Diagnostics and prognostic evaluation in renal cell tumors: the German S3 guidelines recommendations

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Abstract
The German guidelines on renal cell carcinoma (RCC) have been developed at highest level of evidence based on systematic literature review. In this paper, we are presenting the current recommendations on diagnostics including preoperative imaging and imaging for stage evaluation as well as histopathological classification. The role of tumor biopsy is further discussed. In addition, different prognostic scores and the status of biomarkers in RCC are critically evaluated.

Keywords Renal cell carcinoma · S3 guideline · Prognosis · Tumor biopsy · Imaging

Introduction
During the last 2 decades, therapeutic options in renal cell tumors changed not only in metastatic but also in organ confirmed disease due to a broader range of systemic therapies as well as surgical techniques. In addition, more and more small renal masses are detected, and therefore, surveillance strategies and ablative therapies are under discussion. Accordingly, exact diagnosis by imaging as well as histopathology and prognostic evaluation are necessary to select the optimal treatment for each individual patient. In addition, there is an urgent need for molecular biomarkers to further increase diagnostic accuracy including non-invasive markers as well as prognostic markers to individualize treatment. In this manuscript, we present the German highest level systematic literature review-based interdisciplinary guidelines concerning imaging, histopathological classification, renal tumor biopsy, prognostic evaluation, and biomarkers for renal cell tumors (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms, Langversion 2.0,2020, AWMF Registernummer: 043/017OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/Nierenzellkarzinom) [1].

Methods
The methodological approach is described in detail in the guidelines [1]. Briefly, evidence grade is based on the Scottish Intercollegiate Guidelines Network (SIGN) system. Three grades of recommendation have been used (A: strong recommendation; B: recommendation; 0: recommendation not defined). Four categories were used to define grade of consensus (strong consensus: > 95%; consensus: > 75%–95%; consensus by majority: 50–75%; dissent: < 50% agreement). If systematic search was not performed, recommendations are based on expert consensus.

Diagnostics: imaging

With the increasing number of incidentally detected renal cell carcinomas (RCC), the average size is decreasing continuously. The differential diagnosis of smaller lesions is difficult, as typical signs such as cava thrombus, necrosis, or metastasis are missing.

High-resolution imaging in CT and MRI can delineate even small and chromophobe carcinomas [2]. Staging
accuracy of small RCC is similar in MRT and CT with staging accuracy between 0.78 and 0.87 [3]. CT is used routinely for small carcinomas [4], whereas tumor with caval thrombus should be staged with MRI [5] (Table 1).

The CT scan should include an unenhanced spiral of the complete abdomen and a spiral in the early arterial phase of renal perfusion of the upper abdomen and a delayed scan of the complete abdomen. For the CT, a reconstructed slice thickness of 2 mm should be used. An enhanced scan of the thorax in a venous phase can be added for staging. Especially for planning of nephron sparing surgery, high-resolution 3D reconstructions are mandatory. CT has a good accuracy in the evaluation of infiltration into the perirenal fat [6], but has a limited accuracy in the evaluation of intrarenal infiltration [7].

MRI as diagnostic modality is recommended in case of allergic reactions to iodine containing contrast media (CT) or suspected caval thrombus. The complete abdomen including the atrium and the lower pole of the kidneys should be scanned. The scans should include axial T2w images, axial enhanced T1w images and a coronal multiphase acquisition with an unenhanced scan, an early arterial phase, and a parenchymal phase. In case of urogenital bleeding a delayed scan for complete urothelium including bladder should be added. Especially, the high-resolution T2w images allow a delineation of the tumor thrombus [4].

Sensitivity and specificity of caval thrombus evaluation are 1.0 and 0.83 for MRI [5].

For grading, RCC diffusion and perfusion imaging seem to be a promising tool [8–10]. As imaging can hardly differentiate between histologic subtypes, despite of classic AMI, additional biopsy might be useful for therapy planning.

Although prospective trials provide high level of evidence, more data are desirable to corroborate the recommendations.

