Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2026-B-125-z Enfortumab vedotin

Stand: Juli 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Enfortumab vedotin in Kombination mit Pembrolizumab [zur Behandlung des muskelinvasiven Blasenkarzinoms] **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“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht-medikamentöse Behandlungen: - Operation (Zystektomie, transurethrale Resektion (TUR)) - Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Nivolumab: Beschluss vom 20. Oktober 2022 - Durvalumab: Beschluss vom 22.01.2026 - Nivolumab: Beschluss vom 04.06.2026
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:	
Enfortumab vedotin L01FX13 Padcev	<u>Anwendungsgebiet:</u> Enfortumab vedotin ist in Kombination mit Pembrolizumab als neoadjuvante Therapie und anschließend als adjuvante Therapie nach einer radikalen Zystektomie zur Behandlung von erwachsenen Patienten mit resektablem muskelinvasivem Blasenkarzinom (MIBC) indiziert, die für eine Cisplatin-haltige Chemotherapie nicht in Frage kommen.
Zytotoxische Chemotherapien	
Cisplatin L01XA01 generisch	Cisplatin wird angewendet zur Behandlung des: - fortgeschrittenen oder metastasierten Harnblasenkarzinoms
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: - Systemische Therapie des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Methotrexat L01BA01 generisch	Methotrexat medac 25 mg/ml wird angewendet bei: - Harnblasenkarzinomen - in Kombination mit anderen zytotoxischen Arzneimitteln
Gemcitabin L01BCO5 generisch	Gemcitabin wird angewendet bei: - lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms in Kombination mit Cisplatin.
Monoklonale Antikörper	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Durvalumab L01FF03 Imfinzi	Muskelinvasives Blasenkarzinom (muscle-invasive bladder cancer, MIBC) IMFINZI in Kombination mit Gemcitabin und Cisplatin zur neoadjuvanten Behandlung gefolgt von IMFINZI als Monotherapie zur adjuvanten Behandlung nach radikaler Zystektomie ist angezeigt zur Behandlung von Erwachsenen mit resezierbarem muskelinvasivem Blasenkarzinom (MIBC).
Nivolumab L01FF01 Opdivo	Opdivo ist als Monotherapie zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms (MIUC) mit Tumorzell-PD-L1-Expression ≥ 1 % bei Erwachsenen mit hohem Rezidivrisiko nach radikaler Resektion des MIUC indiziert (siehe Abschnitt 5.1).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2026-B-125-z (Beratung nach § 35a SGB V) Enfortumab Vedotin

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	18. Juni 2026

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouacil
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AC	Adjuvant Chemotherapy
CI	Confidence Interval
CM	Cisplatin und Methorexat
CMV	Cisplatin, Methotrexat und Vinblastin
CPS	Combined Positive Score
CT	Computed Tomography
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GC	Gemcitabin und Cisplatin
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray (Einheit für ionisierende Strahlung)
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MIBC	Muscle-invasive Bladder Cancer
MVAC	Methotrexat, Vinblastin, Doxorubicin und Cisplatin
MVEC	Methotrexat, Vinblastin, Epirubicin und Cisplatin
NAC	Neoadjuvant Chemotherapy
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall Survival
PFS	Progression-Free Survival
PD-L1	Programmed Cell Death-Ligand 1
RC	Radical Cystectomy
RCT	Randomized Controlled Trial
RT	Radiotherapy
SCC	Squamous Cell Carcinoma
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
UC	Urothelial Carcinoma
UTUC	Upper Urinary Tract Urothelial Cacinoma
WHO	World Health Organization

1 Indikation

Neoadjuvante/adjuvante Behandlung nach radikaler Zystektomie für die Behandlung von Patienten mit resektablem muskelinvasivem Blasenkarzinom (MIBC), die für eine platinbasierte Chemotherapie nicht geeignet sind.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Harnblasenkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 13.01.2026 abgeschlossen. Am 05.06.2026 erfolgte eine Überprüfung der iterativen Handsuche. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1570 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten Systematischen Reviews identifiziert

3.3 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)), 2025 [2, 3].

Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms; S3-Leitlinie, Langversion 3.0

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: gültig bis März 2030.

Recherche/Suchzeitraum:

- Suche nach qualitativ hochwertigen LL im März 2021 in Medline via Pubmed, Guidelines International Network (G-I-N), UK National Health Service Evidence und Webseiten einzelner fachübergreifender und fachspezifischer Organisationen
- Der Suchzeitraum lag zwischen Mai 2012 und März 2021, um an den letzten Suchzeitraum der alten Leitlinienversion anzuknüpfen.
- Die Suchen für die de novo-Recherchen zu den palliativen und perioperativen Fragestellungen wurden am 14.09.2021 mit einem Suchzeitraum von 01.01.2021-14.09.2021 durchgeführt. Eingeschlossen wurden klinische Studien, RCTs, systematische Übersichtsarbeiten, Metaanalysen und multizentrische Kohortenstudien in englischer und deutscher Sprache. Die Suchen erfolgten in der Cochrane Library und in MEDLINE via Ovid
- Bezüglich der perioperativen Systemtherapie erfolgte eine Updaterecherche für den Zeitraum 09/2021 – 01/2024, für die anderen in der ersten Suche gefundenen Leitlinien-Themen erfolgte keine Update-Recherche, da sich hier im Wortlaut der jeweiligen Leitlinien inhaltlich keine Veränderungen ergaben.

LoE/GoR

Tabelle 6: Schema der Evidenzgraduierung nach SIGN 1999-2012 [7]

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 7: Verwendete Empfehlungsgrade

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

Tabelle 8: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	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

Die Kapitel 5 (Diagnostik), 9 (perioperative Therapie des muskelinvasiven Blasenkarzinoms), 11 (Rehabilitation, Lebensqualität, Psychosozial Aspekte und Palliativmedizin) sowie 12 (Nachsorge) wurden überarbeitet.

De novo-Recherchen wurden lediglich zu den palliativen und perioperativen Fragestellungen durchgeführt. Das Update der weiteren Kapitel erfolgte über eine Recherche nach Leitlinien.

8 Leitlinien wurden berücksichtigt, die in der Domäne 3 des AGREE-II Instruments („Genauigkeit der Leitlinienentwicklung“) einen Wert von mindestens 0,5 Punkten erreichten.

Empfehlungen

9 Perioperative Systemtherapie

9.1 Perioperative Systemtherapie beim lokalisierten muskelinvasiven Harnblasenkarzinom

9.1	Konsensbasierte Empfehlung	modifiziert 2025
EK	Patienten mit muskelinvasivem Harnblasenkarzinom (≥T2) sollen über die Möglichkeiten, Chancen und Risiken einer neoadjuvanten und / oder adjuvanten Systemtherapie unter Berücksichtigung ihrer individuellen Situation aufgeklärt werden.	
	Starker Konsens	

9.2	Konsensbasierte Empfehlung	modifiziert 2025
EK	Bei Patienten mit muskelinvasivem Harnblasenkarzinom (≥T2) soll das Therapiekonzept multidisziplinär in einer Tumorkonferenz vor Therapiebeginn festgelegt werden.	
	Starker Konsens	

9.3	Konsensbasierte Empfehlung	neu 2025
EK	Bei folgenden Patienten soll nach radikaler Zystektomie das weitere postoperative Therapiekonzept multidisziplinär in einer Tumorkonferenz festgelegt werden: • ≥pT3a und/oder pN+ und/oder R1 nach alleiniger radikaler Zystektomie, • ≥ypT2 und/oder ypN+ und/oder R1 nach radikaler Zystektomie mit vorangegangener Chemotherapie.	
	Starker Konsens	

Hintergrund zu 9.1 bis 9.3
Die Entscheidung für eine perioperative Systemtherapie ist wesentlich von individuellen Patientenfaktoren (z.B. Allgemeinzustand, Komorbiditäten, klinischer Verlauf der Tumorerkrankung, etc.) sowie den Vortherapien abhängig. Dieses geschieht individuell für jeden Patienten in einem interdisziplinären Konsens zwischen Urologen, internistischen Onkologen und Radiotherapeuten unter Berücksichtigung des Pathologen, der Interpretation der Bildgebung durch den Radiologen und ggf. weiterer Einschätzungen der Bildgebung durch z.B. den Nuklearmediziner. Da jedes Fachgebiet einen speziellen Blick auf die Patientenproblematik entwickelt, ist die Einbeziehung aller beteiligten Disziplinen essentiell, auch wenn es hierfür keine randomisierten Studien mit hoher Evidenz gibt. Im Rahmen retrospektiver Arbeiten und nicht-randomisiserter prospektiver Studien bestätigt sich allerdings, dass Entscheidungen in einer Tumorkonferenz zu Veränderungen der spezifischen Diagnose (z.B. genauere Beschreibung des Tumorstadiums und der Therapie (patientenindividuellere Vorgehensweisen), aber auch die Überlebensrate positiv beeinflussen können [912]. In diesem Kontext konnte speziell für das Harnblasenkarzinom in einer deutschen Registerstudie gezeigt werden, dass bei Patienten, deren Therapieplanung ohne Beteiligung einer Tumorkonferenz erfolgt, eine höhere Wahrscheinlichkeit aufweisen, keine perioperative Systemtherapie zu erhalten.

9.3 Neoadjuvante Chemotherapie beim lokalisierten muskelinvasiven Harnblasenkarzinom

9.5	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad **A**	Patienten mit einem lokalisierten muskelinvasiven Harnblasenkarzinom (T2-T4a N0 M0), die für eine cisplatin-basierte Chemotherapie geeignet sind, soll eine neoadjuvante cisplatin-basierte Kombinationstherapie angeboten werden.	
Level of Evidence **1+**	[924]	
	Starker Konsens	

9.6	Evidenzbasierte Empfehlung	geprüft 2025
Empfehlungsgrad **A**	Eine neoadjuvante Chemotherapie soll 3-4 Zyklen einer cisplatinhaltigen Kombinationschemotherapie beinhalten.	
Level of Evidence **1++**	[925]	
	Starker Konsens	

9.7	Evidenzbasiertes Statement	neu 2025
Level of Evidence **1++**	Bei geeigneten Patienten kann eine Chemotherapie mit sechs Zyklen ddMVAC durchgeführt werden.	
	[926], [927], [928], [929]	
	Starker Konsens	

9.8	Konsensbasierte Empfehlung	geprüft 2025
EK	Bei der neoadjuvanten Chemotherapie soll alle 2 Zyklen ein bildgebendes Restaging erfolgen, um eine Progression auszuschließen.	
	Starker Konsens	

Hintergrund 9.5. bis 9.8.
Zur Beantwortung der Schlüsselfragen zum Themenkomplex der neoadjuvanten Therapie erfolgte eine Leitlinienadaptation der EAU Leitlinie „Muscle-invasive and metastatic bladder cancer“) aus dem Jahr 2023 [251]. Weiterhin wurde die für die Version V1.0 der S3-Leitlinie Harnblasenkarzinom durchgeführte systematische De Novo Literaturrecherche mit einer Metaanalyse zur Beantwortung der Schlüsselfragen herangezogen [Leilinienprogramm Onkologie [930], [931].

Metaanalyse 2016
Im Rahmen der Leitlinienerstellung 2016 wurde zur Untersuchung der Schlüsselfragen zur neoadjuvanten Chemeotherapie eine systematische De Novo Literaturrecherche mit einer Subgruppenanalyse durchgeführt [930], [931]. Da diese umfassende Untersuchung der Leitliniengruppe nicht als englische Volltextpublikation vorliegt und somit nicht in die EAU -Leitlinie einfließen konnte, sollen an dieser Stelle die Ergebnisse kurz zusammengefasst werden.
In dieser Analyse wurden Studien mit 3135 Patienten, die bis 2014 im Rahmen von insgesamt 12 auswertbaren Studien mit neoadjuvanten Therapien behandelt wurden, eingeschlossen [843], [932], [933], [444], [934], [935], [936], [937], [938], [939], [940], [941], [942], [943]. Zur Wirksamkeit lagen für die Endpunkte „Gesamtmortalität“ und „progressionsfreies Überleben“ bzw. „Rezidiv“ gepoolte Ergebnisse aus MetaAnalysen vor. Zu subgruppenspezifischen Unterschieden lagen Ergebnisse aus Interaktionstests vor. Zu tumorassoziierter Mortalität lagen nur Ergebnisse aus einer Studie vor und zur Toxizität wurden die Daten nur sehr unvollständig berichtet: Sie wurden daher deskriptiv abgehandelt.
Es zeigte sich, dass eine neoadjuvante Kombinations-Chemotherapie vor Zystektomie zu einer relativen Reduktion der Gesamtmortalität von 14 % (95 % KI 2-25 %) während einer medianen Nachsorgezeit von 6,4 Jahren führte, d. h. von 1000 behandelten PatientInnen würden während dieser Zeit 54 (95 % KI 7-103) PatientInnen weniger versterben. Somit hätte jeder 18. Patient (number needed to treat (NNT) = 18) von der Behandlung in Bezug auf das Gesamtüberleben profitiert. Bezüglich des absoluten Progressionsrisikos konnte eine Verbesserung von 22 % (95 % KI 0,71-0,86) gezeigt werden, dies entspricht einer NNT von 13. Die Qualität der Evidenz nach GRADE (d. h. Vertrauen in die Studienergebnisse) wurde mit „moderat“ bewertet. Eine bevorzugte Kombination von Chemotherapeutika konnte nicht identifiziert werden, eine Behandlung mit 3-4 Zyklen war die übliche Behandlung in den Studien. Belastbare Daten konnten nur für Kombinationstherapien mit Cisplatin identifiziert werden, also nur für Patienten mit guter Nierenfunktion (GFR > 60 ml/min/1,73 qmKO) und mit gutem Allgemeinzustand (ECOG 0-1).

