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Renal Cell Carcinoma (Hyper-nephroma)

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 is one of the more common malignant tumors in adults. In Europe, men are significantly more frequently affected with an incidence of approx. 26/100,000 than women with an incidence of approx. 12/100,000. The average age of onset is between 65 and 70 years for men and over 70 years for women. In recent years, renal cell carcinomas have increasingly been discovered incidentally as part of abdominal diagnostics for other indications using sonography or cross-sectional imaging. The age-standardized incidence and mortality rates have been falling slightly since 2006.

The most effective treatment methods are surgery, especially in the localized stage, and drug therapy. Surgery with complete tumor removal is the only curative option. In the last 15 years, numerous new drugs in the field of antiangiogenesis, tyrosine kinase and immune checkpoint inhibition have been approved as mono- and combination therapies for drug-based tumor therapy in the metastatic situation. Radiotherapy is also used in palliative situations, especially in symptomatic inoperable metastases.

2 Basics

2.1 Definition and basic information

Renal cell carcinoma accounts for around 85% of malignant kidney tumors. Other forms include urothelial carcinoma originating from the renal pelvis (10%), non-Hodgkin's lymphomas, sarcomas and, in children, nephroblastomas (Wilms' tumor). The topic of this chapter is renal cell carcinoma.

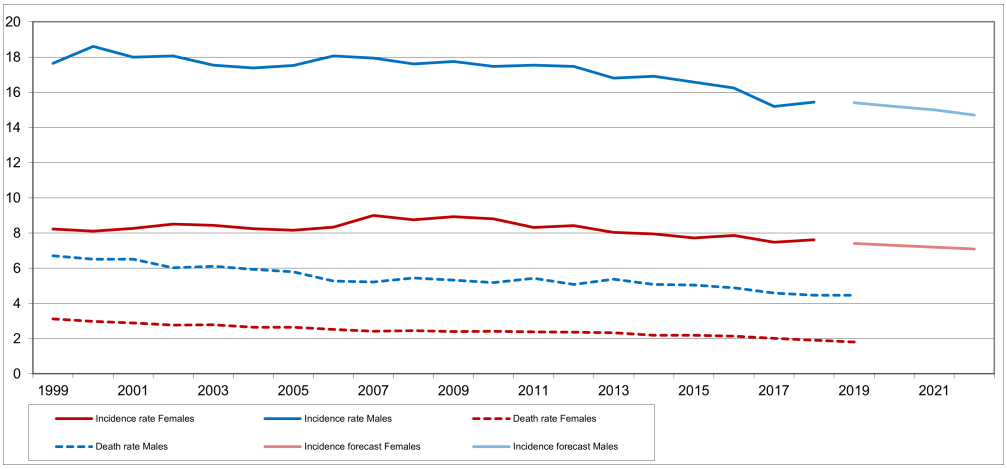
2.2 Epidemiology

Every year, around 15,000 new cases of kidney cancer are diagnosed in Germany [1], around 1,350 in Austria [2] and around 1,000 in Switzerland in the years 2012-2016 [3]. Almost 110,000 people living in Germany have been diagnosed with kidney cancer in the last 10 years. More than 90% of all diagnosed kidney cancers are histologically carcinomas, of which more than 95% are adenocarcinomas. Kidney cancer is responsible for just over 5,000 deaths per year in Germany. Men are affected about twice as often as women.

The absolute 5-year survival rate is given as 65% (men) and 71% (women), the relative 5-year survival rate, which takes into account mortality in the general population, is 76% (men) and 78% (women). The relative 10-year survival rate is 69% (men) and 72% (women) [1].

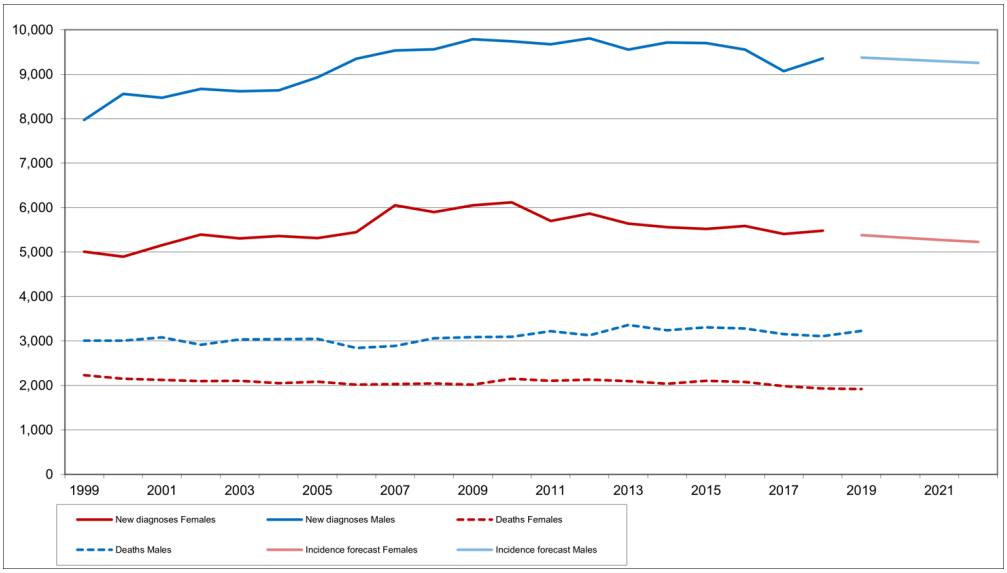
The age-standardized disease rates, as well as mortality rates, have been falling slightly in men for years, see Figure 1. In the last 14 years, the rates have fallen by an average of 0.8% (incidence rate) and 1.5% (mortality rate) per year. In women, the incidence rate is largely constant (-0.5% per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

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



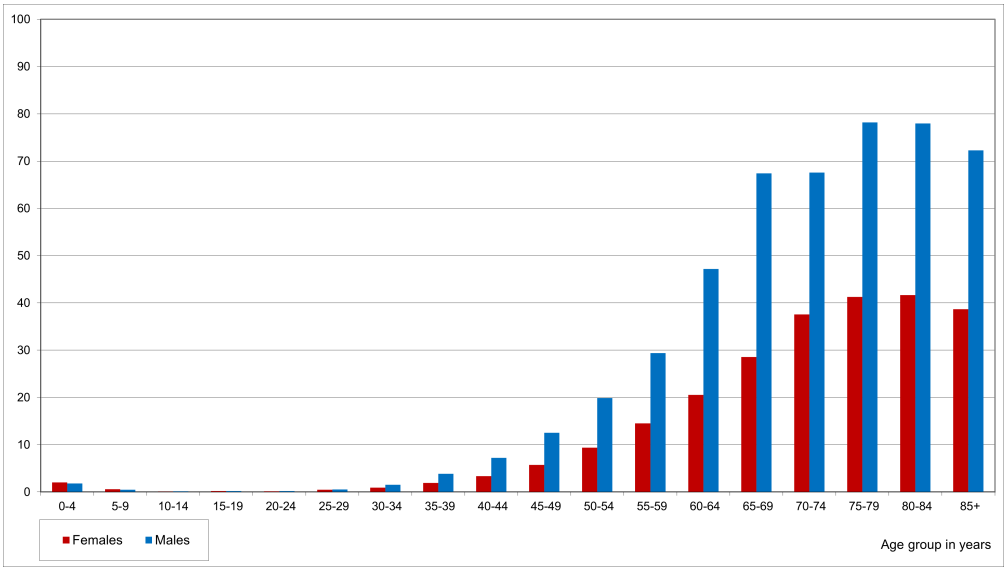
Despite the falling risk of illness and death in men, the number of cases is rising slightly. On average, the number of new cases is increasing by 0.8% per year and the number of deaths by 0.9% per year. This discrepancy is due to the change in the population structure with an increase in people of an older age at risk of developing the disease. Among women, the number of new cases and deaths remained constant, see Figure 2.