### Table 1 Evidence-based recommendations for diagnostic imaging

| Evidence-based recommendation                                                                 | Level of evidence (LoE) | Grade of recommendation | Consensus |
|-----------------------------------------------------------------------------------------------|-------------------------|-------------------------|-----------|
| For preoperative workup for local staging and for planning of nephron sparing surgery of renal cell carcinoma a triphasic CT has to be performed: unenhanced CT scan from the dome of the liver to the symphysis, in the early arterial phase from the dome of the liver to the lower pole of the kidneys in a parenchymal phase from the dome of the liver to the symphysis | 1 +                     | A                       | Strong    |
| Patients with renal cell carcinoma and suspected caval thrombus or venous infiltration should undergo MRI of the abdomen as a primary diagnostic modality. The MR should be performed according to a standard protocol | 1 +                     | B                       | Strong    |

### Imaging for evaluation of metastasis

In patients with tumor size of 3 cm and higher, unenhanced and enhanced thin slice CT (2 mm) of the thorax should be performed, because the risk of metastasis is increasing. CT has a much higher sensitivity and specificity to detect lung metastases than conventional chest X-ray as CT allows to detect small calcifications and fat in pulmonary lesions, and can therefore differentiate the pulmonary lesions [4, 11–13]. For detection of abdominal lesions, MRI and CT have similar detection rates. If brain metastases are suspected, MRI should be used due to its better capability to detect metastases and edema in the brain (Table 2).

### Biopsy

In cases of uncertain renal lesions, it would be helpful to perform biopsies for histopathological evaluation, especially in patients who are candidates for active surveillance or renal tumor ablation (Table 3). Volpe et al. described a 16% reduction of surgery [14]. However, there is the possibility of false-negative results.

Under local anaesthetics, percutaneous sampling can be performed as core biopsy or fine needle aspiration, alone or in combination, US or CT-guided. Fine-needle aspiration shows lower diagnostic yield and accuracy [14, 15], which can be improved by adding 18 Gauge core biopsy [16–18].

Systematic reviews reported a comparatively high diagnostic yield, sensitivity, and specificity for the diagnosis of malignancy (99.1% and 99.7%) when using core biopsy [14, 19, 20].

In tumors > 4 cm, peripheral ultrasound guided biopsies are recommended to avoid sampling of central areas with tumor necrosis [21].
An issue of renal lesion biopsy emphasizes the problem of managing negative biopsy results (0–22.6%). Repeat biopsy is diagnostic in most patients (83–100%) [22, 23]. Therefore, an indeterminate or negative biopsy result but suspicious imaging findings should prompt a repeat biopsy or be interpreted as RCC if repeated biopsy is impossible.

Core biopsy of cystic renal lesions has a lower diagnostic yield and accuracy compared to solid lesions and is therefore not recommended [24].

The morbidity of percutaneous biopsy is low [14, 19]. Tumor cell seeding along the needle tract is unlikely. In a recent pooled analysis, spontaneously resolving and clinically insignificant subcapsular perinephric hematoma was reported in 4.3% of biopsies [25].

### Histopathological classification

The recommendations are based on the consensus conference and the most recent guidelines [26–28] (Table 4). The WHO Classification of 2004 presented a comprehensive histopathological classification of RCC, which were revised in 2013 by the International Society of Urological Pathology (ISUP) in the Vancouver Classification [28]. In the consensus conference of the S3-Guidelines the diagnosis of the following new entities was recommended: Tubulocystic RCC, Acquired cystic disease-associated RCC, Clear cell papillary RCC, MiT-family translocation RCC with Xp11 translocation or t(16; 11) translocation, Hereditary leiomyomatosis, and renal cell carcinoma-associated RCC.

| Table 2 | Expert consensus-based recommendations for evaluation of metastasis by imaging |
|---------|---------------------------------------------------------------|
| Consensus-based recommendation | Grade of consensus |
| In asymptomatic patients with malignant tumors exceeding 3 cm, an enhanced CT of the thorax should be performed | Consensus |
| In case of suspected bone lesions, imaging has to be performed preferably by whole body CT (low dose) or MRI and not by scintigraphy | Consensus |
| In case of suspected brain lesions, an enhanced MR scan of the skull/brain has to be performed | Strong |

