Virchows Arch (1999) 434:281–290

MEETING REPORT

Rodolfo Montironi · Gregor Mikuz · Ferran Algaba
Antonio Lopez-Beltran · Peter W. Hamilton
Constance Parkinson

Epithelial tumours of the adult kidney

Received: 3 December 1998 / Accepted: 3 December 1998

Abstract The epithelial tumours of the adult kidney, in particular renal cell carcinoma (RCC), are a variety of neoplasms that can be classified by morphology and genotype. Although most are well characterised, typical and less typical tumour variants are recognised. There is evidence to indicate that stage is one of the most important prognostic factors, irrespective of tumour subtype. However, the appropriate handling of nephrectomy specimens is essential for accurate evaluation of diagnostic and prognostic factors in RCC. The problem of how to achieve more objective nuclear grading is still unresolved. The use of diagnostic decision support systems offers the possibility of a flexible approach to this problem, while still utilising morphological criteria. The histopathological analysis remains important, but new techniques of molecular and cell biology will be providing new tools of extraordinary power to sharpen the diagnosis and give it a biological interpretation.

Key words Renal parenchymal carcinoma · Renal cell carcinoma · Classification · Staging · Grading

R. Montironi (✉)
Institute of Pathological Anatomy,
University of Ancona School of Medicine, Regional Hospital,
I-60020 Torrette di Ancona, Italy
e-mail: r.montironi@popcsi.unian.it
Tel.: +39-0715964830, Fax: +39-071889985

G. Mikuz
Department of Pathology, University of Innsbruck,
Innsbruck, Austria

F. Algaba
Department of Pathology, Fundacio Puigvert, Barcelona, Spain

A. Lopez-Beltran
Unit of Anatomic Pathology, University Medical School,
Cordoba, Spain

P.W. Hamilton
Institute of Pathology, The Queen's University of Belfast,
Belfast, Northern Ireland, UK

M.C. Parkinson
U.C.L. Hospitals Trust and Institute of Urology,
University College London Medical School, London, UK

Introduction

The Seminar on Renal Tumour Pathology was held in Ancona, Italy, on 27 and 28 February, 1998. The purposes of this meeting were:

- To outline the successive steps the pathologist should follow in the histological assessment of the nephrectomy specimens;
- To give an overview of the most recently proposed classifications of renal cell tumours;
- To compare the 1997 revision of the TNM staging system with the previous revision made in 1992 and with the Robson scheme; and
- To outline the existing problems with the grading systems usually adopted by practising pathologists.

Subsequent sections of this paper contain the presentations given by the authors and a summary of the conclusions reached.

Assessment of nephrectomy specimens (Table 1)

Useful clinical information prior to examination includes the kidney laterality, the size and site of the lesion and the type of surgical operation performed by the urologist [48, 52, 59]. The side of origin is usually apparent from the supero-medial location of the adrenal, the ureter extending to the inferior pole and the relationship of hilar structures. The latter, usually located by the presence of terminal ligatures, include the renal vein, artery and pelvis in an anterior-to-posterior distribution. The latter guide is not so clear as the anatomy diagrams, as branches and tributaries of both artery and vein may be found in a different plane from the main vessel and can easily be easily mistaken for it [30].

Fresh tissue, both tumour and normal kidney away from the neoplasm, is easily located by palpation, and a tissue cube can then be removed without undue distortion of the specimen. Removal of a segment of macroscopically normal ureter does not compromise the diagnosis and provides one of the few opportunities to obtain

Table 1 Aims in the assessment of lesions diagnosed clinically as renal cell tumour

1. Production of a tissue diagnosis (very few patients have a pre-operative biopsy)
2. Generation of prognostic information (currently stage and grade)
3. Examination of the non-tumour kidney to exclude pathology, albeit rare, which may be bilateral and clinically relevant to a patient with only one kidney
4. Production of a detailed macroscopic description to allow comparison with imaging studies and to facilitate audit of these techniques (a copy of the pathology report should be sent to the radiologist who essentially made the clinical diagnosis)
5. A combination of (1) and (2) are of value in surgical audit and allow accurate epidemiological information to be collected (especially relevant as the mode of presentation and classification of renal tumours are changing)
6. Preservation of tissue for future research investigations

normal control urothelium. A fresh specimen or one that has been in formalin for only a few hours should be bisected longitudinally through the hilum to facilitate fixation.

In agreement with recent views expressed by Eble [14], inking and weighing of radical nephrectomy specimens is not a logical practice. Tumours extending to the limits of resected adipose tissue are rare. Furthermore, in contrast to the situation with a relatively smooth dense tissue surface (e.g. prostate), the ink applied to a lobular fatty contour spreads extensively into the tissue, thereby defeating its purpose. The only exceptions are various forms of partial nephrectomy specimens. These are inked to establish the tumour status of the renal limit.

After fixation and before any further dissection, the limits of the artery, vein and ureter are sampled [54]. If these structures are macroscopically normal, the justification for microscopical assessment can be questioned. However, if one returns to sample these components after initial microscopic examination, they are frequently difficult to find. The ureteric length and diameter are recorded, the ureter is opened, and any abnormality is described and sampled (these are rare). Inspection of the hilar area occasionally reveals lymph nodes. These should be described, bisected and sampled. The absence or presence of the adrenal is noted, any abnormalities described and the gland sampled in one block.

If the initial bivalving incision has passed through the centre of the tumour it can be described at this point; otherwise a complete assessment awaits later slicing. The neoplasm is measured, and a third dimension can be added when the adipose tissue has been removed. It is described in terms of location (relationship to upper, middle or lower pelvi-calyceal system, renal vein, hilar adipose tissue, medulla, cortex, renal outline and perirenal adipose tissue) and morphology (colour, necrosis, calcification and cystic change). The blocks selected should reflect the above relationships and different macroscopic appearances of the tumour. There are no recommendations relating tumour size to microscopic heterogeneity from which rules may be derived as to a tumour size/block ratio. The most frequent error in sampling renal tumours is to take blocks from the surfaces revealed by bisection and not to sample the most highly infiltrative areas, which only become apparent on further slicing. This is noted especially at the interface between tumour and compressed kidney or fibrous “capsule” and Gerota’s fascia (perirenal adipose tissue).

