Clinical manifestations, evaluation, and staging of renal cell carcinoma

Author: Michael B Atkins, MD
Section Editor: Jerome P Richie, MD, FACS
Deputy Editor: Sonali Shah, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Aug 2022. | **This topic last updated:** Jan 21, 2022.

INTRODUCTION

Malignant neoplasms involving the kidney may be primary or secondary tumors. Secondary renal neoplasms are usually clinically insignificant and discovered at postmortem examination.

Renal cell carcinomas (RCCs), which originate within the renal cortex, constitute 80 to 85 percent of primary renal neoplasms. Transitional cell carcinomas of the renal pelvis are the next most common (approximately 8 percent). Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, are rare. Nephroblastoma or Wilms tumor is common in children (5 to 6 percent of all primary renal tumors). (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma" and "Malignancies of the renal pelvis and ureter".)

The clinical and radiographic presentation of RCC and the methods used for tumor staging, as well as their potential application for screening, will be reviewed here. The prognosis and treatment of RCC are discussed separately. (See "Prognostic factors in patients with renal cell carcinoma".)

CLINICAL MANIFESTATIONS

Patients with RCC can present with a range of symptoms; unfortunately, many patients are asymptomatic until the disease is advanced. At presentation, approximately 25 percent of

individuals either have distant metastases or advanced locoregional disease [1].

Patients with localized disease can present with a wide array of symptoms and/or laboratory abnormalities, or they may be diagnosed incidentally. In one review of 309 consecutive patients with RCC, the most common presenting symptoms were hematuria, abdominal mass, pain, and weight loss [2]. In contemporary series, fewer patients have the typical symptoms and there is an increased frequency of incidental diagnosis due to radiologic procedures performed for other indications. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Epidemiology' and "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

This shift in pattern of presentation along with improvements in therapy have contributed to better outcomes in RCC. In a series of 701 patients, those who were diagnosed incidentally had a significantly better disease-specific survival at five years (76 versus 44 percent in those with symptoms) [3]. Multivariate analysis showed that the difference was due to the lower stage and histologic grade at the time of diagnosis. (See "Systemic therapy of advanced clear cell renal carcinoma".)

Symptoms and signs — For patients not diagnosed incidentally, symptoms and signs are generally related to invasion of adjacent structures or distant metastases.

- The classic triad of RCC (flank pain, hematuria, and a palpable abdominal renal mass) occurs in at most 9 percent of patients; when present, it strongly suggests locally advanced disease [2,4].

- Hematuria is observed only with tumor invasion of the collecting system. In an early series, hematuria was observed in almost 40 percent of patients [5]. When severe, the bleeding can cause clots and "colicky" discomfort. Clot formation does not occur with glomerular bleeding; thus, the presence of clots is a significant finding in patients with otherwise unexplained hematuria. (See "Etiology and evaluation of hematuria in adults", section on 'Blood clots'.)

- An abdominal or flank mass, which is associated with lower pole tumors, is more commonly palpated in the thin adult. The mass is generally firm, homogeneous, nontender, and moves with respiration.

- Scrotal varicoceles, the majority of which are left sided, are observed in as many as 11 percent of males with RCC [6]. Varicoceles typically fail to empty when the patient is recumbent. This finding should always arouse suspicion for a kidney tumor that has obstructed the gonadal vein where it enters the renal vein.

- Inferior vena cava involvement can produce a variety of clinical manifestations, including lower extremity edema, ascites, hepatic dysfunction (possibly related to a Budd-Chiari syndrome), and pulmonary emboli.

- Among patients with disseminated disease, signs or symptoms may be due to metastatic tumor; the most common sites of involvement include the lungs, lymph nodes, bone, liver, and brain. In this setting, the diagnosis is often made by biopsy of an accessible metastasis in the setting of a renal mass on abdominal computed tomography (CT). (See "Surveillance for metastatic disease after definitive treatment for renal cell carcinoma", section on 'Sites of metastasis'.)

Paraneoplastic symptoms — Patients with RCC can present with or subsequently develop systemic symptoms or paraneoplastic syndromes [7-9]. In some instances, these may be due to ectopic production of various hormones (eg, erythropoietin, parathyroid hormone-related protein [PTHrP], gonadotropins, human chorionic somatomammotropin, an adrenocorticotropic hormone [ACTH]-like substance, renin, glucagon, insulin) [9].

Anemia — Anemia, which can precede the diagnosis of RCC by several months, has been reported in 29 to 88 percent of patients with advanced disease [6,9-11]. The anemia is often disproportionately severe, can be either normocytic or microcytic, and is frequently associated with iron studies typical of those observed with the anemia of chronic disease. (See "Anemia of chronic disease/anemia of inflammation".)

Hepatic dysfunction — Hepatic dysfunction is an uncommon occurrence in patients with RCC, which is called Stauffer syndrome when it occurs in the absence of liver metastases [12-14]. In a series of 365 patients, 21 percent had a paraneoplastic elevation in serum alkaline phosphatase [14].

When hepatic dysfunction is present, it frequently is associated with fever, weight loss, fatigue, and a poor prognosis [15]. The dysfunction may result from tumor production of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and possibly interleukin 6 (IL-6) [16-18].

Nephrectomy may result in the amelioration of hepatic dysfunction [12,13]. Recurrent elevations of liver enzymes in such patients may herald local recurrence or distant metastatic disease [14].

Fever — Fever, which occurs in up to 20 percent of patients, is usually intermittent and is frequently accompanied by night sweats, anorexia, weight loss, and fatigue [9,19]. Its origin is unclear [9].

Hypercalcemia — Hypercalcemia occurs in up to 15 percent of patients with advanced RCC and can result from a number of different mechanisms:

- Lytic bone metastases.
- Overproduction of PTHrP [20-23]. Concurrent production of IL-6 may enhance the action of PTHrP [24,25].
- Increased production of prostaglandins that promote bone resorption [26,27]. In such patients, the hypercalcemia can respond to administration of a nonsteroidal anti-inflammatory drug (NSAID), such as indomethacin [26].

