CANCER EDUCATION DAY

Management of Renal Malignancies

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WINDSOR REGIONAL HOSPITAL
OUTSTANDING CARE – NO EXCEPTIONS!

Erie St. Clair
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The management question is not “how do I remove it?”

Balance four competing domains

Tumour biology

Size / stage
Imaging phenotype
Histology + grade

Renal function

Baseline eGFR / proteinuria
Solitary kidney
Future CKD risk

Competing mortality

Age + comorbidity
Life expectancy
Other-cause mortality

Patient priorities

Tolerance for uncertainty
Procedure burden
Follow-up preference

Shared decision → AS / biopsy / PN / RN / thermal ablation / SBRT

CUA 2022; AUA 2021.

AJCC 8th edition: anatomy still drives the first branch

T1a	≤4 cm, kidney-confined
T1b	>4–7 cm, kidney-confined
T2	>7 cm, kidney-confined
T3a	**renal vein/branches, collecting system, sinus or perirenal fat**
T3b/c	IVC below / above diaphragm or IVC wall
T4	beyond Gerota fascia / contiguous ipsilateral adrenal

Stage groups

I = T1 N0 M0
II = T2 N0 M0
III = T3 N0 or T1–3 N1 M0
IV = T4 or M1

Imaging implication

Multiphasic contrast CT/MRI for local characterization; chest staging is risk-adapted. Look specifically for sinus/venous invasion and nodes.

Pearl

"T1 by size" is not T1 if renal sinus fat, collecting system, or venous invasion is present.

Pathology: subtype and grade modify the meaning of “small”

Clear cell RCC

Most clinically familiar subtype. WHO/ISUP grade applies. Sarcomatoid/rhabdoid differentiation and necrosis signal adverse biology.

Papillary RCC

WHO 2022 no longer recommends “type 1 vs type 2.” Several former type 2 tumours are now distinct molecular entities.

Chromophobe / oncocytic

Chromophobe RCC plus a broader oncocytic family; biopsy interpretation may be limited by overlap in oncocytic neoplasms.

WHO 2022 shift

- Morphology remains central, but molecularly defined RCCs are now a formal category.
- Clear cell papillary RCC renamed “clear cell papillary renal cell tumour” reflecting indolent behaviour.
- WHO/ISUP grade is used for clear cell and papillary RCC; not validated the same way for chromophobe RCC.

Renal mass biopsy: use it when the answer can change the plan

Strongest use cases

- Before thermal ablation
- AS vs intervention is equivocal
- Suspected metastasis, lymphoma, inflammatory/infectious lesion
- Histology will alter systemic/local strategy

What it does well

2026 meta-analysis: ~90% diagnostic yield; sensitivity for malignancy 99%; benign/malignant concordance 96%; subtype concordance 89%.

What it does less well

Grade is less reliable: four-tier concordance ~64%. A nondiagnostic biopsy is not a benign biopsy; repeat sampling can be useful.

Technique Multiple core biopsies are preferred over FNA (AUA).

Safety Recent pooled complication rate ~3%; major complications <1%; bleeding ~1%.

Decision rule **Do not biopsy merely to "have pathology" if management will be unchanged.**

Fox Chase nomograms: quantify the risk you are actually treating

RCC Competing Risk Model

- Estimates kidney-cancer death vs other-cancer death vs non-cancer death.
- Original model uses age, sex, race and tumour size; a comorbidity-adjusted version incorporates Charlson Comorbidity Index (CCI).
- Most useful when deciding whether immediate treatment offers meaningful survival value in older/comorbid patients.

Why it matters

In the comorbidity-based cohort of patients ≥66 with localized RCC, competing-cause mortality substantially exceeded kidney-cancer mortality over time. The model is a counselling aid—not a treatment threshold.

