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Renal cell carcinoma: staging and surveillance

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Abstract

Renal cell carcinoma is a common malignancy with many histologic subtypes. Appropriate treatment depends not only upon the specific subtype but also the size of the tumor and extent of spread at time of presentation. Approximately 5% of RCCs are part of a hereditary syndrome which must also be considered in the therapeutic decisions. Although some RCCs are detected with ultrasound, CT or MR is required for staging. CT is used most commonly as it is most readily available and relatively less expensive than MR imaging. The TNM classification of the American Joint Committee on Cancer has largely replaced the Robson classification. Early detection, accurate staging, and improved treatment options have resulted in improved 5-year survival of patients with renal carcinoma.

Key words: Renal carcinoma—Papillary carcinoma—Chromophobe carcinoma—Hereditary renal cancers—Renal carcinoma staging

Renal cell carcinoma (RCC) is the 7th most common cancer among American males and the 9th most common among females [1]. The most common histology of RCC is clear cell adenocarcinoma which accounts for 70% to 80% of cases. Other histologies include papillary (15%), chromophobe (5%), and rare tumors such as renal medullary, Xp11 translocation, and collecting duct carcinomas. Any subtype of RCC can undergo sarcomatoid differentiation, which is associated with early metastases and a poor prognosis. In addition to sarcomatoid RCC, renal medullary RCC and collecting duct carcinomas are particularly aggressive [2, 3]. Histological subtyping helps determine therapy, as some tumors, such as papillary carcinomas, do not respond to antiangiogenic therapy [4].

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As many as 5% of patients with RCCs are associated with inherited syndromes. These include hereditary papillary renal cell carcinoma (papillary cancers), hereditary leiomyomatosis renal cell carcinoma (papillary cancers), von-Hippel Lindau Disease (clear cell cancers), tuberous sclerosis complex (clear cell cancers), and Birt–Hogg–Dube Syndrome (chromophobe renal cancers) [5]. Although not a hereditary cancer, renal medullary carcinomas develop in patients with sickle cell trait.

With the increasing use of cross-sectional imaging, RCC is discovered as an incidental finding in more than 50% of cases [6]. This is likely the cause of the stage migration seen in recent years. From 1993 to 2004, the percent of patients with Stage I disease increased from 43% to 57% [7]. Patients with newly diagnosed renal cancers are living longer after diagnosis, and the 5-year relative survival continues to increase [8]. Although many indolent cancers are now being detected, many patients with clinically significant cancers still often present with advanced disease. Nonetheless, staging of renal cancer is essential, not only to define the most appropriate treatment but also to determine the prognosis. The 5-year survival among patients without metastases is now over 50%, while it is only 10% among those with distant metastases [1]. Among patients with RCCs discovered incidentally, the 5-year survival is 85% compared with only 53% in those patients who were symptomatic [1]. Imaging has played a major role in this significant improvement through earlier detection and better staging.

Staging

Accurate staging is essential to define the most appropriate treatment and to determine the prognosis. For many years, renal carcinomas were staged using the Robson classification [9], which has now been largely replaced by the TNM staging of the American Joint Committee on Cancer (Tables 1 and 2).

The TNM staging system is briefly summarized as follows: Stage I disease is confined to the kidney, within the renal capsule. The tumor is considered T1a if it is smaller than 4 cm and stage T1b if it is between 4 and 7 cm in diameter. With the increasing number of small

Table 1. TNM staging of the American Joint Committee on Cancer

Primary tumors (T)	
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 the Gerota 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 the 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 the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 2. Stage Grouping

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1-2	N1	M0
	T3	N0-1	M0
IV	T4	N2	M0
	Any T	Any N	M1

RCCs found on cross-sectional imaging studies, some authors have suggested further refinement of these tumor sized stages to T1a for tumors smaller than 2.5 cm, T1b for tumors between 2.5 and 5.0 cm, and T1c for tumors from 5.0 to 7.0 cm [1].

Stage 2 tumors are still confined to the kidney, but are larger than those classified as Stage 1 tumors. Stage T2a tumors are larger than 7 cm but less than 10 cm, while stage T2b tumors are larger than 10 cm.

