Nierenzellkarzinom

Medizinische Leitlinie

Tumorzentrum Oberösterreich

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Diese Leitlinie ist eine Grundlage für die Diagnostik und Therapie innerhalb des Tumorzentrums Oberösterreich und erhebt nicht den Anspruch auf Vollständigkeit.
Darüberhinaus von den jeweiligen Fachgesellschaften festgelegte Qualitätsstandards sind dem Stand der Wissenschaft entsprechend einzubeziehen.

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1 Allgemeines

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2 Diagnostik und Scoring

2.1 Staging

- Klinische Untersuchung
- Labor zumindest:

  Differential Blutbild, Serum Kreatinin, Kalzium, Albumin, TSH, AP, LDH

- CT Thorax/Abdomen/Becken, ev. Abdomen-MRI (Unklarheit bei Cava Thrombus)
  CAVE: nur das klassische Angiomyolipom kann vom RCC unterschieden werden

- Knochenscan nur bei Klinik oder unklar erhöhter AP

- Perkutane Biopsie im Falle von:
  1. Surveillance geplant
  2. Histologie würde die die vorgesehene Behandlung modifizieren
  3. vor einer lokalablativen Maßnahme (RFA, Kryotherapie)
  4. vor einer systemischen Therapie und bislang fehlender Histologie

2.2 Bosniak Klassifikation adaptiert aus EAU Guidelines 2019[1]

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intra-renal, non-enhancing, high attenuation renal lesions > 3 cm. Generally well-marginated.	Follow-up, up to five years. Some are malignant.
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance - Over 50% are malignant.
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

2.3 TNM-Klassifikation aus UpToDate[2]

Kidney cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
T1	N0	M0	I
T1	N1	M0	III
T2	N0	M0	II
T2	N1	M0	III
T3	NX, N0	M0	III
T3	N1	M0	III
T4	Any N	M0	IV
Any T	Any N	M1	IV

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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UpToDate®

Grading nach Fuhrmann	
Grad 1	kleine Kerne (~10µm), keine oder unscheinbare Nucleoli N0
Grad 2	größere Kerne (~15µm), leicht unregelmäßig, kleine Nucleoli N0
Grad 3	noch größere Kerne (~20µm), deutlich irregulär, große Nucleoli
Grad 4	pleomorphe, bizarre Kerne, polylobuliert oder spindelig

Histologische Subtypen (WHO 2016) entnommen aus ESMO Guidlines 2019[3]

Table 1. WHO 2016 classification of renal cell tumours

Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal cell carcinoma
Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
MiT family translocation renal cell carcinomas
Succinate dehydrogenase-deficient renal cell carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

MiT, microphthalmia-associated transcription factor; WHO, World Health Organization.
Reprinted with permission from [6].

2.4 Prognose-Scores

2.4.1 Im lokalisierten Stadium entnommen aus ESMO Guidelines 2019[3]

Table 3. SSIGN score for localised RCC [19]

Feature		Score
Pathological T category of primary tumour (as per 2002 TNM staging)	pT1a	0
	pT1b	2
	pT2	3
	pT3a-pT3c	4
	pT4	4
Regional lymph node status (as per 2002 TNM staging)	pNx or pN0	0
	pN1 or pN2	2
Tumour size	<10 cm	0
	10 cm or more	1
Nuclear grade	1 or 2	0
	3	1
	4	3
Histological tumour necrosis	No	0
	Yes	1

Scores	Group	5-year metastasis-free survival rate (%)
0–2	Low risk	97.1
3–5	Intermediate risk	73.8
6 or more	High risk	31.2

RCC, renal cell carcinoma; SSIGN, size, stage, grade and necrosis; TNM, tumour, node, metastasis.
Adapted from [19], with permission from John Wiley & Sons, Inc.