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



The mean (median) age at diagnosis is 68 years for men and 72 years for women, which is 1 year (men) and 2 years (women) above the mean age at diagnosis for cancer overall. The median age at death is 75 years (men) and 79 years (women). Most cases occur in both sexes in the age group 70 to 79 years. The higher incidence of men can be seen in practically all age groups. Only among the over 85s is the number of cases higher among women due to demographic factors. The incidence rate for men in this age group is also around twice as high as that for women. 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 kidney cancer by age in Germany [1]



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

2.3 Pathogenesis

Renal cell carcinoma is a heterogeneous disease. Histologically, clear cell, papillary and chromophobe carcinoma dominate [5]. The pathophysiology of renal cell carcinoma is characterized by the dysregulation of different signal transduction pathways.

Clear cell carcinomas account for around 75-80% of tumors. They show great inter- and intratumoral heterogeneity. Functional inactivation of the von Hippel-Lindau (VHL) gene is found in about 80%. This leads to the activation of hypoxia-inducible factor (HIF)-1α and 2α, and increases the expression of neoangiogenesis and cell proliferation genes. However, inactivation of the *VHL gene* is not sufficient for the development of renal cell carcinoma. Mutations are also found with lower frequency in the *PBRM1* (40%), *SETD2* (15%) and *BAP1 genes* (15%) [6]. In a subgroup of clear cell renal cell carcinomas, components of the mTOR (mechanistic Target Of Rapamycin) signal transduction pathway are altered at different levels. Furthermore, there are a large number of epigenetic changes that have shown prognostic and predictive value in studies [7].

Papillary renal cell carcinomas (pRCC) are associated with alterations of the *MET gene.* The rare hereditary form is based on a germline mutation of the *MET oncogene* on chromosome 7 [8].

In chromophobe renal cell carcinoma, aneuplodia with loss of specific chromosomes occur in particular [9]. Mutations are frequently found in *TP53*, *PTEN*, *FAAH2*, *PDHB*, *PDXDC1* and *NZF765*.

In the microenvironment, neoangiogenesis and immune response offer starting points for targeted forms of therapy.

2.4 Risk factors

The risk of developing renal cell carcinoma is increased by the following factors:

- Hereditary [10, 11, 12]:

    - Hereditary renal cell carcinomas account for around 5% of patients. More than 12 genetically defined clinical pictures have now been identified. Germline mutations can be detected in 6-9% of newly diagnosed renal cell carcinomas [13]. The best known syndromes are
        - von Hippel - Lindau syndrome [OMIM, 193300, autosomal dominant]: predisposition to clear cell renal cell carcinoma
        - Birt-Hogg-Dubé syndrome [OMIM 135150, autosomal dominant]: predisposition to chromophobe renal cell carcinoma
- Acquired [14]
    - Obesity
    - Chronic renal insufficiency
    - Smoking
    - Arterial hypertension
    - Occupational exposure: halogenated hydrocarbons, long-term exposure to X-rays

3 Prevention and early detection

3.1 Prevention

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

- Do not smoke
- Avoid being overweight

3.2 Early detection

There is no early detection program. Genetic counseling and an individual monitoring strategy are recommended for members of families with Hippel-Lindau syndrome and young patients with renal cell carcinoma.

4 Clinical characteristics

4.1 Symptoms

Renal cell carcinoma is asymptomatic in most cases. Local symptoms may include painless macrohematuria, flank pain, a palpable mass or a new varicocele. General signs of the disease include weight loss, fatigue, anemia and paraneoplastic syndromes such as polycythemia, fever of unknown origin, neuropathy or hypercalcemia. Many renal cell carcinomas remain asymptomatic for a long time.

4.2 Incidental findings

In recent years, up to 50% of renal cell carcinomas have been discovered incidentally during abdominal diagnostics 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 the predilection sites: Bone pain in skeletal involvement, cough and dyspnea in pulmonary, neurological deficits in cerebral/spinal manifestation.

5 Diagnosis

5.2 Diagnostics

Thorough anamnesis and complete physical examination are the basis of rational diagnostics. The next step is to confirm the suspected clinical and/or imaging diagnosis, see Table 1.

Table 1: Diagnostics for new symptoms

Procedure	Recommendation
Sonography kidneys and abdomen	Method of first choice for clinical symptoms
CT[1] abdomen with contrast medium	Method of first choice if kidney function is adequate
MRI[2] abdomen with contrast medium	Method of first choice for renal insufficiency, allergy to iodine-containing contrast medium, vena cava infiltration, and regional availability
Laboratory - Blood	Blood count, electrolytes (Na, K, Ca), lactate dehydrogenase, kidney function, liver values incl. albumin, coagulation
Laboratory - Urine	Status
Laboratory - Blood and urine	eGFR

Legend:
[1] CT - multiphase computed tomography; [2] MRI - magnetic resonance imaging; eGFR - estimated glomerular filtration rate

If the suspected diagnosis of renal cell carcinoma has been confirmed by imaging diagnostics, staging is indicated, see Table 2. Distant metastases can occur in almost all regions of the body. The most common sites are the lungs, skeleton, liver and brain.

Table 2: Staging procedures

Procedure	Recommendation
CT[1] Thorax and abdomen including the true pelvis	Multiphase technology
Skeletal scintigraphy	in case of clinical suspicion of osseous metastases outside the areas already examined in the sectional image diagnosis alternatively: bone CT or MRI
Cerebral CT or MRI[2]	In case of clinical suspicion
Laboratory - Urine	Status
PET-CT/-MRI	No significance in routine diagnostics or follow-up care
PSMA-PET-CT	Conditional indication for determining the degree of metastases (relevance not yet confirmed)

Legend:
[1] CT - multiphase computed tomography; [2] MRI - magnetic resonance imaging; PSMA - prostate-specific membrane antigen

A biopsy is indicated if it has an impact on the further therapeutic procedure, e.g., before local ablative procedures or before systemic therapy for primary metastatic disease. A biopsy to assess malignancy in small renal tumors <2cm, so-called *small renal masses*, may also be indicated as the basis of a potential active surveillance strategy, especially in elderly and comorbid patients [15].

Furthermore, histological confirmation is not required prior to surgical intervention.

5.3 Classification

5.3.1 Histology

The histopathological classification is based on the current WHO classification [5], see Table 3.

Table 3: Histological classification of renal cell carcinomas (according to WHO 2022)

Entity	Frequency (%)
Clear cell renal cell carcinoma	70-80
Papillary renal cell carcinoma, type I and II Chromophobe renal cell carcinoma	~ 15 ~ 6
Oncocytoma Ductus Bellini (collecting duct) Carcinoma Clear cell papillary renal cell carcinoma Mucinous tubular and spindle cell carcinoma Tubulocystic renal cell carcinoma Renal cell carcinoma with acquired cystic disease Eosinophilic and cystic renal cell carcinoma Renal cell carcinoma, unclassifiable, NOS TFE3-rearranged renal cell carcinoma TFEB-altered renal cell carcinoma ELOC-mutated renal cell carcinoma Fumarate hydratase-deficient renal cell carcinoma Hereditary leiomyomatosis and associated renal cell carcinoma Succinate dehydrogenase-deficient renal cell carcinoma ALK-rearranged renal cell carcinoma Medullary carcinoma, NOS SMARCB1-deficient medullary-like renal cell carcinoma SMARCB1-deficient undifferentiated renal cell carcinoma, NOS SMARCB1-deficient dedifferentiated renal cell carcinoma of other subtypes	each ≤1

Sarcomatoid dedifferentiation can occur in all histological subgroups and should be documented. Other pathohistological classifications are prognostically relevant, but have so far had no impact on the surgical strategy or the selection of systemic tumor therapy.

5.3.2 Stages

Classification is based on the TNM and UICC criteria [16, 17], 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 for 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 [18, 19], see Table 5.

Table 5: MSKCC (Motzer) score

- Karnofsky Performance Status (KPS) <80%
- Time from initial diagnosis to start of systemic therapy in recurrence <1 year
- Hemoglobin below the gender-specific normal range
- Calcium (corrected value) >2.5 mmol/l (>10 mg/dl)
- LDH >1.5 of the upper normal range

In more recent studies, the IMDC score (International Metastatic Renal-Cell Carcinoma Database Consortium score) is primarily used. It was developed in the tyrosine kinase inhibitor era and is based on the identification of 6 independent prognostic factors, see Table 6 [20].

Table 6: IMDC prognostic score

- Karnofsky Performance Status (KPS)
- Time from initial diagnosis to start of drug therapy in recurrence <1 year
- Hemoglobin below the gender-specific normal range
- Calcium (corrected value) >2.5 mmol/l (>10 mg/dl)
- Absolute neutrophil count above normal range
- Absolute platelet count above normal range

Each risk factor is given a point, the IMDC score summarizes this [20].

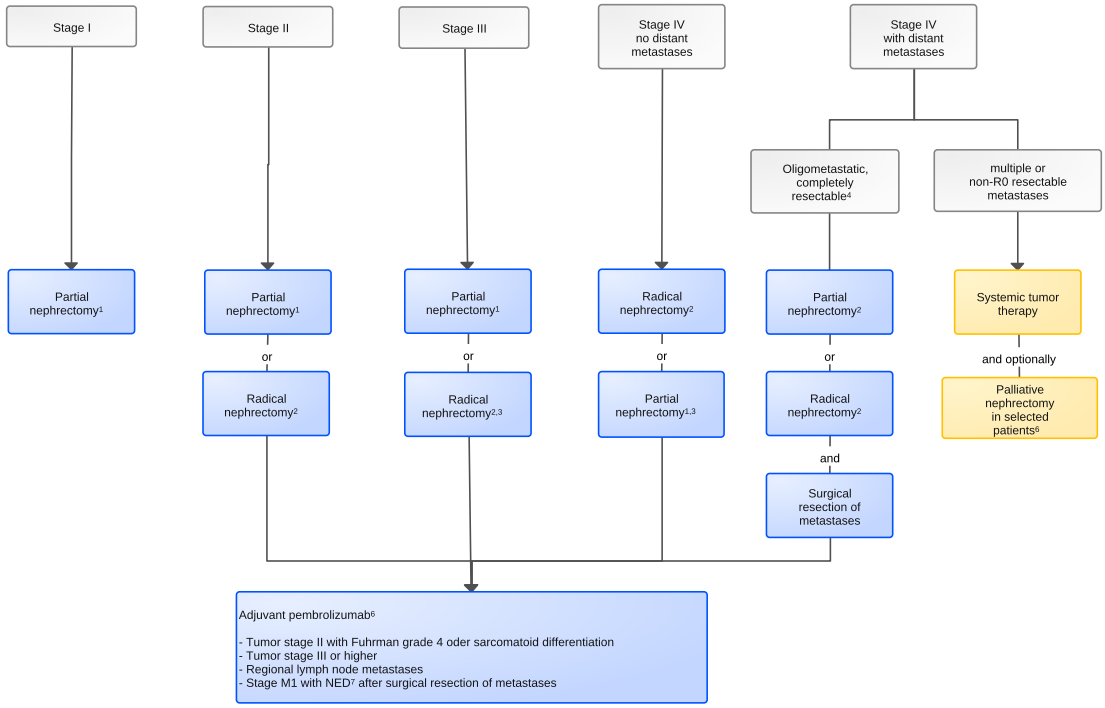
The IMDC score is predictive for the selection of systemic therapy.

6 Therapy

6.1 Treatment structure

The most effective causal treatment modalities are surgery and drug therapy. Surgery is the only curative option. The overall treatment concept should be determined before the first therapeutic measure is taken. A treatment algorithm is shown in Figure 4.

Figure 4: Algorithm for primary therapy of renal cell carcinoma



Legend:
curative intention; non-curative intention;
[1] if surgically possible; [2] minimally invasive, if possible; [3] in individual cases; [4] Indication depends on general condition, risk group, histology and other factors; [5] no benefit in intermediate and high risk compared to sunitinib alone; [6] significant prolongation of disease-free survival (DFS) and overall survival (OS); [7] NED – no evidence of disease

6.1.1 Localized stages

Surgical resection is the treatment of choice for localized renal cell carcinoma.

6.1.1.1 Surgery

6.1.1.1.1 Kidney

Alternatively, radical and partial nephrectomy are available. The former gold standard was open radical nephrectomy with resection of Gerota's fascia, the ipsilateral adrenal gland and the regional lymph nodes. The aim of partial nephrectomy is to preserve functional kidney tissue. Postoperative renal insufficiency is a negative prognostic factor [22].

In a randomized EORTC study including patients with clinical and imaging suspicion of renal cell carcinoma in stage cT1/2 N0, the survival rate after 10 years was 81.1% for radically vs. 75.7% for partially nephrectomized patients. While a significant difference (p=0.03) was calculated in the intention-to-treat (ITT) analysis, it was not significant for the renal cell carcinoma patients after matching the inclusion criteria (p=0.07). The following recommendations can be derived from these data, from phase II studies with long-term follow-up and from a systematic review [23]:

Indications for a partial nephrectomy [23]

- Anatomical or functional single kidney

- Increased risk of renal insufficiency due to other causes (e.g., hypertension, diabetes mellitus)
- Hereditary renal cell carcinoma syndromes
- T1 stage

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

Both radical and partial nephrectomy can be performed open or minimally invasive (retroperitoneoscopic, laparoscopic, robot-assisted). Laparoscopic nephrectomy is less invasive and can reduce the risk of perioperative morbidity [24]. However, there is a lack of large randomized studies on the equivalence of open and laparoscopic partial nephrectomy with respect to the oncological outcome. Endoscopic procedures should be performed at selected centers with appropriate expertise. Whenever oncologically justifiable, kidney preservation by means of partial nephrectomy should be given preference over the radical procedure.

6.1.1.1.2 Adrenal gland

Adrenalectomy is only necessary if there is imaging or intraoperative suspicion of tumor infiltration or metastases [24].

6.1.1.1.3 Lymph nodes

Lymph node resection has no impact on overall prognosis [25, 26]. It is only recommended in patients with imaging or intraoperative suspicion of infiltration to confirm the TNM stage and in the case of local symptoms.