Stage 3 disease includes carcinomas that have invaded the veins or have extended beyond the renal capsule but are still within Gerota's fascia. Stage 3a tumors have extended into the renal vein or its segmental branches or have involved the perinephric fat or adrenal gland. Stage 3b tumors have extended into the inferior vena cava, but are still below the diaphragm. Stage 3c tumors have extended into the vena cava above the diaphragm or invaded the wall of the vena cava.

Stage 4 tumors have spread beyond Gerota's fascia. Involvement of the ipsilateral adrenal gland by contiguous spread is considered Stage T4 disease.

Lymph node metastases are divided into stage N1 in which the involvement is limited to regional lymph nodes and stage N2 where the tumor has spread beyond regional lymph nodes.

Patients with M1 disease have distant metastases.

Renal cell carcinoma tends to metastasize through either the venous or lymphatic systems. RCC often invades the veins where it may spread to the lungs and then to other tissues. With tumor thrombus in the IVC, there may be reflux into the adrenal and gonadal veins. Thus, metastases to the adrenal glands, testes, or ovaries may be seen [10]. Within the lymphatic system, metastases are first seen regionally, in the renal hilar lymph nodes or paraaortic/paracaval nodes. The most common sites of distant metastases from RCC are lung (45%), bone (30%), lymph nodes (22%), liver (20%), adrenal gland (9%), and brain (8%) [11].

Nuclear grading of the renal carcinoma, which is performed using the Fuhrman grading system (on a scale of 1–4), also helps determine the prognosis, as patients with a higher Fuhrman nuclear grade tumor are more likely to develop metastases.

Imaging

Renal carcinomas are often detected on ultrasound and the diagnosis confirmed on CT or MR examinations. Staging may be done with either CT or MR, but CT is more commonly used due to its greater availability and lower cost. When imaging with CT, it is recommended to obtain both arterial and nephrographic phase images. Metastases tend to enhance in a manner similar to the primary tumor [10]. Clear cell carcinomas tend to be hypervascular and are most easily detected during the arterial phase (Fig. 1), while papillary and other non-clear cell carcinomas enhance to a much lesser degree and are most conspicuous during the nephrographic phase (Fig. 2) [10, 12]. Since the lungs and bones are the most common sites of metastases, the CT examination is protocoled to include the chest, abdomen, and pelvis.

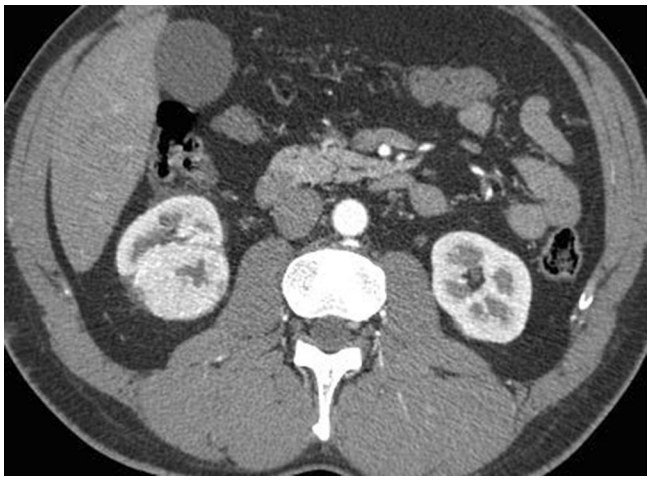

Fig. 1. Hypervascular clear cell carcinoma.

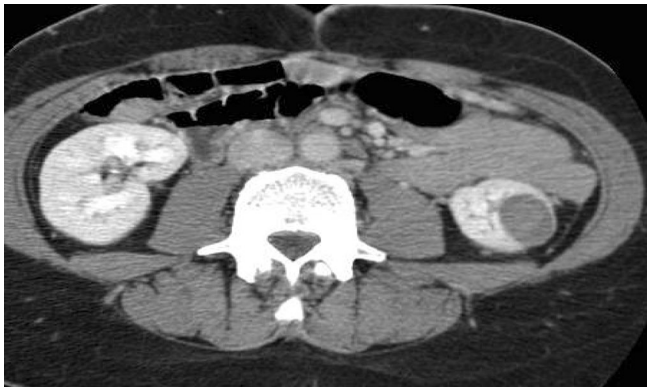

Fig. 2. Stage 1a papillary carcinoma.

