Benefit of metastasectomy in renal cell carcinoma patients with metachronous metastasis: A propensity score analysis

eingereicht von
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Klinische Abteilung für Onkologie

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und
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Graz, den 12.02.2021
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Graz, am 12.02.2021

Franziska Maisel eh
Danksagung

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<td>American Joint Committee on Cancer</td>
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<td>AML</td>
<td>angiomyolipoma</td>
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<td>ARS</td>
<td>age-standardized incidence</td>
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<td>AS</td>
<td>active surveillance</td>
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<td>BHD</td>
<td>Birt-Hogg-Dubé’ syndrome</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>CA</td>
<td>cryoablation</td>
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<td>CAIX</td>
<td>carbonic anhydrase IX</td>
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<td>ccRCC</td>
<td>clear cell RCC</td>
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<td>CEUS</td>
<td>contrast-enhanced US</td>
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<tr>
<td>chRCC</td>
<td>chromophobe renal cell carcinoma</td>
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<td>CKD</td>
<td>chronic kidney disease</td>
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<td>CN</td>
<td>cytoreductive nephrectomy</td>
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<td>CRP</td>
<td>c-reactive protein</td>
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<td>CSS</td>
<td>cancer-specific survival</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>CTLA-4</td>
<td>cytotoxic T-lymphocyte-associated antigen 4</td>
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<td>DFS</td>
<td>disease free survival</td>
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<td>ECOG</td>
<td>Eastern Co-operative Oncology Group</td>
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<td>EGFR</td>
<td>epidermal growth factor receptor</td>
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<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
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<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<td>FU</td>
<td>follow-up</td>
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<td>HIF</td>
<td>hypoxia inducible factor</td>
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<td>HLRCC</td>
<td>hereditary leiomyomatosis and renal cell carcinoma</td>
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<td>HPRC</td>
<td>hereditary papillary renal cell carcinoma</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>IFN-α</td>
<td>interferon alpha</td>
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<td>IKCWG</td>
<td>International Kidney Cancer Working Group model</td>
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<td>IL-2</td>
<td>interleukin-2</td>
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<tr>
<td>IPTW</td>
<td>inverse-probability-of-treatment-weight</td>
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<td>ISUP</td>
<td>International Society of Urological Pathology</td>
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<tr>
<td>IVC</td>
<td>inferior vena cava</td>
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<td>LN</td>
<td>lymph node</td>
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<td>MITF</td>
<td>microphthalmia-associated transcription factor</td>
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<td>MFS</td>
<td>metastasis free survival</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>mRCC</td>
<td>metastatic RCC</td>
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<td>mTOR</td>
<td>mammalian target of rapamycin</td>
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<tr>
<td>nccRCC</td>
<td>non-clear cell renal cell carcinoma</td>
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<td>NSM</td>
<td>nonsurgical management</td>
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<td>OS</td>
<td>overall survival</td>
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<td>PADUA</td>
<td>Padua score</td>
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<td>PD</td>
<td>programmed death</td>
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<td>PD-L1</td>
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<tr>
<td>PD-1</td>
<td>programmed death protein 1</td>
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<td>PFS</td>
<td>progression-free survival</td>
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<td>paraneoplastic syndrome</td>
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<td>papillary renal cell carcinoma</td>
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<td>PS</td>
<td>performance status</td>
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<tr>
<td>RAE</td>
<td>renal artery embolization</td>
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<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
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<tr>
<td>RCC</td>
<td>renal Cell Carcinoma</td>
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<tr>
<td>RCT</td>
<td>randomized control trial</td>
</tr>
<tr>
<td>R.E.N.A.L.</td>
<td>(R)adius, (E)xophytic/endophytic properties of the tumor, (N)earness of tumor deepest portion to the collecting system or sinus, (A)nterior (a)/posterior (p) descriptor and the (L)ocation relative to the polar line - score</td>
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<tr>
<td>RFA</td>
<td>radiofrequency ablation</td>
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<td>RLN</td>
<td>regional lymph nodes</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<td>RTB</td>
<td>renal tumor biopsy</td>
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<tr>
<td>SDH-RCC</td>
<td>succinate dehydrogenase kidney cancer</td>
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<tr>
<td>SEER</td>
<td>Surveillance Epidemiology and End Results (statistic database, U.S.)</td>
</tr>
<tr>
<td>SMD</td>
<td>standardized mean difference</td>
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<tr>
<td>SRM</td>
<td>small renal mass</td>
</tr>
<tr>
<td>SSIGN</td>
<td>Stage, Size, Grade and Necrosis Score</td>
</tr>
<tr>
<td>TCC</td>
<td>transitional Cell Carcinoma</td>
</tr>
<tr>
<td>TKI</td>
<td>tyrosine kinase inhibitor</td>
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<tr>
<td>TSC</td>
<td>tuberous sclerosis complex</td>
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<tr>
<td>TT</td>
<td>targeted therapy</td>
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<tr>
<td>uRCC</td>
<td>unclassified RCC</td>
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<tr>
<td>UICC</td>
<td>Union for International Cancer Control</td>
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<tr>
<td>UISS</td>
<td>University of California, Los Angeles Integrated Staging System</td>
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<tr>
<td>US</td>
<td>ultrasonography</td>
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<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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<tr>
<td>VHL</td>
<td>von Hippel-Lindau gene</td>
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<tr>
<td>vHL</td>
<td>von Hippel-Lindau disease</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Figure Legends

**Figure 1.** Unadjusted and propensity-score-weighted Kaplan-Meier curves of 5-year overall survival according to treatment assignment to metastasectomy (n=106). Panel A – Unadjusted (“crude”) analysis, Panel B – Propensity score analysis (Kaplan-Meier estimators and log-rank test weighted by the inverse-probability-of-treatment-weight (IPTW).

**Figure 2.** Landmark analysis of 5-year overall survival according to whether patients underwent metastasectomy within the first six months after metastasis diagnosis or not. Blue dashed vertical line – Landmark date at 6 months of follow-up.

**Figure 3.** Clinical outcomes according to completeness of metastasectomy. Panel A (left) – Risk of progression (1-Kaplan-Meier estimator due to absence of competing mortality). Panel B (right) – Overall survival. A complete metastasectomy was considered as a metastasectomy that removed all known metastatic lesions within one surgical procedure. Abbreviations: MED – Medical therapy only group (i.e. no metastasectomy), M_{incomplete}+MED – Incomplete metastasectomy group, M_{complete}+MED – Complete metastasectomy group.
Table Legends

Table 1. Major histological RCC subtypes and their characteristics

Table 2. TNM Staging System. RLN are hilar, abdominal para-aortic, and paracaval regional lymph nodes, independent of laterality.

Table 3: Overall Staging System

Table 4. Prognosis for different histological subtypes

Table 5: Comparison of different postoperative prognostic models

Table 6: Comparison of different prognostic models for mRCC

Table 7. Baseline characteristics of the study population – Distribution overall and by treatment assignment to metastasectomy (n=106). Continuous variables are summarized as medians [25th percentile (Q1) – 75th percentile (Q3)], whereas categorical variables are reported as absolute frequencies and percentages. *p-values for difference metastasectomy vs. no metastasectomy are from Pearson’s chi-squared tests (categorical variables with expected cell counts ≥5), Fisher’s exact tests (categorical variables with expected cell counts <5), or Wilcoxon rank-sum tests (continuous variables). **variable from the time of nephrectomy. ***Variable defined as follows: one count for each metastasis, truncated at a maximum value of 9 (=multiple metastases), e.g. a patient with 3 lung metastases + 1 bone metastasis + 2 liver metastases has a value of 6. ****received at any time during follow-up (non-exclusive, i.e. patients can appear both in the aVEGF TKI group and the mTOR inhibitor group). Abbreviations: n (%miss.) – number of patients with fully observed data
(% missing from a total of 80 patients), BMI – Body Mass Index, TNM – Tumor Node Metastasis classification, aVEGF TKI – tyrosine kinase inhibitor targeting the vascular endothelial growth factor receptor pathway, mTOR – mammalian target of rapamycin, RFA – radiofrequency ablation, LDH – lactate dehydrogenase, |ΔS| – Standardized mean difference (SMD), |ΔIPTW| – IPTW-weighted SMD (weighing with the main IPTW based on a 10-variable propensity score model as reported in Supplementary Table 5).

**Table 8. Tabulation of metastasectomy procedures (n=36).** These data represent the first metastasectomy used for assigning patients to the metastasectomy group. Some of these patients received a second or even a third metastasectomy after the index metastasectomy (data reported in Supplementary Table 3).
Zusammenfassung

**Hintergrund:** Die Metastasektomie ist eine häufig praktizierte Behandlungsstrategie beim metastasierten Nierenzellkarzinom (mRCC). Allerdings ist das Ausmaß des Nutzens der Metastasektomie derzeit unklar. **Methoden:** Wir führten daher eine Propensity-Score-Analyse des Gesamtüberlebens (OS) bei 106 mRCC-PatientInnen mit metachroner Metastasierung durch, von denen 36 (34%) mit Metastasektomie und 70 (66%) mit alleiniger medikamentöser Therapie behandelt wurden. **Ergebnisse:** Die häufigsten Metastasektomieverfahren waren Lungenresektionen (n=13) und Kraniotomien (n=6). Die mediane time-to-progression nach Metastasektomie betrug 0,7 Jahre [25.-75. Perzentil: 0.3-2.7]. Nach einem medianen follow-up (FU) von 6.2 Jahren und 63 Todesfällen lag das geschätzte 5-Jahres-Gesamtüberleben in der Metastasektomie- bzw. der medikamentösen Therapie-Gruppe bei 41% bzw. 22% (log-rank p=0.00007; Hazard ratio (HR)=0.38, 95%CI: 0.21-0.68). PatientInnen, die sich einer Metastasektomie unterzogen, hatten eine signifikant höhere Prävalenz günstiger prognostischer Faktoren, wie z. B. weniger bilaterale Lungenmetastasen und längere krankheitsfreie Intervalle zwischen Nephrektomie und Metastasierung. Nach der Propensity-Score-Gewichtung für diese Unterschiede und Adjustierung für immortal time bias, wurde die Assoziation zwischen Metastasektomie und besseren Gesamtüberleben deutlich schwächer (HR=0.62, 95%CI: 0.39-1.00, p=0.050). Das Propensity-Score-gewichtete geschätzte 5-Jahres-Gesamtüberleben betrugen 24% bzw. 20% in der Metastasektomie- und der medikamentösen Therapie-Gruppe (log-rank p=0.001). In explorativen Analysen zeigte sich, dass der Nutzen der Metastasektomie auf PatientInnen beschränkt zu sein schien, die eine vollständige Resektion aller bekannten Metastasen erreichten. **Schlußfolgerung:** Diese gegenständliche Arbeit zeigt einen Zusammenhang zwischen Metastasektomie und verbessertem Gesamtüberleben bei PatientInnen mit metachron metastasiertem mRCC. Metastasektomien, durch die keine vollständige Resektion aller bekannten Läsionen erreicht werden kann, bringen wahrscheinlich keinen Vorteil für das Gesamtüberleben.
Abstract

**Introduction:** Metastasectomy is a frequently practiced treatment strategy in metastatic renal cell carcinoma (mRCC). However, the magnitude of benefit of metastasectomy as compared to medical treatment alone is currently unclear. Methods: We therefore conducted a propensity score analysis of overall survival (OS) in 106 mRCC patients with metachronous metastasis, of whom 36 (34%) were treated with metastasectomy and 70 (66%) with medical therapy alone. **Results:** The most frequent metastasectomy procedures were lung resections (n=13) and craniotomies (n=6). Median time-to-progression after metastasectomy was 0.7 years [25th-75th percentile: 0.3-2.7]. After a median follow-up (FU) of 6.2 years and 63 deaths, 5-year OS estimates were 41% and 22% in the metastasectomy and medical therapy group, respectively (log-rank p=0.00007; Hazard ratio (HR)=0.38, 95%CI: 0.21-0.68). Patients undergoing metastasectomy had a significantly higher prevalence of favourable prognostic factors, such as fewer bilateral lung metastases and longer disease-free intervals between nephrectomy and metastasis diagnosis. After propensity score weighting for these differences and adjusting for immortal time bias, the favourable association between metastasectomy and OS became much weaker (HR=0.62, 95%CI: 0.39-1.00, p=0.050). Propensity-score-weighted 5-year OS estimates were 24% and 20% in the metastasectomy and medical therapy group, respectively (log-rank p=0.001). In exploratory analyses, the benefit of metastasectomy was confined to patients who achieved complete resection of all known metastases. **Conclusion:** Within the limitations of an observational study, these findings support the concept that metastasectomy is associated with an OS benefit in patients with mRCC. Metastasectomies not achieving complete resection of all known lesions are likely without OS benefit.
Publications and presentations based on this thesis


Introduction

Definition of the renal cell carcinoma (RCC)

Renal Cell Carcinoma, formerly known as Grawitz tumor or hypernephroma, is a primary malignant tumor of the kidney.(1-3) It derives from the epithelial cells of the tubulous system or the collecting duct of the nephron; the most common origin is the proximal renal tube.(2, 4) RCC is the most frequent primary tumor of the kidney and is responsible for 80 to 85 percent of its cases. Transitional cell carcinoma (TCC) is the second most common primary neoplasms of the kidney arising from the urothelial cells of the renal pelvis, accounting for 7% of the kidney tumors. In addition, there are rare entities such as mesenchymal tumors.(5, 6) In children the Nephroblastoma (Wilms’ tumor) accounts for 5% of all cases of cancer (39%). Secondary tumors of the kidney are rarely clinically significant and therefore mostly discovered at post-mortem.(7) Oncocytomas and papillary adenomas form part of the group of renal cell tumors which are benign.(8)

Epidemiology

According to most recent estimations for the year 2020 of the American Cancer Society kidney and renal pelvis cancer is the 6th most frequent cancer in men and the 8th in women in the United States, accounting for 5% and 3% of all malignancies respectively.(9) The lifetime risk to develop kidney and renal pelvis cancer is 2.1 in men and 1.2 in women in the US based on the Surveillance Epidemiology and End Results (SEER) cancer registry.(9) In the UK, it represents 4% of total cancer cases in the average of both sexes in 2015–2017.(10) The recently updated World Health Organization GLOBOCAN 2018 database reports the number of new cases of kidney cancer worldwide to be approximately 403,000 (for the age group 0-74 years) and the number of deaths about 175,000 in 2018, with a cumulative risk of 0.20%. That means an age-standardized incidence (ASR) of 4,5 per 100,000 worldwide.(11) Kidney and renal pelvis cancer are the twelfth leading cause of cancer death with a death rate of 3.6 per 100,000 per year in the United states.(40) For females under the age of 20 it is the fifth leading cause of cancer death in the United States of America.(9) The probability of developing RCC is significantly linked to male gender and higher age but ethnicities and geographical factors also seem to be epidemiologically important. Kidney Cancer occurs in men almost twice as often as in women (ARS worldwide 0.6 compared with 3.1).(11) This could be due to the related risk factors, which will be addressed later on.
Kidney cancer is usually diagnosed in ages over 40 years, most frequently among the group of age 65–74.\(^{(10)}\) The median age at diagnosis is 64 with an almost normal distribution.\(^{(12, 13)}\) The median age at presentation for patients with hereditary kidney cancer is significantly lower at 37 years. Early age of onset (<46 years) might therefore be a sign of hereditary RCC.\(^{(12)}\)