Tabelle 45: Neoadjuvante Kombinationschemotherapie plus Zystektomie vs. alleinige Zystektomie

Endpunkt (Qualität der Evidenz nach GRADE)	Absoluter Effekt (95% CI) Kombinations-chemo vs. alleinige Zystektomie	Relativer Effekt (95% CI)	Anzahl der Patienten (Studien)
Gesamtüberleben (moderat)	541 pro 1000 (492 - 588) vs. 595 pro 1000	HR 0,86 (0,75 bis 0.98)	1508 (6 Studien)
Progressionsrisiko (moderat)	603 pro 1000 (550 - 620) vs 676 pro 1000	HR 0,78 (0,71 bis 0,86)	2629 (8 Studien)

9.5 Neoadjuvante Immuntherapie beim lokalisierten muskelinvasiven Harnblasenkarzinom

9.12	Konsensbasiertes Statement	neu 2025
EK	Der Stellenwert einer neoadjuvanten Immuntherapie (Mono- und Kombinationstherapie) ist beim lokalisierten muskelinvasiven Harnblasenkarzinom aufgrund fehlender Ergebnisse randomisierter Studien unklar.	
	Starker Konsens	

Hintergrund zu 9.12
Zur Beantwortung der Schlüsselfragen zum Themenkomplex der perioperativen Immuntherapie erfolgte eine Leitlinienadaptation der EAU Guideline „Muscle-invasive and metastatic bladder cancer) aus dem Jahr 2021 [924]. Zusätzlich wurde eine ergänzende Literaturrecherche für den Zeitraum vom 01.01.2021 bis zum 14.09.2021 durchgeführt. Außerdem gab es eine Update-Leitlinien-Recherche für den Zeitraum 09/2021 und 01/2024.

Daten für den Einsatz einer neoadjuvanten Immuntherapie liegen aus mehreren Phase-II Studien vor. Zu nennen sind hier insbesondere die ABACUS-Studie sowie die PURE-01 Studie [985], [986], [987], [988]. In der einarmigen ABACUS-Studie wurden 95 Patienten mit einem muskelinvasiven Urothelkarzinom, die nicht für einen Cisplatin-basierte Chemotherapie geeignet waren oder diese ablehnten, mit zwei Zyklen Atezolizumab vor einer radikalen Zystektomie behandelt. Primärer Endpunkt war die Rate an pathologischen Komplettremissionen (pCR). Die Ergebnisse ergaben eine pCR-Rate von 31 % (95 % Konfidenzintervall: 21-41 %) [989], [985], [986]. In der einarmigen PURE-01-Studie wurden 55 Patienten mit einem muskelinvasiven Urothelkarzinom unabhängig von ihrer Cisplatin-Eignung, mit drei Zyklen Atezolizumab vor einer radikalen Zystektomie behandelt. Bei Patienten mit einem bildgebenden Nicht-Ansprechen war die Gabe von 3 Zyklen ddMVAC erlaubt. Primärer Endpunkt war auch hier die pCR-Rate. Es zeigte sich eine pCR-Rate von 42 % (95 % Konfidenzintervall: 28-47 %) [987], [988]. Eine weitere Studie (NABUCCO, NCT03387761, Phase I, Daten teilweise nach Abschluss der Literaturrecherche publiziert) wurde der Einsatz einer kombinierten Immuntherapie aus Ipilimumab und Nivolumab bei 54 Patienten mit einem lokal fortgeschrittenen oder primär lymphogen metastasierten Urothelkarzinoms der Harnblase oder des oberen Harntrakts (cT3-4a cN0 cM0 oder cT1-4a cN+ cM0) untersucht. Die Patienten wurden in 2 Kohorten aufgeteilt. In der Kohorte 1 wurde Ipilimumab an Tag 1 und 22 in einer Dosis von 3 mg/kg, Nivolumab an Tag 22 mit 1 mg/kg sowie an Tag 43 mit 3 mg/kg verabreicht. Primärer Endpunkt war die Rate an Patienten, bei denen innerhalb von 9-12 Wochen nach Beginn der Systemtherapie die radikale Resektion erfolgte. Dieser wurde bei 96% der Patienten (95%KI: 79-100) erreicht. Als sekundärer Endpunkt wurde die Rate an pathologischen Komplettremissionen ausgewertet, diese betrug 46 % (95%-KI: 26-67) [990]. In der Kohorte 2 wurden 30 Patienten im Verhältnis 1:1 in 2 Arme randomisiert. Beide Arme erhielten an Tag 1 und 22 Nivolumab und Ipilimumab, in Arm A wurde Ipilimumab mit 3 mg/kg und Nivolumab mit 1 mg/kg, in Arm B wurde Ipilimumab mit 1 mg/kg und Nivolumab mit 3 mg/kg verabreicht. An Tag 43 erhielten die Patienten in beiden Armen Nivolumab mit 3 mg/kg. Die radikale Resektion erfolgte 9-12 Wochen nach Beginn der Systemtherapie. Die Rate an pathologischen Komplettremissionen betrug in Arm A 43% (n=6) und in Arm B 7% (n=1). Der Anteil an partiellen Remissionen zu einem nicht muskelinvasiven Tumorstadium (< ypT1) betrug in Arm A 57% (n=8) sowie in Arm B 29% (n=4) [991]. In den vorgestellten Studien wurden, bei jeweils kleiner Fallzahl, pathologische Remissionsdaten beobachtet, die durchaus mit den Ergebnissen einer neoadjuvanten Cisplatin-basierten Chemotherapie vergleichbar sind. Sollten sich diese Daten in weiteren größeren Phase-II bzw. Phase-III Studien bestätigen, wäre der Einsatz einer neoadjuvanten Immuntherapie eine Option für Cisplatin-ungeeigneten Patienten mit einem muskelinvasiven Harnblasenkarzinom. Da bisher keine Zulassung für eine neoadjuvante Immuntherapie vorliegt, muss eine Kostenübernahme bei den Krankenkassen angefragt werden. In der systematischen Literaturrecherche konnte zusätzlich eine weitere Phase II Studie identifiziert werden, bei dem der Einsatz einer Immuntherapie (Atezolizumab) kombiniert mit einer platinbasierten Chemotherapie (Gemcitabin/Cisplatin) untersucht wurde [992]. In diese Studie wurden 39 Patienten mit einem muskelinvasiven Harnblasenkarzinom eingeschlossen, primärer Endpunkt war das pathologische downstaging.

Tabelle 47: Phase-II-Studien zum neoadjuvanten kombinierten Einsatz der Immun- und Chemotherapie beim Harnblasenkarzinom

Studie	n	Therapie	Endpunkte	Ergebnis
NCT02989584	39	4 x Gemcitabin/Cisplatin + 6 x Atezolizumab 1200 mg (q3w) vor radikaler Zystektomie	**< ypT2 ypN0-Rate** Subgruppe ypt0 ypN0	69% (95%-KI: keine Angabe) 38% (95%-KI: keine Angabe)
NCT03294304 BLASST-1	41	4 x Gemcitabin/Cisplatin + 4 x Nivolumab 360 mg (q3w) vor radikaler Zystektomie	**<= ypT1 ypN0-Rate** Subgruppe ypT0/Tis ypN0	66% (95%-KI: keine Angabe) 49% (95%-KI: keine Angabe)
NCT03674424 AURA Kohorte 1	110	4 x Methotrexat/Vinblastin/Doxorubicin/Cisplatin (q2w) + Avelumab 10 mg/kg (q2w) vor radikaler Zystektomie versus 4 x Gemcitabin/Cisplatin + Avelumab 10 mg/kg (q2w) vor radikaler Zystektomie	**ypT0/Tis ypN0-Rate**	Rekrutierung geschlossen
NCT03674424 AURA Kohorte 1	56	4 x Gemcitabin/Paclitaxel (q3w) + Avelumab 10 mg/kg (q2w) vor radikaler Zystektomie versus 4 x Avelumab 10 mg/kg (q2w)	**ypT0/Tis ypN0-Rate**	18% (95%-KI: 6-37) 46 % (95%-KI: 19-56)
NCT03406650 SAKK 06/17	61	4 x Gemcitabin/Cisplatin +Durvalumab 1500 mg (q3w) vor radikaler Resektion plus Adjuvanz 10 x Durvalumab 1500 mg (q4w)	**EFS nach 2 Jahren** ypT0 ypN0-Rate <=ypT1 ypN0-Rate	76.1% (95%-KI: 62.3-85.3) 34% (95%-KI: 21.5-48.3) 60.4R (95%-KI: 46.0-73.5)

95%-KI: 95%-Konfidenzinterfall; EFS Ereignisfreies Überleben; Primärer Endpunkt **fett** markiert

9.6 Adjuvante Immuntherapie beim lokalisierten muskelinvasiven Harnblasenkarzinom

9.13	Evidenzbasierte Empfehlung	neu 2025
Empfehlungsgrad **A**	Patienten mit einem muskelinvasiven Harnblasenkarzinom soll nach radikaler Zystektomie eine adjuvante Therapie mit Nivolumab angeboten werden, wenn die Tumorzellen eine PD-L1 Expression ≥ 1% (TPS) aufweisen und - wenn bei Patienten mit neoadjuvanter Cisplatin-basierter Chemotherapie ein Tumor mit dem Tumorstadium ypT2-pT4 und/oder ypN1-3 cM0 vorliegt oder - wenn bei Patienten ohne neoadjuvante Chemotherapie ein Tumor mit dem Tumorstadium pT3-pT4 und/oder pN1-3 cM0 vorliegt und diese Patienten nicht für eine Cisplatin-basierte adjuvante Therapie geeignet sind.	
Level of Evidence **1-**	[921]	
	Starker Konsens	

9.14	Konsensbasiertes Statement	neu 2025
EK	Patienten mit einem muskelinvasiven Harnblasenkarzinom sollte nach radikaler Zystektomie eine adjuvante Therapie mit Nivolumab angeboten werden, wenn die Tumorzellen eine PD-L1 Expression ≥ 1% (TPS) aufweisen, ohne neoadjuvante Chemotherapie ein Blasentumor mit dem Tumorstadium pT3-pT4 und/oder pN1-3 cM0 vorliegt und trotz Eignung eine Cisplatin-basierte adjuvante Therapie abgelehnt wird	
	Konsens	

Hintergrund zu 9.13 bis 9.14
Zur Beantwortung der Schlüsselfragen zum Themenkomplex der perioperativen Immuntherapie erfolgte eine Leitlinienadaptation der EAU Guideline „Muscle-invasive and metastatic bladder cancer) aus dem Jahr 2021 [924]. Zusätzlich wurde eine ergänzende Literaturrecherche für den Zeitraum vom 01.01.2021 bis zum 14.09.2021 durchgeführt. Außerdem gab es eine Update-Leitlinien-Recherche für den Zeitraum 09/2021 und 01/2024. Mit der Frage nach der Bedeutung einer adjuvanten Immuntherapie nach radikaler Zystektomie liegen aktuell Daten zweier randomisierter Phase-III Studien (CheckMate 274, IMVigor010) vor. In der randomisierten Phase-III Studie CheckMate 274 [921] wurden 709 Patienten eingeschlossen. Es wurden 2 unterschiedliche Patientengruppen untersucht: In der ersten Gruppe wurden Blasentumorpatienten eingeschlossen, die keine Cisplatin-basierte neoadjuvante Chemotherapie erhalten hatten. Die Patienten hatten entweder keine Cisplatin-Eignung oder eine neoadjuvante Chemotherapie wurde von den Patienten abgelehnt. Nach Zystektomie zeigte sich ein postoperatives Tumorstadium mit pT3-pT4a und/oder pN+. Die zweite Patientengruppe hatte eine Cisplatin-basierte neoadjuvante Chemotherapie erhalten, allerdings zeigte das postoperative Tumorstadium nach radikaler Zystektomie weiterhin einen residuellen Tumorbefund mit ypT2- ypT4a und/oder ypN+ aufweisen. Nach einer 1:1 Randomisierung wurden 353 Patienten mit Nivolumab (240 mg, 14-tägige Gabe, bis zu 1 Jahr) behandelt und 356 Patienten erhielten eine Placeboinfusion. Die beiden primären Endpunkte waren das krankheitsfreie Überleben bei allen Patienten, die randomisiert wurden (intention-to-treatPopulation, ITT), und bei den Patienten mit einer PD-L1-Expression im Tumor von TPS 1 % oder mehr. Hinsichtlich der klinischen Charakteristika waren beide Gruppen ausgeglichen, der Anteil der Patienten mit Urothelkarzinomen des oberen Harntraktes betrug in beiden Kohorten jeweils 21 %. Jeweils 40 % der Patienten wiesen eine PD-L1- Expression im Tumor ≧1 % auf. Insgesamt hatten 43,1 % und 43,5 % der