6.1.1.2 Other local treatment modalities

6.1.1.2.1 Embolization

Embolization of the tumor is used to reduce bleeding complications in the following situations:

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

6.1.1.2.2 Minimally invasive, ablative procedures

Various physical procedures are used for percutaneous, targeted therapy under imaging control [26, 27]. Tumor control rates of up to 85% after one year can be achieved with cryotherapy and radiofrequency ablation. Laser therapy and high-intensity focused ultrasound (HIFU) are less effective. Controlled comparative studies with long-term observation are lacking. These physical procedures are experimental. A prerequisite for their use is prior biopsy confirming the diagnosis. Relative contraindications for local ablative procedures are life expectancy of less than 1 year, multiple metastases, low prospect of success, tumors close to the hilum, tumors >5 cm,

tumors in the immediate vicinity of the renal pelvis or the proximal ureter. Absolute contraindications are coagulation disorders or severe comorbidity.

6.1.1.3 Adjuvant therapy

Most studies in the adjuvant setting for various immunotherapy approaches, e.g., interferon or tumor vaccines, were negative. Several randomized trials with tyrosine kinase inhibitors (Assure, S-TRAC, PROTECT) showed no significant improvement in disease-free survival (DFS), with the exception of sunitinib in the S-TRAC trial [28, 29, 30]. A positive impact on overall survival has not yet been shown.

In the adjuvant study on pembrolizumab for 1 year in patients at 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 no evidence of disease after metastasectomy) after tumor nephrectomy, there was a significant prolongation of disease-free survival compared to placebo (HR 0.68 (0.53-0.87), p=0.002) [31]. After 24 months, the disease-free survival rate was 77.3% vs. 68.1%. The study was only conducted in clear cell renal cell carcinoma. There are now also signs of an advantage for adjuvant therapy with pembrolizumab in terms of overall survival [32].

Adjuvant therapy should therefore be carried out with pembrolizumab in patients with a 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 no evidence of disease after metastasectomy) in renal cell carcinoma [33].

Further phase III trials in adjuvant therapy using checkpoint inhibitors such as atezolizumab [33], or nivolumab plus ipilimumab [34] showed no advantage in DFS and OS compared to placebo. Further studies have not yet been completed.

6.1.2 Locally advanced stages

An open area is the treatment of patients with locally advanced carcinomas where complete resectability appears questionable based on imaging diagnostics. The effectiveness of the newer systemic tumor therapies has led to concepts of primary (neoadjuvant) systemic therapy with subsequent surgery. These 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 substances should be given preference.

6.1.3 Metastatic renal cell carcinoma

The mainstay of treatment is systemic tumor therapy, see Figure 5. Supplementary cytoreductive nephrectomy can be discussed as part of a multimodal treatment concept in the multidisciplinary tumor board, depending on the risk of progression, see Chapter 6. 2. 1. 1. on cytoreductive nephrectomy. Further local therapy procedures such as radiotherapy of osseous metastases or stereotactic radiation can be used as part of symptom-oriented measures, see Chapter 6. 2. 3. on palliative therapy.

6.1.3.1 Systemic tumor treatment

Treatment of metastatic renal cell carcinoma is almost always palliative. Before initiating drug therapy, the possibility of a wait-and-see approach should be examined in patients with low or intermediate risk without clinical symptoms, especially if there is no progression in the follow-

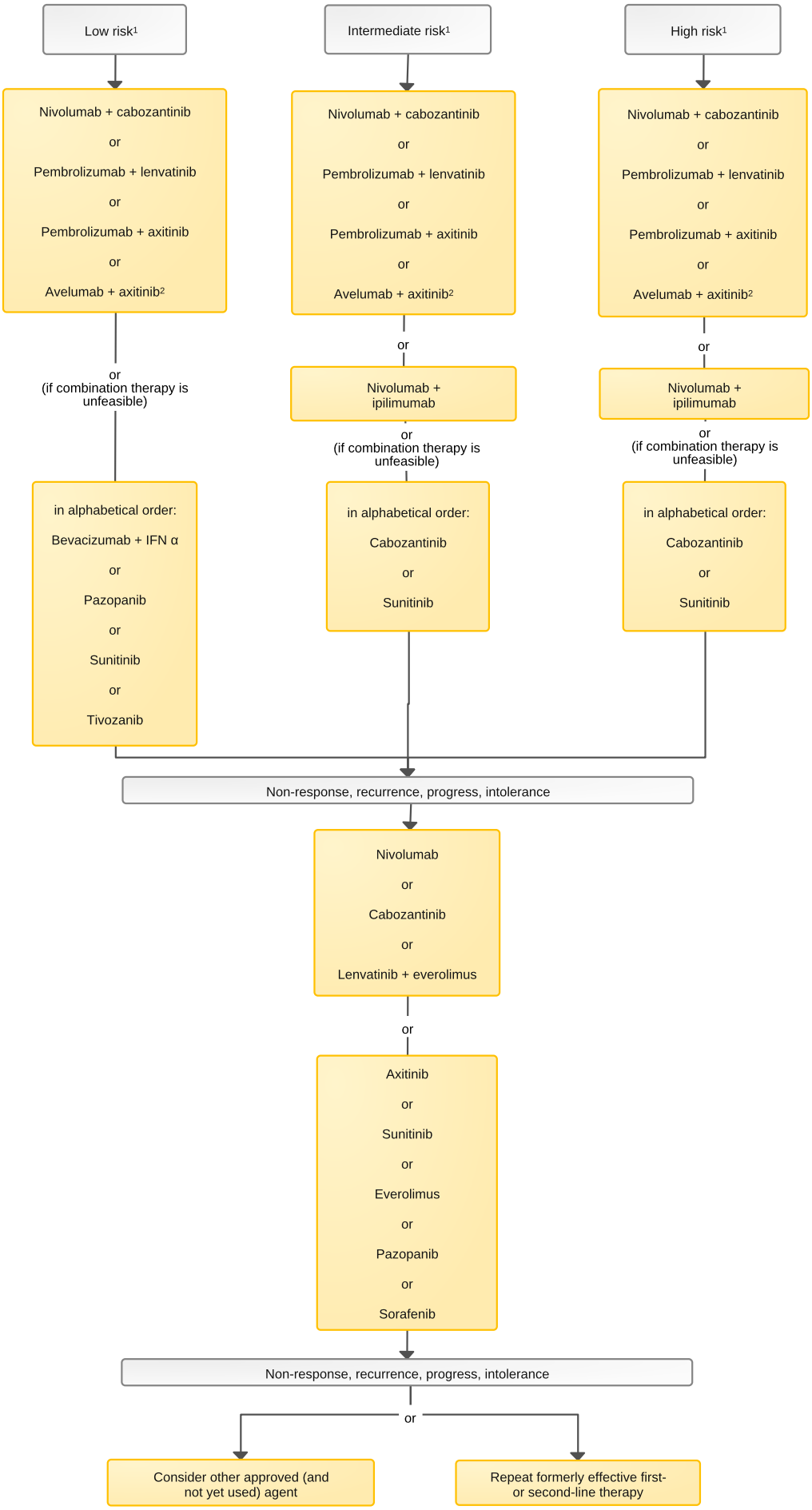
up checks using cross-sectional imaging. In the case of a wait-and-see approach, regular clinical and imaging checks, at least every three months, are recommended. Significant progress with significant prolongation of progression-free survival compared to the previous standard interferon-alpha has been achieved with angiogenesis-inhibiting multi-tyrosine kinase inhibitors (TKIs), mTOR inhibitors [35], the combination of interferon-alpha and the VEGF antibody bevacizumab, and currently with newer TKIs and checkpoint inhibitors. Information on the use of the drugs is summarized in the appendix Approval status.

