 patients surgically treated for Bellini tumours [24].

Table 2.3 Macroscopic, histologic and cytogenetic characteristics of main RCC subtypes

Tumour type	Gross appearance	Microscopic appearance		Cytogenetic alterations
Clear cell	Yellow, well circumscribed and can possess distinct areas of haemorrhage and necrosis	Abundant clear cytoplasm due to deposition of lipid and glycogen		3p (90%), 14q, 8p and 9p and gains at 5q and 12q
Papillary	Mixed cystic/solid consistency. Papillary RCC lesions are often reddish-brown and frequently have a well-demarcated pseudocapsule	Papillary or tubulopapillary architecture. Calcifications, necrosis and foamy macrophage infiltration	Type 1: Thin, basophilic papillae with clear cytoplasm Type 2: Heterogeneous, thicker papillae and eosinophilic cytoplasm	Gains of 7, 8q, 12q, 16p, 17 and 20 and loss of 9p. Papillary type 2 with gains of 8q, loss of 1p and 9p
Chromophobe	Large, well-circumscribed, tan-brown tumour with occasional central scar	Distinct cell borders and a voluminous cytoplasm, nuclear morphology with perinuclear halos, binucleation	Classic: Pale cytoplasm Eosinophilic: Large tumour cells with fine eosinophilic granules	Loss of chromosomes 1, 2, 6, 10, 13 and 17
Oncocytoma	Mahogany colour, well-circumscribed, occasional central scar and rarely with necrosis	Polygonal cell with abundant eosinophilic cytoplasm and uniform, round nuclei		Loss of 1p, loss of Y, often normal karyotype
Collecting duct	Partially cystic, white-grey appearance and often exhibit invasion into the renal sinus	Tubulopapillary pattern, often with cell taking columnar pattern with hobnail appearance, presence of mucinous material, desmoplastic stroma		Losses at 8p, 16p, 1p, 9p and gains at 13q
Medullary	Tan/white, poorly defined capsule, extensive haemorrhage and necrosis	Poorly differentiated, eosinophilic cell; inflammatory infiltrative cells; sheet-like or reticular pattern common		Poorly described, but believed normal karyotype
MiT family	Yellowish tissue often studded by haemorrhage and necrosis	Papillary or nested architecture, granular and eosinophilic cell with voluminous, cytoplasm		Recurrent translocations involving Xp11.2 (TFE3) or 6p21 (TFEB)

Besides tumour characterization according to histological subtype, the most important traditional pathological factors dictating the prognosis of patients with RCCs are the pathological size and extent of the primary tumour, nuclear grading, coagulative necrosis, microvascular invasion and sarcomatoid dedifferentiation.

pT1 tumours based on the latest TNM staging system represent more than 60% of cases included in the largest cohort studies. Specifically, pT1a tumours account for about 35% of cases and pT1b for 27% of cases. The estimated 5-year CSS was approximatively

95% in pT1a tumours and 93% in pT1b. Interestingly, 5-year CSS rates of pT1 tumours were significantly higher compared to pT2a tumours (estimated around 70%) [25]. Moreover, literature data confirm that in pT1 tumours the oncologic outcomes are equivalent after PN and RN [26, 27]. However, when critically examining these data, one has to note that in the subgroup of T1b tumours treated with PN mean tumour size ranged from 5 to 5.5 cm. Interestingly, a multi-institutional study in 2005 showed that 5.5 cm was the most accurate cut-off size to stratify organ-confined RCC in