Patienten eine Cisplatin-basierte neoadjuvante Chemotherapie erhalten. Nach einem medianen Nachbeobachtungszeit von 20,9 (0,1 – 48,3) Monaten zeigte sich in der ITT-Population ein signifikanter Vorteil für die Gabe von Nivolumab. Verglichen mit der Placebo-Gruppe wurde das krankheitsfreie Überleben um 10 Monate verlängert (Nivolumab: 20,8 [95 % KI, 16,5 - 27,6] Monate, Plazebo: 10,8 [95 % KI 8,3 – 13,9] Monate, HR 0,7 [98,72 % KI 0,57-0,86], P<0,001). Bei den Patienten mit einer PD-L1-Expression im Tumor ≧1 % zeigte sich dieser Vorteil ebenfalls (HR 0,55 [98,72 % KI, 0,35 to 0,85], P P<0,001, das mediane krankheitsfreie Überleben für die Nivolumab-Gruppe ist hier noch nicht erreicht. Somit hat die Studie Ihren primären Endpunkt erreicht. Allerdings fehlen noch Daten zum Gesamtüberleben. Bei fehlendem Nachweis eines Überlebensvorteils mit einer adjuvanten Nivolumab Therapie, muss dann eine ausführliche Diskussion mit dem Patienten zur individuellen Entscheidung erfolgen.

Therapiebezogenen Nebenwirkungen ≧ CTCAE Grad 3 wurden bei 17,9 % in der Nivolumab und 7,2 % in der Plazebo-Gruppe beobachtet, therapiebedingte Todesfälle traten bei 2 Patienten (Darmperforation, Pneumonitis) in der Nivolumab-Gruppe auf. In Bezug auf die Lebensqualität, die mit dem EORTC QLQ-C30 Fragebogen erfasst wurde, fand sich kein signifikanter Unterschied bezüglich einer Verschlechterung der Lebensqualität.

In einer explorativen Subgruppenanalyse bei Patienten mit einer negativen PD-L1-Expression (n=414), definiert als TPS von <1 % auf den Tumorzellen, betrug die nichtstratifizierte DFS-Hazard-Ratio-Schätzung 0,83 (95 % KI, 0,64 - 1,08). Dies könnte einen fehlenden Nutzen einer adjuvanten Nivolumab-Therapie bei dieser Patientengruppe hinweisen. Basierend auf dieser Subgruppenanalyse hat die EMA eine Zulassungseinschränkung beschlossen: Es dürfen nur Patienten mit einer positiven PD-L1Expression von ≥ TPS 1 % eine adjuvante Nivolumab-Therapie erhalten. Hingegen hat die FDA eine Zulassung für alle Blasentumorpatienten unabhängig vom PDL1 Status erteilt.
Wichtig zu bemerken ist weiterhin, dass insbesondere Patienten, bei denen eine neoadjuvante Cisplatin-basierte Chemotherapie durchgeführt worden ist, von einer adjuvanten Nivolumab-Gabe zu profitieren scheinen. Während für diese Patienten das Risiko eines Rezidivs und/oder Tod signifikant verringert (-48%) werden konnte (HR 0,52 [95 % KI 0,38-0,71]), war dies bei Patienten ohne vorangegangene neoadjuvante Chemotherapie nicht der Fall (HR 0,92 [95 % KI 0,69-1,21]). Daher sollte bei Cisplatin geeigneten Patienten trotz der Möglichkeit einer adjuvanten Immuntherapie, wenn immer möglich, eine neoadjuvante Cisplatin-basierte Chemotherapie durchgeführt werden. Auch bietet diese Studie keine Grundlage dafür, bei Patienten die Cisplatin geeignet sind, bei denen, aus welchen Gründen auch immer, keine neoadjuvante Chemotherapie durchgeführt worden ist und die nach radikaler Zystektomie einen pT3pT4a und oder pN+ Befund aufweisen, auf eine adjuvante Cisplatin-basierte Chemotherapie zugunsten einer adjuvanten Immuntherapie zu verzichten.

Dieser Einschränkung trägt auch die Nutzenbewertung im Rahmen des AMNOG-Verfahrens des Gemeinsamen Bundesausschuss Rechnung. In seinem Beschluss vom 20. Oktober 2022 [441233 et al. 2022] (https://www.g-ba.de/downloads/39-2615661/2022-10-20_AM-RL-XII_Nivolumab_D-821_BAnz.pdf) erläutert der G-BA, dass bei der Bewertung des Zusatznutzens einer adjuvanten Nivolumab-Therapie in Bezug zur zweckmäßigen Vergleichstherapie (ZVT) zwischen zwei Patientengruppen unterschieden werden muss. Bei „Erwachsene [...], die für eine Cisplatin-haltige Therapie geeignet sind“, ist die ZVT eine platin-basierte Chemotherapie. Da eine solche im Vergleichsarm der CheckMate-274 nicht eingesetzt wurde, ist nach Ansicht des G-BA kein Zusatznutzen für die adjuvante Nivolumab-Gabe belegt. Bei „Erwachsene [...], die für eine Cisplatin-haltige Therapie nicht geeignet sind oder bereits eine neoadjuvante Behandlung erhalten haben“ ist die ZVT ein beobachtendes Abwarten entsprechend dem Vergleichsarm der CheckMate-274-Studie. Hier sieht der G-BA Anhaltspunkte für einen „nicht-quantifizierbaren Zusatznutzen“.

In der randomisierten Phase-III Studie IMVigor010 [993] wurden 809 Patienten eingeschlossen. Die Einschlusskriterien waren mit denen der CheckMate-214-Studie vergleichbar. Patienten, die keine Cisplatin-basierte neoadjuvante Chemotherapie erhalten hatten (Cisplatin-ungeeignete Patienten, Ablehnung einer perioperativen Chemotherapie) mussten nach Zystektomie einen residuellen Tumorbefund im pathologischen Stadium pT3-pT4a oder pN+ aufweisen. Patienten, bei denen eine Cisplatin-basierte neoadjuvante Chemotherapie erfolgt war, mussten einen residuellen Tumorbefund im pathologsichen Stadium ypT2-ypT4a oder ypN+ aufweisen. Nach einer 1:1 Randomisierung wurden 406 Patienten mit Atezolizumab (1200 mg, dreiwöchentliche Gabe, 16 Zyklen oder bis zu 1 Jahr) behandelt, 403 Patienten erhielten keine Therapie und wurden entsprechend dem Nachsorgeschema beobachtet. Der primäre Endpunkt war das krankheitsfreie Überleben (DFS) in der intention-to-treat-Population. Hinsichtlich der klinischen Charakteristika waren beide Gruppen ausgeglichen, der Anteil der Patienten mit Urothelkarzinomen des oberen Harntraktes betrug in beiden Kohorten jeweils 7 % und 6 %. Insgesamt hatten 48 % und 47 % der Patienten eine Cisplatin-basierte neoadjuvante Chemotherapie erhalten. Nach

einer medianen Nachbeobachtungszeit von 21,9 (IQR 13,2-29,8) Monaten zeigte sich in der ITT-Population lediglich ein numerischer, nicht aber ein statistisch signifikanter Vorteil für die Gabe von Atezolizumab verglichen mit der Kontroll-Gruppe (Atezolizumab: 19,4 (95 % KI 15,9– 24,8) Monate, Kontrollgruppe: 16,6 (95 % KI 11.2–24.8) Monate, HR: 0,89 [95 % KI 0,74–1,08]; p=0,24). Der primäre Endpunkt DFS wurde nicht erreicht und die Studie ist damit negativ. Bezüglich weiterer sekundärer Endpunkte wurde sowohl das Gesamtüberleben als auch das Überleben zu verschiedenen vordefinierten Zeitpunkten (nach 12 und 18 Monaten) untersucht. Hier zeigte sich kein Unterschied zwischen der Behandlungs- und der Kontrollgruppe. Schwerwiegende unerwünschte Ereignisse (SAEs) waren in der Atezolizumab-Gruppe häufiger (Atezolizumab: 122/390 (31%), Kontrollgruppe: 71/397 (18%)), Therapie-bezogene SAEs wurden ausschließlich in der Atezolizumab-Gruppe (11% vs. <1%) beobachtet. Ein Patient in der Atezolizumab Gruppe starb aufgrund eines therapiebedingten ARDS.

9.7 Perioperative Radiotherapie beim lokalisierten muskelinvasiven Harnblasenkarzinom

9.15	Evidenzbasiertes Statement	neu 2025
Level of Evidence **2a**	Der Stellenwert einer perioperativen Radiotherapie bei einem operativ behandelbaren, lokalisierten muskelinvasiven Harnblasenkarzinom ist zum aktuellen Zeitpunkt nicht belegt und wird in Studien untersucht.	
	[994], [995]	
	Starker Konsens	

Hintergrund zu 9.15
Zur Beantwortung der Schlüsselfragen zum Themenkomplex der neoadjuvanten Therapie erfolgte eine Leitlinienadaptation der EAU-Leitlinie „Muscle-invasive and metastatic bladder cancer“) aus dem Jahr 2021 [924]. Zusätzlich wurde eine ergänzende Literaturrecherche für den Zeitraum vom 01.01.2021 bis zum 14.09.2021 durchgeführt. Dabei zeigte sich, dass sich die Evidenzlage insbesondere zur adjuvanten Radiotherapie im Vergleich zu vorherigen Leitlinienversion geändert hat und die Empfehlungen somit angepasst werden musste.

Neoadjuvante Radiotherapie
Die systematische Literaturecherche der EAU konnte bezüglich der Frage nach einer neoadjuvanten Radiotherapie sechs randomisierte Studien [996], [997], [998], [999], [1000], [1001] sowie eine Metaanalyse, die die älteren 5 Studien zusammenfasst [1002] als relevant identifizieren. In der Metaanalyse zeigte sich zwar ein Unterschied im 5-Jahresüberleben (OR: 0,71, 95% CI: 0,48–1,06) zugunsten einer neoadjuvanten Radiotherapie. Allerdings muss dabei berücksichtig werden, dass dieser Unterschied wesentlich durch die größte der randomisierten Studien beeinflusst ist, die aus mehreren Gründen einen inhärenten Bias birgt. Nur bei einem kleinen Teil der Patienten wurde eine begleitende Chemotherapie durchgeführt, mehr als die Hälfte der ursprünglichen Patienten wurde von der Effektivitätsanalyse ausgeschlossen, da sie nicht protokollkonform behandelt werden konnten. Wird diese Studie aus der Metaanalyse ausgeschlossen, zeigt sich kein Vorteil für eine neoadjuvante Radiotherapie mehr (OR: 0.94 (95% CI: 0.57–1.55)). Auch die Ergebnisse der neuere Studie [1001] tragen nicht zu einer Verbesserung der Evidenzlage bei. Zum einen wurden in dieser Arbeit Patienten verglichen, die entweder einer neoadjuvanten oder einer adjuvanten Radiotherapie zugeführt wurden, zum anderen waren die Hälfte der Patienten an einem Plattenepithelkarzinom der Harnblase erkrankt, ein Unterschied zwischen den beiden Behandlungsarmen fand sich für keinen der relevanten Endpunkte. Konsistent über die meisten Studien hinweg scheint lediglich zu sein, dass durch eine präoperative Radiotherapie ein downstaging erreicht werden kann [996], [999], [1000], [1001].
Die ergänzende eigene Literaturrecherche konnte eine für die Fragestellung relevante Publikation identifizieren [1003]. In der retrospektiven Multicenter Studie wurden von 5517 eingeschlossenen Patienten mit einem muskelinvasiven Harnblasenkarzinom 195 mit einer neoadjuvante Radiotherapie behandelt. Untersucht wurde die Häufigkeit eines vollständige pathologische Downstagings (≤(y)pT1N0) und das OS bei Patienten mit cT2 versus cT3-4aN0M0 Urothelkarzinom der Harnblase nach radikaler Zystektomie mit oder ohne neoadjuvante Chemo- oder Strahlentherapie. Ein Einfluss der neoadjuvanten Radiotherapie auf das Gesamtüberleben konnte nicht nachgewiesen werden.

