

## Renal Cancer

### Demographics

3% of all cancers in US. 7<sup>th</sup> leading cancer in men and 9<sup>th</sup> leading cancer in females

Peak age 60-70

Male-female ratio ~2:1

Western World

Increasing incidence associated with improved 5YS – presumed 2' to more imaging

### Aetiology

Smoking – RR 1.4-2.3

Obesity

Hypertension

Dialysis – with native kidneys in situ (3-6x increased risk)

Heredity (2% of all RCC)

- VHL disease

- Hereditary Papillary Renal Carcinoma (HPRC)

- Hereditary Leiomyomatosis & Papillary RCC (HLRCC)

- Birt-Hogg Dube syndrome

### Presentation

Incidental finding in over 50% [Novick 1999]

Haematuria

Loin Pain

Palpable Mass

Classical Triad of haematuria, loin pain, mass in 10%

Paraneoplastic syndromes

- Hypercalcaemia (PTHrP) – seen in approximately 25%

- Anaemia

- Hyponatraemia

- Raised ESR

- Polycythaemia - may be associated with increased response to IFN

- Stauffer's syndrome

  - Abnormal LFTs

  - Hepatic necrosis

  - Thrombocytopenia

  - Neutropenia

  - Fever

  - Weight loss

  - ? secondary to elevated IL-6. Majority of cases respond to nephrectomy but poor prognostic sign

Occasionally metastatic disease (found in 30% when looked for)

## Pathology

### Heidelberg Classification 1997

#### Sporadic Renal Cell Carcinoma:

Conventional clear-cell	75%	(60% VHL mutation)
Papillary	12%	(13% MET oncogene mutation)
Chromophobe	4%	
Collecting Duct	1%	
Unclassified*	3-5%	

\* One recently characterised tumour is renal medullary carcinoma

#### Features

Blacks

Almost exclusively with sickle cell disease

Third decade of life

Usually widespread metastasis

Highly aggressive and resistant to conventional Rx

Life expectancy a few months

#### RCC as an inherited syndrome:

VHL disease (clear-cell)

Familial clear cell renal cancer

HPRCC (papillary)

HLRCC (papillary)

Birt-Hogg-Dube (chromophobe or oncocytoma)

VHL gene mutation/deletion

chromosome 3p translocation

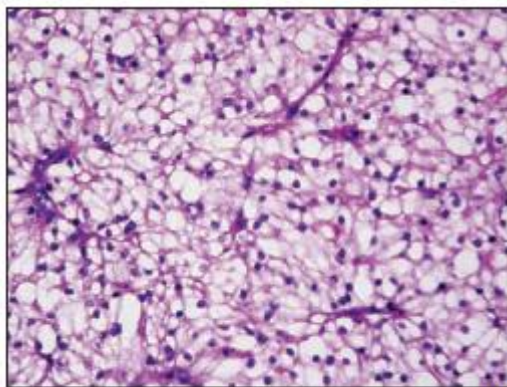
MET oncogene

Fumarate hydratase gene

BHD gene

### Conventional or clear-cell RCC

Derived from cells of proximal convoluted tubule. Large cells typically full of glycogen and cholesterol, do not take up stain, thus clear. Almost always positive for cytokeratin 8/18 and 50% positive for vimentin. Abundant mitochondria on EM. Associated with VHL gene defects in up to 60% of sporadic cases. Presence of spindle cells (sarcomatoid variant – 5% CCRCC) associated with worse prognosis.



A

VHL disease and the hypoxia-inducible factor pathway

Rare autosomal dominant genetic disease

1 in 36,000 live births

Characterised by inheritance of mutated VHL tumour suppressor gene on short arm of chromosome 3 (3p25-26)

50% chance of offspring inheriting defective gene

Disease results from inactivation or silencing of normal (wild-type) allele

25-50% of VHL 'carriers' will get RCC in lifetime. 70% risk aged 60.

3 major manifestations of VHL disease: Clear-cell RCC; CNS haemangioblastomas [retina, cerebellum]; pheochromocytoma

Also hepatic and pancreatic cysts

VHL classification

Type 1	Most common Due to major disrupting mutation e.g. truncation Associated HIF- $\alpha$ upregulation Clear-cell RCC with CNS haemangioblastoma
Type 2	Uncommon More subtle mutations e.g. missense mutations Pheochromocytoma +/- other
2a	Phaeo and CNS haemangioblastoma
2b	Phaeo, clear-cell RCC and CNS haemangioblastoma
2c	Phaeo alone

Hypoxia inducible factor is a crucial regulator of the hypoxic response. Normally, in conditions of low oxygen tension, HIF $\alpha$  binds to HIF $\beta$ , translocates to the nucleus and binds to a specific HIF response element (HRE) on the promoter of a number of hypoxia inducible genes. Examples include VEGF, PDGF, Epo, TGF- $\alpha$ , GLUT-1 (glucose transport) and carbonic anhydrase 9. HIF- $\alpha$  subunits (three have been described to date, HIF-1 $\alpha$ , HIF-2 $\alpha$  and HIF-3 $\alpha$ ) appear to be subject to regulation by VHL, rather than constitutively expressed HIF- $\beta$ .

VHL functions to inhibit HIF-1 $\alpha$ . In normoxia, HIF-1 $\alpha$  is hydroxylated (-OH added) by proline and asparagine hydroxylases. VHL binds to hydroxylated proline residues on HIF- $\alpha$ , and in association with elongins B and C and Cul2, marks it for ubiquitination and subsequent destruction by the 26S proteasome. VHL defects thus lead to inappropriate HIF-1 $\alpha$  upregulation in normoxic conditions.

Papillary RCC (chromophilic)

Associated with loss of chromosome 4 and Y, trisomy 7 & 17

Mutation of C-MET proto-oncogene (C-MET gene identified on chromosome 7q31.1-35) in 13%.

Associated with acquired cystic disease and ESRF

Multicentricity in 40%

Cell of origin controversial. Campbells - proximal convoluted tubule. Others think derived from distal convoluted tubule.

Two types described:

Type 1 (figure B)

Basal cells

Basophilic cytoplasm (H&E)

Benign cf. type 2

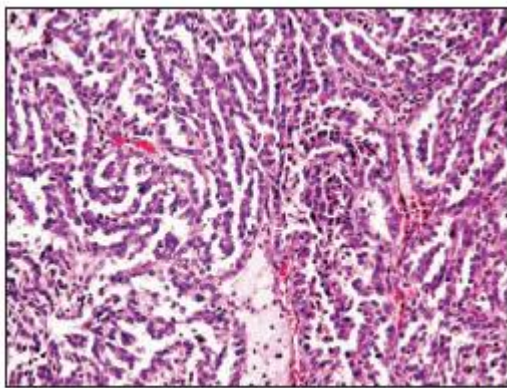
Type 2 (figure C)

Extra cell layers

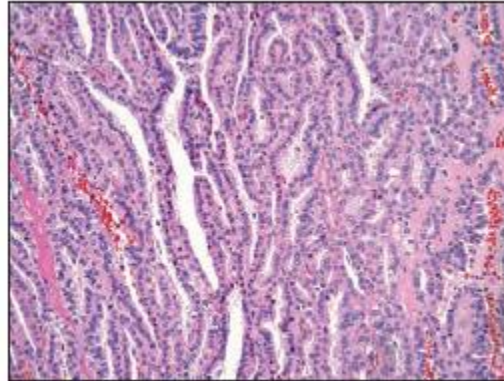
Eosinophilic cytoplasm

Earlier metastasis cf. type 1

Clinical behaviour of papillary RCC controversial. Some authors report improved behaviour vs. CCRCC whilst other do not. Probably due to failure to subdivide papillary RCC into type 1 and 2.