| Table 3 | Expert consensus-based recommendations for renal tumor biopsy |
|---------|---------------------------------------------------------------|
| Consensus-based recommendation | Grade of consensus |
| Biopsy of uncertain lesions of the kidney should be performed only if it impacts clinical management | Consensus |
| Biopsy is recommended before renal tumor ablation | Strong |
| Biopsy of cystic renal lesions should not be performed | Strong |
| Renal tumor biopsy or biopsy of metastases is recommended in patients with primary metastatic disease before systemic therapy if histopathological evaluation was not yet performed | Strong |
| Renal tumor biopsy can be offered before cytoreductive nephrectomy in metastatic patients | Consensus |

| Table 4 | Expert consensus-based recommendations for histopathology |
|---------|---------------------------------------------------------------|
| Consensus-based recommendation | Grade of consensus |
| The histological type of renal cell carcinoma should be defined according to the recent WHO classification | Strong |
| The tumor types recommended by the Vancouver Classification of Renal Cell Carcinoma of the International Society of Urological Pathology (ISUP) should be diagnosed | Strong |
| The diagnosis of the following new tumor types is recommended: Tubulocystic renal cell carcinoma | Strong |
| Acquired cystic disease-associated renal cell carcinoma | Strong |
| Clear cell papillary renal cell carcinoma | Strong |
| MiT-family translocation renal cell carcinoma | Strong |
| Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma | Strong |
| The most recent TNM classification should be used. The tumor grade should be diagnosed in clear cell and papillary renal cell carcinoma according to the WHO-ISUP grading. In addition, the proportion of tumor necrosis should be given | Strong |
| Chromophobe renal cell carcinomas should not be graded | Strong |
| The papillary renal cell carcinoma should be diagnosed in two different types (Type 1 and Type 2) | Strong |
| A sarcomatoid and/or rhabdoid differentiation should be mentioned | Strong |
These entities were also recommended by the WHO classification of 2016.

**Renal cell tumors**

- Papillary adenoma
- Oncocytoma
- Clear cell RCC
- Multilocular cystic renal neoplasm of low malignant potential
- Papillary RCC
- Chromophobe RCC
- Collecting duct carcinoma
- Renal medullary carcinoma
- MiT-family translocation RCC
  - Xp11 translocation RCC
  - t(16; 11) RCC
- Succinate dehydrogenase-deficient RCC
- Mucinous tubular and spindle cell RCC
- Tubulocystic RCC
- Acquired cystic disease-associated RCC
- Clear cell papillary RCC
- Hereditary leiomyomatosis and renal cell carcinoma-associated RCC
- Unclassified RCC.

**Metanephric tumors**

- Metanephric adenoma
- Metanephric adenofibroma
- Metanephric stromal tumors.

**Nephroblastic tumors**

- Nephroblastoma
- Cystic partially differentiated nephroblastoma
- Pediatric cystic nephroma.

**Mesenchymal tumors occurring mainly in children**

- Clear cell sarcoma
- Rhabdoid tumor
- Congenital mesoblastic nephroma
- Ossifying renal tumor of infancy.

**Mesenchymal tumors occurring mainly in adults**

- Angiomyolipoma
- Epitheloid angiomyolipoma
- Leiomyoma
- Hemangioma
- Juxtaglomerular cell tumor
- Renomedullary interstitial cell tumor
- Schwannoma
- Solitary fibrous tumor
- Neuroectodermal tumor
- Synovial sarcoma
- Leiomyosarcoma
- Angiosarcoma
- Rhabdomyosarcoma.

**Mixed epithelial and stromal tumors**

- Adult cystic nephroma/mixed epithelial stromal tumor (MEST).

**Neuroendocrine tumors**

- Low-grade neuroendocrine tumor
- High-grade neuroendocrine tumor/neuroendocrine carcinoma
- Neuroblastoma
- Pheochromocytoma.

**Hematopoietic and lymphoid tumors**

- Lymphoma
- Leukemia
- Plasmacytoma.