The pathogenesis and management of hypercalcemia in patients with malignancy are discussed elsewhere. (See "Hypercalcemia of malignancy: Mechanisms" and "Treatment of hypercalcemia" and "Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumors".)

Cachexia — As with other tumors, patients with RCC may suffer from significant cachexia [9]. (See "Pathogenesis, clinical features, and assessment of cancer cachexia".)

Erythrocytosis — Erythrocytosis occurs in 1 to 5 percent of patients with advanced RCC and appears to be due to constitutive production of erythropoietin [28]. In addition, since the mutated von Hippel-Lindau protein is associated with impaired regulation of hypoxia-induced proteins [29,30], erythrocytosis may be directly related to impaired degradation of hypoxia-inducible transcription factors under normoxic conditions. (See "Regulation of erythropoiesis" and "Epidemiology, pathology, and pathogenesis of renal cell carcinoma".)

Secondary (AA) amyloidosis — Secondary (AA) amyloidosis is found in up to 5 percent of patients [31,32]. This finding reflects a chronic inflammatory response as the amyloid fibrils are composed of fragments of the acute phase reactant serum amyloid A protein. (See "Pathogenesis of AA amyloidosis".)

Thrombocytosis — Thrombocytosis is rare in patients with RCC, but its presence is associated with a poor prognosis [33,34]. The underlying mechanism is not firmly established but could be related to IL-6 production by the tumor.

Polymyalgia rheumatica — A syndrome resembling polymyalgia rheumatica has been reported with RCC [35]. In contrast to idiopathic disease, the symptoms do not respond to prednisone but are often corrected by nephrectomy. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica".)

DIAGNOSTIC EVALUATION

Patients with unexplained hematuria or other symptoms, signs, or findings suggestive of possible RCC must undergo imaging evaluation for the presence of a renal mass. In addition, incidental diagnosis of RCC is becoming more common due to the frequent use of abdominal computed tomography (CT) and/or ultrasonography for evaluation of an unrelated problem. (See "Etiology and evaluation of hematuria in adults" and "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

CT or ultrasonography — The usual first test is abdominal computed tomography (CT) (image 1) or, occasionally, abdominal ultrasound.

Although ultrasonography is less sensitive than CT in detecting a renal mass, it is useful to distinguish a simple benign cyst from a more complex cyst or a solid tumor. The issues surrounding the evaluation of an asymptomatic renal mass or a cyst are discussed in detail separately. (See "Simple and complex kidney cysts in adults" and "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Summarized briefly, there are three major criteria that allow a simple cyst to be differentiated from a tumor or abscess on ultrasonography (table 1):

- The cyst is round and sharply demarcated with smooth walls
- There are no echoes within the cyst ("anechoic")
- There is a strong posterior wall echo, indicating good transmission through a cyst

If all of these criteria are fulfilled, no further evaluation is necessary since the likelihood of a malignancy is extremely small. If the criteria for a simple cyst by ultrasonography are not satisfied, the patient should undergo CT before and after injection of iodinated contrast. On CT, a simple cyst has a smooth appearance without a clearly delineated wall, has no enhancement with intravascular contrast, and is the density of water. CT urography allows imaging of both the renal parenchyma and the collecting system.

By comparison, thickened irregular walls or septa (image 2) and enhancement after contrast injection are suggestive of malignancy (table 1). (See "Simple and complex kidney cysts in adults", section on 'Bosniak classification of kidney cysts'.)

MRI — Magnetic resonance imaging (MRI) may be useful when ultrasonography and/or CT are inconclusive or if iodinated contrast cannot be administered because of allergy or poor renal function (image 3A-B). MRI is particularly helpful in cases where a neoplasm is diagnosed as

it evaluates for tumor growth into the collecting system or the vessels better than the other modalities. (See "Simple and complex kidney cysts in adults", section on 'Category IIF' and "Definitive surgical management of renal cell carcinoma".)

MRI with dynamic gadolinium contrast may be useful in distinguishing papillary or clear cell RCC from other benign and malignant solid renal neoplasms, although the examination does not obviate the need for tissue for diagnosis. In a meta-analysis, contrast enhancement in the corticomedullary phase on MRI diagnosed papillary RCC with a pooled sensitivity of 86 percent (95% CI 68-94 percent) and specificity of 92 percent (95% CI 76-98 percent) [36]. In one large series, clear cell carcinoma was diagnosed with a sensitivity of 85 percent and specificity of 76 percent [37].

Angiography — Catheter-based renal angiography is rarely necessary. If preoperative mapping of the vasculature is required prior to possible nephron-sparing surgery, either CT or MR angiography is preferable.

TISSUE DIAGNOSIS

For patients with localized disease, nephrectomy or partial nephrectomy is used in most cases to obtain tissue for diagnosis of RCC. For patients presenting with metastatic disease who plan to omit or defer cytoreductive nephrectomy, establishing diagnosis via a biopsy of a metastasis is preferred. After the presumptive diagnosis has been made based upon imaging studies, the patient must be evaluated for the extent of local involvement and the presence of metastatic disease prior to surgery. (See 'Staging studies' below.)

In addition to establishing the diagnosis of malignancy, tissue diagnosis provides information about the histopathologic type of RCC, which may have important implications for prognosis and treatment. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Pathology'.)

