STAGING, PROGNOSTIC FACTORS AND SURGICAL TREATMENT OF RCC

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Staging

The clinical staging of renal malignant disease begins with a thorough history, physical examination, and judicious use of laboratory tests.

Systemic symptoms such as significant unintended weight loss (>10% of body weight), cachexia, or poor performance status at presentation suggest advanced disease, as do physical examination findings of a palpable mass or lymphadenopathy. A nonreducing varicocele and lower extremity edema suggest venous involvement.

Significant anemia, hypercalcemia, abnormal liver function parameters or ESR, or elevated serum ALP or LDH level point to the probability of advanced disease.

Metastatic evaluation in all cases should include a routine chest radiograph (chest CT), systematic review of the abdominal and pelvic CT or MRI, and liver function tests.

MRI can be reserved primarily for patients with locally advanced malignant disease, equivocal venous involvement, or allergy to intravenous contrast material.

Overall, the accuracy of CT or MRI for detection of involvement of the perinephric fat is low.

Ipsilateral adrenal involvement can be assessed with reasonable accuracy through a combination of preoperative CT and intraoperative inspection. **Patients with an enlarged or indistinct adrenal gland on CT, extensive malignant replacement of the kidney, or a palpably abnormal adrenal gland are at risk for malignant adrenal involvement and should be managed accordingly**

Enlarged hilar or retroperitoneal lymph nodes (2 cm or more in diameter) on CT almost always harbor malignant change, but this should be confirmed by surgical exploration or percutaneous biopsy if the patient is not a surgical candidate. Many smaller lymph nodes prove to be inflammatory rather than neoplastic and should not preclude surgical therapy

The sensitivities of CT for detection of renal venous tumor thrombus and IVC involvement are 78% and 96%, respectively . CT findings suggestive of venous involvement include venous enlargement, abrupt change in the caliber of the vein, and filling defects.

MRI is well established as the premier study for the evaluation and staging of IVC tumor thrombus, although several studies suggest that multiplanar CT is likely equivalent in many patients.

Bone scintiscan can be reserved for patients with elevated serum alkaline phosphatase, bone pain, or poor performance status.

chest CT scan for patients with pulmonary symptoms or an abnormal chest radiograph.

Biopsy of the primary tumor and/ or potential metastatic sites is also selectively required as part of the staging process.

TABLE 97.12 International TNM Staging System for Renal Cell Carcinoma

T: PRIMARY TUMOR	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤ 4.0 cm and confined to the kidney
T1b	Tumor > 4.0 cm and ≤7.0 cm and confined to the kidney
T2a	Tumor > 7.0 cm and ≤10.0 cm and confined to the kidney
T2b	Tumor > 10.0 cm and confined to the kidney
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota 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 fascia (including contiguous extension into the ipsilateral adrenal gland)

N: REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in regional lymph node(s)

M: DISTANT METASTASES	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

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

TABLE 97.13 Tumor, Node, Metastasis (TNM) Stage and 5-Year Cancer-Specific Survival for Renal Cell Carcinoma

FINDINGS	ROBSON STAGE	TNM (6th ed. 2002)	TNM (7th ed. 2009)	TNM (8th ed. 2016)	5-YEAR SURVIVAL (%)
Organ-confined (overall)	I	T1-2N0M0	T1-2N0M0	T1-2N0M0	70–90
≤4.0 cm	I	T1aN0M0	T1aN0M0	T1aN0M0	90–100
>4.0 cm to 7.0 cm	I	T1bN0M0	T1bN0M0	T1bN0M0	80–90
>7.0 to 10.0 cm	I	T2N0M0	T2aN0M0	T2aN0M0	65–80
>10.0 cm	I	T2N0M0	T2bN0M0	T2bN0M0	50–70
Invasion of pelvicalyceal system	I	T1-2N0M0	T1-2N0M0	T3aN0M0	50–70
Invasion of perinephric or renal sinus fat	II	T3aN0M0	T3aN0M0	T3aN0M0	50–70
Extension into renal vein or branches	IIIA	T3bN0M0	T3aN0M0	T3aN0M0	40–60
Extension into IVC below diaphragm	IIIA	T3cN0M0	T3bN0M0	T3bN0M0	30–50
Extension into IVC above diaphragm or invasion of IVC wall	IIIA	T3cN0M0	T3cN0M0	T3cN0M0	20–40
Direct adrenal involvement	II	T3aN0M0	T4N0M0	T4N0M0	0–30
Locally advanced (invasion beyond Gerota fascia)	IVA	T4N0M0	T4N0M0	T4N0M0	0–20
Lymph node involvement	IIIB	T(Any)N1-2M0	T(Any)N1M0	T(Any)N1M0	0–20
Systemic metastasis	IVB	T(Any)N1-2M1	T(Any)N1M1	T(Any)N1M1	0–10

