

# Renal Cell Carcinoma (Hypernephroma)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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# Renal Cell Carcinoma (Hypernephroma)

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## **Compliance rules:**

- [Guideline](#)
- [Conflict of interests](#)

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## **1 Summary**

Renal cell carcinoma (RCC) is one of the more common malignant tumors in adults. In Europe, men are affected significantly more often than women with an incidence of approximately 26/100,000. The mean age at first diagnosis is between 65 and 70 years in men and over 70 years in women. In recent years, RCCs have increasingly been discovered incidentally in the course of abdominal diagnostics for other indications by means of sonography or cross-sectional imaging. Since 2006, age-standardized incidence and mortality rates have been decreasing slightly.

The most effective therapeutic procedures are surgery, especially in the localized stage, and systemic therapy. Surgery with complete tumor resection is the only curative option. For drug-based tumor therapy in the metastatic situation, numerous new drugs from the field of anti-angiogenesis, tyrosine kinase and immune checkpoint inhibition have been approved for mono- and for combination therapies in the last 15 years. In palliative situations, especially in symptomatic inoperable metastases, radiotherapy is also used.

## **2 Basics**

### **2.1 Definition and basic information**

Renal cell carcinoma accounts for about 85% of malignant renal tumors. Other forms of kidney cancer include urothelial carcinoma originating from the renal pelvis (10%), non-Hodgkin's lymphoma, sarcoma, and, in childhood, nephroblastoma (Wilms' tumor). The subject of this chapter is RCC.

### **2.2 Epidemiology**

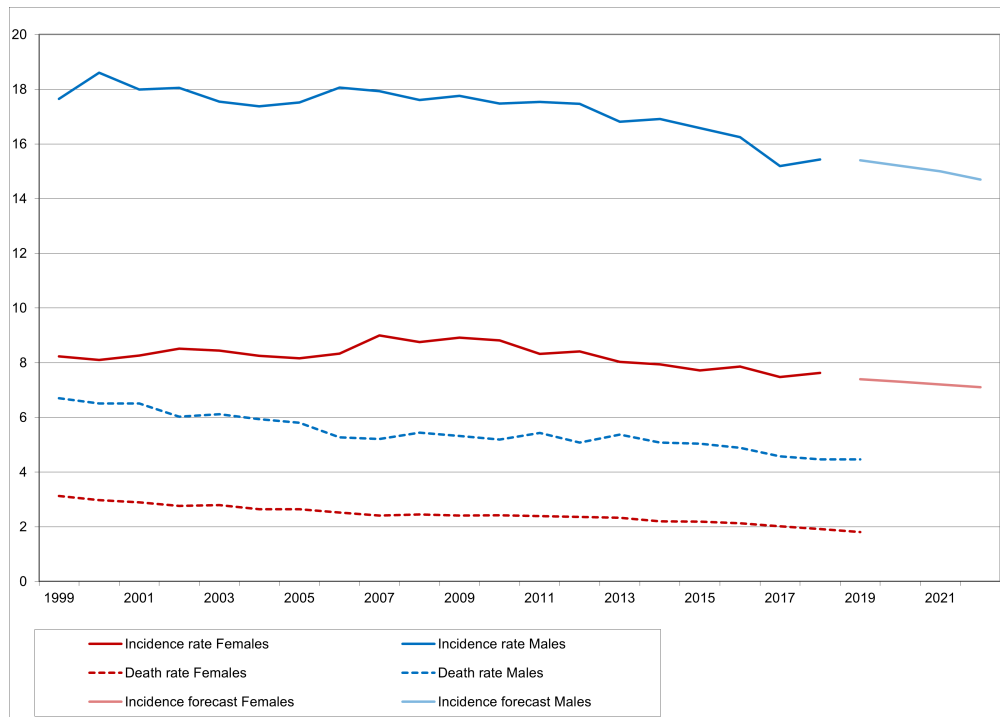
About 15,000 new cases of RCC are diagnosed per year in Germany [1], about 1,350 in Austria [2], and about 1,000 in Switzerland in 2013-2017 [3]. Approximately 110,000 individuals live in Germany who have received the diagnosis of RCC in the last 10 years. More than 90% of all diagnosed renal cancers are histologically carcinomas, of which again more than 95% are adenocarcinomas. Kidney cancer is the cause of slightly more than 5,000 deaths per year in Germany. Men are affected twice as often as women.

The absolute 5-year survival rate is reported to be 65% (men) and 71% (women), respectively, and the relative 5-year survival rate, which takes into account mortality in the general popula-

tion, is 76% (men) and 78% (women). The 10-year relative survival rate is 69% (men) and 72% (women), respectively [1].

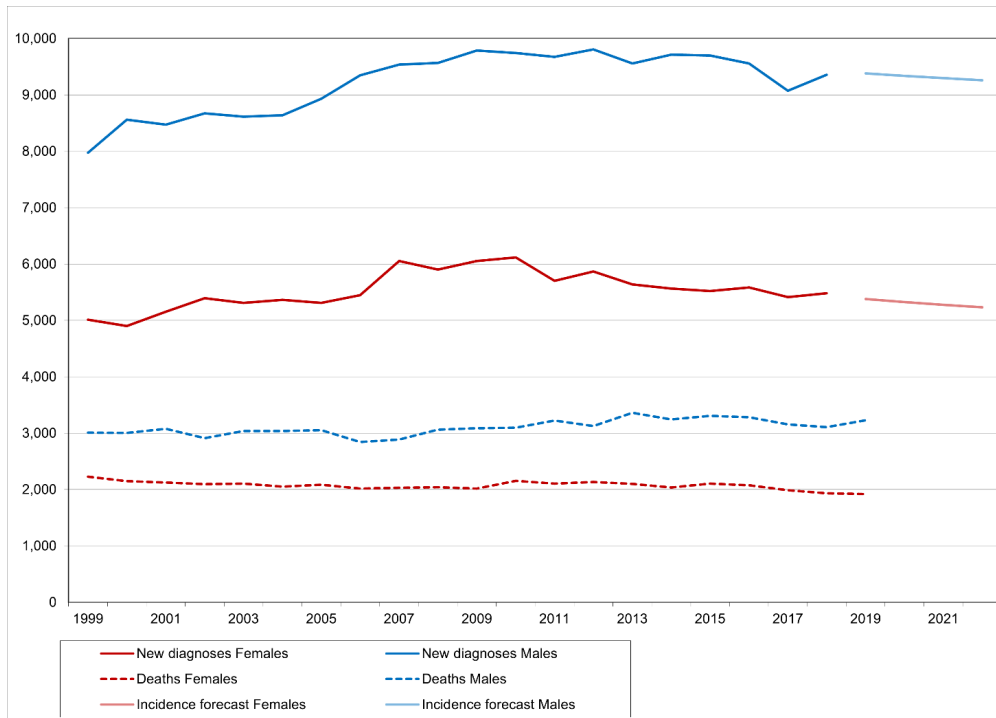
Age-standardized disease rates, as well as mortality rates, have been slightly decreasing in men for years, see Figure 1. In the last 14 years, rates decreased by an average of 0.8% (incidence rate) and 1.5% (mortality rate) per year. In women, the incidence rate has been largely constant (-0.5% per year, which is statistically not significant). Despite constant incidence rates, the mortality rate in women decreased at the same rate as in men (-1.7% per year) [4]. Age-standardized rates of cancer mortality have also declined in Austria and Switzerland in recent decades.

