Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-055 Pembrolizumab

Stand: Juni 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Pembrolizumab
zur adjuvanten Behandlung des Nierenzellkarzinoms

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"* Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use), Stand 26. März 2019: • Inhalatives Interleukin-2 (Proleukin®) zur Therapie des Nierenzellkarzinoms (nicht verordnungsfähig) Beschluss des G-BA vom 15. Oktober 2009 über eine Rücknahme eines Auftrags an die Expertengruppe Off-Label im Fachbereich Onkologie: Interferon-alpha und Interleukin-2-basierte Immunochemotherapien beim metastasierten Nierenzellkarzinom und in der adjuvanten Therapie
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• keine
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01XC18 KEYTRUDA®	Geplantes Anwendungsgebiet laut Beratungsanforderung: „KEYTRUDA ist (als Monotherapie) zur adjuvanten Behandlung des Nierenzellkarzinoms angezeigt.“
Es konnten keine zugelassenen Arzneimittel identifiziert werden.	

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adeverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DFS	Disease free survival
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KCE	Belgian Health Care Knowledge Centre
KI	Konfidenzintervall
LoE	Level of Evidence
MPA	medroxyprogesterone acetate
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	overall survival
PFS	Progression free survival
RCC	renal cell carcinoma
RoB	Risk of bias
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
VEGFR	Vascular Endothelial Growth Factor
WHO	World Health Organization

1 Indikation

zur adjuvanten Behandlung des Nierenzellkarzinoms.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Nierenzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.02.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1580 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 9 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2009 [4].

Beschluss des Gemeinsamen Bundesausschusses über die Rücknahme eines Auftrags an die Expertengruppe Off-Label im Fachbereich Onkologie: Interferon alpha und Interleukin-2-basierte Immunochemotherapien beim metastasierten Nierenzellkarzinom und in der adjuvanten Therapie vom 15. Oktober 2009.

Fazit

Der Auftrag an die Expertengruppe Off-Label im Fachbereich Onkologie zur Erstellung einer Bewertung zum Stand der wissenschaftlichen Erkenntnis über die Anwendung von Interferon alpha und Interleukin-2-basierte Immunochemotherapien beim metastasierten Nierenzellkarzinom und in der adjuvanten Therapie wird zurückgenommen.

Eckpunkte der Entscheidung:

Zwischenzeitlich ist die Zulassung von verschiedenen neuen Arzneimitteln zur Behandlung des metastasierten Nierenzellkarzinoms erfolgt. Aufgrund der somit bestehenden Vielzahl an therapeutischen Alternativen wird der Auftrag an die Expertengruppe zur Bewertung von Interferon alpha und Interleukin-2-basierten Immunochemotherapien beim metastasierten Nierenzellkarzinom zurückgenommen.

G-BA, 2018 [5].

Richtlinie des Gemeinsamen Bundesausschusses über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie/AM-RL). Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use), letzte Änderung in Kraft getreten am 19.01.2019. Teil B - Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) NICHT verordnungsfähig sind: Inhalatives Interleukin-2 (Proleukin®) zur Therapie des Nierenzellkarzinom.

Fazit

Teil B: Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind

- Inhalatives Interleukin-2 (Proleukin®) zur Therapie des Nierenzellkarzinoms

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Sun M et al., 2018 [9].

Adjuvant Vascular Endothelial Growth Factor–targeted Therapy in Renal Cell Carcinoma: A Systematic Review and Pooled Analysis

Fragestellung

To systematically evaluate the current evidence regarding the therapeutic benefit (disease-free survival [DFS] and overall survival [OS]) and grade 3–4 adverse events (AEs) for adjuvant VEGFR-targeted therapy for resected localized RCC.

Methodik

Population:

- Patients diagnosed with non-metastatic RCC who received adjuvant VEGFR-targeted therapy or placebo after nephrectomy

Intervention:

- VEGFR-targeted therapy (sunitinib, sorafenib, axitinib, pazopanib, dovitinib, cabozantinib, tivantinib, and erlotinib)

Komparator:

- Placebo

Endpunkte:

- DFS and overall survival (OS), AEs

Recherche/Suchzeitraum:

- PubMed/Medline, Embase, and the Cochrane Library in January 2018

Qualitätsbewertung der Studien:

- Risk of bias (RoB) was performed using the Cochrane Collaboration RoB tool for RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- The three randomized controlled phase III trials included the following comparisons: sunitinib versus placebo or sorafenib versus placebo (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma [ASSURE] study, n = 1943), sunitinib versus placebo (S-TRAC, n = 615), and pazopanib versus placebo (Pazopanib As Adjuvant Therapy in Localized/Locally Advanced RCC After Nephrectomy study, n = 1135)

Qualität der Studien:

- The RoB was considered low across all included studies.

