Overview and Staging of Renal Neoplasms

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Classification of Renal Neoplasms

The nosology of tumors of renal origin has tremendously evolved during the last three decades. Advancement in our knowledge of histology, immunohistochemistry, genetics, and molecular pathology of renal tumors brought the expansion in its types, particularly within the spectrum of renal cell carcinoma (RCC). The last World Health Organization (WHO) classification of renal tumors was published in 2004 that had evolved mainly from the prior Heidelberg 1996 and Rochester 1997 international consensus conferences. In 2010, the International Society of Urological Pathology (ISUP) conducted a consensus conference in Vancouver, Canada, to modify the 2004 WHO classification of renal tumors [1]. This latest classification scheme known as the *ISUP Vancouver classification of renal neoplasia* (Table 4.1) is the basis for the new WHO classification of renal tumors scheduled for release in 2016.

Several new subtypes of RCC are recognized in the ISUP Vancouver classification such as tubulocystic RCC, acquired cystic disease-associated RCC, clear cell (tubulo) papillary RCC, MiT family translocation RCC (including t(6;11) RCC), and hereditary leiomyomatosis RCC syndrome-associated RCC. Some newly described RCCs are also considered as provisional entities such as thyroid-like follicular RCC, succinic dehydrogenase B deficiency-associated RCC, and ALK-translocation RCC. Additional data are needed to help shed light on the biology of these rare unique tumors. Some innovations were also made on traditional tumor entities, such as renaming multicystic clear cell RCC as a neoplasm of low malignant potential, subtyping papillary RCC into type 1 or 2, accepting the hybrid oncocytic/chromophobe tumor as a discrete subtype of chromophobe RCC, and merging cystic nephroma with mixed epithelial stromal tumor into one tumor spectrum. Despite the inclusion of these novel entities, clear cell RCC, papillary RCC, and chromophobe RCC still comprise >90 % of the RCCs. The proportion of MiT family translocation RCC however is higher in pediatric and young adult patients.

Staging of Renal Cancers

Introduction

The tumor node metastasis (TNM) is the most widely accepted staging system for renal cancer [2]. This approach measures the extent of can-

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Table 4.1 ISUP Vancouver modification of 2004 WHO classification of renal tumors

Renal cell tumors
Papillary adenoma
Oncocytoma
Clear cell renal cell carcinoma
Multilocular cystic clear cell renal cell neoplasm of low malignant potential[a]
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Hybrid oncocytic/chromophobe tumor[a]
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
MiT family translocation renal cell carcinoma[a]
Xp11 translocation renal cell carcinoma
t(6;11) renal cell carcinoma
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma[a]
Acquired cystic disease-associated renal cell carcinoma[a]
Clear cell (tubulo) papillary renal cell carcinoma[a]
Hereditary leiomyomatosis renal cell carcinoma syndrome-associated renal cell carcinoma[a]
Renal cell carcinoma, unclassified
Metanephric tumors
Metanephric adenoma
Metanephric adenofibroma
Metanephric stromal tumor
Nephroblastic tumors
Nephrogenic rests
Nephroblastoma
Cystic partially differentiated nephroblastoma
Mesenchymal tumors
Occurring mainly in children
Clear cell sarcoma
Rhabdoid tumor
Congenital mesoblastic nephroma
Ossifying renal tumor of infants
Occurring mainly in adults
Leiomyosarcoma (including renal vein)
Angiosarcoma
Rhabdomyosarcoma
Malignant fibrous histiocytoma
Hemangiopericytoma
Osteosarcoma
Synovial sarcoma[a]
Angiomyolipoma
Epithelioid angiomyolipoma[a]
Leiomyoma
Hemangioma
Juxtaglomerular cell tumor
Renomedullary interstitial cell tumor
Schwannoma
Solitary fibrous tumor
Mixed mesenchymal and epithelial tumors
Cystic nephroma/mixed epithelial stromal tumor
Neuroendocrine tumors
Carcinoid (low-grade neuroendocrine tumor)
Neuroendocrine carcinoma (high-grade neuroendocrine tumor)
Primitive neuroectodermal tumor
Neuroblastoma
Pheochromocytoma
Hematopoietic and lymphoid tumors
Lymphoma
Leukemia
Plasmacytoma
Germ cell tumors
Teratoma
Choriocarcinoma
Metastatic tumors
Other tumors