Globally, the incidence of RCC varies strongly among world regions with a factor of 12. The highest rates of incidence are documented in more developed countries, as in Northern America, Europe, Australia, and New Zealand, whereas Asian and African countries lie clearly below the average.\(^{(11)}\) It should be noted that mortality, measured by ARS, varies very little between the highest and lowest incidence countries; in North America, the mortality-to-incidence ratio is 0.21, whereas in Central Africa, the ratio is 0.82. The reason for the gender and geographic differences in incidence is unknown. Genetic, occupational, and environmental exposures are likely. In the US and UK, Asian citizens have a significantly lower incidence of RCC; for Black citizens, results are conflicting. American Indian and Alaska Native populations in the US have a 1.4 higher incidence compared with white males.\(^{(9, 10)}\)

In the last decades the incidence of RCC has been rising steadily (in the UK, 87% since the early 90s), accompanied by a decrease in mortality.\(^{(10)}\) These developments are especially evident in developed countries.\(^{(1)}\) Another change is the downward shift of tumor size and stage.\(^{(14)}\) These three aforementioned trends, as well as the geographic differences, can be explained in part by the increased use of radiologic techniques, especially in countries with wealthier health care systems, leading to more incidental detections of renal masses when abdominal imaging is performed as part of health examinations or diagnostically for other indications.\(^{(14)}\)

**Risk factors**

Certain lifestyle factors likely have an influence on disease risk. Countless studies have demonstrated the link between external risk factors and the development of RCC. The triad of the most important risk factors is obesity, smoking and hypertension. All three are strongly lifestyle-dependent and modifiable, which exemplifies the importance of prevention in medicine. According to a British study, 33.5% of kidney cancer cases were due to known risk factors and were therefore preventable.\(^{(15)}\)
Obesity

Obesity has been shown to be a significant RCC risk factor in multiple case-control and prospective cohort studies.(16-23) Obesity alone may be responsible for 24–30% of RCC cases in Europe and 40% in the U.S. and Canada (10, 24), making it the most important risk factor. The relative risk (RR) of developing RCC for obese individuals is 1.83 compared with normal-weight individuals.(22) For every 5 kg/m² increase in BMI, the risk of developing kidney cancer increases by 24% in men and 33% in women.(25) The underlying biological explanation is still largely unknown, but obesity may lead to renal parenchymal damage via a number of pathomechanisms that may ultimately increase the risk of RCC. These mechanisms include oxidative stress, hypertension-induced injury to the renal tubules, renal atherosclerosis, and endocrine changes such as increases in estrogen, steroid hormones, and insulin.(16, 17) Obesity is notoriously associated with increased cardiovascular risk, which in turn can exacerbate the factors listed above.(17) Interestingly, obese metastatic RCC (mRCC) patients might have longer survival and lower mortality compared to normal weight patients, which is called the “obesity paradox”. One reason could be the downregulation in fatty acid metabolism (FASN).(19)

Smoking

Numerous studies have shown that tobacco consumption causes RCC and significantly increases incidence and disease-specific mortality.(24, 26-29) A meta-analysis of 24 studies showed that the RR for RCC was 1.54 for male and 1.22 for female smokers. The same study showed that, as with obesity, there is a strong dose-response correlation.(27) Heavier smoking (longer smoking exposure, higher smoking intensity and greater cumulative exposure) also has a significant association with advanced diseases.(26) The RR of RCC and dying from RCC is highest for current smokers (1.29 and 1.32) and lowest for former smokers (1.14 and 1.01), indicating that smoking cessation reverses the risk. The duration of abstinence is proportional to the decrease in the likelihood of advanced disease.(26, 28) Also environmental tobacco smoke, second-hand smoking increases RR of RCC.(28, 29) Tobacco contains abundant carcinogenic substances such as aromatic hydrocarbons, aromatic amines, and N-nitroso compounds, which damage DNA and favour the emerge of smoke-related cancers such as RCC.(28) Smoking increases cardiovascular risk and damages the renal parenchyma by increasing intraglomerular pressure and altering
endothelial cell function, two additional mechanisms that may indirectly increase RCC risk.(30)

Hypertension

Furthermore, the existence of hypertension or its treatment is positively and strongly related to developing RCC, although it is difficult to distinguish the effect of the disease from that of the drugs.(23, 24, 31-33) In addition, the investigation of the matter is complicated because early-stage RCC itself seems to increase blood pressure.(24) Still, current research suggests that hypertension itself is an independent risk factor, not medication.(24, 34, 35) A dose-response pattern was examined by multiple studies.(32, 33) It is unclear how blood pressure leads to the development of renal cell carcinoma, but the pathomechanism is thought to involve pressure damage to the renal tubules.(24)

Other risk factors

Apart from the three established factors mentioned above, numerous others have been suspected to be associated with RCC and have been investigated in countless studies. A positive association with RCC is suggested for intake of analgesics, height, pre-existing conditions (such as diabetes mellitus, liver and kidney diseases), radiation, hormonal factors (such as hysterectomy and high parity) and occupational exposure (such as asbestos and solvent trichloroethylene (TCE)). Physical activity, special diets (such as fruit and vegetable consumption), use of hormonal contraceptives and alcohol consumption are suggested to be protective factors. A large number of epidemiologic studies have been conducted and yet the research results for most of the factors mentioned are conflicting and inconsistent.(24, 36-40) Only for patients with previous renal transplantation and pre-existing renal disease (such as end-stage renal disease and acquired renal cysts) does an increased risk of renal cell carcinoma appear to be rather clear.(24, 37, 38, 40)

Certain epidemiological groups such as men and older people have a greater risk of being diagnosed with RCC than others (see chapter “Epidemiology”). Patients with a hereditary RCC syndrome have a high risk of RCC (see chapter “Hereditary syndromes”). Heredity plays an important role in pathogenesis, leading to the next risk group. A strongly increased risk applies to family members of an affected individuals, the RR is increased 2–3-fold in first-degree relatives and 1.6-fold in second-degree relatives.(41)
Pathogenesis

Pathways

Most cancers occur sporadically, triggered by hormones, viruses, chemicals and radiation. (41, 42) A small percentage (3–8%) are known to have a hereditary disease. (12, 41, 43, 44) Hereditary cancer refers to a germline mutation in a cancer predisposition gene, 12 of which have been described for renal cancer. (44, 45) Furthermore, spontaneous mutations can lead to mutation of the same genes. (44) Hereditary cancer syndromes are associated with specific mutations and usually predispose to more than one type of cancer. (44) Several have been identified to increase risk of RCC. More recently, it has become known that besides monogenic syndromes multiple susceptibility loci can increase risk and that a large proportion of cancer patients probably have a certain genetic predisposition. (1, 12, 41) Genome-wide association studies (GWAS) of RCC have identified six susceptibility loci to date causing such a predisposition. (46)

Pathology of different histological subtypes

In the following, the pathomechanisms contributing to the development of clear cell RCC (ccRCC) will be explained with some examples in a rather detailed manner to provide an understanding of the mechanism of action of new therapeutic agents. The most frequent genetic aberration in ccRCC is von Hippel-Lindau gene (VHL) inactivation through loss or mutation of the gene located at chromosome 3p25. (1, 47, 48) The cause can be an inherited germline mutation provoking the eponymous von Hippel-Lindau disease (vHL) or simply sporadic mutation. Sporadic ccRCC exhibits loss of the wild-type allele of VHL in over 60%. (47, 48) VHL is a tumor suppressor gene that controls gene transcription. Its loss of function contributes to tumorigenesis by increasing hypoxia-inducible factors (HIFs), leading to a state of pseudohypoxia that ultimately drives angiogenesis, proliferation, and metabolism in response. (1, 44, 47-49) Increased angiogenesis via increased vascular endothelial growth factor (VEGF) expression renders RCC highly perfused and is also the explanation for the efficacy of anti-VEGF therapy (see chapter “Treatment”). (1) Given that VHL loss alone is not enough to cause ccRCC, and considering that only 40–50% of VHL mutation carriers develop RCC, the pathogenesis of ccRCC is likely multifactorial. (1, 32) Multiple genetic losses in tumors are associated with poor prognosis. (48) Other associated mutations include chromatin regulating genes (PBRM1, BAP1, SETD2), histone modifiers
(KDM5a, ARID1a, and UTX), and genes associated with mammalian target of rapamycin (mTOR) pathway signaling (PIK3CA, PTEN, and MTOR). Like VHL, many of these genes (PBRM1, SETD2 and BAP1) are located on the short arm of chromosome 3 (3p). The very frequent 3p loss therefore leads to simultaneous deactivation of several tumor suppressor genes. mTOR promotes tumor growth by activating the mTOR pathway. This is where mTOR inhibitors can intervene (see chapter “Treatment”). The presence of certain mutations has prognostic significance and is therefore the subject of intensive current research. In the future, they could be used as biomarkers. Renal cell carcinomas possess an intrinsic genetic diversity termed tumor heterogeneity. The emergence is the result of selection advantages of different subclonal populations within the tumor as an adaptation to new microenvironmental conditions and metabolic requirements during cancer evolution. By analyzing the expression of immune cell gene signatures in tumors, it is possible to quantify immune cell infiltration in a tumor, which is the expression of the human immune response and is relatively high in RCC. One pathomechanism of cancer is the suppression of this response through the expression of immune checkpoint regulators such as programmed death ligand 1 (PD-L1). RCC uses the programmed death (PD) pathway to downregulate the efficacy of the natural immune response, expressing PD-L1 in two-thirds of tumors. The interaction between programmed death protein 1 (PD-1) on the T cell and its ligands (PDL-1, PDL-2) on the tumor cells triggers inhibitory signals for T cell suppression. The original strong immune response in RCC makes RCC a disease susceptible to immune modulators, such as immune checkpoint inhibitors, which counteract the immunosuppressive effect of the cancer (see chapter “Treatment”). Much less is known about the underlying mechanisms in papillary and chromophobe renal cell carcinomas (pRCC and chRCC). Two syndromes are known to cause pRCC. Activation of the MET proto-oncogene is responsible for the syndrome of hereditary papillary renal cell carcinoma (HPRC), which solely causes papillary renal cell carcinoma type 1. There is also a hereditary equivalent for papillary renal cell carcinoma type 2, the syndrome of hereditary leiomyomatosis and renal cell carcinoma (HLRCC), which is associated with mutations of the FH tumor suppressor gene that can lead to cutaneous and uterine leiomyomas. Sporadic mutations can also cause pRCC but are thought to affect other genes. Type 1 is often associated with epidermal growth factor receptor
(EGFR) mutations and type 2 with SETD2 mutations, CDKN2A mutations or TFE3 fusions.(14)

chrRCC can occur sporadically with loss of whole chromosomes (1, 2, 6, 10, 13, 17, 21) and also with mutations in tumor suppressor genes: such as PTEN and PT53.(12) The associated syndrome is called Birt-Hogg-Dube (BHD) and increases the risk for patients to develop cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothoraces and a variety of renal tumors. It is associated with germline mutations in the FLCN tumor suppressor gene.(32, 44, 47)

Hereditary syndromes

More than 45 types of hereditary cancer syndromes are known, about 10 of them are associated with an increased risk of kidney cancer.(12, 44, 45) Distinct genetic alterations are found in specific familial syndromes. Some but not all patients present with RCC, the probability is expressed by penetrance, which is about 40–50% for vHL and 20–40% for BHD.(32, 44) Carriers also have a higher risk of developing cancer at a young age and multifocally or bilaterally.(44, 45) These syndromes are relatively rare and often overlooked. Common to all syndromes is an autosomal dominant inheritance.(32) The best known is the von Hippel-Lindau disease which is caused by a germline mutation of the von Hippel-Lindau gene. Patients with the VHL disease have an elevated risk to develop ccRCC but also hemangioblastomas of the central nervous system and retina, pancreatic and renal cysts and neuroendocrine tumors, endolymphatic sac tumors and pheochromocytomas.(32, 44) Other syndromes predisposing to kidney cancer are succinate dehydrogenase kidney cancer (SDH-RCC), tuberous sclerosis complex (TSC), Cowden syndrome, and microphthalmia-associated transcription factor (MITF) with germline mutations in SDHB/C/D, TSC1/2, PTEN, or MITF, respectively.(12) The presence of certain characteristics should prompt clinicians to consider referral for genetic counseling (see chapter “Germine Mutation Testing”).(12, 32)

Prevention

As mentioned earlier, approximately a third of kidney cancer cases are reportedly due to attributable known risk factors, therefore they are preventable.(15) Since the triad of major risk factors is known (obesity, smoking, and hypertension), the principles of risk reduction
can be easily concluded. Smoking cessation reduces the risk of RCC. A large retrospective study quantifies this effect, showing that per smoke-free decade, the relative risk of advanced disease decreases by approximately 9% in comparison.(26) Preventing hypertension by avoiding its risk factors reduces the risk of RCC, as does lowering blood pressure.(33) Given what is known about the causal effect of obesity on disease risk, maintaining a normal BMI is an important preventive measure.

Screening

Given the lack of early warning symptoms and the poor prognosis of advanced-stage RCC and rising incidences, the utility of potentially using screening methods in individuals at increased risk is debated. While RCC is surgically curable in early stages, advanced RCC is not, so there is great interest in early detection.

The use of ultrasound screening in combination with urine biomarkers represents a promising screening tool. However, the relatively low prevalence of the disease, possible false-positive results, and potential overdiagnosis of slow-growing RCCs must be considered and make the benefit questionable.(54) Therefore, the optimal screening modalities, survival benefits, and cost-effectiveness of screening need to be further investigated at the country-specific level.(38)

Classification

In order to make treatment decisions and prognoses in individual cases, each tumor must be classified. Pathological entities denote different heterogeneous histological types of RCC with different characteristics, prognoses and therapies. Grading describes the degree of histologic malignancy. Both entities and grading are analyzed by microscopic diagnosis. Staging uses only the anatomic extent of disease to define groups and is usually determined by physical examination combined with imaging.

Subtypes

Renal cell carcinoma is not a uniform disease but a heterogeneous group of cancers that are completely different in terms of sites of origin within the nephron, histologic features, molecular pathways, cytogenetic profiles, and prognoses, implying different treatments. (14, 49) The World Health Organization (WHO) currently lists 13 subtypes of RCC. The subtypes are revised in each new version and novel renal tumor subtypes are added.(5, 8)
The 3 major subtypes (each >5%) of RCC are ccRCC, pRCC and chRCC. Clear cell RCC accounts for the majority of kidney cancer deaths and is the most common subtype. The remaining subtypes have been grouped together as nccRCC (non-clear cell RCC) in clinical trials. There is significantly less research and knowledge on the management of the individual nccRCC subtypes.