B



C

#### Hereditary papillary RCC (HPRCC)

First reported in 1995 (Zbar 1995)

Type 1 papillary RCC

Autosomal dominant transmission

C-MET gene mutation on chromosome 7q31.1-35 (protein product = tyrosine kinase receptor for hepatocyte growth factor)

Early onset, multifocality and aggression common features

Also associated with ca breast, pancreas, lung (SCC)

#### Hereditary leiomyomatosis and renal cell cancer (HLRCC)

Aka Lynch syndrome

Type 2 papillary RCC – most aggressive inherited RCC cancer syndrome

Autosomal dominant transmission (mutated Fumarate Hydratase (FH) gene on 1q42.3-q43)

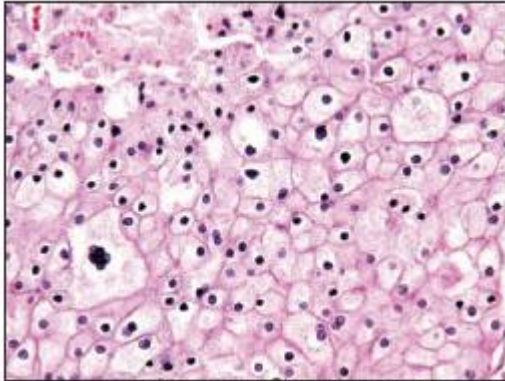
Cutaneous leiomyomata, uterine fibroids, papillary RCC

#### Chromophobe RCC

First reported in 1985

Derived from cortical portion of collecting ducts

Typically large polygonal cells with relatively unstained cytoplasm (chromophobe) and reticular growth pattern reminiscent of plant cells (figure D)  
Eosinophilic variant which can be difficult to distinguish from oncocytoma, but Ultrastructurally packed with microtubules (cf. mitochondria in oncocytoma)  
Associated with LOH 3p, 5p and 17p  
Clinical behaviour poorly characterised. Thought to be of less malignant potential than conventional clear cell RCC and papillary RCC.



#### Birt-Hogg-Dube syndrome

BHD gene identified on chromosome 17p11.2  
Gene encodes ubiquitously expressed protein (folliculin)  
Hair follicle tumours (forehead, ears, nose, cheeks and neck)  
Spontaneous pneumothorax  
Renal tumours: oncocytoma; chromophobe, clear cell, papillary RCC

#### Collecting Duct

Arise from medullary collecting duct  
Usually younger patients  
Aggressive growth  
Positive staining for ulex europeus lectin differentiates collecting duct carcinoma from TCC

#### Oncocytoma

Benign growth  
Mahogany brown tumour  
Derived from distal convoluted tubule  
Uniform round, polygonal cells with dense eosinophilic staining  
Packed with mitochondria at ultrastructural level  
Different genetic profile for sporadic oncocytoma cf. BHD. Defects on chromosome 1, Y, and the long arms of chromosomes 11 and 14  
Little cytological atypia  
May have central necrosis and stellate scar on CT but predictive value poor  
Difficult to differentiate from granular clear-cell RCC or eosinophilic chromophobe RCC on biopsy

Co-exists with RCC in 7-32% of cases [Campbells]. Therefore surgical treatment advocated – partial if strongly suspected (BHD and features) and favourable location

## Radiologic evaluation

### Ultrasound

Simple

Non-ionising

Good for distinguishing solid, cystic and complex masses

Features of benign cyst:

Round/oval shape

No internal echoes

Smooth well-defined wall

Acoustic shadow from wall edges only

Good US transmission

US combined with CT characteristics formed the basis of original Bosniak cyst classification (Bosniak 1986). No problems assigning cysts to Category 1 & 4 assuming good quality USS/CT, but due to difficulties characterising 2 & 3, led to the introduction of intermediate category of 2F (Bosniak 1997)

TABLE 1 The Bosniak classification of renal cysts

Bosniak category	Features
I	A simple benign cyst with a hairline thin wall that does not contain septa, calcification or solid components. It measures as water density and does not enhance with contrast material.
II	A benign cyst that might contain a few hairline thin septa. Fine calcification might be present in the wall or septa. Uniformly high-attenuation lesions of <3 cm that are sharply margined and do not enhance.
IIF	These cysts might contain more hairline thin septa. Minimal enhancement of a hairline thin septum or wall can be seen and there might be minimal thickening of the septa or wall. The cyst might contain calcification that might be nodular and thick but there is no contrast enhancement. There are no enhancing soft-tissue elements. Totally intrarenal non-enhancing high-attenuation renal lesions of $\geq 3$ cm are also included in this category. These lesions are generally well margined.
III	These lesions are indeterminate cystic masses that have thickened irregular walls or septa in which enhancement can be seen.
IV	These lesions are clearly malignant cystic lesions that contain enhancing soft-tissue components.

Reference	Bosniak cat., n malignancies/N in group				TABLE 3 Summary of studies correlating pathology with Bosniak category
	I	II	III	IV	
[5]	0/22	1/8	5/11	26/29	
[15]	-	0/4	4/7	5/5	
[16]	1/2	1/7	4/13	7/10	
[17]	0/7	4/5	4/4	6/6	
[18]	0/15*	-	29/49	18/18	
[19]	-	3/28	8/29	-	
[20]	-	-	28/179†	-	
[21]	-	-	17/28	-	
[23]	0/11	1/2	10/10	12/12	*category I and II combined;
Total	1/57	10/54	109/330	74/80	†category II and IIF combined.
% malignancy	1.7	18.5	33.0	92.5	

Warren 2004

Meta-analysis of all studies validating Bosniak classification shown above. NB. All suffer from retrospective selection bias and surgery selection bias. Thus, values in category 1 and 2 likely to be an over-estimation as do not account for patients entering surveillance without biopsy/extirpation. Also reference 17 above is likely to give an artificially high rate of malignancy for category 2 tumours.

In fact Campbell's quotes quite different rates of malignancy:

Bosniak Classification	Radiographic Features	Risk of Malignancy	Management
I	Water density	None	Only if symptomatic
	Homogeneous		Surveillance not necessary
	No septa		
	No calcification		
	No enhancement		
II	Thin septa	0%-5%	Periodic surveillance
	Thin, curvilinear calcification		
	No enhancement		
	Hypodense lesion with no enhancement	0%-5%	Periodic surveillance
III	Thick or irregular septa	50%	Surgical excision
	Thick or irregular calcification		
	Mild to moderate heterogeneity		
	No enhancement		
IV	Thick walls or nodular areas	75%-90%	Surgical excision
	Marked heterogeneity		
	Enhancement		

#### Other techniques for evaluating indeterminate (category 2/3) cysts?

CT-guided biopsy: Lang 2002 – Bosniak 2F/3. 199 biopsies. Adequate material in 90%. **Sensitivity for malignancy only 70%, positive predictive value 91%**, specificity & negative predictive value (reported as sensitivity and PPV for benign disease approximately 90%); Harisinghani 2003. Bosniak 3, n= 28. adequacy in 100%, incidence of malignancy 61%. No follow-up tumours. Surgery therefore avoided in 39%.

Laparoscopic biopsy: Limb 2002 – Described feasibility (n=57 Bosniak 2&3). 8 (20%) cancers detected. No port site recurrences.

#### Computed tomography

Investigation of choice for staging of renal tumours

CT protocol:

Unenhanced scan

IV contrast runs

Arterial phase	15-30s
Late arterial (portal venous)*	45-60s
Nephrographic phase	75-90s
Excretory phase**	180s



\*evaluation of liver metastases/other organ mets in this phase

\*\* evaluation of urinary tract through to bladder in this phase

3D multiplanar reformats typically 1.5mm slices with 50% overlap

Unenhanced scans important to exclude hepatic mets. RCC mets typically hypervascular. Therefore enhance with rest of liver after IV contrast.