[a]New additions or changes

cer spread at the primary organ site, regional lymph nodes, and distant sites (Table 4.2). The TNM system underwent considerable revisions over the past three decades with its latest edition (seventh) published in 2010, and a new version is being expected within the next 2 years as of 2015. Purely based on the tumor's anatomic extent, the different TNM stage categories are lumped into four main prognostic groups (Table 4.3). The clinical (c) stage is routinely used as a guide in determining the type of primary management, such as nephron sparing surgery (NSS) or ablative therapies for low stage renal tumors or systemic therapy for advanced stage tumors. The pathologic (p) stage mainly provides prognosis of outcome after surgical resection of renal cancer and is important on the decision for adjuvant therapy. TNM stage is often incorporated in the inclusion criteria and in stratifying

Table 4.2 Definitions of the 2010 AJCC TNM staging for renal cancers

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
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 fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node (s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 4.3 2010 AJCC TNM anatomic stage or prognostic groupings

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

patients for clinical therapeutic trials. The accuracy of TNM stage in renal cancer can be further enhanced by its integration in the different prognostic and predictive models such as the MSKCC prognostic nomogram; the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score; and the UCLA integrated staging system (UISS) [3–7].

Historical Background

In 1958, Flocks and Kasdesky [8] introduced one of the first formal stagings for renal cancer based on the tumor's anatomic extent and patterns of spread. A year later, Petkovic [9] proposed a similar classification that subdivided intrarenal tumors into stages I and II (Flocks and Kasdesky's stage I). In the 1960s, Robson modified these systems, incorporated venous involvement, and subdivided localized extrarenal spread [10, 11]. However, Robson's system was hampered by inaccuracies in some of the stage definitions due to the lumping of prognostically different patterns of anatomic spread [11].

First developed in the 1940s by Pierre Denoix in France, the TNM system was adopted by the Union Internationale Contre le Cancer (UICC), while the American Joint Commission on Cancer (AJCC) used a slightly different classification. In 1987, the UICC and AJCC were unified, and the first major revision of the TNM staging was published that incorporated tumor size cutoffs derived from cross-sectional imaging studies. Since then, the TNM system underwent several major revisions published in 1993 (supplement), 1997, 2002, and the latest in 2010, building on experiences and evidences accumulated from each prior version in order to enhance its prognostic accuracies (Table 4.4). Revisions in the 2010 TNM system include T2 tumors divided into T2a (>7 cm but ≤10 cm) and T2b (>10 cm); ipsilateral adrenal gland contiguous invasion classified as T4 and, if not contiguous as M1, renal vein involvement reclassified as T3a; and nodal involvement simplified into N0 and N1 [2].

Table 4.4 Evolution of renal cancer staging system

Stage	Robson (1969)[a]	UICC/AJCC TNM, fourth edition (1987)	UICC/AJCC TNM, fifth edition (1997)	UICC/AJCC TNM, sixth edition (2002)	UICC/AJCC TNM, seventh edition (2010)
T1	(I) Organ confined, any size	Organ confined, ≤2.5 cm	Organ confined, ≤7 cm	–	–
T1a	–	–	–	Organ confined, ≤4 cm	Organ confined, ≤4 cm
T1b	–	–	–	Organ confined, >4–7 cm	Organ confined, >4–7 cm
T2	(II) Into perinephric tissue	Organ confined, >2.5 cm	Organ confined, >7 cm	Organ confined, >7 cm	–
T2a	–	–	–	–	Organ confined, >7–10 cm
T2b	–	–	–	–	Organ confined, >10 cm
T3a	(IIIa) Renal vein	Perinephric tissue or contiguous adrenal gland extension	Perinephric tissue or contiguous adrenal gland extension	Perinephric or sinus tissue or contiguous adrenal gland extension	Perinephric or sinus tissue or renal vein or its segmental branches
T3b	(IIIb) Node involvement	Renal vein	Renal vein or vena cava below diaphragm	Renal vein or vena cava below diaphragm	Vena cava below diaphragm
T3c	(IIIc) Both renal vein and node involvement	Vena cava below diaphragm	Vena cava above diaphragm	Vena cava above diaphragm	Vena cava above diaphragm or wall of vena cava at any level
T4	–	–	Beyond Gerota's fascia	Beyond Gerota's fascia	Beyond Gerota's fascia or contiguous adrenal gland extension
T4a	(IVa) Invasion of adjacent structures	Beyond Gerota's fascia	–	–	–
T4b	(IVb) Distant metastasis	Vena cava above diaphragm	–	–	–

[a]Staged as I, II, IIIa, IIIb, IIIc, IVa, IVb

Components of the TNM Staging System for Renal Cancer

Organ-Confined Tumors

Tumors 7 cm or Smaller (T1)