Studienergebnisse:

- The pooled analysis showed that VEGFR-targeted therapy was not statistically significantly associated with improved DFS (hazard ratio [HR random]: 0.92, 95% confidence interval [CI]: 0.82–1.03, p = 0.16) or OS (HR random: 0.98, 95% CI: 0.84–1.15, p = 0.84) compared with the control group.
- The adjuvant therapy group experienced significantly higher odds of grade 3–4 AEs (OR random: 5.89, 95% CI: 4.85–7.15, p < 0.001).
- In exploratory analyses focusing on patients who started on the full-dose regimen, DFS was improved in patients who received adjuvant therapy (HR random: 0.83, 95% CI: 0.73–0.95, p = 0.005).

Anmerkung/Fazit der Autoren

This pooled analysis of reported randomized trials did not reveal a statistically significant effect between adjuvant VEGFR-targeted therapy and improved DFS or OS in patients with intermediate/high-risk local or regional fully resected RCC. Improvement in DFS may be more likely with the use of full-dose regimens, pending further results. However, adjuvant treatment was associated with high-grade AEs.

Kommentare zum Review

- only three studies with certain degree of heterogeneity
- Siehe auch Sonbol et al., 2018 [8].

Bai Y et al., 2018 [1].

Adjuvant therapy for locally advanced renal cell carcinoma: A meta-analysis and systematic review

Fragestellung

to analyze the role and safety of adjuvant therapy in renal cancer setting

Methodik

Population:

- patients with loco-regional RCC

Intervention:

- adjuvant therapy (chemotherapy, vaccine therapy, immune therapy, and targeted therapy)

Komparator:

- no active treatment after surgery

Endpunkte:

- DFS, OS, PFS, AEs

Recherche/Suchzeitraum:

- PubMed, EMBASE, Web of Science, and the Cochrane Library for relevant studies before 23 April 2017.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twelve trials were identified that were published or presented between 1996 and 2017
- Considering the selected trials, 2 trials tested targeted therapy, 3 trials vaccine therapy, 5 trials immune therapy, 1 trial chemo- therapy, and 1 thalidomide alone. Besides, the Ravaud trial and the Chamie trial made a strict restriction on histologic subtypes that they enrolled only patients who had histologically confirmed RCC with a clear cell component.
- The remaining trials accepted all pathological subtypes. Particularly, the entrance criterion of Ravaud trial that TNM stage III or IV was even higher than other trials. Among the analyzed patients, approximately 18% had pT2, 68% pT3, 2%pT4, while 10% of patients had node-positive disease. Moreover, most eligible trials accepted patients with all subtypes of renal cancer except 1 trial.

Qualität der Studien:

- Our analyzed trials were of sufficient quality. Most studies reported random sequence generation but allocation concealment, for some studies were designed with open- label, may result to some uncertain bias. Regarding out- come reporting, some studies reported intention-to-treat analysis of OS and DFS; for 1 trial, the data of OS have not yet matured for meta-analysis.

Studienergebnisse:

- Adjuvant therapy did not contribute to overall survival or disease-free survival when compared to placebo or observation.
- No survival benefit was observed according to subgroup analyses (targeted therapy, vaccine therapy, and immune therapy).
- Moreover, adjuvant therapy increased obviously the risk of toxicities:
  - hypertension (OR = 3.22; 95% CI: 1.90–5.46,P= 0.000),
  - fatigue (OR = 3.43; 95% CI: 2.03–5.79,P = 0.000),
  - rash (OR = 6.18; 95% CI: 1.51–25.33,P = 0.011),
  - hand-foot syndrome (OR = 11.38; 95% CI: 2.40–53.91, P = 0.000),
  - diarrhea (OR = 14.17; 95% CI: 1.68–119.55; P = 0.015),
  - pain (OR = 3.24; 95% CI: 2.34–4.47; P = 0.000), and
  - infection (OR = 1.88; 95% CI: 1.06–3.33, P = 0.030).