6.1.3.1.1 First-line therapy

The concepts for first-line systemic tumor therapy of locally advanced and metastatic renal cell carcinoma have changed fundamentally in recent years. Various combination and monotherapies are now available. It should be noted that most first-line studies only included clear cell renal cell carcinoma (ccRCC) or renal cell carcinoma with a clear cell component. For non-clear cell renal cell carcinoma (nccRCC), on the other hand, there are only a few studies and the number of cases is limited, which means that the evidence here is significantly lower. However, there are some studies that have predominantly included these patients in a phase II setting. It was found that the modalities used in the treatment of clear cell carcinoma are also effective in the other subtypes, albeit with slightly lower clinical response than in the clear cell variant [36].

The effectiveness of systemic tumor therapy, particularly in terms of overall survival, differs in the various risk groups according to the IMDC score. A treatment algorithm for systemic tumor treatment is shown in Figure 5.

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



Legend:
curative intention; non-curative intention
[1] Risk scores see chapter 5.4.1
[2] Axitinib + avelumab: OS benefit over sunitinib is only shown in the subgroup of high-risk patients

The majority of currently available results of randomized studies compare the respective new therapy with sunitinib monotherapy. Based on these data and the approval status, the combinations of nivolumab with cabozantinib [36], pembrolizumab with axitinib [37], pembrolizumab with lenvatinib [38] or, with restrictions, avelumab with axtitinib [39], are considered the new standard in first-line therapy, regardless of risk score or histological entity, although there is insufficient data for non-clear cell renal cell carcinomas and no universal OS benefit for the combination of axitinib with avelumab. For patients with intermediate and high risk, the combination of ipilimumab and nivolumab [40] represents an equivalent alternative. A clear preference cannot currently be recommended due to the lack of comparative studies. Data are summarized in Table 7.

Table 7: Comparison of studies on first-line systemic therapy for renal cell carcinoma

Study	Checkmate 214 [40]	Checkmate 9ER [36]	Keynote 426 [37]	CLEAR [38]	JAVELIN Renal 101 [39]
Immune combination therapy	Ipilimumab/ nivolumab	Nivolumab/ cabozantinib	Pembrolizumab/ axitinib	Pembrolizumab/ lenvatinib	Avelumab/ axitinib
Primary study endpoints	ORR, PFS, OS in patients with intermediate and poor risk	PFS	OS and PFS in the ITT cohort	PFS	PFS and OS of patients with PD-L1 pos. tumor (>1% of immune cells)
ORR (%)	39.0*	55.7	59.3	71.0	51.4
CR (%)	10.2*	8,0	5.8	16.1	3.4
Primary progress (%)	20*	5.6		5.4	11.5
Median PFS (months) immune combination therapy vs. sunitinib	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
OS (months) immune combination therapy vs. sunitinib	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 with intermediate and poor risk; ORR - overall response rate; CR - complete remission; OS - overall survival; PFS - progression-free survival; ITT - intention-to-treat; NR - not yet reached*

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

- Low risk of progression
  - The combinations nivolumab/cabozantinib, axitinib/pembrolizumab and pembrolizumab/lenvatinib lead to a significant increase in the remission rate and prolongation of progression-free survival in the low-risk group compared to sunitinib; a significant prolongation of overall survival when compared to sunitinib has not yet been shown, as there are still too few events for this to be the case
  - Axitinib/avelumab leads to an increase in remission rate and prolongation of progression-free survival in low- and intermediate-risk patients when compared to sunitinib (a significant prolongation of overall survival compared to sunitinib has not yet been demonstrated)
  - Nivolumab + ipilimumab is inferior to sunitinib in terms of remission rate and progression-free survival (HR 2.18; median - 9.8 months), the difference in overall sur-

vival is not significant.
Alternatives for contraindications to these combinations are

- Tyrosine kinase inhibitors: sunitinib, pazopanib and tivozanib have been approved. The comparator arms of the respective approval studies were different.
  - Compared to interferon-alpha, sunitinib increases the remission rate and prolongs progression-free survival (median 6 months)
  - In a non-inferiority study, pazopanib showed no significant difference in progression-free and overall survival when compared to sunitinib, but a slightly different side effect profile
  - Compared to sorafenib, tivozanib leads to a higher remission rate and longer progression-free survival (HR 0.795; median 2.4 months), but not to prolonged overall survival

- Bevacizumab + interferon-alpha: as compared to interferon-alpha, this combination increases the remission rate and prolongs progression-free survival (median 3.3 months), but also leads to a higher rate of serious adverse events of CTCAE grade 3 / 4.
- Intermediate and high risk of progression
  - The combinations nivolumab/cabozantinib, axitinib/pembrolizumab and pembrolizumab/lenvatinib led to a significant increase in the remission rate, prolongation of progression-free survival and overall survival when compared to sunitinib in the intermediate- and high-risk group
  - Nivolumab + ipilimumab leads to an increase in the remission rate and a prolongation of overall survival (HR 0.697; median not yet reached) for intermediate-risk patients when compared to sunitinib; the difference in progression-free survival is not significant
  - Axitinib + avelumab leads to an increase in the remission rate and prolongation of progression-free survival (HR 0.87; median survival time not yet reached) in low- and intermediate-risk patients when compared to sunitinib
    Alternatives for patients with contraindications to these combinations are tyrosine kinase inhibitors:
    - Compared to interferon-alpha, sunitinib led to an increase in the remission rate and a prolongation of progression-free survival (median 6 months)
    - In a small study, cabozantinib increased the remission rate and prolonged progression-free survival (HR 0.48; median 3.3 months) when compared to sunitinib, but not overall survival.

Details of the respective pivotal studies including assessment of the 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 Second-line systemic tumor therapy

Due to the introduction of combination therapies for first-line treatment and the lack of controlled studies in the second line after combination therapy, an evidence-based recommendation cannot be given. The second line should therefore be chosen on an individual basis (e.g., previous therapy, response, course, comorbidity).

- After first-line therapy with immune checkpoint inhibitors and their combination with a TKI or another immune checkpoint inhibitor, there is currently no evidence-based data for the further therapy sequence. Substances not used in primary therapy can be reiterated in the second and subsequent lines.

- In patients who were primarily treated with a TKI, nivolumab leads to an increase in the remission rate, a prolongation of progression-free survival (HR 0.40; median 4.6 vs. 4.2 months), a prolongation of overall survival (HR 0.51; median 25.5 vs. 19.6 months) and a reduction in the rate of severe adverse events in CTCAE grade 3 / 4 when compared to everolimus [41].
- Cabozantinib also increases the remission rate, prolongs progression-free survival (HR 0.58; median 7.4 vs. 3.8 months) and prolongs overall survival (HR 0.7; median 21.4 vs. 17.1 months) when compared to everolimus in patients who were primarily treated with a TKI. The rate of severe side effects in CTCAE grade 3 / 4 is higher [42, 43].
- Lenvatinib + everolimus increased the remission rate, 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) when compared to everolimus in a small study in patients treated primarily with a TKI. The rate of severe side effects in CTCAE grade 3 / 4 was higher. Data from a follow-up study with a lower dose 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 [44, 45].

Agents not used in primary therapy can be tried in second and subsequent lines. It can therefore be assumed that drugs that are effective in first-line treatment or after VEGF-directed therapy will also retain their effectiveness after failure of new combinations. Prospective studies or at least registry data are urgently needed here. A randomized study comparing tivozanib versus sorafenib in patients after prior treatment with VEGFR and immune checkpoint inhibitors showed a slight increase in progression-free survival (HR 0.73; median 1.7 months), but not in overall survival. Currently, the treatment recommendation is primarily based on the type of previous treatment, the patient's general condition and side effects of previous therapies, see Figure 5.

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

Belzutifan is a new agent that has been approved by the Food and Drug Administration (FDA) in the USA for patients with familial renal cell carcinoma due to a von Hippel Lindau (VHL) gene mutation and for patients with advanced renal cell carcinoma after previous therapy with a PD-1 or PDL-1 inhibitor and a VEGF-TKI [46, 47].

Details of the respective pivotal studies including assessment of the clinical benefit according to the ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS) and the early benefit assessment of the German Federal Joint Committee (G-BA) can be found in the fact sheets.

6.2 Treatment modalities

6.2.1 Surgical approaches

6.2.1.1 Cytoreductive nephrectomy

In patients with advanced renal cell carcinoma, nephrectomy can lead to regression of metastases, but this phenomenon was observed in less than 2% of patients. When used with systemic interferon-alpha therapy, nephrectomy prolonged the median survival time by 3 to 10 months.

In a non-inferiority trial in 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 [48]. The value of sequential tumor nephrectomy was also investigated in the SURTIME trial. The study did not reach the primary endpoint; a total of

99 patients were randomized [49]. By selecting patients with a response to TKI therapy, additional surgery could be avoided in patients with an unfavorable prognosis (PD within 4 months).

The results of modern treatment strategies with TKIs or immune checkpoint inhibitors have mainly been achieved in nephrectomized patients. No data are available to date 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, particularly in lungs, liver or brain. Therefore, this measure is recommended after careful staging for patients in whom R0 resection is possible [28, 33, 50, 51, 52]. The decision on surgical treatment must be made on an individual basis and must take into account factors such as comorbidities, prognosis and patient preferences. A follow-up to detect any new metastases should be performed before metastatic surgery in order to assess the dynamics of the disease and the appropriateness of metastatic resection. Surgical resection of metastases should be performed with the aim of complete resection of the tumor or for palliation alone. Debulking surgery should only be used for symptom control or in the event of imminent/manifest complications. Even after systemic therapy, a long-term treatment-free interval can still be achieved through a subsequent complete metastasectomy.

Adjuvant therapy with pembrolizumab is indicated in cases of initially complete resection of the primary tumor and metastases ("no evidence of disease", NED) (see chapter 6.1.1.3 above).

6.2.1.3 Radiotherapy of metastases

Renal cell carcinoma is not very sensitive to radiation. Randomized studies are not available. Nevertheless, there may be indications for Cyberknife or stereotactic radiotherapy for solitary or oligometastases. This mainly concerns brain metastases or, in individual cases, other organ metastases [28, 53, 54, 55].

Current data show that inoperable localized renal cell carcinoma can also be successfully treated with stereotactic radiotherapy, resulting in long-term local control and low toxicity. However, there is a lack of randomized studies to further elucidate the value of this treatment [56].

6.2.2 Systemic tumor therapy (in alphabetical order)

6.2.2.1 Avelumab

Avelumab is a human monoclonal IgG1 antibody. It binds to the programmed cell death ligand 1 (PD-L1) and prevents binding to its receptor PD-1. A PD-1/PD-L1 receptor/ligand interaction leads to the inhibition of CD8+ T cells and thus to the inhibition of an immune response. Avelumab is approved in combination with axitinib for the first-line treatment of metastatic renal cell carcinoma. Compared to sunitinib, the combination leads to a higher response rate (51.4% vs. 25.7%) and a prolongation of progression-free survival (13.8 vs. 8.4 months; HR 0.69). Side effects of avelumab monotherapy are relatively mild. In patients on monotherapy for Merkel cell carcinoma, severe side effects of CTCAE grade 3 / 4 severity exclusively affected clinical chemistry parameters. The most frequent side effects of all grades were fatigue (24%), infusion reaction (17%), diarrhea (9%), asthenia (8%), exanthema (7%) and loss of appetite (6%). Possibly immune-mediated reactions occurred of grade 1 / 2: hypothyroidism (3%), hyperthyroidism (2%), pneumonitis (1%), type 1 diabetes mellitus (1%). The side effects of the com-

bination therapy correspond 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 the control were achieved. Survival time was not prolonged. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients, were hypertension (16%), diarrhea (11%) and fatigue (11%). Patients treated long-term with multikinase inhibitors may experience endocrine (hypothyroidism), hematologic or cardiac side effects.

6.2.2.3 Belzutifan

Belzutifan is an inhibitor of hypoxia-inducible factor 2-alpha (HIF-2α). It is an oral so-called "small molecule" drug. In patients with renal cell carcinoma in VHL syndrome, the overall response rate was 49% (CI 36% to 62%). In patients pre-treated with a PD-1 or PDL-1 inhibitor and a VEGF-TKI, the overall response as compared to everolimus was significantly improved at 21.9% vs. 3.5%, as was the PFS rate at 12 and 18 months at 33.7% vs. 17.6% and 22.5% vs. 9.0% respectively. The OS was not significantly different.

6.2.2.4 Bevacizumab

Bevacizumab is a monoclonal, anti-angiogenic antibody. In cytokine-pretreated patients, monotherapy can delay progression. In combination with interferon-alpha, remission rates of 25-30% and a significant extension of progression-free survival were achieved compared to monotherapy with interferon-alpha. The analysis by prognostic subgroups showed a benefit for patients with low and intermediate risk scores. Severe adverse events (grade 3 / 4) occurring in more than 5% of patients in the pivotal trials, were fatigue (12-35%), asthenia (10-17%), proteinuria (7-13%) and hypertension (3-13%). Rare critical complications include thromboembolic events and gastrointestinal tract perforations.

6.2.2.5 Cabozantinib

Cabozantinib is a multikinase inhibitor. In contrast to anti-VEGFR1, -VEGFR2 and -VEGFR3 kinases, it also inhibits AXL and MET. Cabozantinib is approved for advanced renal cell carcinoma as monotherapy in the first line (not applicable in Switzerland) for patients with intermediate and high risk, and in the second line at a dose of 60 mg/day. In the pivotal study, cabozantinib after prior VEGFR-directed therapy led to a prolongation of survival (HR 0.67; median 4.9 months), progression-free survival (HR 0.52; median 3.5 months) and an increase in the remission rate when compared to everolimus. The rate of severe therapy-associated side effects is significantly higher with cabozantinib than with everolimus; side effects of CTCAE grade 3 / 4 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 trial, 60% of patients on cabozantinib required a dose reduction.

6.2.2.6 Everolimus

Everolimus is an oral mTOR inhibitor. The pivotal study was conducted in patients in second or later line therapy after pre-treatment with sorafenib and / or sunitinib and showed a significant prolongation of progression-free survival as compared to a placebo control group. Two thirds of the patients were also pretreated with cytokines. Serious adverse events (grade 3 / 4), which occurred in more than 5% of patients in the pivotal trial, were infections (10%) and dyspnea (7%). Pneumonitis is a rare but troublesome side effect of mTOR inhibitors.

6.2.2.7 Interferon-alpha (IFN-alpha)

IFN-alpha is a member of the interferon family. The exact mechanism of its antitumor efficacy has not been clearly elucidated. IFN-alpha stimulates NK cells, increases the immunogenicity of tumor cells, induces apoptosis, has an antiangiogenic effect and also has an antiproliferative effect via the induction of cyclin-dependent kinase inhibitors. In monotherapy, remission rates of 12-13% (0-39) are achieved, with complete remissions in around 2-3% of patients. The median survival time is 13 months (6-28 months). Some of the studies on the superiority of newer substances (bevacizumab, sorafenib, sunitinib, temsirolimus) were conducted in comparison with IFN-alpha monotherapy. Severe side effects (grade 3 / 4), which occurred in more than 5% of patients in the pivotal study, were asthenia (4-26%), anemia (5-22%), fatigue (13%).

6.2.2.8 Ipilimumab

Ipilimumab is a humanized monoclonal antibody directed against the CTLA-4 protein. Its use can reverse negative immune regulation by CTLA-4 and achieve an anti-tumor effect through T-cell stimulation. In renal cell carcinoma, ipilimumab was tested in combination with nivolumab in a phase III trial based on studies in other tumors, particularly melanoma. The combination showed a significantly increased response rate (42% vs. 27%), prolonged progression-free survival (HR 0.83) and overall survival (HR 0.63) when compared to sunitinib in intermediate- and high-risk patients. In patients with a low risk of progression, the combination of nivolumab/ipilimumab 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%), lipase elevation (10%) and diarrhea (4%). Due to side effects, treatment was discontinued in 22% of patients in the nivolumab/ipilimumab arm.

6.2.2.9 Lenvatinib

Lenvatinib is a multikinase inhibitor and inhibits the VEGFR1, VEGFR2 and VEGFR3 kinases. Lenvatinib is approved for first-line treatment of advanced renal cell carcinoma 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 leads to a significant prolongation of 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; $p=0.005$)). The rate of severe grade 3 / 4 adverse events was slightly higher with the combination (82.4% vs. 71.8%), with hypertension (27.6%), diarrhea (9.7%) and weight loss (8.0%) being the most common.

In second-line treatment, lenvatinib is approved as a combination therapy with everolimus at a dose of 18 mg/day plus everolimus at a dose of 5 mg/day. The early benefit assessment was based on a three-arm phase II study with a total of 153 patients. In second-line therapy, lenvatinib/everolimus leads to an improvement of survival (HR 0.51; median 10.1 months), progression-free survival (HR 0.40; median 9.1 months) and response rate when compared to everolimus. The rate of severe treatment-related side effects 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%).

6.2.2.10 Nivolumab

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

Nivolumab is approved for monotherapy as second-line treatment of metastatic renal cell carcinoma. Compared to everolimus, nivolumab leads to an increase in survival time (HR 0.73; median 5.4 months), an increase in the remission rate and an increase in the time until clinical symptoms worsen in second-line therapy. The progression-free survival time is not significantly prolonged. The rate of severe treatment-related side effects is significantly lower with nivolumab than with everolimus, and the rate of treatment discontinuation is also lower. CTCAE grade 3 / 4 adverse events 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 side effects with nivolumab.

6.2.2.11 Pazopanib

Pazopanib is another oral tyrosine kinase inhibitor with a slightly different kinase profile from sorafenib and sunitinib. Patients were included in the pivotal study both in first-line therapy and after prior treatment with cytokines. The response rate was 30% and the progression-free survival time was significantly higher than the placebo control. Survival time was not prolonged. There were no severe side effects (grade 3 / 4) occurring in more than 5% of patients in the pivotal study. Regular monitoring of ALT and bilirubin should be considered for early detection of hepatic toxicity. Endocrine (hypothyroidism), hematologic or cardiac side effects may occur in patients treated long-term with multikinase inhibitors.

6.2.2.12 Pembrolizumab

Pembrolizumab is a humanized monoclonal IgG4 antibody. It binds to the programmed cell death receptor (PD-1) and prevents the binding of its ligands such as PD-L1. A PD-1/PD-L1 receptor/ligand interaction leads to the inhibition of CD8+ T cells and thus to the inhibition of an immune defense; Pembrolizumab counteracts this negative regulation. Pembrolizumab is approved in combination with axitinib for first-line treatment of metastatic renal cell carcinoma. Compared to sunitinib, the combination leads to a higher response rate (59.3% vs. 35.7%), a prolongation of progression-free survival (15.1 vs. 11.1 months; HR 0.69) and a prolongation of overall survival (HR 0.53; median not yet reached). The side effects correspond to those of other immune checkpoint inhibitors (see under nivolumab).

6.2.2.13 Sorafenib

Sorafenib is an oral inhibitor of several tyrosine kinases, including the VEGF receptors, PDGFRB, Flt-3 and c-KIT. In signaling, it also blocks serine-threonine kinases of the Raf family in the MAPK pathway. In the largest study to date with sorafenib, it was investigated as a second-line therapy in patients with low or intermediate risk. Progression-free survival was significantly prolonged. In first-line therapy, there was no significant difference in the remission rate and progression-free survival when compared to interferon-alpha. A severe side effect (grade 3 / 4), which occurred in more than 5% of patients in the pivotal study, was hand-foot syndrome (grade 3 / 4). Patients treated long-term with multikinase inhibitors may experience endocrine (hypothyroidism), hematologic or cardiac side effects.

6.2.2.14 Sunitinib

Sunitinib is an oral inhibitor that blocks several VEGF, PDGF receptors as well as c-KIT and Flt-3 at the tyrosine kinase level. In the approval study, sunitinib was used in patients in first-line therapy in comparison with IFN-alpha. The progression-free survival time was significantly longer and the remission rate was 47% in the final evaluation. 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%). Patients treated long-term with multikinase inhibitors may experience endocrine (hypothyroidism), hematologic or cardiac side effects.

6.2.2.15 Temsirolimus

Temsirolimus was the first approved mTOR kinase inhibitor for the treatment of renal cell carcinoma. The drug is administered intravenously. Its efficacy was investigated in a randomized phase III trial in patients with at least three of six risk factors (Table 5). Patients in the comparator arm were treated with IFN-alpha, patients in a third arm with temsirolimus + IFN-alpha. Treatment with temsirolimus led to remission rates of 8.6%, median progression-free survival and overall survival were significantly prolonged as compared to monotherapy with IFN-alpha. The combination showed no benefit over monotherapy with temsirolimus, although the dose of temsirolimus was reduced to 15 mg per week in the combination arm. Severe adverse events (grade 3 / 4) occurring in more than 5% of patients in pivotal trials were anemia (20%), asthenia (11%), hyperglycemia (11%) and dyspnea (9%). Pneumonitis is a rare but troublesome side effect of mTOR kinase inhibitors.

6.2.2.16 Tivozanib

Tivozanib is another oral tyrosine kinase inhibitor with selective inhibition of VEGF receptors. In the approval study, tivozanib was tested against sorafenib and led to a prolongation of progression-free survival in first-line therapy of 12.7 vs. 9.1 months, and of 11.9 vs. 9.1 months overall (hazard ratio 0.756 for first-line therapy, p=0.037). The remission rate was increased to 33.1 vs. 23.4%. Survival was not prolonged by tivozanib, but the data are of limited value due to a switching (crossover) rate of 61% from the sorafenib to the tivozanib arm. Grade 3 / 4 adverse events, which occurred in ≥5% of patients on tivozanib in the pivotal study, were hypertension (27%), fatigue (5%) and lipase elevation (9%). Dysphonia is another common side effect.