Adjuvante Radiotherapie

Bezüglich der Fragestellung nach einer adjuvanten Radiotherapie konnte die EAU Leitliniengruppe eine aktuellere Phase II Studie [994] sowie eine aktuelle systematische Übersichtsarbeit [995] als relevant identifizieren. In der Phase II Studie von Zaghloul und Mitarbeitern wurden Patienten mit mindestens einem Risikobefund (≥ pT3b, grade 3, oder pN+) nach radikaler Zystektomie eingeschlossen. Nach Ranndomisation wurden 75 Patienten mit einer adjuvanten Chemotherapie (Gemcitabin/Cisplatin, q4w) und einer adjuvanten Radiotherapie (2x1,5 Gy/Tag, 3 Wochen, max. 45Gy) behandelt, 45 Patienten alleine mit einer adjuvanten Chemotherapie. 53% der Patienten waren an einem Urothelkarzinom, die übrigen an einem Plattenepithelkarzinom der Harnblase erkrankt. Für die lokale Tumorkontrolle gemessen am lokales rezidivfreies Überleben nach 2 Jahren zeigte sich ein statistisch signifikanter Vorteil zugunsten der Radiotherapie (96% vs. 69% [HR, 0,08; 95% CI, 0,02-0,39; P < .01]). Auch in Bezug auf das tumorspezifische sowie das Gesamtüberleben scheint die Radiotherapie im Vorteil zu sein, allerdings waren die Unterschiede im Vergleich zur alleinigen Chemotherapie nicht signifikant (DFS: HR, 0,53; 95% CI, 0,27-1,06; P = 0,07; OS: HR, 0,61; 95% CI, 0,33-1,11; P = 0,11). Nur wenige Patienten (7%) waren von relevanten (CTCAE ≧ Grad 3) gastrointestinalen Toxizitäten betroffen. Die systematische Übersichtsarbeit konnte 14 Studien zur adjuvanten Radiotherapie bei Harnblasenkarzinompatienten identifizieren. Für eine Metaanalyse war die Datengrundlage der identifizierten Studien zu heterogen. Die Autoren kommen zum Schluss, dass für eine klare Empfehlung in jedem Fall weitere prospektive Studie erforderlich sind, dass bei ausgewählten Patienten mit einem lokal fortgeschrittenen Tumor eine adjuvante Radiotherapie wahrscheinlich sinnvoll ist.
In der eigenen ergänzenden Literaturrecherche konnten weiterhin zwei retrospektive Untersuchungen der National Cancer Data Base identifiziert werden [1004], [1005], die die Empfehlung der EAU zu einer möglichen Radiotherapie bei Patienten mit einem erhöhten Rezidivrisiko unterstützen. In der Arbeit von Bateni et al. wurden Patienten mit und ohne adjuvante Radiotherapie verglichen, die nach einer radikalen Zystektomie ungünstige pathologische Risikofaktoren aufwiesen (pT3/pT4 und/oder positive Schnittränder). Während sich im Gesamtüberleben insgesamt kein Unterschied zwischen den beiden Patientengruppen zeigte, profitierten Patienten mit positiven Schnitträndern hinsichtlich de Gesamtüberlebens von einer adjuvanten Radiotherapie (Hazard ratio 0.73; p=0,047). Eine Analyse potentieller Nebenwirkungen einer adjuvanten Radiotherapie wurde in dieser Arbeit nicht durchgeführt. Fischer-Valuck et al. untersuchten ein vergleichbares Patientenkollektiv. Zusätzlich zum direkten Vergleich der gesamten Patientenkohorten mit und ohne adjuvante Radiotherapie (kein Unterschied hinsichtlich des Gesamtüberlebens) wurde in dieser Arbeit ein Vergleich nach propensity-score matching der beiden Patientengruppen durchgeführt. Hier zeigte sich ein signifikanter Überlebensvorteil zugunsten einer adjuvanten Radiotherapie (medianes OS 19,8 Monate (95% CI, 18,0-21,6) vs. 16,9 Monaten (95% CI, 15,6-18,1, p = 0,030). Insbesondere In Urothelkarzinom-Patienten mit einem pT4-Befund, pN+-Befund und/oder positiven Schnitträndern profitierten hinsichtlich des Gesamtüberlebens von einer adjuvanten Radiotherapie. Auch in dieser Arbeit wurde keine Analyse potentieller Nebenwirkungen der adjuvanten Radiotherapie durchgeführt.

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van der Heijden AG et al., 2026 [4].

European Association of Urology (EAU)

Muscle-invasive and Metastatic Bladder Cancer

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Konsensusprozesse nicht beschrieben, externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert gesichert.

Recherche/Suchzeitraum:

- A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between 1 May 2024 and 1 May 2025.

LoE

- Currently, the EAU GO uses a modified level of evidence/strength of recommendation table from the Oxford Centre for Evidence-based Medicine Levels of Evidence (modified March 2009)

Table 4. EAU Guideline's levels of evidence

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

GoR

- Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference.

- Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference.

Sonstige methodische Hinweise

Die als “EAU-ESMO consensus statement” gekennzeichneten Empfehlungen basieren nicht auf einer systematischen Suche, Auswahl und Bewertung der Evidenz. Sie wurden für Therapiesituationen angefertigt für die laut der Autoren hochwertige Evidenz fehlt oder widersprüchlich ist.

Empfehlungen

6.5 6.5.1

Perioperative systemic therapy Neoadjuvant

6.5.1.a Neoadjuvant chemotherapy

6.5.1.c Summary of evidence and recommendations for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves OS (8% at five years).	1a
Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0N0 or ≤ ypT2N0.	2a
Perioperative durvalumab plus neoadjuvant GC improves EFS and OS compared to neoadjuvant GC alone.	1b
Perioperative EV + P improves EFS and OS compared to surgery followed by observation in patients with cisplatin-ineligible MIBC.	1b
There are still no reliable tools available to select patients who have a higher probability of benefitting from NAC. In future, genomic markers in a personalised medicine setting might facilitate the selection of patients for NAC and differentiate responders from non-responders.	-

Recommendations	Strength rating
Offer perioperative chemoimmunotherapy with cisplatin/gemcitabine and durvalumab to patients with muscle-invasive bladder cancer (MIBC) (T2-T4a, cN0 M0) who are eligible for cisplatin-based chemotherapy (glomerular filtration rate > 40mL/min. allowed) and immunotherapy.	Strong
Offer perioperative enfortumab vedotin plus pembrolizumab to patients with MIBC who are ineligible for cisplatin-based chemotherapy.	Strong
Offer neoadjuvant cisplatin-based combination chemotherapy to patients with MIBC (T2-T4a, cN0 M0) who are eligible for cisplatin-based chemotherapy.	Strong
Do not offer neoadjuvant carboplatin-containing combination chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong

Hintergrundinformationen

6.5.1.a Neoadjuvant chemotherapy

The standard surgical treatment for patients with urothelial MIBC and MIBC with subtypes is RC. However, RC only provides five-year survival in about 50% of patients [217-219]. To improve survival in patients with nonmetastatic disease, cisplatin-based NAC has been used since the 1980s [217-221].

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive cN0M0 UC of the bladder:

- Chemotherapy is delivered at the earliest point in time, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of in vivo chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0, ≤ ypT1, ypN0 and negative surgical margins. An analysis to identify the optimal definition of pathological response reported a significantly higher risk of recurrence in patients with

ypTaN0 or ypT1N0 disease (with or without Tis) at RC and thus proposed that optimal pathological response after NAC be defined as attainment of ypT0N0/ypTisN0 at RC [222]. However, the definition of pathological responses remains unclear.

- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [223-225]. A comparative survival analysis of patients treated with NAC and RC versus RC alone based on data from the United States (U.S.) National Cancer Database showed that organ-confined disease (≤ pT2) after NAC was associated with decreased risk of death (HR: 0.85; 95% CI: 0.79-0.91) compared to RC alone, whereas > pT2 was associated with increased risk of death (HR: 1.46; 95% CI: 1.34-1.60) [226]. However, there are no prospective trials indicating that delayed surgery due to NAC has a negative impact on survival.
- Neoadjuvant chemotherapy does not appear to affect the outcome of surgical morbidity. In a large multicentre retrospective analysis, NAC did not lead to an increased risk of postoperative complications after RC [227]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm with 71% of patients receiving all three chemotherapy cycles [228].
- Sex may have an impact on chemotherapeutic response and oncologic outcomes [229, 230]. Female patients tend to have a better cancer-related response to NAC compared to male patients.
- Neoadjuvant chemotherapy should only be used chemotherapy [231-238].

Several phase III RCTs addressed the potential survival benefit of NAC administration [231-235, 239-241]. As these studies differed considerably for patient numbers, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [236-238]. In a meta-analysis including patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC [238]. Another meta-analysis included four additional RCTs and used the results from the Nordic I, Nordic II and BA06 30894 trials, including data from 427 new patients and information from 1,596 patients. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in survival at five years with a needed-to-treat number of 12.5 [242].

The analysis of a large phase III RCT [232] with a median follow-up of eight years confirmed previous results and provided additional findings:

- 16% reduction in mortality risk;
- improvement in ten-year survival from 30% to 36% with neoadjuvant Cisplatin, Methotrexate and Vinblastin (CMV);
- benefit regarding distant metastases; and
- the addition of neoadjuvant CMV provided no benefit for locoregional control and locoregional DFS, independent of the definitive treatment.

Based on retrospective data alone, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [243]. A retrospective analysis of clinicopathologic outcomes comparing 245 patients with clinical T2-4a N0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (multivariable OR: 0.4; 95% CI: 0.18-0.84; p = 0.02). The results of the retrospective analysis also showed that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone (p = 0.002).

More-modern chemotherapeutic regimens such as GC have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses [244-247]. Modified dd-MVAC was tested in two small single-arm phase II studies. The studies demonstrated high rates of pathologic complete remission (CR) [248, 249]. Moreover, a large cross-sectional analysis showed higher rates of downstaging and pathological complete response for dd-MVAC [250].

In the GETUG/AFU V05 VESPER RCT of perioperative chemotherapy, 500 patients were randomised to either six cycles of dd-MVAC versus four cycles of GC before surgery (neoadjuvant group) or after surgery (adjuvant group) with a primary endpoint of PFS at three years. Eighty-nine percent of participants received neoadjuvant therapy, and similar pathologic response rates (ypT0N0) were observed in patients treated with dd-MVAC (42%) and GC (36%; p = 0.2). The < ypT2N0 rate was 63% in the dd-MVAC patients and 50% in the GC patients. Organconfined response (< ypT3N0) was observed more frequently in the dd-

MVAC arm (77% vs. 63%; p = 0.001). For all patients in the trial, intention-to-treat (ITT) included neoadjuvant and adjuvant therapy and three-year PFS was improved in the dd-MVAC arm, although the study did not meet its primary endpoint (three-year rate for ITT: 64% vs. 56%; HR: 0.77; 95% CI: 0.57-1.02; p = 0.066). At five-year follow-up, however, a significant benefit for the neoadjuvant group in favour of dd-MVAC with regards to PFS (HR: 0.74; 95% CI: 0.55-0.99) and OS (HR: 0.71; 95% CI: 0.52-0.97) was seen [251]. Dose-dense MVAC was associated with more severe asthenia and GI side effects than GC [89, 252]. In a single-centre retrospective analysis in patients with MIBC, neoadjuvant accelerated MVAC was safe and efficacious irrespective of age, provided that patients were fit and deemed suitable candidates for cisplatin [253]. Another dose-dense regimen using GC was reported in two small phase II trials [254, 255]. While pathological response rates (< pT2) in the range of 45-57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [254]. This approach is therefore not recommended outside of clinical trials.

As an alternative to the standard dose of cisplatin-based NAC with 70mg/m2 on day one, split-dose modification regimens are often used with 35mg/m2 on days one and eight, or days one and two. In a retrospective analysis, the standard schedule was compared to a split-dose schedule to assess complete and partial pathological response. A lower number of complete and partial response rates was seen in the split-dose group, but these results were not statistically significant [256].
For responders to NAC, especially in those with a complete response (ypT0N0), treatment has a major positive impact on OS [257, 258]. Therefore, reliable predictive markers to identify patients most likely to benefit from chemotherapy are needed. Molecular tumour profiling might guide the use of NAC in the future, but as yet, this is not applicable in routine practice [259-261].
It is unclear whether patients with non-UC histology will also benefit from NAC. A retrospective analysis demonstrated that patients with NE tumours had improved OS and lower rates of non-organ-confined disease when receiving neoadjuvant cisplatin/etoposide chemotherapy. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ-confined disease were found, but no statistically significant impact on OS. Patients with SCC did not benefit from NAC [262]. A 2019 systematic review showed benefit of NAC for patients with micropapillary, plasmacytoid, sarcomatoid and mixed variants, but especially for patients with NE tumours [52]. A U.S. National Cancer Database study evaluating potential associations between receipt of NAC, pathological downstaging and OS for patients with histological subtype MIBC demonstrated that NAC was associated with pathological downstaging for all MIBC histological subtypes (UC, sarcomatoid UC, micropapillary UC, SCC, NE carcinoma and adenocarcinoma), with improved OS for patients with UC, sarcomatoid variant UC and NE carcinoma [263]. An analysis of the VESPER trial showed no impact of subtypes on the outcome of NAC, with the exception of SCC and micropapillary subtypes that appeared to have inferior outcome [264]. In a recent systematic review and meta-analysis of NAC prior to RC in MIBC subtypes, better survival outcomes and higher pathologic downstaging were associated with NAC when compared to surgery alone [265].

6.5.1.b Neoadjuvant combination therapies
Checkpoint inhibitors have been tested in the neoadjuvant setting, either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials using single-agent CPIs demonstrated encouraging results [112, 266]. The PURE-01 study, using the PD-1 inhibitor pembrolizumab, reported a complete pathological remission (pT0) in 42% and pathological response (< pT2) in 54% of patients [267], whereas in the ABACUS trial, with the PD-L1 inhibitor atezolizumab, the pathologic complete response rate was 31% [114]. The combination of anti-CTLA4 and anti-PD1 therapy has also been investigated in the neoadjuvant setting. In the NABUCCO study using preoperative ipilimumab and nivolumab, the pathologic complete response was 46%, with 58% having no remaining invasive disease (< ypT2N0) [268]. In a study using preoperative tremelimumab and durvalumab in cisplatin-ineligible patients, the pathological complete response was 37.5% and downstaging to < ypT2N0 was seen in 58% of patients who completed surgery [269].
Three phase II studies have been published investigating the use of neoadjuvant chemoimmunotherapy in patients with MIBC. In a phase II study of gemcitabine plus split-dose cisplatin and pembrolizumab in patients with MIBC, 22 of 39 patients (56% [95% CI: 40-72]) achieved < ypT2N0 and 14 of 39 (36% [95% CI: 21-53]) achieved ypT0N0 [270]. In another phase II study evaluating neoadjuvant atezolizumab with gemcitabine and cisplatin, 27 of 39 patients (69%) were < ypT2N0 and 16 (41%) ypT0N0. [271]. A third phase II study evaluating NAC with GC plus durvalumab including adjuvant durvalumab with a primary endpoint of event-free survival (EFS) demonstrated EFS at three years of 73% (95% CI: 59-83). Complete pathologic response was achieved in 17 of 52 patients (33%), and 31 (60%) had pathologic response < ypTN0. A phase II trial demonstrated promising results using a stringent definition of clinical complete response rate for an organ-sparing treatment for MIBC with the combination of GC plus nivolumab [272].

The first randomised phase III trial (NIAGARA) testing perioperative addition of durvalumab to neoadjuvant cisplatin/gemcitabine chemotherapy has demonstrated significantly improved EFS and OS and higher pathological CR rate [273]. Patients with estimated glomerular filtration rate (eGFR) of 40mL/min. or higher were eligible, with cisplatin split-dose (day one and eight) given in case of eGFR 40-60mL/min. 1,063 patients underwent randomisation and received either four cycles of GC or the same chemotherapy plus durvalumab for four cycles every three weeks in the neoadjuvant part and durvalumab alone for eight cycles every four weeks in the adjuvant part. With a median follow-up of 42.3 months, the estimated EFS at two years was 67.8% with durvalumab compared to 59.8% without durvalumab (HR for progression, recurrence, not undergoing RC or death from any cause: 0.68; 95% CI: 0.56-0.82; p < 0.001) and the estimated OS at two years was 82.2% and 75.2% (HR: 0.75; 95% CI: 0.59-0.93; p = 0.01), respectively. There was no difference between groups in grade 3/4 treatment-related adverse events (AEs), RC rates or in the safety of surgery. The perioperative regimen of cisplatin/gemcitabine and durvalumab, as applied in the NIAGARA study, has been approved by the EMA in July 2025, and it is also FDA approved.
At the European Society of Medical Oncology (ESMO) 2025 Annual Meeting, the results from the phase III KEYNOTE-905/EV-303 study evaluating perioperative EV + P in patients with cisplatin-ineligible MIBC was presented [274]. In this, 344 patients with cisplatin-ineligible (or -declining) MIBC were randomised to perioperative EV + P versus RC with pelvic LND followed by observation. At a median follow-up of 25.6 months, perioperative EV + P was associated with a significant improvement in EFS (HR: 0.40; 95% CI: 0.28-0.57; P < 0.001) and OS (HR: 0.50; 95% CI: 0.33-0.74; P = 0.0002) as compared to surgery followed by observation. Pathologic complete response rate was 57.1% versus 8.6%, respectively. Perioperative EV + P did not impact the ability of participants to undergo surgery, and the safety profile was manageable [274]. The result of this trial supports a new standard of care with perioperative EV + P for patients with cisplatin-ineligible MIBC.

6.5.2 Adjuvant therapy

6.5.2.a Adjuvant chemotherapy

6.5.2.c Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
Two studies using immune CPI in the adjuvant setting for high-risk MIBC patients have demonstrated an improvement in DFS (CheckMate 274 with nivolumab, AMBASSADOR with pembrolizumab). In contrast, one study (IMvigor 010 with adjuvant atezolizumab) failed to show a DFS benefit.	1b
In patients with MIBC, ctDNA-guided adjuvant therapy with atezolizumab improves DFS and OS.	1b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant systemic therapy has been given.	Strong
Offer adjuvant nivolumab to patients with high-risk muscle-invasive urothelial carcinoma (≥ ypT2N0 after NAC or pT3/4 and/or pN+) who are not eligible for, or who declined, adjuvant cisplatin-based chemotherapy. Of note: FDA approval irrespective of PD-L1 status, EMA approval only for PD-L1 tumour cell expression ≥ 1%.	Strong

EMA = European Medicines Agency; FDA = United States Food and Drug Administration; PD-L1 = programmed death-ligand 1.

Hintergrundinformationen
6.5.2.a Adjuvant therapy
Adjuvant chemotherapy
Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (pN+) disease without clinically detectable metastases (M0) is still under debate. The general benefits of adjuvant chemotherapy include:

- chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micro-metastases is avoided; and
- no delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- assessment of in vivo chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem; and
- delay of or intolerability to chemotherapy, due to postoperative morbidity [275].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [276-281]. An individual patient data meta-analysis [282] of survival data from six RCTs of adjuvant chemotherapy [283-285] included 491 patients. All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws [276]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with three additional studies [279-281] resulting in the inclusion of 945 patients from nine trials [278]. None of the trials had fully accrued and individual patient data were not used in the analysis. None of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. The HR for OS was 0.77 (95% CI: 0.590.99; p = 0.049) and for DFS was 0.66 (95% CI: 0.45-0.91; p = 0.014). A systematic review and meta-analysis of individual patient data from RCTs in patients treated with adjuvant cisplatin-based chemotherapy for MIBC has more recently been conducted [286]. In an analysis of ten RCTs (n = 1,183), an OS benefit was demonstrated for cisplatin-based adjuvant chemotherapy (HR: 0.82; 95% CI: 0.70-0.96; p = 0.02). This translates into an absolute improvement in survival of 6% at five years, from 50% to 56%, and a 9% absolute benefit when adjusted for age, sex, pT stage, and pN category (HR: 0.77; 95% CI: 0.65-0.92; p = 0.004).
A retrospective cohort analysis including 3,974 patients after cystectomy and LND showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) (HR: 0.75; CI: 0.62-0.90) [287]. Although not fully accrued, a publication of the largest RCT (European Organisation for Research and Treatment of Cancer [EORTC] 30994) showed a significant improvement of PFS for immediate, compared with deferred, cisplatinbased chemotherapy (HR: 0.54; 95% CI: 0.4-0.73, p < 0.0001), but there was no significant OS benefit [288]. Furthermore, a large observational study including 5,653 patients with pathological T3-4 and/or pathological node-positive BC treated between 2003 and 2006. compared the effectiveness of adjuvant chemotherapy versus observation. Twenty-three percent of patients received adjuvant chemotherapy with a five-year OS of 37% for the adjuvant arm versus 29.1% (HR: 0.70; 95% CI: 0.64-0.76) in the observation group [289]. Another large retrospective analysis based on the U.S. National Cancer Database, including 15,397 patients with locallyadvanced (pT3/4) or LN-positive disease, also demonstrated an OS benefit in patients with UC histology [290]. In patients with concomitant histological subtypes, however, no benefit was found.

Patients should be informed about potential chemotherapy options before RC and the limited evidence for adjuvant chemotherapy.

6.5.2.b Adjuvant immunotherapy
Four phase III RCTs have evaluated CPI monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC (MIUC). CheckMate 274, a phase III, double-blind RCT of adjuvant nivolumab versus placebo for up to one year in 709 patients with MIUC with a high risk of recurrence (≥ ypT2 or ypN+ after NAC or pT3, pT4a, or pN+ without neoadjuvant therapy), demonstrated a significant improvement in median DFS (20.8 months [95% CI: 16.5-27.6] with nivolumab and 10.8 months [95% CI: 8.3-13.9] with placebo). The percentage of patients who were alive and disease-free at six months was 74.9% with nivolumab and 60.3% with placebo (HR for disease recurrence or death: 0.70; 98.22% CI: 0.55-0.90; p < 0.001). Among patients with a PD-L1 expression level of ≥ 1% (tumour cell [TC] score), the percentage of patients was 74.5% and 55.7%, respectively (HR: 0.55; 98.72% CI: 0.35-0.85; p < 0.001) [291]. In an analysis using both PD-L1 TC score and CPS, more patients had CPS ≥ 1 than TC ≥ 1% and patients with CPS ≥ 1 had improved DFS with nivolumab which may have contributed to the benefit seen with adjuvant nivolumab in patients with TC < 1% and CPS ≥ 1 [292]. There was no clinically meaningful deterioration in health-related QoL with adjuvant nivolumab compared to placebo [293]. With extended median follow-up of 36 months, interim OS data were reported demonstrating a promising trend (i.e. not meeting the prespecified boundary for statistical significance at the time of the analysis) in favour of nivolumab with an HR for OS with nivolumab versus placebo of 0.76 (95% CI: 0.61-0.96) in the ITT population and 0.56 (95% CI: 0.36-0.86) in the PD-L1 ≥ 1 population [294].

A second phase III trial evaluated adjuvant pembrolizumab for one year versus observation in patients with high-risk MIBC after radical surgery (Alliance A031501 AMBASSADOR). Adjuvant pembrolizumab demonstrated a significant improvement in median DFS compared to observation 29.6 months (95% CI: 20.040.7) with pembrolizumab and 14.2 months (95% CI: 11.0-20.2) with observation (HR for disease progression or death: 0.73; 95% CI: 0.59-0.90; two-sided p = 0.003) [295]. The primary endpoint of DFS was not achieved in a multicentre RCT of adjuvant atezolizumab versus observation (IMvigor010). Median

DFS was 19.4 months (95% CI: 15.9-24.8) with atezolizumab and 16.6 months (11.2-24.8) with observation (stratified HR: 0.89; 95% CI: 0.741.08; p = 0.24) [296].
The FDA has approved nivolumab for adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing surgery [297] whereas EMA has approved adjuvant nivolumab in the same population only if tumour cell PD-L1 expression is ≥ 1%. A promising report (see Section 4.9) has suggested a potential role for ctDNA to guide the use of adjuvant IO for UC [298].
The recently published phase III IMvigor011 trial evaluated a ctDNA-guided strategy for adjuvant treatment selection. Patients underwent serial ctDNA testing for one year following surgery [108]. Those who developed ctDNA positivity in the absence of radiographic recurrence were randomized to receive atezolizumab or placebo, whereas patients who remained ctDNA-negative received no adjuvant therapy. Among patients with ctDNApositive status, adjuvant atezolizumab significantly improved both DFS and OS compared with placebo. Median DFS was 9.9 months with atezolizumab and 4.8 months with placebo, corresponding to a HR for recurrence or death of 0.64. Median OS was 32.8 months versus 21.1 months, respectively, with a HR for death of 0.59. Persistent ctDNA negative status was associated with excellent survival outcomes with a DFS of 95% at the end of the one-year monitoring period.

6.6 Perioperative radiotherapy

6.6.3 Summary of evidence and recommendations for pre- and postoperative radiotherapy

Summary of evidence	LE
No contemporary data exists to support that preoperative RT for operable MIBC increases survival.	2a
Preoperative RT for operable MIBC, using a dose of 45-50Gy in fractions of 1.8-2Gy, results in downstaging after four to six weeks.	2
Limited evidence supports the safe use of pre- and postoperative RT if a neobladder is planned or *in situ*.	3
Limited high-quality evidence supports the use of preoperative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT is associated with an improvement in local relapse-free survival following cystectomy for locally advanced BC (pT3b-4 or node-positive).	2a

Recommendations	Strength rating
Do not offer preoperative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will not improve survival.	Strong
Adjuvant RT to the cystectomy bed and local pelvic nodes can be offered following radical cystectomy (pT3b-4 or positive nodes or positive margins) to improve locoregional relapse free survival, but not overall survival.	Weak

6.7 Radical cystectomy with pelvic lymph node dissection

6.7.1 Removal of the tumour-bearing bladder

Recommendation	Strength rating
Offer radical cystectomy to patients with T2-T4a N0M0 disease.	Strong

6.7.2.a.3 Summary of evidence and recommendations for sexual-preserving techniques in males

Summary of evidence	LE
The majority of eligible patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2a
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve-sparing) have shown to be superior, and no particular technique can be recommended.	3

Recommendations	Strength rating
Only offer sexual-preserving techniques to eligible male patients who are highly motivated to preserve their sexual function.	Strong

Select patients based on: • organ-confined disease; and • absence of malignancy at the level of the prostate, prostatic urethra or bladder neck.	Strong

6.7.2.b.3 Summary of evidence and recommendation for sexual-preserving techniques in females

Summary of evidence	LE
The risk of gynaecological organ involvement in female patients undergoing RC without clinical evidence of non-organ-confined disease is low.	3

Recommendation	Strength rating
Perform sexual organ-preserving techniques in eligible female patients. Select patients based on absence of tumour in the area to be preserved to avoid positive soft tissue margins.	Strong

6.7.3.a Summary of evidence and recommendations for lymphadenectomy

Summary of evidence	LE
An extended LND is not superior to a standard LND - it does not improve survival and increases the risk of morbidity.	1a
Radical cystectomy includes removal of regional LNs.	3

Recommendations	Strength rating
Perform a lymph node dissection (LND) as an integral part of radical cystectomy.	Strong
Perform a standard LND, because an extended LND does not improve survival and increases the risk of morbidity.	Strong

6.7.4 Robotic-assisted laparoscopic cystectomy

6.7.4.a Summary of evidence and recommendations for robotic-assisted laparoscopic cystectomy

Summary of evidence	LE
Robot-assisted radical cystectomy and open RC provide similar 90-day complication rates, surgical margin rates, median-term oncological outcomes and QoL outcome.	1a
Operative time is longer for RARC compared to open RC (1 to 1.5 hours), but with less blood loss and possibly shorter length of hospital stay compared to open RC.	1a
Surgeon experience and institutional volume are considered the key factors for outcome of both RARC and open RC, not the technique.	4

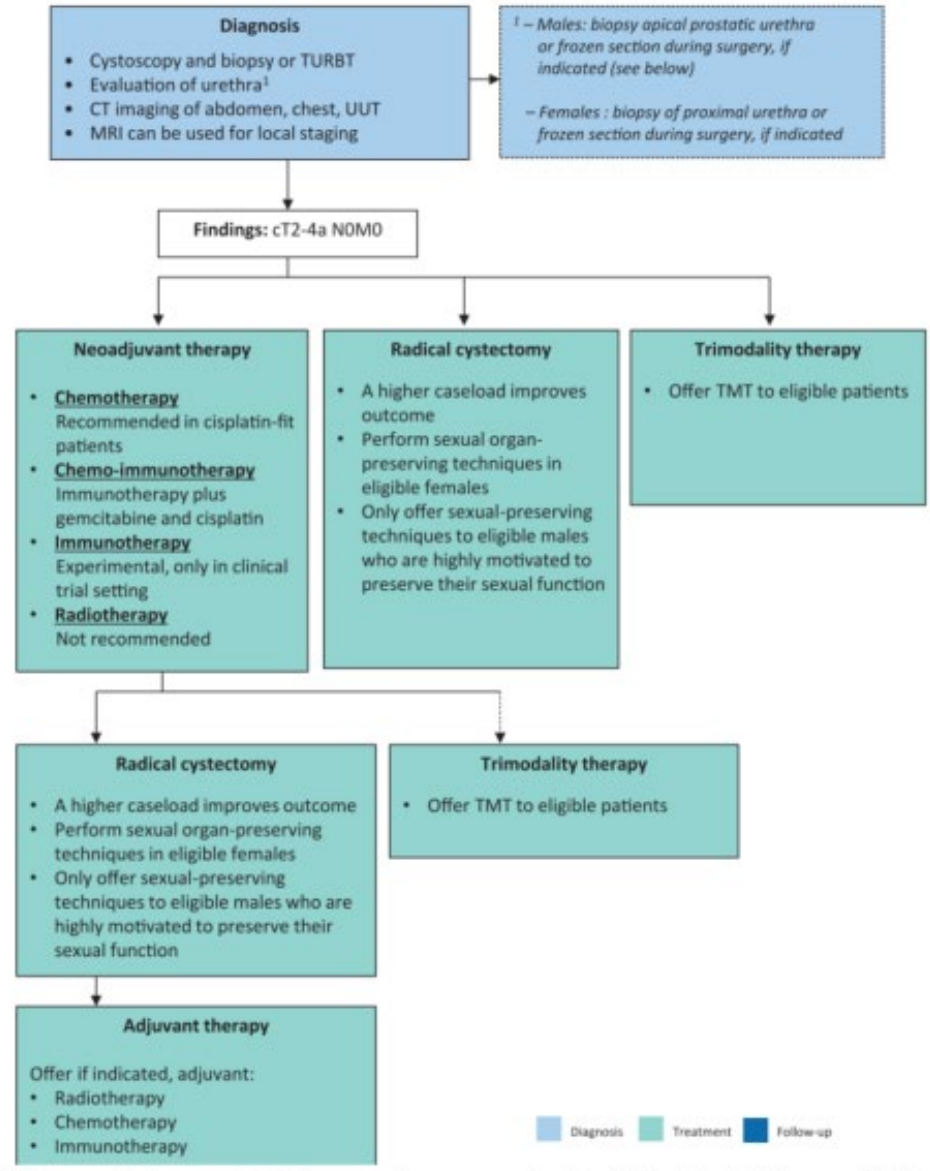
Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (RC) and robotic assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select centres for both RARC and open RC based on experience, rather than the technique used.	Strong
Do not delay RC for more than three months, as this increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong

6.7.5.d Summary of evidence and recommendations for urinary diversion after radical cystectomy

Summary of evidence	LE
Ensuring that patients are well informed about the various urinary diversion options prior to making a decision may help prevent or reduce decision regret, independent of the method of diversion selected.	3
The type of urinary diversion does not affect oncological outcome.	3

Recommendations	Strength rating
Do not offer an orthotopic bladder substitute diversion to patients who have an invasive tumour in the urethra or at the level of urethral dissection.	Strong
Do not offer preoperative bowel preparation.	Strong
Employ 'fast track' measurements to reduce the time to bowel recovery.	Strong

Figure 6.2: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; TMT = trimodality therapy; TURBT = transurethral resection of bladder tumour; UUT = upper urinary tract.

Chang SS et al., 2024 [1].

American Urological Association (AUA)/ American Society of Clinical Oncology (ASCO)/ American Society for Radiation Oncology (ASTRO)/ Society of Urologic Oncology (SUO)

Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline (2017, amended 2020, 2024)

Methodik

Grundlage der Leitlinie

- Grundlage der Leitlinie
- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- Last systematic review in November 2023

LoE

TABLE 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• 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
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

GoR

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Empfehlungen

TREATMENT

Neoadjuvant/Adjuvant Chemotherapy

6. Utilizing a multidisciplinary approach, clinicians should offer cisplatin-based neoadjuvant chemotherapy (NAC) to eligible radical cystectomy patients prior to cystectomy. (Strong Recommendation; Evidence Level: Grade B)

Hintergrund:
The Panel advocates cisplatin-based chemotherapy prior to radical cystectomy based predominantly on two large phase III randomized trials that evaluated the effects of NAC versus no NAC on mortality. The largest trial (n=976) tested neoadjuvant cisplatin, methotrexate and vinblastine (CMV) or no NAC prior to radical cystectomy, radiation therapy, or both.91 This trial demonstrated a decreased risk of cancer-specific mortality for the combined approach (NAC followed by cystectomy) versus cystectomy or radiation therapy alone, or both without NAC. After an initial reported median follow up of four years, the difference was not statistically significant (HR: 0.85; 95% CI: 0.71 to 1.02), but longer follow up (median 8 years)92 of this study reported NAC led to a significantly decreased risk of cancer-specific mortality (HR: 0.74; 95% CI: 0.57 to 0.96) in the subgroup of patients who underwent radical cystectomy (n=428). There was also a 16% reduction in cancer-specific mortality in those patients who received three cycles of CMV before radical cystectomy or radiation therapy. This led to an increase in 3-year cancer-specific survival from 50-56%, an increase in 10-year survival from 30-36%, and a median survival advantage of 7 months (from 37 to 44 months). Another trial93 (n=307) of neoadjuvant methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) plus radical cystectomy with regional lymphadenectomy was associated with a decreased risk of all-cause mortality (59% versus 65%; HR: 0.75; 95% CI: 0.57 to 1.00) and bladder cancer mortality (35% versus 50%; HR: 0.60; 95% CI: 0.41 to 0.82) versus cystectomy plus lymphadenectomy without NAC after a median of 8.7 years follow up. Neoadjuvant MVAC was also associated with longer median duration of survival (77 versus 46 months, p=0.05). Several other trials were unable to show significant differences in survival; however, many of them used regimens that are no longer used in clinical practice.94-97 Several non-randomized single arm phase II clinical trials have evaluated doseintensified (dose-dense) regimens of MVAC and gemcitabine and cisplatin (GC), and have reported significant clinical activity.98, 99 These regimens have been evaluated in the metastatic setting and found to have similar activity with comparable or decreased toxicity.100102

• There are no validated predictive factors or clinical characteristics (including age) associated with an increased or decreased probability of response and benefit using neoadjuvant cisplatin-based chemotherapy

Multiple retrospective studies have evaluated predictive biomarkers for response to NAC for MIBC, but none have been prospectively validated. One prospective trial testing MVAC prior to cystectomy in high-risk organ confined bladder cancer with p53 alterations by immunohistochemistry did not find any association with outcome.103 Several retrospective series have each suggested clinical and molecular parameters to identify patients who might benefit from NAC. However, these have not been prospectively tested and validated, and thus, the Panel does not recommend any at this time.37, 42, 104-106 One national prospective trial is examining this issue, but results are not available.

• The best regimen and duration for cisplatin-based NAC remains undefined Although there are ongoing prospective randomized trials, such as the VESPER trial, there are no definitive data suggesting that one regimen is superior to another at this time (GC versus ddMVAC).107

The optimal duration of NAC remains undefined. Most studies have evaluated three to four cycles of preoperative chemotherapy over about three months, although several smaller studies have tested shortened intensified regimens using six to eight weeks of chemotherapy.98, 99 There have been no randomized trials comparing outcomes between different durations of therapy. A recent large retrospective study did demonstrate that those patients who did not receive cisplatin-based chemotherapy or fewer than 3 cycles of chemotherapy had worse outcomes.108

• The decision regarding eligibility for cisplatin-based NAC should be based on comorbidities and PS, including cardiac status and presence of peripheral neuropathy, hearing loss, and renal dysfunction
Cisplatin eligibility is a major determinant of candidacy for NAC. Toxicities of cisplatin, including nephrotoxicity, diminished cardiac function, neurotoxicity, and hearing loss, preclude 30-50% of MIBC patients from safe receipt of cisplatin-based chemotherapy.109 In addition, reduced PS (World Health Organization or Eastern Cooperative Oncology Group PS ≥2 or Karnofsky PS of ≤60-70%) is associated with

increased toxic effects of cisplatin. Baseline renal dysfunction with an estimated or calculated creatinine clearance < 60ml/min is generally felt to preclude patients from cisplatin-based chemotherapy, although selected patients may be treated by using splitdosing of cisplatin and aggressive hydration. New York Heart Association Class III-IV heart failure (marked or severe limitation in activity) is felt to be exclusionary due to the volume of intravenous fluid required for safe cisplatin administration. Hearing loss at baseline consisting of a decrease of >25 dB in at least one ear at two contiguous frequencies (CTCAE v4.0 grade 2 hearing loss) is also considered a contraindication, as cisplatin may lead to an additional 20 dB loss in patients, resulting in severe hearing loss. Cisplatin-induced peripheral neuropathy is increased in patients with pre-existing sensory neuropathy and may preclude treatment.

7. Clinicians should not prescribe carboplatin-based NAC for clinically resectable stage cT2-T4aN0 bladder cancer. Patients ineligible for cisplatin-based NAC should proceed to definitive locoregional therapy or clinical trial. (Expert Opinion)

Hintergrund:

There is insufficient data to recommend non-cisplatinbased regimens as either NAC or adjuvant chemotherapy (AC) for MIBC. Although some suggestive cohort and clinical trial data exist,110 there is no high level evidence that carboplatin-based regimens lead to increased survival in this setting for MIBC. Downstaging rates in these series appear lower than with cisplatin-based chemotherapy, and comparative data is lacking with either radical cystectomy alone or neoadjuvant cisplatinbased combinations. In the metastatic setting, carboplatin-based combinations are felt to be inferior based on the results of small randomized trials.111, 11

8. Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from NAC (ideally within 12 weeks unless medically inadvisable). (Expert Opinion)

Hintergrund:

Patients who receive NAC must be medically fit to undergo cystectomy. The exact time frame when it is optimal to proceed with cystectomy after chemotherapy has not been defined. However, there are observational studies that suggest that if cystectomy is delayed more than 12 weeks after the completion of chemotherapy, outcomes may be worse.113, 114

9. Patients who have not received cisplatin-based NAC and have pT3-4and/or N+ disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy or adjuvant immunotherapy. Patients who have received cisplatinbased chemotherapy and have pT2-4and/or N+ at cystectomy should be offered adjuvant immunotherapy. (Moderate Recommendation; Evidence Level: Grade C)

Hintergrund:

No single randomized clinical trial has demonstrated a significant improvement in overall survival with adjuvant chemotherapy (AC). Four trials reported AC with an associated decreased risk of mortality versus no AC, but no trial reported a statistically significant benefit.115-118 One trial (n=50) found no difference between adjuvant CMV versus no AC in 5-year survival (52% versus 32%; RR: 0.71; 95% CI: 0.43 to 1.15).115 There was also no difference in the subgroup of patients (n=15) found to be node-negative (71% versus 25%; RR: 0.38; 95% CI: 0.11 to 1.31). Another trial (n=183) found no difference between adjuvant cisplatin and gemcitabine versus no AC in 5-year survival among all patients (43% versus 54%, p=0.24) or in the subgroup of node-negative patients (65% versus 73%, p=0.65).116 One trial (n=83) found no difference between adjuvant cisplatin and methotrexate versus no AC in survival among node-negative patients after a median follow up of 69 months (49% versus 38%).118

The largest trial randomized 284 patients to either immediate adjuvant cisplatin-based combination chemotherapy with either MVAC, dose intensified MVAC, or GC versus treatment at relapse.119 This trial did not demonstrate a significant improvement in overall survival with immediate versus deferred treatment (adjusted HR: 0.78; 95% CI: 0.56 to 1.08; p=0.13). However, immediate treatment did prolong progression-free survival by an estimated 1.12 years (HR: 0.54; 95% CI: 0.4 to 0.73; p<0.0001).

All of the AC trials were terminated early, and therefore are underpowered to provide sufficient evidence to state definitively the benefit of AC in MIBC. However, metaanalyses have suggested a possible benefit, albeit based on data of variable quality.120, 121 Thus, the Panel advocates that cisplatin-eligible patients with high-risk pathologic features who do not receive NAC be offered adjuvant therapy following radical cystectomy on

the basis of a multi-disciplinary consultation with a thorough informed consent. In patients who are non-cisplatineligible, consideration of referral to clinical trials is reasonable.

In 2021, the CheckMate274 trial, which used adjuvant nivolumab administered to patients with high-risk disease after cystectomy, was published.122 This randomized phase III trial allowed patients who had received neoadjuvant cisplatin-based chemotherapy and had ypT2-ypT4 and/or N+ disease or no NAC and had pT3pT4 and/or N+ disease to receive nivolumab every 2 weeks for 1 year. The study found that patients who received adjuvant nivolumab had a significantly improved disease-free survival. Based on this, the recommendation is for patients with high-risk features after cystectomy, with or without NAC, to receive adjuvant nivolumab. Retrospective analysis of the data suggests that the greatest benefit for adjuvant treatment is when it is initiated within 90 days of cystectomy. However, some benefit was still seen even after 90 days post cystectomy.

In contrast, the IMvigor010 trial which examined the use of adjuvant atezoluzimab in a similar population to the CheckMate274 trial failed to demonstrate a statistically significant improvement in disease free survival (DFS).123 Therefore, this drug has not been recommended for adjuvant use.

The AMBASSADOR trial using adjuvant pembroluzimab has reported that it met its endpoint for improvement in DFS, however, the published results and additional endpoints are still pending at this time.124

Radical Cystectomy

10. Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) muscle-invasive bladder cancer. (Strong Recommendation; Evidence Level: Grade B)

Hintergrund:

For non-metastatic MIBC, radical cystectomy combined with NAC is the standard of treatment.125 Radical cystectomy either alone or in combination with chemotherapy in patients with clinically non-metastatic MIBC has been compared to bladder sparing therapy in one RCT,126 seven retrospective cohort studies127-133 and one non-randomized controlled clinical trial.134 Seven studies evaluated overall survival with bladder sparing therapies versus radical cystectomy.126-132 A populationbased cohort study (n=1,843) found that bladder preserving therapy was associated with decreased 5-year survival compared to radical cystectomy (27.9% versus 46.5%).127 The lower probability of mortality associated with cystectomy was observed in the multivariable analysis adjusting for individual clinic-pathologic variables (HR for mortality: 0.79; 95% CI: 0.67 to 0.93) as well as in a propensity-adjusted analysis (HR 0.79; 95% CI: 0.65 to 0.95). However, the AHRQ review found that these trials had methodological issues as well as bias in terms of survival comparisons; none evaluated QOL.1

A retrospective cohort study (n =108) also found radical cystectomy associated with a higher likelihood of survival (50% versus 58% at 10 years) after adjustment for age, tumor stage, nodal status, grade, and tumor multiplicity, though the difference was not statistically significant (HR: 0.62: 95% CI: 0.28 to 1.43).132 Four other cohort studies evaluated all-cause mortality but did not attempt to adjust for potential confounders.128-131While differences in several studies were not statistically significant, one study (n=145) found radiotherapy associated with decreased likelihood of survival at 3 years versus radical cystectomy (39% versus 69%, p=0.03).130 Another study (n=148) found bladder preserving radiation therapy or maximal TURBT each associated with increased risk of 5-year bladder cancer-specific mortality versus radical cystectomy in patients with T2 or T3 tumors (82% versus 75% versus 57%), though the difference was only statistically significant for radiation therapy (RR: 1.44; 95% CI: 1.02 to 2.05).129

While both open and robotic approaches to cystectomy are currently employed, there is insufficient evidence to recommend for or against robotic cystectomy based on oncologic and/or functional outcomes. Based on three small randomized trials135-137 as well as observational data and systematic reviews, robotic cystectomy is associated with longer operative time, higher cost, decreased blood loss, similar lymph node yield, and no clear difference in major complication rates.138

Patients considering a radical cystectomy should be counseled regarding the high rate of complications, both acute and chronic, as outlined previously in this guideline.139, 140 This is particularly critical given that patients undergoing cystectomy are usually older and have multiple comorbid conditions. Coupled with the complexity of the procedure itself, the rate of perioperative complications is high, and readmission to the hospital is as high as 26% at 30 days.72, 141 Therefore, an assessment of anesthetic and surgical fitness is a key component of the decision process in patients with MIBC. This is a multifactorial assessment and often requires a multidisciplinary team, including an anesthesiologist and primary care clinician and, when appropriate, geriatric specialists, pulmonologists, and/or cardiologists.

11. When performing a standard radical cystectomy with curative intent, clinicians should remove the bladder, prostate, and seminal vesicles in males; clinicians should remove the bladder in females and should consider removal of adjacent reproductive organs based on individual disease characteristics and need to obtain negative margins. Organ sparing procedures in females should be considered based on disease location and characteristics on an individual basis. (Clinical Principle)

Hintergrund:

Radical cystectomy involves removal of the bladder (cystectomy) along with the organs at highest risk of harboring tumors that extend beyond the bladder. In males, this includes the prostate and seminal vesicles. In females this may include the anterior vaginal wall, uterus, cervix, fallopian tubes, and ovaries. Recently, the necessity of removing adjacent reproductive organs in all patients has been re-evaluated. Considering the overall low incidence of urothelial cancer involvement of the uterus, ovaries, and vagina and the absence of conclusive evidence suggesting a measurable outcome difference in removing these organs, this scrutiny is appropriate. In women when performing ovarian/uterine sparing who do not desire fertility, consideration to salpinectomy should be given to reduce the risk of ovarian cancer. In select women with early-stage disease and a desire to preserve fertility and/or sexual function, organ preservation may be considered as long as complete tumor resection can be achieved. This is based on Clinical Principle and can be modified as specified below in selected patients (see statement 12). Preoperative counseling should be performed for patients who have invasive cancer at the bladder neck or trigone region in regards to risk of organ sparing surgery.56, 142 If a prostatectomy is performed and there is high-grade cancer at the margin of resection at the apical urethra, a urethrectomy should be performed (immediate or delayed). This can be assessed with a frozen section or final pathology performed at the time of radical cystectomy.143 A urethrectomy should be performed for women not undergoing reconstruction with a neobladder in order to reduce the likelihood of a positive surgical margin or tumor recurrence.

12. Clinicians should discuss and consider sexual function preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Moderate Recommendation; Evidence Level: Grade C)

Hintergrund:

Preservation of sexual function is safe and feasible in many patients undergoing radical cystectomy. In all patients who desire sexual function preservation and are sexually active, a nerve-sparing procedure should be discussed and offered as long as it will not compromise oncologic control.144 In women, vaginal sparing radical cystectomy can be performed when doing so will not compromise tumor control, such as in the absence of cancer in the trigone or bladder base.145 Consideration may also be given to preserving the ovaries for hormonal homeostasis, and the anterior vaginal wall and/or uterus may be preserved in the absence of direct tumor extension. Preservation of the ovaries has not been associated with bladder cancer recurrence, and in patients with no known hereditary risk of ovarian or breast cancer, oophorectomy may not be necessary.146 In men, prostate-sparing and prostate-capsule sparing cystectomy may be offered to highly select individuals with negative prostatic urethral and transrectal prostate biopsies in whom fertility and sexual function are important considerations. Data on the safety of prostate preservation is based on limited observational data, indicating the need for improved data on oncologic outcomes and to guide its use and understand efficacy for preserving sexual function.86, 147 It should be noted that nerve sparing procedures in men may offer similar rates of sexual function preservation when compared to prostate-sparing cystectomy.

Urinary Diversion

13. In patients undergoing radical cystectomy, ileal conduit, continent cutaneous, and orthotopic neobladder urinary diversions should all be discussed. (Clinical Principle)

Hintergrund:

The choice of urinary diversion has a significant impact on long-term QOL for patients who undergo radical cystectomy, and each type of diversion is associated with its own unique potential complications. Discussing the pros and cons of each approach is an important component of preoperative education. The Panel emphasized that clinicians should first determine whether or not a patient is a candidate for each of the diversion options, and patients should be counseled regarding all three categories of urinary diversion, if not contraindicated. The suitability of the appropriate bowel segments is a critical determining factor for creation

of either a continent cutaneous reservoir or ileal neobladder. If there is limited available bowel or the patient is unwilling to perform self-catheterization, then an ileal conduit may be the most appropriate diversion. If ileum is not available, then a colon conduit or continent cutaneous diversion may be the preferred diversion choice.148

Absolute contraindications to continent diversion include 1) Insufficient bowel segment length; 2) Inadequate motor function or psychological issues that limit the ability to perform self-catheterization; 3) Inadequate renal or hepatic function that increases the risk metabolic abnormalities as a consequence of reabsorption of urine from continent diversions (e.g., an eGFR < 45); 4) Cancer at the urethral margin (specifically for orthotopic neobladder); and 5) Significant urethral stricture disease that is not correctable. 76

Patients should understand that the ileal conduit is the most commonly utilized urinary diversion type. It is an incontinent diversion using a short segment of distal ileum; preservation of the most distal 15 cm can reduce issues related to absorption of B12, fat soluble vitamins, and bile salts.149 Orthotopic urinary diversions, or neobladders, represent the most common type of continent diversion. While there are several different techniques, the principle of connecting a segment of detubularized and folded bowel to the urethra is a common principle. The main rationale for this approach is to mimic as closely as possible the functional aspects and body image of a native bladder. Although studies have drawn different conclusions, and most show that wellcounseled patients have equivalent levels of satisfaction regardless of diversion type, several studies have reported better or marginally better QOL outcomes with neobladders than other diversion types.150, 151

The last diversion type is the continent cutaneous reservoir. While there are many techniques for creating continent catheterizable reservoirs, the goal is to create a low-pressure reservoir from detubularized bowel with a continent catheterizable channel to the skin that will avoid involuntary efflux of urine. This type of reservoir is used in patients who want to avoid a stomal appliance and preserve continence but either are not candidates for or do not desire a neobladder. These diversions still require the same selection criteria as for patients with neobladders, including the ability/willingness to catheterize and adequate renal function.152

14. In patients receiving an orthotopic urinary diversion, clinicians must verify a negative urethral margin. (Clinical Principle)

Hintergrund:

Pathologic assessment of urethral margin status at the time of surgery is a best practice to determine if a patient is eligible for an orthotopic diversion. The average risk of the development of cancer in the retained urethral is reported as between 1-17% overall in multiple contemporary cystectomy series, with the majority occurring within the first two years after surgery.153, 154 Reported risk factors include tumor multiplicity, papillary pattern, CIS, tumor at the bladder neck, prostatic urethral involvement, and prostatic stromal invasion. Although prostate involvement is the most significant risk factor for cancer in the urethra, it should not preclude orthotopic diversion, provided that intraoperative frozen section analysis of the urethral margin is without evidence of tumor.155, 156 Preoperative prostatic urethral biopsies have not proved to be as reliable as urethral frozen sections and should not exclude patients from orthotopic diversion.157

In women with MIBC, a comprehensive literature review found that urethral tumor involvement occurs in only approximately 12% of patients undergoing cystectomy.158 Involvement of the bladder neck, posterior bladder base, or anterior vaginal wall with urothelial carcinoma is an important risk factor for urethral tumor involvement, and intraoperative frozen section analysis of the proximal urethra is a reliable approach to confirm the appropriateness of female candidates for orthotopic diversion. In patients with palpable masses (stage ≥T3b) on bimanual examination, intraoperative frozen sections of the urethral and vaginal margins should also be obtained if a neobladder is being considered.159

Perioperative Surgical Management

15. Clinicians should attempt to optimize patient performance status (PS) in the perioperative setting. (Expert Opinion)

Hintergrund:

Given the significant risk of morbidity and prolonged recovery time associated with radical cystectomy, the Panel recommends perioperative patient optimization in accordance with enhanced recovery pathway principles.160 While a specific enhanced recovery after surgery protocol was not recommended, there are a number of important components that should be considered for any patient undergoing radical cystectomy. A substantial percentage of patients with MIBC are malnourished at the time of diagnosis, and preoperative malnutrition is associated with a significant increase in the risk of postoperative mortality.57, 161, 162

Cystectomy patients at high risk for malnutrition should undergo nutritional counseling in preparation for surgery with the goal of optimizing nutritional status prior to surgery. In addition, all patients undergoing treatment for bladder cancer should receive smoking cessation counseling. This is based on multiple studies supporting the importance of smoking cessation prior to cystectomy, both for reducing postoperative complications and improving long-term oncologic control.163-165 In the immediate perioperative period, clinicians may consider not routinely prescribing a mechanical bowel preparation when only small bowel will be used for urinary tract reconstruction. While data from prospective RCTs supports not using a bowel preparation prior to colorectal surgery, there is also some data suggesting a potential benefit in the setting of colorectal resection.166-169 Additionally, limited data suggest that there is no increased risk of perioperative complications in the absence of a mechanical bowel preparation prior to cystectomy.170, 171 There are also data to support consideration of preoperative carbohydrate loading in order to diminish postoperative insulin resistance and shorten length of stay.172, 173 Carbohydrate loading does not appear to lead to an increase in anesthetic risk, despite oral fluid intake within hours of surgery, and it may improve patient comfort and speed recovery of bowel function. During and immediately following surgery, a restrictive transfusion strategy should be utilized in the absence of coronary artery disease or other mitigating factors following American Association of Blood Bank guidelines.174 While there are no cystectomy-specific randomized trials evaluating disparate transfusion strategies, a restrictive strategy does not appear to increase the risk of adverse events or mortality compared to a liberal transfusion strategy.175-177 Other intraoperative considerations should include maintenance of normothermia and normal blood glucose during cystectomy in order to minimize postoperative infection risk. Additionally, fluid management during surgery should seek to avoid fluid excess, and hypovolemia may be utilized to reduce blood loss and expedite recovery of bowel function. Overall, utilization of clinical pathways is associated with decreased narcotic usage, lower incidence of postoperative ileus, and shorter hospital length of stay.178

16. Perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)

Hintergrund:

Thromboembolic risk following a major pelvic surgery such as radical cystectomy is significant and exposes patients to a potentially life-threatening postoperative complication. Many patients undergoing cystectomy possess several of the risk factors associated with the development of a thrombosis as described in the AUA Best Practice Statement for the Prevention of Deep Vein Thrombosis for patients undergoing a urologic surgery.179 The use of intermittent pneumatic compression along with pharmacologic agents such as low-dose unfractionated heparin and low molecular weight heparin have been shown to reduce venous thromboembolic risk in patients undergoing a variety of general surgical, urological, and orthopedic procedures.180-183 Thus, given the significant risk of morbidity and mortality, and the strong evidence to support the efficacy of prophylaxis, the Panel recommends the use of combined mechanical and pharmacologic prophylaxis in patients undergoing radical cystectomy. Strong consideration should be given to initiating pharmacologic prophylaxis just prior to induction of anesthesia; however, the risks of bleeding need be weighed against the benefits of prophylaxis in determining the timing of heparin administration. The optimal timing and duration of chemoprophylaxis for venous thromboembolism prevention has yet to be defined for patients undergoing radical cystectomy. However, increasing evidence suggests that a preoperative dose may decrease venous thromboembolism risk. Perioperative coverage with up to four weeks of treatment following surgery may be beneficial.184, 185

17. In patients undergoing radical cystectomy μ -opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

Hintergrund:

Delayed return of bowel function is a common event following radical cystectomy and a source of morbidity and prolonged hospital stay. The use of peripherally active μ-opioid receptor antagonists has been shown to enhance the recovery of bowel function and decrease hospital length of stay in patients undergoing radical cystectomy and other abdominal surgical procedures.186188 Data supporting the use of μ-opioid receptor antagonists includes a prospective RCT of 277 patients that demonstrated a significant improvement in time to bowel function recovery after radical cystectomy (5.5 versus 6.8 days, $p<0.001$), and shortened hospital length of stay (7.4 versus 10.1 days; $p=0.005$). The first dose is given just prior to surgery and then continued until diet is tolerated or for a maximum of 15 doses. Other postoperative complications are similar in patients receiving μ-opioid receptor antagonists, although these therapies are contraindicated in patients who have taken opioids for one week or greater prior to surgery.

18. Patients should receive detailed teaching regarding care of urinary diversion prior to discharge from the hospital. (Clinical Principle)

Hintergrund:

Urinary diversion following radical cystectomy can have a significant impact on health-related QOL, and patient education, including preoperative stoma marking with an enterostomal therapist, has a critical role in preparing patients for the long-term care of their reconstructed urinary tract. Appropriate stoma education with nurse specialists can shorten the hospital length of stay and reduce subsequent stomal-related complications.189 Detailed teaching may also improve health-related QOL or patients undergoing stoma surgery.190 In addition, patient-directed education for other diversion types, such as continent cutaneous diversions and orthotopic diversions, is essential in preparing patients for their postcystectomy care.

Pelvic Lymphadenectomy

19. Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Strong Recommendation; Evidence Level: Grade B)

Hintergrund:

Mapping studies from patients with invasive bladder cancer have documented the pathways of progression of invasive bladder cancer.191, 192 Sequential dissemination from the lower pelvic to the more proximal lymph nodes in the pelvis and retroperitoneum is the general pattern of spread, and the risk of regional lymph node metastases is associated with the depth of invasion of the primary tumor. Data from a variety of studies have shown that a pelvic lymphadenectomy can improve disease specific survival and pelvic recurrence risk compared to no pelvic lymphadenectomy at the time of radical cystectomy.193-196 Bilateral pelvic lymphadenectomy should be performed in all patients, including those with unilateral bladder wall involvement, due to documented crossover risk to the contralateral lymphatic chain. Complete bilateral pelvic lymphadenectomy may be difficult or not possible in subsets of patients who have undergone extensive prior pelvic surgery, prior pelvic radiation therapy, or those with extensive vascular disease.

Data on pelvic lymphadenectomy at the time of partial cystectomy are limited; however, complete bilateral pelvic lymphadenectomy should be performed in patients undergoing partial cystectomy for curative intent. A number of series have reported that lymphadenectomy is underutilized and often less extensive in patients undergoing partial cystectomy.197, 198 Nevertheless, given the well documented role of a complete bilateral pelvic lymphadenectomy at the time of radical cystectomy, there is a strong rationale to extrapolate the same data to the partial cystectomy setting

20. When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy). (Clinical Principle)

Hintergrund:

The quality of the evidence does not currently support a uniform recommendation for the optimal extent of the pelvic lymphadenectomy to maximize therapeutic benefit. However, in order to facilitate adequate staging, a standard lymphadenectomy (bilateral external iliac, internal iliac and obturator lymph nodes), at a minimum, needs to be completed with >12 lymph nodes evaluated.199 The number of lymph nodes identified by the pathologist is a surrogate for the adequacy of the lymphadenectomy. It reflects the quality and completeness of the surgical dissection as well as the quality of the pathologic examination.200 Submission of separate nodal packets appears to facilitate identification of lymph nodes and is associated with an increased number of reported lymph nodes.

Earlier cohort studies reported that more extensive lymphadenectomy (with boundaries extending above the common iliac bifurcation up to or beyond the aortic bifurcation) to be associated with improved all-cause or bladder cancer-specific mortality versus less extensive lymphadenectomy, but these studies had methodological limitations, including variability in the lymphadenectomy techniques evaluated, and inconsistency in results.193-196, 201-208 Previous cohort studies found that more extensive lymphadenectomy (above the bifurcation of the common iliac arteries) was associated with a lower risk of bladder cancer recurrence or progression, but again most studies had methodological limitations and inconsistent results.209-214

A 2019 randomized trial (n=401) reported that there was no improvement with an extended LND in recurrence-free survival (primary endpoint of this study) cancer specific survival or overall survival.220 More recent observational and cohort studies have varying results with several showing no benefit, but in those that did report an advantage with a more extensive lymph node dissection (LND), this advantage was noted

in patients who had not received neoadjuvant chemotherapy.215-218 The largest observational study (n=19,020), using data SEER, did report statistically significant associations between the extent of pelvic LND and cancer-specific mortality (HR= 0.99; P<.001) and rates of lymph node invasion (OR=1.01; P=.001) in a mixed population of patients with MIBC and NMIBC; however, the effect sizes were very small.218

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2026) am 09.01.2026

#	Suchschritt
1	[mh "Urinary Bladder Neoplasms"]
2	[mh "Carcinoma, Transitional Cell"]
3	(bladder OR urotheli* OR transitional):ti,ab,kw
4	(tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR neoplas* OR cancer*):ti,ab,kw
5	#1 OR #2 OR (#3 AND #4)
6	#5 with Cochrane Library publication date from Jan 2021 to present, in Cochrane Reviews
7	#5 with Cochrane Library publication date from Jan 2024 to present, in Cochrane Reviews
8	#6 NOT #7

Leitlinien und systematische Reviews in PubMed am 09.01.2026

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026

#	Suchschritt
	Leitlinien
1	urinary bladder neoplasms[mh]
2	carcinoma, transitional cell[mh]
3	bladder[ti] OR urotheli*[ti] OR transitional[ti]
4	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR cancer*[ti]
5	#1 OR #2 OR (#3 AND #4)
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2021/01/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
9	"urinary bladder neoplasms/therapy"[mh]
10	"carcinoma, transitional cell/therapy"[mh]
11	urologic*[ti] OR urinary[ti] OR genitourinary[ti] OR urogenital[ti]

#	Suchschritt
12	bladder[tiab] OR urotheli*[tiab] OR transitional[tiab]
13	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
14	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] OR chemotherap*[tiab] OR immunotherap*[tiab] OR radiotherap*[tiab]
15	#3 AND #4 AND #14
16	#11 AND #12 AND #13 AND #14
17	(#12 AND #13 AND #14) NOT medline[sb]
18	#9 OR #10 OR #15 OR #16 OR #17
19	(#18) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
20	(#19) AND ("2021/01/01"[PDAT] : "3000"[PDAT])
21	(#20) NOT "The Cochrane database of systematic reviews"[Journal]
22	(#21) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
23	(#22) NOT (#8)
24	(#23) AND ("2024/01/01"[PDAT] : "3000"[PDAT])
25	#23 NOT #24

Iterative Handsuche nach grauer Literatur, abgeschlossen am 13.01.2026, überprüft am 05.06.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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2. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms; S3-Leitlinie, Langversion 3.0 [online]. AWMF-Registernummer 032-038OL. Berlin (GER): Leitlinienprogramm Onkologie; 2025. [Zugriff: 05.06.2026]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Blasenkarzinom/Version_3/LL_Harnblasenkarzinom_Langversion_3.0.pdf.

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO