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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 Definition und Basic Information

The renal cell carcinoma (formerly hypernephroma) comprises approx. 85% of all malignant kidney tumors. Other forms are the urothelium carcinoma originating from the renal pelvis (10 %), non-Hodgkin lymphomas, sarcomas, and the nephroblastomas occurring in childhood (Wilms' tumor). The renal cell carcinoma is the subject of this chapter.

1.1 Epidemiology

In Germany, the rate of newly diagnosed diseases is estimated to be at 15,000 /year. Men are about 1.5-times more often afflicted than women. Together with the carcinomas of the renal pelvis and the ureters, renal cell carcinomas account for 3.6% and 2.5% of the newly diagnosed malignancies in men and women, respectively. The incidence rate increased until the middle of the 1990s and has since remained constant. The median age of the patients at diagnosis ranges between 65 and 70 years for men, and lies over 70 years for women [1].

1.2 Risk Factors

The factors below increase the risk of acquiring renal cell carcinoma:

- genetic risk factors [2]
  - von Hippel-Lindau disease [OMIM, 193300, autosomal dominant]: predisposition for a clear-cell renal cell carcinoma
  - Birt-Hogg-Dubé syndrome [OMIM 135150, autosomal dominant]: predisposition for a chromophobe renal cell carcinoma
- acquired risk factors
  - obesity
  - chronic renal insufficiency
  - smoking
  - antihypertensive therapy
  - occupational exposure to halogenated hydrocarbons, long-term exposure to X-rays.

2 Prevention and Early Detection

2.1 Prevention

The general recommendations relate to the acquired risk factors hitherto identified:

- No smoking

- Avoidance of obesity

2.2 Early Detection

An early detection program does not exist. Genetic counseling is recommended to members of families with Hippel-Lindau disease.

3 Clinical Presentation

The renal cell carcinoma is a disease poor in symptoms. Local symptoms might consist of painless macrohematuria, flank pain, a palpable tumor, or a new appearing varicocele. General symptoms of the disease include weight loss, fatigue, anemia, and paraneoplastic syndromes such as polycythemia, fever of unknown origin, neuropathy, or hypercalcemia. Many renal cell carcinoma patients remain asymptomatic over a long period of time. In recent years up to 50% of all renal cell carcinomas were discovered incidentally by means of sonography or tomographic imaging performed in the scope of abdominal diagnostics due to other indications. These asymptomatic tumors are tendentially in an earlier stage [3]. Symptoms due to metastases correlate with the predilection sites: bone pain in case of skeletal involvement, coughing and dyspnea in case of pulmonary, and neurological failure in case of cerebral manifestation.

4 Diagnosis

4.1 Diagnostics

The first step consists in the confirmation of the suspected diagnoses based on clinical findings and/or image scanning techniques, see Table 1.

Table 1: Diagnostics - Basics

• Sonography of the kidneys and the abdomen • Multiphase computer tomography (CT) of the abdomen with contrast medium (in case of regular renal function) • Magnetic resonance imaging (MRI) with contrast medium (second-choice method in case of renal insufficiency or allergic response to contrast medium containing iodine) • Laboratory analyses of the blood: differential blood cell counts, electrolytes (Na, K, Ca), LDH, renal function, liver values including albumin, coagulation • Laboratory analyses: urinary status • Laboratory analyses of the blood and urine: creatinine clearance (in case of suspected kidney insufficiency)

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

Table 2: Diagnostics – Staging

• Computer tomography (CT) of the chest • Bone scan in case of clinical suspicion of osseous metastases outside areas already examined in the course of sectional-imaging diagnostics • CT or MRI of the brain in case of clinical symptoms

A biopsy is indicated if it will bear an influence on further therapeutic proceedings. This is the case, for example, prior to local ablative procedures or systemic therapy in case of a primarily metastasized disease. However, a biopsy is not required prior to a planned surgical procedure of the kidney.

4.2 Classification

4.2.1 Stages

Classification is done on the basis of TNM and UICC criteria [4], see Table 3.

Table 3: Classification of Tumor Stages (Update 2011)

Stage	Primary Tumor	Lymph Nodes	Distant Metastases
I	T1 T1a T1b	N0	M0
II	T2 T2a T2b	N0	M0
III	T3 T3a T3b T3c T1 – 3	N0 N1	M0
IV	T4 all T	N0, N1 all N	M0 M1

4.2.2 Histology

Histology distinguishes the following common subtypes of the renal cell carcinoma [5]

- clear-cell (80 - 90 %)
- papillary (10 - 15 %) - Type I small cells with pale cytoplasm,
- low malignancy
    - Type II large cells with eosinophilic cytoplasm,
    - higher malignancy
- chromophobe (3 - 5 %)
- Bellini duct carcinoma (0.6 %)

A sarcomatous differentiation might appear in all histological subgroups. Other pathohistological classifications are relevant to prognosis, however, they neither have an impact on the surgical strategy nor the choice of systemic therapy.

4.2.3 Prognostic Score of Metastatic Renal Cell Carcinoma

Various models have been developed to calculate risk factors and risk scores. The so-called Motzer score was validated in patients treated with interferon [6]. It was used in a modified form to stratify patients included in the randomized clinical studies on the new substances, see Table 4.

Table 4: Memorial Sloan - Kettering Cancer Center Prognostic Score

• LDH > 1.5 of the upper reference value • Karnofsky Index < 80 % • Hemoglobin below the lower, sex-specific reference value • Calcium (corrected value) > 2.5 mmol / l (> 10 mg / dl) • Time between initial diagnosis and onset of systemic therapy in relapse < 1 year
One score point is attributed to each criterion:

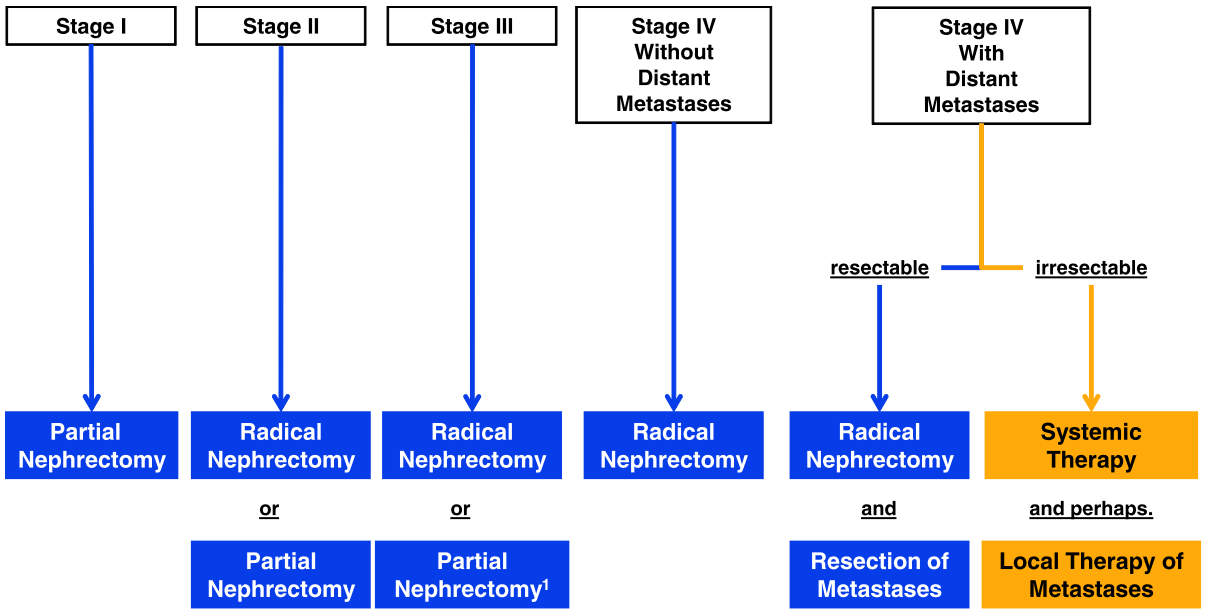
Number of Risk Factors	Prognosis
0	Good
1	Intermediate
≥ 2	Poor

A modification of this score system included the additional criterion "*metastases in two or more organs*". According to this system patients who fulfill three or more criteria are to be considered as having an unfavorable prognosis [7].

5 Therapy

Surgical operation and systemic therapy are the most effective causal therapies. Surgery is the only curative option. The overall therapy concept must be defined before the first therapeutic measure is applied. A treatment algorithm is shown in Figure 1.

Figure 1: Algorithm for Primary Therapy



Legend:
[1]only in case of stages T1 or T2

5.1 Localized Disease

The therapy of choice in case of locally limited renal cell carcinoma is surgical resection.

5.1.1 Surgery

5.1.1.1 Kidney

Radical or partial nephrectomy are available as alternative strategies. The former gold standard used to consist in an open, radical nephrectomy with resection of Gerota's fascia, the ipsilateral adrenal, and the regional lymph nodes. A partial nephrectomy is performed to retain functional kidney tissue. A postoperative renal insufficiency is a negative prognostic factor [8].

Long-term results from randomized clinical trials on radical vs partial nephrectomy are not available [9]. However, it can be concluded from phase-II studies with long observational periods that the cancer-specific survival rates in stage I are comparable after partial and radical nephrectomy. Hence follow the indications for partial nephrectomy [3]:

- anatomical or functional solitary kidney
- increased risk of a renal insufficiency due to other causes (e.g. hypertension, diabetes mellitus)
- hereditary renal cell carcinoma – syndrome
- T1

In stage T2, the success of a partial nephrectomy depends on the careful selection of patients.

Both radical and partial nephrectomy can be performed by open or laparoscopic surgery. Laparoscopic nephrectomy is less invasive and can reduce the risk of perioperative morbidity [9]. However, large randomized studies on the oncologic long-term results of open surgery versus laparoscopic nephrectomy have not yet been made.

5.1.1.2 Ipsilateral Adrenal

Adrenalectomy is only required if tumor infiltration or metastases are suspected based on imaging or intraoperative findings [3].

5.1.1.3 Lymph Nodes

The resection of lymph nodes has no influence on the prognosis of the disease [10]. It is recommended only to confirm the TNM stage when infiltration is suspected on account of imaging or intraoperative findings, and in case of local symptoms.

5.1.2 Other Local Therapeutic Procedures

5.1.2.1 Embolization

Tumor embolization is indicated

- as a palliative action in case of persisting macrohematuria, when neither surgery nor systemic therapy is possible because of poor general health condition
- prior to surgical resection of locally advanced tumors in individual cases.

5.1.2.2 Minimally Invasive Measures

Various physical procedures are applied as percutaneous targeted therapy under imaging control [10]. Tumor growth control rates of up to 85% can be achieved by cryotherapy and radiofrequency ablation, whereas laser therapy and high intensity focused ultrasound (HIFU) are less effective. Controlled comparative studies with long-term follow-up observations do not exist. These physical methods are experimental. A previous histological confirmation of the diagnosis is therefore conditional for their application. Relative contraindications for locally ablative methods consist of a life expectancy under one year, multiple metastases, little chances of success, tumors located close to the hilus, tumors larger than 5cm, tumors of the proximal ureter. Absolute contraindications are coagulation disorders or serious comorbidities.

5.1.3 Adjuvant Therapy

Results obtained from randomized clinical studies are available for various aspects of immunotherapy, see Study Results. They did not show a significant decrease of the relapse risk or an improvement of overall survival. The results of phase-III studies using the new substances are still awaited.

5.2 Locally Advanced Disease

The therapy of patients with locally advanced renal cell carcinomas, whose complete resectability appears questionable on account of imaging diagnostics, is an open field. The effectivity of the newer drugs has resulted in concepts of primary (neoadjuvant) systemic therapy with subsequent surgery. These patients should be treated in the scope of clinical trials.

5.3 Metastatic Disease

5.3.1 Systemic Therapy

Therapy of metastatic renal cell carcinoma is almost always applied for palliative reasons. Immunotherapy with interferon alpha or interleukin-2 used to be the standard in the last two decades, however, the efficacy of this therapy is rather low [11]. Distinct progress including a significant prolongation of progression-free survival was made with the multikinase inhibitors axitinib, pazopanib, sorafenib, and sunitinib, the mTOR kinase inhibitors everolimus and temsirolimus, as well as the angiogenesis-inhibitory VEGF antibody bevacizumab [12], see Study Results.

5.3.1.1 Substances (in Alphabetical Order)

Bevacizumab

Bevacizumab is a monoclonal, angiogenesis-inhibiting antibody. Monotherapy can delay progression of the disease in patients pretreated with cytokines. In combination with interferon alpha, remission rates of 25-30% and a significant prolongation of progression-free survival have been obtained, as compared to interferon-alpha monotherapy [13, 14]. When prognostic subgroups were considered study evaluation revealed a benefit for patients who had a low or intermediate risk score. Serious adverse effects (grade 3/4), which appeared in more than 5% of the patients in the pivotal trial, were fatigue (12-35 %), asthenia (10-17%), proteinuria (7–13%) and hypertension (3-13%). Rather seldom critical complications were thromboembolic events and perforations of the gastrointestinal tract.

Everolimus

Everolimus is an oral mTOR-kinase inhibitor. The marketing authorization study, which was conducted with patients in second-line therapy or later after treatment with sorafenib and/or sunitinib, revealed a significant prolongation of progression-free survival as compared to the placebo control group [15]. Two-thirds of the patients had also been pretreated with cytokines. Serious adverse effects (grade 3/4), which appeared in more than 5% of the patients included in the marketing authorization study, did not exist. Pneumonitis is a more seldom albeit stressful adverse effect induced by mTOR kinase inhibitors.

Interferon α (IFN alpha)

IFN alpha is a member of the interferon family. The exact mechanism of its antitumor efficacy is unknown. IFN alpha stimulates NK cells, enhances the immunogenicity of tumor cells, induces apoptosis, inhibits angiogenesis, and also inhibits cell proliferation by means of an induction of cycline-dependent kinase inhibitors. When applied in monotherapy, remission rates of 12-13% (0-39) are obtained, complete remissions are achieved in about 3% of the patients. The median survival period amounts to 13 months (6-28 months) [11]. Some of the studies on the superiority of the new substances (bevacizumab, sorafenib, sunitinib, temsirolimus) were carried out in comparison with IFN alpha monotherapy. Serious adverse effects (grade 3/4), which appeared in more than 5% of the patients in the marketing authorization studies, were [7, 16, 17, 18]: asthenia (4–26 %), anemia (5-22%), fatigue (13%).

Interleukin-2 (IL-2)

Interleukin-2 is produced by activated T lymphocytes. IL-2 stimulates T lymphocytes as well as NK cells and is a cofactor in the activation of monocytes/macrophages and B lymphocytes. IL-2 was applied in various doses and forms of application. Long-lasting remissions were obtained in 5-7% of the patients with high-dose therapy, complete remissions with long survival periods were achieved in individual cases. A prolongation of the total survival period was observed in randomized studies occasionally [16], however, not consistently [17]. Serious adverse effects (grade 3/4), which appeared in more than 5% of the patients in the marketing authorization study [16] were hypotension (68%), fever (43%), asthenia (36%), diarrhea (28%), anemia (17%), pulmonary symptoms (16%), renal symptoms (15%), neurological symptoms (12%), cardiac symptoms (12%), cutaneous symptoms (10%), and infections (8%).

Pazopanib

Pazopanib is another oral tyrosine kinase inhibitor, which displays a somewhat different kinase profile than that of sorafenib and sunitinib. The marketing authorization study included both patients in first-line therapy and such who had received a pretreatment with cytokines [19]. The RR was at 30%, the progression-free survival period was significantly longer than under placebo. Overall survival was not improved. Serious adverse effects (grade 3/4), which appeared in more than 5% of the patients in the marketing authorization study, did not exist. Attention should be paid to hepatic toxicity by regularly checking ALT and bilirubin. Endocrine (hypothyroidism), hematological or cardiac side effects might occur in patients if they are treated with multikinase inhibitors over a longer period of time.

Sorafenib

Sorafenib is an oral inhibitor of several tyrosine kinases, for example, of the VEGF receptors, PDGFRB, Flt-3 and c-KIT. In signal transduction, it also blocks the serine-threonine kinases of the Raf family in the MAPK pathway. In the pivotal trial, sorafenib was investigated as a second-line therapy option for low and intermediate-risk patients. Progression-free survival was found to be significantly prolonged. In first-line therapy, no significant difference in the remission rate and progression-free survival could be revealed in comparison with interferon alpha. A serious adverse effect (grade 3/4), which appeared in more than 5% of the patients in the marketing authorization study, consisted in a hand-foot syndrome (grade 3/4). Endocrine (hypothyroidism), hematological or cardiac side effects might occur in patients if they are treated with multikinase inhibitors over a longer period of time.

Sunitinib

Sunitinib is an oral inhibitor which blocks several VEGF, PDGF receptors as well as c-KIT and Flt-3 on the level of tyrosine kinase. In the marketing authorization study sunitinib was applied to patients in first-line therapy and compared with IFN alpha [19]. Progression-free survival was significantly longer, the rate of remission was at 47% according to the final evaluation. Serious adverse effects (grade 3/4), which appeared in more than 5% of the patients in the marketing authorization study, consisted of hypotension (12%), fatigue (11%), diarrhea (11%), hand – foot syndrome (9%), and asthenia (7%). Endocrine (hypothyroidism), hematological or cardiac side effects can occur in patients if they are treated with multikinase inhibitors over a longer period of time.

Temsirolimus

Temsirolimus was the first authorized mTOR kinase inhibitor to be applied in cases of renal cell carcinoma. The drug is administered intravenously. Its efficacy was investigated in a randomized phase-III study with patients who had at least three out of six risk factors (Table 4) [7]. Patients in the comparison arm of the study were treated with IFN alpha, whereas patients allocated to a third arm were treated with temsirolimus + IFN alpha. Therapy with temsirolimus produced remission rates of 8.6%. The median progression-free survival and the total survival period were significantly longer as compared with IFN alpha monotherapy. The combination of temsirolimus and IFN alpha was not superior to monotherapy with temsirolimus, however, the dose of temsirolimus was reduced to 15mg per week in the combination arm. Among the serious side effects (grade 3 / 4) reported in over 5% of the patients in the marketing authorization studies were anemia (20%), asthenia (11%), hyperglycemia (11%) and dyspnea (9%). Pneumonitis is a more seldom albeit serious adverse effect induced by mTOR kinase inhibitors.

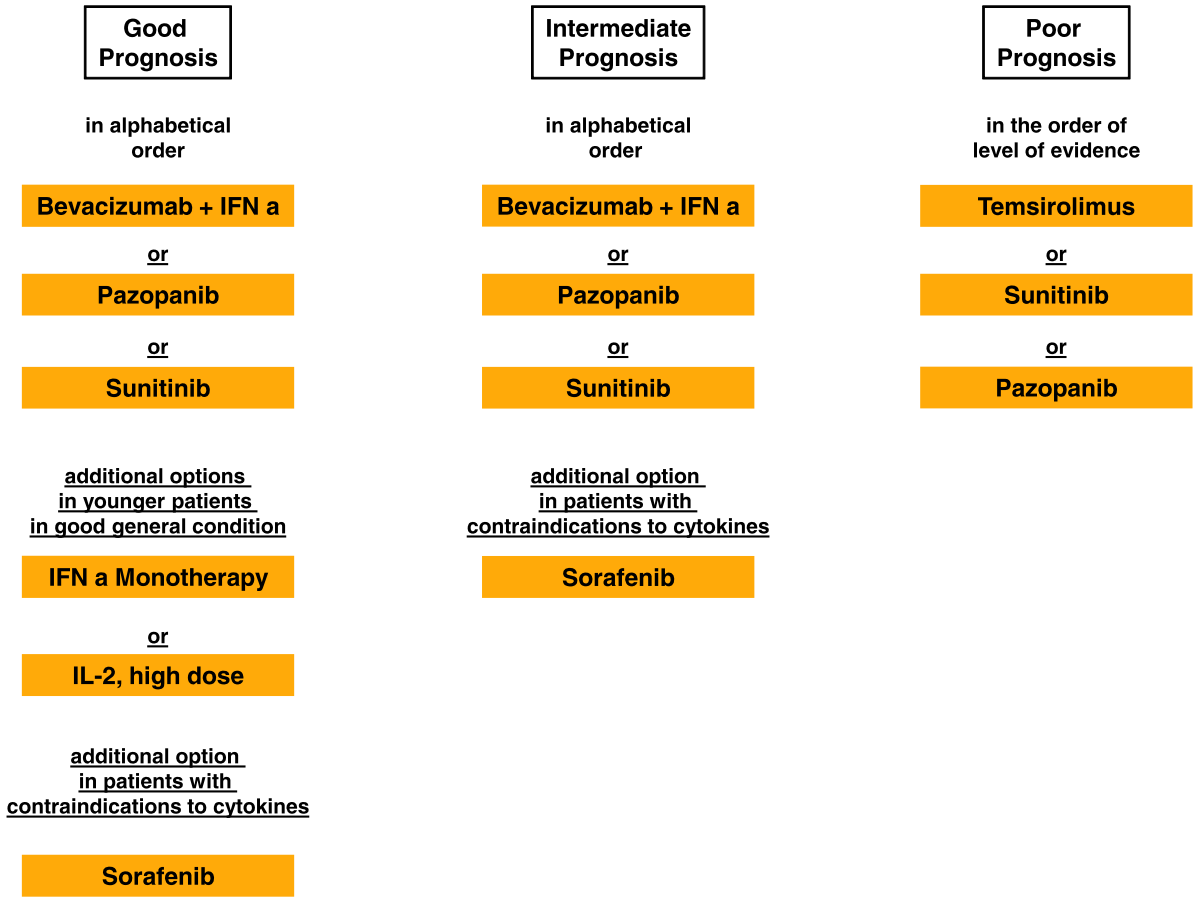
Cytostatic Agents

Conventional cytostatic agents have only little effect in cases of renal cell carcinoma. Applied were, apart from other drugs, 5-fluorouracil in combination with immunotherapy or vinblastine. Remission rates of chemotherapy were below 5%, see Renal Cell Carcinoma Study Results.

5.3.1.2 First-Line Therapy

At present, there are drugs that have been tested against placebo or interferon alpha, but not relative to each other. Neither have the inclusion criteria been consistent as far as risk factors, histology, and previous treatment were concerned. Figure 2 below shows an algorithm for first-line therapy.

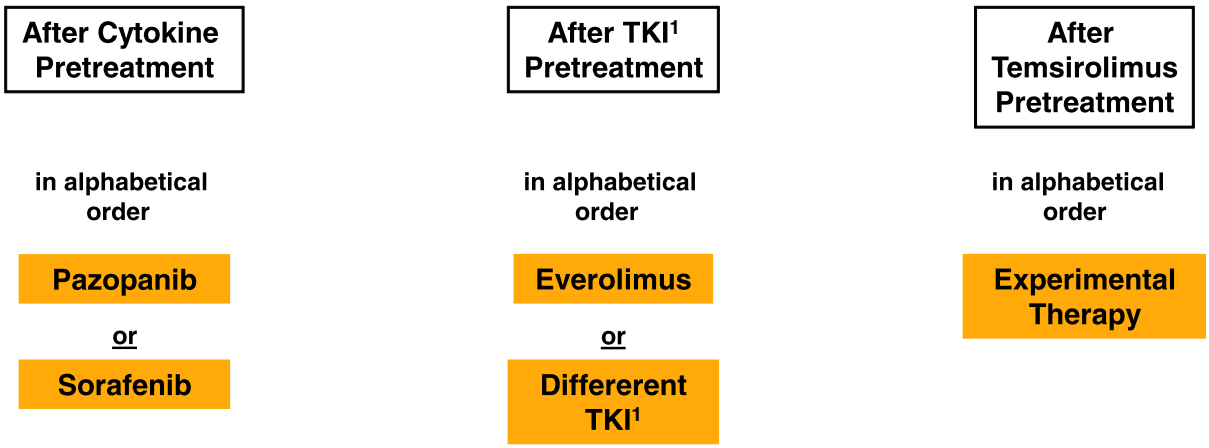
Figure 2: Algorithm for First-Line Systemic Therapy



5.3.1.3 Second-Line Therapy

Drugs used in first-line therapy are effective in second-line therapy as well, others have only been tested in pretreated patients. The algorithm primarily depends on the type of the pre-treatment applied and the physical status of the patient, Figure 3.

Figure 3: Algorithm for Second-Line Systemic Therapy



5.3.1.4 Sequential Therapy, New Options

The new drug treatment options available to patients with metastatic renal cell carcinoma have profoundly altered the course of the disease and patient management. The majority of patients

now receives substances with different cellular targets in a sequential therapy during the course of the disease. The optimal sequence has not been established yet.

New options are additional kinase inhibitors (e.g. axitinib) and the targeted therapy of subgroups (e.g. lapatinib in case of HER2 positivity).

5.3.1.5 Non-Clear Cell Renal Cell Carcinoma

The clear cell renal cell carcinoma is the dominant histological entity. The majority of studies focusing on the newer drugs were exclusively conducted in this entity. Patients with type-II papillary renal cell carcinoma display a more aggressive course of the disease and have a shorter life expectancy. Analyses suggest that this subgroup responds to kinase inhibitors and antiangiogenic therapy, however, displaying lower remission rates and shorter progression-free survival periods. It is recommended to treat patients with non-clear cell renal cell carcinoma according to the algorithm that applies to the clear cell carcinomas.

5.3.2 Surgery

5.3.2.1 Nephrectomy

Nephrectomy might result in the regression of metastases in patients with advanced renal cell carcinomas, however, this phenomenon has been observed in less than 2% of the patients. Under systemic therapy with interferon alpha nephrectomy prolongs the medium survival period by 3 to 10 months, see Study Results. It is not certain whether these data can also be applied to systemic therapy when other substances are used. The results of large randomized studies on this question are still awaited. Modern therapy strategies originate predominantly from results obtained from nephrectomized patients.

When a decision has to be made concerning nephrectomy, the local symptoms induced by the non-resected tumor on the one side and the additional perioperative morbidity as well as a delay of systemic therapy on the other side must be taken into consideration, see also Locally Advanced Stages.

5.3.2.2 Resection of Metastases

Long term remissions have been observed subsequent to the resection of metastases which were predominantly located in the lungs and in the brain. For this reason, the procedure is recommended after careful staging to patients in whom a R0 resection can be achieved [3].

5.3.3 Palliative Therapy – Symptom-Oriented

Palliative therapy should include the treatment of physical and mental symptoms. Its nature is multidisciplinary. The necessity and the possibilities of palliative medicine should be discussed with all persons involved at an early stage. The following specific symptoms occur often particularly in patients who have an advanced-stage renal cell carcinoma.

5.3.3.1 Bone Metastases

Local and systemic procedures are available for the treatment of patients with bone metastases. In the event of pain symptoms or imminent risk of pathological bone fracture radiation will be the therapy of choice. It can be applied hypofractionated under continued systemic ther-

apy. An additional option consists in the surgical treatment of pathological fractures, instable vertebral fractures, or for purposes of relief in case of spinal compression.

Systemic methods consist in a causal therapy and the administration of bisphosphonates. Bisphosphonates reduce the risk of skeletal related complications and delay the progression of osseous metastization. Prospective randomized studies conducted exclusively with renal cell carcinoma patients or a sufficiently large RCC trial population do not exist. The application of these agents is also indicated for the treatment of hypercalcemia.

5.3.3.2 Liver and Lung Metastases

Causal, systemic therapy is of central importance. A local therapy may be indicated in the individual case. Apart from surgical resection, local ablative methods are also available. Conditions are:

- no disseminated metastases
- no local relapse or clinically limiting second neoplasia.

Making decisions on the local treatment of hepatic or pulmonary metastases is a task of multidisciplinary tumor boards.

5.3.3.3 Brain Metastases

The first step to take in case of symptomatic metastization is to administer steroids, in order to reduce the perifocal edema. Local surgical therapy is recommended in case of isolated, resectable brain metastases. An alternative consists in a targeted local radiation (gamma-knife, cyber-knife, stereotactic radiation) or partial brain radiation. The data pertaining to the efficacy of newer drugs are limited to smaller populations of patients [22].

6 Follow-Up

A generally applicable follow-up program does not exist. The relapse risk depends on the stage of the tumor at the time of initial diagnosis. The majority of relapses occur within the first two months. As the patient's life expectancy in relapse is influenced by the extent of metastization, monitoring the course of the disease with imaging techniques appears to be a reasonable course of action. However, there is no evidence that a structured follow-up in the sense of regular staging analyses will result in an improvement of survival. The objective pursued by examinations subsequent to curative therapy is to recognize complications and late biological effects, i.e. especially symptoms of renal insufficiency and hypertension in patients subsequent to nephrectomy.

7 Prognosis

The five-year survival rates in Germany range between 65 and 75%. Decisive for the prognosis are the tumor stage at the time of initial diagnosis and the histological subtype. A chance of cure is only given in case of the surgical extirpation of the tumor in a locally limited stage. Patients with a non-clear cell carcinoma have a less favorable prognosis. The median life expectancy of patients with a metastasized carcinoma has increased in recent years from 6-10 months to 15-24 months and longer.

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10 Active Studies

10.1 First-Line

- RECORD3: Phase-III study on the sequential therapy of sunitinib and everolimus; ClinicalTrials.gov identifier: NCT00903175. http://clinicaltrials.gov/ct2/show/NCT00903175?term=RECORD3&rank=2
- SWITCH: Phase-III study on the sequential therapy of sunitinib and sorafenib; ClinicalTrials.gov identifier: NCT00732914. http://clinicaltrials.gov/ct2/show/NCT00732914?term=00732914&rank=1
- CESAR C-II-006: Phase-II study comparing temsirolimus with sunitinib in cases of non-clear cell renal cell carcinoma; ClinicalTrials.gov identifier: NCT00979966. http://clinicaltrials.gov/ct2/show/NCT00979966?term=00979966&rank=1

10.2 Second-Line

- TORISEL 404: Phase-III study comparing sorafenib with temsirolimus after first-line therapy with sunitinib; ClinicalTrials.gov identifier: NCT00474786. http://clinicaltrials.gov/ct2/show/NCT00474786?term=00474786&rank=1
- Phase-III study comparing dovitinib (TKI258) with sorafenib after antiangiogenic therapy; ClinicalTrials.gov identifier: NCT01223027. http://clinicaltrials.gov/ct2/show/NCT01223027?term=01223027&rank=1

- START: Phase-II study on sequential therapy with pazopanib, everolimus and bevacizumab; ClinicalTrials.gov identifier: NCT01217931. http://clinicaltrials.gov/ct2/show/NCT01217931?term=01217931&rank=1
- MARC-2: Study on temsirolimus in second line after TKI; ClinicalTrials.gov identifier: NCT01266837. http://clinicaltrials.gov/ct2/show/NCT01266837?term=01266837&rank=1

11 Systemic Therapy – Protocols

- Renal Cell Carcinoma - Systemic Therapy - Protocols

12 Study Results

- Renal Cell Carcinoma - Study Results (RCT, Metaanalysis)

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17 Disclosures

according to the rules of the responsible Medical Societies.

17 Disclosures

According to the rules of the German Association of Hematology and Medical Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.

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