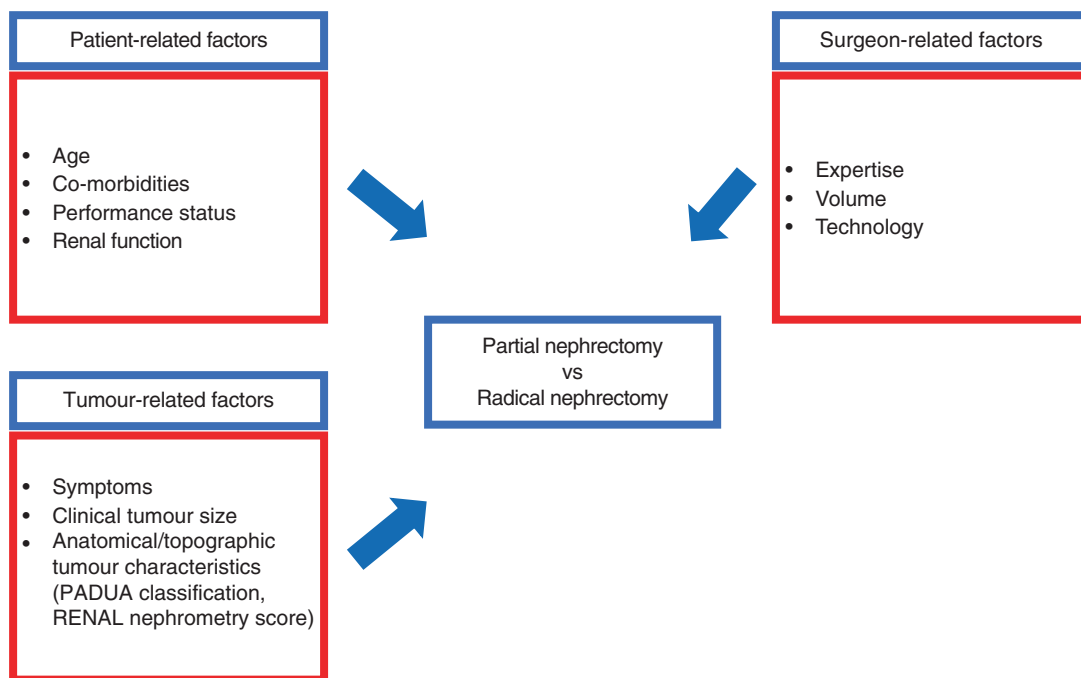


Fig.2.3 Factors influencing the decision-making for partial or radical nephrectomy

two different categories according to CSS probabilities [28]. These data should be considered at the time of preoperative counselling of patients with cT1b tumours larger than 5 cm and suitable for NSS.

The four-tiered Fuhrman grade classification has been the most frequently used system in the last decades. Interestingly, looking at pT1 tumours, some authors reported a direct correlation between tumour size and nuclear grading. Indeed, Ficarra et al. showed that mean tumour size was 4 cm for grade 1, 5.5 cm for grade 2, 7 cm for grade 3 and 9 cm for grade 4, respectively. Therefore, pT1a tumours have more frequently grade 1 or grade 2. Conversely, grade 3 or grade 4 tumours are more frequent in the pT1b or pT2 cases [29]. Interestingly, several studies confirmed the independent role of the Fuhrman nuclear grading to predict CSS and progression-free survival in patients with clear cell RCC. Conversely, the prognostic role of nuclear grade is controversial for papillary or chromo-

phobe RCC [4]. With all these limitations, results of large multi-institutional studies showed that 5-year survival probabilities were 86–89% for grade 1 tumours, 72–79% for grade 2 tumours, 50–60% for grade 3 tumours and 28–30% for grade 4 tumours [4].

Similarly, the prognostic role of coagulative necrosis has uniformly been shown in several retrospective studies including clear cell RCC, but it is still controversial in other histological subtypes [4]. Clearly, the presence of coagulative necrosis is more common in patients with larger tumours. Data from the Mayo Clinic showed that tumour necrosis was present in less than 30% of clear cell RCC, in around 45% of papillary RCC and in 20% of chromophobe RCCs. The risk ratio for death from RCC in patients with necrotic compared with non-necrotic tumours was 5.27 for clear cell, 4.20 for chromophobe and 1.49 (absent) for papillary RCC [30]. Figure 2.3 shows the factors influencing the choice of surgical treatment.

2.4 Predictive Mathematical Models

Several mathematical models have been developed to estimate the risk of disease recurrence or progression as well as of CSS and OS in patients with RCC. Some of these models are based on preoperative clinical factors only, others combine clinical and pathological variables and others consider pathological variables only [8]. Notably, none of these predictive tools have been specifically designed for patients with localized renal tumours suitable for PN.

Age, gender, presence of symptoms, clinical tumour size and clinical stage according to TNM classification are the most relevant preoperative variables combined in the context of the most important preoperative mathematical models. Race was only included in the Kutikov nomogram [31]. Most of these tools have been tested to

predict recurrence-free survival, CSS and/or OS after PN or radical nephrectomy.

Table 2.4 summarizes the characteristics and the accuracy rates of the most common preoperative tools proposed to predict the prognosis of patients suitable for PN or radical nephrectomy [31–34]. The Karakiewicz nomogram seems to be the best tool to predict CSS in patients suitable for radical nephrectomy or PN.

