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Collaborative Review – Kidney Cancer

Reassessing the Current UICC/AJCC TNM Staging for Renal Cell Carcinoma

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Abstract

Context: The outcome prediction for renal cell cancer (RCC) remains controversial, and although many parameters have been tested for prognostic significance, only a few have achieved widespread acceptance in clinical practice. The TNM staging system defines local extension of the primary tumour (T), involvement of regional lymph nodes (N), and presence of distant metastases (M).
Objective: This review focuses on reassessing the current TNM staging system for RCC.
Evidence acquisition: A literature search in English was performed using the National Library of Medicine database and the following keywords: *renal cell cancer, kidney neoplasm*, and *staging*. We scrutinized 1952 references, and 62 were selected for review based on their pertinence, study size, and overall contribution to the field.
Evidence synthesis: The prognostic significance of tumour size for localized RCC has been investigated in a large number of studies. As a consequence, many modifications of the TNM staging system were primarily made to the size cut points between stage I and II tumours. The latest three revisions of the TNM system are systematically reviewed. For the heterogeneous group of locally advanced RCCs, involving different anatomic structures surrounding the kidney, the situation is still the subject of controversial scientific dispute. In detail, perirenal fat invasion, direct infiltration of the ipsilateral adrenal gland, invasion of the urinary collecting system, infiltration of renal sinus fat, and vena cava and renal vein thrombosis are disputed. Finally, staging of lymph node metastases and distant metastatic disease is discussed.
Conclusions: Special emphasis should be put on renal sinus invasion for stage evaluation. Retrospective studies relying on material collected at a time when no emphasis was placed on adequate sampling of the renal sinus should be treated with caution. In view of new treatment opportunities, the current TNM staging system of RCC and any other staging system must be dynamic.

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1. Introduction

Cancers are classified at different stages depending on how advanced tumours have progressed. Staging describes the severity of an individual's cancer based on the extent of the original (primary) tumour and the extent of spread in the body, providing a common language to facilitate the planning of treatment and to predict the outcome of the disease. The American Joint Committee on Cancer (AJCC) staging system [1] is a classification system for describing the extent of disease progression in cancer patients. It uses TNM (tumour, node, metastasis) staging, one of the most commonly used scoring systems. Based on certain standardized criteria, the TNM system was developed and is maintained by the AJCC and the International Union Against Cancer (Union internationale contre le cancer; UICC). The TNM staging system defines local extension of the primary tumour (T), involvement of regional lymph nodes (N), and presence of distant metastases (M).

Contemporaneous with the development of the TNM classification by the UICC, the International Federation of Gynaecology and Obstetrics (FIGO) developed the FIGO staging classification for gynaecological malignancies. A little later, the AJCC began publishing separate definitions of TNM categories. In 1987, the UICC and the AJCC TNM classifications were unified. Currently, an agreement between UICC, the AJCC, and FIGO ensures compatibility of staging classifications for cancers.

Cancer staging can be divided into a clinical stage and a pathologic stage. In the TNM system, clinical stage and pathologic stage are denoted by a small "c" or "p", respectively, before the stage (eg, pT2N0). Of note is that pathologic upstaging of malignant renal neoplasms occurs in about 31% of patients following radical nephrectomy [2].

In 1997, a work group at the RCC Consensus Conference in Rochester, Minnesota, evaluated a variety of putative prognostic parameters for renal cell carcinoma (RCC) [3]. Besides pTNM stage, positive surgical margins, metastatic spread, tumour grade/sarcomatoid architecture, and tumour type were considered to be well supported in the literature and generally used in patient management. Although it is widely acknowledged that tumour staging is the most powerful prognostic indicator for RCC, a number of questions remain regarding the application of the TNM staging in clinical practice. Interestingly, the TNM staging system is contained in many of the proposed integrated staging systems for RCC. These integrated staging systems combine multiple clinical and histopathologic parameters (eg, histologic subtype) and have a higher prognostic accuracy than the TNM system alone (reviewed in Ficarra et al [4]). Nonetheless, anatomic extent of the tumour is a key factor in both the TNM staging system and all integrated prognostic systems. In general, an ideal cancer staging system should communicate critical characteristics of the disease, aid clinicians in selecting most appropriate therapeutic options, stratify a patient's risk of cancer progression and death, and eventually determine the selection criteria for clinical trials. The aim of the current review was to reassess the current TNM staging for RCC, with special emphasis on tumour staging of advanced RCC.

2. Evidence acquisition

A search of the English literature was performed using the National Library of Medicine database and the following keywords: *renal cell cancer, kidney neoplasm*, and *staging*. A free-text strategy was applied without limiting the year of publication. A total of 1952 references were initially scrutinized. Pertinent publications were identified and reviewed rigorously. Reference lists of retrieved articles were also checked for additional relevant articles. A grade of evidence was assigned to the different articles. On the basis of large multicentre studies with level II-2 or II-3 evidence, possible revisions of the TNM staging system were discussed. Sixty-two papers were selected for this review based on their pertinence (favouring recent publications), study size, and overall contribution to the field.

3. Evidence synthesis

3.1. Brief historical review

Former studies have shown that metastatic spread, infiltration of the renal vein, and perirenal fat invasion are poor prognostic features for carcinomas of the kidney [5]. In 1958, Flocks and Kadesky proposed the first formalized staging system for RCC [6]. Subsequently, Petkovic published a similar classification in 1959, dividing intrarenal tumours (stage I in Flocks and Kadesky's system) into stages I and II of his new system [7]. Robson suggested a revision of these previous classification systems in 1963 [8] and 1969 [9], subdividing localized extrarenal invasion according to the structures involved. The prognostic significance of Robson's staging system has been validated in subsequent survival studies. However, significant differences in survival between the various staging categories could not always be observed, and renal vein infiltration was not found to be a significant prognostic feature [10].

Using these classifications as a starting point, the UICC and the AJCC proposed the first TNM staging system for RCC in 1978 [11]. On the basis of new evidence, the TNM system was subsequently modified in 1987, 1993 (supplement), 1997, and 2002 [1,12–14] to improve its prognostic accuracy.

The Robson system emphasized outcome in patients with tumours that were apparently incurable. In the current TNM system, however, increased emphasis was placed on the subdivision of localized tumours in an attempt to predict the outcome of patients with RCC who are more likely to be treated by surgery. For the first time, dimensional criteria were used to stratify confined RCC in two or more prognostic categories in the TNM classification. Considering the promising opportunities of antiangiogenic treatment, the prognostic value of the TNM staging system has to be critically reviewed and tested in prospective clinical trials.

Table 1 – Changes in the TNM staging system of renal cell cancer*

Staging	Classification	Hermanek et al, 1987 [12]	Sobin et al, 1997 [14]	Greene et al, 2002 [1]
Tumour size/extension				
Localized RCC	T1	Tumour ≤2.5 cm, limited to kidney	*Tumour ≤7.0 cm, limited to kidney*	*NA*
	T1a	NA	NA	*Tumour ≤4 cm, limited to kidney*
	T1b	NA	NA	*Tumour >4 cm and ≤7 cm, limited to kidney*
	T2	Tumour >2.5 cm, limited to kidney	*Tumour >7 cm, limited to kidney*	Tumour >7 cm, limited to kidney
Locally advanced RCC	T3	Tumour extends into major veins or invades adrenal or perinephric tissues but not beyond Gerota fascia	Tumour extends into major veins or invades adrenal or perinephric tissues, but not beyond Gerota fascia	Tumour extends into major veins or invades adrenal or perinephric tissues but not beyond Gerota fascia
	T3a	Perinephric or adrenal extension	Perinephric or adrenal extension	*Perinephric or sinus fat or adrenal extension*
	T3b	Renal vein involvement	*Renal vein or vena cava involvement below diaphragm*	Renal vein or vena cava involvement below diaphragm
	T3c	Vena cava involvement below diaphragm	*Vena cava involvement above diaphragm*	Vena cava involvement above diaphragm
	T4	Outside Gerota fascia	Outside Gerota fascia	Vena cava involvement above diaphragm
	T4a	Vena cava involvement above diaphragm	*NA*	NA
	T4b	NA	NA	NA
Regional lymph nodes	Nx	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
	N0	No regional lymph node metatases	No regional lymph node metatases	No regional lymph node metatases
	N1	Metastasis in one lymph node ≤2 cm in greatest dimension	*Metastases in one regional lymph node*	Metastases in one regional lymph node
	N2	Metastasis in one lymph node >2 cm but not >5 cm in greatest dimension	*Metastases in more than one regional lymph node*	Metastases in more than one regional lymph node
	N3	Metastasis in one lymph node >5 cm in greatest dimension	*NA*	NA
Distant metastases	Mx	Distant metastases cannot be assessed	Distant metastases cannot be assessed	Distant metastases cannot be assessed
	M0	No distant metastases	No distant metastases	No distant metastases
	M1	Distant metastases	Distant metastases	Distant metastases

NA = not applicable.
* Dark orange boxes with italics represent changes between the different classification systems.

3.2. *Staging of localized renal cell carcinoma (T1-2)*

The prognostic significance of tumour size for localized RCC has been investigated in a large number of studies. As a consequence, many modifications of the TNM staging system were primarily made to the size cut points between stage I and II tumours. Table 1 reviews the past three revisions of the TNM system.

Although prognostic significance was shown for various cut points (4.0, 4.5, 5.5, and 6.5 cm) [15–18], the association between survival and tumour size was found to be significant irrespective of the TNM classification. Importantly, size was also shown to have a significant association with outcome when modelled continuously. The probability of death increased 3.5 times for each doubling of tumour size [19]. Accordingly, any given cut point will be significantly associated with survival if the sample size is large enough.

In the 1987 edition of the TNM classification, the cut point was defined at 2.5 cm, assuming that smaller tumours had a very low risk of metastases prior to surgery. This categorization, comprising 1–8% of reported cases, however, was found to be lacking in discrimination because few tumours are < 2.5 cm [20]. In the 1993 supplement, the T2 category was expanded into four subcategories (T2a: >2.5–5 cm; T2b: >5–7.5 cm; T2c: >7.5–10 cm; T2d: >10 cm). Finally, this subclassification was replaced in 1997, recommending that the T1/T2 cut point should be at 7 cm. In 2008, Bedke et al reevaluated the optimal tumour size cutoff point that independently differentiates patient prognosis [21]. Patients (n = 398) who underwent radical nephrectomy for localized RCC (T1-2N0M0) were followed prospectively. Univariate and multivariate analyses showed no cutoff point other than 7 cm to be more suitable for distinguishing between T1 and T2 tumours, supporting the current TNM classification.

The most recent revision of the TNM staging system for RCC [1] introduced the subdivision of T1 neoplasms into categories pT1a and pT1b with a cut point at 4 cm. At present, the cut point for determining suitability for partial nephrectomy is set at 4 cm. Hafez et al [15] performed a retrospective analysis of nephron-sparing surgery for localized sporadic RCC in 485 patients. Patients with tumours ≤4.0 cm compared with those with larger tumours showed significantly longer recurrence-free survival times. Subsequently, Uzzo and Novick undertook a systematic review to evaluate the outcome after partial nephrectomy [22]. Long-term cancer-free survival was comparable with that after radical nephrectomy, particularly for patients with low-stage RCC. A large European multicentre study confirmed that the 2002 TNM staging system allowed significant stratification of the cancer-related outcomes in the subgroup of patients with clear cell RCC. The authors analyzed the clinical data of 2217 patients who had undergone radical or partial nephrectomy for localized RCC in seven urologic centres. Patients with early stage RCC were correctly stratified into three distinct prognostic groups (pT1a, pT1b, and pT2) [23]. In a retrospective study, Antonelli et al compared the outcomes of nephron-sparing surgery versus radical nephrectomy in intrarenal RCC (n = 642) [24]. The comparison between tumours <4 cm or ≥4 cm in diameter showed a more rapid progression and a shorter disease-free survival time for the latter. Interestingly, the type of surgery (nephron-sparing or radical) had no significant impact on survival interval.

Other data suggest the necessity of a revision of the current T category for organ-confined RCC. In a study published by Delahunt et al [19], the 5-yr death rate for patients with tumours ≤4 cm was 6.7%, suggesting that the 4-cm cut point should be reduced in the 2002 TNM staging system. In 2004, two independent studies reported a similar rate of local relapse and metastasis-free and disease-specific survival in patients who had undergone either radical or partial nephrectomy with stage pT1b disease (diameter: 4–7 cm) compared with pT1a patients [25,26]. This suggests that the subdivision of pT1 tumours would no longer be necessary if nephron-sparing surgery can be extended to neoplasms with a diameter of 4–7 cm. Two other studies have shown that patients with intrarenal RCC could be dichotomized around a tumour diameter of 5–6 cm [27,28]. Ficarra et al [28] analyzed the data from 1138 patients who had undergone partial or radical nephrectomy for localized RCC (T1-2N0M0) at seven European urologic centres. The optimal pathologic size break point of 5.5 cm was calculated using the Martingale residuals from a Cox proportional hazards regression model. The authors proposed to cluster patients into three subgroups: (1) patients with incidentally detected RCC ≤5.5 cm, (2) patients with symptomatic RCC ≤5.5 cm, and (3) patients with RCC >5.5 cm.

Ficarra et al [29] provided a systematic literature review on staging of organ-confined RCC, highlighting that a correct definition of the staging of organ-confined RCC is far from being achieved. The authors reported that according to the 1987 version of TNM classification, no paper showed statistically significant cancer-specific survival probability differences between stage I and stage II RCC. According to the 1997 TNM version, however, results were controversial; although a few papers found significantly different cancer-specific survival rates between stage I and stage II RCC, several others failed to do so.

Taking into account the increasing rate of small and incidental RCCs [30,31], there is a need for the tumour diameter break point for localized disease to be reviewed regularly before the publication of future versions of the TNM classification.

3.3. *Staging of locally advanced renal cell carcinoma (T3-4)*

For the heterogeneous group of locally advanced RCCs (T3-4), involving different anatomic structures surrounding the kidney, the situation is very different. Fig. 1 shows an example of a clear cell RCC of the upper pole invading into perinephric fat. Although the 2002 and 1997 TNM staging categories for locally advanced RCC are not substantially different (Table 1), classification of locally advanced RCC into the distinct T categories is still the subject of controversial scientific dispute.

3.3.1. *Perirenal fat invasion*

The prognostic impact of focal versus extensive perinephric fat invasion has been discussed controversially. Roberts et al [32] reported that patients with clinically classified cT1 lesions and finally classified as pT3a because of focal perirenal invasion had the same recurrence-free survival

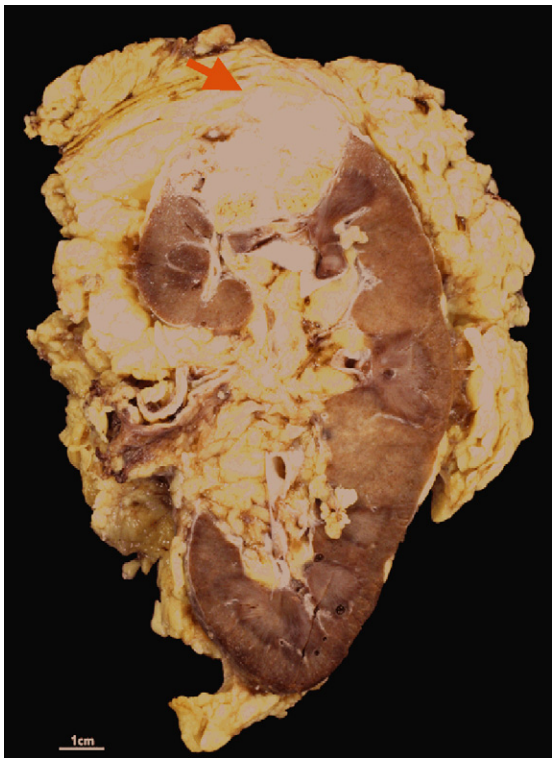

Fig. 1 – Macrophotograph of a clear cell renal cell carcinoma of the upper pole invading the perinephric fat (arrow) but not beyond the Gerota fascia.

rate as patients with pathologically confirmed pT1 lesions. In contrast, Jung et al [33] found no difference between focal or extensive perirenal fat invasion. Moreover, size has been discussed as a prognostic indicator in pT3a tumours [34–36], which could not be confirmed by the Mayo clinic data reported by Siddiqui et al [37].

3.3.2. *Direct infiltration of the ipsilateral adrenal gland*

Based on renal capsule and vascular invasion, the T3 category of the 1978 TNM classification was divided into five subcategories. Of note is that infiltration of the adrenal gland was not considered. This omission was corrected in 1987 [12]. Accordingly, adrenal gland invasion or invasion into perirenal tissues (not beyond the Gerota fascia) was classified as T3a. However, the outcome of RCC patients with direct ipsilateral adrenal invasion was found to be significantly worse than for patients with tumours infiltrating the perirenal fat, and it was similar to the outcome for patients with tumours infiltrating beyond the Gerota fascia [38,39]. These data suggest to reclassify tumours with ipsilateral adrenal gland invasion as pT4 [40].

In a large multicentre European study including 1969 patients with locally advanced RCC, Ficarra et al propose another subclassification of locally advanced RCC with adrenal gland invasion [41]. The authors showed that patients with adrenal gland invasion might be divided into two groups with different prognoses. The first group included patients with only adrenal gland invasion (median survival: 24 mo), and the second included patients with adrenal gland invasion associated with venous involvement (median survival: 12 mo). According to Ficarra et al, only this latter category should be classified as pT4 [41].

3.3.3. *Infiltration of renal sinus fat*

The renal sinus is the fatty compartment located within the confines of the kidney not delineated from the renal cortex by a fibrous capsule. Because it contains numerous veins and lymphatics, invasion into this compartment may permit dissemination of a tumour otherwise regarded as renal-limited (Fig. 2A–C). RCCs infiltrating the renal pelvis were categorized as T3pel in the 1978 TNM classification, although this subclassification of T3 was deleted from subsequent editions (Table 1). According to the 2002 TNM system, perinephric and renal sinus fat invasion are now classified as pT3a.

Many studies have specifically addressed the prognostic significance of infiltration into the tissues of the renal sinus. Bonsib and colleagues [42] showed in a prospective study that the renal sinus is the most common site for extrarenal extension. They identified a patient at risk for metastases even in a putative renal-limited tumour and suggested that all cases should be extensively examined for this feature [42]. Furthermore, Thompson et al [43] investigated the prognostic significance of each of these pathologic features using a cohort of 205 pT3a RCC patients. Regarding cancer-specific death, clear cell tumours invading the renal sinus fat were more aggressive than tumours with perinephric fat involvement [43]. In contrast to these findings, Margulis et al have reported similar survival rates for perirenal and renal sinus fat invasion [44]. Bonsib et al have also shown that infiltration of lymphatics and small blood vessels in the renal sinus has prognostic impact [45,46].

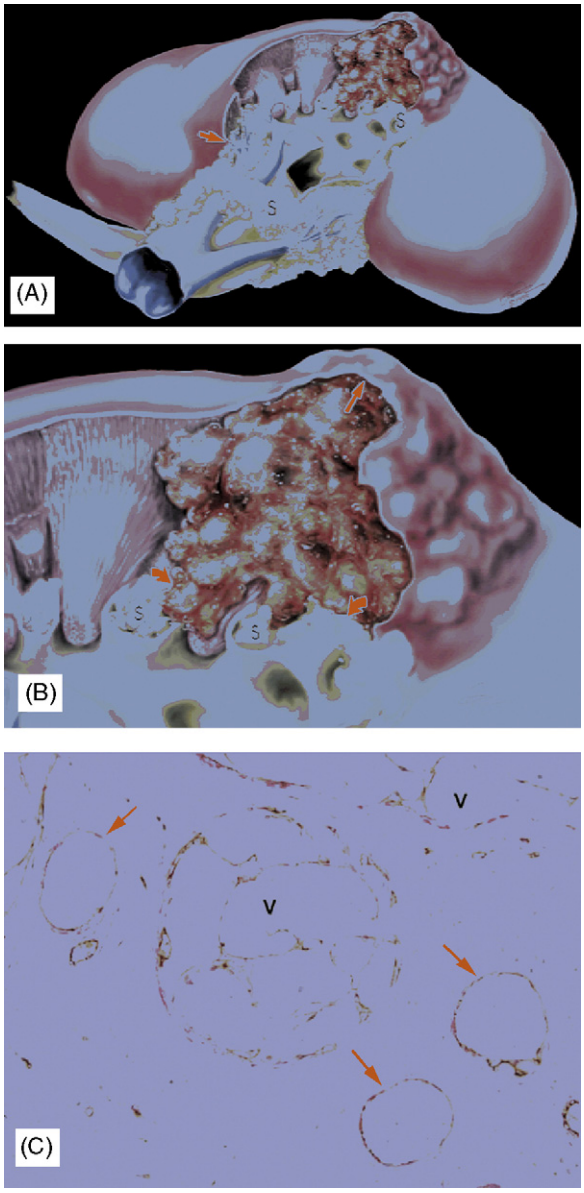

Fig. 2 – (A) Diagram showing the renal sinus fat (S) and its rich venous system that envelopes the collecting system. The renal capsule terminates (arrow) just inside the vestibule of the hilus. (B) A renal cell carcinoma (RCC) is constrained by the renal capsule (arrow), yet no fibrous capsule impedes its growth into the vascular tissue of the renal sinus (curved arrows). (C) Intravenous RCC within larger involved veins (V) is nourished by a delicate capillary plexus. The three other involved lymphovascular structures (arrows) lacking a capillary plexus could be of haematogenous or lymphatic origin. Immunoperoxidase staining for smooth muscle actin (red) and CD31 (black). Fig. 2A and B reprinted with permission from Lippincott Williams & Wilkins [42]. Fig. 2C reprinted with permission from the Nature Publishing Group [45].

Despite these few conflicting reports, renal sinus invasion is an important prognostic parameter that justifies its inclusion in the UICC/AJCC classification [1]. It is important to note that many studies relating to the prognosis of RCC were based on tumour material collected

at a time when no emphasis was made on adequate sampling of the renal sinus. These reports should therefore be treated with caution, and the definition of a standard method of sampling the renal sinus appears mandatory for future trials.

3.3.4. Vena cava and renal vein thrombosis

The prognostic significance of the level of venous involvement (T3b) in RCC is also controversial. Based on a retrospective study by Kim et al ($n = 880$) [47], patients with subdiaphragmatic vena cava thrombosis are grouped together with patients with thrombosis of the renal vein. The disease-specific survival of patients with localized RCC (N0M0) was similar in patients with renal vein and inferior vena cava involvement below the diaphragm (T3b). Patients with inferior vena cava involvement above the diaphragm (T3c) had a significantly worse survival rate even in a multivariate analysis [47].

In contrast, other studies have shown that the survival rate of patients with subdiaphragmatic thrombosis of the vena cava is worse when compared with that of patients with thrombosis of the renal vein [48,49]. Furthermore, large retrospective studies with patients who had undergone partial or radical nephrectomy for pT3-4 RCC showed that simultaneous infiltration of subdiaphragmatic veins and perirenal fat was associated with a substantially worse prognosis than the presence of the single features [40,41,50].

In 2008, Terrone et al [51] showed that the prognostic accuracy of the current TNM 2002 staging system for locally advanced RCC (pT3) is limited. The correlation between patterns of invasion in the pT3 category and outcomes in a large multi-institutional series ($n = 513$) was assessed retrospectively. According to Terrone et al [51], the current TNM classification was not a significant outcome prognosticator. Groups of tumours with distinct patterns of invasion and significantly different survival probabilities were identified: Patients with a tumour invading only the perirenal or sinus fat were at the lowest risk for death from the disease. Patients at intermediate risk had tumours with invasion of the venous system alone. Simultaneous perirenal fat and sinus fat invasion or perirenal fat and vascular invasion as well as adrenal gland involvement characterized high-risk tumours.

3.3.5. Urinary collecting system invasion

The prognostic role of the invasion of the urinary collecting system by RCC has not attracted a notable amount of attention and is considered controversial. Terrone et al [52] have studied the incidence and prognostic value of urinary collecting system involvement in RCC in two centres ($n = 671$). The invasion of the urinary collecting system by RCC was unusual (8.8%), particularly in small tumours, and did not represent an independent prognostic factor [52].

In contrast, Klatte and coworkers [53] examined the prognostic relevance of capsular involvement with no invasion of the perinephric fat and collecting system invasion in a series of 519 patients with intracapsular RCC. Capsular involvement and collecting system invasion were reported in 21.6% and 7.5% of patients, respectively. Collecting system invasion was significantly associated only with microvascular invasion. In addition, capsular involvement and collecting system invasion were not associated with each other, but they had a significant impact on recurrence-free survival ($p = 0.007$ and $p < 0.001$, respectively). In multivariate analysis, both capsular involvement and collecting system invasion were independent predictors of recurrence-free survival with reported risk ratios of 1.84 and 3.78, respectively.

In view of these controversial data, further studies on the prognostic impact of urinary collecting system invasion are indispensable. Ficarra et al have systematically summarized the proposed revisions of the TNM staging system for locally advanced RCC [4].

3.4. Metastatic disease

Regional lymph node metastases or distant metastases are of particular interest in RCC patients. Approximately 10% of RCC patients are nodal positive. In general, patients with exclusive lymph node involvement show a significantly worse prognosis compared with patients without metastatic disease [54]. According to the 2002 TNM staging system [1], patients with one affected lymph node (N1) and those with multiple affected nodes (N2) are distinguished (Table 1).

Other studies, however, could not demonstrate a significant difference in survival between pN1 and pN2 cases, raising a question regarding the prognostic value of this staging subcategory [55,56]. Terrone et al [56] could demonstrate that a cutoff of either four positive lymph nodes or at least 60% of all lymph nodes in the resected tissue positive for metastases better reflects the impact of the disease on survival. Furthermore, a Mayo Clinic study [55] showed that extranodal extension provides prognostic information in addition to the current regional lymph node classification.

In a prospective randomized phase 3 trial managed by the European Organization for Research and Treatment of Cancer [57], radical nephrectomy with complete lymphadenectomy was compared with radical nephrectomy alone. No survival advantage of complete lymph node dissection in conjunction with radical nephrectomy could be demonstrated. Of note is that only patients with clinically inconspicuous nodes were enrolled, and the rate of micrometastases in the lymphadenectomy arm after proper preoperative staging was only 4%. Consequently, if any survival benefit could be expected from lymphadenectomy in nodal-positive patients, much larger study populations would be needed to obtain adequate statistical power. Moreover, performing a lymphadenectomy routinely after proper preoperative staging would result in unnecessary overtreatment of 96% of patients.

RCC with distant metastases was once considered a cancer with a poor outlook, with treatment options limited to cytokines (ie, interferon) [58]. Clinical data have clearly shown that the localization and number of metastases have

an independent prognostic value distinct from other clinical and pathologic variables [59]. In particular, bone or liver metastases are associated with a worse prognosis compared with lung metastases. Novel agents, for example, vascular endothelial growth factor and platelet-derived growth factor tyrosine kinase inhibitors, have recently provided new options for therapy and have improved prognosis [60]. Ongoing studies are currently exploring the role of these agents in reducing tumour recurrence, improving survival, and changing the natural history of the disease for high-risk patients in an adjuvant setting [61]. In view of these adjuvant treatments, adequate prognostic parameters including the TNM system are of utmost importance for proper patient selection.

4. Conclusions

Outcome prediction for RCC remains controversial, and although many parameters have been tested for prognostic significance, only a few have achieved general acceptance in clinical practice. Accurate tumour staging in RCC is essential for prognostic projections, follow-up schedules, clinical trials, and potential systemic therapies. However, correct classification of locally advanced RCC requires a better definition of the various anatomic structures that are involved by the primary tumour. Special emphasis should be put on renal sinus invasion for stage evaluation.

On the basis of new evidence from large multicentre clinical studies, the TNM system of RCC must be a staging method that continually changes [62], becoming a more refined and advanced instrument for clinicians and researchers, respectively. Multivariate Cox proportional hazards regression analyses including multiple clinical and pathologic covariates were more accurate in predicting patient outcome when compared with the TNM staging system. However, the TNM staging system remains the most used tool to classify RCC patients in clinical practice.

Author contributions: Holger Moch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Moch, Wild.
Acquisition of data: Wild, Moch.
Analysis and interpretation of data: Moch, Wild.
Drafting of the manuscript: Wild, Moch, Ficarra.
Critical revision of the manuscript for important intellectual content: Knuechel, Delahunt, Artibani, Patard, Stief, Sulser, Ficarra.
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