Contiguous extension of tumor into the ipsilateral adrenal gland is classified as T4 and noncontiguous involvement of either adrenal as M1, reflecting likely patterns of dissemination.

The only change in the eighth edition (2016) relates to stage pT3a, which now includes invasion of the pelvicalyceal system, based on multiple reports indicating this finding has independent prognostic significance in RCC

Prognostic factors

Pathologic stage has proved to be the single most important prognostic factor for RCC

TABLE 97.13 Tumor, Node, Metastasis (TNM) Stage and 5-Year Cancer-Specific Survival for Renal Cell Carcinoma

FINDINGS	ROBSON STAGE	TNM (6th ed. 2002)	TNM (7th ed. 2009)	TNM (8th ed. 2016)	5-YEAR SURVIVAL (%)
Organ-confined (overall)	I	T1-2N0M0	T1-2N0M0	T1-2N0M0	70–90
≤4.0 cm	I	T1aN0M0	T1aN0M0	T1aN0M0	90–100
>4.0 cm to 7.0 cm	I	T1bN0M0	T1bN0M0	T1bN0M0	80–90
>7.0 to 10.0 cm	I	T2N0M0	T2aN0M0	T2aN0M0	65–80
>10.0 cm	I	T2N0M0	T2bN0M0	T2bN0M0	50–70
Invasion of pelvicalyceal system	I	T1-2N0M0	T1-2N0M0	T3aN0M0	50–70
Invasion of perinephric or renal sinus fat	II	T3aN0M0	T3aN0M0	T3aN0M0	50–70
Extension into renal vein or branches	IIIA	T3bN0M0	T3aN0M0	T3aN0M0	40–60
Extension into IVC below diaphragm	IIIA	T3cN0M0	T3bN0M0	T3bN0M0	30–50
Extension into IVC above diaphragm or invasion of IVC wall	IIIA	T3cN0M0	T3cN0M0	T3cN0M0	20–40
Direct adrenal involvement	II	T3aN0M0	T4N0M0	T4N0M0	0–30
Locally advanced (invasion beyond Gerota fascia)	IVA	T4N0M0	T4N0M0	T4N0M0	0–20
Lymph node involvement	IIIB	T(Any)N1-2M0	T(Any)N1M0	T(Any)N1M0	0–20
Systemic metastasis	IVB	T(Any)N1-2M1	T(Any)N1M1	T(Any)N1M1	0–10

Tumor-related factors such as pathologic stage, tumor size, nuclear grade, and histologic subtype have the greatest individual predictive ability.

Patient-related factors such as age, presence of chronic kidney disease, and comorbidities have a significant impact on overall survival and should be a primary consideration during treatment planning for patients with localized RCC.

Clinical findings that suggest a compromised prognosis in patients with presumed localized RCC include symptomatic presentation, unintended weight loss of more than 10% of body weight, and poor performance status .

Anemia, thrombocytosis, hypercalcemia, albuminuria, elevated ALP, CRP, LDH, or ESR, as well as other paraneoplastic signs or symptoms, have also correlated with poor outcomes for patients with RCC

Histologic subtype of RCC also carries prognostic significance. The presence of sarcomatoid or rhabdoid differentiation or collecting duct, renal medullary, or unclassified histologic subtype denotes a poor prognosis