How to use in clinic

1 Enter patient + tumour variables

2 Compare RCC vs competing mortality

3 Add biopsy if biology remains uncertain

4 Choose intensity proportional to net benefit

Fox Chase Cancer Prediction Tools: nephrometry.com/nomograms/

Active surveillance is an active management strategy

Best fit

CUA: preferred for suspected malignancy <2 cm; reasonable option for 2–4 cm. AUA: AS may be elected for solid masses <2 cm; prioritize expectant management when competing risks exceed oncologic benefit.

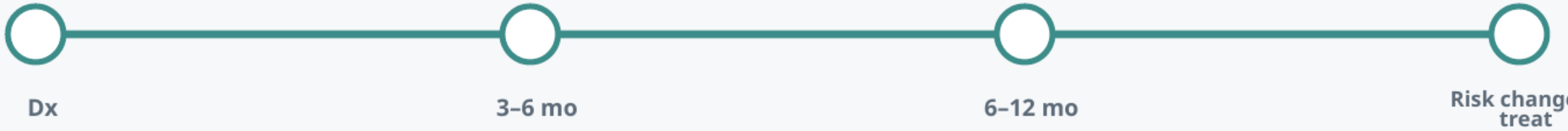
Follow-up

CUA panel: imaging commonly 3–6 months in year 1, then 6–12 months if stable; modality can be ultrasound when measurements are reliable, with cross-sectional confirmation of suspected growth.

Triggers to reconsider

CUA: size >4 cm, consecutive growth >0.5 cm/year, metastasis, or patient choice. AUA uses a somewhat more intervention-oriented risk framework; biopsy can refine uncertainty.

Key distinction **AS = serial assessment with intent to intervene if risk changes. Watchful waiting = symptom-directed care when definitive treatment is no longer expected to improve outcomes.**



Surgery: nephron preservation when oncologically sound

Partial nephrectomy

CUA: recommended over RN for suspected malignant SRM. AUA: prioritize PN for cT1a when intervention is indicated; prioritize nephron-sparing with solitary kidney, bilateral/familial disease, CKD or proteinuria.

Radical nephrectomy

AUA: appropriate when oncologic potential is higher and PN is challenging, particularly with no CKD/proteinuria, normal contralateral kidney, and predicted post-RN eGFR >45 mL/min/1.73 m^2.

Approach

Minimally invasive PN when technically feasible and oncologically safe. For RN, minimally invasive surgery generally reduces morbidity when appropriate; open surgery remains necessary for selected complex disease.

Operative priorities

- Negative margin, not a wide margin.
- Preserve nephron mass; avoid unnecessarily prolonged warm ischemia.
- Clinically suspicious nodes → remove clinically positive nodes for staging.
- Do not routinely remove a radiographically normal adrenal gland.

Thermal ablation: lower procedural burden, more local uncertainty

Who fits

Best evidence in cT1a, especially small peripheral lesions and patients with surgical risk, limited renal reserve, prior ipsilateral surgery, or strong preference for a percutaneous approach.

Cryo vs RFA

CUA: both are acceptable with similar oncologic outcomes/adverse events. Most series are in tumours <3 cm; for 3–4 cm lesions, recurrence/complication risk rises.

Counselling

Compared with PN, ablation generally has lower peri-procedural burden and better short-term renal functional preservation, but evidence is largely nonrandomized and local retreatment is more common.

Non-negotiable	**Obtain renal mass biopsy before (preferred) or at ablation so surveillance is anchored to histology.**
Technical selection	Tumour size, endophytic/central location, collecting system/ureter/bowel proximity, and operator experience determine feasibility more than modality labels alone.

Primary renal SBRT: now a credible non-operative local therapy

Where it fits

Patients with biopsy-confirmed localized RCC who are medically inoperable, technically high-risk for surgery, or decline surgery. Particularly useful when percutaneous ablation is anatomically difficult.

Evidence signal

ISRS 2024 systematic review: 36 studies / 822 patients. IROCK data showed low 5-year local failure. FASTRACK II prospectively treated 70 biopsy-confirmed patients unsuitable for surgery.