**Figure 1: Estimated incidence of renal cell carcinoma Germany - age-standardized rate [1].**



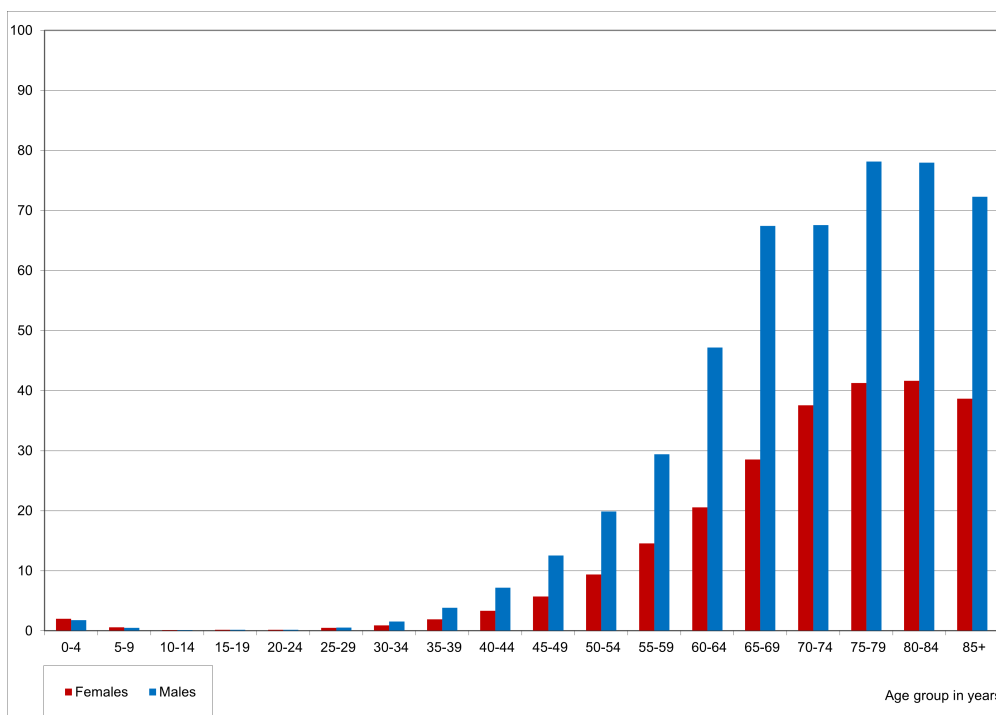
Despite the decreasing risk of disease and death in men, the number of cases is increasing slightly. On average, the number of new cases is increasing by 0.8% per year, and the number of deaths by 0.9% per year. This discrepancy is due to the change in population composition with an increase in persons of older age. Among women, the numbers of both new cases and deaths remain constant, see Figure 2.

**Figure 2: Absolute number of new cases and deaths with renal cell carcinoma in Germany [1].**



The mean (median) age at diagnosis is 68 years for men and 72 years for women, 1 year (men) and 2 years (women) above the median age of onset for cancer overall. The median age at death is 75 years (men) and 79 years (women). Most cases of RCC occur in the 70 to 79 age group for both sexes. The higher incidence in men is evident in virtually all age groups. Only in individuals over 85 years of age is the number of cases higher in women due to demographic factors. The rate of RCC in men is also about twice that of women in this age group. In relation to the underlying population, the highest disease rates for both sexes are in the 80-84 age group, see [Figure 3](#).

**Figure 3: Estimated incidence of renal cell carcinoma in Germany - new cases and deaths [1].**



Based on the current incidence of RCC and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2 - moderate), an increase in the number of cases by about 24% to approximately 18,200 new cases (2040) can be expected in the next 20 years, solely due to the shift in age structures in the population [4].

## 2.4 Pathogenesis

Renal cell carcinoma is a heterogeneous disease. Histologically, clear cell, papillary, and chromophobe carcinoma predominate [5]. The pathophysiology of RCC is characterized by dysregulation of various signal transduction pathways.

Clear cell carcinomas account for approximately 75-80% of renal cell carcinomas. They show a large inter- as well as intratumoral heterogeneity. Functional inactivation of the von Hippel-Lindau (VHL) gene is found in about 80%. This leads to activation of hypoxia-inducible factor (HIF)-1 $\alpha$  and 2 $\alpha$ , and increases expression of neoangiogenesis and cell proliferation genes. However, inactivation of the *VHL* gene is not sufficient for the development of RCC. Mutations are also found at lower frequencies in the *PBRM1* (40%), *SETD2* (15%), and *BAP1* (15%) genes [6]. In a subset of clear cell RCCs, components of the mTOR (mechanistic Target Of Rapamycin) signal transduction pathway are altered at multiple levels. Furthermore, there are a large number of epigenetic alterations, some of which have shown prognostic and some predictive value in studies [7].

Papillary RCC type 1 is associated with alterations of the *MET* gene. The rare hereditary form is based on a germline mutation of the *MET* oncogene on chromosome 7. Papillary RCC type 2 can be genetically differentiated into 3 prognostically relevant subgroups [8]:

- *CDKN2A* mutations
- *ETD2*, *BAP1* and *PBRM1* mutations
- CpG Island Methylator Phenotype (CIMP)

In chromophobe RCC, aneuploidies with loss of specific chromosomes occur in particular [9]. Mutations are clustered in *TP53*, *PTEN*, *FAAH2*, *PDHB*, *PDXDC1* and *NZF765*.

In the tumor microenvironment, neoangiogenesis and immune response provide points of attack for targeted therapies.

## 2.5 Risk factors

The risk of developing RCC is increased by the following factors:

- hereditary [10, 11, 12]:
  - Hereditary RCCs account for approximately 5% of cases. More than 12 genetically defined disease patterns have now been identified. Germline mutations can be detected in 6-9% of newly diagnosed RCCs [13]. The best known syndromes are:
    - von Hippel - Lindau syndrome [OMIM 193300, autosomal dominant]: Predisposition to clear cell RCC.
    - Birt-Hogg-Dubé syndrome [OMIM 135150, autosomal dominant]: Predisposition to chromophobe RCC.
- acquired [14]
  - Obesity
  - chronic renal failure
  - Smoking
  - arterial hypertension



- occupational exposure: halogenated hydrocarbons, extended radiation exposure

## **3 Prevention and early detection**

### **3.1 Prevention**

The effect of prevention is unclear. However, based on the underlying risk factors of RCC, general recommendations for prevention apply:

- do not smoke (nicotine abstinence)
- avoid excess weight

### **3.2 Early detection**

There is no early detection program. Genetic counseling and an individual surveillance strategy are recommended for members of families with Hippel-Lindau (VHL) syndrome and young cancer patients.

## **4 Clinical characteristics**

### **4.1 Symptoms**

RCC is often asymptomatic. Local symptoms may include painless macrohematuria, flank pain, a palpable mass, or a new-onset varicocele. General signs of disease include weight loss, fatigue, anemia, and paraneoplastic syndromes such as polycythemia, fever of unclear etiology, neuropathy, or hypercalcemia. Many RCCs remain asymptomatic for long time.

### **4.2 Incidental findings**

In recent years, up to 50% of RCCs were discovered incidentally during abdominal diagnosis for other indications using sonography or cross-sectional imaging. These asymptomatic tumors tend to be at an earlier stage [10]. Metastasis-related symptoms correspond to predilection sites: Bone pain in skeletal involvement, cough and dyspnea in pulmonary, neurologic deficits in cerebral/spinal manifestation.

## **5 Diagnosis**

### **5.1 Diagnostic criteria**

Not relevant

### **5.2 Diagnostics**

Careful history taking and complete physical examination are the basis of rational diagnosis. The next step is confirmation of the suspected clinical and / or imaging diagnosis, see [Table 1](#).

**Table 1: Diagnostic procedures for new-onset symptoms**

Procedure	Recommendation
Sonography kidneys and abdomen	Method of first choice for clinical symptoms
CT <sup>1</sup> Abdomen with contrast medium	Method of first choice with sufficient renal function
MRI <sup>2</sup> Abdomen with contrast medium	Method of first choice in cases of renal insufficiency, allergy to iodine-containing contrast medium, vena cava infiltration, and regional availability
Laboratory - blood	Blood count, electrolytes (Na, K, Ca), LDH <sup>3</sup> , renal function, liver values incl. albumin, coagulation
Laboratory - urine	Status
Laboratory - blood and urine	eGFR <sup>4</sup>

Legend:

<sup>1</sup> CT - multiphase computed tomography; <sup>2</sup> MRI - magnetic resonance imaging; <sup>3</sup> LDH - lactate dehydrogenase; <sup>4</sup> eGFR - estimated glomerular filtration rate

If the suspected diagnosis of RCC has been confirmed by imaging techniques, staging is indicated, see [Table 2](#). Distant metastases can evolve in almost all regions of the body. The most common localizations are lungs, skeleton, liver and brain.