Further slices parallel to the initial incision can be taken at 2–5 mm through both halves of the kidney with Gerota’s fascia intact. This sequence makes subsequent removal of the capsule to look for additional abnormalities difficult. It is easier to strip the capsule and fascia from both halves while they are intact. This blunt dissection should start from the normal kidney and, on approaching the surface of the tumour, any points of adherence or tumour infiltration of adipose tissue can be sampled. The presence of scars, cysts and additional tumours is noted, together with the distribution and size of the latter two, which are sampled. Finally, a block of normal kidney away from the tumour is taken, to include cortex, medulla and associated papilla.

There are few occasions when conventional RCC comprising nodular yellow, haemorrhagic necrotic tumour fails to be evident on “bivalving ” of the kidney. It is important for block selection to be aware of the differential diagnoses of space-occupying lesions defined by imaging techniques that may prompt nephrectomy. Occasionally, a tumour that proves to be RCC microscopically is white or grey rather than yellow. This macroscopic appearance is usually associated with higher grade (spindle-cell) tumours. Other white tumours include transitional cell and collecting duct (medullary) carcinomas. The transitional cell carcinoma likely to be confused with an RCC on imaging is one arising from flat carcinoma in situ of the pelvis with extensive infiltration of the kidney but without an intrapelvic component. When this last diagnosis is a possibility, additional pelvic and ureteric blocks are helpful, and the ureteric limit becomes essential. A collecting duct tumour should be suspected in a young person with sickle cell disease. Its consideration should prompt close inspection and sampling of the papillae to confirm or exclude the necrosis that is associated with this haemoglobinopathy.

A multicystic mass commonly proves to be cystic RCC, but on imaging techniques and macroscopy multicystic nephroma may have a similar appearance. As microscopic interpretative difficulties may be predicted, additional blocks from the lesion are valuable. An oncocytoma is rarely diagnosed pre-operatively. The characteristic “cartwheel” on arteriography reported in the literature has rarely been seen, and arteriography is now infrequently performed for the investigation of tumours. Oncocytomas are brown/tan in colour, and homogeneous except for a central scar. It is valuable to submit tissue for electron microscopy, as the numerous mitochondria replacing the usual cell organelles are a characteristic finding. Angiomyolipomas are usually submitted as such, as they are recognised on imaging techniques by virtue of their fat content. However, in those where the

Table 2 Renal cell neoplasms. Comparison between the Heidelberg and UICC/AJCC classifications [36, 60]

Heidelberg 1997	UICC/AJCC 1997
Benign	Benign
Metanephric adenoma and adenofibroma	Metanephric adenoma and adenofibroma
Papillary renal cell adenoma	Papillary adenoma
Renal oncocytoma	Renal oncocytoma
Malignant	Malignant
Common or conventional renal cell carcinoma	Conventional (clear cell) renal carcinoma
Papillary renal cell carcinoma	Papillary renal cell carcinoma
Chromophobe renal cell carcinoma	Chromophobe renal cell carcinoma
Collecting duct carcinoma (variant: medullary carcinoma)	Collecting duct carcinoma (variant: medullary carcinoma)
Renal cell carcinoma, unclassified	Renal cell carcinoma, unclassified

vascular and muscle components predominate a preoperative diagnosis of RCC may be made.

Xanthogranulomatous pyelonephritis can present as a space-occupying mass. This benign inflammatory condition is usually suspected clinically because of its association with stones and urinary tract infections. Macroscopically, the normal renal architecture is effaced and the pelvi-calyceal system is ulcerated and replaced by soft bright yellow tissue, which in the later stages forms frank nodules extending into perirenal adipose tissue. In this context the staging blocks are redundant.

Very rarely, equivocal imaging appearances and urine cytology reports prompt nephrectomy for haematuria and no obvious lesion is seen when the specimen is halved. Before the kidney is sliced further, it is important to establish the exact site of the imaging abnormality. It is very easy to miss a papillary hamartoma or pericalyceal haemangioma. When no lesion consistent with the imaging abnormality can be found and subsequent microscopical appearances on haematoxylin and eosin-stained sections are normal, medical causes of haematuria must be considered (although these commonly cause bilateral symptoms).

Classification of renal epithelial tumours

There have been many attempts to devise an accurate classification system for renal cell tumours that could be applied in every pathology laboratory and which is really meaningful to pathologists and urologists in their daily clinical practice. In past decades, widely used classifications for renal cell tumours were based on traditionally held ideas on histogenesis and differentiation. The World Health Organization (WHO) and the Armed Forces Institute of Pathology suggested a proximal tubular origin of renal cell tumours and described the cellular phenotype and growth pattern [5, 46, 50]. Thoenes et al. extrapolated the presumed cellular origin by comparing the tumour cells with their counterparts in different areas of the mature nephron [61].

Renal cell tumours display a heterogeneous morphology, being composed of admixtures of clear, granular or chromophilic and spindle-shaped cells, and their phenotype may change during progression. Thus, they do not necessarily retain the phenotype of their supposed progenitor cell. These findings suggest that a transition between different phenotypes takes place during progression and that the cell type cannot therefore be used as an adequate parameter for accurate diagnosis [13].

Advances in the understanding of the genetics underlying the development of renal cell neoplasms have led to the recognition of distinctive types of tumours. In fact, genetic alterations transmitted during cell division play a part in determining both the morphology and the behaviour of tumours. This means that a histopathological classification, which is based on the genetic abnormalities involved, is robust in terms of biology, clinical behaviour and response to therapy [35].