6.2.2.17 Cytostatic drugs

Conventional cytostatic drugs are only slightly effective in renal cell carcinoma. Among others, 5-fluorouracil in combination with immunotherapy or vinblastine were used. The remission rates achieved with chemotherapy were below 5%.

6.2.3 Sequence therapy, new options

The new drug treatment options for metastatic renal cell carcinoma have profoundly changed the picture of the disease and the treatment of patients. In a majority of patients, several substances with different efficacy profiles are used as sequential therapy during the course of the disease. The optimal sequence has not yet been established. The choice of medication should therefore be based on the treatment goal and the general clinical condition or concomitant diseases, taking into account the expected treatment-related side effects.

6.3 Special situations

6.3.1 Non-clear cell renal cell carcinoma

Clear cell renal cell carcinoma is histologically the dominant entity. The majority of studies with the newer drugs were conducted exclusively in this entity. Patients with papillary renal cell carcinoma type II have a more aggressive course and a 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 that patients with non-clear cell renal cell carcinoma be treated according to the algorithm for clear cell carcinomas. This also applies to the use of immune checkpoint inhibitors.

If possible, therapy should be considered in the context of clinical trials. In these patients, a short-term evaluation is indicated in order to be able to change the mechanism of action if there is no response.

6.3.2 Palliative therapy - symptom-oriented

Palliative therapy involves the individualized, symptom-oriented treatment of physical and psychological complaints at every stage of the course of the disease. It is carried out on a multidisciplinary basis, and psycho-oncological support in particular should be considered. The necessity and possibilities of palliative therapy should be discussed comprehensively with all patients already at an early stage. The following specific symptoms occur particularly frequently in patients with advanced renal cell carcinoma.

6.3.2.1 Bone metastases

In addition to sufficient and adapted pain therapy, local and systemic measures are available for the treatment of patients with bone metastases. In case of a single bone metastasis, surgical treatment should primarily be performed with curative intent. Radiotherapy is the treatment of choice for pain or fracture risk. It can be hypofractionated with ongoing systemic therapy. An additional option is surgical treatment for pathological fractures, unstable vertebral body fractures or to relieve spinal compression.

Systemic measures include causal therapy and the administration of bone-modifying substances (bisphosphonates, anti-RANKL antibodies). They reduce the risk of complications and delay the progression of bone metastasis. There are no prospective randomized studies exclusively in patients with renal cell carcinoma or in a sufficiently large number of patients. Information on the approval status of bone-modifying substances can be found in the appendix Approval for renal cell carcinoma. Bisphosphonates are also indicated for treatment of hypercalcemia.

6.3.2.2 Liver and lung metastases

The focus is on causal, systemic therapy. In individual cases, local therapy may be indicated. In addition to surgical resection, local ablative procedures are also available. Prerequisites are

- No disseminated metastases
- No local recurrence or clinically limiting second carcinoma

Decisions on the local treatment of liver or lung metastases are the task of multidisciplinary tumor conferences.

6.3.2.3 Brain metastases

The first measure in symptomatic metastasis is the administration of corticosteroids to reduce perifocal edema. Local surgical therapy is recommended for isolated, resectable brain metastases. An alternative is targeted local, conformal irradiation (stereotactic irradiation, Gamma-Knife, Cyber-Knife). Partial or whole brain irradiation can be discussed for disseminated brain metastases in patients with good general condition and no extracerebral progression, a life expectancy of more than 3 months and, if possible, with hippocampal sparing to avoid cognitive toxicities. Data on the efficacy of the newer drugs are limited to small patient populations.

7 Rehabilitation

All patients should be offered specialist rehabilitation in the form of follow-up treatment (AHB)/ follow-up rehabilitation (ARH, AR) after local treatment for renal cell carcinoma. If symptoms persist, patients should be informed about further rehabilitation measures. Patients with metastatic disease can also benefit from specialist rehabilitation. The aim of medical rehabilitation is to maintain or restore the patient's ability to work, to lead a self-determined everyday life and to participate.

Depending on the patient's comorbidity, rehabilitation should be multidisciplinary and based on multimodal therapy concepts. As part of the rehabilitation program, patients should be offered targeted physiotherapy, psycho-oncological support to help them cope with their illness, socio-medical advice and, in the case of functional limitations, occupational therapy. With regard to the rehabilitation clinic, the patient's preferences should be taken into account (§9 SGB IX, German Law). Nevertheless, a recommendation should be made for a clinic with an oncological focus in order to ensure optimal rehabilitation success.

8 Post-treatment follow-up

8.1 Progress monitoring

Follow-up care after primary tumor therapy in the non-distant metastatic stage should be risk-adapted [33]. A 3-monthly check-up (clinical examination, laboratory and sonography) is rec-

ommended in the first year, a six-monthly check in the second year and an annual follow-up check in years 3 through 5. Particularly after partial resection of the kidney, sonographic assessment is complex and difficult, therefore risk-adapted cross-sectional imaging (CT abdomen) is recommended for the assessment of these patients, see also the recommendations of the German S3 guideline [33].

During ongoing systemic therapy, sectional imaging should be performed every 6 to 12 weeks. Therapy with checkpoint inhibitors can initially lead to an increase in tumorous masses, so-called early pseudo-progression. For this reason, the first cross-sectional imaging is often not indicated in these patients until 12 weeks after the start of therapy.

8.2 Postoperative follow-up care for patients with localized renal cell carcinoma

There is no universal follow-up program. The risk of recurrence depends on the stage at initial diagnosis. The majority of recurrences occur within the first two years. As the life expectancy after recurrence depends on the extent of the metastasis, follow-up with cross-sectional imaging appears to make sense. However, there is no evidence that structured follow-up care in the form of regular staging examinations leads to an improvement in survival. The aim of examinations after curative therapy is to detect complications and late effects. In patients who have undergone nephrectomy, these primarily 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[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License [4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Bauernhofer, Thomas	Medizinische Universität Graz	**Yes** Adboards AstraZeneca, Merk, Janssen-Cilag, MSD	**No**	**No**	**Yes** Pflegefortbildung 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	**Yes** Bestimmung des HRD Status bei Patienten mit Prostatakarzinom Investigator initiated Study mit Unterstützung durch AstraZeneca	**No**	**No**
Bergmann, Lothar	Selbstständig	**Yes** Teilnahme an einzelnen Advisory Boards/ Expertenmeetings (ohne Honorar!) von Pfizer, Ipsen, EUsa Pharm, BMS, Roche	**No**	**No**	**No**	**No**	**No**	**No**
Bokemeyer, Carsten	Conflict of interest declarations pending							
Casper, Jochen	Klinikum Oldenburg, Oldenburg	**Yes** Pfizer, Merck, Medac, Ipsen	**No**	**No**	**Yes** Pfizer, Merck, Ipsen, Medac	**Yes** Pfizer, medac	**Yes** Pfizer, Merck, Medac, Ipsen	**No**
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Gauler, Thomas	Conflict of interest declarations pending							
Grünwald, Viktor	Conflict of interest declarations pending							
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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** Reisekostenerstattung 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							

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