**Table 2: Staging procedures**

Procedure	Recommendation
CT <sup>1</sup> Thorax and abdomen including the small pelvis	Multiphase technique
Bone scintigramm	In case of clinical suspicion of osseous metastases outside the areas already examined in the cross-sectional diagnosis alternatively: bone CT or MRI
CT or MRI <sup>2</sup> skull	In case of clinical suspicion
Laboratory - urine	Status
PET-CT <sup>3</sup> /MRI	No relevance in routine diagnostics or follow-up care

Legend:

<sup>1</sup> CT - multiphase computed tomography; <sup>2</sup> MRI - magnetic resonance imaging; <sup>3</sup> PET-CT - positron emission tomography combined with CT

A biopsy is indicated if it will have an impact on the future therapeutic approach, e.g., before local ablative procedures or before systemic therapy in primary metastatic disease. Similarly, biopsy for malignancy assessment in small renal masses (< 2 cm) may be indicated as the basis of a potential active surveillance strategy, especially in elderly and comorbid patients [15].

Otherwise, histologic confirmation prior to surgical intervention is not required.

## 5.3 Classification

### 5.3.1 Histology

Histopathological classification is made according to the current WHO classification [16], see [Table 3](#).

**Table 3: Histological classification of renal cell carcinomas**

Entity	Frequency (%)
Clear cell renal cell carcinoma	70-80
Papillary renal cell carcinoma, type I and II	~ 15
Multilocular cystic renal cell carcinoma of low malignancy Hereditary leiomyomatosis associated renal cell carcinoma Chromophobe renal cell carcinoma Ductus Bellini (collecting tube) carcinoma Medullary renal cell carcinoma MiT familial translocation carcinoma of the kidney Succinate dehydrogenase-deficient renal cell carcinoma Tubulocystic renal cell carcinoma Acquired cystic renal cell carcinoma Clear cell papillary renal cell carcinoma Renal cell carcinoma, unclassifiable Papillary adenoma	each ≤1

Sarcomatous dedifferentiation may occur in all histologic subgroups and should be documented. Other pathohistological classifications are prognostically relevant, but do not yet have an impact on surgical strategy or forms of drug therapy.

### 5.3.2 Stages

Classification is based on TNM and UICC criteria [17, 18], see Table 4.

**Table 4: Classification of tumor stages [17, 18].**

Stage	Primary tumor	Lymph nodes	Distant metastases
I	T1 T1a T1b	N0	M0
II	T2a T2b	N0	M0
III	T3a T3b T3c T1-3	N0  N1	M0
IV	T4 All T	N0, N1 All N	M0 M1

## 5.4 Prognostic factors

### 5.4.1 Prognosis score in metastatic renal cell carcinoma.

Various models have been developed for the calculation and standardized assessment of risk factors. The so-called MSKCC or Motzer score has been validated in chemotherapy and interferon-treated patients [19, 20], see Table 5.

**Table 5: MSKCC (Motzer) Score**

<ul style="list-style-type: none"> <li>• Karnofsky Performance Status (KPS) &lt; 80%</li> <li>• Time from first diagnosis to initiation of systemic relapse therapy &lt; 1 year</li> <li>• Hemoglobin below the lower, sex-specific normal value</li> <li>• Calcium (corrected value) &gt; 2.5 mmol/l (&gt; 10 mg/dl)</li> <li>• Serum lactate dehydrogenase (LDH) &gt; 1.5 of the upper normal value</li> </ul>
--

In recent studies, the IMDC score (International Metastatic Renal-Cell Carcinoma Database Consortium score) is most commonly used. It was developed in the current tyrosine kinase inhibitor

(TKI) era and is based on the identification of 6 independent prognostic factors, see [Table 6 \[21\]](#).

**Table 6: IMDC prognostic score**

- Karnofsky Performance Status (KPS) < 80%
- Time from initial diagnosis to initiation of systemic relapse therapy < 1 year
- Hemoglobin below the lower, sex-specific normal value
- Calcium (corrected value) > 2.5 mmol/l (> 10 mg/dl)
- Absolute neutrophil count above normal value
- Absolute platelet counts above normal value

Each risk factor is given a point, and the IMDC score summarizes this [22].

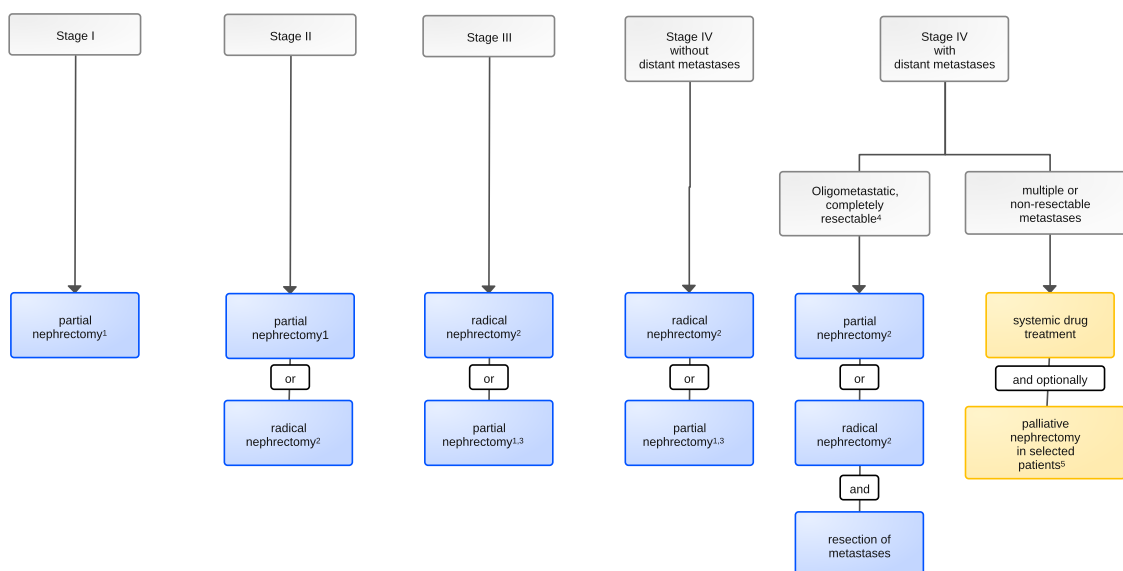
The IMDC score is predictive for the selection of systemic therapy. The calculator is provided online (<https://www.mdcalc.com/calc/3008/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma>).

## 6 Therapy

### 6.1 Treatment structure

The most effective causal therapies are surgery and drug therapy. Surgery is the only curative option. The overall treatment concept should be established before the first therapeutic intervention. A first-line treatment algorithm is shown in [Figure 4](#).

**Figure 4: Algorithm for first-line therapy**



Legend:

— curative intention; — palliative intention;

<sup>1</sup> if surgically possible;

<sup>2</sup> minimally invasive, if possible;

<sup>3</sup> in individual cases;

<sup>4</sup> indication dependent on general condition, risk group, histology and other factors;

<sup>5</sup> no benefit in intermediate and high risk compared to sunitinib alone;

#### 6.1.1 Localized stages

The treatment of choice for localized RCC is surgical resection.

### **6.1.1.1 Surgery**

#### **6.1.1.1.1 Kidney**

Radical or partial nephrectomy are available as treatment alternatives. The former gold standard was open radical nephrectomy with resection of Gerota's fascia, ipsilateral adrenal gland, and regional lymph nodes. Partial nephrectomy has the goal of preserving functional renal tissue. Postoperative renal insufficiency is a negative prognostic factor [23].

In a randomized EORTC trial in patients with clinical and imaging suspicion of stage cT1/2 N0 RCC, survival at 10 years was 81.1% for the radically vs 75.7% for the partially nephrectomized patients. While a significant difference ( $p=0.03$ ) was calculated in the intent to treat (ITT) analysis, it was not significant ( $p=0.07$ ) for the RCC carcinoma patients after controlling for inclusion criteria. Based on these data, phase II studies with long-term follow-up and a systematic review [24], following recommendations can be made:

Indications for partial nephrectomy [24].