The most recent classifications taken into consideration in the Ancona meeting were the "Heidelberg Classification of Renal Cell Tumours" presented at the workshop on "Impact of Molecular Genetics on the Classification of Renal Cell Tumours" held in Heidelberg in October 1996 [36], the "Classification of Renal Cell Carcinoma" presented at the conference on "Diagnosis and Prognosis of Renal Cell Carcinoma" held in Rochester, Minnesota, in March 1997 and sponsored by the WHO in collaboration with the Union Internationale Contre le Cancer (UICC), the American Joint Committee on Cancer (AJCC), Mayo Clinic and Mayo Foundation, the Pacific Northwest Cancer Foundation and other sponsoring groups [8, 60], and the histological classification of the epithelial tumours of renal parenchyma published in 1998 by the World Health Organization [45].

The Heidelberg Classification of Renal Cell Tumours was based on current genetic knowledge and was judged to correlate with recognisable histological findings. The proposed classification subdivides renal cell tumours into benign and malignant parenchymal neoplasms and, where possible, limits each sub-category to the most commonly documented genetic abnormalities. Benign tumours were subclassified into metanephric adenoma and adenofibroma, papillary renal cell adenoma, and renal oncocytoma. Malignant tumours were subclassified into common or conventional renal cell carcinoma; papillary

renal cell carcinoma; chromophobe renal cell carcinoma; collecting duct carcinoma, with medullary carcinoma of the kidney; and renal cell carcinoma, unclassified.

The "Classification of Renal Cell Carcinoma" proposed at the Mayo Clinic Meeting is based on morphology and is in line with genetic facts as they are presently understood and with the evolution of the neoplasms. The proposed classification took into consideration the following items: the terms should be simple, unambiguous, and reflect a salient morphological feature of the neoplasm; the terms should be consistent with historical usage where possible, but when the meaning has changed significantly they should be replaced with new terms; a term is not a description and cannot encompass all of the morphological variations of a neoplasm. The classification proposed by UICC and AJCC shows many similarities with the "Heidelberg Classification" [36]; it represents a further refinement of this (Table 2), still based on a strong genetic background. In both classification proposals, sarcomatoid carcinoma was viewed as a manifestation of high-grade carcinoma of the type from which it arose. The term "granular cell renal cell carcinoma" must no longer be used (descriptive terms previously used as diagnosis).

The histological classification of the epithelial tumours of renal parenchyma published in 1998 by the WHO [45] is based on the microscopic characteristics of tumours. Therefore, this classification is concerned with morphologically identifiable cell types and histological patterns as seen with conventional light microscopy. Since the tumour may show more than one cell type, the predominant cell determines the category.

The neoplasms are divided into benign and malignant. Papillary/tubulopapillary adenoma, oncocytic adenoma (oncocytoma) and metanephric adenoma are included in the group of benign epithelial tumours of the renal parenchyma. The carcinomas are subdivided into renal cell carcinoma (clear cell, granular cell, chromophobe cell, spindle cell, cyst-associated renal cell, and papillary renal cell carcinomas) and collecting-duct carcinoma.

The basic difference from the first two classifications reported above is that the WHO classification lists granular cell carcinoma, spindle cell carcinoma (synonym: sarcomatoid carcinoma) and renal medullary carcinoma as distinct entities, whereas it does not identify renal cell carcinoma, unclassified, as a separate entity. Medullary carcinoma is not classified by the WHO as a variant of collecting duct carcinoma, but it is placed among the epithelial tumours of renal pelvis. In addition, the WHO classification introduces two separate categories to encompass renal cell carcinoma originating in renal cysts and cystic renal cell carcinoma (i.e. cyst-associated renal cell carcinoma).

Tumour stage

Numerous parameters have been evaluated as prognostic markers for RCC, with conflicting results [3, 11, 34, 58] (Table 3). At present only tumour stage has gained widespread acceptance among pathologists and urologists as in indicator of patient outcome.

Ultrasonography, computed tomography and, recently, magnetic resonance imaging have dominant roles in the diagnosis of RCC and its clinical staging [10, 37, 40]. All these methods have a low sensitivity (about 40%) but a high specificity (95–100%) [10].

At the end of the 1950s two very simple staging systems derived from pathological findings were presented by urologists [15, 51]. In both systems the main prognostic factors were tumour extension (organ confined or not), regional lymph node involvement and distant metastases. Although the morphological variables used were rather crude, some correlation with survival was demonstrated. Robson et al. [53] presented a more elaborate staging system. Gross vein or/and lymphatic involvement and transgression of the Gerota's fascia were introduced as new staging criteria.

Combining Robson's staging and their own histological (pattern) grading system, Hermanek et al. [27] elaborated a classification scheme with better accuracy than stage and grade alone. The so-called Erlangen classification distinguished good cancer (grade 1, stages I/II) from bad cancer (any grade, stage IV or grade 3, stages II/III). All other combinations (grade 1, stage III or grade 2–3, stage I or grade 2, stages I/II/III) were called intermedi-

Table 3 Prognostic factors for renal cell carcinoma (tumour-related; subdivided according to the College of American Pathologists Working Classification for Prognostic Markers) [24, 34, 58]

I: Well supported by the literature; generally used in patient management	Positive surgical margins; multiple metastases, or solitary metastasis unresectable, located in the lung or liver; stage; grade; histological type; architecture (sarcomatoid)
II: Extensively studied biologically and/or clinically	IIA: Tested in clinical trials None IIB: Biological and correlative studies performed: few clinical outcome studies Histological type (collecting duct carcinoma); nuclear morphometry; DNA content; proliferation markers such as Ki-67 and AgNORs
III: Currently do not meet criteria for category I or category II	S-phase fraction; PCNA, apoptotic markers; growth factors; cell adhesion molecules; angiogenesis; host response factors; tumour suppressor genes and oncogenes; cytokines; cytogenetic abnormalities/loss of heterozygosity