The primary tumor in the kidney is readily detected with a dedicated renal CT examination including nephrographic phase images. Lesions with macroscopic fat can be classified confidently as angiomyolipomas. This is best determined with unenhanced images and lesions of at least 19 mm^3 [13]. Tumors smaller than this may be too small for an accurate density measurement or to clearly identify contrast enhancement and may be best followed with serial CT examinations until they can be better characterized. The distinction of T1 tumors from T2 tumors (Fig. 3) was increased from 2.5 to 7.0 cm in the TNM revision of 1997 to better distinguish survival differences [14]. Using the 1997 version, Tsui and colleagues demonstrated 5-year survivals ranging from 91% for stage I disease to 32% for patients with stage IV disease [15].

Invasion of the perinephric fat is more challenging than determination of the size of the primary tumor. This was the most common error in prior studies [16]. Ergen and colleagues reported on the use of perinephric stranding on MR examinations, but the renal capsule is difficult to identify and microscopic invasion will remain a challenge for macroscopic imaging [17]. Irregularity of the tumor margin or thick, soft tissue stranding in the perinephric space suggests extension beyond the renal capsule (Fig. 4).

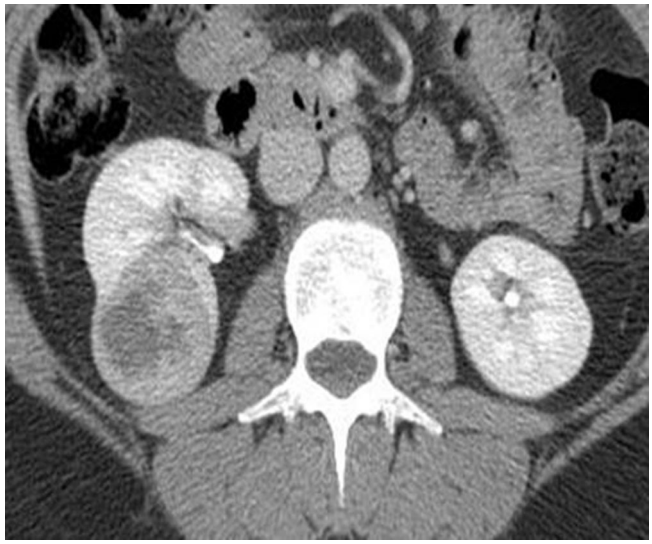

Fig. 3. Stage 2a carcinoma is between 7 and 10 cm but still within the kidney.

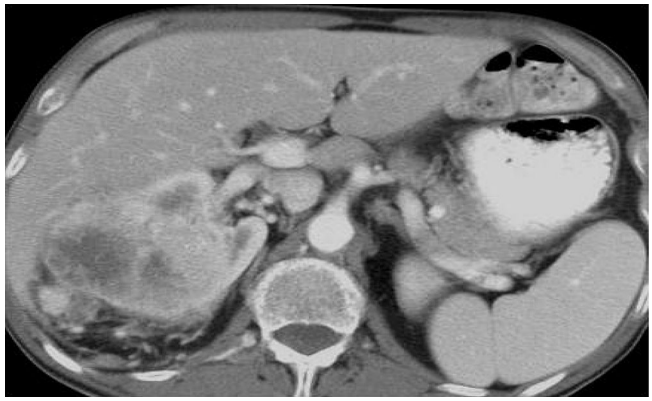

Fig. 4. Stage 3a carcinoma with extension into the perinephric fat.

