Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-10-01-D-314 Atezolizumab

Stand: März 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Atezolizumab **[zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms]** **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 „Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*„nicht angezeigt“*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Beschluss vom 21. Dezember 2017 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab*
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:	
Atezolizumab N.N. Tecentriq®	Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC) nach vorheriger platinhaltiger Chemotherapie oder bei erwachsenen Patienten, die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden (siehe Abschnitt 5.1).
Pembrolizumab L01XC18 Keytruda®	KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind, angezeigt. KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms nach vorheriger Platin-basierter Therapie bei Erwachsenen angezeigt (siehe Abschnitt 5.1).
Nivolumab L01XC17 Opdivo®	Anwendungsgebiet laut Zulassung: OPDIVO ist als Monotherapie zur Behandlung des lokal fortgeschrittenen nicht resezierbaren oder metastasierten Urothelkarzinoms bei Erwachsenen nach Versagen einer vorherigen platinhaltigen Therapie indiziert.
Vinflunin L01CA05 Javlor®	Zur Monotherapie bei fortgeschrittenem oder metastasierendem Übergangszellkarzinom des Urothels bei erwachsenen Patienten, nach Versagen einer platinhaltigen Behandlung. Die Wirksamkeit und Sicherheit von Vinflunin in Patienten mit einem Performance Status ≥ 2 wurden nicht untersucht. (FI Javlor®, Stand: Juni 2014)
Cisplatin L01XA01 generisch	Cisplatin Teva wird angewendet zur Behandlung des: – fortgeschrittenen oder metastasierten Harnblasenkarzinoms Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. (FI Cisplatin Teva® 1 mg/ml Konzentrat, Stand: März 2015)
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: – Systemische Therapie des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms (FI Adrimedac® 2 mg/ml Infusionslösung, Stand: September 2013)
Gemcitabin L01BC05 generisch	Gemcitabin ist in Kombination mit Cisplatin zur Behandlung des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms angezeigt. (FI Gemcitabin Kabi 38 mg/ml Konzentrat, Stand: Mai 2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Methotrexat L01BA 01 generisch	Methotrexat medac 25 mg/ml Injektionslösung wird angewendet bei: Harnblasenkarzinomen – in Kombination mit anderen zytotoxischen Arzneimitteln (FI Methotrexat medac 25 mg/ml Injektionslösung, Stand: April 2015)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Urothelkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.06.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, ESMO, NCCN, NCI. 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 910 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 10 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation

Patienten mit lokal fortgeschrittenem oder metastasierendem Urothelkarzinom.

Berücksichtigte Wirkstoffe/Therapien

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen

AE	Adverse events
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCG	Bacillus Calmette-Guerin
CBC	complete blood count
CCO	Cancer Care Ontario
CIS	carcinoma in situ
CMV	cisplatin, methotrexate, vinblastine
Cr	creatinine
CT	computer tomography
CUA	Canadian Urology Association
CXR	chest x-ray
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
EAU	European Association of Urology
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GCa	gemcitabine plus carboplatin
GIN	Guidelines International Network
GT	Gemcitabine
Gy	unit of radiation dose
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, 6driamycin, and cisplatinum
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PLND	pelvic lymph node dissection
RR	Response Rate
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TURBT	transurethral resection of bladder tumour
UC	urothelial cancer
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

In der Recherche wurden keine relevanten IQWiG-Berichte oder G-BA-Beschlüsse identifiziert.

Cochrane Reviews

Shelley M et al., 2011 [8]. Gemcitabine for unresectable, locally advanced or metastatic bladder cancer (Review)	**1. Fragestellung** Evaluate the effectiveness and toxicity of gemcitabine for the management of unresectable, locally advanced or metastatic bladder cancer.
	2. Methodik *Population* Patients of any age or gender, with measurable or evaluable histologically proven, unresectable locally advanced (T3b-T4b) or metastatic (N2,N3,M1) transitional cell carcinoma of the bladder; Studies were assessable for relevance regardless of the performance status and malignancy status of the enrolled patients. *Intervention / Komparator* • single agent gemcitabine versus placebo; • gemcitabine combined with one cytotoxic versus the same cytotoxic alone; • gemcitabine combined with one cytotoxic versus gemcitabine combined with a different cytotoxic; • a multiple combination regime containing gemcitabine versus the same regime without gemcitabine; • a multiple combination regime containing gemcitabine versus a different multiple combination regime. *Endpunkt* Primary outcome Overall survival Secondary outcomes Progression-free survival, disease-specific survival, tumour response, toxicity, quality of life *Suchzeitraum (Aktualität der Recherche)* MEDLINE (from 1966), EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, LILACS, Web of Science up to March 2010 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 6 trials *Qualitätsbewertung der Studien:* Cochrane risk of bias tool

3. Ergebnisdarstellung

Study/ Com-para-tors	Overall survival			Disease progression			Tumour response		Grade 3-4 toxicities (%)			
	Rate %	Median months	HR (95% CI)	Rate %	Median months	HR (95% CI)	OR	CR	Neutro	Thrombo	Anaemia	Other (%)
Von der Masse 2005 GCis (n= 203) versus MVAC (n = 202)	5 year 13.0 15.3	14.0 15.3	1.09 (0.88-1.34, P = 0.44)	5 year 9.8 11.3	7.7 (6.8 to 8.8) 8.3 (7.3 to 9.7)	1.09 (0.89 to 1.34, P = 0.41)	49 46 P=0.51	12 12	71 82	57 21	27 17	sep Muc td 1* 1* 1 12 22 3
Doglottii 2007 GCis (n = 55) versus GCarbo	64 37 (NS)	12.8 9.8 (NS)	-	-	8.3 (7.5 to 9.1) 7.3 (5.1 to 10.3) NS	-	66 56	20 3	35 45	31 38	20 25	- -
Lorusso 2005 GCis versus GCis-Pac	- -	12.3 15.3 (NS)	-	33 29	6.5 8.0 (NS)	-	44 43 (NS)	7 12	Leuco 35* 49	21* 36	24 20	Muc neuro 5 5 0 0
DeSantis 2009 GCarbo versus MCarboV	- -	- -	-	-	-	-	38 20	3 3	6 14	3 0	- -	Muc Fever 1 6 6 14
Fechner 2006 GPac 2-weekly versus GPac 3-weekly	- -	9.0 13 (NS)	-	-	6.0 11.0 (NS)	-	39 50 (NS)	8 50*	Leuco 16 38	16 0	16 23	Alopecia 32 76*
Albers 2008 GPac 2-weekly versus GPac 3-weekly	- -	6.8 7.5 (P = 0.8)	-	-	3.3 4.5 (P = 0.5)	-	50 35 (NS)	- -	- -	- -	- -	- -

HR = Hazard Ratio, OR Overall Response, CR = Complete Response, GCis = Gemcitabine /Cisplatin, MVAC = Methotrexate/Vinblastine/Doxorubicin/Cisplatin, Neutro =Neutropenia, Thrombo = Thrombocytopenia, sep = neutropenic sepsis, Muc = Mucositis, td = toxic deaths, * statistically significant $p < 0.05$, GCarbo = gemcitabine/Carboplatin, NS =Not Significant (no p value given), Pac = Paclitaxel, Leuco = leucopenia, Neuro = neurotoxicity, MCarboV = Methotrexate/Carboplatin/Vinblastine

Critical appraisal

The studies of von der Masse et al. and de Santis et al. were considered at low-to-intermediate risk of bias. The other four studies of Albers et al., Doglotti et al., Lorusso et al., and Fechner et al. were considered at intermediate risk of bias.

	4. Anmerkungen/Fazit der Autoren A review of the published evidence found that one trial reported gemcitabine plus cisplatin had a better safety profile than MVAC and may be considered the first choice for treatment of metastatic bladder cancer. However, the data are limited to one trial only. Patients unable to tolerate cisplatin may benefit from gemcitabine plus carboplatin. **5. Hinweise durch FB Med** Albers et al. sowie Fechner et al. untersuchten in ihren Studien Patienten, die bereits zuvor eine Erstlinientherapie erhalten hatten. Von der Masse et al. sowie Lorusso et al. verabreichten in beiden Studienarmen Cisplatin-haltige Therapien.

