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THE CURRENT TNM STAGING SYSTEM OF RENAL CELL CARCINOMA: ARE FURTHER IMPROVEMENTS NEEDED?

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Summary.- *Objective of the study is to review the current 7th edition of the TNM classification of renal tumors and to perform a critical analysis of the recent evidence in order to identify the limitations of this new staging system. A search of the english literature was performed through the Medline and Pubmed database using the following keywords: renal cell carcinoma, staging system and TNM. Overall, 2600 references were initially scrutinized. Forty papers were selected based on their pertinence with the topic of the review, level of evidence provided and overall contribution to the field. Few changes have been made in the current version of the TNM staging system of renal tumors. pT2 tumors have been divided in 2 subgroups based on tumor size with a cut-off at 10 cm; the invasion of the renal vein was classified as pT3a; finally, the invasion of the ispsilateral adrenal gland was classified as pT4. However, other changes were suggested by the analysis of the recent literature and have not been introduced in this new version. Further improvements of the TNM classification for renal tumors are needed especially with regard to locally advanced tumors and node-positive disease, in order to improve the accuracy of this important prognostic tool in renal oncology.*

Keywords: *Renal cell carcinoma. Review. TNM. Staging.*

Resumen.- *El objetivo del estudio es revisar la 7ª edición de la clasificación TNM actual de los tumores renales y hacer un análisis crítico de la evidencia reciente para identificar las limitaciones de este nuevo sistema de estadificación. Se realizó una búsqueda bibliográfica de la literatura inglesa en las bases de datos Medline y Pubmed utilizando las siguientes palabras clave: carcinoma de células renales, sistema de estadificación y TNM. En total, se examinaron 2600 referencias inicialmente. Se seleccionaron 40 artículos basados en su relación con el tema de la revisión, nivel de evidencia ofrecido y contribución global al campo. Se han hecho pocos cambios en la versión actual del sistema de estadificación TNM para tumores renales. Los tumores pT2 se han dividido en 2 subgrupos basándose en el tamaño del tumor con un valor de corte de 10 cm; la invasión de la vena renal se clasifica como pT3a; finalmente, la invasión de la glándula suprarrenal ipsilateral*

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se clasifica como pT4. Sin embargo, otros cambios sugeridos tras el análisis de la literatura reciente no han sido introducidos en esta nueva versión. Para mejorar la precisión de esta importante herramienta pronóstica en oncología renal son necesarias mejoras adicionales de la clasificación TNM de los tumores renales, especialmente con respecto a los tumores localmente avanzados y la enfermedad con ganglios linfáticos positivos.

Palabras clave: *Carcinoma de células renales. Revisión. TNM. Estadiaje.*

INTRODUCTION

The TNM classification system was historically developed as a staging method to stratify patients with cancers into groups with different risks of disease progression. TNM is a globally accepted method to describe the local anatomic extension of a cancer (Tumor stage), its spread to lymph nodes (Nodal stage) or to distant organs (Metastasis stage).

The first TNM classification for renal cell carcinoma (RCC) was proposed in 1974 and has been revised several times in the following years (1).

In fact, evidence from the literature proved that each previous TNM edition had not sufficient accuracy to predict cancer-specific survival (CSS) when the system was applied in clinical trials (2).

Moreover, in the last few years new clinical and pathological prognosticators of cause-specific death for RCC have been identified, including microvascular invasion, tumor necrosis, mode of presentation and performance status (3-5). Therefore, recently, some Authors proposed new integrated staging prognostic models and nomograms for RCC such as the UCLA Integrated Staging System, the Mayo Clinic's SSIGN score and the Karakiewick's and Sorbellini's monograms (6-8). These models include the TNM classification and other prognostic variables and proved to be more accurate to predict CSS when compared to the TNM classification alone (9).

Recently, the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) released the 7th edition of the TNM classification for RCC (10). However, this last edition does not take into account some controversial issues that have been debated in the literature in recent years and has introduced some questionable modifications. Aim of the present paper is to review the current 7th edition of TNM of renal tumors and to perform a critical analysis of the recent evidence that highlights the limitations of this new staging system.