Since the 2002 TNM version, T1 tumors are subdivided into T1a and T1b using 4 cm size cutoff (Figs. 4.1 and 4.2). This was mainly based on the study by Hafez et al. [12] wherein they reviewed 485 patients with localized renal cancer treated with NSS and showed a more favorable cancer-free survival in tumors ≤4 cm compared to larger tumors. Since then, the prognostic impact of this subdivision has been validated in subsequent studies [13–17]. Despite of several studies suggesting a different optimal size cutoff for T1a and T1b and T1 versus T2, the 4 and 7 cm cutoffs are retained in the current 2010 TNM system [18–22]. By incidence, most renal cancers are diagnosed as T1 tumors (~55 to 70 %) and with greater T1a (35–45 %) than T1b cases (19–27 %) (Table 4.5) [23–25]. A practical usefulness of this T1 grouping is that most of the current guidelines recommend NSS for T1 renal cancer when technically feasible, and this recommendation is generally accepted for T1a tumors.

Tumors Larger Than 7 cm (T2)

One of the revisions in the 2010 TNM system is the subdivision of T2 into T2a and T2b using 10 cm cutoff (Fig. 4.3). In an earlier study by Frank et al. [17] on 544 patients with organ confined >7 cm renal cancers treated with radical nephrectomies or NSS, tumors ≥10 cm in size had a significantly better cancer-specific survival (CSS) than with <10 cm tumors even after adjusting for regional lymph node involvement and distant metastasis. The 10 cm cutoff outperformed the 9 cm cutoff [17]. The 10 cm cutoff for T2 tumors was supported by data obtained from the National Cancer Data Base (NCDB), wherein T2a and T2b showed 5 years observed survival of 57 % and 47.5 %, respectively [2].

Locally Aggressive Tumors

Perinephric or Sinus Fat, Renal Vein, and Vena Caval Extension (T3)

T3 tumors are subdivided into three categories: T3a defined by invasion of the perinephric or sinus tissues or of the renal vein and both T3b and T3c defined by extension into vena cava subdivided by the level of tumor thrombus relative to the diaphragm (Figs. 4.4, 4.5, 4.6, 4.7, and 4.8). Renal vein invasion includes involvement of its muscle-containing segmental branches. T3c also includes tumor invasion of the vena caval wall regardless if present at any level. The distribution of T3 tumors is disproportionate with most tumors falling under the T3a category (12–36 % overall). Only ~2 and ~0.5 % of renal cancers overall are staged as T3b and T3c, respectively. Contributory to the increase in T3a is the incorporation of sinus invasion into this category [26–28]. Renal sinus invasion is diagnosed pathologically by tumor involvement of any of structures of the renal sinus, including sinus fat, loose connective tissue, or any sinus-based endothelium-lined space [29]. In contrast, perinephric fat invasion is defined pathologically as either tumor touching the fat or extending as irregular tongues into the perinephric tissue, with or without the presence of desmoplasia [29]. Bonsib [28] showed that the frequency of renal sinus invasion is closely related to the tumor size, having a cutoff point of 4 cm, after which the frequency of sinus invasion increases sharply. He also showed that T2 (>7 cm) clear cell RCCs are uncommon if careful examination of the renal sinus for tumor invasion is performed [28]. Renal sinus invasion was shown to have a negative impact on CSS in renal cancers without nodal or distant metastasis [30]. With increasing tumor size, sinus invasion was also shown to be more frequent than perinephric fat invasion. It is possible that the uncommon T1 renal cancers with aggressive course may have unrecognized renal sinus fat invasion that was missed on sampling, particularly for small tumors close to the renal hilum [31, 32]. Since

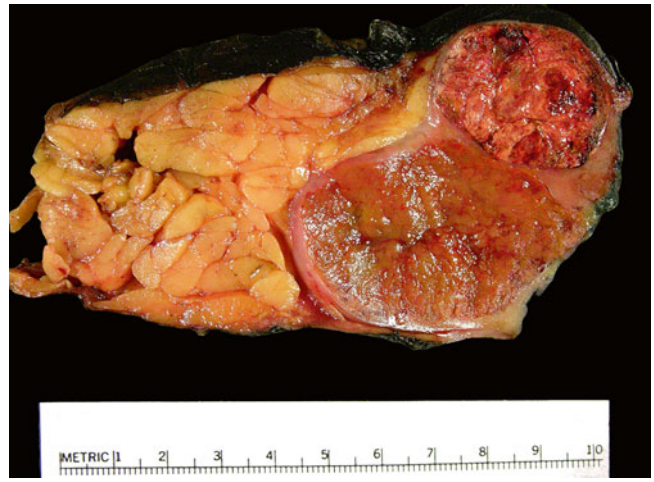

Fig. 4.1 Kidney with two synchronous organ-confined tumors. The smaller tumor (*top*) is T1a and the larger tumor (*bottom*) is T1b. Multiple tumors are staged according to the highest T stage, in this case as T1b