<table>
<thead>
<tr>
<th>Entities</th>
<th>ccRCC</th>
<th>pRCC</th>
<th>chRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of origin</td>
<td>Proximal tubule</td>
<td>Proximal tubule</td>
<td>Intercalated cell of cortical collecting duct</td>
</tr>
<tr>
<td>Frequency</td>
<td>75–85%</td>
<td>12–14%</td>
<td>4–6%</td>
</tr>
<tr>
<td>Histological features</td>
<td>Cytoplasm clear or eosinophilic, architecturally diverse growth pattern: alveolar and acinar, delicate vascular network</td>
<td>Growth pattern: papillary or sarcomatoid further divided into type 1 and 2</td>
<td>Growth pattern: Solid, tubular, or sarcomatoid, large pale cells with prominent cell membranes</td>
</tr>
<tr>
<td>Age in years median (range)</td>
<td>65 (25–90)</td>
<td>68 (36–89)</td>
<td>64 (28–83)</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>1,9:1</td>
<td>2,9:1</td>
<td>1,7:1</td>
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Table 1. Major histological RCC subtypes and their characteristics

The rare subtypes (<1% each) together account for only about 6% and include, for example, clear cell papillary, mucinous tubular, and spindle cell carcinomas, collecting duct carcinomas (Bellini), and tubulocystic. The remaining cancers that do not fulfill no subtype diagnostic criteria, are referred to as unclassified RCC (uRCC) and account for the remaining 4–5%. No standard therapy exists for this large category.

Staging

The most commonly used system for staging tumors is the TNM system, which was established by the Union for International Cancer Control (UICC), is supported by the American Joint Committee on Cancer (AJCC), and is recommended for use in all current guidelines. It contains three components: T measures the size of the primary
tumor and extent of invasion; N indicates the status of metastasis to regional lymph nodes (RLN); and M gives further information about whether there is distant metastasis. Information about the subcategories are combined to assign a stage of 1–4, which allow conclusions to be drawn about prognoses. The current version was published 2017 in its 8th edition and includes following values for RCC.(59) T, N and M are assessed by clinical examination and imaging. If T or N is preceded by p, the information refers to the postoperative situation when the information has been confirmed histologically.

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
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<tbody>
<tr>
<td>X</td>
<td>Cannot be assessed</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>0</td>
<td>No evidence of primary tumor</td>
<td>No RLN metastasis</td>
</tr>
<tr>
<td>1</td>
<td>Primary is limited to kidney, ≤7cm 1a, ≤4cm 1b, 4–7 cm</td>
<td>Metastasis in RLN*</td>
</tr>
<tr>
<td>2</td>
<td>Primary is limited to kidney, &gt;7cm 2a, 7–10 cm 2b, &gt;10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>extends into major veins / perinephric tissues, not into the ipsilateral adrenal gland, not beyond Gerota fascia 3a, extends into the renal vein/ peripelvic fat, not beyond Gerota fascia 3b, extends into vena cava below diaphragm 3c, extends into vena cava below diaphragm</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>invades beyond Gerota fascia or ipsilateral adrenal gland</td>
<td>-</td>
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Table 2. TNM Staging System(59)

In addition, it is possible to classify the disease into overall stages based on the information from the TNM system, which are divided into stages I–IV.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
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Grading

Grading is used to describe and categorize tumors according to their histological differentiation grade. The higher the grade, the less differentiated the tumor, i.e. the more alterations can be found compared to normal cells of the original tissue, indicating abnormal growth and a less favorable prognosis. The grading for a heterogeneous tumor refers to the cells with the highest grade.

The Fuhrman grading system distinguishes four different grades for RCCs, depending on nuclear size, irregularity, and nucleolar prominence. This classification system has been widely criticized for its lack of reproducibility and the low prognostic significance of its components, except for nucleolar prominence. This led the International Society of Urological Pathology (ISUP) to propose a new grading system, the ISUP grading system, which was established by expert consensus at the 2012 ISUP conference in Vancouver. Based on nucleolar prominence, tumors are assigned to grades 1–3; if there is evidence of nuclear anaplasia (including tumor giant cells, sarcomatoid differentiation and/or rhabdoid morphology), the finding is defined as G4 defining. The ISUP system is more reproducible compared to the Fuhrman system and is therefore recommended. WHO has implemented it in the latest version of the WHO Bluebook, its fourth classification of urogenital tumors published in 2016.

Diagnosis

More than half of all renal cell carcinomas are discovered incidentally when abdominal imaging is performed for other indications, most frequently by ultrasound and computed tomography (CT). Consequentially more tumors are detected at a small, localized and respectable stage. This results in better disease-specific survival rates for incidentally detected RCCs compared with symptomatic disease. The prevalence of

<p>| | | | |</p>
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<tbody>
<tr>
<td>II</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>or</td>
<td>1/2/3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>Any N</td>
<td>Any M</td>
</tr>
<tr>
<td>or</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Table 3. Overall Staging System

Grading

Diagnosis
asymptomatic RCCs is highlighted by a study by Hellsten et al. They found RCCs in 2.1% of autopsies, two-thirds of which were undiagnosed during lifetime.(67)

Clinical Diagnosis

RCC has been referred to as the “internist's tumor” and the “great masquerader” because it is not easily recognized clinically due to its multiple systemic manifestations: very common symptoms are absent, and the signs of a relatively common paraneoplastic syndrome are varied and may be difficult to identify as such.(14, 48, 68)

The “classic triad” is well known: gross hematuria, flank pain, and a palpable abdominal mass. However, only in a few cases (in less than 10%) are all three symptoms actually present, not least because an increasing number of tumors are detected at an early stage, and so it is considered obsolete to expect this pathognomonic configuration.(48) Nevertheless, individually, they remain the most important signs and symptoms that occur in 50–60, 40 and 30–40 percent, respectively.(69)

Symptoms are a rarity at an early stage and are more indicative of advanced disease and histologic subtypes with a poorer prognosis.(48, 50, 66) Interestingly, it is males and younger patients who are more likely to be diagnosed based on symptoms, as their counterparts (female patients and older patients) are significantly more likely to attend health check-ups.(66)

B symptoms such as fever, night sweats and weight loss may be present, they generally indicate a consumptive disease.(48, 65) Fatigue and weight loss are non-specific but may be more common than the classic triad, especially in patients with metastatic disease and therefore need careful attention.(67) 2% of male patients present with a usually left-sided non-reducing varicocele due to obstruction of the testicular vein.(48) Bilateral lower extremity edema may be an indicator of RCC as a sign of venous involvement.(66, 70)

At the moment of initial presentation 25–30% of patients already have metastasis (synchronous metastasis) due to the lack of early warning symptoms.(10, 48, 71) Common metastatic sites include lungs (50–60%), bones (in 30–40%), liver (in 30–40%), brain (in 5%) and adrenal glands.(7) But RCC, and ccRCC in particular, is also known to affect unusual sites (sinuses, penis, skin, etc.) and to spread widely.(3, 72) A few patients present
because of with signs and symptoms caused by metastasis, such as cough, bone pain, or deterioration in performance status (PS). (50)

Paraneoplastic syndrome (PNS) is a relatively common phenomenon in RCC patients, observed in 10–40%. It can facilitate initial diagnosis or indicate recurrence after nephrectomy. PNS refers to a set of extrarenal manifestations, signs and symptoms that are indirect, i.e. secondary to tumor disease. PNS includes constitutional symptoms such as the above-mentioned B-symptoms as an indirect consequence of tumor disease, but also specific metabolic, hematologic, neuromuscular, and hepatic syndromes. (50, 68, 73) Various mechanisms such as hormone production by the tumor and formation of immune complexes due to the tumor, explain the development of paraneoplastic symptoms but large parts of the pathophysiology remain unresolved. It seems reasonable that hormones (erythropoietin, renin) and metabolism (calcium) regulated by the kidney can be disturbed by RCC. (48, 68)

The most common PNS in RCC patients is hypercalcaemia, which may be clinically manifested by lethargy, nausea, fatigue, confusion, muscular weakness, lower reflex levels, constipation, and impaired level of consciousness. Recent-onset hypertension as PNS might be caused by increased renin secretion. Similarly, increased production of erythropoietin can lead to erythrocytosis and polycythemia. Stauffer’s syndrome is a liver dysfunction without liver metastases (elevations of liver enzymes such as ALT, AST, and abnormal levels of hepatic synthesis products such as prothrombin). Other symptoms include amyloidosis, neuromyopathies, and hyper-/hypoglycemia. The presence of PNS does not necessarily imply the presence of metastases, nor that the tumor is inoperable. (14, 48, 68)

Physical examination has a subordinate position. If the above findings are present, imaging and laboratory testing should follow quickly. (14, 70)

Laboratory findings

After the patient has been physically examined and a medical history has been taken, urine and blood should be tested. The most important laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, C-reactive protein (CRP), alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium and urinary microhematuria. These values allow conclusions to be drawn about renal function, differential diagnoses, possible PNS, or in
some cases have prognostic significance. Urine cytology can help to exclude malignancies of the bladder. (70)

**Imaging Investigation**

When renal cancer is suspected, preoperative imaging is the most important tool and, in most cases, the only one required for diagnosis and treatment planning, especially for the surgical approach. (70, 74, 75)

Renal cell carcinomas can vary widely morphologically. They range from small indolent lesions up to large aggressive masses, with local extension into adjacent tissues and metastases. (74) In part, it is possible to determine the histological subtype radiologically; ccRCCs in particular have characteristic features that can be recognized (heterogeneous consistency, high signal intensity on T2-weighted MRI, hypervascularity on contrast-enhanced computed tomography). (74-76) However, the primary purpose of imaging is to differentiate between benign and malignant tumors to determine whether surgery is necessary. But it remains one of the biggest challenges because in some cases it is barely possible to distinguish between them using imaging techniques. An example is angiomyolipoma (AML), the most common benign renal tumor; its main identifying feature is its high fat content, but this is absent in about 5%. These fat-free AML are hardly identifiable as such radiologically. Oncocytomas, which are the second most common benign tumor are difficult to distinguish from chRCC due to their strong similarity. (50, 74)

Renal cysts are very common and usually simple to identify by ultrasonography imaging (US); they are anechogenic and have well-defined margins. They can be classified into one of 5 categories based on their appearance in CT according to the Bosniak classification. Based on these categories, a conclusion can be made about malignancy and therapy. Bosniak I, II cysts are benign and do not require further treatment, Bosniak IV cysts are nearly certainly malignant and should be resected surgically. Bosniak IIF and III cysts cannot be clearly classified, they are malignant in 6–18% and 51–55%, respectively. Bosniak IIF cysts should be followed up (after 3 to 6 months), category III cysts should be removed by operation but can also be under active surveillance initially. Specifically for cystic lesions, magnetic resonance imaging (MRI) and contrast-enhanced US (CEUS) are recommended because they have higher sensitivity and specificity than CT. Biopsies of cystic lesions are generally not recommended. (50, 70, 77) However, if malignancy cannot be excluded with certainty, surgery must be performed. As a result, approximately 16% of resected renal
masses are benign. The most common of these are, in descending order, AMLs, oncocytomas, and benign cysts. More knowledge about optimal preoperative imaging modalities is therefore necessary to avoid as many unnecessary surgeries as possible.(48, 74, 78) In addition to reliable confirmation of malignancy, especially in small renal masses, tumors with less than 4 cm in diameter (SRM), identification of multifocal lesions in preoperative imaging is to date in many cases impossible.(75, 79)

It is also crucial to assess the size, stage, location, and organ confinement of the tumor as accurately as possible in order to plan for the surgical modality.(75) CT or MRI are best suited to diagnose RCC and show no significant differences in accuracy.(64, 70, 76)

Ultimately, it is important in preoperative imaging to identify lymph node and/or visceral metastases and to reliably predict the presence and extent of potential thrombus in the vena cava.(75)

Angiography can provide detailed information about vascular supply of the kidney but is no longer recommended for routine use. Nevertheless, it can be utilized in selected cases for surgical planning and is used for tumor embolization (see chapter “Treatment”).(48, 70, 75, 76)

**Ultrasonography**

If urologic symptoms are present, an ultrasound scan is often performed first, often followed by a CT scan if the findings are suspicious. (14, 80). US is widely accessible, including the peripheral area, inexpensive, and has negligible side effects, so basic knowledge of ultrasonography in renal masses is important practitioners in the general practice field. On ultrasonography, RCCs appear very heterogeneous. Solid, but also partially cystic and hypo-, iso- or hyperechoic appearance are possible.(80)

In recent years, the usefulness of CEUS has been increasingly pointed out in the literature. It uses a contrast agent composed of small gas bubbles of phospholipids that is harmless to the kidney, and of course CEUS has the advantage of being non-ionizing. It is particularly useful in differentiating SRM that are difficult to detect on conventional US, as well as identifying benign cystic lesions, which can help reduce unnecessary biopsies. It can also be used in FU examinations and to guide biopsies.(50, 79, 81)
Computed tomography

CT is the most important imaging modality when RCC is suspected and is mandatory in all cases for preoperative diagnostic, local staging, and resection planning according to all current guidelines.(14, 50, 64, 75, 76)

Unenhanced imaging of the abdominal region must be performed from the dome of the liver to the symphysis. For this purpose, usually 100–150 mL of iodinated contrast medium is administered intravenously to allow visualization of different tissue enhancement patterns. In the arterial, late arterial (corticomedullary and portal venous) and nephrographic phases, images should be obtained 15–30, 45–60 and 80–90 seconds after injection, respectively. RCC may appear iso-, hyper-, or hypodense, but the main diagnostic criteria is intratumoral enhancement.(14, 50, 64, 75) CT stages correctly in over 90% and is particularly useful for providing information on tumor size, function and morphology of the contralateral kidney and the condition of the adrenal glands and other solid organs.(75, 82) Particularly for SRM, it is difficult to make reliable diagnoses. Here CT is the gold standard with a sensitivity of 94% compared to 79% archived by ultrasound.(64, 83) In detecting minimally enlarged local lymph nodes, CT has a false-negative rate of 10%; MRI is superior in this regard.(75) In case of allergy to iodinated contrast media, MRT or also CEUS can be used.(76)

Magnetic resonance imaging

If involvement of the renal vein or inferior vena cava (IVC) is suspected, MRI must be performed. MRI is superior to CT for assessing the degree of extension of the tumor into the vein.(14, 48, 50, 76, 82) Precise knowledge of the cranial tumor-thrombus margin is important for planning the resection approach. The presence of IVC tumor thrombus has a significant negative impact on prognosis.(75, 80) For patients with a hereditary syndrome who require frequent radiological examinations, the lower radiation of MRI is an advantage.(70) Abdominal MRI is further indicated when there is a contradiction to intravenous CT contrast agent, e.g. because of an allergy or in pregnancy. (48, 76)

The combination of coronal and axial, T1- and T2-weighted images from the atrial level to the inferior border of the kidney allow accurate determination of tumor extent and detection of SRM.(64) Intravenous injection of gadolinium as a contrast agent to obtain contrast-enhanced images allows for better accuracy but in patients with acute hepatorenal syndrome or dialysis-dependent chronic renal failure it can cause nephrogenic systemic fibrosis, a rare condition associated with multiorgan fibrosis within weeks after the procedure (84).
**Diagnostics of metastases**

Any patient with renal cell carcinoma greater than 3 cm in diameter or locally aggressive growth should undergo chest CT to exclude pulmonary metastases and mediastinal lymph node involvement, as the likelihood of metastatic disease is high in this setting. For detection of pulmonary metastases, CT is the most accurate tool.\(^{(50, 64, 76)}\)