The role of percutaneous biopsy is more limited, although it may be used for a small renal mass if there is a high index of suspicion for a metastatic lesion to the kidney, lymphoma, or a focal kidney infection. A biopsy can also be used to confirm a diagnosis of RCC in patients who are not surgical candidates, although biopsy of a metastatic lesion, if present, is often preferable. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

STAGING STUDIES

Abdominal CT — The extent of local and regional involvement is determined primarily by abdominal computed tomography (CT), which is extremely accurate in staging RCC. In a retrospective study of 100 RCCs, for example, preoperative CTs were compared with the findings obtained at surgery [38]. The following results were obtained:

- For the detection of renal vein invasion, CT was 78 percent sensitive and 96 percent specific.
- For the detection of metastatic adenopathy, CT was 83 percent sensitive and 88 percent specific.
- For the detection of perinephric invasion, CT was only 46 percent sensitive but was 98 percent specific.
- For the detection of adjacent organ invasion, CT was 100 percent specific.

The sensitivity and specificity of CT for detecting nodal metastasis depend upon the size criterion used to define suspicious nodes. At least some data suggest that approximately 50 percent of patients with radiographically enlarged nodes in the 1 to 2 cm size range do not harbor metastases [39].

The limitations of imaging for the detection of renal vein or perinephric invasion may result in upstaging in patients who undergo nephrectomy. In a series of 1448 patients with clinical T1 lesions, 134 (9 percent) were upstaged to pathologic T3a disease [40]. Patients with pathologic T3a disease had a worse three-year recurrence-free survival compared with those with pathologic T1 disease (76 versus 93 percent).

Other imaging studies — Other imaging studies that may be useful for assessing for distant metastases include bone scan, CT of the chest, magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT:

- **Bone scan** – Bone scan is indicated only in patients with bone pain and/or an elevated serum alkaline phosphatase. In one series, for example, less than 5 percent of such patients had occult bone metastases [41]. Bone scan can be falsely negative since bone metastases are frequently osteolytic rather than osteoblastic.
- **Chest CT or radiograph** – CT of the chest is useful to evaluate for evidence of pulmonary or mediastinal lymph node metastases. Alternatively, patients with a small renal mass may be offered a chest radiograph. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass", section on 'Definition'.)

- **MRI** – MRI scanning with gadolinium is superior to CT for evaluation of the inferior vena cava and right atrium when tumor involvement is suspected [42].

- **PET/CT** – PET scanning has high sensitivity and specificity for the primary lesion. Although PET/CT may be more sensitive than radionuclide scanning for the detection of bone metastases, it is expensive and has limited use for routine staging [43-45].

Pathology

Isolated renal mass — For patients with isolated solid renal masses, resection with either a partial or complete nephrectomy is preferred over biopsy because it provides the diagnosis, pathologic tumor (T) and nodal (N) staging (table 2), and definitive treatment. Preoperative needle biopsies are usually not used for resectable renal lesions because of their low specificity [46] and concerns about tumor seeding of the peritoneum.

Although solid renal masses less than 3 cm were once thought to represent benign adenomas, distinctions based upon size are no longer used, since even small tumors frequently represent carcinomas that will grow over time [47]. Most solid renal masses require a histologic diagnosis; in patients with significant comorbidities, "watchful waiting" might be appropriate. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass" and "Simple and complex kidney cysts in adults".)

Metastatic disease — When metastatic disease is suspected at initial presentation, pathologic confirmation is required prior to starting therapy. Biopsy of a metastatic site is often easier and more informative than biopsy of the primary tumor.

In patients with a previously diagnosed nonrenal malignancy, metastatic disease is more likely than a new primary RCC. If the renal mass is nonenhancing and there is clinical evidence of progression of the nonrenal malignancy, biopsy confirmation may be unnecessary [48].

- **Is there a role for upfront cytoreductive nephrectomy in staging?** – The role of upfront cytoreductive nephrectomy is evolving in the era of effective treatments such as checkpoint inhibitor immunotherapy and antiangiogenic agents for patients with metastatic RCC (algorithm 1).

  In general, initial cytoreductive nephrectomy may be indicated in select patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)-favorable or low-intermediate risk features (ie, no or one risk factor) (table 3). Palliative cytoreductive nephrectomy may also be indicated in those experiencing symptoms from the primary tumor (eg, pain, intractable hematuria). Further details on the approach to cytoreductive

nephrectomy and supporting randomized trial data in patients with metastatic clear cell RCC are discussed separately. (See "Role of surgery in patients with metastatic renal cell carcinoma", section on 'Cytoreductive nephrectomy' and "Role of surgery in patients with metastatic renal cell carcinoma", section on 'Palliative nephrectomy'.)

For those with IMDC-high-intermediate or poor risk features (≥2 risk factors) (table 3), initial systemic therapy is indicated, and a decision about cytoreductive nephrectomy should be delayed until more information about disease responsiveness and treatment tolerability is available. (See "Systemic therapy of advanced clear cell renal carcinoma" and "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma".)

TNM STAGING SYSTEM

The eighth (2017) Tumor, Node, Metastasis (TNM) staging system is used for staging all histologic variants of RCC. This system is supported by both the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) [49]. These TNM criteria use the anatomic extent of disease to define prognostic stage groups. (See "Prognostic factors in patients with renal cell carcinoma".)

The TNM system is shown in the table (table 2). In this system, tumors limited to the kidney are classified as T1 or T2 based upon size. T3 tumors extend into the renal vein or perinephric tissues but not beyond the Gerota fascia, while T4 tumors extend beyond the Gerota fascia, including direct extension into the ipsilateral adrenal gland. Nodal and distant metastases are simply classified as absent or present.

SOLID RENAL MASSES

The optimal management of solid renal parenchymal masses is incompletely understood and relies upon both the ability of imaging studies to identify simple renal cysts and the likelihood of the lesion to exhibit clinically malignant behavior. The evaluation and initial management of a patient with a solid renal mass are discussed separately. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

SCREENING

Screening of asymptomatic individuals is not recommended because of the low prevalence of RCC in the general population. However, individuals at high risk for the development of RCC should undergo periodic monitoring with abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) to detect early disease [50].