Systematische Reviews

Necchi A et al., 2016 [6]. Efficacy and Safety of Gemcitabine Plus Either Taxane or Carboplatin in the First-Line Setting of Metastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis	**1. Fragestellung** A trial-level meta-analysis of phase II and III studies that reported on GCa or GT in the first line setting of metastatic UC […]
	2. Methodik Population: Patients with metastatic UC Intervention/Komparator: Gemcitabine plus either carboplatin or a taxane (including paclitaxel or docetaxel only). *Hinweis*: The administration of prior perioperative chemotherapy was allowed. Endpunkte: median OS (primärer Endpunkt), 1-year OS, Response rate (RR), median progression-free survival (PFS), and the rate of adverse events (AEs) Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche zwischen 1990 und 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 27 arms of trials accounting for a total of 1032 patients were selected for the meta-analysis → including 26 prospective and 1 retrospective studies (14 arms with a gemcitabine + carboplatin [n = 548], 13 with gemcitabine + taxane [n = 484]. Two trials were 2-arm randomized controlled trials in which 1 arm was included in this analysis; the remaining trials were single-arm trials *Hinweis*: A sub-analysis was performed including only those trials with no patients having received prior chemotherapy in the perioperative (ie, neoadjuvant/adjuvant) setting. Qualitätsbewertung der Studien: I^2 für Heterogenität. Publication bias was evaluated by visually inspecting funnel plots and using the Egger test for bias.--> keine weiteren Angaben.
	3. Ergebnisdarstellung (Univariable and Multivariable) Meta-Analyses for Response and Survival Outcome: • In univariable analyses, the median RR was not statistically different between the GT and GCa groups. Median PFS was also similar between the 2 groups. • The same results were observed for OS outcome across the 22 evaluable arms. → When considering studies not allowing prior perioperative treatment only, the results were confirmed.

	Subgruppenanalysen: Comparing GCa and GT groups after the removal of patients who had received prior perioperative chemotherapy: o the results did not change substantially for any outcome o Regarding the primary endpoint, there seemed not to be any difference between the GT and the GCa group (P = .79), whereas ECOG PS and the presence of visceral metastases seemed to attain statistical significance (P = .015 for both). Incidence of Grade 3 to 4 Acute Toxicities: *Hinweis*: Focus on Grade 3 to 4 toxicity due to the lack of information on all-grade side effects in most cases! • Statistically significant differences in the frequency of Grade 3 to 4 anaemia (P = .010), thrombocytopenia (P = .010), and peripheral neuropathy (P = .040) were observed. • Trials containing carboplatin had higher incidence of Grade 3 to 4 anaemia (median, 25.5% vs. 8.7%) and thrombocytopenia (28.0% vs. 5.3%), but lower rates of Grade 3 to 4 peripheral neuropathy (median, 0% vs. 8.3%). • Multivariably, the differences in the safety outcomes were confirmed: anaemia (P = .066), thrombocytopenia (P = .030), and peripheral neuropathy (P = .008).
	4. Fazit der Autoren: *In conclusion, the present trial-level meta-analysis supports the comparability of efficacy outcomes between GCa and GT chemotherapy in cisplatin-unfit patients with metastatic UC, with a nonoverlapping safety profile. As a consequence, GT may be included in the guidelines together with GCa as an option for the first-line therapy of cisplatin-ineligible patients. Additionally, the present study provides support to the advice that inclusion in trials of salvage investigational drugs may not be exclusively allowed to patients who have failed platinum-based chemotherapy but also to those who have received GT combination in first-line therapy. In routine clinical practice, our study may help physicians in the decision-making process and to tailor patient's information in the clinic.*
Raggi D et al., 2016 [7]. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic	1. **Fragestellung** We aimed to study the survival impact of single-agent compared with doublet chemotherapy as second-line chemotherapy of advanced UC.
	2. **Methodik** Population: Patients with metastatic UC Intervention/ Komparator: single-agent vs. doublet chemotherapy as second-line chemotherapy (konkretere Angaben siehe Ergebnisteil)

urothelial cancer: a systematic review and meta-analysis	Endpunkte: • primary endpoints: objective response rate (ORR), PFS, and OS; • secondary end point: incidence of acute (grade 3–4) toxicities Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche zwischen 1990 und 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt):46 arms of trials including 1910 patients were selected: 22 arms with single agent (n = 1202) and 24 arms with doublets (n = 708). Qualitätsbewertung der Studien: I^2 für Heterogenität. Publication bias was evaluated by visually inspecting funnel plots and using the Egger test for bias. --> keine weiteren Angaben.
	3. **Ergebnisdarstellung** • The pooled ORR with single agents was 14.2% [95% CI: 11.1–17.9] versus 31.9% [95% CI 27.3–36.9] with doublet chemotherapy. • Pooled median PFS was 2.69 and 4.05 months, respectively. • The pooled median OS was 6.98 and 8.50 months, respectively. • Multivariably, the odds ratio for ORR and the pooled median difference of PFS were statistically significant (P < 0.001 and P = 0.002) whereas the median difference in OS was not. • When including single-agent vinflunine or taxanes only, differences were significant only for ORR (P < 0.001) favouring doublet chemotherapy. • No statistically significant differences in grade 3–4 toxicity were seen between the two groups.
	4. Fazit der Autoren: *In conclusion, in the present meta-analysis comparing single agent to doublet second-line chemotherapy for UC, we identified a better activity of the latter in terms of ORR and PFS, but we did not find any statistically significant difference in OS. The general recommendation is to continue administering single agent taxanes or vinflunine outside of clinical trials, although a significant improvement of PFS and the trending-to-significance improvement of OS are suggesting a potentially meaningful benefit from combining agents with proven activity in UC. In addition to the development of novel compounds such as PD1 and PD-L1 inhibitors as single agents, the prospective evaluation of tolerable combinations of chemotherapeutic drugs as well as chemobiologic combinations is rational.*
Wu XJ et al., 2016 [10]. Comparison of	1. **Fragestellung** Systematic review of published clinical trials of single agent versus combined chemotherapy as salvage treatment in previously treated UC

single agent versus combined chemotherapy in previously treated patients with advanced urothelial carcinoma: a meta-analysis	patients.
	2. **Methodik** Population: Patients with UC who were refractory to previous chemotherapy Intervention/Komparator: combined chemotherapy vs. single agent chemotherapy *Hinweis*: patients who received molecular agent alone or chemotherapy plus molecular targeted agents were excluded for analysis in our study Endpunkte: objective response rate (ORR), disease control rate (DCR), median progression-free and overall survival (PFS, OS), and grade 3/4 toxicities Suchzeitraum (Aktualität der Recherche): Trials published between 1994 and 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 50 cohorts with 1,685 patients were included for analysis: 814 patients were treated with single agent chemotherapy and 871 with combined chemotherapy Qualitätsbewertung der Studien: Newcastle-Ottawa quality assessment scale. I^2 für Heterogenität.
	3. **Ergebnisdarstellung** • Pooled OS was significantly higher at 1 year for combined chemotherapy than for single agent (RR: 1.52; 95% CI: 1.01–2.37; P=0.03) but not for 2-year OS. • Additionally, combined chemotherapy significantly improved ORR (RR: 2.25; 95% CI: 1.60–3.18; P= 0.001) and DCR (RR: 1.12; 95% CI: 1.01–1.25, P=0.033) compared to single agent for advanced UC patients. • As for grade 3 and 4 toxicities, more frequencies of leukopenia and thrombocytopenia were observed in the combined chemotherapy than in single agent group. • Equivalent frequencies of anemia, nausea, vomiting, and diarrhea were found between the two groups.

Table 4 Comparison of higher than grade 3 toxic effect event rates for single agent versus combined chemotherapy

Toxicities	Included study	Events	Total	Events rate (95% CI)	I^2	RR (95% CI)	*P*-value
Hematologic toxicity							
Anemia							
Single agent	13	84	520	13.5 (9.2–19.4)	67.7	1	
Combination	26	110	765	14.6 (9.9–20.9)	49.7	1.08 (0.64–1.83)	0.39
Leukopenia							
Single agent	14	182	534	17.9 (9.2–32.1)	80.8	1	
Combination	26	327	724	45.5 (35.8–55.5)	88.0	2.54 (1.31–4.93)	<0.001
Thrombocytopenia							
Single agent	13	37	520	9.0 (6.6–12.1)	77.7	1	
Combination	26	118	724	15.9 (8.8–22.9)	40.3	1.77 (1.00–3.11)	0.024
Non-hematologic toxicity							
Nausea							
Single agent	9	16	399	5.6 (2.3–12.8)	61.1	1	
Combination	17	18	457	7.0 (4.6–10.3)	0	1.25 (0.48–3.23)	0.32
Vomiting							
Single agent	12	24	480	6.4 (3.5–11.6)	49.1	1	
Combination	16	12	419	6.0 (3.8–9.5)	0	0.93 (0.44–1.99)	0.43
Diarrhea							
Single agent	10	10	224	7.8 (4.4–13.5)	45.7	1	
Combination	12	11	327	4.9 (2.9–8.2)	0	0.63 (0.29–1.35)	0.12
Fatigue							
Single agent	9	74	372	17.7 (9.8–29.9)	70.3	1	
Combination	10	4	282	3.0 (1.5–6.1)	0	0.17 (0.07–0.42)	<0.001

Abbreviations: RR, relative risk; CI, confidence interval.