Caveat

No randomized comparison with PN, RN, or thermal ablation. Renal function declines after treatment and requires longitudinal monitoring; selection should be multidisciplinary.

2026 update

Long-term FASTRACK II and pooled FASTRACK 5-year outcomes further strengthen durability data, but do not erase the comparative-evidence gap.

Surgery remains reference standard → SBRT is an expanding option when surgery is not appropriate

MODALITY COMPARISON

For cT1a disease, the “best” option depends on what you optimize

	AS	Partial Nx	Cryo / RFA	SBRT
Oncologic certainty	Low initially	Highest	High; retreatable	Promising; non-RCT
Procedure burden	None	Highest	Low–moderate	Low
Renal preservation	Excellent	Good	Excellent	Good; dose-dependent
Pathology needed	Selective	Not always	Yes	Usually / ideally yes
Best fit	<2 cm / competing risk	Fit, treatable cT1a	Small lesion / higher surgical risk	Inoperable / high-risk

Comparative evidence is mostly observational; selection bias is substantial.

DECISION PATHWAY

The 2–4 cm renal mass is where decision quality matters most

1. Confirm phenotype

Multiphasic CT/MRI; stage; renal function; hereditary flags.

→

2. Estimate net benefit

Age, comorbidity, Fox Chase competing risk, CKD consequences.

→

3. Add biology

Biopsy if benign/indolent/aggressive histology would alter choice.

Then choose the least burdensome strategy that adequately controls the patient's actual oncologic risk

AS

Small / indolent
High competing risk

PN

Fit patient
Nephron-sparing feasible

RN

High complexity / higher risk
PN not prudent

Ablation

Small lesion
Higher surgical risk

SBRT

Inoperable / high-risk
Ablation unsuitable

T1B–T4 / N+

Beyond the small renal mass: surgery dominates localized higher-stage disease

cT1b	PN when technically/oncologically appropriate; RN when complexity or risk makes PN imprudent.
cT2	RN is common; PN is selective (solitary kidney/CKD or expert-center feasibility).
cT3 venous / fat	Surgical extirpation with thrombectomy as indicated; approach and team depend on thrombus extent.
cN+	Remove clinically suspicious regional nodes for staging/local control during surgery.
T4 / M1	Multidisciplinary systemic-therapy strategy; role/timing of nephrectomy is individualized.

This talk focuses on localized primary management; metastatic systemic therapy is a separate treatment framework.

Case: 78-year-old, 2.6 cm enhancing cortical mass, eGFR 52

What changes the recommendation?

Tumour

Growth? complexity? cystic? suspicious nodes?

Patient

CCI / frailty / life expectancy / CKD trajectory?

Biopsy

Would oncocytoma vs low-grade RCC vs aggressive subtype change choice?

Preference

Accept surveillance uncertainty vs procedure burden?

Reasonable first discussion

AS is guideline-supported; RMB can reduce biologic uncertainty; ablation is reasonable if treatment is preferred; PN remains definitive if operative risk and anatomy are favourable.

Fox Chase contribution

If predicted non-RCC mortality dominates, the threshold for immediate intervention rises. If biopsy shows aggressive biology, that balance may shift back toward treatment.

The nomogram does not choose the treatment—it makes the trade-off visible.

Start with histology, IMDC risk, and tempo

The metastatic decision tree is different from the localized renal-mass algorithm.

CLEAR-CELL | NON–CLEAR-CELL | IMDC | BURDEN / SYMPTOMS | PATIENT GOALS

IMDC: six clinical variables

1. <1 year from diagnosis to systemic therapy
2. Karnofsky performance status <80%
3. Hemoglobin below LLN
4. Corrected calcium above ULN
5. Neutrophils above ULN
6. Platelets above ULN

Favorable

0 factors

Intermediate

1–2 factors

Poor

≥3 factors

Guideline nuance

AUA’s kidney-cancer guideline is explicitly a localized renal-mass guideline; it does not function as a dedicated systemic mRCC guideline. For Canadian practice, the CUA-accredited KCRNC advanced-kidney-cancer consensus and the 2024 CUA–KCRNC non–clear-cell report provide the most directly relevant Canadian framework. Contemporary phase III trials then update the systemic-therapy evidence base.

Clinical implication: biopsy a metastatic site or renal primary when histology is not already established and the result will alter systemic therapy.

Cytoreductive nephrectomy: selective, not reflexive

Systemic therapy now defines the default trajectory for most synchronous mRCC.

Consider upfront CN

- Good performance status
- Resectable primary
- Minimal systemic symptoms
- Limited metastatic burden
- Oligometastatic disease where complete local control is plausible

After CN: surveillance, metastasis-directed therapy, or systemic therapy depending on residual disease.

Systemic therapy first

- Most intermediate presentations
- Need for prompt disease control
- Uncertain biology / burden

Reassess for deferred CN after meaningful response or durable disease control. This is a multidisciplinary selection decision—not a mandatory sequence.

Avoid upfront CN

- Poor performance status
- Rapidly progressive disease
- Major systemic symptoms
- Active CNS metastases
- High extrarenal burden relative to primary
- Limited life expectancy

Oligometastatic / oligoprogressive disease

Metastasectomy, SBRT, or other local therapy can be considered in selected patients to achieve local control or defer a systemic-therapy change.

First-line systemic therapy: four durable standards

No head-to-head randomized comparison establishes one doublet as universally superior.

Nivolumab + ipilimumab

Best-established for IMDC intermediate/poor risk

Immune-only strategy; potential for long treatment-free intervals after response

Less attractive when very rapid cytoreduction is essential

Nivolumab + cabozantinib

All IMDC risk groups

High response probability + durable OS/PFS benefit

Chronic TKI toxicity and dose modification are common practical issues

Pembrolizumab + axitinib

All IMDC risk groups

Long-term OS/PFS benefit sustained at ≥5 years

Axitinib offers a short half-life that can help toxicity attribution

Pembrolizumab + lenvatinib

All IMDC risk groups

High ORR and long PFS in CLEAR

Requires active management of hypertension, diarrhea, fatigue, proteinuria and other TKI toxicities

Choose by IMDC risk, disease tempo/site, autoimmune or cardiovascular comorbidity, toxicity priorities, logistics, and patient preference—not cross-trial ORR/PFS ranking.

What the long-term phase III updates show

The signal is durable across different immunotherapy backbones; the toxicity/kinetics trade-offs remain clinically relevant.

CheckMate 214 — NIVO + IPI

9.3-y median follow-up
OS HR 0.71 (ITT) | 0.69 (IMDC I/P)
108-mo OS: 31.4% vs 19.5%
96-mo PFS: 22.7% vs 9.0%
Grade 3–4 treatment-related AE: 48.6% vs 64.1%

CheckMate 9ER — NIVO + CABO

5.6-y median follow-up
PFS HR 0.58 | median 16.4 vs 8.3 mo
OS HR 0.79 | median 46.5 vs 35.5 mo
ORR 55.7% vs 27.4% | CR 13.9% vs 4.6%

KEYNOTE-426 — PEMBRO + AXI

≥5-y follow-up
OS HR 0.84
PFS HR 0.69
ORR 60.6% vs 39.6%
Benefit remains sustained despite a narrowing late OS effect.

CLEAR — PEMBRO + LENVA

Final prespecified OS analysis
OS HR 0.79
PFS 23.9 vs 9.2 mo | HR 0.47
ORR 71.3% vs 36.7%
36-mo OS 66.4% vs 60.2%

Do not infer superiority across trials: populations, follow-up, endpoint timing, subsequent therapy, and censoring differ.

Switch mechanism; routine ICI rechallenge has not delivered

The post-ICI era now has randomized evidence that is directly relevant to sequencing.

CONTACT-03 (2023)

Atezolizumab + cabozantinib vs cabozantinib after prior ICI

No PFS or OS improvement; more toxicity.

Takeaway: do not reflexively add another PD-(L)1 agent after progression.

TiNivo-2 (2024)

Tivozanib + nivolumab vs tivozanib after prior ICI

No PFS benefit for ICI rechallenge.

Together with CONTACT-03, supports changing mechanism rather than continuing checkpoint blockade by default.

LITESPARK-005 (2024)

Belzutifan vs everolimus after prior PD-(L)1 + antiangiogenic therapy

18-mo PFS 24.0% vs 8.3%; ORR 21.9% vs 3.5%.
OS endpoint not significant at the reported interim analysis.

LITESPARK-011 (2026)

Belzutifan + lenvatinib vs cabozantinib after prior anti–PD-(L)1
PFS HR 0.74; ORR 53.1% vs 40.2%; DOR 22.0 vs 11.9 mo.
Final OS favored combination but did not cross the prespecified significance boundary.

Practical sequencing

After an IO/TKI doublet → use an active VEGFR-TKI or another non-cross-resistant mechanism.
After NIVO/IPI → a VEGFR-TKI remains a core next step.
Belzutifan-based therapy expands later-line options, but access and exact placement are jurisdiction-dependent.

2026 caution: first-line “triplet escalation” has not proven that more drugs are better; COSMIC-313 and LITESPARK-012 did not establish a routine triplet standard.

Histology matters again

The 2024 CUA–KCRNC report emphasizes clinical trials and subtype-specific treatment rather than extrapolating clear-cell data wholesale.

Papillary RCC

- Use IMDC risk stratification
- Clinical trial preferred when available
- If systemic therapy is needed: an ICI-based combination or cabozantinib are Canadian expert-report options
- Consider CN or metastasis-directed therapy only in appropriately selected patients

Chromophobe RCC

- No single established systemic standard
- Clinical trial strongly preferred
- Biology and therapeutic responsiveness differ from papillary and clear-cell RCC
- Low-volume asymptomatic disease can sometimes be observed in selected patients

Aggressive / rare variants

- Sarcomatoid or rhabdoid dedifferentiation → favour an ICI-based combination
- FH-deficient, medullary, collecting-duct, translocation and other rare entities warrant expert pathology review and histology-specific multidisciplinary planning
- Trial referral is particularly important

Selected low-volume, asymptomatic or minimally symptomatic metastatic nccRCC may be candidates for active surveillance or metastasis-directed therapy before systemic treatment.

TAKE-HOME

Five points to take back to clinic

1	**Stage precisely**	Sinus fat, collecting system and venous invasion can upstage a “small-looking” tumour.
2	**Biopsy for utility**	Histology is valuable when it changes AS vs treatment, modality, or surveillance.
3	**Competing risk is part of staging the patient**	Use Fox Chase tools to quantify other-cause mortality rather than relying on age alone.
4	**PN is the surgical default for cT1a**	But ablation and AS are guideline-supported in appropriately selected patients.
5	**SBRT has arrived—but with a different evidence tier**	Strong prospective/local-control data in non-operative patients; no randomized equivalence to surgery.

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- Mjaess G, et al. Systematic review/meta-analysis of renal tumour biopsy. Eur Urol. 2026.
- Yanagisawa T, et al. Ablation vs partial nephrectomy comparative meta-analysis. 2023.

Guidelines are the management backbone; newer studies are used where they materially update biopsy, ablation, or SBRT evidence.

Metastatic RCC — selected contemporary sources

Guideline/consensus documents and randomized trials used in the added section.

Canadian / guideline framework

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Contemporary randomized evidence

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AUA note: the formal AUA renal cancer guideline is scoped to localized renal masses; metastatic systemic-therapy recommendations in this section therefore rely primarily on the Canadian KCRNC/CUA framework plus phase III trial data.