2.4.2 Im metastasierten Stadium

The Metastatic Renal Cancer Database Consortium (IMDC) risk model[4]:

Risikofaktor	Cut-off
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal

Favourable (low) Risk **0 Risikofaktoren**
Intermediate Risk **1-2 Risikofaktoren**
Poor (high) Risk **>2 Risikofaktoren**

Medianes OS nach IMDC entnommen aus ESMO Guidelines 2019[3]

Table 5. Median OS estimates in first- and second-line RCC according to IMDC risk groups

Number of risk factors	Risk category	Median OS (months)	
		First line [24]	Second line [23]
0	Favourable	43.2	35.3
1–2	Intermediate	22.5	16.6
3–6	Unfavourable	7.8	5.4

IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma.

5-Jahres Überlebenswahrscheinlichkeit entnommen aus ESMO Guidelines 2019[3]

UISS (UCLA Integrated Staging System)

Table 4. UISS risk groups and 5-year disease-specific survival [20]

Patient group		Prognostic group			
		T stage	Fuhrman grade	ECOG status	5-year disease-specific survival (%)
Localised disease (N0, M0)	Low risk	1	1–2	0	91.1
	Intermediate risk	1	1–2	1 or more	80.4
		1	3–4	Any	
		2	Any	Any	
		3	1	Any	
		3	2–4	Any	
	High	3	2–4	1 or more	54.7
		4	Any	Any	
Metastatic disease	Low risk	N_1M_0	Any	Any	32
		N_2M_0/M_1	1–2	0	
	Intermediate risk	N_2M_0/M_1	1–2	1 or more	19.5
			3	0, 1 or more	
			4	0	
	High	N_2M_0/M_1	4	1 or more	0

ECOG, Eastern Cooperative Oncology Group; UISS, University of California Los Angeles Integrated Staging System.
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3 Behandlungsplan

3.1 Auf die Niere Beschränkte Tumore (RCC)

3.1.1 Empfehlungen lt. EAU Leitlinien 2019[1]

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy to patients with T1 tumours.	Strong
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Offer an extended lymph node dissection to patients with adverse clinical features, including a large diameter of the primary tumour.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

Recommendations	Strength rating
Offer laparoscopic radical nephrectomy (RC) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological, functional and peri-operative outcomes.	Strong

Recommendation	Strength rating
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	Weak

Recommendations	Strength rating
In patients with clinically enlarged lymph nodes (LNs), perform LN dissection for staging purposes or local control.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong

3.1.2 Adjuvante Therapie

Aufgrund der aktuellen Studienlage kann keine Empfehlung für eine adjuvante Therapie ausserhalb von Studien gegeben werden. Dies trifft auch bei Z. n. kompletter Metastasektomie zu.[1][3]

3.2 Metastasiertes RCC

3.2.1 Zusammenfassung der Evidenz und Empfehlungen bzgl. lokaler Therapie bei mRCC lt. EAU Leitlinien 2019[1]

Summary of evidence	LE
Cytoreductive nephrectomy (CN) followed by sunitinib is non-inferior to sunitinib alone in patients with metastatic ccRCC.	1a
Deferred CN with presurgical sunitinib in intermediate-risk patients with metastatic ccRCC leads to a survival benefit in secondary endpoint analysis and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform *immediate* CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).	Weak
Start systemic therapy without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

3.2.2 Empfehlung zur lokalen Behandlung von Metastasen bei metastasierten RCCs lt. EAU Guidlines 2019[1]

Summary of evidence	LE
All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	Strength rating
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone or brain metastases for local control and symptom relief.	Weak

3.2.3 Systhemische Therapie

3.2.3.1 Therapie Empfehlung first line mccRCC lt. EAU Update 2020[5]

	Standard of care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	Nivolumab/cabozantinib [1b] Pembrolizumab/axitinib [1b]	Sunitinib [1b] Pazopanib [1b]
IMDC intermediate and poor risk	Nivolumab/cabozantinib [1b] Pembrolizumab/axitinib [1b] Nivolumab/ipilimumab [1b]	Cabozantinib [2a] Sunitinib [1b] Pazopanib* [1b]

Nach: Updated Eurpean Association of Urology guideline recommendatios for the first-line treatment of metastatic clear-cell renal cancer. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium. [1b] = based on a randoised controlled phase 3 trial. [2a] = based on a well-designed study withaut randomisation, or a subgroup analysis of a randomised controlled trial. * Pazopanib for intermediate-risk disease only.

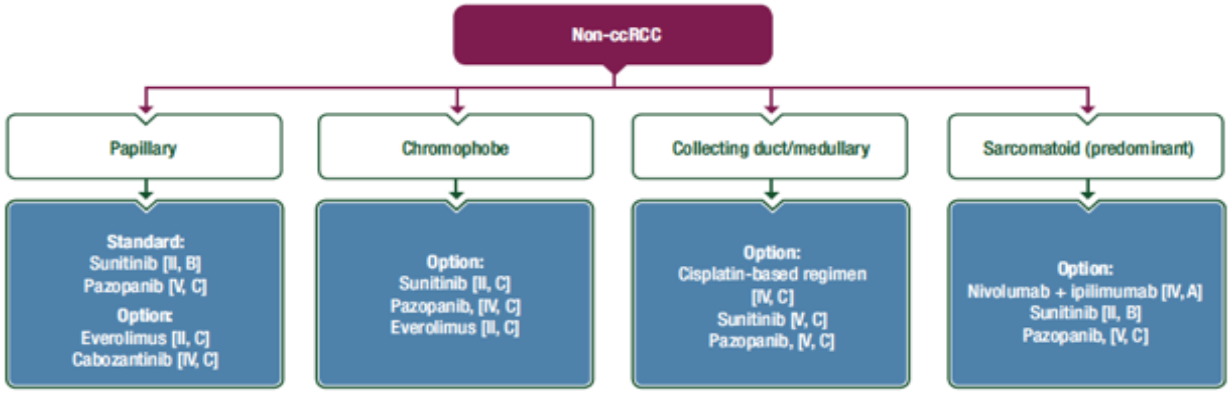
Tivozanib stellt einen Nebenwirkungsarme TKI alternative in der first line dar[6]
Bei cerebralen SBL sollte eine Therapie mittles Cabozantinib erwogen werden[7]
Erhöhte Entzündungsmarker (wie CRP, erhöhte NLR,...) weisen auf eine immunsuopresive Mircoinviroment des Tumors hin was zu einem schlechteren Ansprechen der Immuntherapie führen kann. In diesen Fällren wäre wohl eine kombinationtherapie mit einem TKI zu bevorzugen.[8][9]

3.2.3.2 Therapie Empfehlung second line mccRCC lt. EAU Update 2019[10]

	Standard of care	Alternative
Prior IO	Any VEGF targeted therapy that has not been used previously in combination with IO [4]	
Prior TKI	Nivolumab [1b] Cabozantinib [1b]	Axitinib[a] [2b]

Owohl TITAN-RCC in der 2L Population nicht den Primären Endpunkt von ORR von 40% mit Ipilimumab Boost nach 8-16 Wochen Nivolumab 240mg q2w erreicht zeigt sich doch eine deutlich verbesserte ORR von 18% auf 28% [11]. Das Protokoll ist bei den Quellenangaben angefügt.

3.2.3.3 Empfehlungen first line non ccRCC lt. ESMO Guidline 2019[3]



3.2.3.4 Auflistung der Immunkombinationen in der first line mRCC lt. EAU Update 2020[5]

Table 1 – First-line immune checkpoint inhibitor combination trials for clear-cell RCC[a]

Study	*N*	Experimental arm	Primary endpoint	Risk groups	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
KEYNOTE-426 **NCT02853331** **Median follow-up 30.6 mo** [3,5]	861	Pembrolizumab 200 mg. IV Q3W plus axitinib 5 mg. PO BID vs. sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI: 15.4 (12.7–18.9) SUN: 11.1 (9.1-12.5) HR 0.71 (95% CI 0.60–0.84) $p < 0.0001$	(ITT) PEMBRO + AXI: NR SUN: 35.7 (33.3–NE) HR 0.68 (95% CI 0.55–0.85) $p = 0.0003$
JAVELIN 101 **NCT02684006** **Median follow-up 19 mo** [6,7]	886	Avelumab 10 mg/kg IV Q2W + AXI 5 mg PO BID vs sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1$^+$ population and OS in the ITT by BICR	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.8 (10.1–20.7) SUN: 7.0 (5.7–9.6) HR 0.62 (95% CI 0.49–0.78) $p < 0.0001$	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4–NE) HR 0.83 (95% CI 0.60–1.15) $p = 0.1301$
IMmotion 151 **NCT02420821** **Median follow-up 24 mo** [8]	915	Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1$^+$ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 69% POOR 12%	(PD-L1+) ATEZO + BEV: 11.2 (8.9–15.0) SUN: 7.7 (6.8–9.7) HR 0.74 (95% CI 0.57–0.96) $p = 0.0217$	(ITT) ATEZO + BEV: 33.6 (29.0–NE) SUN: 34.9 (27.8–NE) HR 0.93 (95% CI 0.76–1.14) $p = 0.4751$
CheckMate214 **NCT02231749** **Minimum follow-up of 48 months** [2,4]	1096	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the IMDC intermediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/POOR) NIVO + IPI: 11.2 (8.4–16.1) SUN: 8.3 (7.0–10.8) HR 0.74 (95% CI 0.62–0.88)	(IMDC IMD/poor) NIVO + IPI: 48.1 (35.6-NE) SUN: 26.6 (22.1-33.5) HR 0.65 (0.54–0.78) $p < 0.0001$
CheckMate 9ER **Median follow-up of 18.1 months** **NCT03141177** [1]	651	Nivolumab 240 mg fixed dose IV every 2 wk + cabozantinib 40 mg PO daily vs sunitinib 50 mg PO QD4/2 wk	PFS in the ITT by BICR	IMDC FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO + CABO: 16.6 (12.5–24.9) SUN: 8.3 (7.0–9.7) HR 0.51 (95% CI 0.41–0.64) $p < 0.0001$	(ITT) NIVO + CABO: NR SUN: NR (22.6–NE) HR 0.60 (98.9% CI 0.40–0.89) $p = 0.0010$

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PO = by mouth; BID = twice a day; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks.

[a] Cross trial comparison is not recommended and should occur with caution.

3.2.4 Auflistungen TKI first line und anderer Substanzen second line

Trial design	Line of treatment/ patient characteristics	Benefit
Sunitinib vs IFN[12]	1st line (good/interm. risk)	Median PFS: 11 vs 5 mo. Median OS: 26 vs 22 mo. NS
Bevacizumab+IFN vs placebo+IFN [13]	1st line (good/interm. risk)	Median PFS: 10.2 vs 5.4 mo. Median OS: 23 vs 21 mo. NS
Temsirolimus vs IFN[14]	1st line (poor risk)	MedianPFS: 5.5 vs 3.1 Median OS: 11 vs 7 mo.
Sorafenib vs placebo[15]	2nd line (post IFN/IL2)	Median PFS: 5.5 vs 2.8 mo. OS: 17.8 vs 14.3 mo. (censoring crossed-over placebo)
Everolimus vs placebo[16]	2nd line (post TKI)	Median PFS: 4.0 vs 1.9 mo. Median OS: nr vs 9 mo. NS
Pazopanib vs placebo [17]	1st line and after cytokine	Median PFS: 11.1 vs 2.8 mo. (naïve) Median PFS: 7.4 vs 4.2 mo. (after cytokine)
Axitinib vs Sorafenib [18]	2nd line	Median PFS: 6.7 vs 4.7 mo.
Nivolumab vs Everolimus [19]	2nd line post TKI	Median PFS: 4,6 vs 4,4 mo Median OS: 25 vs 19,6 mo (bis 75a)
Cabozantinib vs. Everolimus [20]	2nd line	Median OS: 21,4 vs 16.5 mo
Levantinib + Everolimus vs. Everolimus [21]	2nd line	Median PFS: 14,6 vs 5,5 mo Median OS: 25,5 vs 15,4 mo
Tivozanib vs. Sorafenib [6]	1st line	Median PFS: 12,7 vs 9,1 mo Median OS: idem

3.2.5 Knochenprotektive Substanzen

Bei Knochenmetastaen sollte eine protektive Therapie erfolgen. Denosumab ist der Vorzug zu geben, da die Therapie nicht durch Einschränkungen der Nierenfunktion beeinträchtigt wird. Vor Therapiebeginn sollte eine Zahnärztliche Begutachtung erfolgen um das Risiko für ONJ zu reduzieren[3]. Zusätzlich soll eine Kalziumsubstitution eingeleitet werden.

3.2.6 Generelle Empfehlungen TKI betreffend

Dosis und Intervall Modifikationen können zur besseren Verträglichkeit und Therapieadhärenz erwogen werden.[22]

3.3 Andere corticale Nierentumore mit entsprechender Therapieempfehlung adaptiert lt. EAU Guidlines 2019[1]

Entity	Clinical relevant notes	Malignant potential	Treatment of localised tumour/metastatic tumour
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity.	High	Surgery. Nivolumab and ipilimumab. Sunitinib, gemcitabine plus doxorubicin is also an option [73].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC	Benign	Surgery, nephron-sparing surgery (NSS).
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1, 33% at diagnosis). The hazard ratio (HR) CSS in comparison with ccRCC is 4.49 [26].	High, very aggressive. Median survival 30 months [74].	Surgery; Platin basierte CTX[23]; Response to targeted therapies is poor [75].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [74].	Surgery. Different chemotherapy regimes, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. It constitutes with TRCC 6p21 MiT translocation RCCs [76].	High	Surgery. Vascular endothelial growth factor (VEGF)-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS. VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle.	Intermediate	Surgery, NSS.
Acquired cystic disease-associated RCC		Low	Surgery.
Clear cell papillary RCC	Also reported as renal angiomyomatous tumour (RAT).	Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, new entity in the 2016 WHO classification, caused by a germline mutation of the fumarate hydratase gene [23].	High	Surgery. No data about treatment of metastatic disease.
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Variable	Surgery.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS.
Cystic nephroma/Mixed epithelial and stromal tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS.
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard [77,78].	Benign	Observation (when histologically confirmed) [71,72,79]. NSS.
Renal cysts	Simple cysts are frequently occurring, while occurring septa, calcifications and solid components require follow-up and/or management.	Malignant or benign	Treatment or follow-up recommendation based on Bosniak classification.

4 Verlaufskontrolle und Nachsorge

4.1 Lokalisiertes Stadium und tumorfrei nach Metastasektomie lt. EAU Guidelines 2019[1]

Risk profile	Surveillance				
	6 mo	1 y	2 y	3 y	> 3 y
Low	US	CT	US	CT	CT once every 2 years; Counsel about recurrence risk of ~10%
Intermediate / High	CT	CT	CT	CT	CT once every 2 years

CT = computed tomography of chest and abdomen, alternatively use magnetic resonance imaging for the abdomen; US = ultrasound of abdomen, kidneys and renal bed.

4.2 Metastasiertes Stadium mit nachweisbaren Herden

Alle 3 Monate CT-Thorax/Abdomen (alternativ Sono oder MRI-Abdomen).

5 Genetische Abklärung und Empfehlung zu heriditären Tumor Syndromen

Empfehlungen zur Erwägung einer weiterführenden genetischen Abklärung:

- Patienten jünger als 45 Jahre bei ED eines malignen Nieren Tumors
- bilaterale oder multifokale Tumore
- heriditäre leiomyomatose und RCC (HLRCC)
- Birt-Hogg-Dubé Syndrome assozierte Histologie (multiple chromophobe RCC, Oncocytome, oder Hybrid Tumore)
- Angiomyolipome der Niere und einem weiteren Krieterium des TSC Komplex den Patienten betreffend
- Succinat-Dehydrogenase(SDH)-defizientes Nierenzellkarzinom

5.1 Übersicht über hereditäre Tumorsyndrome mit Auftreten von Nierenzellkarzinomen (RCC) modifiziert nach A. Agaimy & A. Hartmann[24]

Syndrom	Gen (chromosomale Lokalisation)	Histologische Typen der RCC	Andere Tumoren oder klinische Symptome
Von-Hippel-Lindau-Erkrankung	VHL (3p25-26)	ccRCC	Hämangioblastome (Gehirn, Retina, spinal) Phäochromozytome Endokrine Tumoren des Pankreas Pankreaszysten Papilläres Zystadenom des Nebenhodens u. des Pankreas Endolymphatischer Tumor Papilläres Zystadenom der Mesosalpinx
Hereditäres pap. RCC	MET (7q31)	Papilläres RCC Typ 1	Keine
Bird-Hogg-Dubé-Syndrom	BHD (17p11.2)	Unterschiedliche hist.Subtypen Typisch: Hybrid-onkozytischer Tumor Auch: Klarzelliges RCC, Onkozytom, papilläres RCC	Fibrofollikulom der Haut Trichodiskom der Haut Achrochordon der Haut Lungenzysten mit Pneumothorax Schilddrüsenadenom oder -karzinom Onkozytom der Glandula parotis Andere Neoplasien
Hereditäre Leiomyomatose und Nierenzellkarzinom (HLRCC)	FH (1q42-43)	Überwiegend: Papilläres RCC Typ 2 Heterogenes Bild mit unterschiedlichen Histomorphologien	Nierenzellkarzinom Leiomyome der Haut und des Uterus Selten: Leiomyosarkom des Uterus Nebennierenrindenadenome Paragangliome Andere Karzinome
Tuberöse Sklerose (TSC)	TSC1/TSC (9q34/16p13)	Angiomyolipom Auch: Renale Zysten, papilläres RCC, klarzelliges RCC, Onkozytom	Kutane Angiofibrome Subunguale Fibrome Lymphangioleiomyomatose der Lunge Kardiale Rhabdomyome Adenome von Duodenum und Dünndarm Subependymales Riesenzellastrozytom Epilepsie und mentale Retardierung Knollenartige kortikale Veränderungen (sog. Tuber) Retinale Hamartome Nierenzysten

Syndrom	Gen (chromosomale Lokalisation)	Histologische Typen der RCC	Andere Tumoren oder klinische Symptome
Hereditäres Paragangliom-Phächromozytom-Syndrom	SDHB/SDHC/SDHD/SDHA (1p36/1q21/11q23/5p15.33)	Succinat-Dehydrogenase-defizientes (SDH) NZK	Paragangliome Phäochromozytome Gastrointestinale Stromatumoren
Cowden-Syndrom (PTEN-Hamartom-Tumorsyndrom)	PTEN (10q22-23)	Klarzelliges NZK Papilläres NZK Chromophobes NZK	Trichilemmome der Haut Papillomatöse Läsionen und Keratosen, besonders der Akren Schilddrüsenadenom und -karzinom Endometriumkarzinom Hamartome der Mamma Mammakarzinom Hamartöse intestinale Polypen
Hereditäres Hyperparathyreodismus-Kiefertumor-Syndrom (HPT-JT)	HRPT (1q21-32)	Gemischter epithelialer und Stromatumor (MEST) Papilläres RCC Wilms-Tumor	Nebenschilddrüsenadenome und -karzinome Fibroossäre Kieferläsionen
BAP1-assoziiertes familiäres Nierenzellkarzinom	BAP1 (3p21)	Klarzelliges RCC	Melanome (Haut und Uvea) Mesotheliom Melanozytischer BAP1-mutierter atypischer intradermaler Tumor Selten: cholangiozelluläre Karzinome, Mammakarzinome, etc.
Konstitutionelle Chromosom-3-Translokation	Unbekannt, Chromosom 3	Klarzelliges RCC	Noch keine definiert

5.2 Empfehlungen zur operativen Intervention bei bestätigten heriditären Tumorsyndromen lt. NCCN[25]

- Preoperative alert: Patients with a suspected or known diagnosis of PGL/PCC or VHL are at increased risk of pheochromocytomas and should have blood and/or urine screening for this prior to any surgical procedure.