TABLE 97.14 Adverse Prognostic Factors for Renal Cell Carcinoma

CLINICAL	ANATOMIC	HISTOLOGIC
Poor performance status	Larger tumor size	High nuclear grade
Systemic symptoms	Venous involvement	Certain histologic subtypes
Anemia	Extension into contiguous organs, including adrenal gland	Sarcomatoid features
Hypercalcemia	Lymph node metastases	Presence of histologic tumor necrosis
Elevated lactate dehydrogenase	Distant metastases and greater metastatic burden	Vascular invasion
Elevated erythrocyte sedimentation rate		Invasion of perinephric or renal sinus fat
Elevated C-reactive protein		Collecting system invasion
Thrombocytosis		Positive surgical margin
Elevated alkaline phosphatase		

Data from Lane BR, Kattan MW: Prognostic models and algorithms in renal cell carcinoma. *Urol Clin North Am* 35(4):613–625, 2008; Sun M, Vetterlein M, Harshman LC, et al.: Risk assessment in small renal masses: a review article. *Urol Clin North Am* 44(2):189–202, 2017.

Table 6.4: Anatomical, histological, and clinical variables in the commonly used prognostic models for localised and metastatic RCC

Prognostic Models	Variables													
		TNM Stage [151]	ECOG PS [202]	Karnofsky PS [203]*	RCC related symptoms	Fuhrman grade [154]**	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Haemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS [192]***	x	x			x								
	SSIGN [193]	x				x	x	x						
	Post-operative Karakiewicz's nomogram [196]	x			x	x		x						
Metastatic RCC	MSKCC prognostic system [204]****			x					x	x	x	x		
	IMDC [205]			x					x		x	x	x	x

ECOG-PS = Eastern Cooperative Oncology Group - performance status (see details; Section 7.4.2.1, Table 7.1); IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; SSIGN = Stage Size Grade Necrosis; TNM = Tumour, Node Metastasis (classification); UISS = University of California Los Angeles integrated staging system.

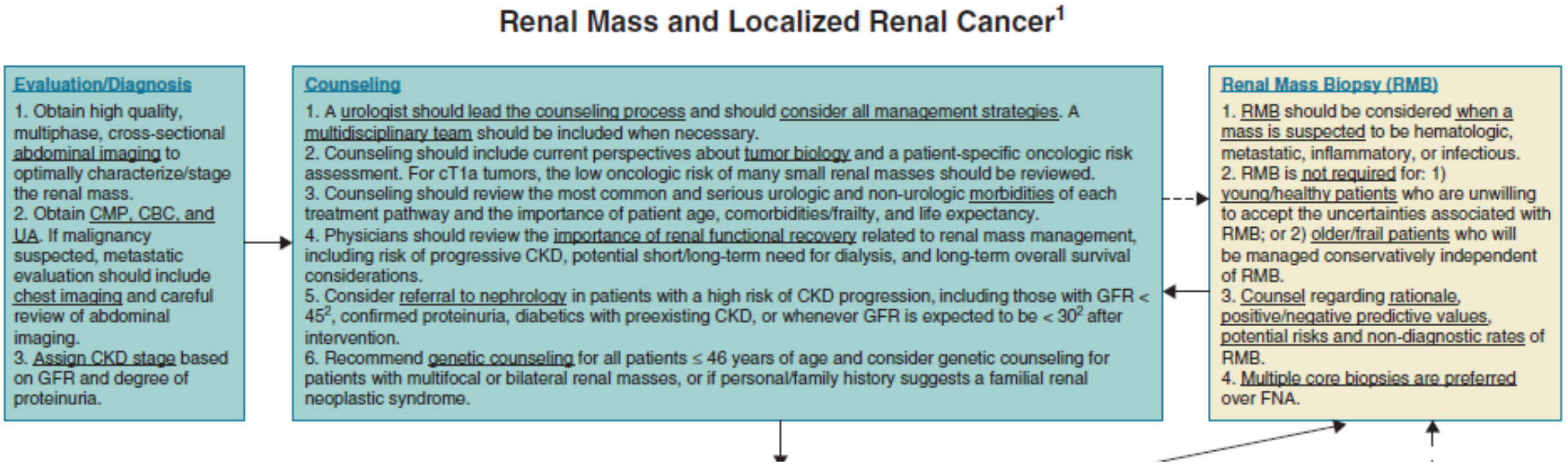
**Karnofsky score calculator: https://www.thecalculator.co/health/Karnofsky-Score-for-Performance-Status-Calculator-961.html*

***Fuhrman nuclear grade: https://www.mdcalc.com/fuhrman-nuclear-grade-clear-cell-renal-carcinoma*

****UISS: https://qxmd.com/calculate/calculator_170/prognosis-in-renal-cell-carcinoma-uiss*

*****MSKCC: https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-metastatic-renal-cell-carcinoma-rcc*

Algorithm for evaluation, counseling, and management of patients presenting with a renal mass or localized renal cancer.



Renal Mass Biopsy

- RMB should be considered when a mass is suspected to be **hematologic, metastatic, inflammatory, or infectious**.
- Perform a RMB before **ablative therapy** and **systemic therapy** without previous pathology.
- Perform a RMB in **select patients who are considering active surveillance**.

RMB is not required for

1. young/healthy patients who are unwilling to accept the uncertainties associated with RMB;
2. older/frail patients who will be managed conservatively independent of RMB.

Multiple core biopsies are preferred over FNA.

Do not perform a RMB of cystic renal masses.

A positive biopsy is reliable with high specificity (96%) and positive predictive value (99.8%).

The nondiagnostic rate for RMB is approximately 14%, which can be substantially reduced with repeat biopsy.

Recent meta-analyses suggest that RMB is generally safe and accurate.

RMB is safe with relatively low rates of hematoma (4.9%), clinically significant pain (1.2%), gross hematuria (1.0%), pneumothorax (0.6%), and hemorrhage requiring transfusion (0.4%).

There have been *no* reported cases of RCC tumor seeding in the contemporary literature.

Management

Partial Nephrectomy (PN) and Nephron-Sparing Approaches

1. Prioritize PN for the management of the cT1a renal mass when intervention is indicated.
2. Prioritize nephron-sparing approaches for patients with an anatomic or functionally solitary kidney, bilateral tumors, known familial RCC, preexisting CKD, or proteinuria.
3. Consider nephron-sparing approaches for patients who are young, have multifocal masses, or comorbidities that are likely to impact renal function in the future.

Radical Nephrectomy (RN)

1. Physicians should consider RN for patients where increased oncologic potential is suggested by tumor size, RMB, and/or imaging characteristics. In this setting, RN is preferred if all of the following criteria are met:
1) high tumor complexity and PN would be challenging even in experienced hands;
2) no preexisting CKD/proteinuria; and
3) normal contralateral kidney and new baseline eGFR will likely be > 45[2].

Thermal Ablation (TA)

1. Consider TA an alternate approach for management of cT1a renal masses <3 cm in size. A percutaneous approach is preferred.
2. Both radiofrequency ablation and cryoablation are options.
3. A RMB should be performed prior to TA.
4. Counseling about TA should include information regarding increased likelihood of tumor persistence/recurrence after primary TA, which may be addressed with repeat TA if further intervention is elected.

Active Surveillance (AS)

1. For patients with renal masses suspicious for cancer, especially those <2cm, AS is an option for initial management.
2. Prioritize AS/Expectant Management when the anticipated risk of intervention or competing risks of death outweigh the potential oncologic benefits of active treatment.
3. When the risk/benefit analysis for treatment is equivocal and the patient prefers AS, physicians should repeat imaging in 3-6 months to assess for interval growth and may consider RMB for additional risk stratification.
4. When the oncologic benefits of intervention outweigh the risks of treatment and competing risks of death, physicians should recommend active treatment. In this setting, AS may be pursued only if the patient understands and is willing to accept the associated oncologic risk

Factors Favoring AS/Expectant Management

Patient-related	Tumor-related
Elderly Life expectancy <5 years High comorbidities Excessive perioperative risk Frailty (poor functional status) Patient preference for AS Marginal renal function	Tumor size <3cm Tumor growth <5mm/year Non-infiltrative Low complexity Favorable histology

Principles Related to PN

1. Prioritize preservation of renal function through efforts to optimize nephron mass preservation and avoidance of prolonged warm ischemia.
2. Negative surgical margins should be a priority. The extent of normal parenchyma removed should be determined by surgeon discretion taking into account the clinical situation; tumor characteristics including growth pattern, and interface with normal tissue. Enucleation should be considered in patients with familial RCC, multifocal disease, or severe CKD to optimize parenchymal mass preservation.