Imaging studies of the skeleton and brain should be performed only in the presence of symptoms or laboratory findings suggestive of metastases.\(^{(14, 76)}\)

If osseous metastases are suspected, whole-body CT (low dose) or MRI should be preferred to skeletal scintigraphy. Positron emission tomography (PET) CT should not be used routinely. Contrast-enhanced cranial MRI is the best tool for visualizing cerebral metastases and possible edema in the brain.\(^{(50, 64)}\)

**Biopsy**

The basic rule for biopsies is “no invasive diagnostics without a potential resulting consequence”. Accordingly, in the case of an unclear renal mass, a biopsy should only be performed if the result might have an influence on the therapy, therefore possible results and consequences should be discussed with the patient beforehand.\(^{(64)}\)

A percutaneous renal tumor biopsy (RTB) prior to treatment is used to histologically confirm and classify a malignancy.\(^{(14, 64)}\) A biopsy is essential, especially in SRMs, a high proportion of which are benign and, as discussed above, often not radiologically assessable. By performing biopsies, these benign tumors, as well as lymphomas, renal abscesses, and metastases from another primary tumor, can be excluded. As a result, up to 16% of surgeries can be avoided. If ablative therapy or active surveillance (AS) is planned, a biopsy should be performed when no pathologic report is yet available. In advanced and metastatic renal cell carcinoma, the tumor should be biopsied as well before cytoreductive surgery is planned or systemic therapy is initiated. In individual cases, targeted therapy may also vary depending on the subtype.\(^{(14, 50, 64, 85)}\)

For cystic tumors, the study landscape is mixed, but in view of the higher risk of biopsy failure, false-negative results, and possible tumor seeding, biopsy is not recommended except for Bosniak IV lesions with a solid pattern.\(^{(50, 64, 85)}\)
RTB can be performed on an outpatient basis. Under local anesthesia and ultrasound or CT guidance, at least two samples are extracted. Needle core biopsy has been shown to be more accurate than fine needle aspiration.\(^{(50, 85, 86)}\) A 18-gauge needle is used in coaxial technique to reduce tumor seeding.\(^{(64)}\) The specimen should be taken peripherally and from the primary tumor rather than from a metastasis.\(^{(50)}\)

RTB has a high diagnostic yield; Marconi et al. found sensitivity and specificity to be 99.1% and 99.7%, respectively, by meta-analysis. The histologic subtype usually corresponds to the surgical specimen, but statements about Fuhrman grading are less reliable. It should be noted that there are a small number of false-negative results.\(^{(85, 86)}\) A major problem is that approximately 15–22% of biopsies are nondiagnostic; endophytic, cystic, and hypoenhancing lesions are particularly affected.\(^{(50, 79, 85, 87)}\) Further diagnostic procedure after an unsuccessful biopsy is unclear, but it should be considered to repeat biopsy, as high diagnostic rates have been reported for re-biopsies.\(^{(50, 64, 87)}\)

RTB with its latest technology is relatively safe with low morbidity and very rare occurrence of complications. No cases of tumor seeding have been reported for RTB with coaxial technology.\(^{(64, 70, 85)}\) In particular, ccRCC is a well-vascularized tumor so mild perirenal and subcapsular hematomas may be commonly observed, but relevant bleeding requiring transfusion is rare. Development of significant pneumothorax occurs in less than 1% and is largely avoidable with proper technique.\(^{(70, 85)}\)

Histological differentiation in biopsies between oncocytomas and malignant chromophobe tumors is very difficult and often not clearly possible. 4% of RCC-suspected tumors resected surgically, oncocytomas.\(^{(5, 8, 61)}\) The final histopathologic diagnosis is derived from the results of the nephrectomy specimen.\(^{(14)}\)

**Molecular profiling**

The Cancer Genome Atlas program was founded in 2006 under the direction of the National Cancer Institute and the National Human Genome Research Institute. In this milestone genome project, major cancer entities have been genetically analyzed and information about somatic genomic and epigenomic alterations occurring in these malignancies has been listed in a database that is available to the public.\(^{(22, 88)}\) The insights gained into chromosomal alterations, gene mutations, copy number alterations, extent of DNA hypermethylation and gene expression have significantly expanded the understanding of the underlying tumor
biology of RCC. The presence of certain aberrations thus found has enabled research on molecular markers that have predictive value, e.g. in terms of patient survival and response to certain targeted therapies for specific genetic aberrations (49, 89). Molecular markers such as carbonic anhydrase IX (CAIX), VEGF, hypoxia-inducible factor (HIF), Ki67 and p53 could be used to improve prognostic modelling and individualize treatment decisions (35, 90-92). The new approach is promising, but there is no clear evidence of improved predictive accuracy using molecular markers compared with current prognostic systems and no external validation. The current RCC guidelines do not recommend the utilization of molecular markers for prognosis assessment in routine clinical use as their evidence is insufficient.(64, 70, 93)

Germline mutation testing

Germline mutation testing can be performed if a hereditary kidney cancer syndrome is suspected. Knowledge of genetic syndromes can help adjust diagnosis, treatment, and screening depending on specific recommendations for individual syndromes to improve outcomes.(45) Radiologic imaging should be performed more frequently in these patients to detect other primary carcinomas of the kidney and other organs early. If applicable, nephron-sparing surgery should be preferred to preserve renal function.(43, 44, 94) Certain characteristics are commonly observed in patients with hereditary syndromes, including younger age at presentation, family history of RCC, bilateral or multifocal tumors, and concomitant presence of other typical cancer manifestations (such as cerebellar hemangioblastoma in patients with VHL syndrome or pulmonary cysts in patients with BHD).(12, 43, 94) Also, certain histologic subtypes particularly associated with hereditary RCC syndromes.(12, 94) All of these findings should prompt a clinician to consider a hereditary syndrome and recommend genetic testing to the patient.(93) Unfortunately, there is no guideline for RCC that explicitly defines how to select suitable candidates for genetic testing, as is the case for breast and colorectal cancer.(12) Shuch et al. performed a detailed analysis of the age distribution of patients with renal cancer and discovered that patients with hereditary RCC syndromes are on average 27 years younger and therefore recommend considering germline testing in patients younger than 46 years of age.(12)
Prognosis

The prognosis of renal cell carcinoma is comparatively favorable, with a 5-year relative survival rate of 82.1% in men and 79.3% in women, which is relatively high compared to other tumor diseases and is currently increasing. (93, 95) Localized RCC can be cured by surgical resection. Unfortunately, early-stage RCC has few symptoms, so the diagnosis is often made at an advanced stage with inoperable tumors. The prognosis of locally advanced or metastatic RCC is still generally poor despite remarkable improvement in recent years. Up to 30% of operated patients suffer a recurrence. (35)

Prognostic Factors

This chapter will briefly review factors that affect prognosis in patients with renal cell carcinoma.

Stage

The tumor stage is the most consistent factor influencing prognosis in patients with renal cell carcinoma (RCC). Depending on the stage of the disease, the 5-year relative survival rate, for patients diagnosed with renal cell carcinoma between 1998 and 2019, for UICC stages I, II, III, and IV ranged from 98.1% to 89.0%, 73.3% and 17.8%, respectively, according to data from the German Tumor Registry of Munich. (95) Based on SEER data from 2010–2016, the 5-year relative survival rates for kidney and pelvic cancer for all stages, localized tumors (confined to primary site), regional tumors (spread to regional lymph nodes), and distant tumors (cancer has metastasized) in the United States were 75.2%, 92.6%, 70.4% and 13.0%, respectively. The age-adjusted mortality rate was 3.6 per 100,000 men and women per year for 2014–2018. (13) More specific and effective drugs have strongly prolonged median survival for patients with metastatic disease. (see chapter “Treatment”)

Histological characteristics

Histological subtypes are an independent prognostic factor (96). ccRCC has a poorer prognosis then nccRCC (96, 97). Most studies show that patients with chRCC vs. pRCC vs. ccRCC have a better prognosis (97, 98), but the prognostic advantage for chRCC compared with pRCC is controversial (96). A large retrospective study by Patard et al. that included more than 4000 RCC patients showed the same trend for lower stage, lower histologic grade,
lack of metastasis, and higher 5-year survival. The results are shown in the following table.(97)

<table>
<thead>
<tr>
<th></th>
<th>ccRCC</th>
<th>pRCC</th>
<th>chRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low stage (I to II)</td>
<td>50.3%</td>
<td>62.9%</td>
<td>74.8%</td>
</tr>
<tr>
<td>Fuhrman grades 1 and 2</td>
<td>55.8%</td>
<td>66.9%</td>
<td>68%</td>
</tr>
<tr>
<td>Distant Metastasis</td>
<td>21.5%</td>
<td>14.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>5-year OS in months</td>
<td>73.2%</td>
<td>79.4%</td>
<td>87.9%</td>
</tr>
</tbody>
</table>

**Table 4. Prognosis for different histological subtypes(97)**

In papillary RCC type 1, prognosis is better than in type 2.(70) Presentation of a sarcomatoid pattern can be found in all RCC subtypes and correlates with a poorer prognosis.(56, 70) Rare collector duct RCC (Bellini duct carcinoma) has a very poor prognosis with a median overall survival (OS) of 3 months (compared to 48 for ccRCC).(57) Eventually, the predictive value of histologic subtypes after adjustment for TNM stage and other covariates, however, remains nonsignificant.(96-98) Histologic grading is an independent predictive value for prognosis.(70, 99) Tumor necrosis is an independent risk factor and its percentage should be documented. The future implementation of tumor necrosis in the classification is discussed.(64, 100)

In addition to the aforementioned prognostic factors (TNM staging, histologic subtype, presence of necrosis, sarcomatoid and/or rhabdoid differentiation) ISUP consensus and WHO recommend reporting the presence of microscopic vascular invasion, description of non-neoplastic renal tissue, and ISUP nuclear grade (ccRCC and papillary RCC only). (63)

**Clinical Features**

In addition to the anatomical extend and histological characteristics, survival is strongly related to various clinical factors. The presence of symptoms is an independent predictor of prognosis in renal cell carcinoma and increases the risk of cause-specific death at each stage of disease.(97) Adverse prognostic factors also include a short interval between initial diagnosis and development of metastases, poor Karnofsky or Eastern Co-operative Oncology Group (ECOG) PS, high LDH, low serum hemoglobin, and high corrected serum calcium.(101, 102) Hematologic parameters as hemoglobin, platelet and neutrophil count
but also calcium and lactate dehydrogenase levels are prognostically relevant and have thus been included in several prognostic models.(93)

Prognostic Models

Multivariable prognostic models combining information on anatomic extent, histopathologic features, and various clinical factors have been designed to simplify and standardize risk assessment in patients with RCC. The use of validated prognostic models is more precise and accurate than the use of univariable prognostic factors.(93) The various nomograms should be used according to disease progression and therapy and can be used to counsel patients on prognosis, individualize FU, select treatment modalities in clinical practice, and determine eligibility for clinical trials. Numerous validated predictive models with different outcome variables (i.e. disease free survival (DFS), metastasis free survival (MFS), or OS) exist for different settings: i.e. before surgery, after surgical resection of a localized tumor (N0, M0), and for patients with metastatic cancer before initiation of systematic therapy. The routine use of risk models for localized disease in clinical practice is not recommended, but EAUss, although they may stratify patients for enrollment in clinical trials.(70) The main criteria for validation of prognostic models is the concordance index (C-index), which is defined as the increase in predictive accuracy over that of a univariable parameter with respect to its endpoint. Values from 0 to 1 are possible, with 1 being the optimum. Values between 0.5–0.7 represent low precision, 0.7–0.9 are acceptable and values >0.9 represent a very precise model.(93) Several models are applicable to patients of all stages, such as the Stage, Size, Grade and Necrosis Score (SSIGN score), they are mostly used for research purposes.(35)

Preoperative

For the preoperative setting, the Cindolo and the Yaycioglu model have been developed to predict the risk of recurrence in surgical planning.(103, 104) Both are relatively weak prognostically and, with a C-index of 0.589 for Yaycioglu and 0.615 for Cindolo only slightly superior to chance.(35, 105, 106) A working group from Montreal has published 5 nomograms for different settings, all named Karakiewicz.(93) The preoperative Karakiewicz model is superior to that of Yaycioglu and Cindolo; an external validation indicated a concordance of 86.8% at both 2 and 5 years.(107) The nomogram integrated age, sex, clinical T category, presence of metastasis, tumor diameter and symptoms into its model which predicts cancer-specific survival (CSS).(93)
There are two other scores for the preoperative setting (R.E.N.A.L. and PADUA) that provide predictions of surgical outcome. Both algorithms use comprehensive information about the anatomical behaviour of the tumor from the CT scan, to estimate the risk of bleeding and postoperative complications after partial nephrectomy order to provide patients with advice and select them for surgery in an evidence-based manner.

**Postoperative**

The following nomograms are designed to improve the prognosis of patients who have had localized RCC and have already undergone surgery. All postoperative nomograms use the parameters T-stage and grading combined with other factors, but they have different endpoints. The University of California, Los Angeles Integrated Staging System (UISS) was introduced by Zisman et al. in 2001 with the aim of predicting survival (2- and 5-year OS) in postoperative renal cell carcinoma patients. In the following year, the authors modelled the algorithm of the existing system and expanded its capabilities. Since then, it has been able to determine additional endpoints such as disease-specific survival, freedom from recurrence and freedom from progression, as well as a user-friendly “decision box” that guides clinicians through the process. It was externally validated several times and achieved satisfying results. In general, the concordance indices vary widely in different externally validating studies. In the aforementioned large-scale comparative study by Petard et al. the UISS system was confirmed as a sufficient predictor of survival and achieved a C-index of 0.809, although it has a slight weakness in accuracy in metastatic patients. The Leibovich model was published in 2003 and, along with the UISS system, is the most commonly used postoperative prognostic model for adjuvant trials. Probably the most useful prognostic model, with very good predictive accuracy, is Karakiewicz's postoperative nomogram. In several internal and external validations, the concordance is always above 0.8. In a comparative study by Tan et al. the Karakiewicz nomogram exceeded the Kattan nomogram, the Sorbellini nomogram, and the Leibovich model. Lastly, the Kattan nomogram has questionable validity, with external validations yielding values of 0.607 and 0.807 as C-indices. The following table compares different predictive models for initially localized diseases.

<table>
<thead>
<tr>
<th>Leibovich</th>
<th>UISS</th>
<th>Karakiewicz postoperative</th>
<th>Kattan</th>
</tr>
</thead>
</table>

<p>| | | | |
| | | | |</p>
<table>
<thead>
<tr>
<th>Setting</th>
<th>Only ccRCC, only localized tumors</th>
<th>All histological subtypes</th>
<th>All histological subtypes</th>
<th>ccRCC, pRCC, chRCC, only localized tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint(s)</td>
<td>MFS</td>
<td>OS, tumor-specific survival, freedom from progression</td>
<td>CSS, OS, freedom from recurrence</td>
<td>5-year progression-free survival (PFS)</td>
</tr>
<tr>
<td></td>
<td>- N (pN0/ pNx vs. pN1-2)</td>
<td>- N category</td>
<td>- N and M status (0 vs. 1 each)</td>
<td>- Diameter</td>
</tr>
<tr>
<td></td>
<td>- Diameter (&gt; vs. &lt;10 cm)</td>
<td>- M category</td>
<td>- Diameter</td>
<td>- Histological subtype</td>
</tr>
<tr>
<td></td>
<td>- Fuhrman grade</td>
<td>- ECOG PS</td>
<td>- Fuhrman grade</td>
<td>- Symptoms</td>
</tr>
<tr>
<td></td>
<td>- Tumor necrosis</td>
<td>- Fuhrman grade</td>
<td>- Symptoms</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Comparison of different postoperative prognostic models (93)

Other scores such as the SSIGN score by Frank et al.(113), the Sorbellini nomogram of the MSKCC group and the papillary nomogram should only be mentioned by name here.