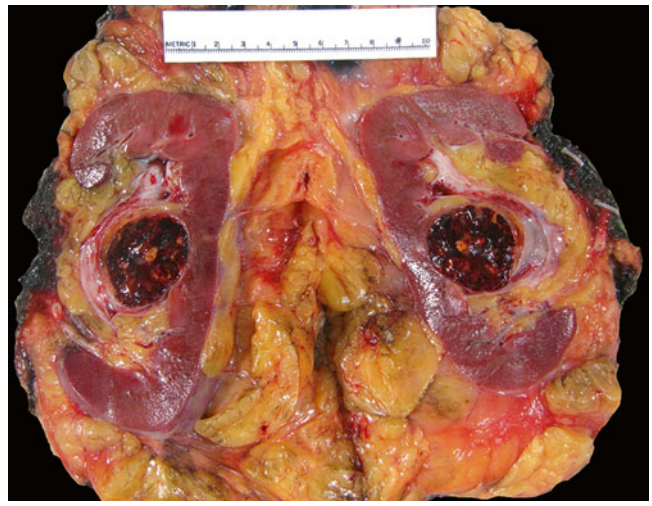

Fig. 4.2 T1a clear cell RCC that is very close to the hilum. In this case, adequate sampling of the tumor-sinus interface is important to ascertain the absence of invasion (T3a)

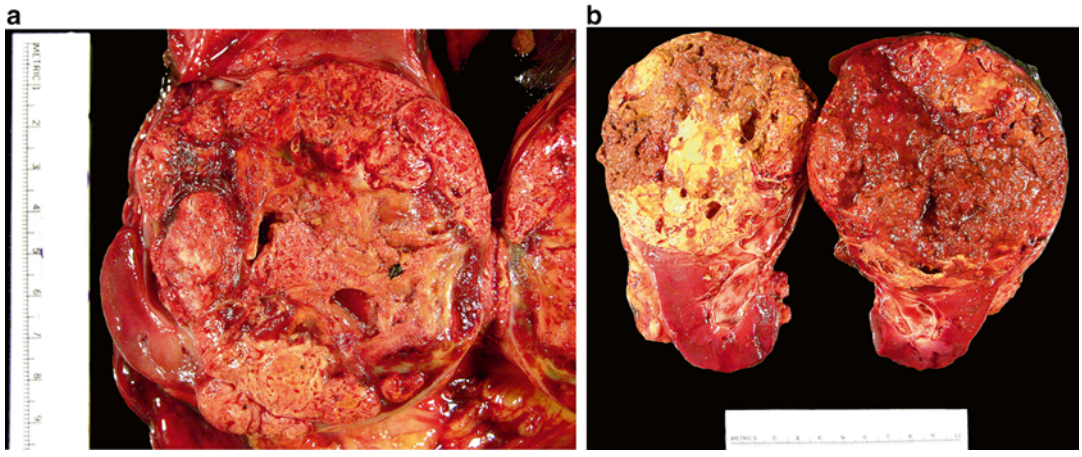

Fig. 4.3 Large organ-confined tumors. (**a**) T2a clear cell RCC and (**b**) T2b papillary RCC

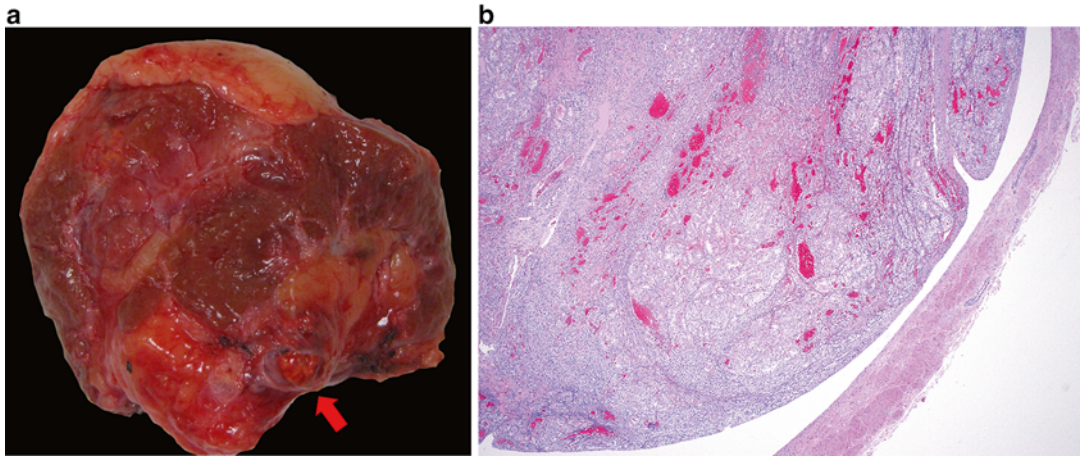

Fig. 4.4 (**a**) T3a clear cell RCC with tumor thrombus in a segmental branch of renal vein (*arrow*) seen at the cut margin of a partial nephrectomy. (**b**) The tumor does not infiltrate into the vessel wall