Candidates for screening include patients with any of the following conditions:

- Inherited conditions associated with an increased incidence of RCC or other renal tumors, including Von Hippel-Lindau syndrome and tuberous sclerosis. (See "Clinical features, diagnosis, and management of von Hippel-Lindau disease" and "Renal manifestations of tuberous sclerosis complex" and "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis".)
- End-stage kidney disease, especially younger subjects without serious comorbid diseases who have been on dialysis for three to five years or more.
- A strong family history of RCC. (See "Hereditary kidney cancer syndromes".)
- Prior kidney irradiation.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cancer of the kidney and ureters".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a

variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient education: Renal cell carcinoma (kidney cancer) (Beyond the Basics)")

SUMMARY

- **Clinical manifestations** – Patients with renal cell carcinoma (RCC) can present with a range of symptoms due to the tumor itself (eg, mass, pain), invasion of the urinary tract (eg, hematuria), paraneoplastic syndromes, or the presence of metastases. In addition, RCC is more frequently being diagnosed incidentally as a consequence of increased use of imaging procedures for other reasons. (See 'Clinical manifestations' above.)

- **Diagnostic evaluation** – Patients with symptoms, signs, or other findings suggestive of RCC should undergo evaluation for the presence of a renal mass. Abdominal computed tomography (CT) or ultrasound can confirm the presence of a mass, distinguish RCC from a benign cyst, and assess the extent of disease. (See 'Diagnostic evaluation' above.)

- **Approach to a solitary small renal mass** – In the setting of a solitary small renal mass, imaging studies **cannot** reliably distinguish a benign renal tumor from RCC. Thus, it is generally recommended that lesions other than simple cysts be resected. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

- **Staging** – The tumor, node, metastasis (TNM) staging system, which is based upon the extent of the primary tumor and the presence or absence of regional lymph node involvement or distant metastases, is used for staging all histologic variants of RCC (table 2). This staging system correlates with prognosis and provides important information for patient management. (See 'TNM staging system' above and 'Tissue diagnosis' above and 'Staging studies' above and "Prognostic factors in patients with renal cell carcinoma".)

- **Screening for individuals at high risk for RCC** – Individuals thought to be at increased risk for the development of RCC should undergo routine screening with abdominal ultrasound, CT, or magnetic resonance imaging (MRI). (See 'Screening' above.)

REFERENCES

1. Garnick MB. Primary neoplasms of the kidney. In: Therapy in Nephrology and Hypertensio n: A Companion to Brenner and Rector's the Kidney, Brady HR, Wilcox CS (Eds), WB Saunder s, Philadelphia 1998.
2. Skinner DG, Colvin RB, Vermillion CD, et al. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. Cancer 1971; 28:1165.
3. Gudbjartsson T, Thoroddsen A, Petursdottir V, et al. Effect of incidental detection for survival of patients with renal cell carcinoma: results of population-based study of 701 patients. Urology 2005; 66:1186.
4. DeKernion JB. Real numbers. In: Campbell's Urology, Walsh PC, Gittes RF, Perlmutter AD (Ed s), WB Saunders, Philadelphia 1986. p.1294.
5. Gibbons RP, Monte JE, Correa RJ Jr, Mason JT. Manifestations of renal cell carcinoma. Urology 1976; 8:201.
6. PINALS RS, KRANE SM. Medical aspects of renal carcinoma. Postgrad Med J 1962; 38:507.
7. Chisholm GD, Roy RR. The systemic effects of malignant renal tumours. Br J Urol 1971; 43:687.
8. Laski ME, Vugrin D. Paraneoplastic syndromes in hypernephroma. Semin Nephrol 1987; 7:123.
9. Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol 1996; 14:216.
10. Cherukuri SV, Johenning PW, Ram MD. Systemic effects of hypernephroma. Urology 1977; 10:93.
11. Sufrin G, Mirand EA, Moore RH, et al. Hormones in renal cancer. J Urol 1977; 117:433.
12. Walsh PN, Kissane JM. Nonmetastatic hypernephroma with reversible hepatic dysfunction. Arch Intern Med 1968; 122:214.
13. Utz DC, Warren MM, Gregg JA, et al. Reversible hepatic dysfunction associated with hypernephroma. Mayo Clin Proc 1970; 45:161.
14. Chuang YC, Lin AT, Chen KK, et al. Paraneoplastic elevation of serum alkaline phosphatase in renal cell carcinoma: incidence and implication on prognosis. J Urol 1997; 158:1684.
15. Boxer RJ, Waisman J, Lieber MM, et al. Non-metastatic hepatic dysfunction associated with renal carcinoma. J Urol 1978; 119:468.
16. Chang SY, Yu DS, Sherwood ER, et al. Inhibitory effects of suramin on a human renal cell carcinoma line, causing nephrogenic hepatic dysfunction. J Urol 1992; 147:1147.