- anatomical or functional single kidney
- increased risk of renal failure from other causes (e.g., hypertension, diabetes mellitus)
- hereditary renal cell carcinoma syndromes
- T1 stage

In stage T2, the success of partial nephrectomy depends on careful patient selection and surgical expertise.

Both radical and partial nephrectomy can be performed open or minimally invasive (retroperitoneoscopic, laparoscopic, robotic-assisted). Laparoscopic nephrectomy is less invasive and may reduce perioperative morbidity [25]. However, large randomized trials of the equivalence of open and laparoscopic partial nephrectomy from an oncologic perspective are not available. Endoscopic procedures should be performed at selected centers with appropriate expertise. Whenever oncologically justifiable, renal preservation by partial nephrectomy should be preferred over the radical procedure.

#### **6.1.1.1.2 Adrenal gland**

Adrenalectomy is required only when tumor infiltration or metastases are suspected on imaging or intraoperatively [26].

#### **6.1.1.1.3 Lymph nodes**

Lymph node resection has no impact on prognosis [27]. It is recommended only in patients with imaging or intraoperative suspicion of infiltration to confirm TNM stage, and in the presence of local symptoms.

### 6.1.1.2 Other local treatment options

#### 6.1.1.2.1 Embolization

Tumor embolization is used to reduce bleeding complications in the following situations:

- as the sole palliative measure for persistent macrohematuria when neither surgery nor systemic therapy is possible due to poor general condition
- in individual cases before surgical resection of locally advanced tumors
- in preparation of resection of bone metastases

#### 6.1.1.2.2 Minimally invasive ablative measures

Various physical procedures are used for percutaneous targeted therapy under imaging guidance [28]. Tumor control rates of up to 85% at one year can be achieved by cryotherapy and radiofrequency ablation. Laser therapy and high-intensity focused ultrasound (HIFU) are less effective. Controlled comparative studies with long-term follow-up are lacking. These physical procedures are experimental. A prerequisite for their use is prior histological confirmation of the diagnosis. Relative contraindications for local ablative procedures are life expectancy of less than 1-year, multiple metastases, low chance of success, tumors close to the hilus, tumors > 5 cm, tumors in close proximity to the renal pelvis or proximal ureter. Absolute contraindications are coagulation disorders or severe comorbidity.

#### 6.1.1.3 Adjuvant therapy

Most trials in the adjuvant setting for various immunotherapeutic approaches, e.g., interferon or tumor vaccines, have been negative. Several randomized trials on adjuvant tyrosine kinase inhibitor therapy (Assure, S-TRAC, PROTECT) showed no significant improvement in disease-free survival (DFS), with the exception of sunitinib in the S-TRAC trial [29, 30, 31], and a positive impact on overall survival has not yet been shown.

Grade	Definition
1	Tumor nucleoli are absent or inconspicuous and basophilic at 400x magnification
2	Tumor nucleoli are conspicuous and eosinophilic at 400x magnification but not prominent at 100x magnification
3	Tumor nucleoli are eosinophilic and clearly visible at 100x magnification
4	Tumors showing extreme nuclear pleomorphism and/or containing neoplastic giant cells and/or the presence of any proportion of sarcomatoid and/or rhabdoid dedifferentiation

In the adjuvant trial on pembrolizumab for 1 year in patients at high risk of recurrence (i.e., tumor stage 2 with Fuhrman grade 4 (tumors with extreme nuclear polymorphism and/or neoplastic giant cells and/or sarcomatoid and/or rhabdoid dedifferentiation) or sarcomatoid differentiation; tumor stage 3 or higher, regional lymph node metastases, or stage M1 with NED after metastasectomy) after tumor nephrectomy, a significant prolongation of disease-free survival vs placebo was shown (HR 0.68 (0.53-0.87), p=0.002) [32]. At 24 months, the rate of disease-free survival was 77.3% vs 68.1%. The study was performed only in clear cell RCC. Overall survival data are not significantly different at this time with still relatively short follow-up. An adjuvant trial with Atezolizumab did not demonstrate a significant prolongation of disease-free interval [50]. Further phase III trials with checkpoint inhibitors are pending.

Adjuvant therapy should therefore be given to patients with high risk of recurrence (i.e., tumor stage 2 with Fuhrman grade 4 or sarcomatoid differentiation; tumor stage 3 or higher, regional lymph node metastases, or stage M1 with NED after metastasectomy) in RCC [33].

### **6.1.2 Locally advanced stages**

An open field of clinical research is the treatment of patients with locally advanced RCCs in whom complete resectability appears questionable based on diagnostic imaging. The effectiveness of systemic therapies has led to concepts of primary (neoadjuvant) systemic therapy followed by surgery. Such patients are to be treated in trials. An advantage of neoadjuvant therapy in terms of patient-relevant endpoints such as operability, progression-free and overall survival has not yet been demonstrated. It is also unclear which of the available systemic agents should be preferred.

### **6.1.3 Metastatic renal cell carcinoma**

The main focus of treatment is systemic drug treatment, see [Figure 5](#). An additional cytoreductive nephrectomy can be discussed as an element of a multimodal therapy concept depending on the risk of progression in the multidisciplinary tumor board, see chapter [6.2.1.1](#). Further local therapy methods such as irradiation of osseous metastases or stereotactic irradiation can be used in the context of symptom-oriented measures, see chapter [6.2.3](#).

#### **6.1.3.1 Systemic drug treatment**

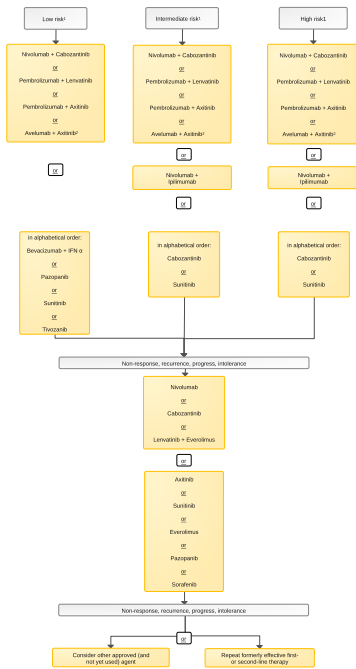
Therapy of metastatic RCC is almost always palliative. Before initiating drug therapy, the possibility of a watch-and-wait approach should be considered in low-risk or intermediate-risk patients without clinical symptoms, especially in the absence of progression on follow-up imaging. Under a watch-and-wait modality, regular clinical and imaging follow-up at least every three months is recommended. A clear benefit with significant prolongation of progression-free survival compared to the former standard of interferon alpha could be achieved with angiogenesis-inhibiting multityrosine kinase inhibitors (TKIs), mTOR inhibitors [33, 34], the combination of interferon alpha and the VEGF antibody bevacizumab as well as currently with newer TKIs and checkpoint inhibitors. Information on the use of these drugs is summarized in the [Approval Status Appendix](#).

##### **6.1.3.1.1 Systemic first-line therapy**

The concepts for first-line systemic treatment of locally advanced and metastatic RCC have changed fundamentally since the last 3 years. Different drug combinations and monotherapies are now available. It should be noted that most first-line trials included only clear cell renal cell carcinoma (ccRCC) or RCC with a clear cell component. In contrast, for non-clear cell renal cell carcinomas (nccRCC), studies are sparse and limited by case numbers, so the evidence here is much lower. However, there are also studies that have preferentially included these patients, predominantly in the phase II setting. It was found that essentially the approaches used in the treatment of clear cell carcinoma are also effective in the other subtypes, albeit with somewhat lower effectiveness than in the clear cell variant [35].

The efficacy of drug therapy, especially in terms of overall survival, differs between different risk groups according to the IMDC score. A treatment algorithm for drug therapy is shown in [Figure 5](#).

**Figure 5: Algorithm for systemic drug therapy of advanced/metastatic renal cell carcinoma**



**Legend:**

— curative intention; — palliative intention;

<sup>1</sup> For risk scores see chapter 5.4.1;

<sup>2</sup> Axitinib plus avelumab: overall survival advantage over sunitinib has been shown only in the subgroup of patients at high risk

The majority of currently published randomized trials compare the respective new therapy against sunitinib monotherapy. Based on these data and approval status, the combinations of nivolumab with cabozantinib [36], pembrolizumab with axitinib [37], pembrolizumab with lenvatinib [38], or, with limitation, avelumab with axitinib [40] are considered the new standard of care in first-line therapy regardless of risk score or histological entity, although insufficient data are available for non-clear cell renal cell carcinomas and no overall survival data are available for the combination of axitinib with avelumab. For intermediate- and high-risk patients, the combination of ipilimumab and nivolumab [40] is an equivalent alternative. Prioritization cannot be made at this time in the absence of comparative studies. Data are summarized in Table 7.



**Table 7: Comparison of studies on systemic first-line therapy**

Study	Checkmate 214 [40]	Checkmate 9ER [36]	Keynote 426 [37]	CLEAR [38]	JAVELIN Renal 101 [39]
<b>Combination immunotherapy</b>	Ipilimumab/nivolumab	Nivolumab/cabozantinib	Pembrolizumab/axitinib	Pembrolizumab/lenvatinib	Avelumab/Axitinib
<b>Primary study endpoints</b>	ORR, PFS, OS in intermediate- and poor-risk patients	PFS	OS and PFS in the IIT cohort	PFS	PFS and OS of patients with PD-L1 pos. tumor (>1% of immune cells)
<b>ORR (%)</b>	39.0*	55.7	59.3	71.0	51.4
<b>CR (%)</b>	10.2*	8.0	5.8	16.1	3.4
<b>Primary progress (%)</b>	20*	5.6		5.4	11.5
<b>Median PFS (months) Combination immunotherapy vs. sunitinib</b>	12.4* vs. 12.3 p<0.001	16.6 vs 8.3 p<0.001	15.1 vs. 11.1 p<0.001	23.9 vs. 9.2 p<0.001	13.8 vs 8.4 p<0.0001
<b>OS (months) Combination immunotherapy vs. sunitinib</b>	NR vs. 32.0 p<0.001	Median NR p<0.001	Median NR p<0.001	Median NR p=0.005	Median NR n.s.

Legend:

\*Results for patients at intermediate and poor risk. ORR – overall response rate; CR – complete response; OS – overall survival; PFS – progression-free survival; PD-L1 – programmed cell death ligand 1; ITT – intention-to-treat

The results for the different risk groups can be summarized as follows:

- Low risk of progression
  - The combinations nivolumab/cabozantinib, axitinib/pembrolizumab, and pembrolizumab/lenvatinib significantly increase the remission rate and prolong progression-free survival in the low-risk group compared with sunitinib; a significant prolongation of overall survival compared with sunitinib has not yet been shown because too few events are available for this purpose.
  - Axitinib/avelumab results in increased remission rates and prolonged progression-free survival at low and intermediate risk compared with sunitinib, (significant prolongation of overall survival compared with sunitinib has not been shown to date
  - Nivolumab + ipilimumab is inferior to sunitinib in remission rate and progression-free survival (HR 2.18; median - 9.8 months), and the difference in overall survival is not significant.
- Alternatives in case of contraindications regarding these combinations are:
  - Tyrosine kinase inhibitors: sunitinib, pazopanib and tivozanib are approved. The comparator arms of the respective pivotal studies were different.
    - Sunitinib leads to increase in remission rate and prolongation of progression-free survival (median 6 months) compared to interferon-alpha.
    - Pazopanib showed no significant difference in progression-free and overall survival in a non-inferiority trial versus sunitinib, but a somewhat different side effect profile.
    - Compared with sorafenib, tivozanib results in a higher remission rate and longer progression-free survival (HR 0.795; median 2.4 months), but no longer overall survival.
  - Bevacizumab + interferon alpha: Compared to interferon alpha, this combination leads to an increase in remission rate, prolongation of progression-free survival

(median 3.3 months), but also to a higher rate of severe adverse events of CTCAE grade 3/4.

- Intermediate and high risk of progression
  - The combinations of nivolumab/cabozantinib, axitinib/pembrolizumab, and pembrolizumab/lenvatinib significantly increased remission rates, progression-free survival, and overall survival compared with sunitinib in the intermediate and high-risk groups
  - Nivolumab + ipilimumab results in an increase in remission rate and prolongation of overall survival (HR 0.697; median not reached yet) in intermediate-risk patients compared with sunitinib; the difference in progression-free survival is not significant.
  - Axitinib + avelumab leads to increase in remission rate and prolongation of progression-free survival), not overall survival (HR 0.87; median survival not yet reached), in low and intermediate risk versus sunitinib.
- Alternatives for contraindications regarding these combinations are tyrosine kinase inhibitors:
  - Sunitinib resulted in increased remission rates and prolonged progression-free survival (median 6 months) compared with interferon-alpha.
  - Cabozantinib leads to increased remission rate and prolonged progression-free survival (HR 0.48; median 3.3 months), not overall survival, in a small study versus sunitinib.

Details of the respective pivotal studies including assessment of clinical benefit according to the ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS) and the early benefit assessment of the G-BA can be found in the [Fact Sheets](#).

#### **6.1.3.1.2 Systemic second-line therapy**

Due to the introduction of combination therapies in the first line and the lack of controlled studies in the second line after combination therapy, an evidence-based recommendation cannot be given. Therefore, the second line should be based on individual consideration (e.g., prior therapy, response, course, comorbidity).

- After first-line therapy with immune checkpoint inhibitors and their combination with a TKI or another immune checkpoint inhibitor, there are currently no evidence-based data for the subsequent treatment sequence. Agents not used in primary therapy may be tried in second and subsequent lines.
- Nivolumab leads to an increase in remission rate, prolongation of progression-free survival (HR 0.40; median 4.6 vs 4.2 months), prolongation of overall survival (HR 0.51; median 25.5 vs 19.6 months), and a decrease in the rate of severe adverse events in CTCAE grade 3/4 compared to everolimus in patients treated primarily with a TKI.
- Cabozantinib also results in increased remission rates, prolonged progression-free survival (HR 0.58; median 7.4 vs 3.8 months), and prolonged overall survival (HR 0.7; median 21.4 vs 17.1 months) compared with everolimus in patients treated primarily with a TKI. The rate of serious adverse events of CTCAE grade 3/4 is higher [41, 42].
- Lenvatinib + everolimus leads to increased remission rates, prolonged progression-free survival (HR 0.4; median 14.6 vs 5.5 months), and prolonged overall survival (HR 0.51; median 25.5 vs 15.4 months) compared with everolimus in a small study of patients treated primarily with a TKI. The rate of serious adverse events of CTCAE grade 3/4 is higher. Data from a follow-up study with lower doses of lenvatinib (14 mg vs 18 mg) show

similar toxicity but a trend in favor of the higher dose with respect to ORR, PFS, and OS [43, 44].

Substances not used in the primary therapy can be tried in the second and subsequent lines. Thus, it may be presumed that drugs effective in first-line treatment or after VEGF-targeted therapy retain their efficacy after the new combinations. Here, prospective studies or at least registry data are urgently needed. A randomized trial comparing tivozanib versus sorafenib in patients after pretreatment with VEGFR and immune checkpoint inhibitors showed a slight prolongation of progression-free survival (HR 0.73; median 1.7 months), not overall survival. Currently, treatment recommendation is primarily based on the type of prior treatment, the patient's general condition, and side effects of prior therapies, see [Figure 5](#).

Depending on the therapeutic goal, comorbidity, and side effects of prior therapies, other TKIs and the mTOR inhibitor everolimus may also be used.

Details of the respective pivotal studies including assessment of clinical benefit according to the ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS) and the early benefit assessment of the G-BA can be found in the [Fact Sheets](#).

## **6.2 Treatment modalities**

### **6.2.1 Surgical treatment**

#### **6.2.1.1 Cytoreductive nephrectomy**

In patients with advanced RCC, nephrectomy may lead to regression of metastases, but this phenomenon has been observed in less than 2% of patients. In combination with systemic therapy using interferon alpha, nephrectomy prolongs median survival by 3 to 10 months.

In a non-inferiority trial including intermediate- and high-risk metastatic patients, sunitinib alone was non-inferior to cytoreductive tumor nephrectomy followed by sunitinib, and there was even a trend in OS in favor of sunitinib alone [45]. The value of sequential tumor nephrectomy was also investigated in the SURTIME trial. The trial did not meet the primary endpoint, and a total of 99 patients were randomized [46]. By selecting for patients with response to TKI therapy, additional surgery could be avoided in patients with an unfavorable prognosis (progressive disease within 4 months).

