Chapter 24
Renal Cell Carcinoma

Sunanda Pejavar, James Rembert, and Alexander R. Gottschalk

PEARLS

- Two percent of all new cancers diagnosed in the US (54,390 new cases 2008).
- Steady increase in incidence not explained by incidental diagnoses (~7% of cases) made from increased diagnostic imaging.
- Male predominance (M:F 1.5:1).
- Most common in sixth to eighth decades; peak incidence in sixth decade.
- Ninety-five percent diagnoses made with imaging – characteristic solid, hypervascular mass.
- Metastatic disease in 30% at diagnosis, and eventually in 50% (lung, liver, bone, distant LN, adrenal, brain, opposite kidney, soft tissue).
- Stage at diagnosis is the most important prognostic factor.
- Predominant histologic type: adenocarcinoma arising from tubular epithelium.
  - Adenocarcinoma subtypes: clear cell (75–85%), chromophilic/papillary (10–15%), chromophobe (5–10%), oncocytic (rare)
  - Sarcomatoid (1–6%; poor prognosis)
- Risk factors: tobacco, urban environmental toxins (cadmium/asbestos/petrols), obesity, high dietary fat intake, acquired cystic renal disease from renal failure (premalignant condition with 4–9% incidence RCC; US surveillance q2 years).
- Association with von Hippel-Lindau disease: autosomal dominant, loss of 3p, >70% chance developing RCC (almost all clear cell histology) in addition to risk of developing multiple other benign and malignant tumors (retinal angiomas, CNS hemangioblastomas, pheochromocytoma, pancreatic cancer).
- Possible association with lymphoma, based on two large cancer database studies.

- RCC has low response rates to traditional chemotherapy (~6–7%). Response rates to immunotherapy (IL-2, interferon alpha) are slightly higher (~10–15%).

WORKUP

- H&P
  - Common signs and symptoms: hematuria (80%), flank pain (45%), flank mass (15%), classic triad of prior three only present in 10%, normocytic/normochromic anemia, fever, weight loss
  - Less common signs and symptoms: hepatic dysfunction without mets, polycythemia, hypercalcemia (occurs in 25% of patients with RCC mets)
- Labs: CBC, LFT, BUN/Cr, LDH, urinalysis
- Imaging: CT abdomen. MRI abdomen if CT suggests IVC involvement
- Metastatic evaluation: CXR. Bone scan or MRI brain only if clinically indicated

STAGING: RENAL CELL CARCINOMA

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

(AJCC 6TH ED., 2002)

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor 7 cm or less in greatest dimension, limited to the kidney
- T1a: Tumor 4 cm or less in greatest dimension, limited to the kidney
- T1b: Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney

T2: Tumor more than 7 cm, limited to the kidney
T3: Tumor extends into major veins or invades adrenal gland or perirenal and/or renal sinus fat, but not beyond Gerota's fascia
- T3a: Tumor directly invades adrenal gland or perirenal and/or renal sinus fat, but not beyond Gerota's fascia
- T3b: Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or vena cava below the diaphragm
- T3c: Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava

T4: Tumor invades beyond Gerota's fascia

Regional lymph nodes* (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastases in a single regional lymph node
N2: Metastasis in more than one regional lymph node
*Laterality does not affect the N classification
Regional lymph nodes: Renal hilar, paracaval, aortic (paraaortic, periaortic, lateral aortic), Retroperitoneal NOS.
Note: If a lymph node dissection is performed, pathologic evaluation would ordinarily include at least eight nodes.

(AJCC 7TH ED., 2010)

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor 7 cm or less in greatest dimension, limited to the kidney
- T1a: Tumor 4 cm or less in greatest dimension, limited to the kidney
- T1b: Tumor more than 4 cm, but not more than 7 cm in greatest dimension limited to the kidney

T2: Tumor more than 7 cm in greatest dimension, limited to the kidney
- T2a: Tumor more than 7 cm, but less than or equal to 10 cm in greatest dimension, limited to the kidney
- T2b: Tumor more than 10 cm, limited to the kidney

T3: Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
- T3a: Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat, but not beyond Gerota's fascia
- T3b: Tumor grossly extends into the vena cava below the diaphragm
- T3c: Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the venacava

T4: Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional lymph nodes (N)

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

continued

Distant metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Stage grouping		~5-Years OS by stage	
0:	TisN0M0	I:	~85–90%
I :	T1N0M0	II:	~65–85%
II:	T2N0M0	III:	~40–60%
III:	T3N0M0, T1-3N1M0	IV:	~30% if only 1 metastatic site <10% if >1 metastatic site
IV:	T4N0-1M0, AnyTN2M0 Any M1		

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002), published by Springer Science+Business Media.