Metastatic disease

Unlike for localized cancers, the guidelines give a strong recommendation for the use of prognostic models in patients with metastatic disease, but without further specification (35). In 1999, the first multivariable prognostic model was published by Motzer et al. from Memorial Sloan-Kettering Cancer Center, the MSKCC score for patients with metastatic renal cell carcinoma.(102) It was updated in 2002, changing one of the original prognostic factors. It was developed during the cytokine era of mRCC, but is still applicable in patients treated with targeted therapies,(111, 114) although its accuracy here is not very high (c-index 0.52-0.65).(115)

The first prognostic model developed specifically for patients to be treated with targeted therapies was developed by Heng et al. using data from the International Metastatic Renal
Cancer Database Consortium.(64) It is a dynamic score, allowing values for clinical variables that change over the course of the disease to be reassessed. It can be used for both the naïve and second-line treatment setting. It is used in common recommendations for the management of e.g. systemic treatment and cytoreductive nephrectomy in synchronous mRCC patients.(111)

In addition to the International Kidney Cancer Working Group model (IKCWG) model, which is one of the 3 most important models in advanced RCC stages, there are numerous others, such as the Cleveland Clinic Foundation Model CCF and French model, which are not all mentioned here.(93)

In 2013, Heng et al. published a representative validation study comparing all major prognostic models for mRCC (MSKCC, Heng, IKCWG, CCF, French model). Interestingly, there is hardly any difference in the predictive power of the different models. All concordance indices are between 0.640 and 0.664.(93, 116)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MSKCC 2002</th>
<th>Heng</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic factors</td>
<td>- Karnofsky PS (&lt;80 %)</td>
<td>- Karnofsky PS (&lt;80 %)</td>
</tr>
<tr>
<td></td>
<td>- low hemoglobin</td>
<td>- low hemoglobin</td>
</tr>
<tr>
<td></td>
<td>- high albumin-corrected calcium (&gt;10 mg/dl)</td>
<td>- high albumin-corrected calcium (&gt;10 mg/dl)</td>
</tr>
<tr>
<td></td>
<td>- Period from initial diagnosis to start of</td>
<td>- Period from initial diagnosis to start of</td>
</tr>
<tr>
<td></td>
<td>systemic therapy (≤12 months)</td>
<td>sunitinib (≤12 months)</td>
</tr>
<tr>
<td></td>
<td>- LDH (&gt;1.5 above normal)</td>
<td>- Platelet count higher than normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neutrophil count higher than normal</td>
</tr>
<tr>
<td>Risk groups</td>
<td>3 risk groups: favourable (0 factor), intermediate (1 or 2 factors) and poor (3–5 factors) (with median OS of 20, 10, and 4 months)</td>
<td>3 risk groups: favourable (0 factor), intermediate (1 or 2 factors) and poor (3–6 factors)</td>
</tr>
</tbody>
</table>

Table 6. Comparison of different prognostic models for mRCC (35, 93)
Follow up Management

Recommendations for FU management in RCC vary widely between guidelines and can be based on little existing evidence. However, the objective of the interventions is clear: to monitor and control the development of renal function, possible post-operative or therapy-related complications, recurrence, progression and metastasis. For this purpose, a medical history, physical examination, serum studies and imaging (CT/MRI of the abdomen and pelvis, chest CT, and US) should be performed. The main point of contention is the interval between tests in asymptomatic patients. No specific tumor marker is known; only an increase in inflammatory parameters, transaminases or alkaline phosphatase can unspecifically indicate metastasis. There is agreement that the intensity of FU in non-metastatic patients, depends on the individual risk of recurrence of the patient. Nevertheless, the different guidelines use different risk stratification tools. Before planning an imaging procedure, it is important to consider whether and how its result will influence the therapy discussion, because the general rule for diagnostics with radiation exposure is: “No examination without possible consequences”. For a rough guide in timing the FU, one should keep in mind that 70% of metastases occur within 3 years of primary therapy and only a maximum of 10% of metastases occur after more than 5 years, making the first 3 years particularly important. While in high-risk patients follow-up at 3–6 month intervals for 2 years may be appropriate, in low-risk patients an annual CT scan may be sufficient. In the end, however, it is not proven at all whether regular FU prevents symptomatic local recurrences or improves survival. Important and recommended for every patient is follow-up rehabilitation after oncological treatment, the offer of psycho-oncological care and the handing out of the patient guidelines.

Treatment

RCC is a classically surgical cancer, although more minimally invasive procedures and kidney function-sparing interventions are now available. Contrary to what is often assumed, RCC is not radiotherapy-insensitive, and certain applications are being investigated, nevertheless, it plays a secondary role. Chemotherapeutic agents no longer play a role in the therapy of RCC. For advanced stage patients, prognosis has improved significantly in recent years since new generation drug agents have been introduced.
Local Management

In the localized stage, curative surgery is possible by complete resection of the tumour, which is the desirable ideal case. Due to better developed techniques and tools, a partial nephrectomy is now often enough as it recognised that a clean tumour margin is sufficient. Other approaches such as initial waiting in multimorbid patients or ablative procedures are increasingly being explored and offer alternatives.(47) Therapeutic decisions should therefore be made taking into account the individual characteristics of the patient and his or her priorities. The R.E.N.A.L. and PADUA Nephrectomy Scores systems can help with treatment planning by determining the likelihood of surgical complications in PN (see chapter “Prognostic Models”).(1, 50)

Surgery

In the past, radical nephrectomy (RN) was performed, it includes removal of the kidney, perirenal fat, and gerota fascia.(120) Recently, partial nephrectomy, in which only the tumour with a tumor-free margin is removed, has become increasingly common. For a long time, PN (also referred to as “nephron sparing surgery”) was underused because of criticism of its effectiveness, possible risks and because PN is technically more demanding and requires more experienced surgeons.(121, 122) One of the pioneering studies was a prospective randomized control trial (RCT) by Van Poppel et al. at the European Organization for Research and Treatment of Cancer (EORTC) comparing PN and RN in patients with T1-T2 N0 M0 RCC. Doubts regarding oncologic outcome were eliminated: Both, RN and PN, have a similar, very favourable oncologic outcome in tumors up to 7cm.(123-125) However, PN has a slightly higher risk of complications as perioperative bleeding (3.1%) and urinary fistulas (4.4%).(126) PN, nevertheless, allows the best possible preservation of renal function,(127, 128) while RN poses a significantly higher risk of causing CKD (chronic kidney disease) than PN in tumors smaller than 4 cm.(122) PN is therefore recommended in small, easily resectable, incidentally discovered organ-confined tumors measuring up to 7 cm, if technically feasible.(14, 48)

Instead of open surgery, a laparoscopic approach is also available to perform both RN and PN. Oncologic results (OS and CSS) and functional outcomes are equivalent for open vs. laparoscopic surgery.(125, 129-131) Laparoscopy, also called key hole surgery for its with small hole incisions results in less blood loss and shorter hospital stay(131-133) but is
technically the more difficult procedure requiring more experienced surgeons.(129) There is insufficient data for the use of robotic-assisted nephrectomy.(64)

Lymph node (LN) dissection without evidence of involvement is not recommended in local disease because it does not bring survival advantage compared to RN, only, in high-risk patients it can be considered though.(14, 134, 135) In metastatic disease or when abdominal CT showed LN invasion extended lymph node dissection is important for staging correctly.(70) LN enlargements from 1 to 2 cm may be caused by reactive hyperplasia but lymph nodes of 2 cm in diameter or more nearly always contain metastases and should always be removed surgically.(48)

Likewise, adrenalectomy should only be performed if there is a clinical suspicion of invasion of the adrenal gland by CT imaging suggesting so (14, 70)

Preoperative renal artery embolization (RAE) used to be a common procedure but is no longer recommended. In the palliative setting (inoperable or unresectable renal cell carcinoma) RAE can reduce symptoms as haematuria, reduce flank pain and stabilize hemoglobin levels.(136, 137)

**Nonsurgical management (NSM)**

For small cortical tumors (≤3 cm) and patients with high comorbidity and/or age, who are poor candidates for surgery because of contradictions as fragility, high surgical risk, solitary kidney, renal insufficiency, hereditary RCC, or multiple bilateral tumors there are nonsurgical procedures available.(14) Primary waiting, called active surveillance or various ablative procedures are alternatives that may be suitable for certain groups of patients. However, it should be clearly noted that no prospective data exists only observational studies with certain selection bias regarding these procedures have been performed.(64, 125, 138)

**Ablation**

Radiofrequency ablation (RFA) and cryoablation (CA) are the most common best-studied ablative procedures (133). RFA is a local technique that destroys tissue inserting an applicator percutaneously guided by imaging. High-frequency electricity generates heat and causes thermonecrosis. In CA, a cold applicator is inserted into the tumor percutaneously or after exposing the kidney laparoscopically. Temperatures below -60 degrees cause coagulation necrosis and tumor destruction.(64)
Kunkle et al. analyzed a total of 99 studies representing 6,471 lesions and compared CA and RFA with PN. Ablative procedures had slightly more local progress and an equal rate of progress to metastases (138). The large-scale comparative study by MacLennan et al. found equal CSS, minimally fewer metastases, and also minimally more local recurrence for RFA compared with PN.(125) Incorporating these and other studies, in summary, NSM is probably similar or slightly inferior to PN.(139, 140) Thus, PN should be preferred except in appropriate high-risk patients because more experience and more reliable data exist. The effectiveness is very similar for CA and RFA and is 89% and 90% respectively.(133)

In stereotactic ablative body radiotherapy, hypofractionated doses of radiotherapy are applied from different beams (angles) in multiple sessions to maximally preserve surrounding tissue. First results are comparable to other ablative techniques, but not enough studies are available, especially regarding the exact procedure.(141) There is little evidence on microwave ablation and highly focused ultrasound hence not discussed in detail here.(14, 64)

**Active Surveillance**

AS is possible for small tumors that have not shown an aggressive growth pattern (invasive growth) in a previously obligatory biopsy. The patient should be informed that organ-preserving tumor therapy may no longer be possible in the event of progression and that curative salvage therapy is lacking in the case of metastases.(14, 64)

In RCC patients with short life expectancy, waiting is a legitimate approach because progression/growth and metastasis rates are low.(77) According to a multicentric prospective phase 2 clinical trial for AS by Jewett et al. and other studies, progression occurs in one third of cases and progression to metastatic disease in only 1–2%. The average growth rate is slow (about 0.31 cm/year) and permits AS. Tumors that metastasize at a later time grow faster (0.8 cm/year).(142-144)

However, in contrast to other tumors, there are no objective criteria for the selection of adequate patients in RCC, nor is there a well-defined scheme for the management of AS.(64) Regular FU imaging is recommended at an interval of 3 months for the first year followed by a decreasing frequency to annual imaging by 3 year and thereafter. If the tumor diameter increases rapidly or exceeds 4 cm, treatment should be started.(144)
Systemic Therapy Agents

Systematic therapies are only used in patients with inoperable advanced tumours. In the past, cytokines were used, but 15 years ago they were replaced by new generation agents, i.e. targeted therapies and targeted immunotherapy, which have significantly improved the prognosis of mRCC.

Adjuvant therapies

No clinical approval by the European Medicines Agency exists for neoadjuvant or adjuvant chemotherapies in patients with RCC in the European region. In the USA, sunitinib has been approved for the adjuvant setting. It is based on the S-TRAC trial, which found a DFS benefit without improvement in OS after adjuvant administration of the tyrosine kinase inhibitor (TKI). (14, 145) Other studies could not reproduce this benefit but showed high risk of adverse events due to excessive toxicity. (146, 147)

Chemotherapy

RCC is to resistant to most chemotherapies because it contains high levels of the multidrug resistance protein P-glycoprotein. Due to the very low response rates, chemotherapy is no longer used for mRCC. (65, 71)

Cytokines

Until the 1980s, attempts to treat RCC with hormone therapy and chemotherapy were unsuccessful. Cases of single spontaneous remissions in mRCC suggested an immune-mediated recovery, hence trials started to boost the non-specific immune system by cytokine administration. (148)

The two most important cytokines in RCC therapy are interferon alpha (IFN-α) and high-dose interleukin-2 (IL-2). (149) Until 2004, they were the standard first-line therapy. (64, 118)

Coppin et al. from the Cochrane Collaboration published a meta-analysis of all RCTs in which patients with advanced renal cell carcinoma were given immunotherapeutic agents. For this purpose, 53 studies involving 6117 patients with mRCC were analyzed. The results showed a modest OS benefit of 4.8 months with IFN-α compared with non-immunotherapeutic agents. Partial or complete remission was achieved by cytokine therapy
in only 12.9% of patients, but 28% of these had complete remissions. (148) Other studies confirm equally low objective response rates of about 10–20%. (64, 120, 150) Durable effects and complete remissions were a huge advance but still the vast majority of patients did not respond to therapy. Also, patient-centered endpoint benefits were lacking and toxicity was high. (148) Grade 3 and 4 toxic effects occurred in 36% of patients on IFN-α, (150) and median survival in patients with advanced RCC receiving interferon alfa was nevertheless only 1–1.5 years. (20, 150) Combination therapy of IFN-α + IL-2 + fluorouracil resulted in higher overall response rates but no OS/PFS benefit and serious adverse events were reported that may affect survival, grade 3 and 4 AEs occurred in 56% instead of 36%. (148, 150)

Because better alternatives are now available, they are no longer used as standard of care, but in certain circumstances they may be a second choice option in first-line therapy of RCC. (14) However, IFN-α monotherapy is not recommended, as a combination of bevacizumab and low dose IFN-α is more effective. (64, 151) High dose IL-2 is effective but inferior to immune checkpoint inhibitor combination therapy due to high toxicity. (70)

Targeted Therapy

Around 2005 targeted therapy (TT) agents were introduced, that act more specifically than previous cytokine or chemotherapies on tumor cell activity. TT refers to anti-VEGF drugs and mTOR inhibitors described in more detail below. First, agents targeting VEGF emerged. With this new antiangiogenesis approach, a therapy success (remission or stable disease) was achieved in a much larger proportion (60–70%) of patients. (152, 153) Sorafenib was the first anti-VEGF TKI approved for treatment of mRCC, acting in multiple other targets as well. Sunitinib could provide a better PSF, a higher overall response rate, and more quality of life compared to IFN-α in patients with metastatic disease according to a study by Motzer et al. in 2007 including 750 patients. (154) Pazopanib, tivozanib, and axitinib are other TKIs acting by inhibiting the VEGF receptor. (155) Bevacizumab is a monoclonal antibody, a competing agonist for VEGF receptors inhibiting the VEGF pathway. (155) All the mentioned anti-VEGF agents suppress angiogenesis, an important target, as RCC is a highly vascular tumor, especially in tumors with VHL mutations that activate the hypoxia-induced pathway (see chapter “Pathology of different histological subtypes”). By suppressing VEGF activity, the blood supply of the tumor is inhibited and thus the tumor growth, whereby stable disease or shrinkage is to be aimed at. (152) Inhibitors of mTOR are targeting a different known pathway in RCC pathogenesis (see chapter “Pathology of different histological subtypes”). mTOR is a central regulator of cell regulation, promoting tumor growth through
proliferation and angiogenesis. Temsirolimus and everolimus address this mechanism to hinder progression. (152) All TT agents of both groups improved the PFS and/or OS in RCTs for patients with mRCC although complete remission is rare and therefore TT is not curative in most cases. (14, 152, 154, 156, 157)

Side effects are a result of the fact that the drug does not act selective to cancer cells. The most common adverse effects are hypertension, fatigue, diarrhea and hand–foot syndrome for anti VEGF agents and mucositis, hyperglycemia, hyperlipidemia and rarely interstitial pneumonitis for the mTOR inhibitors. (152)

The introduction of TT prolonged the median OS for mRCC patients from 13–18 months (in the cytokine era) to 43.2 months for patients with a favorable risk profiles, 22.5 months and 7.8 months for patients with intermediate and unfavorable risk profiles, respectively. While a simultaneous combination of agents leads to excessive side effects, sequential drug therapy can be beneficial. (118) Drug resistance plays a major role in TKIs, primary resistance could explain the 20–30% non-responders. Acquired resistance often develops in the first year of therapy and limits the efficiency. (153) A health-related quality of life benefit was not tested in placebo-controlled studies. (155)

**Checkpoint Inhibitors**

Immunomodulation is an important approach in RCC, because typical for this immunogenic tumor is the prominent immune cell invasion of T cells, natural killer cells, dendritic cells and macrophages (see chapter “Pathology of different histological subtypes”). However, the host immune response is dysfunctional and unable to control the tumor because it is inhibited by it. Various agents are used to try to harness this natural immune response. Attempts to boost the immune response have already been made in a non-specific manner by administering cytokines, which mediate the immune response. But clinically relevant responses were missing, because the tumor is able to inactivate the immune response.