Table 4 TNM staging protocol for renal cell carcinoma. Comparison between the TNM 1992 and 1997 revisions [26, 57] (T0, TX, N0, NX, M0 and MX not shown)

1992 revision	1997 revision
Primary tumour (T)	
T1 Tumour ≤2.5 cm in greatest dimension, limited to the kidney	Tumour ≤7.0 cm in greatest dimension, limited to the kidney
T2 Tumour >2.5 cm in greatest dimension, limited to the kidney	Tumour >7.0 cm in greatest dimension, limited to the kidney
T3 Tumour extends into major veins, or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia	Tumour extends into major veins, or invades adrenal or perinephric tissues but not beyond Gerota's fascia
T3a Tumour invades adrenal gland or perinephric tissues but not beyond Gerota's fascia	Tumour invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3b Tumour grossly extends into renal vein(s) or vena cava below diaphragm	Tumour grossly extends into renal vein(s) or vena cava below diaphragm
T3c Tumour grossly extends into vena cava above diaphragm	Tumour grossly extends into vena cava above diaphragm
T4 Tumour invades beyond Gerota's fascia	Tumour invades beyond Gerota's fascia
Lymph node (N)	
N1 Metastasis in a single lymph node ≤2 cm in greatest dimension	Metastasis in a single lymph node
N2 Metastasis in a single lymph node >2 but not >5 cm in greatest dimension, or multiple lymph nodes, none >5 cm in greatest dimension	Metastases in more than one lymph node
N3 Metastasis in a lymph node >5 cm in greatest dimension	(Not identified)
Distant metastasis	
M1 Distant metastasis	Distant metastasis

Table 5 Renal cell carcinoma: staging protocol according to Robson [53]

Stage	Description
1	Confined to kidney
2	Perirenal fat invasion, but confined to Gerota's fascia
3A	Gross renal vein or inferior vena cava involvement
3B	Metastases to regional lymph nodes
3C	Renal vein or vena cava involvement and metastases to regional lymph nodes
4A	Adjacent organs other than adrenal involved
4B	Distant metastases

ate cancer. The classification became obsolete because the grading was based on histological criteria different from those that are now generally accepted [60]. Nevertheless, the Erlangen classification is easy to apply and guarantees low observer variability. The predictive value is good.

The TNM staging system was proposed by UICC and AJCC in the 1970s. The most recent revision of the TNM was published in 1997 (Table 4) [21, 26, 57]. Some pathologists and urologists hold the view that the 30-year-old Robson staging could be still the preferred one. In fact, it is easily applied and allows comparison of recent data with those collected in the past (Table 5). Most urologists suggest that both the TNM and the Robson systems should be included in the pathology reports.

Although the same or similar parameters are used in most of the staging systems developed since the end of the 1950s, the prognostic validity of some individual variables still remain unclear or even controversial.

Tumour size

After Bell published his famous post-mortem study [4], it was generally accepted that tumours smaller than 3 cm in diameter do not metastasise and that such neoplasms should be called adenomas. This arbitrary rule was used although Bell [4] himself and, later on, other authors observed tumours less than 2 cm in diameter, that did metastasise. Apitz [1, 2] described 725 adenomas discovered at autopsy. In this study the size of the tumour was not used, the classification being based on the histological features.

The TNM staging system uses the size as one of the prognostic factors. In the second revision of 1992 [26] the breakpoint between T1 and T2 was set at 2.5 cm. A year later, a subdivision or "telescopic ramification" of the T2 tumours, with four subcategories (T2a–T2d) related to a 2.5-cm increment, was adopted [28]. This was based on the evaluation of 872 cases [25], which showed significantly different 5-year survival rates among the proposed subcategories. The sub-categorisation of T2 is no longer included in the 1997 revision of the TNM [57]. In addition to this, the threshold between T1 and T2 has been increased from 2.5 cm to 7 cm, provided that the tumour is still limited to the kidney. The breakpoint of 7 cm does not seem to be fully justified by the data published in the literature. The T1 category should be split into subcategories to accommodate tumours of intermediate size. Alternatively, both the categories T1 and T2 and the corresponding "telescopic ramifications" proposed in 1992 and 1993 [26, 28] should be used in association with the 1997 revision until enough cases can be evaluated to prove which revision is superior for prediction of patient survival or disease-free time. These suc-

cessive changes in the cut-off values can create uncertainty among urologists and pathologists about the prognostic value of the size of a RCC.

The Robson staging scheme does not take into account the tumour size, but only whether or not the RCC is confined to the kidney. However, the tumour size shows some relationship with the level of tumour extension. Golimbu et al. [20] were able to show that in all Robson stages the 5-year mortality was higher for RCC larger than 5 cm in diameter. Other investigators found survival differences only in tumours smaller or greater then 10 cm [42].

Extension of RCC beyond the renal capsule

Extension of the RCC beyond the renal capsule into the perinephric tissue or adrenal gland while still confined to the Gerota's fascia (T3a; Robson stage 2) is a noncontroversial prognostic factor. The pathologists agree with the urologists that extension through the capsule diminishes the patient's chance of survival. Care must be taken not to mistake the pseudocapsule of the tumour for the true renal capsule, because the infiltration of the pseudocapsule is not prognostically important [14, 32]. In addition, bulging above the renal contour does not qualify as invasion beyond the confines of the kidney. This pattern is still considered either T1 or T2, based on the size of the tumour. Infiltrative growth into the perirenal fat is required for stage T3. The renal capsule is interrupted in the renal sinus, and in that location, RCC may abut on or be in direct contact with fat without showing infiltrative growth. This does not make the lesion stage T3. Penetration into the renal pelvis probably reflects the tumour stage more closely than does the biological behaviour [20]. Involvement of the pelvis is mostly encountered in advanced stages. There is enough evidence to suggest that pelvic involvement does not affect survival [20, 41].