17. Blay JY, Rossi JF, Wijdenes J, et al. Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal-cell carcinoma. Int J Cancer 1997; 72:424.
18. Stadler WM, Richards JM, Vogelzang NJ. Serum interleukin-6 levels in metastatic renal cell cancer: correlation with survival but not an independent prognostic indicator. J Natl Cancer Inst 1992; 84:1835.
19. Cranston WI, Luff RH, Owen D, Rawlins MD. Studies on the pathogenesis of fever in renal carcinoma. Clin Sci Mol Med 1973; 45:459.
20. O'Grady AS, Morse LJ, Lee JB. Parathyroid hormone-secreting renal carcinoma associated with hypercalcemia and metabolic alkalosis. Ann Intern Med 1965; 63:858.
21. LYTTON B, ROSOF B, EVANS JS. PARATHYROID HORMONE-LIKE ACTIVITY IN A RENAL CARCINOMA PRODUCING HYPERCALCEMIA. J Urol 1965; 93:127.
22. GOLDBERG MF, TASHJIAN AH Jr, ORDER SE, DAMMIN GJ. RENAL ADENOCARCINOMA CONTAINING A PARATHYROID HORMONE-LIKE SUBSTANCE AND ASSOCIATED WITH MARKED HYPERCALCEMIA. Am J Med 1964; 36:805.
23. Sandhu DP, Munson KW, Harrop JS, et al. Humoral hypercalcaemia in renal carcinoma due to parathyroid hormone related protein. Br J Urol 1993; 72:848.
24. de la Mata J, Uy HL, Guise TA, et al. Interleukin-6 enhances hypercalcemia and bone resorption mediated by parathyroid hormone-related protein in vivo. J Clin Invest 1995; 95:2846.
25. Weissglas M, Schamhart D, Löwik C, et al. Hypercalcemia and cosecretion of interleukin-6 and parathyroid hormone related peptide by a human renal cell carcinoma implanted into nude mice. J Urol 1995; 153:854.
26. Brereton HD, Halushka PV, Alexander RW, et al. Indomethacin-responsive hypercalcemia in a patient with renal-cell adenocarcinoma. N Engl J Med 1974; 291:83.
27. Robertson RP, Baylink DJ, Marini BJ, Adkison HW. Elevated prostaglandins and suppressed parathyroid hormone associated with hypercalcemia and renal cell carcinoma. J Clin Endocrinol Metab 1975; 41:164.
28. Da Silva JL, Lacombe C, Bruneval P, et al. Tumor cells are the site of erythropoietin synthesis in human renal cancers associated with polycythemia. Blood 1990; 75:577.
29. Iliopoulos O, Levy AP, Jiang C, et al. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proc Natl Acad Sci U S A 1996; 93:10595.
30. Wiesener MS, Seyfarth M, Warnecke C, et al. Paraneoplastic erythrocytosis associated with an inactivating point mutation of the von Hippel-Lindau gene in a renal cell carcinoma. Blood 2002; 99:3562.

31. Pras M, Franklin EC, Shibolet S, Frangione B. Amyloidosis associated with renal cell carcinoma of the AA type. Am J Med 1982; 73:426.
32. Chisholm GD. Nephrogenic ridge tumors and their syndromes. Ann N Y Acad Sci 1974; 230:403.
33. Symbas NP, Townsend MF, El-Galley R, et al. Poor prognosis associated with thrombocytosis in patients with renal cell carcinoma. BJU Int 2000; 86:203.
34. O'Keefe SC, Marshall FF, Issa MM, et al. Thrombocytosis is associated with a significant increase in the cancer specific death rate after radical nephrectomy. J Urol 2002; 168:1378.
35. Sidhom OA, Basalaev M, Sigal LH. Renal cell carcinoma presenting as polymyalgia rheumatica. Resolution after nephrectomy. Arch Intern Med 1993; 153:2043.
36. Chiarello MA, Mali RD, Kang SK. Diagnostic Accuracy of MRI for Detection of Papillary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol 2018; 211:812.
37. Kay FU, Canvasser NE, Xi Y, et al. Diagnostic Performance and Interreader Agreement of a Standardized MR Imaging Approach in the Prediction of Small Renal Mass Histology. Radiology 2018; 287:543.
38. Johnson CD, Dunnick NR, Cohan RH, Illescas FF. Renal adenocarcinoma: CT staging of 100 tumors. AJR Am J Roentgenol 1987; 148:59.
39. Studer UE, Scherz S, Scheidegger J, et al. Enlargement of regional lymph nodes in renal cell carcinoma is often not due to metastases. J Urol 1990; 144:243.
40. Nayak JG, Patel P, Saarela O, et al. Pathological Upstaging of Clinical T1 to Pathological T3a Renal Cell Carcinoma: A Multi-institutional Analysis of Short-term Outcomes. Urology 2016; 94:154.
41. Koga S, Tsuda S, Nishikido M, et al. The diagnostic value of bone scan in patients with renal cell carcinoma. J Urol 2001; 166:2126.
42. Semelka RC, Shoenut JP, Magro CM, et al. Renal cancer staging: comparison of contrast-enhanced CT and gadolinium-enhanced fat-suppressed spin-echo and gradient-echo MR imaging. J Magn Reson Imaging 1993; 3:597.
43. Ramdave S, Thomas GW, Berlangieri SU, et al. Clinical role of F-18 fluorodeoxyglucose positron emission tomography for detection and management of renal cell carcinoma. J Urol 2001; 166:825.
44. Wu HC, Yen RF, Shen YY, et al. Comparing whole body 18F-2-deoxyglucose positron emission tomography and technetium-99m methylene diphosphate bone scan to detect

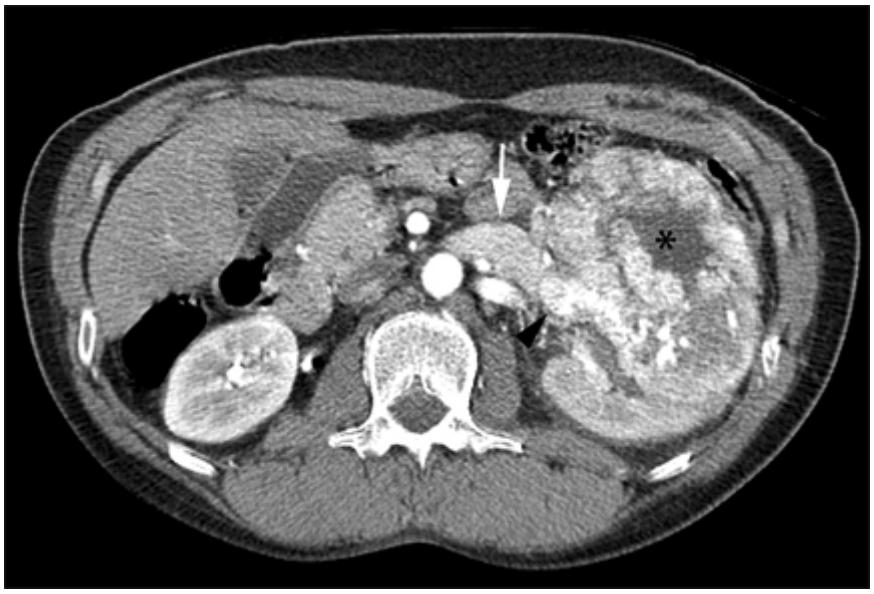
bone metastases in patients with renal cell carcinomas - a preliminary report. J Cancer Res Clin Oncol 2002; 128:503.

45. Goldberg MA, Mayo-Smith WW, Papanicolaou N, et al. FDG PET characterization of renal masses: preliminary experience. Clin Radiol 1997; 52:510.
46. Dechet CB, Zincke H, Sebo TJ, et al. Prospective analysis of computerized tomography and needle biopsy with permanent sectioning to determine the nature of solid renal masses in adults. J Urol 2003; 169:71.
47. Bosniak MA, Birnbaum BA, Krinsky GA, Waisman J. Small renal parenchymal neoplasms: further observations on growth. Radiology 1995; 197:589.
48. Sánchez-Ortiz RF, Madsen LT, Bermejo CE, et al. A renal mass in the setting of a nonrenal malignancy: When is a renal tumor biopsy appropriate? Cancer 2004; 101:2195.
49. Rini BI, McKiernan JM, Chang SS, et al. Kidney. In: AJCC Cancer Staging Manual, 8th, Amin M B (Ed), Springer, New York 2017. p.739.
50. Vogelzang NJ, Stadler WM. Kidney cancer. Lancet 1998; 352:1691.

Topic 2983 Version 31.0

GRAPHICS

CT image of large clear cell carcinoma of the kidney



Axial contrast-enhanced CT image shows a large enhancing mass in the left kidney with central necrosis (asterisk). A patent left renal vein (arrow) is noted medially. A low-grade (Fuhrman nuclear grade 2) clear cell renal cell carcinoma was identified pathologically after nephrectomy.

CT: computed tomography.

Courtesy of Ivan Pedrosa, MD.

Graphic 60352 Version 4.0

Definition of Bosniak classification of cystic kidney masses by CT scanning

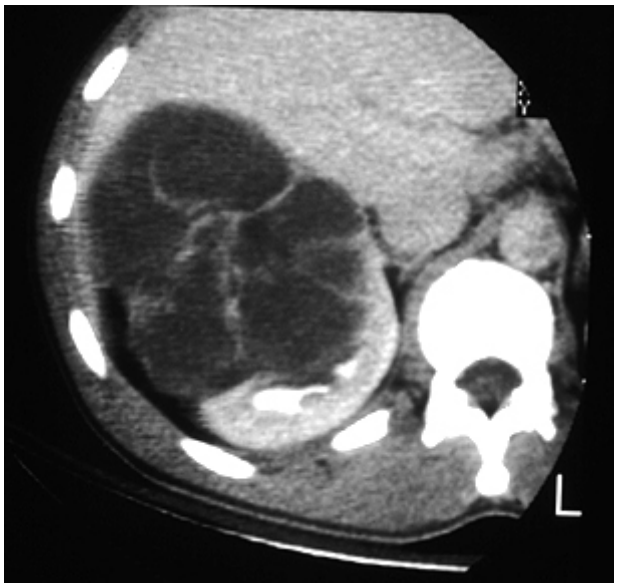
Category I - Simple benign cyst with the following features:
Hairline thin wall.
Density less than 20 Hounsfield units (similar to water).
Does not contain septa, calcification, or solid components.
Does not enhance.
Category II - Cystic lesions with the following features:
A few hairline thin septa.
"Perceived" enhancement may be present. There is no measurable enhancement.
Uniformly high attenuation lesions <3 cm that are well marginated and do not enhance fall into this category.
Category IIF - Minimally complicated cysts that do not neatly fall into category II. These lesions are generally well marginated but have some suspicious features that require follow-up:
Multiple hairline thin septa or minimal smooth thickening of the wall or septa.
"Perceived" enhancement of septa or wall may be present.
Thick and nodular calcification of the wall or septa, but no measurable contrast enhancement is present.
Totally intrarenal, nonenhancing, high attenuation lesions >3 cm in diameter fall into this category.
Category III - True indeterminate cystic masses that typically undergo surgical evaluation, although many lesions are benign. These lesions show the following:
Thickened irregular or smooth walls or septa in which measurable enhancement is present.
Category IV - These mostly malignant lesions have the following features:
All category III criteria.
Enhancing soft-tissue components adjacent to, but independent of, the wall or septum.

CT: computed tomography.

Adapted from Israel GM, Bosniak MA. An update of the Bosniak Renal Cyst Classification System. Urology 2005; 66:484.

Graphic 67087 Version 5.0

CT scan demonstrating cystic renal cell carcinoma



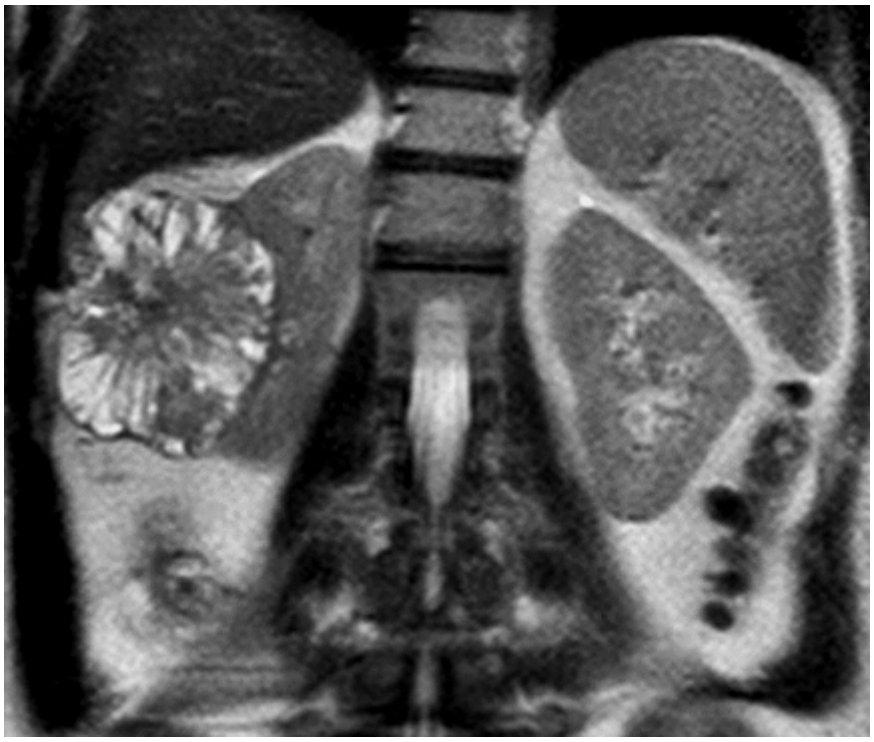
Single axial contrast-enhanced CT scan through the right kidney demonstrates a large, multiloculated cystic mass containing irregular septations.

CT: computed tomography.

Courtesy of Jonathan Kruskal, MD.

Graphic 77721 Version 4.0

MRI of clear cell carcinoma of the kidney



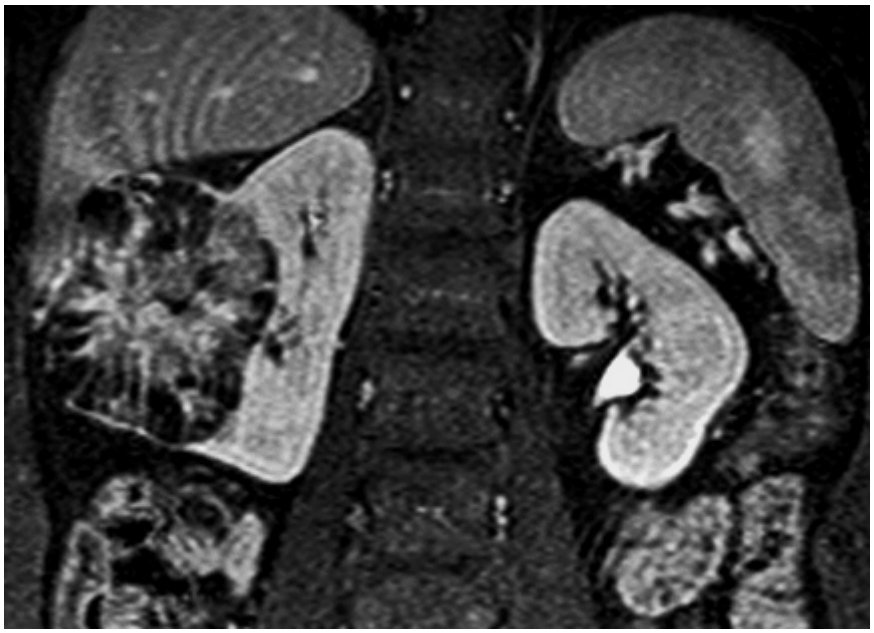
Coronal T2-weighted single-shot fast spin echo image shows a heterogeneous mass in the right kidney.

MRI: magnetic resonance imaging.

Courtesy of Ivan Pedrosa, MD.

Graphic 73120 Version 3.0

MRI of clear cell carcinoma of the kidney



Coronal three-dimensional T1-weighted fat-saturated gradient echo image after administration of gadolinium obtained during the excretory phase confirms the presence of enhancement (compared with precontrast, not shown) within the mass. After nephrectomy, a low-grade (Fuhrman nuclear grade 2) clear cell renal cell carcinoma was confirmed.

MRI: magnetic resonance imaging.

Graphic 51129 Version 4.0

Kidney cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >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 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's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

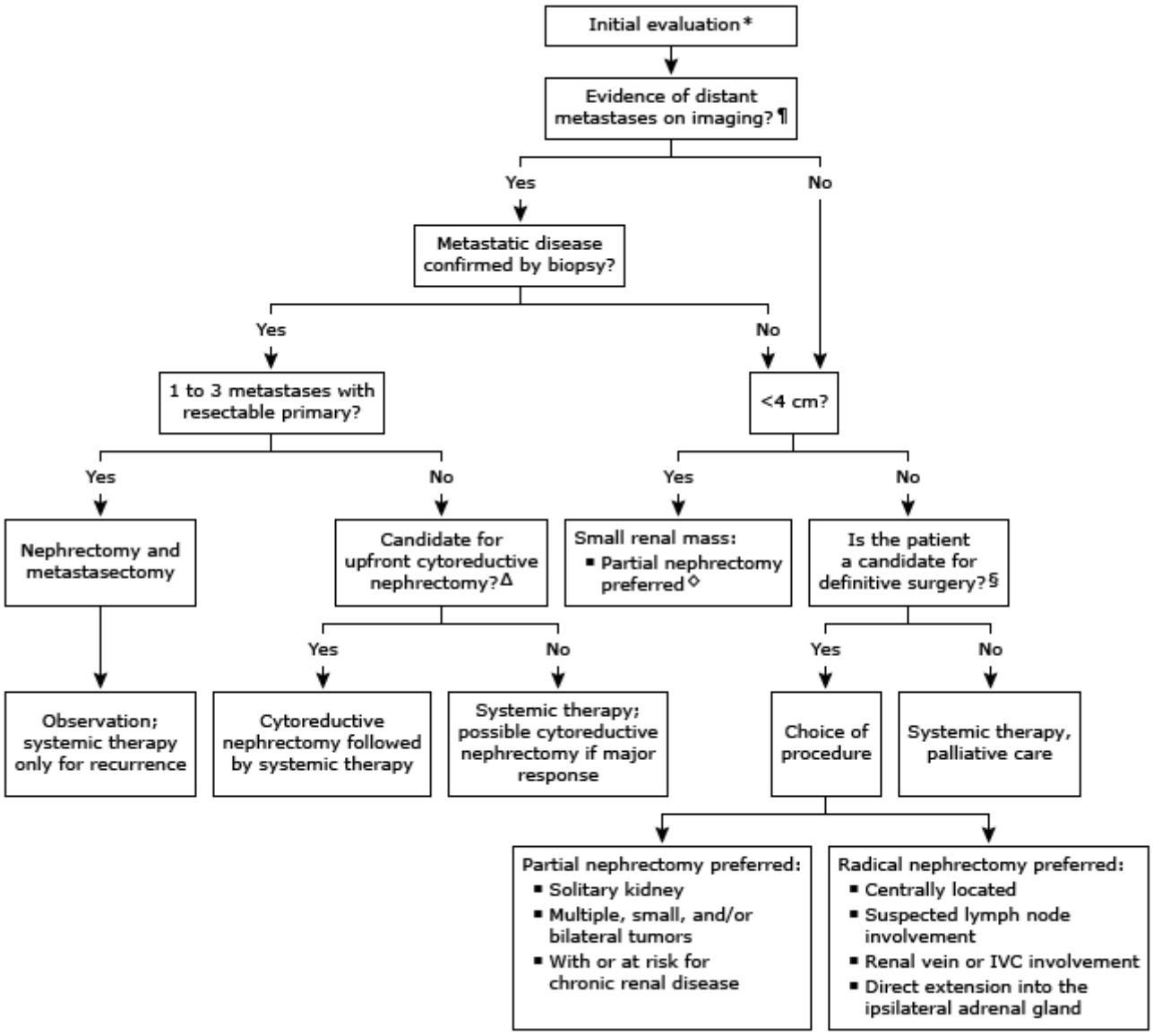
Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group**

			is...
T1	N0	M0	I
T1	N1	M0	III
T2	N0	M0	II
T2	N1	M0	III
T3	NX, N0	M0	III
T3	N1	M0	III
T4	Any N	M0	IV
Any T	Any N	M1	IV

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110735 Version 10.0

Initial evaluation and treatment of renal cell carcinoma



IVC: inferior vena cava; CT: computed tomography; MRI: magnetic resonance imaging.

* Preliminary diagnosis is based upon characteristic findings on imaging studies (CT/MRI); tissue diagnosis is generally obtained at time of definitive surgery.

¶ Chest imaging, additional studies as clinically indicated to look for evidence of metastases.

Δ Selection of patients should be done with considerable care so that appropriate patients can proceed with systemic therapy; important factors include good performance status, ability to perform adequate debulking, and favorable- or low-intermediate-risk diseases. Refer to UpToDate topic on the role of surgery in patients with metastatic renal cell carcinoma.

◇ Partial nephrectomy is the preferred approach to confirm the diagnosis and treat a renal mass <4 cm. However, thermal ablation (cryotherapy, radiofrequency ablation) or active surveillance may be appropriate alternatives for patients who are not surgical candidates. The choice between these approaches is guided by local expertise and patient preference. Refer to UpToDate topic on the diagnostic approach, differential diagnosis, and treatment of a small renal mass.

§ Based upon factors including patient preference, age, and comorbidities.

Graphic 109427 Version 4.0

International Metastatic Renal Cell Carcinoma Database Consortium criteria

Karnofsky performance status score <80
Time from original diagnosis to initiation of targeted therapy <1 year
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Favorable risk: None of the above risk factors present.
- Intermediate risk: 1 or 2 of the above risk factors present.
- Poor risk: 3 or more risk factors present.

Adapted from: Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013; 14:141.

Graphic 116130 Version 3.0

Contributor Disclosures

Michael B Atkins, MD Equity Ownership/Stock Options: Pyxis [Immunotherapy];Werewolf Therapeutics [Immunotherapy]. Grant/Research/Clinical Trial Support: AstraZeneca [RCC];Bristol Myers Squibb [Melanoma and RCC];Merck [Melanoma and RCC]. Consultant/Advisory Boards: Adagene [Melanoma, RCC, immunotherapy];Agenus [Melanoma, RCC, immunotherapy];Apexigen [Melanoma, RCC, immunotherapy];Asher Bio [Melanoma, RCC, immunotherapy];AstraZeneca [Melanoma, RCC, immunotherapy];Aveo [Melanoma, RCC, immunotherapy];Bristol Myers Squibb [Melanoma, RCC, immunotherapy];Eisai [Melanoma, RCC, immunotherapy];Exelixis [Melanoma, RCC, immunotherapy];Fathom [Melanoma, RCC, immunotherapy];Idera [Melanoma, RCC, immunotherapy];Iovance [Melanoma, RCC, immunotherapy];Leads [Melanoma, RCC, immunotherapy];Merck [Melanoma, RCC, immunotherapy];Novartis [Melanoma, RCC, immunotherapy];PACT [Melanoma, RCC, immunotherapy];Pfizer [Melanoma, RCC, immunotherapy];Pneuma [Melanoma, RCC, immunotherapy];Roche [Melanoma, RCC, immunotherapy];SAB Bio [Melanoma, RCC, immunotherapy];SeaGen [Melanoma, RCC, immunotherapy];Simcha [Melanoma, RCC, immunotherapy];Surface [Melanoma, RCC, immunotherapy];Symphogen [Melanoma, RCC, immunotherapy];Takeda [Melanoma, RCC, immunotherapy]. All of the relevant financial relationships listed have been mitigated. **Jerome P Richie, MD, FACS** No relevant financial relationship(s) with ineligible companies to disclose. **Sonali Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy