Invasive Carcinoma of Renal Tubular Origin Histopathology Reporting Guide Family/Last name Date of birth DD – MM – YYY) Given name(s) Patient identifiers Date of request Accession/Laboratory number DD – MM – YYYY Elements in **black text** are REQUIRED. Elements in grey text are RECOMMENDED. **PRE-OPERATIVE TREATMENT** (Note 1) TUMOUR SITE(S) (Note 5) Tumour embolization Not specified Upper pole) Not provided Cryoablation Mid zone Cannot be assessed Radio frequency ablation Lower pole External-beam radiation therapy (EBRT) Cortex Other, *specify* Medulla Other, specify **SPECIMEN LATERALITY** (Note 2) TUMOUR FOCALITY (Note 6) 🔵 Left Not specified Unifocal Cannot be assessed Right Multifocal Other eg horseshoe kidney, specify Specify number of tumours (if possible) **OPERATIVE PROCEDURE** (Note 3) MAXIMUM TUMOUR DIMENSION (Note 7) Radical nephrectomy Not specified (If multiple tumours the maximum dimension of the Simple nephrectomy largest five should be recorded.) Partial nephrectomy Other, specify Tumour 1 mm Tumour 4 mm Tumour 2 Tumour 5 mm mm Tumour 3 mm ACCOMPANYING/ATTACHED STRUCTURES Adrenal gland None submitted Lymph nodes, *provide details* HISTOLOGICAL TUMOUR GRADE - WHO/ISUP (Note 8) Not applicable) Grade X - Cannot be assessed Uther organs, *provide details* Grade 1 - Nucleoli absent or inconspicuous and basophilic at 400x magnification Grade 2 - Nucleoli conspicuous and eosinophilic at 400x magnification, visible but not prominent at 100x magnification Grade 3 - Nucleoli conspicuous and eosinophilic at 100x magnification TISSUE REMOVED FROM SPECIMEN PRIOR TO SUBMISSION (Note 4)

Grade 4 - Extreme nuclear pleomorphism and/or multi nuclear giant cells and/or rhabdoid and/or sarcomatoid differentiation

)Yes, provide details

) No

Not stated

HISTOLOGICAL TUMOUR TYPE**					
(Value list from the World Health	EXTENT OF INVASION (Note 16)				
of Tumours of the Urinary System and Male Genital Organs, Fourth edition (2016) classification of renal cell tumours and the International Society of Urological Pathology Vancouver classification of renal neoplasia)		Tumour limited to the kidney			
		Tumour spread b	eyond renal	capsule	
**Occasionally more than one histologic type of carcinoma occurs within the same kidney specimen. Each tumour type		○ Not identified	OPresent	Cannot be assess	ed
should be separately recorded.		Tumour in renal	sinus		
Clear cell renal cell carcinom	Clear cell renal cell carcinoma		Not identified Cannot be assessed		
	ell neoplasm of low malignant	OPresent in fat		\bigcirc	
potential		Present in vascular spaces			
Papillary renal cell carcinoma		Present in fat and vascular spaces			
Type 1					
Type 2		Tumour extends	beyond Ger	ota's fascia	
Oncocytic			~		
NOS		Not identified	OPresent	Cannot be assess	sea
	Chromophobe renal cell carcinoma		voine (rone	l voin or ite commoni	
Hybrid oncocytic chromo	phobe tumour	Tumour in major veins (renal vein or its segmental branches, inferior vena cava)			
Collecting duct carcinoma		○ Not identified	O Present	Cannot be assess	ad
Renal medullary carcinoma MiT family translocation rena		O Not identified	OPresent		eu
		Tumour in renal			
Xp11 translocation renal t(6;11) renal cell carcino				\bigcirc	
\Box ((6;11) renal cell carcino \Box Other, <i>specify</i>	ma	 Not identified 	O Present	Cannot be assess	ed
Other, specify					
		Tumour in pelvic	alyceal syste	em	
		Not identified	Present	Cannot be assess	ed
Mucinous tubular and spindle		Tumour in adrena	al gland		
 Tubulocystic renal cell carcinoma Acquired cystic disease associated renal cell carcinoma 		Not provided		Cannot be asses	sed
Clear cell papillary/tubulopap		Not identified			Jea
Hereditary leiomyomatosis a		Present - direct	ovtoncion		
associated renal cell carcinon		Present - metas			
Succinate dehydrogenase (SI		Present - metas	stasis		
Renal cell carcinoma, unclass					
Other, <i>specify</i>		Tumour in other	organs/stru	ctures	
• • • • • • • • • • • • • • • • • • •		Not provided		Cannot be asses	sed
		Not identified			
		Present, specify	' sites		
		▼			
SARCOMATOID MORPHOLOGY (Note 10)				
Not identified					
Present					
Extent of environmeteral		LYMPHOVASCULAR	INVASION (Note 17)	
Extent of sarcomatoid	%	LYMPHOVASCULAR I	INVASION (Note 17)	
Extent of sarcomatoid component (Note 11)	%		INVASION (Note 17)	
	%	ONot identified	INVASION (Note 17)	
	%	ONot identified	INVASION (Note 17)	
component (Note 11)		○Not identified ○Present	, , , , , , , , , , , , , , , , , , ,	,	
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○ T0 ○ T1	No evidence of primary tumour Tumour \leq 7 cm in greatest dimension, limited to
\bigcirc	Tumour \leq 7 cm in greatest dimension, limited to
○ T1a	che Runey
	Tumour \leq 4 cm in greatest dimension, limited to the kidney
○ T1b	Tumour > 4 cm but \leq 7 cm in greatest dimension, limited to the kidney
○ T2	Tumour > 7 cm in greatest dimension, limited to the kidney
() T2a	Tumour > 7 cm but \leq 10 cm in greatest dimension, limited to the kidney
○ T2b	Tumour >10 cm, limited to the kidney
⊖ T3	Tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
◯ ТЗа	Tumour extends into the renal vein or its segmental branches, or invades pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
⊖ T3b	Tumour extends into the vena cava below the diaphragm
⊖ T3c	Tumour extends into the vena cava above the diaphragm or invades the wall of the vena cava
⊖ T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regiona	al lymph nodes (pN)
	Regional lymph nodes cannot be assessed.
<u>́</u> N0	No regional lymph node metastasis
○ N1	Metastasis in regional lymph node(s)
Distant	metastasis (pM)
🔵 Not a	applicable
○ M1	Distant metastasis
Clis	sed with permission of the American College of Surgeons, hicago, Illinois. The original source for this information the AJCC Cancer Staging Manual, Eighth Edition (2016) ublished by Springer Science+Business Media.
	 T2a T2b T3 T3a T3a T3b T3c T4 Regiona NX N0 N1 Distant M1 ## Uic Gis

Scope

This dataset has been developed for excision specimens of the kidney. Urothelial carcinoma arising from the upper renal tract, Wilms tumours and other nephroblastic and mesenchymal tumours are not included. This dataset is designed for the reporting of a single laterality of specimen ie left or right. If both lateralities are submitted then separate datasets should be completed

Note 1 - Preoperative treatment (Recommended)

Reason/Evidentiary Support

Pre-operative treatments may significantly alter the gross and microscopic appearance of the tumour.

1 Back

Note 2 – Specimen laterality (Required)

Reason/Evidentiary Support

Specimen laterality information is needed for identification and patient safety purposes.

1 Back

Note 3 - Operative procedure (Required)

Reason/Evidentiary Support

The type of surgical procedure is important in determining the assessment of surgical margins. Specifically in the case of partial nephrectomy specimens it is important that the intra-renal surgical margin be carefully evaluated so as to ensure that no residual tumour is present in the remaining kidney.

A radical nephrectomy specimen is defined as a resection of Gerota's fascia and its entire contents including the kidney, perinephric fat and lymphatics and a length of ureter, and may or may not be accompanied by the adrenal gland.

A simple nephrectomy is the removal of a kidney only with a small length of ureter.

A partial nephrectomy specimen may vary from a simple enucleation of the tumour to part of a kidney containing variable portions of calyceal or renal pelvic collecting system.

1 Back

Note 4 - Tissue removed from specimen prior to submission (Recommended)

Reason/Evidentiary Support

Pathologic evaluation requires a detailed examination of the complete surgical specimen. If tissue has been removed prior to examination this could compromise diagnosis, staging and prognostic assessment.

Note 5 - Tumour site(s) (Recommended)

Reason/Evidentiary Support

The position of the tumour in relation to the boundaries of the kidney and the surgical resection margin for radical nephrectomy and partial nephrectomy specimens is important for staging purposes. The position of the tumour in relation to the renal cortex or medulla may also have diagnostic importance. This is especially important for small tumours where a site of origin within the medulla would support a diagnosis of collecting duct carcinoma or medullary carcinoma.¹

Locations of medulla and renal cortex should be mentioned under 'other (specify)'.

1 Back

Note 6 - Tumour focality (Required)

Reason/Evidentiary Support

Renal cell carcinomas are usually solitary, however, if multifocal tumours are present, this is important to record. Carcinomas in the setting of acquired cystic kidney disease are often multifocal. Multifocality may also be a clue that one may be dealing with hereditary renal cell carcinoma. Von Hippel Lindau, Birt-Hogg-Dube and hereditary papillary carcinoma syndromes are characteristically associated with multiple tumours.

In a case of multiple carcinomas, it is important to record the diagnostic and prognostic parameters associated with the most significant tumours (largest, highest pT-category, highest grade). The histological subtype of the tumours may be similar or different and occasionally diverse morpho-types may be found. When numerous carcinomas are present some authors have suggested that the details of the 5 largest tumours should be recorded.⁴

1 Back

Note 7 - Maximum tumour dimension (Required)

Reason/Evidentiary Support

The maximum dimension of the tumour is required for staging purposes as it constitutes the defining feature of the pT1 and pT2 categories of the TNM staging classification.² Further it has been shown that for clear cell renal cell carcinoma tumour size correlates with outcome as a continuous variable.³

Measurement of tumour size should be undertaken following detailed dissection of the gross specimen and the greatest dimension should be recorded. Tumour extending into extracapsular tissue and/or the renal sinus, in continuity with the primary tumour intra-renal should be included in the measurement. Tumour within the real vein should not be included in this measurement. If multiple tumours are present the greatest dimension of the five largest tumours should be recorded.⁴

🕇 Back

Note 8 - Histological tumour grade - WHO/ISUP (Required)

Reason/Evidentiary Support

Grade should be assigned based on the single high power field showing the greatest degree of nuclear pleomorphism.

This grading system is the World Health Organization/ International Society of Urological Pathology (WHO/ISUP) grading system for renal cell carcinoma which is recommended in the 2016 WHO.^{1,15} This system has been validated as a prognostic parameter for clear cell and papillary renal cell carcinoma.^{15,19,20} It has not been validated for other types of renal cell carcinoma but may be used for descriptive purposes.²¹ The current recommendation is that chromophobe renal cell carcinoma is not graded.^{1,22}

1 Back

Note 9 - Histological tumour type (Required)

Reason/Evidentiary Support

Many of the various sub-types of renal epithelial neoplasia exhibit differing clinical behaviour and prognosis.^{1,2,10-15} This has been confirmed in large single and multicentre studies for the main tumour sub-types. Several series have also clearly demonstrated that many of the newly described entities of renal malignancy have a prognosis that differs from that of clear cell renal cell carcinoma.¹⁵ In addition to this protocols for the various types of adjuvant anti-angiogenic therapy relate to specific tumour sub-types.¹⁶

The 2013 International Society of Urological Pathology (ISUP) Vancouver Classification of adult renal tumours identified an emerging/provisional category of renal cell carcinoma (RCC).⁹ While appearing distinctive, these rare tumours had not been fully characterized by morphology, immunohistochemistry and molecular studies. This category was also included in the fourth edition of the World Health Organization (WHO) classification of renal neoplasia. In the WHO classification oncocytoid RCC post-neuroblastoma, thyroid-like follicular RCC, anaplastic lymphoma kinase (ALK) rearrangement-associated RCC and RCC with (angio) leiomyomatous stroma are included in this category. These entities should be classified under 'other' with the name specified.

Papillary RCC has traditionally been subdivided into Type 1 and Type 2.¹⁷ Recent studies have shown these tumours to be clinically and biologically distinct. Type 1 tumours are associated with alterations in the MET pathway while type 2 tumours are associated with activation of the NRF2-ARE pathway. On the basis of molecular features type 2 tumours may be sub-divided into at least 3 subtypes.¹⁸ Type 1 and type 2 tumours show differing immunohistochemical staining with type 1 tumours more frequently expressing cytokeratin 7 in comparison to type 2.^{19,17,18}

Oncocytic papillary renal cell carcinoma is a category included in the fourth edition of the WHO renal tumour classification.¹ While not fully characterized, this tumour is best included in the broader papillary category.

Papillary RCC is associated with a more favourable outcome than clear cell renal cell carcinoma (ccRCC), collecting duct carcinoma and hereditary leiomyomatosis and renal cell carcinoma (HLRCC)^{1,15} Papillary subtyping is also of prognostic significance with type 1 tumours having a better prognosis then those with type 2 morphology.^{15,17,18}

Note 10 - Sarcomatoid morphology (Required)

Reason/Evidentiary Support

The presence of sarcomatoid morphology is seen in approximately 5% of renal cell carcinomas and is associated with a poor prognosis.^{15,23-26} Numerous studies have confirmed that sarcomatoid morphology may occur within any of the main subtypes of renal cell carcinoma and represents high grade disease.^{1,9} The five year survival for patients with sarcomatoid morphology is of the order of 15 to 22%.^{1,9,23-26} The outcome associated with sarcomatoid morphology is stage dependent.²⁷ The presence of sarcomatoid morphology is incorporated into the WHO/ISUP grading system (Grade 4).¹⁵

1 Back

Note 11 - Extent of sarcomatoid component (Recommended)

Reason/Evidentiary Support

While there is no recommended or agreed method to calculate the sarcomatoid component at this stage.¹⁵ It has been suggested that the proportion of tumour showing sarcomatoid differentiation has prognostic significance. In particular, significantly different survivals were demonstrated for tumours divided with a cutpoint of 50% sarcomatoid component.²⁶

1 Back

Note 12 - Rhabdoid morphology (Required)

Reason/Evidentiary Support

Similar to the sarcomatoid morphology, rhabdoid morphology is a feature of high grade disease.^{15,28} Tumours showing this phenotype resemble rhabdoid cells having bulky eosinophilic cytoplasm and an eccentric nucleus, often with a prominent nucleolus.^{1,9} Rhabdoid change is associated with a poor prognosis. It has been shown that 71% of patients with rhabdoid morphology developed metastases with a mean follow-up of 4.5 months. Within 2 years it was also noted that 43% of patients in this series had died, with a median survival rate of 8-31months.^{15,28-30} In approximately 25% of tumours with rhabdoid morphology, there is co-existing sarcomatoid carcinoma.¹ The presence of rhabdoid morphology is incorporated into the WHO/ISUP grading system (Grade 4).¹⁵

1 Back

Note 13 - Extent of rhabdoid component (Recommended)

Reason/Evidentiary Support

There is currently no firm evidence to demonstrate that the volume of cells showing rhabdoid morphology is of prognostic significance.¹⁵

Note 14 - Necrosis (Required)

Reason/Evidentiary Support

The presence of tumour necrosis has been shown to be a prognostic indicator for clear cell renal cell carcinoma and chromophobe renal cell carcinoma independent of tumour stage.^{15,35} Papillary renal cell carcinoma typically contains foci of necrosis, however the prognostic significance of this is, at best debated. At present it is recommended that the presence of both macroscopic and microscopic (coagulative) necrosis be recorded.¹⁵ For patients who have undergone pre-surgical renal embolization, the degree of tumour-related necrosis cannot be assessed.

1 Back

Note 15 - Extent of necrosis (Recommended)

Reason/Evidentiary Support

The presence of tumour necrosis has been shown to be a prognostic indicator for clear cell renal cell carcinoma and has limited or no prognostic implications for papillary renal cell carcinoma. It has been shown that tumour necrosis >10% is associated with a less favourable outcome, while for TNM stage 1 and 2 tumours a cutpoint of 20% of the area of the tumour showing necrosis has been suggested to have prognostic significance.³⁶ At present the prognostic significance of the amount of necrosis within a tumour is uncertain. Despite this it has been recommended that this be recorded as a percentage.¹⁵

1 Back

Note16 - Extent of invasion (Required and recommended)

Reason/Evidentiary Support

Macroscopic extent

The identification of tumour directly infiltrating the renal sinus or large vessels has prognostic significance and this information is required for staging purposes.^{2,5} Careful gross examination of the specimen to assess large vessel invasion for example of the renal vein or beyond (if applicable) should be undertaken.

The renal sinus is an important pathway of spread of renal cell carcinoma and is often an under-recognized phenomenon.⁶ The renal sinus fat should be carefully assessed and generously sampled in order to detect renal sinus fat involvement. There is evolving literature suggesting that renal sinus fat involvement predicts a more aggressive outcome than peripheral perinephric fat invasion.^{7,8}

When renal carcinoma involves the adrenal gland, it is important to document whether the involvement is contiguous spread of tumour or a separate (noncontiguous) nodule of carcinoma, the latter representing metastatic disease (pM1).²

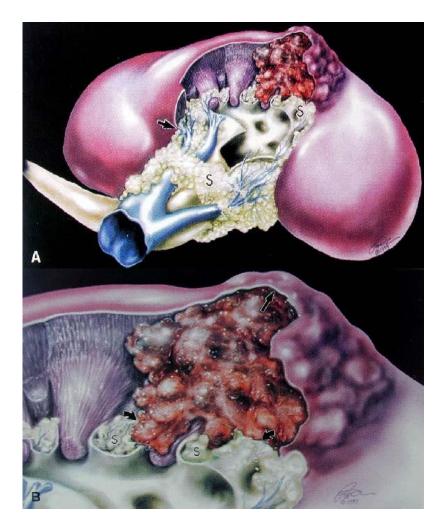


Figure 1.

A: Diagram showing the renal sinus fat (S) and its rich venous system that envelops the collecting system. The renal capsule terminates (arrow) just inside the vestibule of the hilus.

B: A renal malignancy is constrained by the renal capsule (arrow), yet no fibrous capsule impedes its growth into the vascular tissue of the renal sinus (curved arrows).

From Bonsib et al.⁶ The American Journal of Surgical Pathology. © 2000 Wolters Kluwer Health. Reproduced with permission.

Microscopic extent

Extra-renal extension of tumour is a feature of pT3 and pT4 staging categories of the TNM staging classification. Extension of tumour beyond Gerota's fascia is a feature of the pT4 staging category of the TNM staging system.²

The renal sinus is the compartment that lies between the renal parenchymal and the renal pelvis and calyces. This compartment contains varying amounts of fat and is rich in lymphatics. As a consequence infiltration of the renal sinus is the principal route for the extension of tumour beyond the kidney.³⁰ Renal sinus invasion is present when there is tumour in contact with renal sinus fat, loose connective tissue clearly beyond the renal parenchyma of the renal sinus and in endothelial-lined spaces (with or without mural smooth muscle) within the renal sinus.³⁰ This is most commonly seen in clear cell renal cell carcinoma and appears to be associated with tumour size. In particular it has been noted that in clear cell renal cell carcinomas \geq 7cm in diameter, renal sinus invasion was seen in > 90% of cases.^{7,8} Involvement of the renal sinus by tumour is a feature of pT3a tumour staging category of the TNM classification. It is likely that renal sinus invasion is preceded by involvement of renal sinus veins. It has also been shown that involvement of lymphatics within the renal sinus is of prognostic significance.³¹

If renal sinus invasion is seen on gross inspection of the specimen, then only one confirmatory section need be taken. If there is no evidence of renal sinus invasion grossly, then sampling should consist of at least three blocks of tissue.⁴

Macroscopic infiltration rather than microscopic evidence of invasion of the renal vein was a feature of pT3a in earlier editions of the TNM classification³², however, it has been shown that microvascular invasion correlates with outcome independent of T category, grade and perirenal fat invasion.⁴⁵ Further, it is appreciated that infiltration of the renal vein may be overlooked on gross examination. For this reason the qualifier "grossly", in relation to renal vein invasion, was removed as part of the definition of the pT3a staging category in the eighth edition of the AJCC staging system.

Adrenal gland: It is now recognized that direct spread of tumour to the ipsilateral adrenal gland has an outcome similar to pT4 tumour.^{33,34} In earlier TNM classifications this was included in the pT3a category, however, in view of these recent findings this was included as a feature of the pT4 category. In contrast a discrete, separate nodule in the adrenal gland is considered M1 disease.²

Other organs: The presence of metastatic disease is a feature of the pM1 staging category of the TNM staging classification.²

1 Back

Note 17 - Lymphovascular invasion (Recommended)

Reason/Evidentiary Support

Lymphovascular invasion includes intratumoral, peritumoral and perirenal space invasion.⁴ In the renal sinus, it may be difficult to distinguish microscopic lymphovascular invasion from involvement of thin walled veins lacking smooth muscle. From a practical perspective, the presence of either pattern should be considered as renal sinus involvement (pT3a).

Microvascular invasion has been shown to correlate with the development of metastases and with survival, independent of tumour size, primary tumour category, and grade.⁴⁰

In both clear cell and papillary RCC, tumour spread is predominantly haematogenous via the sinus veins, renal vein and vena cava to the lung. Infiltration of the perirenal fat can result in retroperitoneal spread. Lymphatic spread to the nodes of the renal hilum may also occur and is more common in papillary RCC than with ccRCC.²

1 Back

Note 18 - Lymph node status (Required and recommended)

Reason/Evidentiary Support

In earlier editions of the UICC/AJCC of the TNM classification, the number of lymph nodes infiltrated by tumour was used to differentiate the different pN categories. This has been simplified to now consist of presence or absence of lymph node involvement by tumour.¹ It has, however been shown that survival does decrease with an increase in the number of lymph nodes involved (>4).³⁷

Note 19 - Margin status (Required)

Reason/Evidentiary Support

Assessment of surgical margins is important in determining if residual tumour is present. In a partial nephrectomy specimen, the renal parenchymal margin should be inked and histologically assessed. Most partial nephrectomy specimens also contain a portion of perinephric fat overlying the tumour site. The perirenal fat margin should also be assessed. In situations where no perirenal fat is submitted, the renal capsular margin should be inked and examined histologically. In radical nephrectomy specimens the ureteric, major vascular (renal vein, renal artery) and soft tissue (Gerota's fascia, renal sinus) margins should be examined and documented in the report.

1 Back

Note 20 - Co-existing pathology in non-neoplastic kidney (Required)

Reason/Evidentiary Support

It is important to recognize that medical kidney diseases may be present in nonneoplastic renal tissue in nephrectomy and nephroureterectomy specimens.^{38,39} Arterionephrosclerosis (or hypertensive nephropathy) and diabetic nephropathy are seen in approximately 30% and 20% of cases, respectively. Other medical renal diseases that have been identified include thrombotic microangiopathy, focal segmental glomerulosclerosis, and IgA nephropathy. The findings of greater than 20% global glomerulosclerosis or advanced diffuse diabetic glomerulosclerosis are predictive of significant decline in renal function 6 months after radical nephrectomy.³⁹ Evaluation for medical renal disease should be performed in each case; PAS and/or Jones methenamine silver stains should applied if necessary. Consultation with a nephropathologist should be pursued as needed.

1 Back

Note 21 - Ancillary studies (Recommended)

Reason/Evidentiary Support

Ancillary studies are being increasingly utilized for subtyping of renal cell neoplasms. Fluorescent in-situ hybridization (FISH) can be used to confirm a diagnosis of translocation carcinoma (MiT family tumour) and has been shown to be of utility in distinguishing oncocytoma from chromophobe renal cell carcinoma.¹ Cytogenetics may be undertaken in some instances; however, this is not usually performed as part of the routine assessment of a renal tumour. It is now recognized that immunohistochemical assessment of tumours can be diagnostically helpful. There are currently no ancillary tests that are accepted as having prognostic significance for renal cell neoplasms.^{41,42}

Note 22 - Pathologic Staging (TNM 8th edition) (Required)

Reason/Evidentiary Support

This dataset includes the AJCC TNM 8th edition² definitions. The implementation of AJCC TNM 8th edition has been deferred until January 2018 in some jurisdictions. UICC 7th edition⁴³ or AJCC 7th edition⁴⁴ may be useful in the interim.

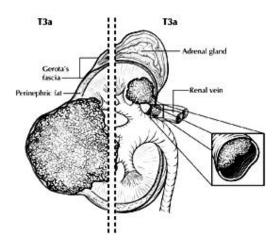


Figure 2: T3a Invasion into perirenal and/or renal sinus fat but not beyond Gerota's fascia.

Figure 3: T4 Invasion beyond Gerota's fascia.

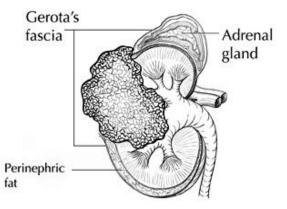
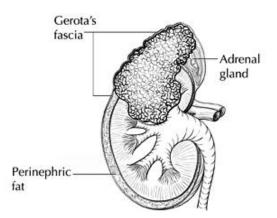


Figure 4: T4 Direct extension of tumour into ipsilateral adrenal gland.



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