Venous extension into the main renal vein is readily detected on either CT or MR examinations, though MR may have a slight advantage due to its multiplanar capability [17]. Karlo and colleagues found that if the renal carcinoma is separated from the renal sinus fat on CT, the likelihood of muscular venous branch invasion was significantly reduced, and the patient was more likely to undergo partial nephrectomy [18]. Extension into the renal vein or inferior vena cava is detected in 25% and 10% of patients, respectively (Fig. 5) [19]. The presence of tumor thrombus or bland thrombus in the renal vein or IVC has little effect on prognosis as it usually slides out as "a finger from a glove" and is relatively easy to remove surgically. However, accurate delineation of the thrombus extent is critical to planning the surgical approach, as extension into the right atrium indicates the need for cardiopulmonary bypass.

Lymph node involvement is determined by size criteria. Renal hilar, paraaortic, and paracaval (regional) lymph nodes with a short-axis diameter greater than 1 cm are considered to be involved (Fig. 6). Although sensitivities for detecting involvement are high, false positives are common and are usually due to benign reactive changes [20, 21]. Regional lymph node involvement is most common when the primary tumor is large, stage 2 [17].

Metastatic disease may occur anywhere, but the most common sites are the lungs (Fig. 7), liver, and bones (Fig. 8). Thus, imaging studies must include the chest and abdomen. Using both arterial and nephrographic phase images may enhance tumor conspicuity and increase the likelihood of detection [22].

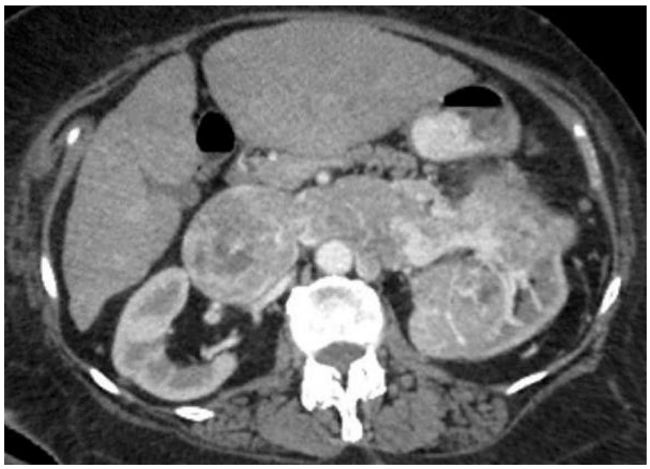

Fig. 5. A large left renal carcinoma is extending through the left renal vein into the inferior vena cava.

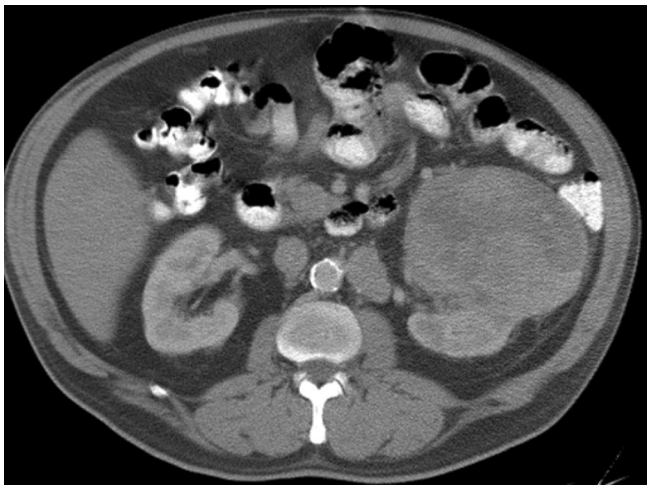

Fig. 6. Stage T2, N1 an enlarged par aortic lymph node suggest tumor involvement.

Tumor surveillance

Renal cell carcinomas may be treated with surgery, ablation, or chemotherapy, and the protocol for surveillance differs with stage, grade, and method of therapy. Patients with negative surgical margins are considered differently from patients with positive margins. Early detection of metastases is important as solitary lesions may be treated with ablation or surgical resection [23].