The results of modern therapeutic strategies with TKIs or immune checkpoint inhibitors have been predominantly achieved in nephrectomized patients. No data are yet available on the value and sequence of tumor nephrectomy with immune checkpoint inhibitors and combination therapies (IO/TKI or IO/IO).

#### **6.2.1.2 Resection of metastases**

Long-lasting remissions have been observed after resection of metastases, especially from lungs, liver, and brain. Therefore, after careful staging, this measure is recommended for patients in whom R0 resection is possible [33, 47, 48, 49]. The decision for surgical therapy must be made on an individual basis and must take into account factors such as comorbidities, prognosis, and patient preferences. Follow-up to detect any new metastases should be performed before surgical resection of metastases to assess the dynamics of the disease and usefulness of metastasis resection. Conceptually, surgical metastasectomy should be performed with the goal of complete resection of the tumor burden or for palliation alone. Debulking surgery should be used only for symptom control or when complications are imminent/mani-

fest. Even after systemic therapy, a long-term treatment-free interval may still be achieved by subsequent complete metastasectomy.

In case of initial complete resection of the primary and metastases ("no evidence of disease", NED), adjuvant therapy with pembrolizumab is indicated (see chapter 6.1.1.3).

## **6.2.2 Agents for systemic treatment (in alphabetical order)**

### **6.2.2.1 Avelumab**

Avelumab is a human IgG1 monoclonal antibody. It binds to [programmed cell death ligand 1](#) (PD-L1) and prevents binding to its receptor PD-1. PD-1/PD-L1 receptor/ligand interaction leads to inhibition of CD8+ T cells and thus inhibition of immune response. Avelumab is approved in combination with axitinib for first-line treatment of metastatic RCC. The combination results in a higher response rate (51.4% vs. 25.7%) and prolonged progression-free survival (13.8 vs. 8.4 months; HR 0.69) compared with sunitinib. Side effects of avelumab monotherapy are relatively rare. In Merkel cell carcinoma monotherapy, serious adverse events of CDTAE grade 3/4 severity related exclusively to laboratory findings. Most common adverse reactions of all grades were fatigue (24%), infusion reaction (17%), diarrhea (9%), asthenia (8%), exanthema (7%), and loss of appetite (6%). Possible immune-mediated reactions were of grade 1-2: Hypothyroidism (3%), hyperthyroidism (2%), pneumonitis (1%), type 1 diabetes mellitus (1%). The side effects of combination therapy are similar to those of axitinib and other immune checkpoint inhibitors (see also under nivolumab).

### **6.2.2.2 Axitinib**

[Axitinib](#) is a second-generation tyrosine kinase inhibitor. It selectively blocks VEGF receptors 1-3. In second-line therapy, remission rates of 19% and a significantly longer progression-free survival time compared to control were achieved. Survival was not prolonged. Serious adverse events (grade 3/4) occurring in more than 5% of patients were hypertension (16%), diarrhea (11%), and fatigue (11%). Endocrine (hypothyroidism), hematologic, or cardiac side effects may occur in patients treated long-term with multikinase inhibitors.

### **6.2.2.3 Bevacizumab**

[Bevacizumab](#) is a monoclonal antibody with antiangiogenic activity. In cytokine-pretreated RCC patients, monotherapy can delay progression. In combination with interferon alpha, remission rates of 25-30% and significant prolongation of progression-free survival were achieved compared with interferon alpha monotherapy. Analysis by prognostic subgroups showed a gain for patients with low and intermediate risk scores. Serious adverse events (grade 3/4) that occurred in more than 5% of patients in the pivotal studies were: Fatigue (12-35%), asthenia (10-17%), proteinuria (7-13%), and hypertension (3-13%). Less common critical complications included thromboembolic events and gastrointestinal tract perforations.

### **6.2.2.4 Cabozantinib**

[Cabozantinib](#) is a multikinase inhibitor. In addition to VEGFR1, VEGFR2 and VEGFR3 kinases, it also inhibits AXL and MET. Cabozantinib is approved in advanced RCC as monotherapy in the first-line setting (not applicable in Switzerland) for intermediate- and high-risk patients and in the second-line setting at a dose of 60 mg/day. In the pivotal trial, cabozantinib led to increased survival (HR 0.67; median 4.9 months), progression-free survival (HR 0.52; median 3.5

months), and remission rates after VEGFR-targeted prior therapy compared with everolimus. The rate of serious therapy-associated adverse events is significantly higher with cabozantinib than with everolimus; CTCAE grade 3/4 adverse events that occurred more frequently than in the everolimus arm were hypertension (15%) and fatigue (9%). The most common adverse events leading to dose reduction with cabozantinib were diarrhea (16%), palmoplantar erythrodysesthesia (11%), and fatigue (10%). In the pivotal study, 60% of patients on cabozantinib required dose reduction.

#### **6.2.2.5 Everolimus**

Everolimus is an oral mTOR inhibitor. The pivotal study was conducted in RCC patients in second or later line therapy after pretreatment with sorafenib and / or [sunitinib](#) and showed a significant prolongation of progression-free survival compared to the placebo control group. Two-thirds of patients were also pretreated with cytokines. Serious adverse events (grade 3/4) that occurred in more than 5% of patients in the pivotal trial were infection (10%) and dyspnea (7%). A less frequent but more burdensome side effect of mTOR inhibitors is pneumonitis.

#### **6.2.2.6 Interferon alpha (IFN alpha)**

IFN alpha is a member of the interferon family. The exact mechanism of its antitumor activity is not clear. IFN alpha stimulates NK cells, increases the immunogenicity of tumor cells, induces apoptosis, has an anti-angiogenic effect and also an antiproliferative effect via the induction of cyclin-dependent kinase inhibitors. In monotherapy of RCC patients, remission rates of 12-13% (0-39) are achieved, complete remissions in around 2-3% of patients. Median survival is 13 months (6-28 months). Part of the studies on the superiority of the newer agents ([bevacizumab](#), sorafenib, [sunitinib](#), temsirolimus) were performed in comparison to monotherapy with IFN alpha. Serious adverse events (grade 3/4) occurring in more than 5% of patients in the pivotal study were: asthenia (4-26%), anemia (5-22%), fatigue (13%).

#### **6.2.2.7 Ipilimumab**

Ipilimumab is a humanized monoclonal antibody directed against the Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4). Its use can reverse negative immune regulation by CTLA-4 and achieve anti-tumor effects through T-cell stimulation. In RCC, ipilimumab has been tested in combination with nivolumab in a phase III trial, following studies in other tumors, particularly in melanoma. The combination showed significantly increased response rate (42% vs 27%), prolonged progression-free survival (HR 0.83), and overall survival (HR 0.63) compared with [sunitinib](#) in intermediate- and high-risk patients. In patients at low risk of progression, the nivolumab/ipilimumab combination was inferior to sunitinib. CTCAE grade 3/4 adverse events that occurred in more than 1% of patients in the nivolumab/ipilimumab arm were fatigue (4%), elevation of lipase (10%), and diarrhea (4%). Due to adverse events, therapy was discontinued in 22% of patients in the nivolumab/ipilimumab arm.

#### **6.2.2.8 Lenvatinib**

[Lenvatinib](#) is a multikinase inhibitor and inhibits VEGFR1, VEGFR2 and VEGFR3 kinases. Lenvatinib is approved in first-line advanced RCC in combination with [pembrolizumab](#) at a dose of 20 mg/day p.o. in combination with pembrolizumab 200 mg i.v. every 21 days. Compared to [sunitinib](#), the combination significantly prolongs overall response (71.0% vs 36.1%), progression-free survival (23.9 months vs 9.2 months; HR 0.39:0.32-0.49; p<0.001) and overall survival (HR 0.66:0.49-0.88; p=0.005). Rates of grade 3/4 serious adverse events were slightly higher with

the combination (82.4% vs 71.8%), predominantly hypertension (27.6%), diarrhea (9.7%), and weight loss (8.0%).