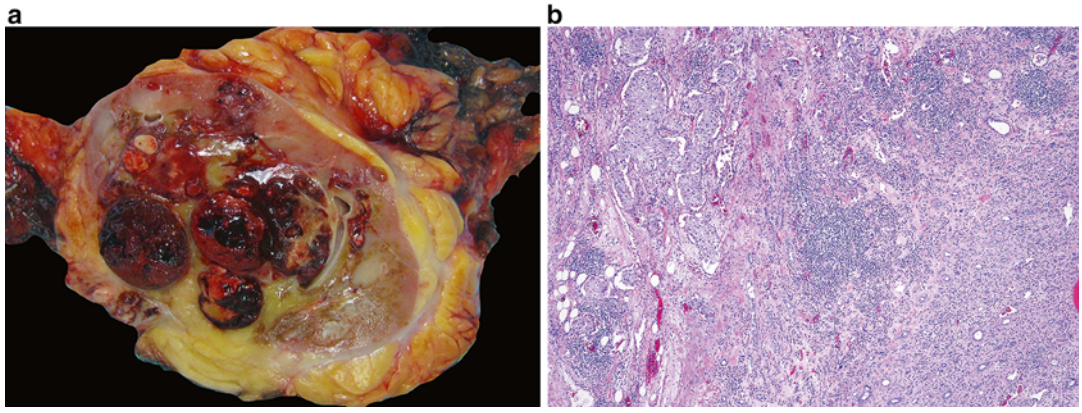

Fig. 4.5 (**a**) T3a clear cell RCC with concomitant renal vein invasion and sinus fat invasion. (**b**) Infiltration of tumor into the renal sinus tissue

T3a has three different inclusion criteria (i.e., sinus invasion, perinephric invasion, and renal vein invasion) and has a relatively larger proportion of tumors among the different T categories (Table 4.5), this large group may also be prognostically heterogeneous. Thompson et al. [33], in a study of 205 T3a renal cancers treated with radical nephrectomy, showed that renal tumors invading the sinus are more aggressive than those invading into the perinephric fat. It is suggested that access by tumor to the lymphatic and vascular channels present at the sinus is responsible for the more aggressive course. Subsequent

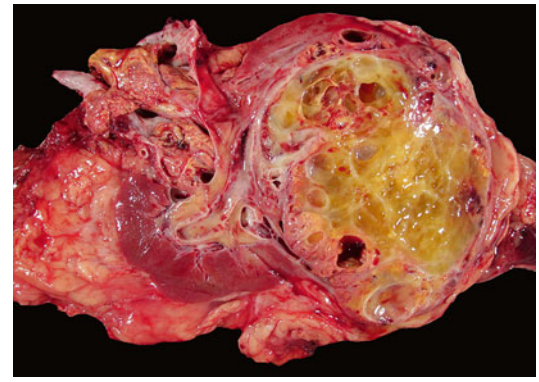

Fig. 4.6 T3b Clear cell RCC with a tumor thrombus within the renal vein that extends into the vena cava

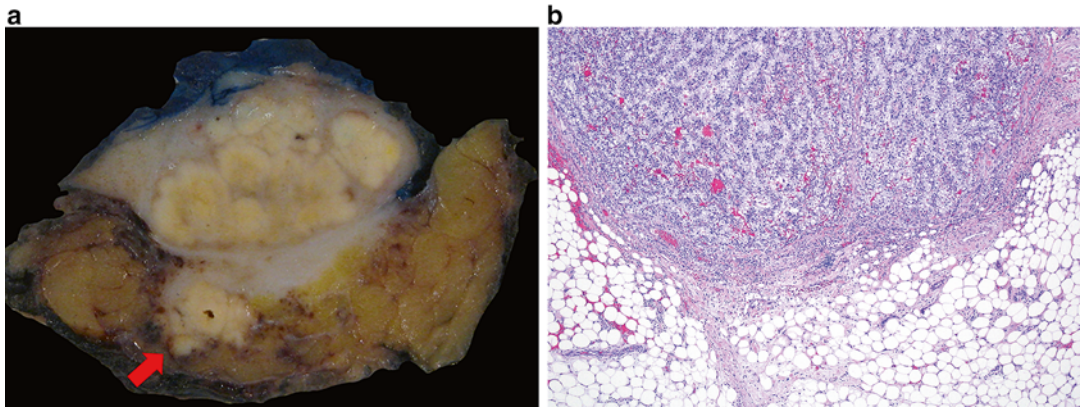

Fig. 4.7 T3a clear cell RCC in a partial nephrectomy with invasion into the perinephric fat (**a**, *arrow*, and **b**)

Table 4.5 Distribution of renal cancer patients by pathologic T stage

pTstage	Novara et al. (2010) [23]	Lee et al. (2011) [24]	Pichler et al. (2013) [25]
N	5339	1691	2739
T1a (%)	35.5	45.3	35.7
T1b (%)	27	24.8	19.2
T2a (%)	8	8.5	4.5
T2b (%)	3	4	1.6
T3a (%)	20	12.8	36.5
T3b (%)	2	2.2	1.6
T3c (%)	0.5	0.5	0.3
T4 (%)	4	1.8	0.7

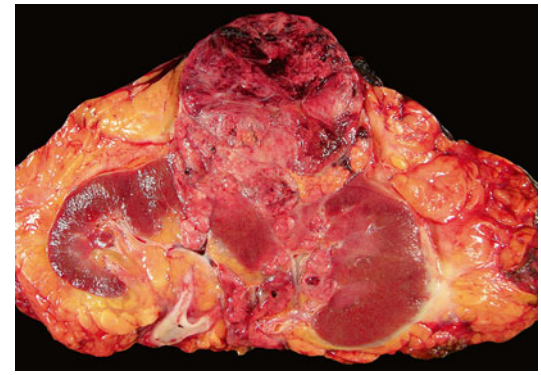

Fig. 4.8 T3a clear cell RCC with concomitant perinephric fat and renal sinus invasion

studies also showed differences in outcome between sinus and perinephric fat invasion (see validation studies below).

In the 2010 TNM system, both T3b and T3c encompass extension of the tumor into the vena cava. Studies have shown that prognoses are different for tumors involving the renal vein (T3a) and sub- (T3b) and supradiaphragmatic (T3c) levels of the vena cava [34–36]. Kim et al. [36] showed that patients with tumor thrombus involving the vena cava above the diaphragm had a significantly worse survival than with renal vein involvement and vena

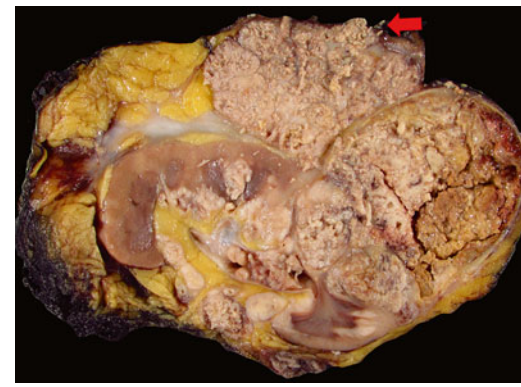

Fig. 4.9 T4 renal cancer extending into Gerota's fascia (*arrow*)

cava involvement below the diaphragm. Leibovich et al. [35] showed that renal cancer with tumor thrombus in renal vein only has better prognosis than patients with T3 renal cancers with tumor thrombus extending 2 cm or less above the renal vein or beyond to the level above the diaphragm. Ficarra et al. [34] showed survival differences between renal cancers with tumor thrombus in renal vein (T3a) or vena cava below the diaphragm (T3b) versus vena caval thrombus above the diaphragm (T3b). These studies led to the reclassification of renal vein invasion into pT3a in the 2010 TNM system (vs. pT3b in 2002 TNM system).

Invasion into Ipsilateral Adrenal Gland or Beyond Gerota's Fascia (T4)

Previous studies have shown that direct ipsilateral adrenal gland extension has poorer behavior than tumors involving the perinephric or sinus fat and is now lumped with tumor extending beyond Gerota's fascia (Fig. 4.9) [37–39]. Direct adrenal gland invasion is defined as contiguous spread of renal tumor through the peripheral perinephric fat into the ipsilateral adrenal gland [38]. Han et al. [37] showed a median survival of 12.5 months and 0 % 5-year CSS in renal cancer patients with adrenal gland involvement in contrast to a median survival of 36 months and a 36 % 5-year CSS for T3a renal cancer patients with perinephric or sinus fat invasion. The median survival of direct adrenal gland involvement is about similar to the median survival of tumors extending beyond Gerota's fascia (11 months) [37]. Thompson et al. [38] studied 424 renal cancer patients who underwent nephrectomy and adrenalectomy and showed that the CSS for tumors that directly invaded the adrenal gland (T4) was significantly worse compared with that of patients with perinephric, renal sinus, renal vein, or vena caval extension and without adrenal gland involvement (T3a–b). There was no difference in the 5-year CSS of patients with adrenal gland extension (20 %) and patients with extension beyond Gerota's fascia (14 %) [38]. Thus, ipsilateral adrenal gland extension was eventually designated as a T4 disease in the 2010 TNM system.

Regional Lymph Nodes and Distant Metastasis

The regional lymph nodes for renal cancers include the hilar, caval (paracaval, precaval, and retrocaval), interaortocaval, and aortic (paraaortic, preaortic, and retroaortic) lymph nodes. The primary landing zone considered for right-sided renal tumors is the interaortocaval zone and for left-sided tumors is the aortic region; however, the patterns of tumor spread can be unpredictable. The 2010 TNM system lumps any positive lymph nodes altogether (N1 vs. N0), since most studies showed that any extent of lymph node involvement portends a poorer outcome.

Common distant metastatic sites for renal cancer are the bone, liver, lung, and brain. Involvement of distant or non-regional lymph nodes is staged as M1.

Pathologist Handling of Kidney Resections for Staging Adequacy

Appropriate specimen handling is critical to the adequate pathologic staging of tumor nephrectomy specimens. In 2012, the ISUP held a consensus conference for the new classification of renal neoplasia [1]. Also covered in the consensus meeting is the pathological staging and specimen handling of renal tumors [29]. For specimen handling, it was agreed that kidneys with tumor should be sectioned along the long axis and perinephric fat extension should be determined by examining multiple perpendicular sections of the tumor/perinephric fat interface as well as areas that are suspicious for invasion. When measuring a renal tumor, the renal vein/vena caval thrombus, if present, is discounted from the measurement. Renal tumors should be sampled 1 block/cm with a minimum of 3 blocks per tumor. Recognizing the difficulty in identifying sinus invasion, the consensus recommended that at least 3 blocks of tumor-renal sinus interface should be submitted. If renal sinus invasion is grossly discernable, examination of one block of renal sinus tissue with tumor will suffice. When a caval thrombus is submitted by the surgeons for

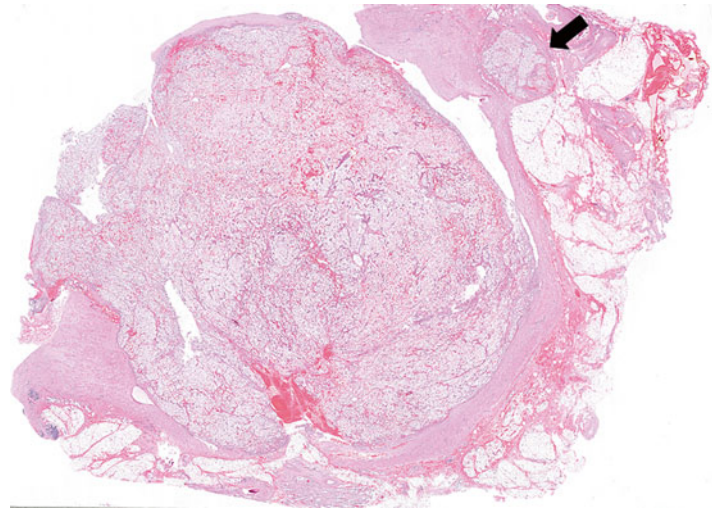

Fig. 4.10 Section of the renal vein margin containing a tumor thrombus. This margin is considered positive because of tumor infiltration to the wall that is present at the margin (*arrow*)

Table 4.6 Cancer-specific survival of renal cancer patients by pathologic T stage

pT stage	5-Year CSS		10-Year CSS
	Novara et al. (2010) [23]	Lee et al. (2011) [24]	Kim et al. (2011) [40]
T1a (%)	94.9	–	96
T1b (%)	92.6	–	80
T2a (%)	85.4	83.2	66
T2b (%)	70	83.8	55
T3a (%)	64.7	62.6	36
T3b (%)	54.7	41.1	26
T3c (%)	17.9	50	25
T4 (%)	27.4	26.1	12

pathological examination, the recommendations is to submit at least two sections to look for wall invasion (classified as pT3c if present). Another recommendation is regarding the definition of a positive renal vein/caval margin in the presence of a tumor thrombus. It is not uncommon that a tumor thrombus when present may hang freely beyond the renal vein/caval resection margin, and such should not be automatically considered as a positive renal vein/caval margin. Renal vein/caval margin is considered positive only when there is adherent tumor visible microscopically at the actual cut margin (Fig. 4.10) [29].

Validation Studies of the 2010 TNM Staging System

After its publication, several studies were conducted assessing the prognostic ability across all or select categories of the 2010 TNM system. The CSS of the different T categories in recent studies is presented in Table 4.6. While these studies were able to demonstrate the prognostic ability of the 2010 TNM system, its differences from the 2002 TNM system are only modest at best.

In a large multi-institutional study in Italy that included 5339 renal cancer patients, the 2010 TNM system was shown to be a strong predictor of CSS [23]. The substratification of T1 (T1a vs. T1b) tumors however was not retained as an independent prognostic variable. When only the non-metastatic tumors were considered, the survival differences between T1a and T1b, T2b and T3a, T3a and T3b, and T3c and T4 were not statistically significant. T3a was shown to be heterogeneous with renal vein invasion having a significantly higher CSS, followed by tumors with perirenal involvement and by those with both of these features present. The differences in the CSS of renal cancers with renal vein (T3a), infradiaphragmatic (T3b), and supradiaphragmatic vena caval thrombus (T3b) were statisti-

cally significant; however, these differences did not hold true in non-metastatic renal cancers.

In the study by Kim et al. [40] of 3996 renal cancer patients from a large tertiary institution, the 2010 TNM system likewise retained its robust predictive ability for CSS; however, it showed only modest improvement compared to the 2002 TNM system. The aggregation of nodal involvement to N0 or N1 did not contribute to any increase in the predictive ability than in the prior N subcategories. The T3a category was again shown to be heterogeneous where renal cancers with level 0 thrombus and no fat invasion had better CSS than patients with fat invasion only, while renal cancers with both level 0 thrombus and fat invasion had the poorest CSS.

In the study by Lee et al. [24] of 1691 renal cancer patients from Korea, the 2010 TNM system offered a good statistical power in predicting CSS; however, the findings suggested that the predictive ability of 2010 TNM system is not superior to that of the 2002 TNM system. The study also showed that the CSS of T2a and T2b renal cancers did not differ significantly. Pichler et al. [25] in another study of 2739 renal cancer patients from Austria showed the predictive ability of the 2010 TNM system for overall survival, CSS, and metastasis-free survival in renal cancers. However, the use of the 2010 TNM system was not associated with a net benefit in predicting these three clinical end points when compared with the 2002 TNM system [25]. In terms of metastasis-free survival, significant differences were observed for T1a versus T1b, T3a versus T3b, and T3b versus T3c [25]. The same authors showed similar lack of predictive advantage of the 2010 TNM system, specifically in clear cell RCC or in papillary RCC, regarding CSS compared to the 2002 TNM system [41].

Other studies focused only on some of the categories of the 2010 TNM system. Ingimarsson et al. [42] showed that the probability for synchronous metastases increased in a nonlinear fashion with increasing tumor size according to the 2010 TNM size cutoffs (T1a, T1b, T2a, and T2c) and that tumor size affected the probability of the disease-specific mortality. Bianchi et al. [43] showed the 10 cm cutoff for T2 tumors as an independent predictor of cancer-specific mortality; however, higher discrimination was achieved with either 9 or 11 cm cutoffs. In contrast, Waalkes et al. [44] in a study of 579 T2 renal cancer patients showed no significant difference in CSS between T2a and T2b.

Chevinsky et al. [45] in a study of 1809 T1–T3 renal cancer patients showed that T3a tumors had a greater risk of tumor recurrence than T1/T2 tumors. The risk of disease recurrence increased more rapidly as tumor size increased only with the presence of perinephric fat invasion. Veeratterapillay et al. [46] likewise showed that T3a and T3b were both significantly worse than T1 in the 2010 TNM system that were not demonstrated with the 2002 TNM stage. In a large multi-institutional study of 7384 T1a–T3a renal cancer patients pooled from 12 centers, the T3a tumors were grouped into those with perinephric fat invasion only (group 1) and those with renal vein invasion with or without perinephric fat invasion (group 2) [47]. The cancer-specific mortality was significantly higher for both group 1 and group 2 renal cancers compared to T1–T2 renal cancers. The cancer-specific mortality for group 1 and group 2 renal cancers did not differ, thus supporting the merging of perinephric fat invasion and renal vein invasion under a single stage category (pT3a) in the 2010 TNM system.

In a multi-institutional study that included 1215 renal cancer patients who underwent radical nephrectomy and tumor thrombectomy, the tumor thrombus level was shown to be an independent predictor of survival [48]. The 5-year survival of renal vein involvement (T3a), vena cava below diaphragm (T3b), and vena cava above diaphragm (T3c) were 43.2 %, 37 %, and 22 %, respectively. This finding supported the separation of these levels of vascular involvement in the 2010 TNM system.

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