The lungs are the most common site of metastatic disease and follow-up chest CT has replaced chest radiography, with or without tomography, as the most appropriate imaging modality. Other common sites of metastases include the bones, liver, and brain [23, 24]. Metastases to the pelvis are uncommon and routine pelvic CT examinations are seldom recommended. However, metastases may develop many years after treatment [25]. Miyao and colleagues reported that 6.6% of patients developed recurrent disease more than 10 years after nephrectomy [26].

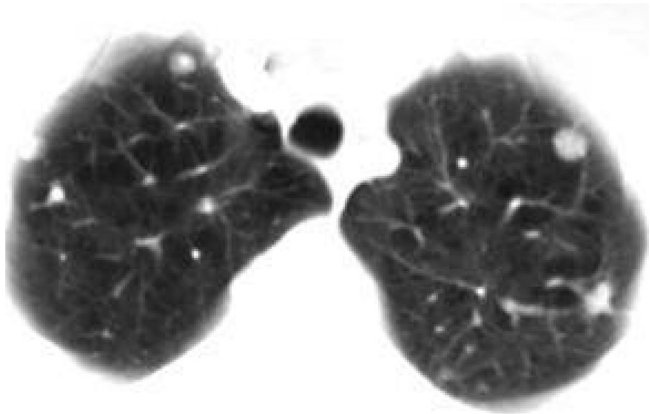

Fig. 7. Stage N1. Pulmonary metastases.

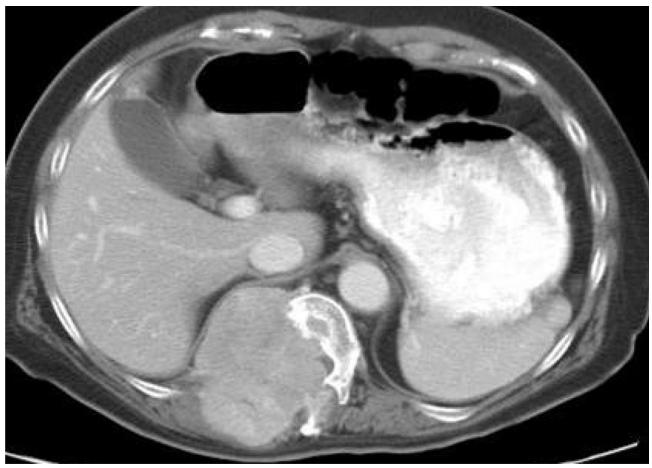

Fig. 8. Stage N1. Metastatic involvement of a lumbar vertebral body.

After nephrectomy

Patients who have undergone nephrectomy of stage T1 or T2 tumors and negative surgical margins may not need routine surveillance, though the American College of Radiology recommends chest radiography and follow-up abdominal CT examinations. Patients treated with partial nephrectomy or who have positive surgical margins deserve more aggressive follow-up and often undergo annual abdominal CT examinations. Abdominal CT examinations should be performed with imaging in the portal venous phase to enhance lesion conspicuity. Since metastases to the brain or bones are usually symptomatic, routine surveillance imaging of the bones and brain is not recommended [27].

After thermal ablation

Renal cell carcinoma may be effectively treated with either radiofrequency ablation or cryoablation. Risk stratification is more difficult with these less invasive techniques as neither surgical margins nor as extensive a histological evaluation are available as compared with surgery, and more aggressive imaging surveillance is needed. The American College of Radiology recommends enhanced and unenhanced abdominal CT scanning at 1, 3, 6, and 12 months after ablative therapy. Early follow-up scanning is needed as the majority of incomplete treatments are detected within the first 3 months after ablation [28]. Effectively treated tumors eventually develop a ''bull's eye'' appearance consisting of a central dense (>40H) mass surrounded by a halo of fat (Fig. 9).

Surveillance imaging demonstrates a decrease in the size of the tumor mass, but the ablation beds of even successfully treated tumors usually show an increase in size in the first few months following therapy. Decrease in size of the ablation cavity occurs slowly and seldom disappears. Enhancement is an important criterion in following these lesions, as successfully treated tumors do not enhance. Benign rim enhancement surrounding the ablation bed may occur, but has a smooth margin. Enhancement of the residual nodule by 20H or more, especially if accompanied by enlargement, is a strong indication of residual or recurrent active tumor [29].