CCRCC enhances > other histologic subtypes: Kim 2002 = increased attenuation of  $\geq 84$ HU highly specific (100%) for clear cell RCC cf. other subtypes

Central stellate scar not unique to oncocytomas – can be seen in necrotic CCRCC

Oral contrast typically given to identify duodenum

Many centres give 2 doses of IV contrast 3-5 mins apart (double-dose contrast scanning) and scan after second dose, thereby gaining portal venous and excretory information in one scan, limiting radiation dose.

NB. Metastatic non-renal cancer involving kidney 8-13% in some series.

Enhancement and absence of other non-renal mets increases likelihood of primary RCC. In one series of 100 patients with primary extrarenal cancer and a lump in the kidney, 86% of non-enhancing tumours and 31% on enhancing tumours were secondary deposits. All patients had evidence of other non-renal mets. In those with a primary non-metastatic cancer and solitary renal mass, the solitary renal mass was a RCC in all cases (Campbell's).

CT very good for determining renal vein/IVC involvement and involvement of adjacent organs. Higher false positives for lymph node metastases and capsular breach.

### MRI

Equivalent staging accuracy to CT (Beer 2006)

Less sensitive for solid lesion < 3 cm

Better cf. CT and Doppler USS for determining superior extent of IVC involvement (coronal plane)

Clinically used for patients with renal insufficiency/pregnancy in whom CT/iodinated contrast contraindicated

NB. Increasing awareness of risk of nephrogenic systemic fibrosis (NSF) with gadolinium based contrast agents: severe multisystem disease associated with fibrosis and skin rashes – usually in patients with significantly reduced GFR and multiple exposure.

### Renal mass biopsy for non-cystic mass lesions

Limited usage until recently for a number of reasons:

- High false negative rates

- High perceived rate of complications

- 80-90% solid enhancing renal masses malignant

- No suitable alternative to surgical extirpation so would not change Mx

Recent advances have led to a desire for pre-operative diagnosis

Minimally invasive NSS, particularly ablative therapies such as cryoablation and RFA  
 Observation that a significant proportion of SRMs are benign or low grade, raising prospect of surveillance vs. surgery (Frank 2003)  
 TKI therapy currently subtype specific  
 Recent marked improvements in renal mass biopsy. Excellent review article by Lane 2008 assessing role of biopsy in multiple studies before and after 2001:

	<2001	2001 +
Technical failure rate	8.9%	3.5%
Inadequate/indefinite	5.5%	11%
False negative rate	4.4%	0.7%
Accuracy*	88%	88%

\* Accuracy is the number of correct diagnoses (true positive and true negative / all results and all indeterminate)

**Prognostic factors**

Most important prognostic factors:

- T stage
- Fuhrman grade
- Cell type

**Staging**

Robson staging system (1968) historically used

- Stage 1 – Tumour confined to kidney
- Stage 2 – Tumour invasion of perinephric fat
- Stage 3 – Tumour involvement of regional LN, renal vein or IVC
- Stage 4 – Tumour beyond Gerota's or distant mets

Fell out of favour – limited as survival in stages 2 and 3 could be equivalent.  
Therefore TNM developed for renal cancer in 1978

**T - Primary tumour**

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Tumour  $\leq$  7 cm in greatest dimension, limited to the kidney

T1a Tumour  $\leq$  4 cm in greatest dimension, limited to the kidney

T1b Tumour  $>$  4 cm but  $\leq$  7 cm in greatest dimension

T2 Tumour  $>$  7 cm in greatest dimension, limited to the kidney

T2a Tumour  $>$  7 cm but  $\leq$  10 cm in greatest dimension

T2b Tumours  $>$  10 cm limited to the kidney

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

T3a Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia

T3b Tumour grossly extends into the vena cava below the diaphragm

T3c Tumour grossly extends into 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)

**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

**M - Distant metastasis**

M0 No distant metastasis

M1 Distant metastasis

**Stage grouping and prognosis**

Stage 1	Tumour 7cm or less confined to kidney	95% 5YS
Stage 2	Tumour greater than 7cm confined to kidney	88% 5YS

Stage 3	Into perinephric fat, adrenal or major veins, or 1 LN	59% 5YS
Stage 4	Beyond Gerota's or >1 LN involved or M1	20% 5YS

### Staging stats

Asymptomatic	>80% 5YS	
Symptomatic	50% 5YS	
Size < 5cm	84% 5YS	
Size 5-10 cm	50% 5YS	
Size > 10cm	0% 5YS	(Guinan 1995)
Fuhrman grade		
	1	76% 5YS
	2	72% 5YS
	3	51% 5YS
	4	35% 5YS (Bretheau 1995)
Venous tumour thrombus	45-69% 5YS	(provided tumour confined to kidney)
Venous wall invasion	25% 5YS	(Hatcher 1991)
LN positivity	5-30% 5YS	
	0-5% 10YS	
Systemic mets	50% 1YS	
	5-30% 5YS	
	0-5% 10YS	

### Histology

Fuhrman grade (Fuhrman 1982) most widely accepted histological grading system. Four nuclear grades defined in order of increasing nuclear size, irregularity and nucleolar prominence (see below). Independently prognostic on long-term multi-centre evaluation (Lang 2005); improved intra- and inter-observer correlation when grouped into low grade (Fuhrman 1&2) and high-grade disease (Fuhrman 3&4) without compromising prognostic significance.

Nuclear grade was determined using the criteria proposed by Fuhrman et al.<sup>3</sup> Grade 1 tumors were composed of cells with small (~10 μm), round, uniform nuclei and inconspicuous or absent nucleoli; Grade 2 tumor cells had larger (~15 μm) nuclei with irregular outlines and nucleoli that were visible under high-power (400×) microscopy; Grade 3 tumor cells had even larger nuclei (~20 μm) with obviously irregular outlines and prominent nucleoli even under low-power (100×) microscopy; and Grade 4 tumors exhibited features similar to those of Grade 3 tumors but also had bizarre, often multilobed nuclei and heavy chromatin clumps.

Cell type: many studies show a trend towards improved prognosis for chromophobe > papillary type 1 > papillary type 2 = CCRCC > collecting duct

carcinoma. NB. Prognostic effect of cell type disappears when controlled for T-stage. Spindle cell component also confers worse prognosis.

ECOG performance status, symptoms and presence of systemic features associated with a worse prognosis (multiple EAU guidelines references)

Molecular markers reported to be associated with a worse prognosis are carbonic anhydrase 9, Ki67 proliferation index, HIF, VEGF, p53, PTEN and E-cadherin. However, none achieved widespread acceptance as not independently prognostic.

DNA ploidy. Potentially useful in organ-confined disease. For stage 1 tumours diploid tumours associated with improved prognosis. Diploid 92% 10YS vs. 63% 10YS

#### Natural history of small renal masses

#### **Overall 20-30% SRM benign (women > men) and often slow growth**

Few studies have assessed natural Hx, as once detected, surgery has usually been performed:

Bennington 1987: incidence of mets in tumours < 3cm ~1-3%

Bosniak 1995: 43 tumours < 3cm. Slow growth up to 1.3 cm/yr. Once > 3cm excised (all RCC, all stage 1, most grade1). \*no mets during observation period of 3.5 years mean follow-up.

Volpe 2004: 32 tumours < 4cm. Significant growth considered to be achieving 4cm or volume doubling within 12 months. Only one-third (11) met criteria at 3yr follow-up. Of nine tumours removed 8 = RCC and 1 oncocytoma. No patient had disease progression during study.

Chawla 2006: Metaanalysis and review of literature. Large number of patients (n=286) but mean follow-up only 36 months. Slow growth rate of 0.28cm yr and low rate of metastasis 1.1%, but mets unpredictable based on growth rate alone. Features such as Fuhrmann grade would therefore be very useful if renal mass biopsy reliable.

Prognostic nomograms

A number of prognostic scoring systems have been proposed in the past, including the SSIGN score, used to predict likelihood of death. Currently there are two pre-eminent scoring systems with the end-point of the development of metastasis: UISS and Mayo clinic prognostic algorithms. Both based on clinico-pathological (post-nephrectomy data). Used to predict likelihood of metastases and thus influence follow-up protocols.

SSIGN score

Mayo clinic scoring system to predict risk of death. Used Stage (T,N &M), Size, Grade and necrosis to assign score. Very good prediction of death from metastases. (see below). However due to increasing survival with TKIs and good survival post-metastasesctomy, endpoint of development of metastasis becomes more appropriate.

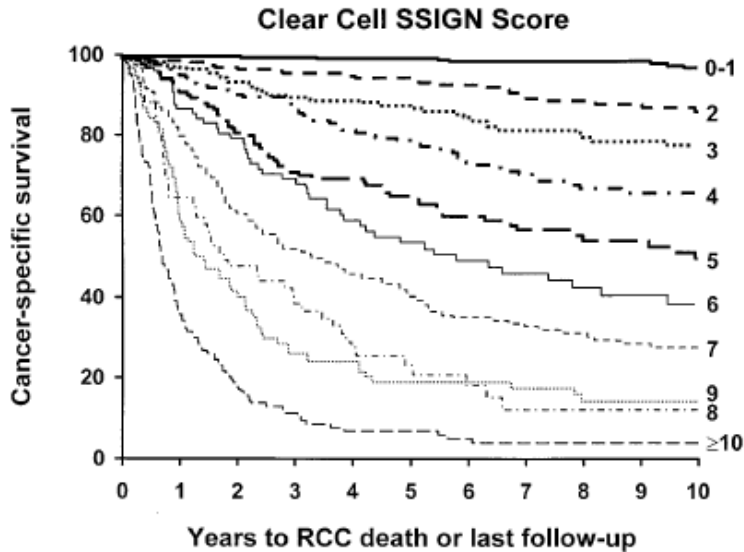


TABLE 5. SSIGN score algorithm  
 The scores in this table are added together and the total is used to determine survival using table 6.

Feature	Score
<b>T stage:</b>	
pT1	0
pT2	1
pT3a	2
pT3b	2
pT3c	2
pT4	0
<b>N stage:</b>	
pNx	0
pN0	0
pN1	2
pN2	2
<b>M stage:</b>	
pM0	0
pM1	4
<b>Tumor size (cm.):</b>	
Less than 5	0
5 or Greater	2
<b>Nuclear grade:</b>	
1	0
2	0
3	1
4	3
<b>Necrosis:</b>	
Absent	0
Present	2

UCLA Risk Stratification (Zisman 2002)

Arie Belledegrin's group at the University of California Hospital Los Angeles. Staging known as the UCLA integrated staging system (UISS). Devised scoring algorithm for 2 subgroups of patients: those with non-metastatic, and those with metastatic (nodal or distant) disease. Non-metastatic algorithm shown below:

Low Risk            T1 G1/2 and ECOG 0  
 Intermediate Risk    T1 G1/2 and ECOG >0  
                           T1 G3/4  
                           T2  
                           T3 G1  
                           T3 G2-4 and ECOG 0  
 High Risk            T3 G2-4 and ECOG >0  
                           T4

Displayed graphically:

T stage	1		2	3		4
Grade	1-2		3-4	1		>1
ECOG PS	0	≥1	0	≥1	0	≥1
Risk	Low		Intermediate		High	

- 0 Fully active
- 1 Self-caring, light work
- 2 Self-caring, no work, bed or chair < 50% of waking hours
- 3 Limited self-care, bed or chair > 50% of waking hours
- 4 Completely disabled, totally confined to bed or chair
- 5 Dead

Patients in the LR, IR, and HR groups following nephrectomy demonstrated 5-year recurrence-free rates of **90.4%, 61.8%, and 41.9%, respectively** ( $p < 0.0001$ ), and median times to recurrence of 28.9, 17.8 and 9.5 months, respectively ( $p < 0.0001$ ). Chest and abdomen recurrences comprised of 75% and 37.5%, 77.4% and 58.1%, and 45.2% and 67.7% of recurrences in the LR, IR and HR groups, respectively. NB. Chest recurrences most common in low and intermediate risk groups, abdomen more common in high risk group.

UCLA follow-up protocol simple and easy to use for non-metastatic and metastatic patients and appears to stratify patients into appropriate prognostic groups. Validated internationally (Patard 2004). Recently simplified by Lam (2005) to take into account nodal disease. However criticised for including all cell types.

Leibovich Cancer 2003; Mayo Clinic scoring system – Clear-cell RCC only.  
 Modified SSIGN score (Blute 2002) No specific post-operative surveillance protocol recommended in this paper.

Feature	Score
<i>Primary tumor / T-stage</i>	
T1a	0
pT1b	2
pT2	3
pT3 - pT4	4
<i>Tumor size</i>	
<10cm	0
>10cm	1
<i>Regional Lymph Node status</i>	
pNx/pN0	0
pN1 - pN2	2
<i>Nuclear grade</i>	
Grade 1-2	0
Grade 3	1
Grade 4	3
<i>Tumor necrosis</i>	
No necrosis	0
Necrosis	1

Risk groups can be stratified by the scoring system, characterized into low-risk 0-2, intermediate risk 3-5 and high-risk >6 according to the Mayo Scoring System (13).

**Table 4: Accumulated risk of metastases (%) after nephrectomy in patients with clear cell renal cell carcinoma as defined in risk groups according to the Mayo Scoring System (13)**

Risk group	Year 1	Year 3	Year 5	Year 10
Low	0.5	2.1	2.9	7.5
Intermediate	9.6	20.2	26.2	35.7
High	42.3	62.9	68.8	76.4



## Management of locally-confined disease

### Radical Nephrectomy

RCC requires surgical cure – chemotherapy resistant (MDR p-glycoprotein ) and poor response to immunotherapy. Reasonable response to radiotherapy but in-situ disease not generally amenable to treatment due to risk of malignant hypertension and innocent bystander effects (small bowel etc.)

Robson first described radical nephrectomy in 1969

Early vessel ligation to limit tumour emboli\*

Resection outside Gerota's fascia\*\*

Ipsilateral adrenalectomy\*\*\*

Complete ipsilateral lymphadenectomy from crus diaphragm to aortic bifurcation\*\*\*\*

\* advantageous, but not always possible

\*\* valid: 25% of localised tumours show perinephric involvement

\*\*\* not routinely necessary unless adrenal involvement of upper pole tumour (Sagalowsky 1994; Tsui 2000; Siemer 2004). Not recommended by EAU unless contiguous involvement cannot be ruled out by imaging/palpation

\*\*\*\* Controversial for a number of reasons:

Equal frequency of LN and haematogenous spread

LN drainage extremely variable

**No evidence that routine complete LND improves survival.**

Recently EORTC 30881 (Blom et al) found low incidence (4%) of occult LN metastases in clinically staged NOMO patients. No survival advantage for routine lymphadenectomy

However:

Useful for staging and prognostication

May have some benefit in selected patients with micrometastases (Giuliani 1990) and with enlarged regional nodes. Golimbu (1986) showed a 10-15% increased 5YS in patients with T3 disease. Also reported improved survival in the setting of cytoreductive Nx (Pantuck 2003)

No apparent value of pre-operative tumour embolisation in terms of reducing blood transfusion requirement. One Polish case-control study (Zielinski 2000) reported significantly improved survival for pre-op embolisation: The overall 5- and 10-year survival for 118 patients embolized before nephrectomy was 62% and 47%, respectively, and it was 35% and 23%, respectively, for the matched group of 116 patients treated with surgery alone ( $p = 0.01$ ). Results controversial however and not repeated.

### Bowel injury at laparoscopic radical nephrectomy

1.3 per 1000 cases (0.1%)

70% unrecognised; 60% small bowel; 50% by electrocautery

Typically pain over nearest port site

N+V, diarrhoea, low grade fever, low or normal WCC

### Nephron-sparing surgery

First described by Czerny in 1890 but high morbidity

Revived by Vermooten in 1950

Indications for nephron-sparing surgery:

- Anatomical or functional single kidney\*

- Bilateral renal cell carcinoma

- Pre-existing condition likely to lead to future loss of nephrons (high risk of metachronous multifocal tumour, renal disease)

\* 20% of one kidney or GFR < 25 ml/min usually sufficient to avoid ESRF

Previously normal contralateral kidney was considered to be a debatable indication for NSS. However recent studies suggest equivalent OS and DSS with radical nephrectomy, albeit with increased local recurrence rates (thought to be a manifestation of undetected multifocal tumour).

### Open partial nephrectomy

Equivalent outcomes for patients undergoing OPN vs. ORN at least for patients with tumours < 4cm (Lerner 1996).

Initial studies with <= 5 years follow-up indicate DSS 78-100% with local recurrence up to 10%. In the study with longest follow-up from Cleveland Clinic Fergany (2000) reported on 107 spontaneous tumours (mean size 4.7 cm) 10YR DSS 73%. Overall local recurrence 10.5%. Local recurrence by stage: T1a - 2%; T1b – 5%; T2+ 10-20%.

NB. No minimum resection margin – as long as clear good enough. Positive margins appear to have negligible impact on subsequent survival (Bensaleh Eur Urol 2010)

### Laparoscopic partial nephrectomy

First transperitoneal LPN performed by Winfield 1993

Relatively few studies with long term follow-up. Longest is Lane 2007: 56 patients, mean size 2.9 cm, T1a 86%. 66% turned out to be malignant. OS and DSS 86% and 100%.

Main difference from OPN is that ischaemia time is limited. Accepted warm ischaemia time 30 mins. Important as WIT significant predictor of post-op impaired renal function.

Complication rate certainly appears higher in LPN – approx 20% (6% bleeding, 2.5% urinary leak; Turna 2008 n =507). Recently, reduced overall (16 vs 37%) and haemorrhagic (3 vs 12%) complication rate associated with use of Floseal (Berger 2008)

Best study comparing LPN and OPN (Gill 2007):

3-centre comparison of 1800 patients. Hospital stay and operative time were shorter in the LPN group. Overall postoperative complications were higher in the LPN group (18.6 vs. 13.7%), particularly hemorrhagic complications (4.2 vs. 1.6%). Positive margins for cancer were similar (1.6 vs. 1%). Local (1.4 vs. 1.5%) and distant (0.9 vs. 2.1%) recurrences were also equivalent. Cancer specific

survival at 3 years was 99.3 and 99.2%, respectively.

### Probe ablative therapies

Minimally invasive techniques appropriate for small tumours (4cm or less) in the infirm and in those with a predisposition to forming multiple tumours.

Contraindicated in those with a bleeding diathesis. Caution should be exercised in those with central tumours encroaching on collecting system. RFA in particular associated with urinary fistulae.

### Radiofrequency ablation

First utilised in 1911, when electrical current used to heat probes for treating bladder tumours.

First use of RFA to treat renal tumours 1997 (Zlotta 1997)

Performed either percutaneously or laparoscopically: px = percutaneously; ax = laparoscopically to avoid visceral injury

Longest follow-up 55 months. (McDougal 2005). Ablative defect gradually fills in – approx 90% at 4 years.

Area of ablation can be increased by injecting conductive agent into tissue to decrease impedance. However eschar tends to decrease impedance.

One advantage of RFA is that radiation directly induced mitoses by a thermal independent mechanism. Therefore no loss of efficacy near to large vessels.

Largest study to date Zagoria et al 2007; A total of 104 patients with 125 biopsy-proven RCC were treated with CT-guided percutaneous RFA. Patients were followed with contrast-enhanced CT or MRI and 93% complete ablation rate was noted over a mean follow-up of 13.8 months. Single-session percutaneous RFA was possible in 109 tumors. 7/16 failures in the study group were eventually salvaged by repeat RFA or cryoablation. When tumors were stratified by size, all 95 tumors smaller than 3.7 cm were completely ablated after a single session (100%). In comparison, only 14/30 tumors larger than 3.7 cm were treated successfully by a single RFA session.

**Table 1 Percutaneous and laparoscopic radio frequency ablation for small renal masses**

Author	RCC/tumor	Tumor size (cm)	Follow-up (months)	Results (CSS, RFS)	Re-treatment rate
<b>Percutaneous</b>					
McDougal <i>et al.</i> [28]	16/20	3.2 (1.1–7.1)	55.2 (48–60)	94% CSS	5/16
Zagoria <i>et al.</i> [29**]	125	2.7 (0.6–8.8)	13.8 (1–75.8)	98% CSS	
Park <i>et al.</i> [30]	38/55	2.4 (1–4.1)	24.3 (12–48)	98.5% CSS	Two reablations, 1 salvage partial/radical
Varkarakis <i>et al.</i> [31]	27/56	2.2 (1–4)	27.5 (12–48)	86.4% RFS	Five reablations, 1 salvage partial/radical
<b>Laparoscopic</b>					
Park <i>et al.</i> [30]	27/39	2.3 (1–4.2)	26 (12–36)	98.5% CSS	0
Hwang <i>et al.</i> [32]	15/15	2.2 (1.5–2.9)	13 (12–23)	93% RFS	0

Mean (range). CSS, cancer-specific survival; RCC, renal cell carcinoma; RFS, recurrence-free survival.

### Cryoablation

First used for palliation of malignancy in 1850 by James Arnott (Lancet 1850)

Dr Irving Cooper neurosurgeon father of modern cryoablation

Beneficial effects of very localised tissue damage with minimal collateral damage now fully appreciated.

First used in urology to treat BPH (Gonder 1965)

Percutaneous for px tumours, laparoscopic for ax tumours.

Two cycles of freeze thaw using argon/helium. Temperatures < -20 degrees necessary, < -40 considered ideal.

Intra-operative monitoring using intra-op USS (lap USS for anterior tumours).

Results:

Largest study to date Gill 2005. mean tumour size 3.3cm (n=39). Careful MRI follow-up and repeat Bx at 6 months. 2/39 had residual RCC at Bx. Resolution of defect in 62% at 3 years. 3 yr DSS 98%.

**Table 2 Laparoscopic and percutaneous cryoablation**

Author	RCC/tumors	Tumor size (cm)	Follow-up (months)	Results (CSS, RFS)	Re-treatment rate
<b>Laparoscopic</b>					
Gill <i>et al.</i> [49]	36/60	3.3 (1–4.5)	36	98% CSS	0
Weld <i>et al.</i> [50]	22/36	2.1 (0.5–4)	45.7 (36–63)	100% CSS	0
Lawatsch <i>et al.</i> [51]	38/81	2.5 (1–5)	25.2 (N/A)	95% RFS	0
Cestani <i>et al.</i> [52]	29/37	2.6 (1–6)	20.5 (1–36)	94.3% RFS	1 salvage partial/radical nephrectomy
<b>Percutaneous</b>					
Silverman <i>et al.</i> [53]	24/26	2.6 (1–4.6)	14 (4–30)	87% RFS	1 salvage radical/partial nephrectomy

Mean (range). CSS, cancer-specific survival; RCC, renal cell carcinoma; RFS, recurrence-free survival.

### RFA vs. Cryo

No direct comparative prospective randomised controlled trials to date

Retrospective single institution comparison (Hegarty 2006 Cleveland Clinic); 246 pts; 164 cryo with 3 years f/up, 82 RFA with one year f/up. DSS 98% and 100% respectively. Larger ablation zone achievable with cryo, higher re-treatment rate with RFA

Best meta-analysis to date Kunkle 2008:

47 studies; 1375 kidney lesions. Pre-Rx bx in approx 70%. Matched for age size of lesion (mean 2.6 cm) and follow-up.

Cryo better than RFA for:

Repeat Rx	1.3% vs 8.5%
Local tumour progression	5.2% vs. 12.9%
Metastasis	1.0% vs. 2.5%

Cryo also has advantage over RFA that it allows real-time monitoring of ice-ball formation whereas RFA does not allow intra-operative measurement of treatment effect and relies on post-operative imaging. Broadly equivalent complication rates: more urinary fistulae with RFA (major); more skin paraesthesia and pain with cryo (minor and improved with insulated needles)

### **Adjuvant treatment for high-risk locally-confined disease**

Neoadjuvant and adjuvant radiotherapy has previously been used for patients with RCC. No evidence to support its use but studies old (Finney 1978) and have not been repeated recently. Currently no evidence to recommend routine adjuvant treatment for high risk locally-confined disease. Also no definite consensus on what constitutes high risk disease, although a number of studies adopting Leibovich's prognostic score.

**EORTC 30955: Phase III Randomized Study of Adjuvant Interleukin-2, Interferon alfa, and Fluorouracil Versus Observation Only in Patients With Renal Cell Carcinoma at High Risk of Relapse After Surgical Resection (Closed/unreported)**

**Inclusion criteria:**

Histologically confirmed primary renal cell carcinoma meeting 1 of the following criteria:

- Stage T3b, T3c, or T4 tumor
- Any pT stage and nodal status pN 1 or 2
- Any pT stage and microscopic positive margins
- Presence of any microscopic vascular invasion

Underwent surgical resection of primary tumor within the past month

Removal of clinical N+ disease required

No evidence of metastatic disease

No evidence of macroscopic residual disease

**RE05/SORCE: A phase III Randomised Controlled Study Comparing Sorafenib With Placebo In Patients With Resected Primary Renal Cell Carcinoma at High or Intermediate Risk of Relapse (EORTC participation protocol #30072) - Recruiting**

**Inclusion criteria:**

All kidney tumour sub-types

No mets on post-Nx CT

Leibovich score 3-11 [most minimal disease = tumour > 4cm with necrosis or Fuhrman 3]

Between 4 weeks and 3 months of surgery

**Trial design**

Patients will be randomly assigned to 3 years of placebo (Arm A), 1 year sorafenib 400mg bd & 2 years placebo (Arm B) or 3 years sorafenib 400mg bd (Arm C).

**Management of locally-advanced disease**

**IVC involvement**

4-10% of patients

**Classification system**

- I Adjacent to ostium of renal vein – able to be milked back
- II Up to lower margin of caudate lobe
- III Behind liver
- IV Above diaphragm

a/w lower extremity oedema, renal dysfunction, hepatic dysfunction (Budd-Chiari) ascites, non-emptying varicocoele, caput medusae, PE, cardiac failure, SVC hypertension.

Coronal MRI investigation of choice for determining cephalad extension (Choyke 1997) – tumour thrombus enhances with gadolinium cf. simple/bland thrombus  
 ~ 40% of cases have arterialised thrombus. Simultaneous MR angiography should therefore be performed as pre-op arterial embolisation may cause tumour shrinkage (Campbells but ? increased likelihood of tumour embolus)  
 IVC involvement without other mets a/w overall survival of ~60%. However;  
 IVC tumour with other mets = overall 10% 5YS (in studies after Nx – Campbells; largest study Swierzewski 1994), but probably much worse as only fit patients included. Therefore only consider ECOG 0 patients with low volume mets (eg. one or two lung nodules).

### Locally invasive, non-metastatic RCC

Relatively uncommon

Often present with pain due to invasion of px abdo wall & nerve roots

Mesenteric organs usually first involved (small bowel/colon) / due to parasitisation of feeding vessels.

Liver, duodenum and pancreatic invasion very uncommon – much more likely to involve liver via haematogenous seeding.

Overall prognosis poor

Complete excision                      5% 5YS

Incomplete excision                    12% 1YS (deKernion 1978)

No role for neoadjuvant or adjuvant radiotherapy

## Management of metastatic disease (mRCC)

### Management of the primary tumour – cytoreductive Nx

Patients with mRCC often have acquired immune dysfunction

- T-cell dysfunction
- Increased T-cell apoptosis
- Impaired proliferative responses
- Tumour associated immunosuppression

Cytoreductive Nx improves all of the above.

In 2001, the results of the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group trial 30947 (Mickish 2001) and the similarly designed Southwest Oncology Group (SWOG) trial 8949 (Flanigan 2001) documented improved overall survival for patients who underwent cytoreductive nephrectomy before systemic immunotherapy with interferon- $\alpha$  (IFN- $\alpha$ ) when compared with patients treated with immunotherapy alone. In a combined analysis of these two trials (326 patients), Flanigan et al. (Flanigan 2004) demonstrated a median survival duration of 13.6 months for patients who underwent cytoreductive nephrectomy and IFN- $\alpha$  versus 7.8 months (**approx 6 months survival advantage**) for patients treated with IFN- $\alpha$  alone.

However, patient selection paramount as:

- Up to 25% of patients in each arm died within 4 months of enrolment\*
- Up to 60% of patients unable to tolerate systemic Rx after CNx

\* Pre-CNx systemic therapy has been used as a 'litmus test' select out responders from non-responders. Bex (2002) used 2 cycles of IFN- $\alpha$  and low dose IL-2 prior to CNx. Responders/stable disease underwent CNx. Non-responders did not have CNx, rapidly progressed and died. Survival post-CNx equivalent to SWOG trial. Currently a number of phase 2 trials investigating value of pre-CNx SMIs (bevacizumab and sunitinib). No evidence that pre-surgery Rx increases morbidity (Margulis 2008)

Value of cytoreductive Nx questioned in era of SMIs. New European trial of CNx + sunitinib vs. sunitinib alone about to start recruiting (? EORTC).

### Management of the primary tumour – tumour embolisation

Simple to perform transarterially following groin puncture. Agents: absolute ethanol, gelfoam, acrylic microspheres (embospheres) and metallic coils. Coils and embospheres most popular, and often used in tandem to achieve large artery and capillary embolisation respectively. Few large studies of efficacy in palliative setting however. Schwartz recently reported experience of 121 RAEs (55% pre-op, 20% bleeding, 12.5% AML, 8% advanced tumour). Complications significant as shown below.

TABLE 5 The morbidity and complications of RAE

Morbidity/complication	N (%)
Post-infarction syndrome:	90 (74.4)
Flank pain	74 (61.1)
Fever	45 (37.2)
Nausea	29 (24.0)
Vomiting	11 (9.1)
Complication:	
Incomplete embolization	2 (1.7)
Coil migration	2 (1.7)
Groin haematoma	2 (1.7)
Adjacent organ necrosis	0
Total	6 (5.0)

Post-infarction syndrome comprising pain, fever and nausea in three-quarters. Reportedly mild and self-limiting however.

### Metastasectomy (Rasco 2006)

Number of reports of long-term survival after metastasectomy, some up to 10 years. Usually after lung/bone mets. Largest pulmonary study with longest follow-up Piltz 2002: 105 patients; 150 lung resections. 5YS 40%; 10YS 33%. Similar 44% 5YS from MSKCC for all locations. Favourable prognostic factors - DFI of longer than 12 months, a solitary metastasis and glandular/soft tissue location. OS did not appear to decrease with recurrent metastases and repeat metastasectomies. Survival by location:

- Bone 15% 5YS; complication rate 40% with prior RT vs. 15%. No studies comparing RT vs. metastasectomy.
- Lung Combined analysis of over 400 pts – 5YS consistently ~40%. Better with longer disease-free interval and few mets. Complications 6-12%. Mortality 1-3%.
- Liver Few studies, small numbers. 56% 2YS. High complication/mortality rates. Fewer studies of pancreas but some reported long-term survival, even after Whipple's.
- Brain Traditionally whole brain irradiation +/- stereotactic RT. Largest series of conventional surgery Wronski 1996: n=50, half had WBRT after surgery (no difference in OS/DSS). Mortality 10%. Median survival 12 months. 5YS 8.5%.

### Systemic therapy

Multiple studies have reported improved response rates in trials of immunotherapy and chemotherapy in metastatic RCC. However response rates thought to poorly correlate with overall survival - thus only overall survival should be primary endpoint.

### Medroxyprogesterone acetate

Early reports from animal studies and subsequent patient studies of MPA therapy in 1970s and early 1980s suggested a treatment response of 10-15% with occasional dramatic long-term responses. However a number of subsequent trials failed to demonstrate a definite benefit:



Two multicenter randomized trials (Medical Research Council Renal Cancer Collaborators, 1999 ; Negrier et al, 2005 ) tested oral medroxyprogesterone acetate as initial therapy for patients with metastatic RCC. In these reports, 174 and 123 patients received medroxyprogesterone acetate, 300 mg/day and 200 mg/day, respectively. Response rates to medroxyprogesterone acetate were uniformly low (2.0% and 2.5%, respectively), and overall median survival of the patients varied from 6.0 months ( Medical Research Council Renal Cancer Collaborators, 1999 ) to more than 15.0 months ( Negrier et al, 2005 ). The difference in survival probably reflects patient entry criteria used in the two studies rather than a true difference in biologic responsiveness. Therefore, whereas progestational agents may be useful for symptom palliation, they do not appear to have any significant value in the treatment of patients with metastatic RCC.

One prospective RCT of MPA (500mg thrice weekly for 12 months) following nephrectomy (Pizzocaro 1987). N= 136, 5 yr follow-up. No survival benefit seen and significant side-effect in 57% of treatment arm due to MPA – predominantly hormonal toxicity. This and the finding of improved survival with IFN- $\alpha$  vs. MPA killed off MPA as a treatment. Occasionally reserved for patients unable to tolerate IFN- $\alpha$  or systemic therapy.

#### Interferon alpha-2a

Mechanism of action poorly understood. 4 RCTs shown increased survival advantage with IFN in metastatic renal cell cancer. Usually vs. medroxyprogesterone. Pooled median survival 3.8 months. Interestingly no difference in partial or complete response rates between groups. Largest trial MRCRCC trial 1999, no author. IFN following cytoreductive nephrectomy associated with prolonged survival in 2 trials compared with IFN alone (see above)

Elevated CRP possibly an independent predictor of reduced survival in interferon therapy Blay 1994.

#### Interleukin-2

No evidence that IL-2 associated with prolonged survival in randomised trials. From Cochrane systematic review: *“We were unable to identify any published randomized study of high-dose interleukin-2 versus a non-immunotherapy control, or of high-dose interleukin-2 versus interferon- $\alpha$  reporting survival”*. Is however associated with overall response rates of 15%. Sometimes prolonged and sustained complete remission in up to 7% of patients [Fyfe 1996; Yang 2003] - reason for drug approval by FDA. Significant toxicity with high dose treatment, reduced responses with low dose treatment.

No survival advantage for combination interferon and IL-2 over monotherapy. Negrier 2001/2005.

### Combination Chemotherapy/Immunotherapy

Atzpodien 2001 reported 40% response rates with INF, IL-2 and 5-FU in metastatic RCC: ? Overall survival advantage. Not been reproduced as yet but currently the focus of closed/unreported RE04 trial. Outcomes of RE04 now reported (Gore et al Lancet 2010). Median overall survival almost identical among the groups, with no other benefit for combination Rx.

IFN-2a 18.8 months

IFN-2a, IL-2, 5-FU 18.6 months

### Small Molecule Inhibitors

Selected examples:

Sorafenib (Nexavar)

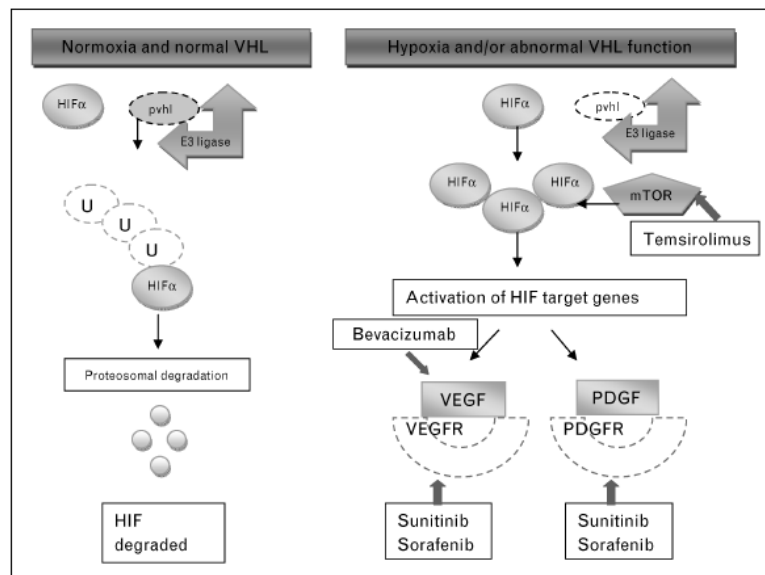
Sunitinib (Sutent)

Bevacizumab (Avastin)

Temsirolimus (Torisel)

Everolimus (Afinitor)

Sorafenib and sunitinib block multiple tyrosine kinases. Temsirolimus blocks mTOR. Erlotinib and lapatinib block EGFR TK. Bevacizumab is a monoclonal antibody vs. VEGF receptor.



Proteasomal degradation of HIF- $\alpha$  is deranged in conditions of hypoxia and altered VHL function, leading to activation of HIF target genes and overexpression of VEGF and PDGF. Mutations of mTOR also enhance angiogenesis by upregulating HIF- $\alpha$  activity. Sites of action of novel targeted therapies are illustrated in the figure above. HIF $\alpha$ , hypoxia-inducible factor alpha; mTOR, mammalian target of rapamycin kinase; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; pVHL, von Hippel-Lindau protein; U, ubiquitin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

### SMLs as second-line for immunotherapy failure

Sorafenib (Nexavar, Bayer pharmaceuticals)

Biaryl urea raf kinase inhibitor of VEGF and PDGF

Treatment dose 400mg po od (small red tablet)

TARGET trial (Escudier 2007); n=903 pts randomised to sorafenib vs. placebo. Objective response rate 10% vs. 2%. PFS 5.5 vs. 2.8 mths. No overall survival data presented.

Side effects – diarrhoea, rash, fatigue, hand-foot reactions.

#### Sunitinib (Sutent, Pfizer)

Inhibitor of VEGF and PDGF

Treatment dose 50mg po od for 4 wks out of six

Biggest trial to date Motzer 2006: 106 patients who underwent prior nephrectomy and cytokine therapy. Overall response rate of 33%. with a 14-month median duration of response. Median PFS and OS were 8.8 and 23.9 months.

Side effects – diarrhoea, rash, fatigue, hand-foot reactions.

NB. Sorafenib and sunitinib most effective vs. CCRCC. Overall response rate 25% in chromophobe and only 5% in papillary RCC (Chouieri 2008)

#### First line monotherapy

##### Sorafenib

No trials to date

##### Sunitinib

Recent phase 3 trial of sunitinib vs. interferon in patients with metastatic disease (90% in each arm had Nx) [Motzer 2006 n=750]. Either 50mg sunitinib od 4wks on, 2wks off, or 9MU interferon x3/wk. Primary endpoint PFS [assessment of imaging studies by independent review, performed cycles 1-4, then every 2 cycles thereafter]. **Median PFS 11 mo in sunitinib group vs. 5 mo in interferon group.** Trend towards increased overall survival in sunitinib group but not enough patients died\*. Improved QOL and SE profile in sunitinib group.