**Germ cell tumors**

**Metastatic renal cell carcinoma** In the consensus meeting, the classical histopathological parameters and the grading system for RCC were discussed. It was recommended that the tumor grade of RCC should be given according to the WHO-ISUP grading system. There is a clear correlation of the grade with the prognosis in clear cell and papillary RCC. Papillary RCC should be separated in two types (Type 1 with low grade and basophilic cytoplasm and Type 2 with high grade and eosinophilic cytoplasm). Papillary RCC Type 1 has an excellent prognosis. Furthermore, it was recommended that chromophobe RCC should not be graded. Other histological features were discussed. A sarcomatoid and rhabdoid differentiation should be mentioned in the histopathological report, because it is clearly associated with a poorer prognosis. The proportion of necrosis is also associated with a poorer prognosis and should be given.

The grading of chromophobe RCC has to be improved. The new grading systems proposed by Paner et al., Avulova et al., and Ohashi et al. are based on the pattern of the tumor and show that necrosis and sarcomatoid dedifferentiation are the most important factors for an adverse outcome [29–31]. Therefore, this should be mentioned in every report, which
is also stated in the guideline. However, prospective data are still lacking. Thus, the grading is still not recommended by the WHO.

The data for microvascular invasion in lymph or blood vessels as a poor prognostic factor are not sufficient. A new edition of the TNM classification is available since 2017 [32].

**Prognostic scores**

TNM staging and grading still represent the most important characteristics for prognostic evaluation. However, these parameters are not sufficient to evaluate the individual prognosis in a given patient. Therefore, several prognostic models have been developed to predict outcome at different time points of disease and therefore select patients for different therapeutic options. These models should improve the prognostic accuracy compared to standard TNM stage and grade (Table 5).

Although some preoperative nomograms exist, majority of models have been developed for postoperative evaluation. The first aim is to evaluate the risk of progression/metastasis and survival in local disease. The following nomograms have been created: UISS (UCLA Integrated Staging Aystem)-model [33], Karakiewicz-nomograms [34, 35], SSIGN-score [36], Leibovich-score [37], Kattan-nomogram [38], Sorbellini-nomogram [39], and papillary nomogram [40]. Some of these nomograms are developed for clear cell RCCs only; others did not differentiate histological subtypes. Most of them are validated in independent patient cohorts (Table 5). The second aim is to predict the outcome of metastatic patients treated with systemic therapy. The Motzer or MSKCC-score is the first and mostly used nomogram developed for patient cohorts treated with interferon [41]. However, it is still used in the tyrosine kinase inhibitors era, too. Additional nomograms include the IMDC or Heng-score [42], the International Kidney Cancer Working Group-Modell (IKCWG)-model [43], the Cleveland Clinic Foundation-Modell (CCF)-model [44], the French model [45], the Sunitinib model [46], and the Leibovich Score before immune therapy [47].

Currently, Motzer score and the IMDC-nomogram are most frequently used models to categorize patients in risk groups and thereof to predict outcome in clinical trials and practice.

**Biomarkers**

Diagnostic biomarkers could improve early detection and differential diagnosis in addition to histopathological evaluation, especially in small renal masses. In addition, there is an urgent need in prognostic biomarkers to define individual outcome of RCC patients and, therefore, to select the most appropriate therapy.

During the last years, several biomarkers on different molecular levels (DNA, RNA, and proteins) have been published that are correlated with metastasis and survival of RCC patients [48–51]. Some of these markers have been analyzed in comparison to existing clinical prognostic parameters or have been incorporated in prognostic scores, and improved prognostic accuracy [52–54]. Due to the lack of independent prospective validation, none of these markers has been introduced in clinical routine (Table 6).

However, it is likely that new prognostic markers will be identified from complex high-throughput analyses on
several molecular levels in parallel considering clinical course [55–58].

Currently, several molecular signatures alone or integrated into clinical models have been published which are partially validated in independent cohorts. Almost all have a superior accuracy to predict individual patient outcome compared to clinically based nomograms [57, 59–62].

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**Declarations**

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**References**

1. S3-Leitlinie Diagnostik, Therapie und Nachsorge der testikulären Keimzelltumoren, Langversion 1.1 [Internet]. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF 2020.

2. Raman SP et al (2013) Chromophobe renal cell carcinoma: multiphase mdtct enhancement patterns and morphologic features. Am J Roentgenol 201(6):1268–1276

3. Hallscheidt PJ et al (2004) Diagnostic accuracy of staging renal cell carcinomas using multidetector-row computed tomography and magnetic resonance imaging—a prospective study with histopathologic correlation. J Comput Assist Tomogr 28(3):333–339

4. Sheth S et al (2001) Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector CT and three-dimensional CT. Radiographics 21:S237–S254

5. Hallscheidt PJ et al (2005) Preoperative staging of renal cell carcinoma with inferior vena cava thrombus using multidetector CT and MRI—prospective study with histopathologic correlation. J Comput Assist Tomogr 29(1):64–68

6. Kim C, Choi HI, Cho KS (2014) Diagnostic value of multidetector computed tomography for renal sinus fat invasion in renal cell carcinoma patients. Eur J Radiol 83(6):914–918

7. Karlo CA et al (2013) Role of CT in the assessment of muscular venous branch invasion in patients with renal cell carcinoma. Am J Roentgenol 201(4):847–852

8. Israel GM, Hecht E, Bosniak MA (2006) CT and MR imaging of complications of partial nephrectomy. Radiographics 26(5):1419–1429

9. Vargas HA et al (2013) Multiphasic contrast-enhanced MRI: single-slice versus volumetric quantification of tumor enhancement for the assessment of renal clear-cell carcinoma fuhrman grade. J Magn Reson Imaging 37(5):1160–1167

10. Hallscheidt P et al (2002) Organ-sparing surgery of renal cell carcinoma—operative technique and findings in radiological follow-up. Rofo-Fortschritte Auf Dem Gebiet Der Rontgen-strahlen Und Der Bildgebenden Verfahren 174(4):409–415

11. Bechtold RE, Zagoria RJ (1997) Imaging approach to staging of renal cell carcinoma. Urol Clin North Am 24(3):507–510

12. Heidenreich A, Ravery V (2004) Preoperative imaging in renal cell cancer. World J Urol 22(5):307–315

13. Miles KA et al (1991) Ct staging of renal-carcinoma—a prospective comparison of 3 dynamic computed-tomography techniques. Eur J Radiol 13(1):37–42

14. Volpe A et al (2012) Rationale for percutaneous biopsy and histologic characterisation of renal tumours. Eur Urol 62(3):491–504

15. Volpe A et al (2007) Techniques, safety and accuracy of sampling of renal tumours by fine needle aspiration and core biopsy. J Urol 178(2):379–386

16. Barwari K et al (2013) What is the added value of combined core biopsy and fine needle aspiration in the diagnostic process of renal tumours? World J Urol 31(4):823–827

17. Li G et al (2012) Combination of core biopsy and fine-needle aspiration increases diagnostic rate for small solid renal tumors. Anticancer Res 32(8):3463–3466

18. Parks GE et al (2011) Benefits of a combined approach to sampling of renal neoplasms as demonstrated in a series of 351 cases. Am J Surg Pathol 35(6):827–835