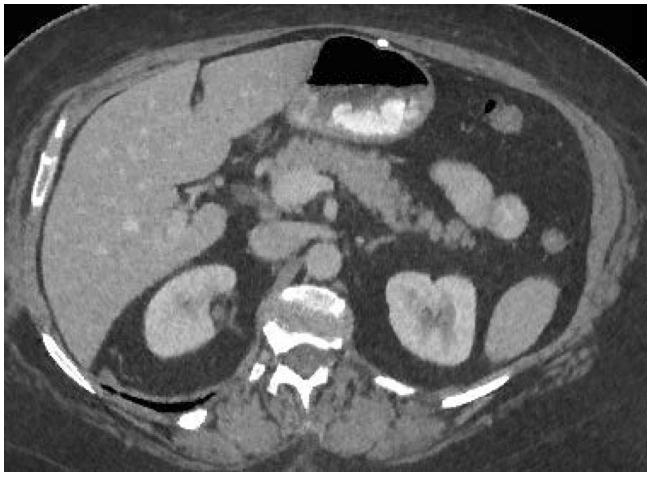

Fig. 9. Past radiofrequency ablation (RFA). A central dense mass is surrounded by fat.

After chemotherapy

Antiangiogenic targeted therapy agents, usually consisting of multi-kinase inhibitors, have been used successfully to treat renal cell carcinomas [6]. Since these antiangiogenic agents primarily inhibit growth, even successfully treated tumors may show only modest decreases in size. While many responding tumors will demonstrate a decrease in size, others will not. In these cases, imaging findings may be limited to a reduction in attenuation and diminished enhancement of the tumor, a finding which should be considered to indicate a successful response to therapy [30].

Treatment and surveillance of inherited renal carcinomas

The most common cause of inherited RCC, von-Hippel Lindau (VHL) Disease, is an autosomal dominant disorder of variable expressivity [5] with a prevalence of 1 per 35,000 to 40,000 people. Image interpretation is particularly challenging, as the kidneys develop both cysts and renal carcinomas (Figure 10) [31]. Tumors can arise de novo or from cystic precursors, even from those cysts that appear benign by the usual imaging criteria [32]. Since the tumors are multiple and usually bilateral, the emphasis has been to surgically remove tumors before they metastasize, usually when they reach 3 cm in size. The frequency of follow-up depends upon the relative aggressiveness of the tumor associated with the

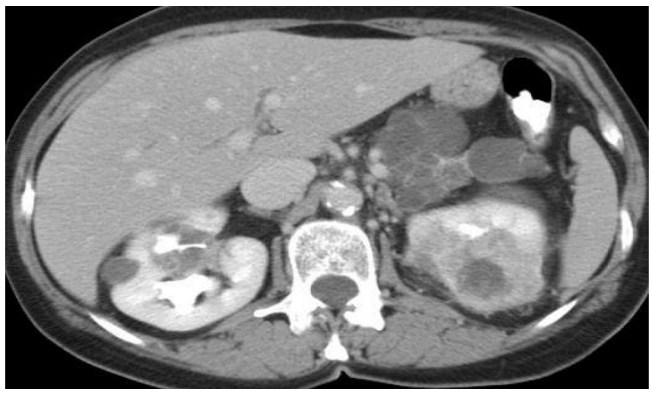

Fig. 10. von-Hippel Lindau disease. Multiple cysts are seen in the kidneys and pancreas. A Renal carcinoma is present in the left kidney.

disease. Since VHL is a life-long disease, MR imaging is generally preferred to avoid the radiation exposure with repeated CT examinations.

Tuberous Sclerosis (TS) is inherited in an autosomal dominant fashion. It has a prevalence of 1 per 10,000 people and is characterized by a diverse array of abnormalities. Renal angiomyolipomas, which are now classified as perivascular epithelial cell tumors (PEComas) are seen in as many as 80% of patients affected by TS. Renal cysts are seen in up to half of TS patients, while clear cell RCC is found in 2% to 4% of patients [33].