Surgical Principles

1. In the presence of clinically concerning regional lymphadenopathy, lymph node dissection should be performed for staging purposes.
2. Adrenalectomy should be performed if imaging and/or intraoperative findings suggest metastasis or direct invasion.
3. A minimally invasive approach should be considered when it would not compromise oncologic, functional and perioperative outcomes.
4. Pathologic evaluation of the adjacent renal parenchyma should be performed after PN or RN to assess for possible nephrologic disease, particularly for patients with CKD or risk factors for developing CKD.

Radical Nephrectomy

Prototypical RN encompasses the basic principles of early ligation of the renal artery and vein, removal of the kidney with primary dissection external to Gerota fascia, excision of the ipsilateral adrenal gland, and performance of an extended lymph node dissection (LND) from the crus of the diaphragm to the aortic bifurcation

Performance of a perifascial nephrectomy is of undoubted importance during RN for preventing postoperative local tumor recurrence because approximately 25% of clinical T1b/T2 RCCs manifest perinephric fat involvement**.**

Preliminary renal arterial ligation remains an accepted practice; however, in large tumors with abundant collateral vascular supply, it is not always possible to obtain complete preliminary control of the arterial circulation.

Removal of the ipsilateral adrenal gland is not routinely necessary except:

Patients with an enlarged or indistinct adrenal gland on CT, extensive malignant replacement of the kidney, or a palpably abnormal adrenal gland

diffuse involvement by tumor, large tumor size (>10 cm), extrarenal tumor extension, tumor thrombus, lymphadenopathy and regional metastasis, or an adrenal mass on imaging.

preoperative CT and MRI may miss 20% to 25% of adrenal metastases

The need for an extensive LND in all patients undergoing RN has also been challenged

1. RCC metastasizes through the bloodstream
2. lymphatic drainage of the kidney is highly variable
3. an extensive retroperitoneal LND may not remove all possible sites of metastasis

AUA Guidelines now recommend that LND should be performed when suspicious lymphadenopathy is identified on imaging or surgical exploration.

Beyond this LND can be selectively considered for locally advanced disease

LND is primarily for staging and prognostic purposes.

Indications for regional lymphadenectomy include

1. enlarged lymph nodes on imaging
2. cytoreductive surgery for metastatic disease
3. tumor size greater than 10 cm
4. nuclear grade 3 or greater, sarcomatoid histology
5. presence of tumor necrosis on imaging
6. extrarenal tumor extension
7. tumor thrombus
8. direct tumoral invasion of adjacent organs.

Radical nephrectomy is reserved for renal tumors that are not amenable to partial nephrectomy.

Indications for radical nephrectomy include

1. tumors in nonfunctional kidneys
2. large tumors replacing the majority of renal parenchyma
3. tumors associated with detectable regional lymphadenopathy
4. tumors associated with renal vein thrombus.

All renal tumors suspicious of malignancy should be staged with abdominopelvic CT or MRI and chest imaging with chest radiograph or chest CT .

If any sign of metastatic disease is present, a bone scan and head CT should also be obtained.

The cross-sectional imaging should be closely evaluated for tumor thrombus, enlarged retroperitoneal nodes, and any embryologic abnormalities of the renal collecting system and vasculature.

Before surgery, percutaneous renal biopsy can be considered in

1. patients with another malignancy to evaluate for potential metastatic disease,
2. to evaluate for the possibility of lymphoma in cases of infiltrative-appearing renal masses on imaging studies
3. solid masses that will be managed nonoperatively with percutaneous modalities (radiofrequency or cryotherapy)
4. in nonoperative cases when the histology may dictate the type of systemic therapy .

In cases of bilateral renal tumors, percutaneous renal biopsy should be considered to guide management.

Partial Nephrectomy

When technically feasible, partial nephrectomy is the preferred method of choice for managing most renal masses to preserve maximum renal function .

Although in the past partial nephrectomy was reserved for specific conditions (bilateral tumors, tumor in a solitary kidney, patient at high risk for future renal failure) and small tumors less than 4 cm in diameter **, indications for partial nephrectomy have considerably widened to include most renal masses that can be safely and completely removed independent of their size.**

Relative contraindications to partial nephrectomy include the following:

Technical issues

- Cold ischemia time greater than 45 minutes (consider extracorporeal approach)
- Less than 20% of global nephron mass retained

Cancer-related issues

- Diffuse encasement of renal pedicle by tumor
- Diffuse invasion of central collecting system
- Tumor thrombus involving major renal veins
- Adjacent organ invasion (stage cT4)
- Regional lymphadenopathy (stage cTxN1)

Hyperfiltration Injury. When a significant portion of renal parenchyma is removed, the renal blood flow is delivered to a smaller number of nephrons, which can lead to increased glomerular capillary perfusion pressure that results in an increased single-nephron glomerular filtration rate called *hyperfiltration* .

Over decades, the hyperfiltration can injure the remaining nephrons, resulting in **focal segmental glomerulosclerosis** and the clinical manifestations of proteinuria and progressive renal failure.

Hyperfiltration injury is most common when the total nephron mass of both kidneys is reduced by more than 80%.

Renal Ischemia and Hypothermia. To minimize blood loss and allow for adequate surgical visibility, it is often necessary to employ vascular compression during partial nephrectomy.

Options include

1. manual compression
2. renal compression clamp (Kaufmann clamp)
3. selective clamping of the renal artery
4. en bloc clamping of the entire renal pedicle.

Manual and clamp compression of renal parenchyma is preferable because vascular clamping is associated with a higher incidence of renal complications.

It is unclear whether leaving the renal vein unclamped for retrograde renal perfusion offers any tangible benefit.

Attempting to limit warm ischemia to 20 minutes and cold ischemia to 35 minutes helps maintain renal function

To help prevent acute postoperative renal failure, intravenous mannitol (12.5 g) and furosemide (20 mg) should be infused about 15 minutes before renal artery clamping

Enucleation and Surgical Margin. Simple tumor enucleation can be safely conducted in small renal tumors while preserving a small rim of normal tissue and a negative surgical margin.

Multifocality and Tumor Size.

The incidence of multifocality is approximately 2% for clear cell and chromophobe RCC and 10% for papillary RCC.

Multifocal tumors are also more common as the primary tumor size increases.

Careful inspection of the entire renal surface should be done at the time of partial nephrectomy to ensure that intraoperative findings corroborate preoperative imaging studies.

If additional unanticipated renal mass(es) are encountered intraoperatively, **partial nephrectomy is still the treatment of choice for multifocal tumors as long as they can be safely resected with clear surgical margins.**

Hereditary Renal Malignancy. Hereditary renal tumors are usually multifocal and bilateral, with high likelihood of recurrence.

Except for patients with hereditary leiomyomatosis and RCC who should be aggressively treated with wide excision, most patients with hereditary syndromes can be safely observed with little chance of metastasis until the renal tumors reach 3 cm in size.

The entire renal surface should be visualized, and all visible tumors should be resected.

TABLE 97.15 Surveillance for Clinically Localized Renal Neoplasms: General Considerations

FOLLOW-UP MEASURE	RECOMMENDATION
Physical examination and history	History and physical examination directed at detecting signs and symptoms of metastatic spread or local progression
Laboratory testing	Basic laboratory testing, including BUN/creatinine, urinalysis, and eGFR, for all patients Progressive renal insufficiency or proteinuria should prompt nephrology referral CBC, LDH, LFTs, alkaline phosphatase, and serum calcium per discretion of the physician
Central nervous system imaging	Acute neurologic signs should lead to prompt neurologic cross-sectional imaging of the head or spine based on localized symptoms
Bone scan	Elevated alkaline phosphatase, clinical symptoms such as bone pain, and/or radiographic findings suggestive of a bony neoplasm should prompt a bone scan Bone scan should not be performed in the absence of these signs and symptoms

TABLE 97.16 Surveillance After Radical or Partial Nephrectomy[a]

FOLLOW-UP MEASURE	RECOMMENDATION
LOW-RISK PATIENTS	
Abdominal imaging	**Partial Nephrectomy:** Obtain a baseline abdominal scan (CT or MRI) within 3–12 months after surgery. If the initial postoperative scan is negative, abdominal imaging (US, CT, or MRI) may be performed yearly for 3 years based on individual risk factors. **Radical Nephrectomy:** Patients should undergo abdominal imaging (US, CT, or MRI) within 3–12 months after surgery. If the initial postoperative imaging is negative, abdominal imaging beyond 12 months may be performed at the discretion of the clinician.
Chest imaging	**Partial and Radical Nephrectomy:** Obtain a yearly CXR for 3 years and only as clinically indicated beyond that time period.