BAP1-TPDS
- No specific guidelines in surgical management for this syndrome (See KID-A).

BHDS
- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.[1]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

HLRCC
- As these tumors can be aggressive, surveillance of renal tumors is not recommended, and total radical nephrectomy should be considered.[2]

HPRC
- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

PGL/PCC
- Malignant tumors absent aggressive histology and early stage should undergo surgical resection; partial nephrectomy can be considered.
- For larger tumors and those with aggressive histology (eg, high grade, sarcomatoid), radical nephrectomy should be considered.[3]

TSC
- AML is a benign lesion associated with TSC and managed separately.[4,5,6]
- Nephron-sparing surgery is the treatment of choice for malignant renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.[7]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

VHL
- Management of localized renal masses in patients with VHL are typically guided under the "3 cm rule."[7]
- The idea is to intervene at a time point of maximal benefit to the patient to limit the chance of development of metastatic disease but also to consider the recurrent and multiple resections many of these patients will have over the course of their lifetime with subsequent development of chronic and progressive renal failure.[7,8]
- Patient should undergo partial nephrectomy if at all possible and consider referral to centers with surgical expertise in complex partial nephrectomies and management of VHL patients.[8]
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

5.3 Empfehlungen zur systhemischen Therapie bei bestätigten heriditären Tumorsyndromen lt. NCCN[25]

HLRCC
- There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab[1] demonstrated benefit in patients with metastatic RCC from HLRCC (See KID-C).[2]

TSC
- Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter.[3]

VHL Disease
- At this time there are no FDA-approved therapies for nonmetastatic RCC arising in VHL disease. However, pazopanib was associated with a >50 % objective response rate in renal lesions in a 31-patient phase II study.[4]

5.4 Empfehlungen zum Follow up bei bestätigten heriditären Tumorsyndromen lt NCCN[25]

General
- Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.
- Whenever possible, screening should be coordinated with other specialist involved in patient's care.
- Women of childbearing age who are planning conception should consider renal imaging prior to pregnancy.
- If there is a family member with an early diagnosis, screening should begin 10 y before earliest age of diagnosis in family member.
- CT of the abdomen can be used for surgical planning but should be limited if possible for surveillance due to lifetime radiation exposure for hereditary syndromic patients.
- Imaging frequency would be increased once lesions are detected based on growth rate and size of lesion(s).
- For surgical recommendations for each syndrome, see HRCC-C; for systemic therapy, see HRCC-D.

***BAP1*-TPDS**
- Abdominal MRI (preferred) or CT with and without IV contrast every 2 y starting at age 30 y[1]

BHDS
- Abdominal MRI (preferred) or CT with and without IV contrast every 3 y starting at age 20 y[2]

HLRCC
- Abdominal MRI (preferred) or CT with and without IV contrast annually starting at age 8–10 y[3]

HPRC
- Abdominal MRI (preferred) or CT with and without IV contrast every 1–2 y starting at age 30 y[4,5]

PGL/PCC
- Abdominal MRI (preferred) or CT with and without IV contrast every 4–6 y starting at age 12 y[5,6,8]

TSC
- Abdominal MRI (preferred) or CT with and without IV contrast every 3–5 y starting at age 12 y[7]

VHL
- Abdominal MRI (preferred) or CT with and without IV contrast to assess kidneys, pancreas, and adrenals every 2 y starting at age 15 y[5]

6 Nebenwirkungsmanagment

Nebenwirkungsmanagment Immuntherapie lt. ESMO[26]

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

Alternativ ein PDF slide set mit besserer Übersicht.

7 Dokumentation und Qualitätsparameter

1. % LL-Konform behandelt (C37)
2. Perioperative Mortalität
3. % Tumorteilnephrektomie/Nephrektomie
4. PFS (Start first line therapy till progression or death)
5. OS

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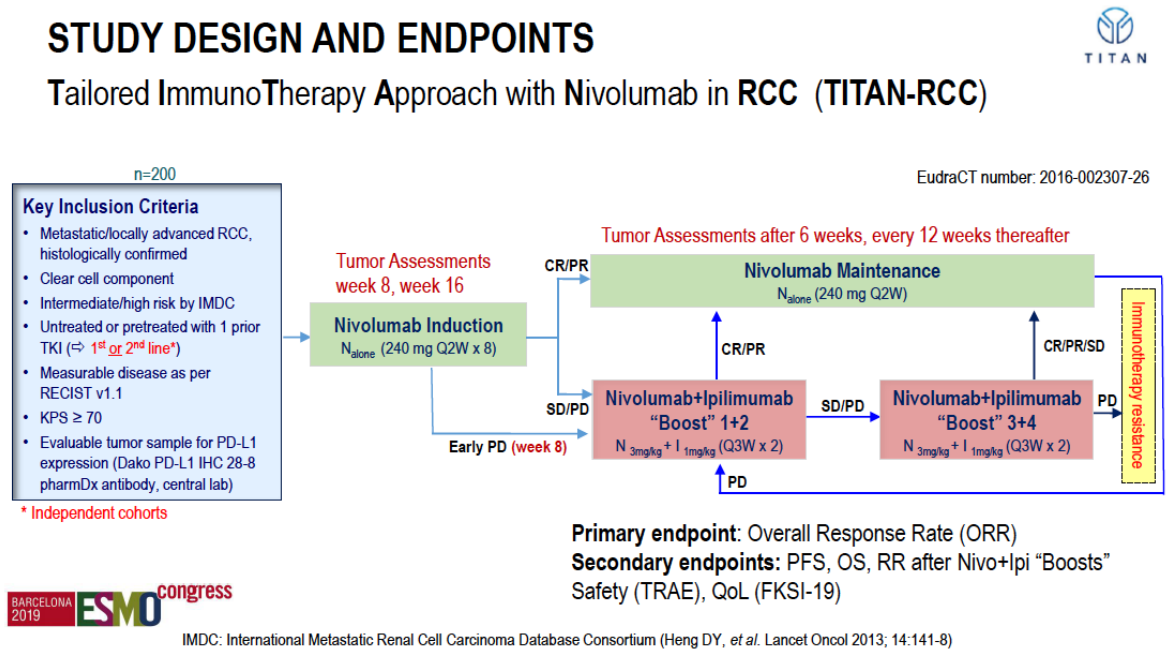
Anhang: Studienblatt

Zentrum	Studie	Präparat/Intervention	Indikation
OKL Eli	POD1UM (Incyte 0012-203)	PD1-Inhibitor (MGA012)	RCC, 1. Linie, M1
OKL Eli	CA209-914 (BMS)	Nivolumab (12x) + Ipilimumab (4x) vs. Placebo	RCC, adjuvant nach Nephrektomie, M0
OKL Eli	BMS FRACTION (CA018-005)	Kombi-Immuntherapien (Nivolumab, Ipilimumab, CCR2/5 dual antagonist,..)	RCC, alle Linien, Progress nach Immuntherapie
OKL Eli	COSMIC-313 (Exilixis)	Cabozantinib + Nivolumab + Ipilimumab vs. Nivolumab + Ipilimumab	RCC, 1. Linie, M1

Anhang: Chemotherapieprotokolle

Chemotherapie Option bei Ductus Bellini Karzinom:
1,250 mg/m ^{2} Gemcitabine Tag 1 und 8 plus 70 mg/m^2 Cisplatin oder Carboplatin (AUC 5) bei eingeschränckter Nierenfunktion am Tag 1; Zykluslänge 21 Tage; 6 Zyklen je nach Toxizität.[23]

URO - RCC: Ipilimumab (1), Nivolumab (3); d1, q3w
URO - RCC: Nivolumab (3) d1; q2w
URO - RCC: Nivolumab (6) d1;q4w
URO - RCC: Temsirolimus (25); q1w