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Anatomic stage/prognostic groups

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

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science+Business Media.

TREATMENT RECOMMENDATIONS

2002 Stage	Recommended treatment
I–III	■ Nephrectomy ■■ Open radical nephrectomy, but laparoscopic gaining popularity. Nephron sparing surgery via partial nephrectomy, if possible (open or laparoscopic) ■■ Possible to spare adrenal gland in ~75% cases ■ No role for adjuvant chemo/immunotherapy ■ No widely accepted role for neoadjuvant or adjuvant radiotherapy. Retrospective data suggest possible utility in select cases: ■■ Positive surgical margins ■■ Locally advanced disease with perinephric fat invasion and adrenal invasion (IVC/renal vein extension alone does not increase local recurrence significantly) ■■ LN+ ■■ Unresectable (pre-op RT)
IV	■ *Cytoreductive nephrectomy*: improved survival with nephrectomy followed by interferon alpha vs. interferon alpha alone (Flanigan et al. 2001) ■ *Systemic therapy* ■■ Immunotherapy (IL-2, interferon alpha, or combination) ■■■ High dose IL-2 only FDA approved treatment for Stage IV RCC ■■ Biologic agents show promise in recent trials ■■■ Bevacizumab ■■■ Sorafenib or sunitinib ■■■ Temsirolimus Consider chemo (gemcitabine ± 5-FU or capecitabine) ■■ Focal palliation of metastases ■■■ RT alone ■■■ Metastasectomy ■■■ Combination of both

TRIALS

RADIOTHERAPY

- Two prospective randomized European trials (Rotterdam trial, Sweden trial) showed no benefit to preoperative radiotherapy in terms of OS or PFS.
- Two prospective randomized trials (Fugitt, Cancer, 1973; Kjaer et al. 1987) showed no benefit to postoperative radiotherapy, yet these trials did not select a patient population that was likely to benefit from adjuvant RT. LR in radical nephrectomy series is

~5%. These excellent results are driven mainly by completely resected stage I/II tumors. However, with incomplete resection or +LN, LR rises dramatically to ~20–30%, suggesting a role for adjuvant RT in these patients. The following two studies retrospectively analyze patients at high risk for local recurrence and support a role for adjuvant RT in select patients.

- Kao et al. (1994): Retrospective study of 12 consecutive patients with locally advanced RCC (perinephric invasion or +margins) who received adjuvant RT 41–63 Gy (1.8–2 Gyfx) – 100% 5-year LC, with 5-year actuarial DFS 75% compared with 30% in 12 consecutive patients of similar stage treated with surgery alone.
- Stein et al. (1992): Retrospective study of 147 patients treated with post-op RT (median 46 Gy) vs. observation. In the T3N0 patients, LR was 10% vs. 37% favoring adjuvant RT. Also, 3/19 recurrences at the scar.

SYSTEMIC THERAPY

- *Escudier/AVOREN* (Escudier et al. 2007b): randomized, phase III trial; 649 patients with untreated metastatic RCC given interferon-alfa with either bevacizumab vs. placebo. PFS 10.2 vs. 5.4 months (HR 0.63, $p = 0.0001$).
- *Escudier/TARGET* (Escudier et al. 2007a): randomized, phase III trial; 903 patients with treatment-resistant RCC given sorafenib vs. placebo. PFS 5.5 vs. 2.8 months (HR 0.44; $p < 0.01$) favoring sorafenib. Toxicity higher in sorafenib arm.
- Motzer et al. (2007): randomized, phase III trial; 750 patients with untreated, metastatic RCC given sunitinib vs. interferon-alfa. PFS 11 vs. 5 months (HR 0.42; $p < 0.001$), RR 31 vs. 6% ($p < 0.001$), favoring sunitinib.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

Primary site

- Supine, arms-up to allow visualization of lateral isocenter marks, immobilize with wing-board or alpha cradle, wire scar, planning CT scan.
- *Volume*: nephrectomy bed (involved kidney if pre-op), lymph-node drainage sites, surgical clips; scar failures reported [Stein], so if not possible to include scar in treatment volume, treat it with electrons to full dose. SRS currently under active study.