Nivolumab is a human monoclonal antibody that binds to the PD-1 receptor as a competitive antagonist and thus blocks the PD signalling pathway, reversing tumour-induced T-cell suppression and thus tumour immunity (see chapter “Pathology of different histological subtypes”). Immune checkpoint inhibitors such as nivolumab hence act more specifically than cytokines. (149)
The largest single-agent nivolumab trial in RCC was conducted in 2015 by Motzer et al. 821 patients received either nivolumab or everolimus after first-line anti-VEGF treatment. Objective response rate was 25% versus 5%, median OS was 25 versus 19.6 months, and treatment duration was 5.5 versus 3.7 months for nivolumab and everolimus, respectively, with no significant difference in PFS. This led to the approval of nivolumab by the US Food and Drug Administration.(158)

Nivolumab has a manageable safety profile. Immune-mediated adverse effects include pneumonitis, colitis, hepatitis, nephritis, renal failure, hypothyroidism and hyperthyroidism.(149) Compared with everolimus, grade 3–4 adverse events occurred in 19% instead of 37% of patients, leading to discontinuation in 8% vs. 13%.(158) Combinations with other agents, such as angiogenesis inhibitors or with other immune checkpoint inhibitors, have demonstrated higher response rates but at the cost of increased toxicity.(149) Checkpoint inhibitor therapy is not recommended as single-agent in first-line treatment.(70) Ipilimumab is an antibody that targets the immune checkpoint protein cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). The combination of ipilimumab + nivolumab was compared with sunitinib in an RCT by Motzer et al. Median OS and overall response rate were significantly better for intermediate- and poor-risk patients who were in the ipilimumab + nivolumab group.(159)

Stage dependent therapy choice

The choice of therapy depends besides the stage of the disease on the patient’s health characteristics, previous therapies and ultimately on the decision of the doctor and the patient.

Non-metastatic disease

For localized tumors, complete surgical removal is the gold standard.(39) For T1 organ preservation is recommended, for T2 tumors it was controversial but is meanwhile recommended.(14, 118) Crucial to this decision is also the consideration of the patient’s comorbidities. For T1a tumors, NSM is a valid alternative. For patients with certain conditions requiring preservation of renal function, e.g. solitary kidney, synchronous bilateral RCC, compromised renal function, and vHL, PN is strongly recommended even in larger tumors, without limiting size.(1) Whether PN is performed openly, laparoscopically, or robotically assisted is up to the surgeon. RN for T2 tumors should be carried out.
laparoscopically as long as it does not negatively affect the outcome.(70) In patients with contraindications to surgery, RAE can provide palliation. In T3 tumors, curation may still be possible by radical tumorectomy.(120) However, removal of tumor thrombi carries a high risk of complications during surgery. There are no solid guidelines for the procedure in tumors with vein involvement as there are only retrospective studies with bias and confounding. For T4 tumors without metastases, RN is recommended when technically feasible.(14, 120)

**Metastatic disease**

Stage IV disease includes all patients with T1 and/or M1 and are almost always incurable.(120) Therefore, treatment is mostly intended for palliation rather than curation (118).

**Systemic therapy**

In asymptomatic patients with a low tumor burden, an initial phase of observation is possible, as early treatment does not seem to be beneficial over delayed treatment.(14) The amount of information on therapy recommendations for mRCC and related studies cannot be fully summarized here. The following two sections therefore only provide a brief orientation. Drug efficacy and eventually resistance should be evaluated regularly in order to adjust the therapy if necessary. For this purpose, a CT scan should be performed every 2–4 months.

RECIST (Response Evaluation Criteria in Solid Tumors) is the most used tool to objectify the response of a tumor to systemic therapy, first release in 2000. Currently, the updated version RECIST 1.1 is utilized, in order to describe the treatment response in a standardized form.(14, 160, 161)

**First-Line Treatment**

Standard treatment in therapy naïve patients with metastatic ccRCC is based on the patient's prognostic profile according to Heng score risk stratification. First line therapy is usually based on a TKI, whereby sunitinib and pazopanib are the most commonly used for patients with a good risk profile.(14) According to recommendations of the European Society for Medical Oncology (ESMO) guidelines bevacizumab + IFN-α and tivozanib are alternatives. All four variations are superior in PSF over either IFN-α or placebo in phase III trials.(14, 151, 154) For the intermediate- and poor-risk population, combination therapy with at least one checkpoint inhibitor such as nivolumab plus ipilimumab should be given if possible.(14, 159)
Second-Line-Treatment
If the therapy is not successful after completing the first line therapy (progression or metastasis), the second line therapy usually requires the use of a different drug. After initial TKI administration, a checkpoint inhibitor should be tried when available, and vice versa, a TKI should be given after unsuccessful initial treatment with nivolumab plus ipilimumab.(14)

_Cytoreductive nephrectomy (CN)_
In mRCC, initial CN is often performed before applying systemic therapy.(162) For certain patient groups, CN is recommended but studies are weak.(14, 64) The idea is to reduce the amount of cancer cells to avoid progression and ultimately improve survival. mRCC patients with IFN-α therapy had a delayed time to progression and longer survival if they received CN beforehand.(163, 164) However, the two landmark clinical trials by Mickisch et al. and Flanigan et al. included only patients with good PS of 0 or 1.(120) In the VEGF era initial CN also seems to show a benefit only for patients with good PS. The CARMENA trial found sunitinib alone not to be inferior to CN + sunitinib in 450 mRCC patients with intermediate or poor PS (165). A retrospective study by Mathieu et al. compared systemic treatment (sunitinib, sorafenib, temsirolimus, interferon, bevacizumab, or IL-2) vs. initial CN + system treatment. OS was longer in the CN group (OS 16.4 vs. 38.1 months, P <0.001), but was only significant among patients with PS 0 or 1 (16.7 vs. 43.3 months, P = 0.03). In addition, it contains the selection bias of a retrospective study; the patients in the non-CN group were older and had poorer PS.(166) Empirical data from an RCT showing the benefit of CN is lacking. But other than improving the oncologic outcome, it can improve life quality and alleviate symptoms caused by the tumor and its ectopic hormone production, and can have a positive psychological effect as well.(120, 162) The decision whether or not to perform cytoreductive nephrectomy must therefore be made on an individual basis, based on factors in favour of CN (symptomatic primary tumor, paraneoplastic syndrome) and those against (contraindications to surgery, high comorbidity), the requirement being good or moderate PS.(64, 162)

_Local treatment of metastases_
In addition to systematic therapies and CN, there is the option to treat metastases locally. Metastasectomy or various radiotherapies can prolong survival in certain patients or intervene symptomatically, i.e. palliatively
Metastasectomy
In RCC, metastasectomy plays a more important role than in other cancers and is often applied. Better oncologic outcomes have been observed after resection of metastases.\(^{118}\) In this context, for ethical reasons, prospective RCTs cannot be conducted in which a patient group would be deprived of metastasectomy. Therefore, the evidence for metastasectomies is limited to retrospective studies containing major selection biases.\(^{14, 119}\) Because there are no guidelines for patient selection, a multidisciplinary decision must be made on a case-by-case basis.\(^{64}\)

If a metastasectomy is considered, the different possible configurations of metastasis must be taken into account. Most research has been done on metachronous solitary metastases. In this case, a metastasectomy, regardless of the affected organ system, is recommended if the patient is suitable for surgery, as long as a R0 resection seems possible, although the level of evidence is very low.\(^{64, 118}\) Long-term remission rates of up to 30%, prolonged OS and CSS can be achieved in certain patients.\(^{14, 48, 120, 167-169}\) Kavolius et al. conducted a large comparative study in the era of Targeted Therapies comparing the outcomes of 278 patients with metachronous mRCC whose metastases were either completely removed, partially removed, or not operated on. The 5-year survival was 44%, 14%, and 11%, respectively.\(^{169}\) The study also suggests that repeated metastasectomy is possible.

Resection can also be performed for metachronous onset of multiple metastases in a single organ system. According to Van der Poel et al., OS does not differ after resection in patients with solitary or multiple metastases.\(^{64, 170}\) Radiotherapy may be considered alternatively in this case. Unfortunately, the prognosis for patients with synchronous metastases is generally poor, even when the primary and metastatic sites are both resected aggressively; hence, the role of metastasectomy here is unclear.\(^{64}\)

Alt et al. studied 887 RCC patients who underwent nephrectomy with multiple metachronous metastases. Complete resection was possible in 125 patients (4%). In this group, disease-free survival was 4.8 years compared with 1.3 years in the group without complete resection. The 5-year CSS was 32.5% after complete resection versus 12.4% without complete resection, and for lung-only metastases the difference was even greater at 73.6% vs. 19%.\(^{171}\)

Adjuvant systemic therapy following metastasectomy is not recommended.\(^{14}\) Long disease-free interval (>12 months) from the time of nephrectomy to the appearance of metastases has a significant benefit on the success of metastasectomy.\(^{120, 169, 170, 172}\)
Patients with solitary pulmonary metastases have the best results from metastasectomy. Pulmonary metastasectomy is safe and it also has the most evidence.(170, 171, 173-175) Auch bei Patienten mit Hirnmetastasen kann die Operation zur Palliation und Behandlung dienen.(176)

Radiotherapy
In patients with oligometastatic disease with only one organ system affected, where metastasectomy is technically difficult, R0 resection is not possible or other contradictions against surgery exist, radiotherapy is a valid alternative to metastasectomy. Particularly in patients with brain or bone metastases, radiotherapy may provide a survival benefit or symptom relief (64, 118). The potential benefits and risks of morbidity from radiotherapy should be assessed individually and discussed with the patient.(118) Possible modalities include high-dose external radiotherapy, radiosurgery, or stereotactic radiotherapy. Stereotactic body radiotherapy has low toxicity (<5%) at a high local control rate at up to 90% following RECIST criteria.(177, 178) In patients with new emerged lesions, it is important to consider that radiotherapy, unlike metastasectomy, does not allow histologic confirmation when metastasis is suspected.(64) In patients with brain involvement, local control rates averaging 85% can be achieved with intracranial stereotactic radiosurgery.(167) For palliative patients with bone metastases local radiation therapy of affected bony lesions is often very effective in alleviating pain.(64)

Aims of this study
Systemic antineoplastic therapies such as tyrosine kinase inhibitors and immune checkpoint inhibitors have significantly improved outcomes of patients with mRCC.(179) Although these treatments can induce tumor responses, delay disease progression,(180) preserve quality-of-life,(181) and improve OS,(158) few patients achieve long-term remissions and mRCC still remains a usually fatal disease.(182) Metastasectomy, i.e. surgery with the intent to remove most or all metastatic lesions, is a frequently practiced strategy in patients with mRCC.(170) Retrospective series have demonstrated that adequately selected patients can experience long-term remissions and favorable survival following metastasectomy. For example, in a meta-analysis by Zhao and colleagues pooling 16 studies on pulmonary metastasectomy in mRCC, a favorable 5-year OS estimate of 43% was observed.(172) Moreover, a recent systematic review of 56 retrospective studies by Ouzaid and colleagues reported a better OS after metastasectomy as compared to treatment concepts without
metastasectomy. However, due to the retrospective and mostly uncontrolled and non-comparative design of the currently available data as well as the absence of any randomized data, the magnitude of benefit of metastasectomy versus treatment without metastasectomy for overall survival in patients with mRCC remains unclear. To improve the understanding about the potential role of metastasectomy for treating patients with mRCC, more data are needed.

Analysis of observational data is an increasingly popular way to explore potential treatment benefits in the absence of randomized data or in settings where randomized studies are infeasible for ethical or logistical reasons. However, a comparison of patients with mRCC with and without metastasectomy using retrospective data has a high inherent risk of bias, because patients are likely selected by their treating physicians and surgeons for metastasectomy according to favorable prognostic criteria, such as low metastatic load, technical feasibility of resection, good performance status, and longer disease-free interval between index nephrectomy and metastasis onset. Consequently, a naive comparison of OS outcomes between mRCC patients who did and did not undergo metastasectomy has a high risk of overestimating the “true” effect of metastasectomy in this setting. Biostatistical research has brought forward comparative effectiveness research methods such as propensity score analysis to address this problem. In this observational study, we perform a propensity score analysis of patients with metachronous metastasis from RCC to quantify the potential benefit of metastasectomy towards OS as compared to treatment strategies without metastasectomy.

**Methods**

**Study Population and Design**

In this single-center, observational study, we retrospectively ascertained baseline and outcome data for all patients who underwent either partial or total nephrectomy at the Department of Urology, Medical University of Graz, Austria, between Jan, 2005 and Nov, 2018 (n=1,190). These data were collected from our electronic health record system as previously described. Subsequently, all patients who developed metachronous metastasis were included in the current analysis (Supplementary Paragraph 1, Supplementary Table 1, and Supplementary Figure 1). The baseline date was defined as the
date of diagnosis of first metachronous metastasis. Metastasectomies were not restricted to a particular site (i.e. we considered any-type metastasectomy including lung, liver, bone, and others). However, interventional procedures without surgical removal of tumor masses (e.g. radiofrequency ablation of lung or liver metastases) were not counted as metastasectomies. Primary endpoint of this study was death-from-any-cause within 5 years after the baseline date. Mortality status was obtained by central query of the Austrian Social Security Database. Data collection and analysis was approved by the local institutional review board (Ethics Committee of the Medical University of Graz, Austria; document number No. 31-082 ex 18/19, ethikkommission@medunigraz.at).

**Statistical methods**

All statistical analyses were performed using Stata 15.0 (Stata Corp., Houston, TX, USA). Continuous variables were reported as medians [25th-75th percentile], and count data as absolute frequencies (%). Differences in means and proportions between patients with and without metastasectomy were quantified using standardized mean differences (SMDs),(189) and tested with rank-sum tests, \( \chi^2 \)-tests, and Fisher’s exact tests, respectively. SMDs >0.30 were considered to indicate relevant imbalance between patients with and without metastasectomy.(189) Median follow-up times were estimated with the reverse Kaplan-Meier method.(190) Overall survival (OS) was estimated with Kaplan-Meier estimators, and compared between patients with and without metastasectomy using log-rank tests. Moreover, landmark analyses (landmark for metastasectomy set at 6 months after metastasis diagnosis) and Mantel-Byar tests were performed to reduce immortal time bias. Uni- and multivariable modeling of the primary endpoint (5-year OS) was performed with Cox proportional hazards models. Metastasectomy was also treated as a time-dependent variable to fully eliminate immortal time bias. We estimated the propensity score with a multivariable logistic regression model for being in the metastasectomy group using a stepwise backward elimination algorithm from all variables that had either a p-value for difference between the metastasectomy and medical therapy group of ≤0.10 or a corresponding SMD ≥ 0.10 (excluding one-by-one the variables with the smallest strength of association as indicated by the t-statistic). This base model was subsequently reduced by stepwise backward elimination to a final propensity score model with a pre-specified number of 10 predictor variables. The propensity score model development was performed after multiple imputation of missing data using a chained equations algorithm with 20 imputation datasets (imputation models on file with FP).(191) The propensity score was then defined as the probability of undergoing
metastasectomy conditional on the included predictor variables, and the inverse-probability-of-treatment-weight (IPTW) was defined as the inverse of the probability of receiving the treatment that the patient actually received.(189) To ascertain whether the IPTW achieved sufficient balance between patients with and without metastasectomy, SMDs were re-estimated after weighing the data with the IPTW.(189) Kaplan-Meier estimators and Cox proportional hazards models were then re-fitted after weighing for the IPTW.(185) The proportional hazards assumption was assessed with Schoenfeld tests and by fitting interactions between metastasectomy and linear follow-up time. Rates of death according to metastasectomy status in the presence of non-proportional hazards were estimated with a flexible parametric regression model with restricted cubic splines on the log(cumulative hazard) scale (4 degrees of freedom for the time-invariant effect and 3 degrees of freedom for the time-varying effect of metastasectomy, Stata routine stpm2).(184) Progression risks after metastasectomy were estimated with 1-Kaplan-Meier estimators (because no competing mortality event occurred prior progression events). Effect modification between baseline variables and metastasectomy were explored in a hypothesis-generating analysis by fitting interactions between metastasectomy and the respective variable in an IPTW-weighted, immortal-time-bias-adjusted Cox model. The full analysis code is available on reasonable request from the corresponding author.

Results

Characteristics of the study population

One-hundred-and-six patients were included in the analysis at the time of diagnosis of metachronous metastasis (Table 7).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=106)</th>
<th>No metastasectomy (n=70)</th>
<th>Metastasectomy (n=36)</th>
<th>p*</th>
<th>ΔS</th>
<th>ΔIPTW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 [62-76]</td>
<td>72 [64-77]</td>
<td>68 [60-74]</td>
<td><strong>0.026</strong></td>
<td>0.41</td>
<td>0.31</td>
</tr>
<tr>
<td>BMI (kg/m²)**</td>
<td>28 [24-319]</td>
<td>27 [24-30]</td>
<td>29 [25-32]</td>
<td>0.224</td>
<td>0.32</td>
<td>0.25</td>
</tr>
<tr>
<td>Female Gender</td>
<td>39 (37%)</td>
<td>22 (31%)</td>
<td>17 (47%)</td>
<td>0.110</td>
<td>0.32</td>
<td>0.04</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (points)**</td>
<td>5 [4-7]</td>
<td>5 [5-7]</td>
<td>5 [4-6]</td>
<td><strong>0.014</strong></td>
<td>0.52</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Procedural features: Nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right side</td>
<td>58 (55%)</td>
<td>38 (54%)</td>
<td>20 (56%)</td>
<td>0.901</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Laparoscopic nephrectomy</td>
<td>19 (18%)</td>
<td>12 (18%)</td>
<td>7 (19%)</td>
<td>0.821</td>
<td>0.05</td>
<td>0.35</td>
</tr>
<tr>
<td>Partial nephrectomy</td>
<td>25 (24%)</td>
<td>17 (24%)</td>
<td>8 (22%)</td>
<td>0.813</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Surgical access: transperitoneal</td>
<td>67 (64%)</td>
<td>44 (64%)</td>
<td>23 (66%)</td>
<td>0.845</td>
<td>0.04</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Tumor features: Nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuhrmann grade: G3-G4</td>
<td>47 (44%)</td>
<td>32 (46%)</td>
<td>15 (42%)</td>
<td>0.691</td>
<td>0.08</td>
<td>0.27</td>
</tr>
<tr>
<td>Non-clear-cell histology</td>
<td>8 (8%)</td>
<td>5 (7%)</td>
<td>3 (8%)</td>
<td>0.999</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Sarcomatoid features</td>
<td>6 (6%)</td>
<td>6 (9%)</td>
<td>0 (0%)</td>
<td>0.175</td>
<td>0.43</td>
<td>0.41</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td>50 (48%)</td>
<td>34 (49%)</td>
<td>16 (46%)</td>
<td>0.782</td>
<td>0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Macro- or microscopic vascular invasion</td>
<td>51 (48%)</td>
<td>35 (50%)</td>
<td>16 (44%)</td>
<td>0.588</td>
<td>0.11</td>
<td>0.05</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>6.0 [4.5-8.5]</td>
<td>6.5 [5.0-8.5]</td>
<td>6.0 [4.5-8.0]</td>
<td>0.3366</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>TNM pT stage: pT3-4</td>
<td>59 (56%)</td>
<td>43 (61%)</td>
<td>16 (44%)</td>
<td>0.096</td>
<td>0.34</td>
<td>0.16</td>
</tr>
<tr>
<td>TNM pN stage: N0</td>
<td>19 (18%)</td>
<td>14 (20%)</td>
<td>5 (14%)</td>
<td>0.437</td>
<td>0.16</td>
<td>0.14</td>
</tr>
<tr>
<td>TNM M stage: M1</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.999</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Tumor features: Time of metastasis diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from nephrectomy to metastasis diagnosis (years)</td>
<td>2.0 [0.7-4.3]</td>
<td>1.5 [0.6-3.9]</td>
<td>3.3 [1.5-6.5]</td>
<td><strong>0.011</strong></td>
<td>0.48</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of organs/sites affected by metastases***</td>
<td>9 [2-9]</td>
<td>9 [6-9]</td>
<td>1 [1-2]</td>
<td>&lt;0.0001</td>
<td>2.16</td>
<td>1.04</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>---Lung</td>
<td>71 (67%)</td>
<td>48 (69%)</td>
<td>23 (64%)</td>
<td>0.627</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>-----Bilateral lung mets</td>
<td>45 (64%)</td>
<td>37 (77%)</td>
<td>8 (35%)</td>
<td><strong>0.001</strong></td>
<td>0.93</td>
<td>0.72</td>
</tr>
<tr>
<td>-----Number of lung mets</td>
<td>5 [2-6]</td>
<td>6 [3-6]</td>
<td>2 [1-2]</td>
<td>&lt;0.0001</td>
<td>1.22</td>
<td>0.41</td>
</tr>
<tr>
<td>---Liver</td>
<td>26 (25%)</td>
<td>23 (33%)</td>
<td>3 (8%)</td>
<td><strong>0.005</strong></td>
<td>0.63</td>
<td>0.54</td>
</tr>
<tr>
<td>-----Number of liver mets</td>
<td>3 [1-6]</td>
<td>3 [1-6]</td>
<td>1 [1-6]</td>
<td>0.473</td>
<td>0.34</td>
<td>0.62</td>
</tr>
<tr>
<td>---Adrenal gland: ipsilateral</td>
<td>10 (9%)</td>
<td>7 (10%)</td>
<td>3 (8%)</td>
<td>0.999</td>
<td>0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>---Adrenal gland: contralateral</td>
<td>5 (5%)</td>
<td>4 (6%)</td>
<td>1 (3%)</td>
<td>0.660</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>---Contralateral kidney</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0.340</td>
<td>0.24</td>
<td>0.21</td>
</tr>
<tr>
<td>---Distant lymph nodes</td>
<td>36 (34%)</td>
<td>26 (37%)</td>
<td>10 (28%)</td>
<td>0.335</td>
<td>0.20</td>
<td>0.21</td>
</tr>
<tr>
<td>---Bone</td>
<td>28 (26%)</td>
<td>20 (29%)</td>
<td>8 (22%)</td>
<td>0.483</td>
<td>0.14</td>
<td>0.23</td>
</tr>
<tr>
<td>---Central Nervous System</td>
<td>17 (16%)</td>
<td>9 (13%)</td>
<td>8 (22%)</td>
<td>0.213</td>
<td>0.25</td>
<td>0.47</td>
</tr>
<tr>
<td>---Soft tissue</td>
<td>18 (17%)</td>
<td>13 (19%)</td>
<td>5 (14%)</td>
<td>0.543</td>
<td>0.13</td>
<td>0.42</td>
</tr>
<tr>
<td>---Others</td>
<td>19 (18%)</td>
<td>11 (16%)</td>
<td>8 (22%)</td>
<td>0.408</td>
<td>0.16</td>
<td>0.46</td>
</tr>
<tr>
<td>---Mediastinal bulk</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0.340</td>
<td>0.24</td>
<td>0.18</td>
</tr>
<tr>
<td>Any local recurrence</td>
<td>16 (15%)</td>
<td>13 (19%)</td>
<td>3 (8%)</td>
<td>0.252</td>
<td>0.31</td>
<td>0.52</td>
</tr>
</tbody>
</table>

| Treatments for metastatic disease****          |         |         |         |          |      |      |
| Radiotherapy                                   | 28 (26%) | 15 (21%) | 13 (36%) | 0.111    | 0.33 | N/A  |
| aVEGF TKI                                      | 56 (53%) | 37 (53%) | 19 (53%) | 0.999    | 0.00 | N/A  |
| mTOR inhibitor                                 | 16 (15%) | 12 (17%) | 4 (11%)  | 0.569    | 0.17 | N/A  |
| Immune checkpoint inhibitor                    | 14 (13%) | 8 (11%)  | 6 (17%)  | 0.547    | 0.15 | N/A  |
| Local ablation (e.g. RFA)                      | 7 (7%)   | 4 (6%)   | 3 (8%)   | 0.687    | 0.10 | N/A  |

<table>
<thead>
<tr>
<th>Laboratory parameters: Time of metastasis diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
</tr>
<tr>
<td>12.8 [11.5-14.1]</td>
</tr>
<tr>
<td>Platelet count (G/L)</td>
</tr>
<tr>
<td>240 [180-291]</td>
</tr>
<tr>
<td>Absolute neutrophil count (G/L)</td>
</tr>
<tr>
<td>5.4 [4.1-6.5]</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>LDH (U/L)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
</tr>
<tr>
<td><strong>Comorbidities: Time of metastasis diagnosis</strong></td>
</tr>
<tr>
<td>Charlson Comorbidity Index (points)</td>
</tr>
</tbody>
</table>

Table 7. Baseline characteristics of the study population – Distribution overall and by treatment assignment to metastasectomy (n=106)
At baseline, the median age of the cohort was 70 years [25\textsuperscript{th}-75\textsuperscript{th} percentile: 62-76], and 39 patients (37%) were female. Most patients had clear-cell histology (n=98, 92%) with a median number of 9 [2-9] organs/sites affected by metastases. Most frequent organs/sites affected by metastasis were the lungs (67%), distant lymph nodes (34%), and bones (26%). After metachronous metastasis diagnosis, the median follow-up interval was 6.2 years (25\textsuperscript{th}-75\textsuperscript{th} percentile: 2.5-8.1). During the pre-specified study period of 5 years after metachronous metastasis diagnosis, we observed 63 deaths-from-any-cause. One-, 2-, 3-, and 5-year OS estimates after metachronous metastasis diagnosis were 69% (95\%CI: 59-77), 52% (41-62), 41% (30-51), and 28% (19-39), respectively (Supplementary Figure 2).

**Metastasectomy procedures**

Thirty-six (34%) patients had at least one metastasectomy procedure after diagnosis of metastasectomy. The most frequent first metastasectomy procedures included pulmonary metastasectomy (wedge resections (n=10) lobectomy (n=2), bilobectomy (n=1), craniotomies (n=6), and bone surgery (n=4), while liver resection was only performed in 1 patient (Table 8).

<table>
<thead>
<tr>
<th>Metastasectomy procedure</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung: Wedge resection</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Craniotomy / Brain surgery</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Bone surgery</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Lung: Lobectomy</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Skin / Soft tissue surgery</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Lung: Bilobectomy</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Liver resection</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Table 8. Tabulation of metastasectomy procedures (n=36)

Metastasectomy achieved macroscopic complete excision of all known tumor lesions in 27 (75%) out of the 36 patients. Ten patients and 3 patients underwent a second and third metastasectomy, respectively (Supplementary Table 2). Thirty-day mortality of metastasectomy was 0%. Non-metastasectomy treatment procedures, including systemic and local-ablative therapies are reported in Table 7.
**Crude analysis of 5-year overall survival according to metastasectomy**

Median and 5-year OS estimates were 4.2 years (95%CI: 2.7-7-not reached) and 41% (21-60) in patients who were treated with metastasectomy ± medical therapy ("metastasectomy group"), and 1.3 years (0.8-1.9) and 22% (12-34) in patients who were treated with medical therapy alone ("medical therapy group"), respectively (log-rank p=0.0007, Hazard Ratio (HR)=0.38, 95%CI: 0.21-0.68, **Figure 1 Panel A**).

![Panel A - Crude analysis](image1)

![Panel B - Propensity score analysis](image2)

**Figure 1**: **Unadjusted and propensity-score-weighted Kaplan-Meier curves of 5-year overall survival according to treatment assignment to metastasectomy (n=106).**

The median time from diagnosis of metachronous metastasis to metastasectomy was 1.5 months [25th-75th percentile: 1.0-2.3]. To reduce and eliminate this immortal time bias, landmark analysis (with a landmark date at 6 months) and time-dependent Cox regression were performed. In landmark analysis, 1-, 3-, and 5-year OS estimates were 71%, 41%, and 30% in the 35 patients who underwent metastasectomy within the first six months after metachronous metastasis diagnosis, and 96%, 58%, and 38% in the remaining 71 patients who did not undergo metastasectomy within this time window, respectively (Mantel-Byar p=0.014, **Figure 2**).
Figure 2. Landmark analysis of 5-year overall survival according to whether patients underwent metastasectomy within the first six months after metastasis diagnosis or not. In univariable Cox regression treating metastasectomy as a fully time-dependent variable, metastasectomy was associated with a 0.5-fold lower relative risk of death as compared to medical therapy alone (HR=0.48, 95%CI: 0.27-0.87, p=0.016).

Development of the propensity score and the IPTW

As expected, patients who underwent metastasectomy had a significantly higher prevalence of favorable prognostic factors (Table 7). For example, the median number of organs/sites affected by metastasis were 9 [6-9] and 1 [1-2] in the patients who did not and did undergo metastasectomy, respectively (rank-sum p<0.0001; standardized mean difference (SMD)=2.16, with SMDs>0.30 indicating a potentially important imbalance between study groups). Further, patients in the metastasectomy group had, among others, lower c-reactive protein (CRP) levels (SMD=0.48), a lower prevalence of bilateral lung metastases (SMD=0.93) and a longer interval between nephrectomy and metastases diagnosis (SMD=0.48) than patients in the non-metastasectomy group. Several of these differentially distributed variables were associated with a more favorable overall survival experience (Supplementary Table 3). Because this is a major source of bias for the metastasectomy versus medical therapy comparison, we constructed a propensity score to predict probabilities of treatment assignment conditional on covariates at baseline. We constructed the propensity score using a multivariable logistic regression model with 10 predictor variables (Supplementary Table 4, with the model building process described in the statistical methods section). The distribution of the propensity score (Supplementary Figure 3A) covered the whole probability range from 0 to 1, and was then transformed into
the IPTW according to the inverse of the probability of receiving the treatment that the patient actually received (Supplementary Figure 3B). Re-weighing of the data with the IPTW strongly reduced imbalances of baseline covariates between the two treatment groups (Table 7). For example, IPTW-weighing reduced the SMDs for the key prognostic variables (1) time from nephrectomy to metastasis diagnosis from 0.48 to 0.25, (2) number of organ/sites affected by metastases from 2.16 to 1.04, and (3) haemoglobin level at metastases diagnosis from 0.44 to 0.20, respectively.

**IPTW-weighted analysis of 5-year overall survival according to metastasectomy**

After IPTW weighting of the data, median and 5-year OS estimates were 3.5 years and 24% in the metastasectomy group, and 1.0 years and 20% in the medical therapy group, respectively (IPTW-weighted log-rank p=0.001, IPTW-weighted HR=0.45, 95% CI: 0.27-0.73, Figure 1B). In univariable IPTW-weighted Cox regression treating metastasectomy as a fully time-dependent variable in order control immortal time bias, the association between metastasectomy and favorable OS became much weaker (HR=0.62, 95% CI: 0.39-1.00, p=0.050).

**Exploratory analysis: Time-to-disease progression after metastasectomy**

During a median follow-up of 3.7 years after metastasectomy, 28 (78%) of the 36 patients who underwent metastasectomy developed disease progression. This corresponded to a median time-to-disease-progression of 0.7 years, with 75% and 25% of the metastasectomy cohort remaining free from disease progression for at least 0.3 and 2.7 years, respectively (Supplementary Figure 4).

**Exploratory analysis: “Complete” and “incomplete” metastasectomies**

Twenty-seven (75%) of the 36 metastasectomies achieved complete resection of all known metastases within a single metastasectomy procedure (“complete metastasectomy”), whereas 9 (25%) metastasectomies did not achieve this (“incomplete metastasectomy”). Clinical details about “incomplete” metastasectomies are tabulated in Supplementary Table 5. Notably, in an exploratory analysis of unweighted data, the potential benefit of metastasectomy appeared to be confined to complete metastasectomies. In detail, median times-to-disease-progression were 0.3 years and 1.5 years in patients with complete and incomplete metastasectomy (log-rank p=0.0003, Figure 3A). Crude 5-year OS estimates
were 22%, 17%, and 48% in patients with no, incomplete, and complete metastasectomy (log-rank p=0.022, Figure 3B). In an IPTW-weighted Cox model treating both incomplete and complete metastasectomy as a time-dependent variable, we observed HRs of 1.55 (95%CI: 0.84-2.86, p=0.163) for incomplete metastasectomy vs. no metastasectomy, and 0.54 (95%CI: 0.33-0.89, p=0.016) for complete metastasectomy vs. no metastasectomy, respectively.

Figure 3. Clinical outcomes according to completeness of metastasectomy.

Sensitivity analysis: Exploring potential time-dependencies of metastasectomy benefit

The beneficial “effect” of metastasectomy appeared to become progressively smaller during follow-up (Figure 1). Upon further investigation, we found (1) strong evidence for a violation of the proportional hazards assumption for metastasectomy (Schoenfeld test of IPTW-weighted univariable Cox model=0.012), and (2) a 3.7-fold multiplicative decrease of the relative metastasectomy benefit for each year of follow-up time elapsed interaction HR between metastasectomy and linear follow-up time in the IPTW-weighted univariable Cox model=3.68, 95%CI: 1.88-7.17, p<0.0001). Indeed, non-proportional analysis of mortality hazards showed that rates of death between metastasectomy vs. no metastasectomy
crossed at around 2.4 years of follow-up (Supplementary Figure 5). In IPTW-weighted Cox models treating metastasectomy as a time-dependent variable, HRs for metastasectomy and overall survival for prediction horizons of 1, 2, 3, 4, and 5 years were 0.05 (p=0.004), 0.13 (p<0.0001), 0.27 (p=0.003), 0.53 (p=0.027), and 0.62 (p=0.050), respectively.

Hypothesis-generating analysis: Predictive markers for metastasectomy benefit

In a hypothesis-generating, exploratory analysis of interactions between metastasectomy and selected baseline covariates, we found signals towards a greater magnitude of benefit of metastasectomy regarding overall survival in patients with less than 3 metastatic lesions/sites affected by metastasis, and patients with lower comorbidity scores. Otherwise, the beneficial association of metastasectomy was consistent across patients with nephrectomy to metastasis time intervals > and ≤ 2 years (Supplementary Table 6).
Discussion

Randomized evidence assessing the potential benefit of metastasectomy in mRCC is currently not available. In this study, we thus performed a propensity-score-based comparative effectiveness analysis of OS outcomes in a large institutional mRCC population among which approximately one third of the patients underwent metastasectomy in addition to standard medical therapy. Crude analysis suggested that patients who underwent metastasectomy had significantly longer OS than patients who were treated with standard medical therapy alone. However, consistent with the non-random assignment to metastasectomy in this cohort, this finding was confounded by selection bias. Additionally, immortal time bias was present. After controlling for these two biases with propensity score weighting and time-dependent analysis, the association between metastasectomy and favorable OS prevailed, although at a much smaller magnitude of benefit and strength of association. In exploratory analyses, we found a weakening “effect” of metastasectomy over time, and no evidence that “incomplete” metastasectomies associate with improved OS. In summary, these data support the hypothesis that metastasectomy improves OS in mRCC, but that the magnitude of this potential OS benefit weakens over time and appears to be confined to patients who achieve excision of all known metastatic lesions within a single metastasectomy procedure.

Metastasectomy is a frequently practiced treatment strategy in mRCC, and several single-arm non-comparative analyses have demonstrated favorable OS outcomes in mRCC after metastasectomy.(170, 172, 192-195) Nonetheless, systemic antineoplastic therapy for mRCC has become more effective over time due to the advent of tyrosine kinase inhibitors and immune checkpoint inhibitor therapy.(179) It is therefore of high clinical interest to analyze relative merits of a treatment strategy primarily based on medical therapy versus a medical treatment strategy that additionally integrates metastasectomy. At present, a randomized trial of these two treatment strategies appears infeasible in mRCC for ethical and clinical reasons, primarily because many clinicians are convinced that metastasectomy can lead to long-term remissions and even cure.(196) In such a situation, comparative effectiveness analyses of observational data are an increasingly popular and important tool for comparing treatment strategies.(184, 197) In our case, we used propensity score weighting to control for the extensive selection bias present in our data. Given a valid
propensity score model is developed, the assignment to treatment in an observational study is independent conditional on the covariates in the propensity score model. The ensuing pseudo-population mimics a randomized study. As for our study, patients who underwent metastasectomy had a significantly higher prevalence of favorable prognostic factors, such as lower comorbidity, a longer disease-free interval before metastasis diagnosis, a smaller number of organs/sites affected by metastases, a lower prevalence of bilateral lung metastases, a lower prevalence of liver metastases, and lower levels of laboratory variables known to associate with worse outcomes including C-reactive protein. This is consistent with the non-random assignment of patients to metastasectomy, with metastasectomy being indicated by treating physicians generally to patients in good performance status with few metastases that are technically feasible to resect. Moreover, metastasectomy needs time for preparation regarding to tumor board decision making, patient counseling, preoperative anesthesia work-up, and surgical planning and scheduling. Thus, a naïve analysis would artificially inflate the survival time of each metastasectomy by the time it took from metastasis diagnosis to metastasectomy (“immortal time bias”). Ignoring these selection and immortal time biases can be expected to largely overestimate the “true” effect of metastasectomy on OS, and we indeed found a much longer OS with metastasectomy in a crude analysis. When applying propensity score weighting (to control for selection bias) and time-dependent metastasectomy variable specification (to control for immortal time bias), the benefit of metastasectomy became much smaller with regards to both magnitude and strength of association. Nonetheless, in the final fully-adjusted propensity score model, metastasectomy was independently associate with improved OS. Thus our study is consistent with the concept that metastasectomy can be considered as an intervention for improving OS within comprehensive, multi-disciplinary mRCC treatment planning.

Several additional insights could be gained from exploratory and hypothesis-generating analyses. First, although 25% of patients remained free from disease progression for at least 2.7 years, the median time-to-progression after metastasectomy of 0.7 years was quite short. An interpretation of this finding is that the clinical utility of metastasectomy should be further improved by carefully selecting patients for metastasectomy based on prognostic factors. Several authors have already provided hints in this direction. Another interpretation of this finding is that although some patients derive clinically significant long-term freedom-from-disease from metastasectomy, true cure is not as frequent as one may
expect and many patients eventually relapse after metastasectomy. Second, we found a highly time-dependent effect of metastasectomy that weakened over time. In detail, mortality rates between the metastasectomy and medical therapy group crossed after two years, and OS after 5 years of follow-up was not strongly different between the two treatment groups after careful propensity score weighting and time-dependent analysis. This suggests that metastasectomy can be considered as palliative therapy that delays death but does not necessarily lead to a longer proportion of long-term survivors at 5 years of follow-up as compared to medical therapy alone. Oncologists and surgeons should take this into account when discussing metastasectomy with their patients. Third, we found that so-called “incomplete” metastasectomies which did not remove all known metastatic lesions within the first metastasectomy surgery were not associated with any OS benefit. This finding confirms several previous reports who have shown that the most important prognostic factor for OS after metastasectomy is complete resection.\textsuperscript{(192, 193)} A clinical interpretation of this finding is that incomplete metastasectomies can still be performed with a reasonable symptomatic palliative treatment goal (see e.g. the patient vignettes in Supplementary Table 6, such as the patient with pain from femoral bone metastasis who underwent femoral resection for pain relief in the presence of several other bone metastases), but one should not expect that such metastasectomies prolong a patient’s survival. Fourth, we performed subgroup analyses to identify patients with a potentially very high or very low benefit from metastasectomy. Here we found signals towards a greater magnitude of benefit of metastasectomy in patients with less than 3 metastatic lesions / sites affected by metastasis, and patients with lower comorbidity scores. Although we urge readers to consider these results purely hypothesis-generating due to the small patient numbers, arbitrary cut-offs, and high potential for false-positive and false-negative results, they could provide the basis for improved metastasectomy indication once being confirmed by other studies.

Otherwise, our study cohort compares well to other study cohorts in the field with regards to treatment outcomes. In detail, our unadjusted 5-year OS of 41% in the metastasectomy group is similar to the corresponding estimates of and 33%, 36%, and 45% in the pulmonary metastasectomy cohorts of Hofmann et al.,\textsuperscript{(192)} Kawashima et al.,\textsuperscript{(193)} Procházková et al.,\textsuperscript{(195)} and 43% in the pulmonary metastasectomy meta-analysis by Zhao et al.\textsuperscript{(172)} Importantly, 30-day mortality of our metastasectomy cohort was 0%, showing that metastasectomy in mRCC is safe when patients are well selected and treated at an experienced center by experienced surgeons.
While most studies in this field focused on pulmonary metastasectomies, it is noteworthy that pulmonary metastasectomies constituted only one third of metastasectomies in our cohort which included also a significant number of craniotomies and several less frequent procedures such as adrenalectomy, skin/soft tissue surgeries, and thyroidectomies. This is consistent with the study by Adashek and colleagues, (196) who report on mRCC metastasectomies of the brain, the liver, the pancreas, the bone, and the lymph nodes.

Finally, several limitations of the present analysis need to be discussed. First, as with all retrospective analyses, we cannot exclude information bias by miscoding of exposures and outcomes. Second, our propensity score model may not have reduced all imbalances between the two treatment groups, because the assumption that a propensity score model is difficult-to-test. Although balance diagnostics after IPTW weighting showed removal of most differences, some variables still had SMDs >0.3. This means that the “true” causal effect of metastasectomy on OS in mRCC could be even slightly lower than our estimate. Next, we did not consider interventional procedures without removal of tumor masses such as radiofrequency ablations as metastasectomies. Whether these increasingly popular methods are associated with improved OS should thus be addressed in future studies. Fourth, some metastasectomy procedures such as adrenalectomy of skin/soft tissue surgery had small numbers. Thus, we cannot provide specific effect estimates for each individual metastasectomy procedure, but rather for metastasectomy as a whole. Fifth, a limited amount of patients underwent further metastasectomies during follow-up after their first metastasectomy procedure, and with the advent of immunotherapy, the effect of systemic therapies can be expected of having improved over time. Modeling of these two factors was considered not possible within our analysis framework for difficult-to-ascertain time-dependent confounding. A further limitation is that quality-of-life data were not available in our retrospective study. As metastasectomies can be highly invasive surgical procedures requiring post-surgical intensive care unit surveillance and in-hospital stays, future studies should not only focus on overall survival but also on quality-of-life aspects to gain a more patient-oriented picture of the overall utility of metastasectomy in this setting. Finally, we pre-specified to consider only patients with metachronous metastasis after nephrectomy for our study cohort. The reasons for this were that inclusion of patients with synchronous metastases would have led to more immortal time bias and more time-dependent selection (e.g. patients with synchronous metastases who received metastasectomy only after having achieved stable disease on a systemic therapy, or patients treated with cytoreductive
nephrectomy).(198) Although this stringent selection of metachronous metastasis patients can be considered as a strength, we of course cannot generalize our results to patients with synchronous metastasis and future studies should thus also address this sub-population.

**Conclusion**

This comparative effectiveness analysis supports the hypothesis that metastasectomy is associated with an overall survival benefit in patients with mRCC. This benefit slightly weakens over time and appears to be restricted to patients in which complete resection of all known metastatic lesions is achieved within a single metastasectomy procedure. These results can inform cancer specialists and patients when planning comprehensive multi-disciplinary treatment for mRCC.
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