19. Lane BR et al (2008) Renal mass biopsy—a renaissance? J Urol 179(1):20–27

20. Phe V et al (2012) Is there a contemporary role for percutaneous needle biopsy in the era of small renal masses? BJU Int 109(6):867–872
21. Wunderlich H et al (2005) The accuracy of 250 fine needle biopsies of renal tumors. J Urol 174(1):44–46
22. Menogue SR et al (2013) Percutaneous core biopsy of small renal mass lesions: a diagnostic tool to better stratify patients for surgical intervention. BJU Int 111(1B):E146–E151
23. Leveridge MJ et al (2011) Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. Eur Urol 60(3):578–584
24. Lang EK et al (2002) CT-guided biopsy of indeterminate renal cystic masses (Bosniak 3 and 2F): accuracy and impact on clinical management. Eur Radiol 12(10):2518–2524
25. Marconi L et al (2016) Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol 69(4):660–673
26. Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010.
27. Srigley JR et al (2013) The International Society of Urological Pathology (ISUP) vancouver classification of renal neoplasia. Am J Surg Pathol 37(10):1469–1489
28. Delahunt B et al (2013) The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 37(10):1490–1504
29. Avulova S et al (2021) Grading chromophobe renal cell carcinoma: evidence for a four-tiered classification incorporating coagulative tumor necrosis. Eur Urol 79(2):225–231
30. Ohashi R et al (2020) Multi-institutional re-evaluation of prognostic factors in chromophobe renal cell carcinoma: proposal of a novel two-tiered grading scheme. Virchows Arch 476(3):409–418
31. Paner GP et al (2010) A novel tumor grading scheme for chromophobe renal cell carcinoma prognostic utility and comparison with fuhrman nuclear grade. Am J Surg Pathol 34(9):1233–1240
32. Brierley JD, Gospodarowicz MK, Wittekind C (eds) (2017) TNM classification of malignant tumours, 8th edn. Wiley-Blackwell, Oxford
33. Zisman A et al (2002) Risk group assessment and clinical outcome for papillary renal cell carcinoma. J Urol 184(1):53–58
34. Frank I et al (2002) An outcome prediction model for patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. Cancer 110(3):543–550
35. Negrier S et al (2002) Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinoma - treated by cytokines: a report from the groupe francais d’immunotherapie. Ann Oncol 13(9):1460–1468
36. Bansia A et al (2013) Development and validation of a prognostic model in patients with metastatic renal cell carcinoma treated with sunitinib: a European collaboration. Br J Cancer 109(2):332–341
37. Leibovich BC et al (2003) Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma—a stratification tool for prospective clinical trials. Cancer 98(12):2566–2575
38. Eichelberg C et al (2009) Diagnostic and prognostic molecular markers for renal cell carcinoma: a critical appraisal of the current state of research and clinical applicability. Eur Urol 55(4):851–863
39. Tan PH et al (2013) Renal tumors: diagnostic and prognostic biomarkers. Am J Surg Pathol 37(10):1518–1531
40. Junker K et al (2013) Potential role of genetic markers in the management of kidney cancer. Eur Urol 63(2):333–340
41. Finley DS, Pantuck AJ, Belldegrun AS (2011) Tumor biology and prognostic factors in renal cell carcinoma. Oncologist 16(Suppl 2):4–13
42. Klatte T et al (2009) Molecular signatures of localized clear cell renal cell carcinoma to predict disease-free survival after nephrectomy. Cancer Epidemiol Biomarkers Prev 18(3):894–900
43. Parker AS et al (2009) Development and evaluation of BioScore: a biomarker panel to enhance prognostic algorithms for clear cell renal cell carcinoma. Cancer 115(10):2092–2103
44. Sun M et al (2011) Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol 60(4):644–661
45. Cancer Genome Atlas Research, et al (2013) Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 499(7456):43–49
46. Sato Y et al (2013) Integrated molecular analysis of clear-cell renal cell carcinoma. Nat Genet 45(8):860–867
47. Brooks SA et al (2014) ClearCode34: a prognostic risk predictor for localized clear cell renal cell carcinoma. Eur Urol 66(1):77–84
48. Davis CF et al (2014) The somatic genomic landscape of chromophobe renal cell carcinoma. Cancer Cell 26(3):319–330
49. Choueiri TK et al (2007) Clinical factors associated with outcome for papillary renal cell carcinoma treated with radical nephrectomy. Cancer Epidemiol Biomarkers Prev 16(6):1528–1535
50. Negrier S et al (2002) Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the groupe francais d’immunotherapie. Ann Oncol 13(9):1460–1468
51. Rini B et al (2015) A 16-gene assay to predict recurrence after nephrectomy. J Clin Oncol 33(27):3372–3379
52. Manola J et al (2011) Prognostic model for survival in patients with metastatic renal cell carcinoma: results from the international kidney cancer working group. Clin Cancer Res 17(16):5443–5450
53. Chang C et al (2015) Prognostic value of 7 miRNAs in renal cell carcinoma. Nat Genet 47(11):1365–1370
54. Grimm J et al (2019) Metastatic risk stratification of clear cell renal cell carcinoma patients based on genomic aberrations. Genes Chromosomes Cancer. https://doi.org/10.1002/gcc.22749
55. Heinzlmann J et al (2019) 4-miRNA score predicts the individual metastatic risk of renal cell carcinoma patients. Ann Surg Oncol 26(11):3765–3773
56. Rini B et al (2015) A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. Lancet Oncol 16(6):676–685
57. Buttner F et al (2015) Survival prediction of clear cell renal cell carcinoma based on gene expression similarity to the proximal tubule of the nephron. Eur Urol 68(6):1016–1020
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