MODERATE- TO HIGH-RISK PATIENTS (pT2-4N0Mx or pT[any]N1Mx): PARTIAL OR RADICAL NEPHRECTOMY	
Abdominal imaging	A baseline abdominal scan (CT or MRI) within 3–6 months after surgery with continued imaging (US, CT, or MRI) every 6 months for at least 3 years and annually thereafter to year 5. Imaging beyond 5 years may be performed at the discretion of the clinician. Perform site-specific imaging as symptoms warrant.
Chest imaging	Obtain a baseline chest scan (CT) within 3–6 months after surgery with continued imaging (CXR or CT) every 6 months for at least 3 years and annually thereafter to year 5. Imaging beyond 5 years is optional and should be based on individual patient characteristics and tumor risk factors.

Metastatic Renal Cell Carcinoma

Approximately one-third of all patients with newly diagnosed RCC are seen initially with synchronous metastatic disease, and an additional 20% to 40% of patients with clinically localized disease at diagnosis eventually develop metastases.

Metastatic RCC is almost always fatal, with 10-year survival rates of less than 5%.

Prognostic factors

Memorial Sloan Kettering Cancer Center

- Karnofsky performance score < 80%
- Elevated lactate dehydrogenase (>1.5 times upper limit of normal)
- Low hemoglobin (<lower limit of normal)
- Elevated corrected calcium (>10 mg/dL)
- Absence of prior nephrectomy

RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	20 months
Intermediate	1–2	10 months
Poor	3–5	4 months

International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model (IMDC)

- Karnofsky performance score <80%
- Neutrophilia (>upper limit of normal)
- Low hemoglobin (<lower limit of normal)
- Elevated corrected calcium (>upper limit of normal)
- Thrombocytosis (>upper limit of normal)
- <1 yr from diagnosis to VEGF-targeted therapy

RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	43.2 months
Intermediate	1–2	22.5 months
Poor	3–6	7.8 months

SURGICAL MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA

Cytoreductive Nephrectomy

(1) the rare but well-described occurrence of spontaneous regression of metastatic lesions after nephrectomy

(2) preclinical data suggesting that large primary tumors may inhibit T-cell function

1. In a metaanalysis comparing CN+ INF-based immunotherapy vs. INF-based immunotherapy only, increased long-term survival was found in patients treated with CN. However, INF-based immunotherapy is no longer relevant in contemporary clinical practice.

1. CARMENA, a phase III non-inferiority RCT investigating immediate CN followed by sunitinib vs. sunitinib alone, showed that sunitinib alone was not inferior to CN followed by sunitinib with regard to OS. (The trial included 450 patients with metastatic ccRCC of intermediate- and MSKCC poor risk)

2. The randomised EORTC SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS. However, in secondary endpoint analysis a strong OS benefit was observed in favour of the deferred CN approach in the ITT population with a median OS of 32.4 months in the deferred CN arm vs. 15 months in the immediate CN arm .

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-mRCC shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

Resection of Metastases

Several retrospective studies have suggested that patients undergoing complete resection of isolated metastatic foci may experience long disease-free intervals with median overall survival rates of 35% to 50% in some reports.

Several factors are associated with an improved outcome after metastasectomy, including complete resection, presence of solitary metastatic lesions, age younger than 60 years, smaller tumor size, presence of pulmonary metastases, and development of metachronous metastatic disease.

There are no prospective, randomized studies demonstrating a favorable outcome with metastasectomy. It is therefore possible that the favorable outcome after resection of limited metastatic disease may be a reflection of patient selection bias, differences in tumor biology and natural history, or other confounding factors not related to resection.

Thanks for your attention