\* Overall survival advantage over IFN-a of 4.6 months recently reported (Figlin 2008). Median survival 26.4 mo. vs. 21.8 mo. (Only 6% MSKCC poor prognosis patients in the trial; 60% ECOG 0)

#### Temsirolimus (Torisel, Wyeth pharmaceuticals)

mTOR inhibitor

Relatively gentle toxicity profile cf. bevacizumab and TKIs – mainly rash oedema, hyperglycaemia and hyperlipidaemia.

Global ARCC trial (Hudes 2007): n=626 poor prognosis ARCC. 25mg temsirolimus weekly vs. combination Rx with IFNa and IFNa alone. Overall survival with temsirolimus 10.9 mths vs 7.3 for IFNa alone (combination 8.4 mths). Objective response rate only 8.5% however with stable disease in 30%.

#### First-line combination therapy

##### Sorafenib and IFN-alpha 2B

Minimal improved survival vs. either agents but toxicity also synergistic – not currently recommended.

##### Bevacizumab (Avastin, Roche pharmaceuticals)

AVOREN trial (Escudier 2007): 649 patients were randomized to receive bevacizumab (10 mg/kg IV q 2 weeks) and IFN- $\alpha$  (9MU sc thrice weekly) or placebo and IFN- $\alpha$ . Median PFS 10.2 vs. 5.4 mths. Side-effects fatigue asthenia, hypertension and proteinuria.  
Similar results obtained by CALBG 90206.

### Second-line treatment with TKIs

Very little evidence to support sequential treatment with TKIs. Currently Sorafenib given to treatment failures with bevacizumab and sunitinib based on abstract by Rini 2008. Apparently 5% reduced tumour burden in one third of patients receiving second-line sorafenib. However two-thirds had grade three toxicity [ NCI grade 3 toxicity criteria: diarrhoea = > 7 stools/day; rash = symptomatic > 50% body surface area; fatigue = decrease performance by 2 ECOG levels; hand-foot = painful skin changes interfering with function].

### Emerging treatments

Axitinib, Cediranib, pazopanib, volociximab, everolimus

**Table 1 Summary of randomized control trials of targeted therapies in renal cell carcinoma**

Study	Randomization	Number of patients	Objective response rate (%)	PFS (months)
Escudier <i>et al.</i> [12**]	Sorafenib (400mg) p.o. b.i.d. vs. placebo	903	10 vs. 2	5.5 vs. 2.8 ( $P < 0.01$ )
Motzer <i>et al.</i> [22**]	Sunitinib (50 mg) p.o. q.d. vs. IFN- $\alpha$ nine MU s.c. three times weekly	750	31 vs. 6 ( $P < 0.001$ )	11 vs. 5 ( $P < 0.001$ )
Escudier <i>et al.</i> [26**]	Bevacizumab (10mg/kg) i.v. every 2 weeks and IFN- $\alpha$ 2a nine MU s.c. three times weekly vs. placebo and IFN- $\alpha$ 2a nine MU s.c. three times weekly	649	31 vs. 13	10.2 vs. 5.4 ( $P = 0.0001$ )
Rini <i>et al.</i> [27**]	Bevacizumab (10mg/kg) every 2 weeks and IFN- $\alpha$ nine MU s.c. three times weekly vs. IFN- $\alpha$ nine MU s.c. three times weekly	732	25.5 vs. 13.1 ( $P < 0.0001$ )	8.5 vs. 5.2 ( $P < 0.0001$ )
Hudes <i>et al.</i> [29**]	Temsirolimus (25mg) i.v. weekly vs. IFN- $\alpha$ 3–18 MU s.c. three times weekly vs. temsirolimus (15mg) i.v. weekly and IFN- $\alpha$ six MU s.c. three times weekly	626	4.8 vs. 8.6 vs. 8.1	3.1 vs. 5.5 vs. 4.7

### Summary of current Rx (risk stratification below)

#### First-line Rx

Low/intermediate risk	Sunitinib	<b>4.6 mo. improved OS</b> (21-26 mo. Figlin et al 2008)
	Bevacizumab	improved PFS, no OS (Escudier 2007)
Low risk	Temsirolimus	<b>4 mo. improved OS</b> Global ARCC, Hudes 2007

#### Second-line Rx

After cytokines	Sorafenib	Improved PFS, no OS (TARGET, Escudier 2002)
After 1 <sup>st</sup> -line SMI	Everolimus	Improved PFS, no OS (RECORD1, Motzer 2008)

Defining Risk in mRCC

Motzer criteria typically used to predict prognosis in patients with mRCC (Motzer 1999 – MSKCC criteria)

Variable	Good	Poor
Performance status	0-1	>1
Histology	Clear-cell	Other
LDH	<1.5 x ULN	>1.5 ULN
Corrected calcium	Normal	> 10mg/dl
Haemoglobin	Normal	< LLN
Previous nephrectomy	Yes	No
Good prognosis = 0 poor factors		
Intermediate = 1-2		
Poor = >2		

Currently EAU/NCCN recommend sunitinib or bevacizumab/interferon for first-line treatment in good and intermediate disease groups. NCCN recommends sunitinib for poor prognosis disease. Temsirolimus is an alternative. EAU but not NCCN recommends sorafenib for 2nd line treatment.

SMI - Treatment economics

Drug	Six-week cycle	Daily
IFN-a (10 MU 3x/wk)	£778	£18.5
Sunitinib	£3140	£75
Sorafenib	£3190	£76
Bevacizumab/IFN-a	£6300	£150
Temsirolimus	Not listed	Not listed

NB. Assuming a survival advantage of 4.6 months (Figlin 2008) sunitinib 'buys' extra life at a cost of £340/day. (Overall cost of sunitinib therapy ~ £60,000 for survival of median survival of 26.4 months)

## Follow-up

### Suggested UCLA follow-up protocol (Lam J Urol 2005)

#### Low Risk

- Yearly Review
- Hx & Exam
- FBC/UE/LFTs
- CXR (CT chest)
- [Abdo CT @ 2 & 4 yrs - USA]
- Discharge @ 5 yrs

#### Intermediate Risk

- 6 monthly review to 5 yrs, then
- @ 7yrs and 9 yrs
- Hx & Exam
- FBC/UE/LFTs
- CXR (CT chest)
- Yearly CT Chest/Abdo
- Discharge @ 10 yrs

#### High Risk

- 6 monthly review to 5 yrs, then
- @ 7yrs and 9 yrs
- Hx & Exam
- FBC/UE/LFTs
- CT Chest/Abdo
- Discharge @ 10 yrs

Displayed graphically:

<i>UISS risk group based surveillance protocol for patients following surgical resection for localized and locally advanced RCC</i>											
	Mos Followup										
	3	6	12	18	24	30	36	48	60	84	108
<b>Low risk:</b>											
History + physical examination			•		•		•	•	•		
Laboratory studies*			•		•		•	•	•		
Chest CT†			•		•		•	•	•		
Abdominal CT					•			•			
<b>Intermediate risk:</b>											
History + physical examination	•	•	•	•	•	•	•	•	•	•	•
Laboratory studies*	•	•	•	•	•	•	•	•	•	•	•
Chest CT†	•	•	•	•	•	•	•	•	•	•	•
Abdominal CT		•			•		•		•		•
<b>High risk:</b>											
History + physical examination	•	•	•	•	•	•	•	•	•	•	•
Laboratory studies*	•	•	•	•	•	•	•	•	•	•	•
Chest CT†	•	•	•	•	•	•	•	•	•	•	•
Abdominal CT	•	•	•	•	•	•	•	•	•	•	•
<b>Nodal disease:</b>											
History + physical examination	•	•	•	•	•	•	•	•	•	•	•
Laboratory studies*	•	•	•	•	•	•	•	•	•	•	•
Chest CT†	•	•	•	•	•	•	•	•	•	•	•
Abdominal CT	•	•	•	•	•	•	•	•	•	•	•

\* Includes complete blood count, serum chemistries and liver function tests.  
 † A chest radiograph can be alternated with a chest CT after 3 years of followup.