5. Fazit der Autoren:

Currently available clinical evidence for advanced UC patients indicates that combined chemotherapy may be a more efficient regimen for previously treated UC patients, but with more frequencies of grade 3 and 4 myelosuppression toxicities compared with single agent. However, since the overall quantity and quality of data regarding salvage chemotherapy is poor, there might be risk of bias in comparisons between observation studies. No definite conclusions were attained from the results. As a result, prospective randomized studies, definitively comparing the survival and treatment toxicity between combined chemotherapy and single agent, are strongly recommended to clearly determine the role of combined chemotherapy as salvage treatment for previously treated UC patients.

5. Anmerkungen der FBMed:

- First and most importantly, the application of formal meta-analytic methods to observational studies was controversial
- the study was a pooled analysis of primarily single-arm prospective studies and retrospective series, with a small number of patients included that might have overreported the benefit of preoperative treatments
- patients included that were treated with different combination or single agent chemotherapy for analysis, which would increase the clinical heterogeneity among included trials, which also made the interpretation of a meta-analysis more problematic.

Leitlinien

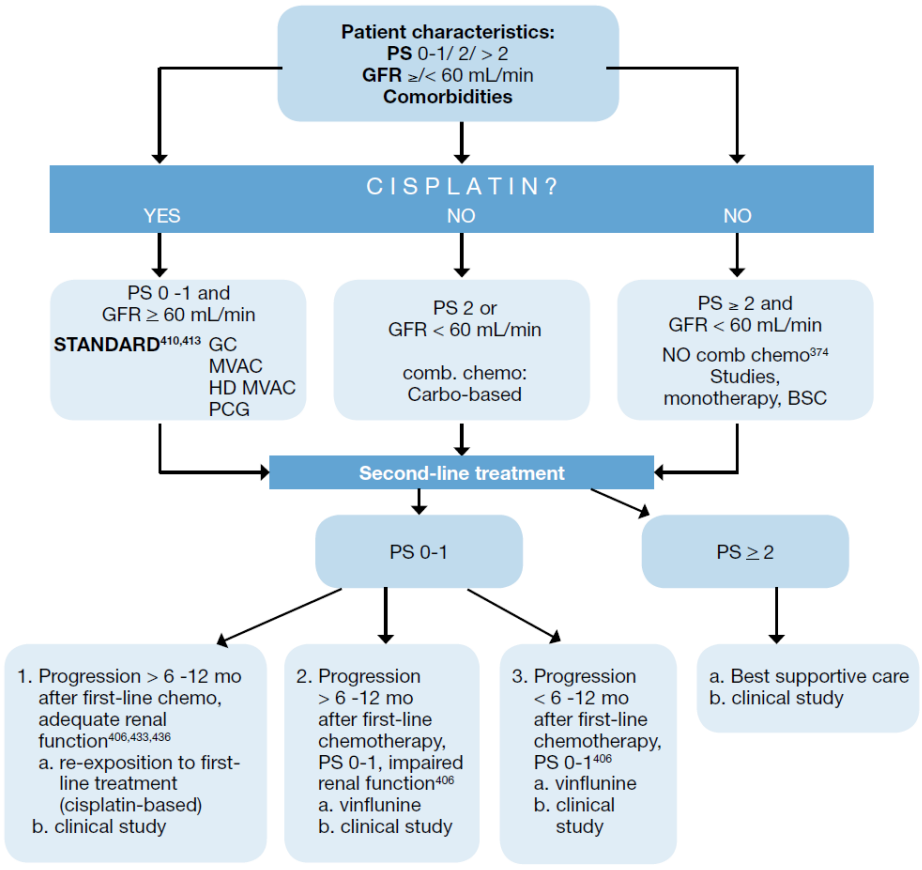
Witjes JA et al, 2015 [9]. European Association of Urology Guidelines on Muscle-invasiveand Metastatic Bladder Cancer	**Fragestellung/ Zielsetzung:** The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) has prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.
	Methodik Grundlage der Leitlinie The recommendations provided in the current guidelines are based on literature searches performed by the expert panel members. A systemic literature search was performed for the systematic review of the role and extent of lymphadenectomy during radical cystectomy for cN0M0 muscle-invasive bladder cancer (see Section 7.4: Radical surgery and urinary diversion. There is clearly a need for continuous re-evaluation of the information presented in the current guidelines by an expert panel. It must be emphasised that these guidelines contain information for the treatment of individual patients according to a standardised approach. In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.
	Freitext/Empfehlungen/Hinweise 7.8.7 Second-line treatment Second-line chemotherapy data are highly variable and prognostic factors have been established recently A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least 6-12 months after first-line cisplatin-based combination chemotherapy. Second-line response rates of paclitaxel (weekly), docetaxel, nab-paclitaxel oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials . Although gemcitabine has also shown excellent response rates in second-line use, most patients already receive this drug as part of their front-line treatment . Paclitaxel/gemcitabine studies have shown response rates of 38-60%. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this secondline combination. Vinflunine, a novel third-generation vinca alkaloid, provided promising

results in phase II trials. A randomised phase III trial compared vinflunine plus best supportive care (BSC) against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment.

Conclusions	LE
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reaches the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival.	3
Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay skeletal related events in metastatic bone disease.	1b

Recommendations	GR
First-line treatment for fit patients:	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	B
Second-line treatment:	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	A*
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

** Grade A recommendation is weakened by a problem of statistical significance.*
GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; GR = grade of recommendation; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; LE = level of evidence; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.

	Figure 7.2: Algorithm for the management of metastatic urothelial cancer  *BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.*
NCCN, 2016 [5]. Bladder Cancer Version 2.2016	Leitlinie des National Comprehensive Cancer Networks **Fragestellung/Zielsetzung:** k.A.
	Methodik Leitlinien-Update von 2015 LoE: k.A. GoR: k.A. GoR Category 1 Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Category 3 Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

	Note: All recommendations are category 2A unless otherwise indicated. Suchzeitraum: bis 2016 Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - eigenes Graduierungssystem - industriefinanziert Sonstige methodische Hinweise Diese Leitlinie entspricht nicht den methodischen Mindestanforderungen. Sie wurde jedoch aufgrund ihres hohen Aktualitätsgrades und ihrer Popularität hier mit aufgenommen.
	Freitext/Empfehlungen/Hinweise *First-line chemotherpapy for metastatic disease* • Regimens o Gemcitabine and cisplatin (category 1) Von der Maase H et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005 Jul 20;23(21):4602-8. Von der Maase H et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000 Sep;18(17):3068-77. Kaufman D et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol. 2000 May;18(9):1921-7. o DDMVAC with growth factor support (category 1) Sternberg CN et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol. 2001 May 15;19(10):2638-46. Sternberg CN et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer. 2006 Jan;42(1):50-4. Epub 2005 Dec 5. • Alternative regimens o Carboplatin- or taxane-based regimens, or single-agent chemotherapy (category 2b) Keine Literaturangaben für single-agent chemotherapy als Erstlinientherapie! De Santis M et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol. 2009 Nov 20;27(33):5634-9. Burch PA et al. Phase II study of paclitaxel and cisplatin for advanced urothelial cancer. J Urol. 2000 Nov;164(5):1538-42. (Anm. FBMed: Einarmige Studie) Meluch AA et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol. 2001 Jun 15;19(12):3018-24. (Anm. FBMed: Einarmige Studie) Bellmunt J et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol. 2000 Sep 15;18(18):3247-55. (Anm. FBMed: Einarmige Studie) Hussain M et al. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol. 2001 May 1;19(9):2527-33. (Anm. FBMed: Einarmige Studie) Pectasides D et al. Weekly chemotherapy with docetaxel, gemcitabine and cisplatin in advanced transitional cell urothelial cancer: a phase II trial. Ann Oncol. 2002 Feb;13(2):243-50. (Anm. FBMed: Einarmige Studie) • The presence of both visceral metastases and ECOG performance score ≥ 2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic

factors have the greatest benefit from chemotherapy.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial

Bellmunt J et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012 Apr 1;30(10):1107-13.

- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
    - Participation in clinical trials of new or more tolerable therapy is recommended.
    - Carboplatin- or taxane-based regimens, or single-agent therapy can be considered for these patients. (category 2b)

Keine Literaturangaben für single-agent chemotherapy als Erstlinientherapie!
De Santis M et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol. 2009 Nov 20;27(33):5634-9.
Burch PA et al. Phase II study of paclitaxel and cisplatin for advanced urothelial cancer. J Urol. 2000 Nov;164(5):1538-42. (Anm. FBMed: Einarmige Studie)
Meluch AA et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol. 2001 Jun 15;19(12):3018-24. (Anm. FBMed: Einarmige Studie)
Bellmunt J et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol. 2000 Sep 15;18(18):3247-55. (Anm. FBMed: Einarmige Studie)
Hussain M et al. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol. 2001 May 1;19(9):2527-33. (Anm. FBMed: Einarmige Studie)
Pectasides D et al. Weekly chemotherapy with docetaxel, gemcitabine and cisplatin in advanced transitional cell urothelial cancer: a phase II trial. Ann Oncol. 2002 Feb;13(2):243-50. (Anm. FBMed: Einarmige Studie)

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or for pelvic recurrence after cystectomy*

- Cisplatin
- Taxane (docetaxel or paclitaxel) (category 2b)
- 5-FU (category 2b)
- 5-FU and mitomycin C (category 2b)
- Capecitabine (category 3)
- Low-dose gemcitabine (category 2b)

*Carboplatin should not be substituted for cisplatin with radiation.

Perioperative chemotherapy (neoadjuvant or adjuvant)

Standard regimens
• DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles[1,2] • Gemcitabine and cisplatin for 4 cycles[3,4] • CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles[5]

- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.[1,6,7]
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.[7]
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,8] Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence showing equivalence to conventional MVAC in the setting of advanced disease.[4,9]
- For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.[10]
- Neoadjuvant chemotherapy may be considered for select patients with upper tract urothelial carcinoma, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
- Carboplatin should not be substituted for cisplatin in the perioperative setting.
  - For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m² on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
  - For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
- For patients with borderline renal function, 24-hr urine creatine clearance should be assessed to estimate GFR.

Second-line systemic therapy for locally advanced or metastatic disease

- No standard therapy exists in this setting; thus, participation in clinical trials of new agents is recommended.
- The standard and alternate options are listed below.

Standard regimens	Alternate regimens for select patients
• Atezolizumab[16] • Paclitaxel or docetaxel[17] • Gemcitabine[12] • Pemetrexed[18]	• Nab-paclitaxel[19] • Ifosfamide[20] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[14] • Gemcitabine and paclitaxel[13] • Gemcitabine and cisplatin[4] • DDMVAC[2]

[2]Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638-2646.

[3]Dash A, Pettus JA, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113:2471-2477.

[4]Von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068-3077.

[12]Stadler WM, Kuzel T, Roth B, et al: Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. J Clin Oncol 15:3394-8, 1997.

[13]Calabro F, Lorusso V, Rosati G, et al: Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 115:2652-9, 2009.

[14]Siefker-Radtke AO, Dinney CP, Shen Y, et al: A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial cancer: final results. Cancer 119:540-7, 2013.

[15]Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012;30:1107-1113.

[16]Rosenberg JE, Hoffman-Censits J, Powles T et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet 2016; 387:1909-1920.

[17]McCaffrey JA, Hilton S, Mazumdar M, et al: Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997;15:1853-7.

[18]Sweeney CJ, Roth BJ, Kabbinavar FF, et al: Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clini Oncol 2008;24:3451-7.

[19]Ko YJ, Canil CM, Mukherjee SD, et al: Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. Lancet Oncol 2013;14:769-76.

[20]Witte RS, Elson P, Bono B, et al: Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol 1997;15:589-93.

Leitlinienprogramm Onkologie, 2016 [2].

Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF

S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms. **Konsultationsfassung** Langversion – Februar 2016. AWMF-Registernummer: 032/038OL

Federführende Fachgesellschaft(en)

Deutsche Gesellschaft für Urologie (DGU)

Interdisziplinäre Arbeitsgruppe BlasenCarcinom der DKG e.V. (IABC)

Fragestellung/Zielsetzung:

Als konsens- und evidenzbasiertes Instrument ist es Ziel dieser interdisziplinären Leitlinie der Qualität S3 zur Früherkennung, Diagnose Therapie und Nachsorge des Harnblasenkarzinoms, die Versorgungsstruktur zu verbessern und damit die Morbiditäts- und Mortalitätsrate von Patienten zu senken.

Methodik

Grundlage der Leitlinie

Die methodische Vorgehensweise bei der Erstellung der Leitlinie ist im Leitlinienreport dargelegt. Dieser ist im Internet z. B. auf den Seiten des Leitlinienprogramms Onkologie (http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html) und den Seiten der AWMF (http://www.awmf.org/) frei verfügbar.

LoE, GoR gemäß dem System des Scottish Intercollegiate Guidelines Network (SIGN)

Tabelle 3: Schema der Evidenzgraduierung nach 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)
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

Tabelle 4: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 5: Konsensusstärke

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

Sonstige methodische Hinweise

Konsultationsfassung! Ist noch nicht in Kraft. Fertigstellung ist erst für Februar 2017 vorgesehen; eine gültige aktuelle Version ist nicht verfügbar.

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

EK = Expertenkonsens

Freitext/Empfehlungen/Hinweise

Erstlinien-Chemotherapie bei Patienten mit einem metastasierten Blasenkarzinom

9.5.1. Prädiktive Faktoren zur Wirksamkeit der Erstlinientherapie

9.9	Evidenzbasiertes Statement
Level of Evidence 1+	Performance Status und viszerale Metastasen (Lunge, Leber, Knochen) sind unabhängige prognostische Faktoren für das Überleben nach einer Erstlinienchemotherapie.
	Literatur: [4, 921, 922]
	Starker Konsens

9.10	Evidenzbasiertes Statement
Level of Evidence 2-	Aktuell existiert für den klinischen Alltag kein verlässlicher prädiktiver Biomarker für den Therapieerfolg einer Chemotherapie beim metastasierten Urothelkarzinom.
	Literatur: [124]
	Starker Konsens

9.5.2. Nutzen der Erstlinien-Chemotherapie bei Patienten mit einem metastasierten Blasenkarzinom

9.11	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Patienten mit metastasiertem Urothelkarzinom der Harnblase soll eine cisplatinhaltige Chemotherapie angeboten werden, wenn der Allgemeinzustand und die Komorbiditäten dies zulassen.
Level of Evidence 1-	Primärrecherche: [938, 939]
	Konsens

9.12	Evidenzbasiertes Statement
Level of Evidence 1+	Ähnliche Wirksamkeit ergibt sich für Gemcitabin/Cisplatin, MVAC und HD-MVAC. Die Toxizität von HD-MVAC ist dabei geringer als unter konventionellem MVAC, aber höher als unter Gemcitabin/Cisplatin.
	Primärrecherche: [4, 925, 940]
	Konsens

9.13	Evidenzbasiertes Statement
Level of Evidence 1-	Eine Intervallverkürzung von MVAC oder Gemcitabin/Cisplatin bringt keinen Zugewinn an Effektivität und geht mit höherer Toxizität einher.
	Primärrecherche: [941]
	Starker Konsens

9.14	Evidenzbasiertes Statement
Level of Evidence 1+	Die Erweiterung des Gemcitabin/Cisplatin-Schemas um Paclitaxel bringt keinen eindeutigen Vorteil bei gering erhöhter Toxizität.
	Primärrecherche: [921]
	Starker Konsens

9.15	Konsensbasierte Empfehlung
EK	Bei der Erstlinienchemotherapie soll ein Restaging nach 2-3 Zyklen (Zyklen à 3-4 Wochen) erfolgen.
	Starker Konsens

9.16	Konsensbasiertes Statement
EK	Bei Patienten, die für eine Cisplatin-haltige Chemotherapie geeignet sind, stellt Carboplatin keinen adäquaten Ersatz dar.
	Starker Konsens

Nicht-cisplatinbasierte Chemotherapie bei Patienten mit fortgeschrittenem und/oder metastasiertem Urothelkarzinom

9.6.1. Patientengruppe

9.17	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Patienten mit zumindest einem der folgenden 5 Parameter sollten nicht mit Cisplatin-basierter Chemotherapie behandelt werden: • WHO oder ECOG Performance Status (PS) von ≥2 oder Karnofsky PS ≤ 60-70% • Kreatinin Clearance (gerechnet oder gemessen) ≤ 40 ml/min (Bei reduzierter Kreatinin Clearance von 40-60 ml/min soll eine Dosisanpassung von Cisplatin stattfinden, siehe Empfehlung 9.18) • CTCAE Version 4, Grad 2 oder höherer Hörverlust in der Audiometrie • CTCAE Version 4, Grad 2 oder höher mit peripherer Neuropathie • NYHA Klasse III Herzinsuffizienz
Level of Evidence **3**	Primärrecherche: [945]
	Starker Konsens

9.18	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Ausgewählte Patienten mit gutem EGOC-Performance Status (0-1), mäßig eingeschränkter Nierenfunktion (GFR 40-60 ml/min) und ohne weitere Komorbiditäten können mit Cisplatin in aufgeteilten Dosen behandelt werden.
Level of Evidence **3**	Primärrecherche: [946-949]
	Starker Konsens

9.6.2. Substanzen, Substanzkombinationen und Anzahl der Therapiezyklen

9.19	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Patienten, die nicht für eine cisplatinbasierte Chemotherapie geeignet sind und einen guten EGOC-Performance Status (0-1) haben, sollten mit Gemcitabin/Carboplatin behandelt werden.
Level of Evidence 1+	Primärrecherche: [928, 950, 951]
	Konsens

9.20	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	Patienten, die nicht für eine cisplatinbasierte Chemotherapie geeignet sind und einen EGOC-Performance Status ≥2 haben, können mit einer Monochemotherapie behandelt werden.
Level of Evidence 1+	Primärrecherche: [928, 951]
	Konsens

9.21	Evidenzbasiertes Statement
Level of Evidence 1+	Die vorliegende Evidenz lässt bezüglich der Frage nach der idealen oder nötigen Anzahl von Therapiezyklen bei Patienten, die für eine cisplatinhaltige Chemotherapie nicht geeignet sind, keine Empfehlung zu.
	Primärrecherche: [928, 950, 952-972]
	Konsens

9.22	Evidenzbasiertes Statement
Level of Evidence 1+	Zur Verwendung von Monotherapien bei Patienten, die nicht geeignet für cisplatinhaltige Kombinationschemotherapien sind, lässt sich aufgrund der mangelnden Evidenz durch randomisierte Vergleichsstudien keine Empfehlung für oder gegen eine einzelne Substanz ableiten.
	Primärrecherche: [950, 973]
	Starker Konsens

Tabelle 28: Konsensusdefinition: Kriterien für Patienten mit fortgeschrittenem Urothelkarzinom, die "nicht fit" für cisplatinbasierte Chemotherapie sind [932]

Vorliegen von zumindest einem Kriterium
- WHO oder ECOG Performance Status (PS) von 2, oder Karnofsky PS 60-70%
- Kreatinin Clearance (gerechnet oder gemessen) < 60 mL/min
- CTCAE Version 4, Grad 2 oder höherer Hörverlust in der Audiometrie
- CTCAE Version 4, Grad 2 oder höher mit peripherer Neuropathie
- NYHA Klasse III Herzinsuffizienz

Legende: WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association

Das Toxizitätsprofil von Cisplatin hat zur Untersuchung von besser verträglichen Carboplatin-Kombinationen geführt. Drei randomisierte Phase II und eine unvollständig rekrutierte Phase III Studie (siehe Tabelle 299) geben den Hinweis, dass Carboplatin-

Kombinationen weniger wirksam sind. Deshalb sind für Patienten, die "fit" für Cisplatin sind, Carboplatin-Kombinationstherapien kontraindiziert [952, 976-978].

Tabelle 29: Cisplatin versus Carboplatin: Randomisierte Phase II/III Studien

Autor/ Jahr	Phase	N	Regime	OR (%)	CR (%)	OS (Monate)
Petrioli 1996 [978]	II	57	MVAC vs. MVECa	71 41	25 11	13 9.5
Bellmunt 1997 [979]	II	47	MVAC vs. M-CAVI	52 39	13 0	16 9
Dogliotti 2007 [976]	II	110	Gem + Cis vs Gem + Carbo	49 40	14.5 1.8	12.8 9.8
Dreicer 2004* [980]	III	85	MVAC vs Paclitaxel + Carbo	36 28	12.8 2.6	15.4 13.8

*Rekrutierung abgebrochen; MVAC: Methotrexat, Vinblastin, Adriamycin, Cisplatin; M-CAVI: Methotrexat, Carboplatin, Vinvlastin; MVECA: Mehtotrexat, Vinblastin, Epirubicin, Carboplatin; Carbo: Carboplatin; Cis: Cisplatin; Gem: Gemcitabin; OR: Odds Ratio; CR: complete response; OS: overall survival; N = Anzahl

Es liegen zwei randomisierte Studien zur Behandlung dieser Patientengruppe vor [928, 950, 951]. Die erste, größte (237 Patienten) und bislang einzige publizierte randomisierte Phase-II/III-Studie zur Chemotherapie (EORTC 30986) von "nicht fitten" Patienten mit fortgeschrittenem UC verglich Gemcitabin/Carboplatin (GCa) mit Methotrexat/ Carboplatin/ Vinblastin (M-CAVI). Die beiden Regime unterschieden sich nicht signifikant in ihrer Wirksamkeit (M-CAVI: medianes OS 8.1 Monate, 21 % ORR; GCa: medianes OS 9.3 Monate, 36.1 % ORR), jedoch war GCa weniger toxisch. "Nicht fit" wurde in dieser Studie wie folgt definiert: glomeruläre Filtrationsrate (GFR) <60 ml/Min und/oder Performance-Status 2.

Patienten, die "nicht fit" für Cisplatin sind, scheinen nach den vorliegenden Daten keine einheitliche Gruppe zu sein. Jene Patienten in dieser EORTC-Studie 30986, die beide Definitionskriterien für "nicht fit" erfüllten (GFR < 60 mL/min und PS 2) oder die der Risikogruppe 2 nach Bajorin zuzuordnen waren, hatten ein medianes OS von nur 5.5 Monaten bei überdurchschnittlich hoher Toxizität. Patienten mit einem ungünstigen Risikoprofil ziehen demnach kaum Nutzen aus einer Carboplatin-Kombinationschemotherapie. Als Alternative kommt für diese Patienten eine Monochemotherapie oder "best supportive care" in Betracht [Monochemotherapie siehe Empfehlung 9.27].

Zweitlinientherapie bei Patienten mit metastasiertem Harnblasenkarzinom

9.7.1. Prädiktive Faktoren zur Wirksamkeit der Zweitlinientherapie

9.23	Konsensbasiertes Statement
Level of Evidence EK	ECOG Performance Status, Lebermetastasen, Hämoglobinwert und die Zeit bis zum Tumorprogress nach Erstlinienchemotherapie sind vor Durchführung einer Zweitlinienchemotherapie unabhängige prognostische Faktoren für das Überleben.
	Starker Konsens

9.24	Konsensbasiertes Statement
EK	Aktuell existiert für den klinischen Alltag kein verlässlicher prädiktiver Biomarker für den Therapieerfolg beim metastasierten Urothelkarzinom.
	Starker Konsens

9.25	Konsensbasierte Empfehlung
EK	Bei Progress nach primärer Chemotherapie oder perioperativer Chemotherapie eines metastasierten Urothelzellkarzinoms kann eine Zweitlinienchemotherapie angeboten werden.
	Konsens

9.26	Evidenzbasierte Empfehlung
Empfehlungsgrad A	In der Zweitlinientherapie sollen Patienten keine Erhaltungstherapie bis zum weiteren Tumorprogress erhalten.
Level of Evidence 2+	Primärrecherche: [996]
	Starker Konsens

9.27	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Patienten mit einem metastasierten Urothelkarzinom, die eine Progression unter bzw. nach einer cisplatinhaltigen Therapie erfahren, sollten als Zweitlinie eine Behandlung mit Vinflunin erhalten.
Level of Evidence 1-	Primärrecherche: [990, 991]
	Konsens

9.28	Konsensbasierte Empfehlung
EK	Eine Wiederaufnahme einer platinhaltigen Primärtherapie nach einem therapiefreien Intervall (mindestens > 6 Monate) und guter Verträglichkeit kann durchgeführt werden.
	Starker Konsens

	<table><tr><td>9.29</td><td>Evidenzbasierte Empfehlung</td></tr><tr><td>Empfehlungsgrad 0</td><td>Nach platinhaltiger Primärtherapie können Gemcitabin und/oder Paclitaxel ggf. auch in Kombinationen eingesetzt werden, insbesondere wenn diese nicht in der Primärtherapie enthalten waren.</td></tr><tr><td>Level of Evidence 1 -</td><td>Primärrecherche: [996-998]</td></tr><tr><td></td><td>Starker Konsens</td></tr></table>
Milowsky MI et al., 2016 [3]. **American Society of Clinical Oncology (ASCO)** Guideline on Muscle-Invasive and Metastatic Bladder Cancer. (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement	**Fragestellung/Zielsetzung:** To endorse the European Association of Urology guideline on muscle-invasive (MIBC) and metastatic bladder cancer. The American Society of Clinical Oncology (ASCO) has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.
	Methodik Grundlage der Leitlinie The ASCO Endorsement Panel considered the methodology used in the EAU guideline by considering the results from the AGREE II review instrument. The methodology review of the EAU guideline (which comprises several modalities including a web-based guideline, a journal publication, and an abbreviated pocket version) was completed independently by two ASCO guideline staff members using the Rigor of Development subscale fromthe AGREE II instrument. Only the webbased guideline was assessed using the AGREEII instrument. Detailed results of the scoring for this guideline are available on request to guidelines@asco.org. Overall, the EAU guideline on MIBC and metastatic bladder cancer itself scored 4.5 of 7, along with a score of 65%on the Rigor of Development subscale, because the methodology for arriving at the body of supporting evidence, the strengths and limitations of that evidence, and the methods used to arrive at the final recommendations were not described in detail in the actual guideline (Methodology Supplement Fig 2).However, the preliminary ASCO content reviewers of the EAU guideline MIBC and metastatic bladder cancer, as well as the ASCO Endorsement Panel, found the recommendations well supported in the original guideline. Each section, including the introduction, summary, and recommendations themselves, was clear and well referenced from the systematic review. This is the most recent information as of the publication date. For updates, the most recent information, and to submit new evidence, please visit http://www.asco.org/endorsements/MIBC or the ASCO Guidelines Wiki (http://www.asco.org/guidelineswiki).

	ASCO guidelines staff updated the EAU guideline on MIBC and metastatic bladder cancer literature search. To identify additional evidence, MEDLINE was searched on March 26, 2015 and was updated in December 2015. The search was restricted to articles published in English and to systematic reviews, meta-analyses, and randomized controlled trials. The updated search yielded 382 records. After a title and abstract review, 20 articles were ordered for full-text review, and five of these were retained for inclusion in this endorsement. Additional articles were also retained for discussion.
	Freitext/Empfehlungen/Hinweise - Bewertungen der EAU-Leitlinien und ASCO-Empfehlungen: siehe Anlage (lists the EAU recommendations and ASCO-endorsed guidelines with qualifying statements (in bold italics). - Multidisciplinary care for patients with MIBC and metastatic bladder cancer is critical. The standard treatment of MIBC (cT2-T4a N0M0) is neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy. In cisplatin-ineligible patients, radical cystectomy alone is recommended. Adjuvant cisplatin-based chemotherapy may be offered to high-risk patients who have not received neoadjuvant therapy. Chemoradiotherapy may be offered as an alternative to cystectomy in appropriately selected patients with MIBC and in some patients for whom cystectomy is not an option. Metastatic disease should be treated with cisplatin-containing combination chemotherapy or with carboplatin combination chemotherapy or single agents in patients ineligible for cisplatin. ASCO Key Recommendations for MIBC and Metastatic Bladder Cancer 1. Multidisciplinary input via tumor board discussions and/or directed consultations is critical to the optimal management of patients with MIBC and metastatic bladder cancer (eg, referral to a medical oncologist should be made for a discussion of neoadjuvant chemotherapy and referral to a radiation oncologist for a discussion of bladder preservation in patients with muscle-invasive disease). Implementation of these guidelines requires the integration of urology and medical and radiation oncology expertise to provide the highest level of care to patients. 2. Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.

	3. Neoadjuvant chemotherapy is not recommended in patients who are ineligible for cisplatin-based combination chemotherapy, unless the goal is downstaging surgically unresectable tumors. 4. Any decision regarding bladder-sparing or radical cystectomy in elderly/geriatric patients with invasive bladder cancer should be based on tumor stage, bladder function, and the ability to tolerate major surgery, radiotherapy, and/or chemotherapy. 5. Radical cystectomy is recommended in T2-T4a, N0M0 and high-risk non-MIBC. Chemoradiotherapy-based organ preservation treatment may be offered to select patients with MIBC. 6. In patients being treated with bladder-preservation therapy with curative intent, combined chemoradiotherapy is superior to, and is recommended over, radiotherapy alone. 7. Although neoadjuvant chemotherapy is recommended, adjuvant chemotherapy may be offered to high-risk patients who have not received neoadjuvant treatment.* 8. First-line treatment of fit patients with metastatic disease: Use cisplatin-containing combination chemotherapy with gemcitabine plus cisplatin, MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), or high-dose MVAC with granulocyte colony-stimulating factor. 9. First-line treatment in patients ineligible (unfit) for cisplatin: use carboplatin combination chemotherapy or single agents. 10. In patients experiencing progression after platinum-based combination chemotherapy for metastatic disease, entry into a clinical trial is preferred. Alternatively, single-agent therapy may be offered (eg, paclitaxel, docetaxel, or vinflunine where available). *The word “offered” should be interpreted as having a detailed discussion with the patient about the risks and benefits of adjuvant chemotherapy. The discussion should include a thorough review of the absolute risk of recurrence in light of the pathologic findings, acknowledging the limitations of the data in the adjuvant setting.
NICE, 2015 [4]. **National Collaborating Centre for Cancer - Commissioned by the National Institute for Health and Care**	This guideline does not include recommendations covering every detail of the diagnosis and treatment of bladder cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact.

Excellence Bladder cancer: diagnosis and management	**Methodik** Grundlage der Leitlinie – systematische Evidenzaufbereitung und Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - GoR werden durch Formulierungen wiedergegeben – The basic steps in the process of developing this guideline: o using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline o forming the GDG o developing clinical questions o identifying the health economic priorities o developing the review protocol o systematically searching for the evidence o critically appraising the evidence o incorporating health economic evidence o distilling and synthesising the evidence and writing recommendations o agreeing the recommendations o structuring and writing the guideline o consultation and validation – Suchzeitraum o The Cochrane Library, Medline and Premedline (1946 onwards), Excerpta Medica (Embase) (1974 onwards), Web of Science (1899 onwards) and Social SciencesCitation Index (1956 onwards), Cinahl (1937 onwards), Allied & Complementary Medicine (AMED) (1985 onwards), and Psychinfo (1806 onwards) were searched in June 2014 Wording of the recommendations – 'Offer' – for the vast majority of patients, an intervention will do more good than harm – 'Do not offer' – the intervention will not be of benefit for most patients – 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.
	Freitext/ Empfehlungen/ Hinweise - *Vgl. auch Anlage : Behandlungsschema -* *Management of locally advanced or metastatic bladder cancer* First-line chemotherapy Clinical question: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic

	bladder cancer? Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [M-VAC] in combination with with granulocyte-colony stimulating factor [G-CSF]) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have a performance status of 0 or 1) and have adequate renal function (typically defined as a glomerular filtration rate [GFR] of 60 ml/min/1.73 m^2 or more). Galsky, MD et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Annals of Oncology 2012; 23(2): 406-410. Bamias, A et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. Journal of Clinical Oncology 2004; 22(2): 220-228. Bellmunt, J et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer 1997; 80(10): 1966-1972. Bellmunt, J et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. Journal of Clinical Oncology 2012; 30(10): 1107-1113. Dogliotti, L et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. European Urology 2007; 52(1): 134-141. Dreicer, R et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer 2004; 100(8): 1639-1645. Lorusso, V et al. Randomised, open-label, phase II trial of paclitaxel, gemcitabine and cisplatin versus gemcitabine and cisplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium. Oncology Reports 2005; 13(2): 283-287. Sternberg, CN et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. Journal of Clinical Oncology 2001a; 19(10): 2638-2646. Sternberg, CN et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. European Journal of Cancer 2006; 42(1): 50-54. von der Maase, H et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. Journal of Clinical Oncology 2000; 18(17): 3068-3077. von der Maase, H et al. Long-term-survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. Journal of Clinical Oncology 2005; 23(21): 4602-4608. Offer carboplatin in combination with gemcitabine to people with locally advanced or metastatic urothelial bladder cancer with a performance status of 0 - 2, if a cisplatin-based chemotherapy regimen is unsuitable, for example because of performance status, inadequate renal function (typically defined as a GFR of less than 60 ml/min/1.73 m^2) or comorbidity. Assess and discuss the risks and benefits with the person. De Santis, M et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of Clinical Oncology 2012; 30(2): 191-199. **Managing symptoms of locally advanced or metastatic bladder cancer**

Bladder symptoms

- Offer palliative hypofractionated radiotherapy to people with symptoms of haematuria, dysuria, urinary frequency or nocturia caused by advanced bladder cancer that is unsuitable for potentially curative treatment

Loin pain or symptoms of renal failure

- Discuss treatment options with people who have locally advanced or metastatic bladder cancer with ureteric obstruction. Include:
    - Prognosis of their cancer and
    - Advantages and disadvantages of the treatment options, including best supportive care
- Consider percutaneous nephrostomy or retrograde stenting (if technically feasible) for people who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment
- If percutaneous nephrostomy or retrograde stenting is not possible at the local hospital, discuss the options with a specialist urology MDT

Intractable haematuria

- Evaluate the cause of intractable bleeding with the local urology team
- Consider hypofractionated radiotherapy or embolisation
- If radiotherapy or embolisation are not suitable treatments, discuss further management with a specialist urology MDT

Intractable pelvic pain

- Evaluate the cause of pelvic pain with the local urology team
- Consider, in addition to best supportive care, one or more of the following to treat pelvic pain caused by incurable bladder cancer:
    - Hypofractionated radiotherapy if the person has not had pelvic radiotherapy
    - Nerve block
    - Palliative chemotherapy

Duchesne, GM et al. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. International Journal of Radiation Oncology, Biology, Physics 2000; 47(2): 379-388.

Second-line chemotherapy

Consider second-line chemotherapy with gemcitabine in combination with cisplatin, or accelerated (high-dose) M-VAC in combination with G-CSF for people with incurable locally advanced or metastatic urothelial bladder cancer whose condition has progressed after first-line chemotherapy if:

- their renal function is adequate (typically defined as a GFR of 60 ml/min/1.73 m_2 or more) and

- they are otherwise physically fit (have an ECOG performance status of 0 or 1)

	Consider second-line chemotherapy with carboplatin in combination with paclitaxel[i] or gemcitabin For recommendations on vinflunine as second-line chemotherapy for people with incurable locally advanced or metastatic urothelial bladder cancer, see NICE's technology appraisal guidance on vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract. For people having second-line chemotherapy for locally advanced or metastatic bladder cancer: • carry out regular clinical and radiological monitoring and • actively manage symptoms of disease and treatment-related toxicity and • stop second-line chemotherapy if there is excessive toxicity or disease progression. e in combination with paclitaxel[j] for people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it.
Alberta Health Services, 2013 [1]. Muscle invasive and locally advanced/ metastatic bladder cancer	This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists. Fragestellung: What is the appropriate stage-specific treatment (i.e., surgery, systemic therapy, radiotherapy) for patients with bladder cancer?
	Methodik Grundlage der Leitlinie: syst. Literaturrecherche Suchzeitraum der syst. Literaturrecherche: bis März 2013 (The original guideline, which was developed in 2005 and updated in 2009, 2010, and 2011, was divided into two distinct documents during the 2013 update: a guideline on noninvasive bladder cancer and a guideline on muscle-invasive and locally advanced or unresectable/metastatic disease.) LoE und GoR: n.a., da bei den Empfehlungen keine LoE und GoR angegeben sind.
	Freitext/Empfehlungen/Hinweise *Management of Stages T3, T4 and/or N1-3 M0* Primary Therapy – If surgery is abandoned because of unresectable N+ or T4b, the patient should be managed as for metastatic disease. *Management of Advanced Unresectable Metastatic Disease (T4b, N1-3, M1)*

	Primary Therapy – In patients who present with *de novo* metastatic disease or for those that develop metastatic disease after a definitive local therapy, the mainstay of treatment is systemic chemotherapy. o Sequential cisplatinum and gemcitabine at the schedule described above, plus paclitaxel (80 mg/m2 days 1 and 8), every 3 weeks. o Cisplatinum in combination with gemcitabine is the primary chemotherapy combination at the dose and schedule described above; an alternative to cisplatinum if clinically indicated is carboplatinum in combination with gemcitabine; patients who respond should be treated for a maximum of six cycles. Carteni, G, Dogliotti, L, Crucitta, E, et al. Phase II randomised trial of gemcitabine plus cisplatinum and gemcitabine plus carboplatinum in patients with advanced or metastatic transitional cell carcinoma of the urothelium (abstract). Proc Am Soc Clin Oncol 2003; 22:384a. Bamias, A, Moulopoulos, LA, Koutras, A, et al. The combination of gemcitabine and carboplatinum as first-line treatment in patients with advanced urothelial carcinoma. A Phase II study of the Hellenic Cooperative Oncology Group. Cancer 2006; 106:297. – For patients with their bladder in situ, radiotherapy to the bladder either as a single modality therapy or combined with a platinum can be administered for (1) palliation in patient unable to receive chemotherapy or (2) in attempt to reduce the risk of local recurrence as an adjunct to systemic chemo-therapy in selected patients who wishes for aggressive treatment after discussion of lack of high level evidence in this area. – Radiotherapy is of value in the management of symptomatic local disease and symptomatic metastases. Bellmunt J, Orsola A, Maldonado X, Kataja V; ESMO Guidelines Working Group. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v134-6. Second-line – There is no phase III data to support recommending one agent over another. – If patients treated with cisplatinum (carboplatinum) + gemcitabine relapse within six months, consider treating with agents not previously administered such as CMV or MVAC, depending on performance status, or single agents. If relapses are greater than six months, then the patient could be considered for re-treatment with original regimen or alternatively with CMV or MVAC. – Paclitaxel in combination with a platinum agent could be considered as second line therapy. **Management of Stage T2a/b** 70 mg/m_2 day 1 and gemcitabine, 1000-1250 mg/m_2 day 1 and 8 q 21 days); patients with contraindications to cisplatinum should

	proceed directly to definitive therapy, as the routine use of carboplatinum-based neoadjuvant combinations is not advised. [45-61] A CT scan of the abdomen and pelvis should precede cystectomy. In patients who have already undergone cystectomy, adjuvant cisplatinum-based combination chemotherapy (as above) should be offered. As most bladder cancer related deaths are due to systemic relapse, chemotherapy in either the adjuvant or neoadjuvant setting can be expected to improve overall survival and disease free survival. 45 Wallace, DM, Raghavan, D, Kelly, KA, et al. Neo-adjuvant (pre-emptive) cisplatinum therapy in invasive transitional cell carcinoma of the bladder. Br J Urol 1991; 67:608. 46 Martinez-Pineiro, JA, Gonzalez Martin, M, Arocena, F, et al. Neoadjuvant cisplatinum chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. J Urol 1995; 153:964. 47 Neoadjuvant chemotherapy for invasive bladder cancer. Cochrane Database Syst Rev 2005; 2:CD005246. 48 Winquist, E, Kirchner, TS, Segal, R, et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004; 171:561. 49 Stockle, M, Wellek, S, Meyenburg, W, et al. Radical cystectomy with or without adjuvant polychemotherapy for non-organ-confined transitional cell carcinoma of the urinary bladder: prognostic impact of lymph node involvement. Urology 1996; 48:868. 50 Schultz, P, Herr, HW, Zhang, ZF, et al. Neoadjuvant chemotherapy for invasive bladder cancer: prognostic factors for survival of patients treated with M-VAC with 5-year follow-up. J Clin Oncol 1994; 12:1394. 51 Neoadjuvant cisplatinum, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised contolled trial. International Collaboration of trialists. Lancet 1999; 354:533. 52 Scher, HI, Yagoda, A, Herr, HW, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatinum) effect on the primary bladder lesion. J Urol 1988; 139:470. 53 Hall, RR. Updated results of a randomised controlled trial of neoadjuvant cisplatinum, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer (abstract). Proc Am Soc Clin Oncol 2002; 21:178a. 54 Freiha, F, Reese, J, Torti, F. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatinum, vinblastine and methotrexate chemotherapy for muscle-invasive bladder cancer. J Urol 1996; 155:495. 55 Skinner, DG, Daniels, JR, Russell, CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991; 145:459. 56 Bajorin, DF. Plenary debate of randomized phase III trial of neoadjuvant MVAC plus cystectomy versus cystectomy alone in patients with locally advanced bladder cancer. J Clin Oncol 2001; 19:17S 57 Grossman, HB, Natale, RB, Tangen, CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003; 349:859. 58 Cortesi, E. Neoadjuvant treatment for locally advanced bladder cancer: A prospective randomized clinical trial (abstract). Proc Am Soc Clin Oncol 1995; 14:237. 59 Millikan, R, Dinney, C, Swanson, D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant m-vac versus cystectomy with both preoperative and postoperative m-vac. J Clin Oncol 2001; 19:4005. 60 Dotan, ZA, Bajorin, DF, Grossman, BH, et al. Optimal combined modality treatment improves outcome of locally advanced bladder cancer: analysis of SWOG 8710 (abstract). J Clin Oncol 2005; 23:385s. 61 Malmstrom, PU, Rintala, E, Wahlqvist, R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. J Urol 1996; 155:1903.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 23.06.2016**

#Suchschritt	Suchfrage
1	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
2	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
3	urotheli*:ti,ab,kw or "transitional":ti,ab,kw or "bladder":ti,ab,kw (Word variations have been searched)
4	neoplasm* or cancer* or tumor* or tumour* or carcinom* (Word variations have been searched)
5	#3 and #4
6	#1 or #2 or #5
7	#6 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 23.06.2016

#Suchschritt	Suchfrage
1	((urotheli*[Title/Abstract]) OR transitional[Title/Abstract]) OR bladder[Title/Abstract]
2	((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR cancer*[Title/Abstract]
3	#1 OR #2
4	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
5	#3 AND #4
6	(("carcinoma, transitional cell/drug therapy"[MeSH Terms]) OR "carcinoma, transitional cell/radiotherapy"[MeSH Terms]) OR "carcinoma, transitional cell/surgery"[MeSH Terms]) OR "carcinoma, transitional cell/therapy"[MeSH Terms]
7	(("urinary bladder neoplasms/drug therapy"[MeSH Terms]) OR "urinary bladder neoplasms/radiotherapy"[MeSH Terms]) OR "urinary bladder neoplasms/surgery"[MeSH Terms]) OR "urinary bladder neoplasms/therapy"[MeSH Terms]
8	#5 OR #6 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	(#9) Filters: Publication date from 2011/06/01 to 2016/06/23

Leitlinien in Medline (PubMed) am 23.06.2016

#Suchschritt	Suchfrage
1	"carcinoma, transitional cell"[MeSH Terms]
2	urinary bladder neoplasms[MeSH Terms]
3	((urotheli*[Title/Abstract]) OR transitional[Title/Abstract]) OR bladder[Title/Abstract]
4	((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR cancer*[Title/Abstract]
5	#3 AND #4
6	#5 OR #2 OR #1
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
8	(#7) Filters: Publication date from 2011/06/01 to 2016/06/23

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4. **National Collaborating Centre for Cancer.** Bladder Cancer: Diagnosis and Management [online]. London (GBR): NICE; 2015. [Zugriff. (NICE Guideline; Band NG2). URL: https://www.nice.org.uk/guidance/ng2/evidence/full-guideline-3744112.

5. **National Comprehensive Cancer Network (NCCN).** Bladder Cancer [online]. Fort Washington (USA): NCCN; 2016. [Zugriff: 27.06.2016]. (NCCN clinical practice guidelines in oncology; Band Version 2.2016). URL: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

6. **Necchi A, Pond GR, Raggi D, Giannatempo P, Vogelzang NJ, Grivas P, et al.** Efficacy and Safety of Gemcitabine Plus Either Taxane or Carboplatin in the First-Line Setting of Metastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis. Clin Genitourin Cancer 2016.

7. **Raggi D, Miceli R, Sonpavde G, Giannatempo P, Mariani L, Galsky MD, et al.** Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. Ann Oncol 2016;27(1):49-61.

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Anlagen

Anlagen 1

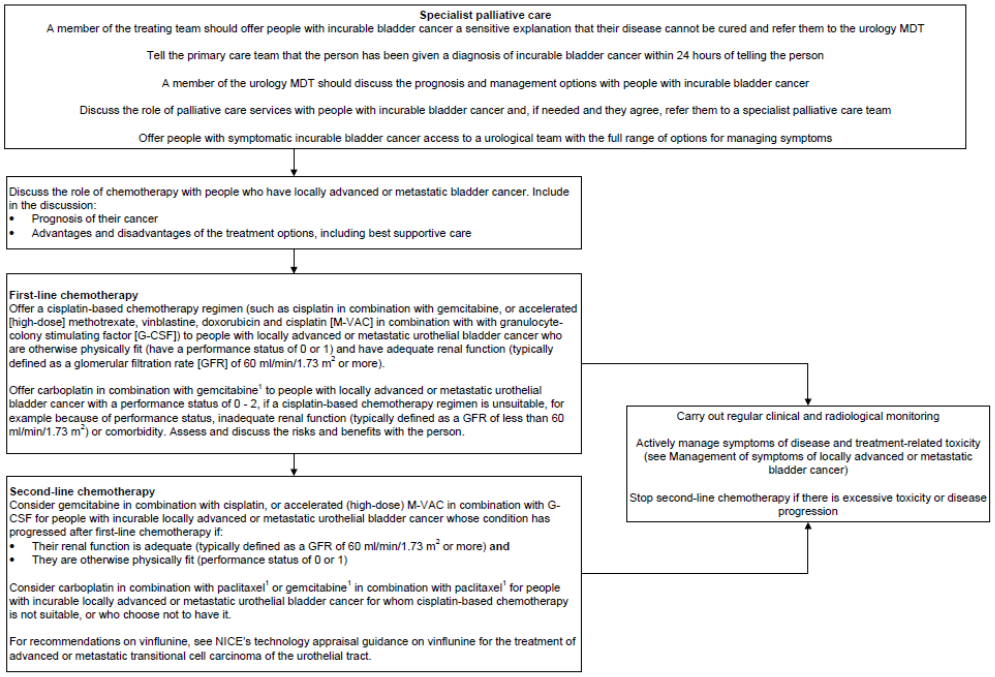
ASCO-Endorsement der EAU-Leitlinie (Milowsky et al., 2016)

EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer Original Recommendations	ASCO Endorsement of EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer Original Recommendations With Qualifying Statements (in bold italics)
Chemotherapy	
Chemotherapy alone is not recommended as primary therapy for localized bladder cancer.	Chemotherapy alone is not recommended as primary therapy for localized bladder cancer.
Multimodality bladder-preserving treatment	
Surgical intervention or multimodality treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.	***Neoadjuvant chemotherapy followed by radical cystectomy or bladder-preserving chemoradiotherapy*** treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.
Multimodality treatment could be offered as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	***Bladder-preserving*** multimodality treatment could be offered as an alternative ***to cystectomy*** in ***appropriately*** selected patients***, and may be appropriate in some patients for whom cystectomy is not an option.***
Adjuvant Chemotherapy	
Adjuvant cisplatin based combination chemotherapy may be offered to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Adjuvant cisplatin based combination chemotherapy may be offered to patients with pT3/4 and/or or pN+) disease if no neoadjuvant chemotherapy has been given. ***While neoadjuvant chemotherapy is recommended, adjuvant chemotherapy may be offered to high-risk patients who did not receive neoadjuvant treatment†***
Metastatic Disease	
First-line treatment for fit patients	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	First-line treatment for fit patients: use cisplatin-containing combination chemotherapy with ***GC, MVAC, or HD-MVAC with G-CSF***.
Carboplatin and nonplatinum combination chemotherapy is not recommended.	Carboplatin and nonplatinum combination chemotherapy is not recommended.
First-line treatment in patients ineligible (unfit) for cisplatin	
Use carboplatin combination chemotherapy or single agents.	Use carboplatin combination chemotherapy or single agents.
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.
Second-line treatment	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	In patients progressing after platinum-based combination chemotherapy for metastatic disease***, entry into a clinical trial is preferred. Alternatively, single-agent therapy may be offered (e.g. paclitaxel, docetaxel, or vinflunine where available).***
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	Zoledronic acid or denosumab ***may be offered*** for treatment of bone metastases†
Follow-Up	
Local recurrence, poor prognosis: treatment should be individualized depending on the local extent of tumor	
Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination.	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination.
Distant recurrence, poor prognosis	
Chemotherapy is the first option, and consider individualized cases for metastatectomy in case of unique metastasis site.	Chemotherapy is the first option, and consider individualized cases for metastatectomy ***when oligometastatic disease is present.***
Secondary urethral tumor: staging and treatment should be done as for primary urethral tumor	
Local conservative treatment is possible for noninvasive tumor.	Local conservative treatment is possible for noninvasive tumor.
Staging and treatment should be done as for primary urethral tumor. In isolated invasive disease, urethrectomy should be performed.	Staging and treatment should be done as for primary urethral tumor. In isolated invasive disease, urethrectomy should be performed.
Staging and treatment should be done as for primary urethral tumor. Urethral washes and cytology are not recommended.	Staging and treatment should be done as for primary urethral tumour. Urethral washes and cytology ***should be considered in high-risk patients.***

Anlage 2

NICE-Leitlinie (2015)

Management of locally advanced or metastatic bladder cancer



[1] Although this use is common in UK clinical practice, at the time of publication (February 2015), this intervention did not have UK marketing authorisation for this indication. . The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information