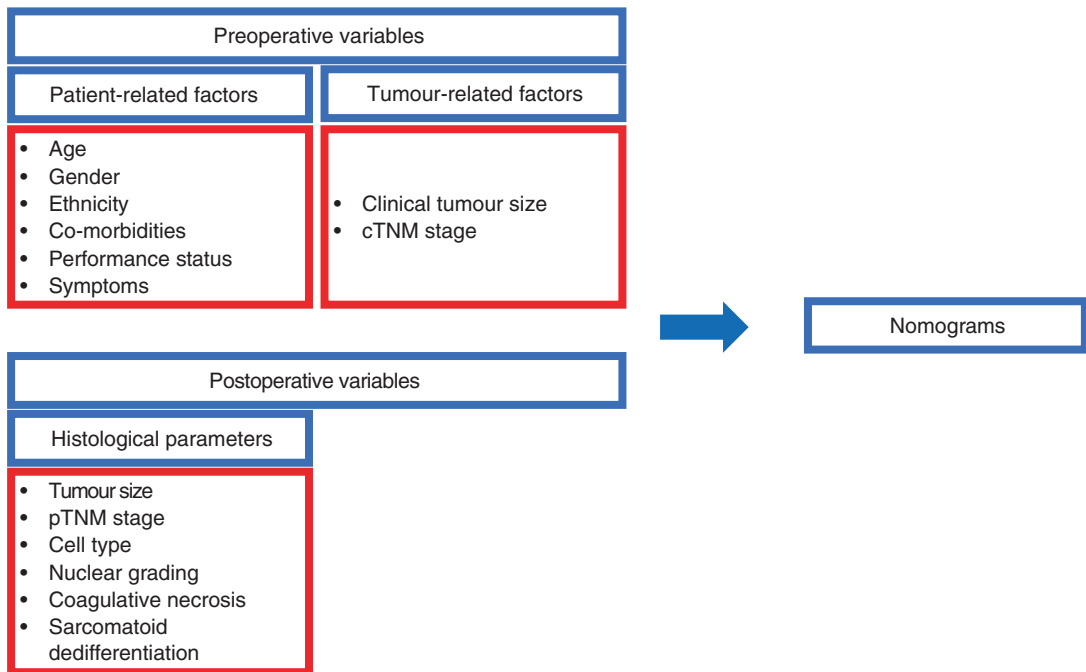
Histological tumour subtypes, pathological tumour size and TNM staging, nuclear grading and coagulative necrosis are the pathological variables most frequently included in the mixed or pure pathological models predicting RFS, CSS or OS [35]. Table 2.5 summarizes the clinical and pathological parameters included in each model and reports the accuracy rates of most common integrated models including pathological information [36–40]. Figure 2.4 summarizes the key prognostic factors of patients with renal cell carcinoma.

Table 2.4 Characteristics and accuracy of the most important preoperative tools proposed to predict the prognosis of patients suitable for partial or radical nephrectomy

Authors	Variables	Treatment	Outcomes	Accuracy
Yaycioglu, 2001 [32]	– Symptoms – Clinical size	Radical and partial nephrectomy	RFS CSS OS	0.65 0.62 0.58
Cindolo, 2003 [33]	– Symptoms – Clinical size	Radical and partial nephrectomy	RFS CSS OS	0.67 0.64 0.61
Karakiewicz, 2009 [34]	– Age – Gender – Symptoms – Clinical size – cT – M	Radical and partial nephrectomy	CSS	0.84–0.88
Kutikov, 2009 [31]	– Race – Age – Gender – Clinical size	Radical and partial nephrectomy	CSS OS	0.70–0.73

Table 2.5 Accuracy of most common integrated models including histopathological information

Authors	Histologic subtypes	Variables	Outcomes	Accuracy [33]
Kattan, 2001 [36]	All	– Symptoms – Histotype – pSize – pT (1997)	RFS CSS OS	0.80 0.77 0.70
Zisman, 2001 [37]	All	– Performance status – pTNM – grading	CSS OS	0.79–0.84 0.64–0.86
Frank, 2002 [38]	Clear cell RCC	– pSize – pT – pN – M – Necrosis – grading	RFS CSS	0.82 0.83–0.88
Sorbellini, 2005 [39]	Clear cell RCC	– Symptoms – pSize – pT (2002) – Grading – Necrosis – Vascular invasion	RFS	0.82
Karakiewicz, 2007 [40]	All	– Symptoms – pSize – pT (2002) – pN – M – Grading	CSS	0.86

**Fig.2.4** Clinical and pathological factors influencing the prognosis of patients with renal cell carcinoma

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