In the second-line setting, lenvatinib is approved for combination therapy with everolimus at 18 mg/day plus everolimus at 5 mg/day. The basis of the early benefit assessment was a three-arm phase 1b/2 trial including a total of 153 patients. Lenvatinib/everolimus lead to increased survival (HR 0.51; median 10.1 months), progression-free survival (HR 0.40; median 9.1 months), and remission rates in second-line therapy compared with everolimus. The rate of serious therapy-associated adverse events was significantly higher with lenvatinib/everolimus than with everolimus. Grade 3/4 adverse events that occurred more frequently than in the everolimus arm were diarrhea (20%), fatigue (14%), hypertension (14%), vomiting (8%), nausea (6%), proteinuria (4%), and back pain (4%).

#### **6.2.2.9 Nivolumab**

Nivolumab is an anti-PD-1 monoclonal antibody. Nivolumab blocks apoptosis of activated T cells and enhances the autologous immune response. Nivolumab is approved in first-line therapy of RCC in combination with ipilimumab. This combination shows significantly increased response rate (42% vs 27%), prolonged progression-free survival (HR 0.83) and overall survival (HR 0.63) in patients at intermediate and high risk of progression compared to sunitinib. CTCAE grade 3/4 adverse events that occurred in more than 1% of patients in the nivolumab/ipilimumab arm were fatigue (4%), lipase elevation (10%), and diarrhea (4%). Due to adverse events, therapy was discontinued in 22% of patients in the nivolumab/ipilimumab arm.

Nivolumab is approved as monotherapy for second-line treatment of metastatic RCC. Nivolumab results in prolonged survival (HR 0.73; median 5.4 months), increased remission rate, and prolonged time to worsening of clinical symptoms in second-line therapy compared with everolimus. Progression-free survival is not significantly prolonged. The rate of serious therapy-associated adverse events is significantly lower with nivolumab than with everolimus, and the rate of treatment discontinuation is also lower. Adverse events of CTCAE grade 3/4 associated with nivolumab were fatigue (2%), anemia (2%), diarrhea (1%), dyspnea (1%), pneumonitis (1%), and hyperglycemia (1%). Fatigue (33%), nausea (14%), pruritus (14%), diarrhea (12%), loss of appetite (12%), and exanthema/acne (10%) were also the most common of all adverse events with nivolumab.

#### **6.2.2.10 Pazopanib**

Pazopanib is another oral tyrosine kinase inhibitor with a slightly different kinase profile than sorafenib and [sunitinib](#). The pivotal study enrolled patients in both first-line therapy and after pretreatment with cytokines. RR was 30% and progression-free survival was significantly higher than placebo control. Survival time was not prolonged. There were no serious adverse events (grade 3/4) occurring in more than 5% of patients in the pivotal study. Attention should be paid to regular monitoring of ALT and bilirubin for early detection of hepatotoxicity. Endocrine (hypothyroidism), hematologic, or cardiac side effects may occur in patients treated long-term with multikinase inhibitors.

#### **6.2.2.11 Pembrolizumab**

[Pembrolizumab](#) is a humanized IgG4 monoclonal antibody. It binds to the [programmed cell death receptor](#) (PD-1) and prevents binding of its ligands such as PD-L1. PD-1/PD-L1 receptor/ligand interaction leads to inhibition of CD8<sup>+</sup> T cells and thus inhibition of an immune response; pembrolizumab counteracts this negative regulation. Pembrolizumab is approved in combination with axitinib for first-line treatment of metastatic RCC. Compared with sunitinib,

the combination results in a higher response rate (59.3% vs. 35.7%), prolonged progression-free survival (15.1 vs. 11.1 months; HR 0.69), and prolonged overall survival (HR 0.53; median not yet reached). Side effects of the combination were consistent with those of axitinib and that of other immune checkpoint inhibitors (see under nivolumab).

#### **6.2.2.12 Sorafenib**

Sorafenib is an oral inhibitor of several tyrosine kinases, including VEGF receptors, PDGFRB, Flt-3, and c-KIT. In signal transduction, it also blocks Raf family serine-threonine kinases in the MAPK pathway. The largest study of sorafenib to date evaluated this agent as second-line therapy in low- or intermediate-risk patients. Progression-free survival was significantly prolonged. In first-line therapy of RCC, there was no significant difference in remission rate and progression-free survival compared with interferon alpha. Serious adverse event (grade 3/4) occurring in more than 5% of patients in the pivotal study was hand - foot syndrome (grade 3/4). Endocrine (hypothyroidism), hematologic, or cardiac side effects may occur in patients treated long-term with multikinase inhibitors.

#### **6.2.2.13 Sunitinib**

**Sunitinib** is an oral inhibitor that blocks multiple VEGF, PDGF receptors as well as c-KIT and Flt-3 at the tyrosine kinase level. In the pivotal study, sunitinib was used in RCC patients for first-line therapy compared with IFN alpha. Progression-free survival was significantly longer, and the remission rate was 47% at final analysis. Serious adverse events (grade 3/4) occurring in more than 5% of patients in the pivotal study were hypertension (12%), fatigue (11%), diarrhea (11%), hand-foot syndrome (9%), and asthenia (7%). Endocrine (hypothyroidism), hematologic, or cardiac side effects may occur in patients treated long-term with multikinase inhibitors.

#### **6.2.2.14 Temsirolimus**

Temsirolimus was the first approved mTOR kinase inhibitor in RCC. The drug is administered intravenously. Efficacy was evaluated in a randomized phase III trial in patients with at least three of 6 risk features ([Table 5](#)). Patients in the comparator arm were treated with IFN alpha, and patients in a third arm were treated with temsirolimus + IFN alpha. Temsirolimus therapy resulted in remission rates of 8.6%, and median progression-free survival and overall survival were significantly prolonged compared with IFN alpha monotherapy. The combination showed no benefit over monotherapy with temsirolimus; however, the dose of temsirolimus was reduced to 15 mg per week in the combination arm. Serious adverse events (grade 3/4) occurring in more than 5% of patients in the pivotal trials were anemia (20%), asthenia (11%), hyperglycemia (11%), and dyspnea (9%). A less common but troublesome side effect of mTOR kinase inhibitors is pneumonitis.

#### **6.2.2.15 Tivozanib**

**Tivozanib** is another oral tyrosine kinase inhibitor with selective inhibition of VEGF receptors. In the pivotal study, tivozanib was tested in the first-line treatment of RCC versus sorafenib in previously untreated or with interferon- $\alpha$  pretreated patients (TIVO-1) and resulted in a prolongation of progression-free survival of 12.7 vs 9.1 months in previously untreated patients, and 11.9 vs 9.1 months in the entire population including interferon-alpha pretreated patients (hazard ratio 0.756 for first-line,  $p=0.037$ ). The remission rate was increased to 33.1 vs 23.4%. Survival was not prolonged by tivozanib, but data are limited due to a switching (crossover) rate of 61% from the sorafenib to the tivozanib arm. Grade 3/4 adverse events that occurred in  $\geq 5\%$  of

patients on tivozanib in the pivotal trial were hypertension (27%), fatigue (5%), and lipase elevation (9%). Another common side effect is dysphonia.

#### **6.2.2.16 Cytostatic drugs**

Conventional cytostatics have only a low efficacy in RCC. Agents used have included [5-fluorouracil](#) in combination with immunotherapy or vinblastine. Chemotherapy remission rates have been less than 5%.

### **6.2.3 Treatment sequence**

The new drug treatment options for metastatic RCC have profoundly changed the picture of the disease and the way patients are treated. In a majority of patients, multiple agents with different efficacy profiles will be used as sequential therapy during the course of the disease. The optimal sequence has not yet been established. The choice of drugs should therefore be based on the treatment goal and the patient's general clinical condition and concomitant diseases, taking into account the expected treatment-related side effects.

## **6.3 Specific settings**

### **6.3.1 Non-clear cell renal cell carcinoma**

Clear cell RCC represents the dominant histological entity. The majority of studies with the newer drugs have been conducted exclusively in this entity. Patients with papillary RCC type II have a more aggressive course and shorter life expectancy. Analyses of this subgroup suggest that they respond to kinase inhibitors and antiangiogenic treatment, but with lower remission rates and shorter progression-free survival.