MATERIAL AND METHODS

A search of the English literature was performed using Medline and Pubmed database including the following keywords: renal cell carcinoma, staging system and TNM. A total of 2600 references were initially scrutinized. Pertinent publications were identified and reviewed rigorously. We discussed thoroughly reviews and multicenter trials concerning the 2002 TNM system edition and we analyzed the recent evidences concerning the 2009 TNM edition. Forty papers were selected for this review based on their pertinence and contribution to the field, favouring recent publications and larger series.

RESULTS

Tumor stage

Tumor stage describes the anatomical extension of a neoplasm within the kidney and the nearby organs. Table I compares the 2002 and 2009 edition of the kidney TNM staging system (Table 1). We will here analyze and critically discuss the issues concerning each tumor stage category.

T1: Tumor ≤ 7 cm in greatest dimension, limited to the kidney

As far as T1 renal tumors are concerned, the current TNM edition does not differ from the previous 2002 edition. In fact, tumors are divided according to tumor size in T1a (<4 cm) and T1b tumors (>4 cm but less than 7 cm) using the 4 cm size as cut-off value. This classification was introduced with the clinical purpose to identify those tumors that are suitable for nephron-sparing surgery (NSS). However, nowadays there is consistent data that supports the feasibility and the safety of nephron-sparing surgery also for larger localized RCCs (11-14). Patard et al retrospectively reviewed 1454 patients with T1a-T1b RCC who underwent radical or partial nephrectomy at 7 international academic urological centers. The Authors observed that, in the subset of patients with pT1b tumors, cancer-specific death rate of patients who underwent partial nephrectomy was not significantly different from the death rate of patients who underwent radical surgery (6.2% vs 9%, p=0.6) (5). More recently, Weight et al analyzed a cohort of 510 pT1b RCCs who were treated with elective

TABLE I. COMPARISON OF THE LAST TWO VERSIONS OF THE TNM STAGING SYSTEM FOR RENAL CELL CARCINOMA.

TNM 6th edition 2002	TNM 7th edition 2009
T - Tumor stage	**T - Tumor stage**
TX Primary tumor cannot be assessed	TX Primary tumor cannot be assessed
T0 No evidence of primary tumor	T0 No evidence of primary tumor
T1. Tumor ≤ 7 cm in greatest dimension, limited to the kidney - T1a: Tumor ≤ 4 cm in greatest dimension, limited to the kidney - T1b: Tumor > 4 cm but ≤ 7 cm in greatest dimension	T1. Tumor ≤ 7 cm in greatest dimension, limited to the kidney - T1a Tumor ≤ 4 cm in greatest dimension, limited to the kidney - T1b Tumor > 4 cm but ≤ 7 cm in greatest dimension
T2. Tumor > 7 cm limited to the kidney	T2. Tumor > 7 cm in greatest dimension, limited to the kidney - T2a Tumor > 7 cm but ≤ to 10 cm in greatest dimension - T2b Tumor > 10 cm limited to the kidney
T3. Tumor extends into major veins or invades adrenal or perinephric tissues, but not beyond Gerota's fascia - T3a: Perinephric or sinus fat or adrenal extension - T3b: Renal vein or vena cava involvement below the diaphragm - T3c: Vena cava involvement above the diaphragm	T3. Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia - T3a: Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches or tumor invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia - T3b: Tumor grossly extends into the vena cava below the diaphragm - T3c: Tumor grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4. Tumor invades beyond Gerota's fascia	T4. Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
N - Regional lymph nodes	**N - Regional lymph nodes**
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in a single regional lymph node N2 Metastasis in more than 1 regional lymph node	NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in a single regional lymph node N2 Metastasis in more than 1 regional lymph node
M - Distant meatstasis	**M - Distant meatstasis**
M0 No distant metastasis M1 Distant metastasis	M0 No distant metastasis M1 Distant metastasis
TNM stage grouping	**TNM stage grouping**
Stage I T1 N0 M0 Stage II T2 N0 M0 Stage III T3 N0 M0 T1, T2, T3 N1 M0 Stage IV T4 Any N M0 Any T N2 M0 Any T Any N M1	Stage I T1 N0 M0 Stage II T2 N0 M0 Stage III T3 N0 M0 T1, T2, T3 N1 M0 Stage IV T4 Any N M0 Any T N2 M0 Any T Any N M1