Birt–Hogg–Dube Syndrome is also an autosomal dominant disorder, but has a prevalence of only 1 per 200,000 people. Approximately 15% to 30% of patients will develop renal carcinomas which are variable in histology with 34% chromophobe, 9% clear cell, 5% oncocytoma, and 2% papillary. In as many as 50% of patients, the tumors will contain mixed elements of oncocytoma and chromophobe RCC [34].

Hereditary Papillary RCC, an autosomal dominant disorder, is very rare, with a prevalence of only 1 per 10,000,000 people. These patients develop multiple and bilateral papillary renal cancers [35].

Hereditary Leiomyomatosis and Renal Cell Cancer is an autosomal dominant disorder that has been reported in more than 200 families [36]. Affected family members develop cutaneous and uterine leiomyomata as well as aggressive papillary RCCs.

Renal Medullary Carcinoma is a rare tumor arising from the distal collecting duct in patients with sickle cell trait [37]. It is found in young adults and is often metastatic at time of presentation. Median survival from time of diagnosis is less than 4 months. There are no other associated abnormalities.

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Compliance with Ethical Standards

Conflict of interest N. Reed Dunnick declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ng C, Wood CG, Silverman P, et al. (2008) Renal Cell Carcinoma: Diagnosis, Staging, and Surveillance. Am J Radiol 191(4):1220–1232
2. Prasad SR, Humphrey PA, Catena FR, et al. (2006) Common and uncommon histologic subtypes of renal cell carcinoma: imaging spectrum with pathologic correlation. RadioGraphics 26:1795–1806
3. Shanbhogue K, Alampady V, Raghunandan P, et al. (2012) Rare (<1%) histological subtypes of renal cell carcinoma: an update. Abdom Imaging 37:861–872
4. Shinagare A, Krajewski Katherine M, Jagannathan JP, Ramaiya N (2012) Genitourinary imaging: part 2, role of imaging in medical management of advanced renal cell carcinoma. Am J Radiol 199(5):W554–W564
5. Northrup EB, Jokerst CE, Grubb RL, et al. (2012) Hereditary renal tumor syndromes: imaging findings and management strategies. Am J Radiol 199:1294–1304
6. Escudier B, Porta C, Schmidinger M, et al. (2012) Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis. Treatment and follow-up. Ann Oncol 23(7):vii65–vii71
7. Kane C, Mallin K, Ritchey J, Cooperberg M, Carroll P (2008) Renal cell cancer stage migration: analysis of the national cancer data base. Am Cancer Soc 113(1):78–83
8. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, (eds). *ERRT cancer statistics review*, 1975–2012. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2012/ (http://seer.cancer.gov/csr/), based on November 2014 SEER data submission, posted to the SEER website, April 2015
9. Robson CJ, Churchill BM, Anderson W (1969) The results of radical nephrectomy for renal cell carcinoma. J Urol 101:297–301
10. Brufau BP, Cergueda CS, Villalba LB, et al. (2013) Metastatic renal cell carcinoma: radiologic findings and assessment of response to targeted antiangiogenic therapy by using multidetector CT. Radiographics 33(6):1691–1715
11. Bianchi M, Sun M, Jeldres C, et al. (2012) Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 23(4):973–980
12. Vikram R, Ng CS, Tamboli P, et al. (2009) Papillary renal cell carcinoma: radiologic-pathologic correlation and spectrum of disease. RadioGraphics 29:741–754
13. Davenport M, Neville A, Ellis J, et al. (2011) Diagnosis of renal angiomyolipoma with hounsfield unit thresholds: effect of size of region of interest and nephrographic phase imaging. Radiology 260(1):158–165
14. Guinana PD, Vogelzang NJ, Fremgen AM, et al. (1995) Renal cell carcinoma: tumor size, stage and survival. J Urol 153:901–903
15. Tsui KH, Shvarts O, Smith RO, Figlin JB (2000) Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. J Urol 163:1090–1095
16. Johnson CD, Dunnick NR, Cohan RH, Illescas FF (1987) Renal adenocarcinoma: CT staging of 100 tumors. AJR 148:59–63
17. Ergen FB, Hussain H, Caoili EM, et al. (2004) MRI for preoperative staging of renal cell carcinoma using the 1997 TNM classification: comparison with surgical and pathologic staging. Am J Radiol 182(1):217–225
18. Karlo C, Donati OF, Marigliano C, et al. (2013) Role of CT in the assessment of muscular venous branch invasion in patients with renal cell carcinoma. Am J Radiol 201(4):847–852
19. Hatcher PA, Anderson EE, Paulson DF, Carson CC, Robertson JE (1991) Surgical management and prognosis of renal cell carcinoma invading the vena cava. J Urol 145:20–24
20. Russo P (2000) Renal cell carcinoma: presentation, staging, and surgical treatment. Semin Oncol 27:160–176
21. Prasad SR, Humphrey PA, Catena JR, et al. (2006) Common and uncommon histological subtype of renal cell carcinoma: imaging spectrum with pathologic correlation. RadioGraphics 26:1795–1806
22. Patel U, Sokhi H (2012) Imaging in the follow-up of renal cell carcinoma. Am J Radiol 198(6):1266–1276
23. Sivaramakrishna B, Gupta NP, Wadhwa P, et al. (2005) Pattern of metastases in renal cell carcinoma: a single institution study. Indian J Cancer 42:173–177
24. Scatarage JC, Sheth S, Corl FM, Fishman EK (2001) Patterns of recurrence in renal cell carcinoma: manifestations on helical CT. Am J Radiol 177:653–658
25. Dunnick NR, Wixson D, Doppman JL, Bokinski G, Javadpour N (1979) Metastatic renal cell carcinoma to the remaining kidney 14 years after nephrectomy—report of 2 cases. Cardiovasc Radiol 2:127–130
26. Miyao N, Naito S, Ozono S, et al. (2011) Late recurrence of renal cell carcinoma: retrospective and collaborative study of the Japanese society of renal cancer. Urology 77:379–384
27. Klatte T, Lam JS, Shuch B, Belldegrum AS, Pantuck AJ (2008) Surveillance for renal cell carcinoma: why and how? When and how often? Urol Oncol 26:550–554