The distinction between direct invasion of the adrenal and haematogenous metastases to the adrenal is prognostically important and is recognised in the difference between T3a and M1 [17, 28, 57]. If carcinoma is present in the adrenal, whether it is a direct extension or a metastasis must be reported. In the Robson scheme, invasion of the adrenal gland is stage 2, whereas metastasis to the adrenal gland is stage 4B.

Gerota's fascia (renal fascia) is the fibro-fatty tissue enveloping the kidney and opening only at the hilum. In general usage it includes the pre- and retro-renal fascia. The pre-renal fascia adheres to the parietal peritoneum, and the cranial part reaches the diaphragm. Transgression of this fascia (T4, Robson stage 4A) is a sign of a poor prognosis. According to the anatomy, invasion of the peritoneum is invasion beyond the pre-renal Gerota's fascia and is classified as T4.

Renal vein or inferior vena cava involvement

It is commonly believed that the prognosis deteriorates when the RCC invades the renal vein(s). It is indeed considered an important prognostic variable in every staging system, including those devised recently [9, 15, 18, 22, 27, 29, 41, 51, 53, 57]. Nevertheless, there are controversial results with this finding. Some authors even claim that invasion of the renal vein(s) is of limited importance as a predictive factor [51, 55, 56, 62]. The divergent opinions might be caused by the extent to which the surgical specimen is examined and sampled.

Tumour extension into renal vein(s) or the vena cava below the diaphragm corresponds to T3b (Robson stage 3A). There are no differences in prognosis between an RCC involving the renal vein(s) alone and a carcinoma growing in the vena cava below the diaphragm. Recent investigations have shown that even tumours extending to the atrium, when surgically removed, do not impair the survival (involvement of the vena cava above the diaphragm corresponds to T3c) [18]. In the TNM Supplement 1993 [25] the presence of microscopic vein invasion was included in the T1-3a classification (*i*=without microscopic venous invasion; *ii*=with microscopic venous invasion) [63]. This subdivision is no longer present in the third revision of the TNM classification [57].
The Erlangen group [25, 29] subdivided vein invasion into histologically and macroscopically determined. The 5-year survival rate was 89% for cases without vein invasion, 62% when the invasion was detected microscopically and only 33% when the vein involvement was visible macroscopically. The Erlangen group found a correlation between vein invasion and tumour size. RCCs smaller than 3 cm showed vein invasion in 36.4% of cases at the histological level. In carcinomas up to 5 cm in diameter, the histological evidence amounted to 39.1%, whereas the macroscopic evidence was 15.2%. In the other size classes (5–10 cm and >10 cm) the percentage of gross invasion increased linearly to more than 70%.

Metastases to regional lymph node

The regional lymph nodes are the hilar, abdominal para-aortic, and paracaval nodes. Some urologists rarely submit para-aortic and paracaval lymph nodes for histological evaluation, because the therapeutic value of regional lymph node dissection is debated. However, the presence of metastasis in these lymph nodes has an adverse effect on prognosis and should be reported to support the correct stage assignment. Lymph node enlargement does not always reflect the presence of metastasis [11, 14].

In the 1997 revision of the TNM system the involvement of the regional lymph nodes is subdivided into N1 and N2, accordings as whether a single lymph node is involved or more than one shows secondary deposits. This is a slightly simplified sub-categorisation in comparison with the previous revision, in which N3 was also

identified, based on the size of the metastatic lesion [26, 57].

The current TNM version does not report any changes in the M classification since the previous version [57].

Tumour grade

Various grading systems have been proposed for RCC, using a variety of nuclear, cytoplasmic, and architectural features [11, 19]. Most of these have shown some degree of correlation with survival. Nuclear grading systems are the most widely used. The evidence available in the literature suggests that nuclear grading is a better prognostic indicator than other systems that do not use nuclear criteria. Nuclear grading has prognostic value for conventional (clear cell) and papillary RCC. The data supporting the validity of nuclear grading for chromophobe carcinoma are not well established, but it seems reasonable to grade these tumours for ongoing clinicopathological studies. Oncocytoma is a benign tumour that should not be graded [43].

Of the several nuclear grading systems that have been proposed, that of Fuhrman et al. is the most widely used system in Europe [16] (Table 6). There are studies that support its clinical relevance as a prognostic factor. It has been suggested that, for those who use the Fuhrman system, collapsing the four grades into three may be useful. The prognostic data indicate that grouping grades 1 and 2 together brings a potential improvement. The TNM Classification of Malignant Tumours includes a grading scheme for RCC consisting of four divisions based on cellular changes [57] (Table 7). Studies have correlated this system with survival with limited success. The scheme of histological grading suggested by the WHO is very similar to this. Only three grades are suggested: grade I applies to tumours that have the least degree of cellular anaplasia compatible with the diagnosis of malignancy; grade III applies to tumours with the most severe degree of cellular anaplasia; grade II applies to those tumours in between [45]. (For a detailed list of RCC grading systems see [19]).

There are two major problems with the proposed grading systems. The first is that the degree of correlation of the various systems with survival is not satisfactory. The other is the lack of observer consistency in the assignment of grades to RCC [39]. There might be several explanations for the first problem. One of these is that the importance of each component of the various grading systems is usually untested as a prognostic parameter in its own right. Although the tumour grade assigned may correlate with survival, it is likely that one or more of the criteria used will have no relationship with survival when considered in isolation, and therefore have the effect of unnecessary compounding an already complicated grading classification.

The poor reproducibility of grading systems for RCC, as for other tumours, relates to the fact that the changes form a morphological continuum. Whenever a tumour specimen is analysed, the pathologist has to identify its exact location along this spectrum. Basically, this is done by comparing the case under investigation with known 'points' along the spectrum that represent diagnostic grades. The case is then allocated to the category to which it is closest or most similar. This is called synthetic or inductive diagnosis making, an important part of which is probably subconscious [38]. This type of diagnosis making has the advantage of speed, but factors may play such a large part that a classification shift in continuous lesions may result and a grade be given that is not strictly correct. This is due, at least in part, to the inadequate description of grading criteria published in some classifications.

The alternative for diagnosis is the so-called analytical process [38]. This is usually applied when the criteria needed in the identification of the grade of a certain lesion are well defined. The analytical process is far better than the synthetic one, because the pathologist has to evaluate a series of features and their degree of changes, and to compare them with prototypes present in the pathologist's memory. The analytical process can be represented as an inference network that allows the pathologist to evaluate the level of certainty associated with a diagnosis or a grade of a lesion. An inference network, or Bayesian belief network (BBN), was developed by Dr. Peter W. Hamilton (Belfast, UK) on the basis of previous experience acquired in the development of decision support systems for the grading of prostate and breast lesions [23, 44]. In these lesions the application of a BBN allowed the achievement of a higher level of reproducibility than when the grading system was applied to a purely morphological evaluation. The BBN developed by Dr Hamilton was based on the Fuhrman system [16].

Table 6 Fuhrman grading system [16]

Grade	Characteristics
I	Nuclei round, uniform, approximately 10 μm; nucleoli inconspicuous or absent
II	Nuclei slightly irregular, approximately 15 μm; nucleoli evident
III	Nuclei very irregular, approximately 20 μm; nucleoli large and prominent
IV	Nuclei bizarre and multilobated, 20 μm or greater; nucleoli prominent; chromatin clumped

Table 7 Histological grading according to UICC (TNM Classification of Malignant Tumours, 1997 revision)[a]

G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated/undifferentiated

[a] Identical to the grading protocol reported in the 1992 revision. An indication of the criteria to be used was given in the TNM Supplement 1993 (grading is generally performed by a combined evaluation of various histological and cytological features, including similarity to tissue of origin, cell arrangement, cellularity, differentiation, cellular and nuclear pleomorphism, mitotic activity, necrosis and others) [26, 28, 57]

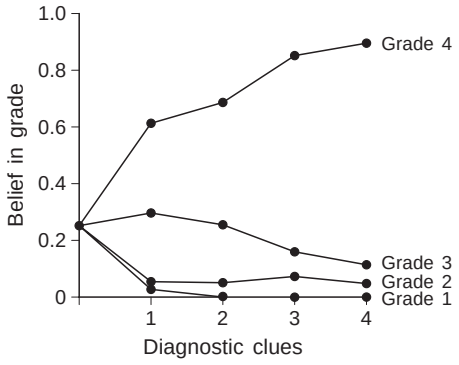

Fig. 1 When evidence is collected for the diagnostic clues (or features), the BBN system points to grade 4, for which the belief value is highest

Four different grades were in fact included in the decision node, and the features and their outcomes for the descendant nodes were also derived from the detailed description given by Fuhrman et al. [16]. On-screen images showing the different morphological features were used to prompt the user and ensure the consistent entry of evidence to the network. Initial data showed that this diagnostic decision support system allowed an accurate analysis of the lesion grade, this being expressed by the corresponding probabilistic measure of belief (Fig. 1). The application of such a system shows a certain number of advantages that are usually not seen with the morphological approach to grading. The most important is the possibility of expanding the BBN whenever new features are available for evaluation and, at the same time, of discarding those that show a poor contribution to the grading results. Different types of features can be included. These can be of purely histomorphological type, or be related to proliferation or morphometrical analysis.

Seminar summary (Table 8)

According to the "Working Classification for Prognostic Markers" proposed by the College of American Pathologists [24], all morphological features (histological type, stage, grade) of RCC belong to category I, which means that their usefulness is well supported by the literature and they are commonly used in patient management. All new factors (proliferation markers, apoptosis, neoangiogenesis, etc.) still need to be tested in large clinical studies and/or meta-analyses [25, 27, 47, 58].

Diagnostic decision support systems, such as Bayesian belief networks, case-based reasoning systems and neural networks, should be developed more extensively. These systems are flexible enough to absorb the analysis factors with well-established prognostic value and new markers as soon as they become available and to incorporate the clinical, epidemiological and aetiological data [6, 7, 12, 31, 33, 49] that characterise the patient. They represent the solution to the problems of the exact prognostic assessment in each individual patient when only histological type, grade and stage are considered.

Table 8 Seminar summary

1. Appropriate handling of nephrectomy specimens is essential for accurate evaluation of diagnostic and prognostic factors in RCC.
2. New classifications have been proposed recently. There are similarities between the Heidelberg classification and that proposed by UICC and AJCC. The advantage of the WHO classification is that it is concerned with morphologically identifiable cell types and histological patterns, as seen with conventional light microscopy.
3. The AJCC and UICC published their revised staging system in 1997. This scheme has some differences from the 1992 revision. The Robson scheme has the advantage that it has remained unchanged since it was proposed over 30 years ago. It is easily applied and allows comparison of recent data with those collected in the past. The pathological report should contain information related to both staging systems.
4. The grade of RCC has prognostic importance essential to patient management. Nuclear grading is preferred, but the optimal system has not been described. Optimal fixation of the tissue is needed to avoid artefacts that can markedly affect nuclear and nucleolar morphology. The problem of a more objective nuclear grading is still unresolved. The use of diagnostic decision support systems offers the possibility of a flexible approach to this problem.
5. Even though histopathological analysis remains important, future prognostic factors should be derived from studies related to genetic and epigenetic phenomena.

Even though histopathological analysis remains important, future prognostic factors should be derived from studies related to genetic and epigenetic phenomena. A fundamental part will be played by new techniques, such as microsatellite analysis and fluorescence in situ hybridisation and by the assessment of the mutation of specific genes and their effects on renal tumorigenesis. The knowledge of the genetic abnormalities in renal cell neoplasms should eventually be incorporated into the evaluation, in an attempt to provide a foundation for diagnosis and perhaps even guide the development of future therapy. The morphological evaluation of precursor lesions and potential precursor lesions together with their molecular analysis should allow better understanding of the natural history of renal cell tumours and the role of chemoprevention strategies.

References

1. Apitz K (1944) Die Geschwülste und Gewebsmißbildungen der Nierenrinde. III. Die Adenome. Virchows Arch [A] 311:328–359
2. Apitz K (1944) Die Geschwülste und Gewebsmißbildungen der Nierenrinde. IV. Strumen, Krebse und Carcinosarkome. Virchows Arch [A] 311:360–431
3. Aronson DC, Medary I, Finlay JL, Herr HW, Exelby PR, La Quaglia MP (1996) Renal cell carcinoma in childhood and adolescence: a retrospective survey for prognostic factors in 22 cases. J Pediatr Surg 31:183–186
4. Bell ET (1950) Tumors of the kidney. In: Bell ET (ed) Renal diseases. Lea & Febiger, Philadelphia, p 411
5. Bennington FL, Beckwith JB (1975) Tumors of the kidney, renal pelvis and ureter. (Atlas of tumor pathology, 2nd ser, fasc 12) Armed Forces Institute of Pathology, Washington, DC
6. Bernstein J, Robbins TO, Kissane JM (1986) The renal lesions of tuberose sclerosis. Semin Diagn Pathol 3:97–105

7. Bosniak MA (1995) Observation of small incidentally detected renal masses. Semin Urol Oncol 13:267–272
8. Bostwick DG, Eble JN, Murphy GP (1997) Diagnosis and prognosis of renal cell carcinoma. Cancer 80:976–977
9. Clayman RV, Gonzalez R, Fraley EE (1980) Renal cell cancer invading the inferior vena cava: clinical review and anatomical approach. J Urol 123:157–163
10. Constantinides C, Recker F, Bruehlmann W, von Schulthess G, Goebel N, Zollikofer C, Jaeger P, Hauri D (1991) Accuracy of magnetic resonance imaging compared to computerized tomography and renal selective angiography in preoperatively staging renal cell carcinoma. Urol Int 47:181–185
11. Delahunt B (1998) Histopathologic prognostic indicators for renal cell carcinoma. Semin Diagn Pathol 15:68–76
12. Dunill MS, Millard PR, Oliver P (1977) Acquired cystic disease of the kidneys: a hazard of long-term intermittent maintenance haemodialysis J Clin Pathol 30:868–877
13. Eble JN (1997) Neoplasms of the kidney. In: Bostwick DG, Eble JN (eds) Urologic surgical pathology. Mosby, St Louis, pp 83–147
14. Eble JN (1998) Recommendations for examining and reporting tumor-bearing kidney specimens from adults. Semin Diagn Pathol 15:77–82
15. Flocks RH, Kadesky MC (1958) Malignant neoplasms of the kidney: an analysis of 353 patients followed five years or more. J Urol 79:196–201
16. Fuhrman SA, Lasky LC, Limas C (1982) Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 6:655–663
17. Gelb AB (1997) Renal cell carcinoma. Current prognostic factors. Cancer 80:981–986
18. Glazer AA, Novick AC (1996) Long-term follow-up after surgical treatment for renal cell carcinoma extending into the right atrium. J Urol 155:448–450
19. Goldstein NS (1997) The current state of renal cell carcinoma grading. Cancer 80:977–980
20. Golimbu M, Joshi P, Sperber A, Tessler A, Al Askari S, Morales P (1986) Renal cell carcinoma: survival and prognostic factors. Urology 27:291–301
21. Guinan P, Sobin LH, Algaba F, Badellino F, Kameyama S, MacLennan G, Novick A (1997) TNM staging of renal cell carcinoma. Cancer 80:992–993
22. Hallscheidt P, Stolte E, Roeren T, Pomer S, Drehmer I, Kauffmann GW (1998) The staging of renal-cell carcinomas in MRT and CT. A prospective histologically controlled study. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 168:165–170
23. Hamilton PW, Anderson NH, Diamond J, Bartels PH, Gregg JB, Thompson D, Millar RJ (1996) An interactive decision support system for breast fine needle aspiration cytology. Anal Quant Cytol Histol 18:185–190
24. Henson DE, Fielding LP, Grignon DJ, Page DL, Hammond ME, Nash G, Pettigrew NM, Gorstein F, Hutter RVP, et al (1995) College of American Pathologists Conference XXVI on clinical relevance of prognostic markers in solid tumors. Summary. Members of the Cancer Committee (review). Arch Pathol Lab Med 119:1109–1112
25. Hermanek P, Schrott KM (1990) Evaluation of the new tumor, nodes and metastases classification of renal cell carcinoma. J Urol 144:238–242
26. Hermanek P, Sobin LH (1992) TNM. Classification of malignant tumours, 4th edn, 2nd rev. Springer, Berlin Heidelberg New York
27. Hermanek P, Sigel A, Chlepas S (1976) Combined staging and grading of renal cell carcinoma. Z Krebsforsch 87:193–196
28. Hermanek P, Henson DE, Hutter RVP, Sobin LH (1993) TNM. Supplement 1993. A commentary on uniform use. Springer, Berlin Heidelberg New York
29. Hoehn H, Hermanek P (1983) Invasion of veins in renal cell carcinoma. Frequency, correlation and prognosis. Eur Urol 9:276–278
30. Hruban RH, Westra WH, Phelps TH, Isacson C (1996) Surgical pathology dissection. An illustrated guide. Springer, Berlin Heidelberg New York
31. Kantor AF (1977) Current concepts in the epidemiology and etiology of primary renal cell carcinoma. J Urol 117:415–417
32. Kay S (1968) Renal carcinoma. A 10-year study. Am J Clin Pathol 50:428–432
33. Keith DS, Torres VE, King BF, Zincki H, Farrow G (1994) Renal cell carcinoma in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 4:1661–1669
34. Klöppel G, Knoefel WT, Bausch H, et al (1986) Prognosis of renal cell carcinoma related to nuclear grade, DNA content and Robson stage. Eur Urol 12:426–431
35. Kovacs G (1993) Molecular differential pathology of renal cell tumours. Histopathology 22:1–8
36. Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CS, Delahunt B, Eble JN, Fleming S, Ljungberg B, Medeiros LJ, Moch H, Reuter VE, Ritz E, Roos G, Schmidt D, Srigley JR, Störkel S, van den Berg E, Zbar B (1997) The Heidelberg classification of renal cell tumours. J Pathol 183:131–133
37. Kreft BP, Muller Miny H, Sommer T, Steudel A, Vahlensieck M, Novak D, Muller BG, Schild HH (1997) Diagnostic value of MR imaging in comparison to CT in the detection and differential diagnosis of renal masses: ROC analysis. Eur Radiol 7:542–547
38. Langley FA, Baak JPA, Oort J (1991) Diagnosis: error sources. In: Baak JPA (ed) Manual of quantitative pathology in cancer diagnosis and prognosis. Springer, Berlin Heidelberg New York, pp 19–27
39. Lanigan D, Loftus B, Barry-Walshe C, Royston D, Leader M (1994) A comparative analysis of grading systems in renal adenocarcinoma. Histopathology 24:473–476
40. McClennan BL (1991) Oncologic imaging. Staging and follow-up of renal and adrenal carcinoma. Cancer 67:1199–1208
41. McNichols DW, Segura JW, DeWeerd JH (1981) Renal cell carcinoma: long-term survival and late recurrence. J Urol 126:17–23
42. Medeiros LJ, Gelb AB, Weiss LM (1988) Renal cell carcinoma. Prognostic significance of morphologic parameters in 121 cases. Cancer 61:1639–1651
43. Medeiros LJ, Jones EC, Aizawa S, Aldape HC, Cheville JC, Goldstein NS, Lubensky IA, Ro J, Shanks J, Pacelli A, Jung SH (1997) Grading of renal cell carcinoma. Cancer 80:990–991
44. Montironi R, Bartels PH, Thompson D, Scarpelli M, Hamilton PW (1995) Prostatic intraepithelial neoplasia (PIN). Performance of Bayesian belief network for diagnosis and grading. J Pathol 177:153–162
45. Mostofi FK, Davis CJ (1998) Histological typing of kidney tumours. International Classification of Tumors, 2nd edn. World Health Organization, Geneva
46. Mostofi FK Sesterhenn IA, Sobin LH, et al (1981) Histological typing of kidney tumors: International Classification of Tumors, no 25. World Health Organization, Geneva
47. Murphy WM, Beckwith JB, Farrow GM (1994) Tumors of the kidney, bladder, and related structures. (Atlas of Tumor Pathology, 3rd ser, fasc 11) Armed Forces Institute of Pathology, Washington DC
48. Novick AC, Streem S, Montie JE, Pontes JE, Siegel S, Montague DK, Goormastic M (1989) Conservative surgery for renal cell carcinoma: a single center experience with 100 patients. J Urol 141:835–839
49. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (1997) Cancer incidence in five continents, vol VII. (IARC Scientific publications no. 143) IARC, Lyon
50. Petersen RO (1992) Urologic pathology, 2nd edn. Lippincott, Philadelphia
51. Petkovic SD (1959) An anatomical classification of renal tumors in the adult as a basis for prognosis. J Urol 81:618–623

52. Rassweiler J, Fornara P, Weber M, Janetschek G, Fahlenkamp D, Henkel T, Beer M, Stackl W, Boeckmann W, Recker F, Lampel A, Fischer C, Humke U, Miller K (1998) Laparoscopic nephrectomy: the experience of the laparoscopy working group of the German Urologic Association. J Urol 160:18–21
53. Robson CJ, Churchill BM, Anderson W (1969) The results of radical nephrectomy for renal cell carcinoma. J Urol 101:297–301
54. Rosai J (1996) Ackerman's Surgical Pathology, 8th edn. vol II. Mosby, St Louis, pp 2668–2669
55. Selli C, Hinshaw WM, Woodard BH, Paulson DF (1983) Stratification of risk factors in renal cell carcinoma. Cancer 52:899–903
56. Skinner DG, Vermillion CD, Colvin RB (1972) The surgical management of renal cell carcinoma J Urol 107:705–710
57. Sobin LH, Wittekind Ch (1997) TNM. Classification of malignant tumors, 5th edn. Wiley, New York
58. Srigley JR, Hutter RV, Gelb AB, Henson DE, Kenney G, King BF, Raziuddin S, Pisansky TM (1997) Current prognostic factors. Renal cell carcinoma. Cancer 80:994–996
59. Stephens R, Graham SD (1990) Enucleation of tumors versus partial nephrectomy as conservative treatment of renal cell carcinoma. Cancer 65:2663–2667
60. Störkel S, Eble JN, Adlakha K, Amin M, Blute ML, Bostwick DG, Darson M, Delahunt B, Iczkowski K (1997) Classification of renal cell carcinoma. Cancer 80:987–989
61. Thoenes W, Störkel S, Rumpelt HF (1989) Histopathology and classification of renal cell tumours (adenomas, oncocytomas and carcinomas). Pathol Res Pract 181:125–143
62. Waters WB, Jerome PR (1979) Aggressive surgical approach to renal cell carcinoma: review of 130 cases. J Urol 122:306–309
63. Van Poppel H, Vandendriessche H, Boel K, Meryteus V, Goethuys H, Haustermans K, van Damme B, Baert L (1997) Microscopic vascular invasion is the most relevant prognosticator after nephrectomy for clinically nonmetastatic renal cell carcinoma. J Urol 158:45–49