Anmerkung/Fazit der Autoren

The systematic review confirms that as a whole, adjuvant therapies-targeted therapy, vaccine therapy, and immune therapy are not effective for RCC, and even harmful.

Kommentare zum Review

- different adjuvant therapies
- absence of adequate data on toxicity

3.4 Leitlinien

AWMF, 2017 [6].

Leitlinienprogramm Onkologie (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe)

Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms; S3-Leitlinie, Langversion 1.2

Leitlinienorganisation/Fragestellung

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms.

Methodik

Grundlage der Leitlinie

- Vorversion aus 2015: Aktualisierung um Themen (Amendement)
  - Systemtherapie des metastasierten klarzelligen Nierenzellkarzinoms
  - Adjuvante Therapie
- Fragestellungen definiert, konkretisiert und konsentiert durch die Leitliniengruppe am 29.10.2012.
- Zur adjuvanten Therapie wurde sich auf Expertenkonsens als primäre Bearbeitungsstrategie verständigt.
- Leitlinienadaption: Suche nach publizierten Leitlinien zu Diagnostik und Therapie des Nierenzellkarzinoms im August 2012, Bewertung mittels DELBI.
- Systematische Literaturrecherchen: Zur adjuvanten Therapie nicht durchgeführt in Version 1.0 und nicht durchgeführt für Amendement 2016
- 3 Konsensuskonferenzen, finale schriftliche Abstimmung, DELPHI- Prozess
- Amendement 2016 erforderlich, weil neue Erkenntnisse durch Publikation zwischenzeitlich abgeschlossener Studien vorlagen, die den Leitlinienautoren bekannt waren.

LoE: Verwendung nach Scottish Intercollegiate Guidelines Network (SIGN)

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
1- -	Alle-oder-Keiner
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z.B. Fallberichte, Fallserien
4	Expertenmeinung

GoR:

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann /kann verzichtet werden

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Dissens	<50% der Stimmberechtigten

- Statements: Als Statements werden Darlegungen oder Erläuterungen von spezifischen Sachverhalten oder Fragestellungen ohne unmittelbare Handlungsaufforderung bezeichnet. Sie werden entsprechend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens verabschiedet und können entweder auf Studienergebnissen oder auf Expertenmeinungen beruhen.

- Expertenkonsens (EK): Statements/Empfehlungen, für die eine Bearbeitung auf der Grundlage von Expertenkonsens (es erfolgt keine systematische Recherche) der Leitliniengruppe beschlossen wurde, sind als „Expertenkonsens“ ausgewiesen. Für die Graduierung der Empfehlungen die auf Expertenkonsens basieren, werden keine Empfehlungsstärken mittels Buchstaben verwendet.

Sonstige methodische Hinweise

- CoI dokumentiert und einsehbar
- Expertenkonsens als primäre Bearbeitungsstrategie zur adjuvanten Therapie festgesetzt. Im Addendum 2016 wurde zusätzlich die Phase-III-Studie (ASSURE-Studie) zu adjuvanten Therapie berücksichtigt. Aufgrund der negativen Ergebnisse wurde die Empfehlung nicht verändert, der Hintergrundtext wurde um die Studienergebnisse ergänzt.

Empfehlungen

9.4.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad A	Eine adjuvante Immuntherapie oder Vakzinierungstherapie soll nicht durchgeführt werden.	
Level of Evidence 1++	Literatur: [483-492]	
	Konsens	

9.5.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad A	Eine adjuvante Behandlung mit Target-Therapie (Multikinase-Inhibitoren, mTOR-Inhibitoren) soll nur in Studien durchgeführt werden.	
Level of Evidence 4	Literatur: [476-478, 481, 492]	
	Starker Konsens	

Hintergrund:

- Kein Vorteil für adjuvante Behandlung (Immuntherapie, Vakzinierung, klassische Chemotherapie, Thalidomid) bezüglich Verlängerung des DFS (disease free survival) oder OS (overall survival) im Vergleich zur unbehandelten Kontrollgruppe in Metaanalyse von 10 RCTs mit 2.609 Patienten [492].
- Metaanalyse von 7 vor allem retrospektiven Arbeiten mit 735 Patienten mit adjuvanter Strahlentherapie zeigte Senkung des Lokalrezidivrisikos bei älteren Bestrahlungstechniken, jedoch kein Einfluss auf Überleben [493].
- Keine Belege für Nutzen einer adjuvanten Immuntherapie mit Interferon-alpha, hochdosiertem Interleukin-2, Interleukin-2 mit CD8-positiven tumorinfiltrierenden Lymphozyten noch einer Kombination von Interferon-alpha und Interleukin-2 allein oder mit Chemotherapie [483-488].
- Keine Belege für den Nutzen einer adjuvanten Vakzinierung mit autologen bestrahlten Tumorzellen plus Bacillus Calmette-Guérin als auch mit HSPPC-96 [489, 490].

- Keine Belege für den Nutzen einer adjuvanten Hormontherapie, z. B. mit Medroxyprogesteronacetat [494].
- Keine Belege für den Nutzen einer adjuvanten Target-Therapie [495].

483. Pizzocaro, G., et al., Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. J Clin Oncol, 2001. 19(2): p. 425-31. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/11208835
484. Messing, E.M., et al., Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. J Clin Oncol, 2003. 21(7): p. 1214-22.
485. Figlin, R.A., et al., Multicenter, randomized, phase III trial of CD8(+) tumor-infiltrating lymphocytes in combination with recombinant interleukin-2 in metastatic renal cell carcinoma. J Clin Oncol, 1999. 17(8): p. 2521-9.
486. Clark, J.I., et al., Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. J Clin Oncol, 2003. 21(16): p. 3133-40. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/12810695
487. Passalacqua, R., et al., Adjuvant low-dose interleukin-2 (IL2) plus interferone-alpha (IFN) in operable renal cell cancer (RCC). A phase III, randomized, multicenter, independent trial of the Italian Oncology Group for Clinical Research (GOIRC). J Clin Oncol, 2007. 25(20 Suppl): p. LBA5028.
488. Atzpodien, J., et al., Adjuvant treatment with interleukin-2- and interferon-alpha2a-based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: results of a prospectively randomised trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). Br J Cancer, 2005. 92(5): p. 843-6. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/15756254
489. Galligioni, E., et al., Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guérin: five-year results of a prospective randomized study. Cancer, 1996. 77(12): p. 2560-6. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/8640706
490. Wood, C., et al., An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. Lancet, 2008. 372(9633): p. 145-54. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18602688
491. Jocham, D., et al., Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. Lancet, 2004. 363(9409): p. 594-9. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/14987883
492. Scherr, A.J., et al., Adjuvant therapy for locally advanced renal cell cancer: a systematic review with meta-analysis. BMC Cancer, 2011. 11: p. 115. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/21453469
493. Tunio, M.A., A. Hashmi, and M. Rafi, Need for a new trial to evaluate postoperative radiotherapy in renal cell carcinoma: a meta-analysis of randomized controlled trials. Ann Oncol, 2010. 21(9): p. 1839-45.
494. Pizzocaro, G., et al., Adjuvant medroxyprogesterone acetate to radical nephrectomy in renal cancer: 5-year results of a prospective randomized study. J Urol, 1987. 138(6): p. 1379-81. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/2824861
495. Haas, N.B., et al., Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet, 2016. 387(10032): p. 2008-16.

Ljungberg B et al., 2017 [7].

European Association of Urology

Guidelines on renal cell carcinoma

Leitlinienorganisation/Fragestellung

Clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

Methodik

Grundlage der Leitlinie

- Limited update of the 2016 publication
- Neue Empfehlungen im Kapitel „Adjuvant therapy“
- Kapitel zur adjuvanten Therapie “updated using a structured literature assessment”
- Peer Review: Chapter 7 ‘Disease management’ [beinhaltet Kapitel zur adjuvanten Therapie] was peer reviewed prior to publication. Publications ensuing from SRs have all been peer reviewed.

- Suchzeitraum (Update): July 2015 - June 2016 in Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase, Ovid MEDLINE

LoE/GoR

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

Summary of Evidence (SOE) tables provided for each recommendation address a number of key elements:

- 1. the overall quality of the evidence which exists for the recommendation;
- 2. the magnitude of the effect (individual or combined effects);
- 3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
- 4. the balance between desirable and undesirable outcomes;
- 5. the impact of patient values and preferences on the intervention;
- 6. the certainty of those patient values and preferences.

The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ and is directional, either ‘do it’ (as represented by arrows pointing upwards) or ‘do not do it’ (arrows pointing downwards).

The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Sonstige methodische Hinweise

- CoI dokumentiert und online einsehbar.
- Evidenz- und konsensbasierte Leitlinie entsprechend deutscher S3-Klassifikation.

Empfehlungen

7.2.5.1.Summary of evidence and recommendations for adjuvant therapy

Summary of evidence		LE
Adjuvant cytokines do not improve survival after nephrectomy.		1b
Adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival, after nephrectomy in selected high-risk patients.		1b
Recommendations	**grade**	
Do not offer adjuvant therapy with sorafenib.	strong	↓↓
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.	weak	↓

Hintergrund

- No evidence from randomised phase III trials for survival benefit of
  - adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas [323-327] (LE: 1b),
  - interferon-alpha (IFN-α) and interleukin-2 (IL-2) [328],
  - heat shock protein-peptide complex-96 (vitespen) [329] in overall sample,
  - girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER) [330],
- ASSURE study on with 1:1:1 to sunitinib, sorafenib, or placebo showed no benefit in DFS and OS [162].
- In S-TRAC study with adjuvant Sunitinib vs placebo the HR was 0.76 (95% CI 0.59–0.98; p = 0.03) for DFS, and OS was immature. Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib.
- The panel, including representatives from a patient advocacy group (IKCC), voted and reached a consensus decision to not recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy [331].

162.Haas, N.B., et al. Initial results from ASSURE (E2805): Adjuvant sorafenib or sunitinib for unfavorable renal carcinoma, an ECOG-ACRIN-led, NCTN phase III trial. ASCO Meeting Abstracts, 2015. 33: 403.
323.Galligioni, E., et al. Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: five-year results of a prospective randomized study. Cancer, 1996. 77: 2560.
324.Figlin, R.A., et al. Multicenter, randomized, phase III trial of CD8(+) tumor-infiltrating lymphocytes in combination with recombinant interleukin-2 in metastatic renal cell carcinoma. J Clin Oncol, 1999. 17: 2521.
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Benahmed N et al., 2015 [2].

Belgian Health Care Knowledge Centre (KCE)

Renal cancer in adults: diagnosis, treatment and follow-up.

Leitlinienorganisation/Fragestellung

This guideline provides recommendations based on current scientific evidence for the diagnosis, treatment, follow-up and supportive care of patients with renal cancer.

Methodik

Grundlage der Leitlinie

- Clinical questions were developed in collaboration with members of the Guideline Development Group.
- Collaboration between multidisciplinary groups of practicing clinicians and KCE experts
- Search for high-quality, recent guidelines in Medline, the NGC and the GIN database
- If high quality guidelines not sufficient, systematic search in MEDLINE, EMBASE and the Cochrane Library + search for primary studies published after the search date of the most complete review performed in MEDLINE, EMBASE and CENTRAL.
- Suchzeitraum: ≥ 2009-2014
- Critical appraisal with AGREE II, AMSTAR, QUADAS-2, Cochrane Collaboration's tool for assessing risk of bias

LoE/GoR

Table 1 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect.	RCTs without important limitations or overwhelming evidence from observational studies.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	RCTs with very important limitations or observational studies or case series.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 4 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice).*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice).*

Table 5 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted.

Empfehlungen

Factor	Comment
Balance between clinical benefits and harms	The balance is clearly negative because of the absence of benefit and the significant toxicity of adjuvant treatment.
Quality of evidence	The quality of evidence is very low. One study on the role of vaccines is very underpowered.

Targeted therapy as adjuvant treatment is out-of-scope of the current guideline. However, a recent published trial (ASSURE) tested sorafenib and sunitinib as adjuvant therapy in patients with locally advanced RCC at high risk of recurrence.[97] The authors concluded that neither sorafenib nor sunitinib offers benefits above or beyond placebo.

Recommendation	Strength of Recommendation	Level of Evidence
• Adjuvant therapy is not recommended outside clinical trials.	Strong	Very low

<u>Radiotherapy</u>

- No recent RCT found on the topic
- Most recent RCT [86]: No benefit in relapse rates and in survival for patients with renal adenocarcinoma, huge complication rate reported in the radiotherapy group (44%)

<u>Hormones</u>

- Adjuvant medroxyprogesterone acetate (MPA) after radically resection of a renal cancer was compared to no adjuvant treatment in 120 Italian patients without metastasis.[91]
- No statistically significant difference in 5-year survival rate

<u>Chemotherapy</u>

- No improvement of the 2- and 3-year[80] or 5-year[90] cancer specific survival found

<u>Immunotherapy and adoptive immunotherapy</u>

- Cytokines as adjuvant treatment of nephrectomy in RCC were tested in four trials.[79, 82, 87, 88]
- No advantage in overall survival, in median survival or in disease free survival in all trials, high toxicity in all but 1 RCT[87]
- No improvement in response rate or survival for adoptive immunotherapy[83]

Immuno-chemotherapy

- 2 trials [71,81] failed to show any statistically significant benefit for the postoperative adjuvant immune-chemotherapy in terms of DFS or OS
- Treatment associated with significant toxicity

Vaccines

- 1 trial[85] with advantage of vaccine for 5-year progression-free survival (in subgroup analysis only noted in T3 tumours)
- 1 RCT with no advantage in terms of recurrence-free survival or OS

Targeted therapy

- ASSURE trial[97]: neither sorafenib nor sunitinib offers benefits above or beyond placebo.

Conclusions

- Adjuvant therapies after nephrectomy in non-metastatic RCC such as radiotherapy, chemotherapy, immunotherapy (cytokines or vaccine) or immuno-chemotherapy did not show any improvement in disease free or overall survival.
- Significant toxicity was generally associated with these adjuvant treatments.

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Gallardo E et al., 2018 [3].

Spanish Society of Medical Oncology (SEOM)

SEOM clinical guideline for treatment of kidney cancer (2017).

Leitlinienorganisation/Fragestellung

to provide recommendations about the management of kidney cancer.

Methodik

Grundlage der Leitlinie

The SEOM guidelines have been developed with the consensus of ten genitourinary cancer oncologists from SEOM (Spanish Society of Medical Oncology) and SOGUG (Spanish Oncology Genitourinary Group).

Table 1 Levels of evidence/grades of recommendation

Levels of evidence
I Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III Prospective cohort studies
IV Retrospective cohort studies or case–control studies
V Studies without control group, case reports, experts opinions
Grades of recommendation
A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages; optional
D Moderate evidence against efficacy or for adverse outcome, generally not recommended
E Strong evidence against efficacy or for adverse outcome, never recommended

Statements without grading were considered justified standard clinical practice by the SEOM/SOGUG faculty and experts.

Sonstige Hinweise:

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Empfehlungen

Local and locoregional disease

- Partial nephrectomy is recommended in T1 tumors, if technically feasible, as well as in bilateral tumors or a single functional kidney. Radical nephrectomy is recommended in T2-4 tumors. Level of evidence: III. Grade of recommendation: A.
- Adjuvant therapy with sunitinib over 1 year after nephrectomy could be an option to consider individually in patients with high-risk features. However, there is still insufficient evidence to recommend this therapy routinely in clinical practice. Level of evidence: II. Grade of recommendation: C.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2019) am 20.12.2019

#	Suchfrage
1	[mh "Carcinoma, Renal Cell"]
2	((renal and cell) or kidney* or nephroid* or hypernephroid* or grawitz* or collecting duct):ti,ab,kw
3	(cancer* or tum*r* or carcinoma* or neoplas* or adenocarcinoma* or sarcoma* or lesion* or malign*):ti,ab,kw
4	#2 and #3
5	(hypernephroma* or rcc):ti,ab,kw
6	#1 or #4 or #5
7	#6 Publication Year from 2014 to 2019

Systematic Reviews in Medline (PubMed) am 19.02.2019

#	Suchfrage
1	((((("carcinoma, renal cell/drug therapy"[mh] OR "carcinoma, renal cell/radiotherapy"[mh] OR "carcinoma, renal cell/therapy"[mh]))))
2	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
3	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	(#5) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
7	#1 OR #6
8	(#7) AND ((Meta-Analysis[ptyp] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND systematic review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (systematic review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence)))

	AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
9	((#8) AND ("2014/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 20.12.2019

#	**Suchfrage**
1	((((("carcinoma, renal cell/drug therapy"[mh] OR "carcinoma, renal cell/radiotherapy"[mh] OR "carcinoma, renal cell/therapy"[mh]))))
2	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
3	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	(#5) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
7	#1 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
9	(((#8) AND ("2014/02/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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