28. Matin SF, Ahrar K, Cadeddu JA, et al. (2006) Residual and recurrent disease following renal energy ablative therapy: a multi-institutional study. J Urol 176:1973–1977
29. Kawamoto S, Permpongkosol S, Bluemke DA, Fishman EK, Solomon SB (2007) Sequential changes after radiofrequency ablation and cryoablation of renal neoplasms: role of CT and MR imaging. Radiographics 27:343–355
30. Smith AD, Shah SN, Rini BI, Lieber ML, Remer EM (2010) Morphology, attenuation, size and structure (MASS) criteria: assessing response and predicting clinical outcome in metastatic renal cell carcinoma on antiangiogenic targeted therapy. Am J Radiol 194:1470–1478
31. Choyke P, Glenn GM, Walther MM, et al. (1995) von Hippel-Lindau disease: genetic, clinical, and imaging features. Radiology 194:629–642
32. Leung R, Biswas SV, Duncan M, Rankin S (2008) Imaging features of von-Hippel-Lindau disease. RadioGraphics 28:65–79
33. Northrup B, Jokerst CE, Grubb RL, et al. (2012) hereditary renal tumor syndromes: imaging findings and management strategies. Am J Radiol 199(6):1294–1304
34. Pavlovich CP, Walther MM, Eyler RA, et al. (2002) Renal tumors in the Birt-Hogg-Dube syndrome. Am J Surg Pathol 26:1542–1552
35. Gupta S, Kang HC, Ganeshan DM, Bathala TK, Kundra V (2015) Diagnostic approach to hereditary renal cell carcinoma. Am J Radiol 204:1031–1041
36. Smit DL, Mensenkamp AR, Badeloe S, et al. (2011) Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. Clin Genet 79:49–59
37. Tsaras G, Owusu-Ansah A, Boaend FO, Amoateng-Adjepong Y (2009) Complications associated with sickle cell trait: a brief narrative review. Am J Med 122:507–512