radical or partial nephrectomy and observed that in the subgroup of patients treated with nephron-sparing surgery CSS was significantly longer than in the subgroup treated with radical nephrectomy (15). Based on these studies, in the most recent versions of the international guidelines the indications to nephron-sparing surgery have already been extended to all T1 tumors, whenever this is technically possible (16).

However, to date there is no large long-term prospective clinical trial that compares the CSS of pT1a and pT1b tumors after nephron-sparing surgery. Other size cut-off within this category may better stratify CSS. For example a multicentre study that analysed 1138 patients with localised RCC (T1–2N0M0) with a medium follow-up of 87 months after radical or partial nephrectomy used a 5.5 cm cut-off for tumor diameter and found that this method of stratification was more accurate than the 2002 TNM version to distinguish between two groups of patients with different prognosis (3).

This data suggests that the present classification for T1 renal tumors may be improved, because it is progressively losing its main clinical relevance, although large clinical trials are needed to assess the long-term oncological safety of nephron-sparing surgery for pT1b renal cancers.

T2: Tumor > 7 cm in greatest dimension, limited to the kidney

In comparison with the 6th edition, the modern TNM classification divides T2 tumors into two subcategories, based on size cut-off of 10 cm (T2a<10 cm, T2b>10 cm).

This new classification is based on the results of a single study by Frank et al who retrospectively analyzed data from 544 patients who underwent radical or partial nephrectomy for pT2 RCCs at the Mayo Clinic between 1970 and 2000 (17). The Authors observed that patients with tumors >10 cm were significantly more likely to die of RCC than patients with tumors < 10 cm even after adjusting for regional lymph node involvement and distant metastases (risk ratio 1.42, 95% CI 1.07 to 1.90, p=0.017).

However, at a thorough review of the literature the best size cut-off for >7 cm renal tumors is controversial. In fact, Klatte et al evaluated a group of 706 patients with pT2 RCC and identified an optimal cut-off to predict CSS at 11 cm (18). On the contrary, Karakiewick and Moch (1, 4) observed that tumor size for pT2 RCC is significantly associated with CSS when modelled continuously, irrespective of a specific cut-off point.

Moreover, Waalkes et al. recently assessed the CSS of 5122 patients who underwent radical or partial nephrectomy for pT2 RCCs (19). Reclassifying all tumors according to the current TNM classification, the Authors observed that there was no significant difference in terms of CSS between pT2a and pT2b tumors (79% vs74.1% respectively, p = 0.38). Moreover, Novara et al., comparing the 5-year CSS of pT2b (70%) and pT3a patients (64.7%), did not observe any statistical significant difference (p>0.05) (20).

Overall, this data suggests that the rationale of the further subdivision of the pT2 category in the 2009 TNM classification is supported by scarce and weak evidence. Furthermore, the first studies that have assessed the performance of this new classification did not confirm an improved prognostic accuracy compared to the previous TNM edition.

T3: Tumor extends into major veins or directly invades perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

The T3 category includes cancers that involve multiple anatomical compartments. This category has been the most complex and controversial in every TNM edition. In fact, there are more than 20 possible patterns of tumor invasion within the T3 stage (21).

As far as the 6th edition is concerned, some Authors observed that the prognostic accuracy for T3 RCCs was highly debatable. This was the main reason to encourage further development of the pT3 classifications in the 2009 TNM edition (2, 21, 22). The category T3a continues to define cancers that involve the perinephric and/or the sinus fat tissue and now includes also tumors with invasion of the renal vein, previously classified as T3b. The direct extension of a tumor to the ipsilateral adrenal gland is now classified as T4 instead of T3a. T3b and T3c categories define cancers that have invaded the IVC below or above the diaphragm respectively. Finally, the extension of the tumor within the atrium is also classified as T3c.

However, although some changes have been introduced, there are still some crucial points of discussion that were not considered in order to further improve T3 subcategorization.

- **Perinephric fat versus renal sinus fat invasion**

There is consistent evidence that the vascular and lymphatic anatomy of the fat tissue located at the

level of the renal sinus is different from the anatomy of the perinephric fat surrounding the kidney, within the Gerota's fascia (23).

The extension of a RCC to the renal sinus or the perinephric fat tissue has been investigated in many studies that reported a different impact on CSS for these two patterns of fat invasion (1, 21, 23, 24).

The renal sinus can be defined as the compartment of fatty tissue that envelopes the collecting system and contains abundant tributary veins and lymphatics (1). Because of this peculiar anatomy, the invasion of this compartment allows the dissemination of a cancer otherwise considered as localized.

Many studies have specifically investigated the prognostic significance of renal sinus fat invasion (RSI). Bonsib et al first observed that the renal sinus was the most common site for extrarenal extension of RCC. In a cohort of 40 patients with locally advanced RCC the invasion of sinus fat was mainly associated with the invasion of sinus veins, likely responsible for hematogenous metastases, the most common route of tumor dissemination in RCC (25). This pathological data supports the idea that RSI negatively impacts CSS.

Thompson et al. confirmed this data in a study of 205 patients with pT3 RCCs. The Authors compared the CSS of patients with RSI or perirenal fat invasion (PFI) and observed a significantly lower 5-year CSS in the subgroup of patients with RSI (24). On the contrary, Terrone et al. analyzed the outcomes of 513 pT3 RCC patients (according to 2002 TNM) and observed that CSS in the subset of cases with PFI was not significantly different from CSS in the RSI subgroup. Moreover, the risk of death for RCC was classified as low when PFI or RSI were present as only site of tumor extension. On the contrary, when the fat invasion was combined with invasion of renal vein or IVC the risk of disease progression and cause-specific death was significantly increased (21).

As far as the PFI is concerned, we can identify 2 different anatomical patterns of invasion (focal or extended). The prognostic impact of these 2 patterns is controversial.

Roberts et al (26) reported that patients with clinically classified T1 lesions and finally classified as pT3a because of focal PFI, had the same recurrence-free survival rate of patients with pathologically confirmed pT1 lesions. In contrast, Jung et al found no difference between focal or extensive PFI (27).

In the current TNM classification the pattern of fat tissue invasion was not used as a variable to differentiate T3a subcategories. This may be due to the lack of sizable studies comparing CSS of patients with PFI and RSI.

• Urinary collecting system invasion

The invasion of urinary collecting system (UCSI) ranges from 7.5%-14% of RCCs and it has been questioned as a prognosticator of CSS (18, 28).

Terrone et al. analyzed the data of 671 RCC specimens from 2 academic urological centers (29). Tumors invading the UCS were usually symptomatic, with high nuclear grade and predominantly high stage. At multivariate analysis UCSI did not represent an independent prognostic factor for CSS. However, in the subgroup of patients with organ-confined tumors UCSI involvement was found to have a prognostic influence. Similar results were observed by Uzzo et al. and Verhoest et al. (23, 30).

On the contrary, Palapattu et al. observed a significant correlation between UCSI and the development of nodal and systemic metastases in a population of 124 T2-T3 tumors. Overall, UCSI was shown to be an independent prognosticator of CSS and to be associated with a 3.78 fold increased risk of tumor recurrence in presence of organ confined tumors (31). Similar results were obtained by Klatte et al in a series of 519 cases (28).

In all TNM classification developed to date UCSI is not considered as a variable in the definition of the local extension of renal tumors and therefore is not included in any T category. This is most likely due to the absence of large cohort studies that assessed the impact of UCSI on CSS. Further studies are therefore needed to clarify this issue and allow the inclusion of this important anatomical variable in the TNM system.

• Tumor thrombus level

It is well known that the presence of a renal tumor thrombus in renal vein, IVC or right atrium is a negative prognostic factor for CSS (32)

The current TNM system divides patients into 3 subcategories based on the level of the venous extension of the tumor. However, the prognostic significance of the level of venous involvement in RCC has been debated and it is nowadays still considered highly controversial. Moreover, all the studies available to date are characterized by a small number of cases with supradiaphragmatic IVC tumor extension (33).

In 2008, Terrone et al analyzed the outcomes of a large series of 513 pT3 RCC cases and concluded that the prognostic accuracy of the 2002 TNM system edition was low. Of note, Terrone et al. identified up to 23 subcategories by considering the possible combinations of each single anatomical structure invaded by the cancer. Nine groups of patients with specific patterns of invasion and significantly different cause-specific death risk were identified. These groups were then divided into 3 categories with different risk of disease progression (low, intermediate and high risk) based on CSS. Patients were classified at intermediate risk in presence of any invasion of the venous system alone or in association with RSI, while the high risk group included tumors with both perirenal fat and venous invasion. The risk of death in the intermediate and high risk group was increased by 1.47 and 1.60 times respectively compared to the low risk group (21).

Other investigators have suggested that the invasion of the renal vein alone has a more favourable outcome when compared to the invasion of IVC, irrespective of tumor thrombus level (2, 9, 34).

Recently, Martinez-Salamanca et al assessed the prognostic accuracy of the 7th edition of the TNM system in an international multicenter study that included the records of 1215 patients who underwent radical nephrectomy with complete thrombectomy for T3 RCC (33). Patients were reclassified according to the modern TNM edition and Kaplan-Meier estimates were obtained. A statistically significant difference of 5-year CSS was observed between pT3a and pT3b patients ($p<0.005$), but this data could not be confirmed after adjusting for lymph nodes invasion and presence of distant metastases ($p=0.72$). On the contrary, a significant difference was observed for 5 and 10-year CSS between pT3b N0M0 and pT3c N0M0 tumors ($p<0.001$).

Novara et al, who first validated the new TNM classification, observed that pT3a patients with isolated PFI and renal vein invasion had similar outcomes, whereas patients with the two concomitant features had significantly lower CSS ($p<0.0001$). Among the 886 pT3aN0M0 RCC cases, patients with renal vein invasion had the highest CSS, followed by those with PFI only and by those with the two concomitant features, with all survival differences being statistically significant. As far as the pT3b and pT3c cases are concerned, 5-year CSS was significantly different. In both these subcategories, the concomitant presence of PFI and IVC invasion was related to a significantly worse prognosis (20).

Overall, once again, this data suggests that the current TNM classification has not improved the prognostic accuracy of this staging system for patients with tumor thrombus. However, it is important to observe that Novara and Martinez-Salamanca are the only Authors that assessed the new TNM system and therefore there is little evidence to support a thorough analysis of the accuracy of this 7th edition.

T4: Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

In the 2009 edition of the TNM system all RCCs presenting with direct infiltration of the ispilateral adrenal gland are classified as stage T4. These cases were identified as pT3a tumors in the previous edition. This change was based on the evidence that the outcomes of pT3a patients with direct adrenal invasion were worse than those of patients with perirenal fat invasion (35).

Moreover, CSS of patients classified as pT3b and pT3c was worse when adrenal gland was invaded by the cancer (36). Finally, the 5 and 10-year CSS of patients classified as pT4 and pT3a (according to 2002 edition) were shown to overlap in presence of adrenal gland invasion (2).

This new classification seems to improve the prognostic accuracy of the TNM system, as recently demonstrated by the results reported by Novara et al (20). These Authors observed that the outcomes of patients with direct adrenal invasion and Gerota's fascia invasion (all classified as pT4 according to the 7th TNM edition) were similar. However, a small number of specimens with direct adrenal involvement were included in this study and therefore these results need to be confirmed in larger series.

Metastatic disease

There is consistent data in the literature showing that the presence of metastases from RCC is related to a poor prognosis (37). Overall, almost 30% of patients presents with metastases at diagnosis, including 10% of cases with nodal metastases (38). As far as nodal and metastatic status are concerned, no changes have been introduced in the new 2009 TNM edition. In the last few years a modification of the N staging system has been advocated by several Authors (39). Terrone et al reviewed 618 RCCs specimens obtained after radical nephrectomy and extended lymphadenectomy (from the crus of the diaphragm to the aortic/caval bifurcation). The

Authors observed that the TNM classification for nodal disease was not able to stratify the outcomes in this series. Conversely, the presence of >4 positive nodes or a positive lymph node density >60% was shown to correlate significantly with CSS. Similar conclusions were drawn also by Lohse et al in a recent review of the literature (40).

CONCLUSION

Few changes have been made in the current, recently released version of the TNM staging system for renal tumors. This new classification will require validation in large series to confirm an improved efficacy for stratification of outcomes. However, other changes suggested by the analysis of the recent literature were not introduced in the recently updated TNM version. Further improvements of this prognostic tool are needed, especially with regard to locally advanced and node-positive tumors.

REFERENCES AND RECOMMENDED READINGS (*of special interest, **of outstanding interest)

*1. Moch H, Artibani W, Delahunt B, Ficarra V, Knuechel R, Montorsi F, Patard JJ, Stief CG, Sulser T, Wild PJ: Reassessing the current UICC/AJCC TNM staging for renal cell carcinoma. Eur Urol 2009, 56(4):636-643.

**2. Ficarra V, Novara G, Iafrate M, Cappellaro L, Bratti E, Zattoni F, Artibani W: Proposal for reclassification of the TNM staging system in patients with locally advanced (pT3-4) renal cell carcinoma according to the cancer-related outcome. Eur Urol 2007, 51(3):722-729; discussion 729-731.

3. Ficarra V, Martignoni G, Maffei N, Brunelli M, Novara G, Zanolla L, Pea M, Artibani W: Original and reviewed nuclear grading according to the Fuhrman system: a multivariate analysis of 388 patients with conventional renal cell carcinoma. Cancer 2005, 103(1):68-75.

4. Karakiewicz PI, Lewinshtein DJ, Chun FK, Briganti A, Guille F, Perrotte P, Lobel B, Ficarra V, Artibani W, Cindolo L et al: Tumor size improves the accuracy of TNM predictions in patients with renal cancer. Eur Urol 2006, 50(3):521-528; discussion 529.

5. Patard JJ, Leray E, Cindolo L, Ficarra V, Rodriguez A, De La Taille A, Tostain J, Artibani W, Abbou CC, Guille F et al: Multi-institutional validation of a symptom based classification for renal cell carcinoma. J Urol 2004, 172(3):858-862.

6. Volpe A, Patard JJ: Prognostic factors in renal cell carcinoma. World J Urol, 28(3):319-327.

7. Sorbellini M, Kattan MW, Snyder ME, Reuter V, Motzer R, Goetzl M, McKiernan J, Russo P: A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol 2005, 173(1):48-51.

8. Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, Cindolo L, De la Taille A, Tostain J, Mulders PF et al: Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol 2007, 25(11):1316-1322.

9. Ficarra V, Galfano A, Mancini M, Martignoni G, Artibani W: TNM staging system for renal-cell carcinoma: current status and future perspectives. Lancet Oncol 2007, 8(6):554-558.

10. Greene FL: American Joint Committee on Cancer (AJCC) staging manual. ed 7 Philadelphia, PA: Springer. In.; 2009.

11. Leibovich BC, Cheville JC, Lohse CM, Zincke H, Kwon ED, Frank I, Thompson RH, Blute ML: Cancer specific survival for patients with pT3 renal cell carcinoma-can the 2002 primary tumor classification be improved? J Urol 2005, 173(3):716-719.

12. Margulis V, Tamboli P, Matin SF, Meisner M, Swanson DA, Wood CG: Location of extrarenal tumor extension does not impact survival of patients with pT3a renal cell carcinoma. J Urol 2007, 178(5):1878-1882.

13. Simmons MN, Weight CJ, Gill IS: Laparoscopic radical versus partial nephrectomy for tumors >4 cm: intermediate-term oncologic and functional outcomes. Urology 2009, 73(5):1077-1082.

14. Becker F, Siemer S, Hack M, Humke U, Ziegler M, Stockle M: Excellent long-term cancer control with elective nephron-sparing surgery for selected renal cell carcinomas measuring more than 4 cm. Eur Urol 2006, 49(6):1058-1063; discussion 1063-1054.

15. Weight CJ, Larson BT, Gao T, Campbell SC, Lane BR, Kaouk JH, Gill IS, Klein EA, Fergany AF: Elective partial nephrectomy in patients with clinical T1b renal tumors is associated with improved overall survival. Urology, 76(3):631-637.

16. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, Patard JJ, Mulders PF, Sinescu IC: EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol, 58(3):398-406.

17. Frank I, Blute ML, Leibovich BC, Cheville JC, Lohse CM, Kwon ED, Zincke H: pT2 classification for renal cell carcinoma. Can its accuracy be improved? J Urol 2005, 173(2):380-384.

*18. Klatte T, Patard JJ, Goel RH, Kleid MD, Guille F, Lobel B, Abbou CC, De La Taille A, Tostain J, Cindolo L et al: Prognostic impact of tumor size on pT2 renal cell carcinoma: an international multicenter experience. J Urol 2007, 178(1):35-40; discussion 40.

19. Waalkes S, Becker F, Schrader AJ, Janssen M, Wegener G, Merseburger AS, Schrader M, Hofmann R, Stockle M, Kuczyk MA: Is There a Need to Further Subclassify pT2 Renal Cell Cancers as Implemented by the Revised 7th TNM Version? Eur Urol.

**20. Novara G, Ficarra V, Antonelli A, Artibani W, Bertini R, Carini M, Cosciani Cunico S, Imbimbo C, Longo N, Martignoni G et al: Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? Eur Urol, 58(4):588-595.

**21. Terrone C, Gontero P, Volpe A, Porpiglia F, Bollito E, Zattoni F, Frea B, Tizzani A, Fontana D, Scarpa RM et al: Proposal of an improved prognostic classification for pT3 renal cell carcinoma. J Urol 2008, 180(1):72-78.

22. Terrone C, Volpe A: The role of pathology for clinical decision-making in renal cell carcinoma is increasing. Eur Urol 2007, 51(5):1166-1168; discussion 1168-1170.

23. Verhoest G, Avakian R, Bensalah K, Thuret R, Ficarra V, Artibani W, Tostain J, Guille F, Cindolo L, De La Taille A et al: Urinary collecting system invasion is an independent prognostic factor of organ confined renal cell carcinoma. J Urol 2009, 182(3):854-859.

24. Thompson RH, Cheville JC, Lohse CM, Webster WS, Zincke H, Kwon ED, Frank I, Blute ML, Leibovich BC: Reclassification of patients with pT3 and pT4 renal cell carcinoma improves prognostic accuracy. Cancer 2005, 104(1):53-60.

25. Bonsib SM: Renal lymphatics, and lymphatic involvement in sinus vein invasive (pT3b) clear cell renal cell carcinoma: a study of 40 cases. Mod Pathol 2006, 19(5):746-753.

26. Roberts WW, Bhayani SB, Allaf ME, Chan TY, Kavoussi LR, Jarrett TW: Pathological stage does not alter the prognosis for renal lesions determined to be stage T1 by computerized tomography. J Urol 2005, 173(3):713-715.

27. Jung SJ, Ro JY, Truong LD, Ayala AG, Shen SS: Reappraisal of T3N0/NxM0 renal cell carcinoma: significance of extent of fat invasion, renal vein invasion, and adrenal invasion. Hum Pathol 2008, 39(11):1689-1694.

*28. Klatte T, Chung J, Leppert JT, Lam JS, Pantuck AJ, Figlin RA, Belldegrun AS: Prognostic relevance of capsular involvement and collecting system invasion in stage I and II renal cell carcinoma. BJU Int 2007, 99(4):821-824.

29. Terrone C, Cracco C, Guercio S, Bollito E, Poggio M, Scoffone C, Tarabuzzi R, Porpiglia F, Scarpa RM, Fontana D et al: Prognostic value of the involvement of the urinary collecting system in renal cell carcinoma. Eur Urol 2004, 46(4):472-476.

30. Uzzo RG, Cherullo EE, Myles J, Novick AC: Renal cell carcinoma invading the urinary collecting system: implications for staging. J Urol 2002, 167(6):2392-2396.

31. Palapattu GS, Pantuck AJ, Dorey F, Said JW, Figlin RA, Belldegrun AS: Collecting system invasion in renal cell carcinoma: impact on prognosis and future staging strategies. J Urol 2003, 170(3):768-772; discussion 772.

32. Moinzadeh A, Libertino JA: Prognostic significance of tumor thrombus level in patients with renal cell carcinoma and venous tumor thrombus extension. Is all T3b the same? J Urol 2004, 171(2 Pt 1):598-601.

**33. Martinez-Salamanca JI, Huang WC, Millan I, Bertini R, Bianco FJ, Carballido JA, Ciancio G, Hernandez C, Herranz F, Haferkamp A et al: Prognostic Impact of the 2009 UICC/AJCC TNM Staging System for Renal Cell Carcinoma with Venous Extension. Eur Urol.

34. Kim HL, Zisman A, Han KR, Figlin RA, Belldegrun AS: Prognostic significance of venous thrombus in renal cell carcinoma. Are renal vein and inferior vena cava involvement different? J Urol 2004, 171(2 Pt 1):588-591.

35. Han KR, Bui MH, Pantuck AJ, Freitas DG, Leibovich BC, Dorey FJ, Zisman A, Janzen NK, Mukouyama H, Figlin RA et al: TNM T3a renal cell carcinoma: adrenal gland involvement is not the same as renal fat invasion. J Urol 2003, 169(3):899-903; discussion 903-894.

36. Thompson RH, Leibovich BC, Cheville JC, Lohse CM, Frank I, Kwon ED, Zincke H, Blute ML: Should direct ipsilateral adrenal invasion from renal cell carcinoma be classified as pT3a? J Urol 2005, 173(3):918-921.

*37. Bensalah K, Pantuck AJ, Crepel M, Verhoest G, Mejean A, Valeri A, Ficarra V, Pfister C, Ferriere JM, Soulie M et al: Prognostic variables to predict cancer-related death in incidental renal tumours. BJU Int 2008, 102(10):1376-1380.

38. Karakiewicz PI, Trinh QD, Bhojani N, Bensalah K, Salomon L, de la Taille A, Tostain J, Cindolo L, Altieri V, Ficarra V et al: Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease: prognostic indicators of disease-specific survival. Eur Urol 2007, 51(6):1616-1624.

39. Terrone C, Cracco C, Porpiglia F, Bollito E, Scoffone C, Poggio M, Berruti A, Ragni F, Cossu M, Scarpa RM et al: Reassessing the current TNM lymph node staging for renal cell carcinoma. Eur Urol 2006, 49(2):324-331.

40. Lohse CM, Cheville JC: A review of prognostic pathologic features and algorithms for patients treated surgically for renal cell carcinoma. Clin Lab Med 2005, 25(2):433-464.