Metastatic site (non-CNS)

- Proper immobilization depending on site; planning CT if 3DCRT needed to spare normal tissue
- *Volume:* focal treatment of metastasis with 2–3 cm margin
- See Chap. 40 for management of CNS metastases

DOSE PRESCRIPTIONS

- Pre-op: 40–50 Gy (1.8–2 Gy/fx)
- Post-op: 45–50 Gy with 10–15 Gy boost to micro/gross disease; total 50–60 Gy
- Metastases: 45–50 Gy in 3–4.5 weeks

DOSE LIMITATIONS

- Contralateral kidney: limit to ≤20 Gy in 2–3 weeks
- Liver: limit to <30% receiving >36–40 Gy
- Spinal cord: <45 Gy
- Small bowel: <40 Gy

FOLLOW-UP (NCCN 2009 RECOMMENDATIONS)

- *Stage I–III*: every 6 months × 2 years, then every 1 year × 5 years – H&P, CXR, Labs with LDH; CT chest/abdomen/pelvis at 4–6 months then as indicated.

REFERENCES

Escudier B, Eisen T, Stadler WM, et al. TARGET study group. Sorafenib in advanced clear-cell renal-cell carcinoma. NEJM 2007;356:125–134.

Escudier B, Pluzanska A, Koralewski P. AVOREN trial investigator. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomized, double-blind phase III trial. Lancet 2007;370:2103–2111.

Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345(23):1655–1659.

Fugitt RB, Wu GS, Martinelli LC. An evaluation of postoperative radiotherapy in hypernephroma treatment - a clinical trial. Cancer 1973;32(6):1332-1334.

Kao GD, Malkowicz SB, Whittington R, et al. Locall advanced renal cell carcinoma: low complication rate and efficacy of postnephrectomy planned with CT. Radiology 1994;193(3):725–730.

Kjaer M, Frederiksen PL, Engelholm SA. Postoperative radiotherapy in stage II and III renal adenocarcinoma. A randomized trial by the Copenhagen Renal Cancer Study Group. Int J Radiat Oncol Biol Phys 1987;13(4):665–672.

Motzer RJ, Hudson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal cell carcinoma. NEJM 2007;356:115–124.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Kidney Cancer. Available at: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. Accessed on May 1, 2009.

Stein M, Kuten A, Halpern J, et al. The value of postoperative irradiation in renal cell cancer. Radiother Oncol 1992;24(1):41–44.

FURTHER READING

Finney R. The value of radiotherapy in the treatment of hypernephroma – a clinical trial. Br J Urol 1973;45(3):258–269.

Greene FL; American Joint Committee on Cancer, American Cancer Society. AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002.

Juusela H, Malmio K, Alfthan O, et al. Preoperative irradiation in the treatment of renal adenocarcinoma. Scand J Urol Nephrol 1977;11:277–281.

Michalski JM. Kidney, Renal Pelvis, and Ureter. In: Halperin EC, Perez CA, Brady LW, et al., editors. Principles and Practice of Radiation Oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. pp. 1397–1411.

Redman BG, Kawachi M, Hurwitz M. Urothelial and kidney cancers. In: Pazdur R, Coia L, Hoskins W., Wagman L, editors. Cancer Management: A Multidisciplinary Approach. 8th ed. New York: CMP Healthcare Media; 2004. pp. 403–418.

Schefter T, Rabinovitch R. Cancer of the Kidney In: Leibel SA, Phiilips TL, editors. Textbook of Radiation Oncology. 2nd ed. Philadelphia: Saunders; 2004. pp. 923–938.

van der Werf-Messing B, van der Heul RO, Ledeboer RC. Renal cell carcinoma trial. Strahlentherapie (Sonderb) 1981;76:169–715.