It is recommended to treat patients with non - clear cell RCC analogous to the clear cell carcinoma algorithm. This also applies to the use of immune checkpoint inhibitors.

If possible, therapy should be managed in the context of clinical trials. In these patients, short-term evaluation is indicated to allow for a change of mechanism of action in case of non-response.

### **6.3.2 Palliative therapy**

Palliative therapy includes individualized, symptom-oriented treatment of physical and psychological complaints in every phase of the course of the disease. It takes place on an interdisciplinary basis and, in particular, psycho-oncological support should be considered. The necessity and the possibilities of palliative therapy should be discussed early and comprehensively with all those affected. The following specific symptoms occur particularly frequently in patients with advanced RCC.

#### **6.3.2.1 Bone metastases**

For the treatment of patients with bone metastases, local and systemic measures are available in addition to appropriate pain therapy. In case of a singular bone metastasis, a primarily surgical therapy should be performed. In case of pain symptoms or fracture risk, radiotherapy is the treatment of choice. This can be applied hypofractionated under continuous systemic therapy.



An additional option is surgical treatment of pathological fractures, instable vertebral body fractures or as a relief in case of spinal compression.

Systemic treatment, i.e., the administration of bone-modifying substances (bisphosphonates, anti-RANKL antibodies), are indicated. They reduce the risk of complications and delay the progression of skeletal metastasis. Prospective randomized trials exclusively in patients with RCC or in a sufficiently large number of patients are not available. For information on the approval status of bone-modifying agents. Bisphosphonates are also indicated for hypercalcemia.

### **6.3.2.2 Liver and lung metastases**

Here, the focus is on systemic treatment. In individual cases, local therapy may be considered. In addition to surgical resection, local ablative procedures are available. Prerequisites are

- no disseminated metastases
- no local recurrence or clinically limiting second cancer

Decisions on local treatment of liver or lung metastases should be made by a multidisciplinary tumor board.

### **6.3.2.3 Brain metastases**

First approach to symptomatic cerebral metastasis is administration of glucocorticosteroids to reduce perifocal edema. Local surgical therapy is recommended for isolated, resectable brain metastases. An alternative is targeted local conformal radiotherapy (stereotactic radiation, gamma-knife, cyber-knife). Partial or whole brain radiotherapy may be discussed for disseminated brain metastases. Data on the efficacy of the newer drugs for systemic treatment are limited due to small numbers of patients studied.

## **7 Rehabilitation**

After local therapy of RCC, all patients should be offered specific rehabilitation in the form of follow-up treatment and rehabilitation. If symptoms persist, patients should be informed about further rehabilitation measures. Patients with metastatic disease can also benefit from specific rehabilitation. The aim of medical rehabilitation is to maintain or restore the ability to work, to lead a self-determined daily life and to participate in social activities. Rehabilitation should be multidisciplinary, taking into account the patient's comorbidity and applying multimodal treatment concepts. As part of the rehabilitation measure, patient should be offered targeted physiotherapy, psycho-oncological care to support coping with the disease and socio-medical counseling, as well as profession-related support, if there are limitations in functional ability. With regard to the choice of the rehabilitation clinic, patient preferences should be taken into account (§9 SGB IX). Nevertheless, a recommendation should be made for a clinic with an oncological focus to optimize rehabilitation success.

## **8 Follow-up**

### **8.1 General follow-up post-treatment**

Follow-up after primary tumor therapy in the non-distant metastatic stage should be risk-adapted [33]. In the first year, a 3-monthly check-up (clinical examination, clinical chemistry, and sonography) is recommended, in the 2nd year a semiannual check-up, and from year 3 through 5, an annual follow-up. Especially after partial resection of the kidney, sonographic

assessment may be difficult, so that risk-adapted cross-sectional imaging (CT abdomen) is useful in these patients (see also recommendations of the current S3 guideline [33]). Under ongoing systemic therapy, cross-sectional imaging should be performed every 6 to 12 weeks. During therapy with checkpoint inhibitors, an initial increase in tumor extension may be observed, which is called early pseudo-progression. Therefore, in these patients, the first cross-sectional imaging is generally not indicated before 12 weeks after start of therapy.

## 8.2 Follow-up postoperatively in patients with localized renal cell carcinoma

There is no universal follow-up program for this cohort of patients. The risk of recurrence depends on the stage at initial diagnosis. The majority of relapses occur in the first two years. Since life expectancy in recurrence is influenced by the extent of metastasis, follow-up with cross-sectional imaging appears reasonable. However, evidence is lacking that structured follow-up in terms of regular re-staging procedures result in improved survival. The aim of examinations after curatively intended therapy is the detection of complications and late sequelae. In patients post-nephrectomy, these examinations include symptoms of renal insufficiency and hypertension.

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## **16 Disclosure of Potential Conflicts of Interest**

according to the [rules of DGHO, OeGHO, SGH+SSH, SGMO](#)

Author	Employer <sup>1</sup>	Consulting / Expert opinion <sup>2</sup>	Shares / Funds <sup>3</sup>	Patent / Copyright / License <sup>4</sup>	Fees <sup>5</sup>	Funding of scientific research <sup>6</sup>	Other financial relations <sup>7</sup>	Personal relationship with authorized representatives <sup>8</sup>
Bauernhofer, Thomas	Medizinische Universität Graz	<b>Yes</b> Adboards AstraZeneca, Merk, Janssen-Cilag, MSD	<b>No</b>	<b>No</b>	<b>Yes</b> Pflegefertbildung der AHOP, Sonderausbildung onkologische Pflege der KeGes, Übersichtsartikel zum Thema Prostatakarzinom mit finanzieller Unterstützung von Janssen-Cilag Vertragshonorare von Janssen-Cilag, BMS, MSD, Astellas, AstraZeneca, Merk, Ipsen	<b>Yes</b> Bestimmung des HRD Status bei Patienten mit Prostatakarzinom Investigator initiated Study mit Unterstützung durch AstraZeneca	<b>No</b>	<b>No</b>
Bergmann, Lothar	Selbstständig	<b>Yes</b> Teilnahme an einzelnen Advisory Boards/ Expertenmeetings (ohne Honorar!) von Pfizer, Ipsen, EUSA Pharm, BMS, Roche	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>
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Casper, Jochen	Klinikum Oldenburg, Oldenburg	<b>Yes</b> Pfizer, Merck, Medac, Ipsen	<b>No</b>	<b>No</b>	<b>Yes</b> Pfizer, Merck, Ipsen, Medac	<b>Yes</b> Pfizer, medac	<b>Yes</b> Pfizer, Merck, Medac, Ipsen	<b>No</b>
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Gauler, Thomas	Conflict of interest declarations pending							
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		MSD Sharp / Dohme GmbH Merck Health-care Germany GmbH Janssen-Cilag GmbH Bristol-Myers Squibb GmbH & Co. KGaA Pfizer Pharma GmbH Photocure GmbH						
Peters, Inga		No	No	No	No	No	No	No
Pritzkuleit, Ron		No	No	No	No	No	No	No
Raida, Martin	VAMED Rehaklinik Bergisch-Land Wuppertal	No	Yes Lanxess	No	No	No	No	No
Schmidinger, Manuela	Medizinische Universität Wien, Universitätsklinik für Urologie	Yes BMS, MSD, Merck, EUSA, EISAI, IPSEN, EXELIXIS, ALKERMES, JANSSEN	No	No	Yes BMS, MSD, Merck, EUSA, EISAI, IPSEN, EXELIXIS, ALKERMES, JANSSEN	Yes IPSEN,	Yes Reisekosten-erstattung IPSEN	No
Stenner-Liewen, Frank	Universitätsspital Basel	Yes Roche MSD BMS Pfizer Pfizer Ipsen	No	No	No	Yes PI einer BMS gesponserten Studie SAKK 07/17	No	No
von Amsberg, Gunhild	Conflict of interest declarations pending							

*Legend:*

<sup>1</sup> - Current employer, relevant previous employers in the last 3 years (institution/location).

<sup>2</sup> - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.

<sup>3</sup> - Ownership of business shares, stocks, funds with participation of companies of the health care industry.

<sup>4</sup> - Relates to drugs and medical devices.

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*matter of the investigation.*

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