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: 2025-B-018 Nivolumab

Stand: April 2025

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

Nivolumab
[zur adjuvanten Behandlung des Urothelkarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe „Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Nivolumab: Beschluss vom 20. Oktober 2022
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:	
Nivolumab L01XC17 Opdivo	<u>Zugelassenes Anwendungsgebiet:</u> 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.
Zytotoxische Chemotherapien	
Cisplatin L01XA01 generisch	Cisplatin Teva 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 Injektionslösung wird angewendet bei: • Harnblasenkarzinomen - in Kombination mit anderen zytotoxischen Arzneimitteln • […]
Gemcitabin L01BCO5 generisch	Gemcitabin ist in Kombination mit Cisplatin zur Behandlung des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms angezeigt.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-018 (Beratung nach § 35a SGB V) Nivolumab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. März 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AUA	American Urological Association
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HG	High-Grade
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LG	Low Grade
LoE	Level of Evidence
MIBC	Muscle-Invasive Bladder Cancer
NAC	Neoadjuvant Chemotherapy
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PD-L	Programmed death-ligand
RNU	Radical nephroureterectomy
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SUP	Society of Urologic Oncology
TRIP	Turn Research into Practice Database
TURBT	Trans Urethral Resection of Bladder Tumor
UTUC	Upper Tract Urothelial Carcinoma
WHO	World Health Organization

1 Indikation

Adjuvante Behandlung des muskelinvasiven Urothelkarzinoms.

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 *Urothelkarzinom* 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 05.03.2025 abgeschlossen. 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 1374 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. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte 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 8 Referenzen eingeschlossen.

Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews im Anwendungsgebiet identifiziert.

3.2 Systematische Reviews

Boutaleb I et al., 2024 [1].

Perioperative chemotherapy and immunotherapy to optimize cystectomy outcomes in the curative intent of non-metastatic muscle-invasive bladder cancer: A systematic review and meta-analysis

Fragestellung

The aim of this study was to perform a systematic literature review and meta-analysis to evaluate the effect of chemotherapy and/or immunotherapy in the neoadjuvant and/or adjuvant setting in patients with non-metastatic muscle-invasive bladder cancer.

Methodik

Population:

- patients with non-metastatic muscle-invasive bladder cancer

Intervention:

- chemotherapy and/or immunotherapy, in the neoadjuvant and/or adjuvant setting

Komparator:

- cystectomy alone or comparison of protocols

Endpunkte:

- overall survival
- progression-free survival
- relapse-free survival
- pathological downstaging
- metastasis-free survival

Recherche/Suchzeitraum:

- A systematic literature review was conducted by two independent authors (IB and GM) using the PubMed, Scopus, and clinicaltrials.gov databases
- search between 1994 and 2023

Qualitätsbewertung der Studien:

- RoB2 für RCT
- Keine Qualitätsbewertung für Beobachtungsstudien

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 studies: 24 prospective (92%), 1 retrospective (4%), and 1 observational (4%).

- 7 studies focused on neoadjuvant chemotherapy (NAC) (27%), eight on adjuvant chemotherapy (31%), nine on neoadjuvant immunotherapy (35%), and two on adjuvant immunotherapy (7%).

Anmerkung: Im Folgenden werden nur die Ergebnisse zur adjuvanten Therapie dargestellt.

Charakteristika und Qualität der Studien:

Adjuvante Chemotherapie (Table 2):

Author and year	Region, Country	Study type	Number of included patients (*n*)	Chemotherapy protocols	Objectives	Results	Risk of bias (Rob2)	Ref.
Studer et al., 1994	Switzerland	Randomized clinical trial	77 patients 40 in the cystectomy-alone arm 37 in the AC arm	3 cycles of 90 mg/m^2 of cisplatin alone	To evaluate overall survival	No significant difference between the two arms in the 5-year overall survival rate (54% vs. 57% in the AC group, $P = 0.65$)	High	[26]
Stöckle et al., 1995	Germany	Randomized clinical trial	49 patients 23 in the cystectomy-alone arm 26 in the AC arm	3 cycles of M-VAC methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, cisplatin 70 mg/m^2 and doxorubicine 30 mg/m^2 or M-VEC (epirubicine 45 mg/m^2)	To evaluate progression-free survival	Significant difference (87% progression in the cystectomy-alone arm vs. 42%, $P = 0.0005$)	Some concerns	[27]
Lehmann et al., 2006	Germany	–	49 patients 23 in the cystectomy-alone arm 26 in the AC arm	–	Long-term results of Stöckle et al's study To assess 10-years progression-free survival, overall survival and tumor-free survival	Progression-free survival of 13% in the cystectomy arm vs. 43.7% (HR: 2.84 (1.46–5.54), $P = 0.002$) Overall survival of 17.4% vs. 26.9% (HR: 1.75 (0.95–3.23), $P = 0.069$) Disease-free survival of 17.4% vs. 41.7% (HR: 2.52 (1.28–4.99), $P = 0.007$)	–	[28]
Freiha et al., 1996	United-States	Randomized clinical trial	50 patients 25 in the cystectomy-alone arm 25 in the AC arm	4 cycles of 21 days with cisplatin (100 mg/m^2), methotrexate (30 mg/m^2) and vinblastine (4 mg/m^2)	To evaluate progression-free survival and risk of recurrence	Improvement in progression-free survival (33% in the cystectomy arm vs. 52%, $P = 0.01$) Decreased risk of recurrence in the CMV arm by 48% vs. 20%	Low	[29]
Cognetti et al., 2012	Italy	Multicenter randomized clinical trial	194 patients 102 in the immediate AC arm 92 in the delayed AC arm	4 cycles of 28 days of gemcitabine (1000 mg/m^2) and cisplatin 70 mg/m^2 2 subgroups: One receiving cisplatin on D2 and the other on D15	To evaluate 5-year overall survival and disease-free survival	No significant difference in overall survival at 5 years (43.4% in the immediate GC arm vs. 53.7%) HR: 1.29 (0.84–1.99) $P = 0.24$ No difference in disease-free survival at 5 years (37.2% vs. 42.3%) HR: 1.08 (0.73–1.59) $P = 0.7$ No difference based on the timing of cisplatin administration	Low	[30]
Sternberg et al., 2014	Europe and Canada	Multicenter randomized clinical trial	284 patients 141 in the immediate AC arm 143 in the delayed AC arm	4 cycles for arm A, 6 cycles for arm B 3 different protocols: M-VAC, high-dose M-VAC and GC	To evaluate 5-year overall survival and progression-free survival	No significant difference in overall survival at 5 years (53.6% in the immediate CT arm vs. 47.7%, HR: 0.78 (0.56–1.08); $P = 0.13$) Significant difference in progression-free survival (47.6% vs. 31.8%, HR: 0.54, (0.4–0.73), $P < 0.0001$)	Low	[31]
Galsky et al., 2016	United-States	Observational study	5653 patients, of whom 23% received adjuvant chemotherapy	–	To assess 5-year overall survival	Improvement in overall survival at 5 years for adjuvant CT (37% vs. 29.1%) HR: 0.70 (0.64–0.76), $P < 0.001$ Data support the use of adjuvant CT, especially in patients who did NOT receive NAC.	–	[32]
Zhegalik et al., 2020	Byelorussia	Randomized clinical trial	100 patients 53 in the immediate AC arm 47 in the delayed AC arm	2 cycles of 28 days of cisplatin 75 mg/m^2 and gemcitabine 1000 mg/m^2	To compare overall survival, cancer-specific survival and disease-free survival	No significant difference in overall survival at 5 years (35% vs. 27%, HR: 0.7 (0.45–1.11), $P = 0.13$) No significant difference in cancer-specific survival (42% vs. 37%, HR: 0.84 (0.50–1.41), $P = 0.51$) No significant difference in disease-free survival (43% vs. 36%, HR: 0.77 (0.46–1.28), $P = 0.31$)	Some concerns	[33]

Adjuvante Immunotherapie

Author and year	Region, country	Study type	Number of included patients (*n*)	Immunotherapy protocols	Objectives	Results	Risk of bias (Rob2)	Ref.
Bellmunt et al., 2021	International	Multicenter, open-label, randomized clinical trial	809 patients 406 in the atezolizumab arm 403 in the cystectomy-alone arm	Atezolizumab 1200 mg every 3 weeks, for 16 cycles or up to 1 year	To evaluate disease-free survival and overall survival	Disease-free survival at 18 months is 51% in the atezolizumab arm vs. 49%, HR: 0.89 (0.74–1.08), $P = 0.24$. Overall survival at 1 year is 88% vs. 81%, and at 18 months is 79% vs. 73%, HR 0.85 (0.66–1.09) No evidence of efficacy of atezolizumab in the adjuvant setting	Low	[42]
Bajorin et al., 2021	International	Multicenter, double-blind, randomized clinical trial	709 patients 353 in the nivolumab arm 356 in the placebo arm	Nivolumab 240 mg every 2 weeks until 1 year or recurrence	To evaluate disease-free survival and metastasis-free survival	Improvement in disease-free survival at 1 year (62.8% in the nivolumab arm vs. 46.6%) HR: 0.70 (0.55–0.90), $P < 0.001$ Metastasis-free survival of 40.5 months vs. 29.5 months. Results even more pronounced in patients with PD-L1 > 1%	Low	[43]

Studienergebnisse:

Adjuvant chemotherapy (AC)

Eight studies evaluating AC were included (Table 2).

Studer et al. used cisplatin monotherapy in 37 out of 77 patients to assess 5-year OS and found no significant results, with a 5-year OS of 57% for AC and 54% for cystectomy alone [22]. Stöckle et al. evaluated the use of 3 cycles of MVAC on PFS and demonstrated progression in 87% of patients without AC compared to 42% with AC [23]. The long-term results of this study were presented by Lehmann et al., with an assessment of 10-year OS and tumor-free survival, which were 26.9% and 41.7% for AC, and 17.4% and 17.4% for cystectomy alone [25].

The study by Freiha et al. evaluated PFS and the recurrence-free survival in 49 patients who received 4 cycles of MVC, and showed an increase in PFS and a decrease in the recurrence-free survival in the AC arm, with rates of 52% and 48%, respectively [24]. Some studies also compared the effect of immediate versus deferred AC. The first study using G/C was conducted by Cognetti et al. and evaluated 5-year OS and disease-free survival and showed no significant difference, with a lower response in the immediate G/C postsurgery arm (43.4% and 37.2%, respectively) compared to the deferred arm (53.7% and 42.3%, respectively) [26]. The same results were observed in the studies by Sternberg et al. [27] and Zhegalik et al. [28] with 284 and 100 patients, respectively, showing no significant difference in 5-year OS.

However, the study by Sternberg showed an improvement in PFS with immediate chemotherapy (47.6% vs. 31.8%), especially in patients without nodal involvement. The observational study by Galsky et al. in 2016 included 5653 patients, 23% of whom received AC [29], and showed an improvement in 5-year OS to 37% in the AC arm compared to 29.1% for cystectomy alone.

Adjuvant immunotherapy

Bajorin et al. (CheckMate 274) evaluated diseasefree survival and risk of metastasis in 709 patients after radical cystectomy, of whom 353 received nivolumab as adjuvant therapy [44]. A significant difference was observed, with a 1-year DFS of 62.8% in the nivolumab arm compared to 46.6%, and a longer metastasis-free survival of 40.5 months compared to 29.5 months. The positive results of the study were even higher in patients with PD-L1 expression > 1%. Overall survival data are pending.

Anmerkung/Fazit der Autoren

This systematic review and meta-analysis confirm the known positive impact of platinum-based chemotherapy in the perioperative setting on improving survival in patients with muscle-invasive bladder cancer.

Studies using immunotherapy and targeted therapies show encouraging results; however, more data are needed before these therapeutic approaches can be fully integrated into our daily practice.

Kommentare zum Review

In dem SR wurden sowohl zugelassene als auch nicht zugelassene Therapien eingeschlossen. Für die Chemotherapien wurde auch die qualitative Analyse der nicht zugelassenen Therapien (z.B. MVAC) extrahiert. Auf eine Extraktion der quantitativen (Meta-) Analysen für zugelassene und nicht zugelassene Therapieoptionen gemeinsam wurde dagegen verzichtet. Für die Immunotherapien wurden nur Ergebnisse zu zugelassenen Therapieoptionen extrahiert.

3.3 Leitlinien

Konsultationsfassung Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms, 2024 [4,5].

Aktuell liegt zur **S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms** eine **Konsultationsfassung** vor. Die geplante Fertigstellung der S3-Leitlinie ist für den 30.06.2025 vorgesehen.

Witjes JA et al., 2024 [8].

European Association of Urology (EAU)

Muscle-invasive and Metastatic Bladder Cancer

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Limited update of the 2023 publication
- 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 the 1st of May 2022 and 1st May 2023.

LoE

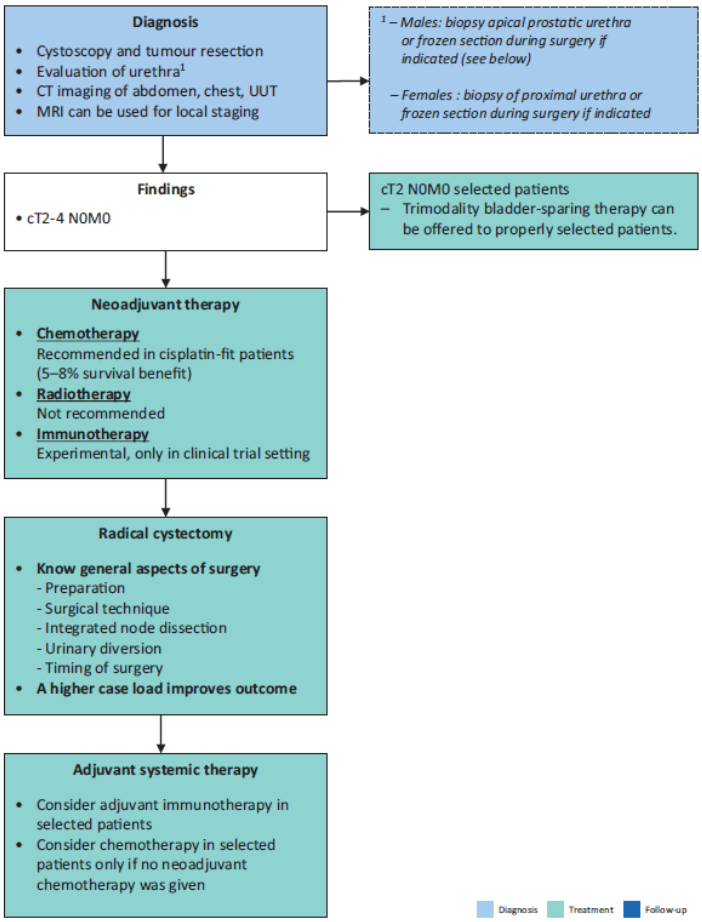
Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental 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

Empfehlungen

Figure 7.1: Flow chart for the management of T2–T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; UUT = upper urinary tract.

7.2 Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

Summary of evidence	LE
No contemporary data exists to support that pre-operative RT for operable MIBC increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45–50 Gy in fractions of 1.8–2 Gy, results in down-staging after 4 to 6 weeks.	2
Limited evidence supports the safe use of pre- and post-operative RT in case a neobladder is planned or *in situ*.	3
Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced bladder cancer (pT3b–4, or node-positive).	2a
There are no randomised trials showing an effect for local therapy in oligometastastic bladder cancer.	1
Retrospective case series show some survival benefit for the additional of local therapy (to the primary and to sites of metastases) in oligometastatic bladder cancer.	3

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant RT in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak
Inform patients with oligometastatic disease about local therapy treatment options. Patients should be carefully selected for treatment and fully informed of the potential benefits and harms of the different treatment modalities as well as the fact that there is no definitive evidence supporting local therapy inoligometastatic disease.	Weak

Hintergrund

7.2.1 Post-operative radiotherapy

Given the high rates of local-regional failure after RC in patients with locally-advanced (pT3–4) BC, estimated at ~30%, as well as the high risk of distant failure and poor survival for these patients, there is an interest in adjuvant therapies that address both the risk of local and distant disease. Data on adjuvant RT after RC are limited and further prospective studies are needed, but a more recent phase II trial compared adjuvant sequential chemotherapy and radiation vs. adjuvant chemotherapy alone in 120 patients with locally-advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive), in a study population with 53% UC and 47% SCC. Addition of adjuvant RT to chemotherapy alone was associated with a statistically significant improvement in local relapse-free survival (at 2 years 96% vs. 69% favouring the addition of RT). Disease-free survival and OS also favoured the addition of RT, but those differences were not statistically significant and the study was not powered for those endpoints. Late-grade ≥ 3 GI toxicity in the chemoradiation arm was low (7% of patients) [309].
A 2019 systematic review evaluating the efficacy of adjuvant radiation for BC or UTUC found no clear benefit of adjuvant radiation following radical surgery (e.g., cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally-advanced disease [310].
Adjuvant radiation might be considered in patients with pT3/pT4 pN0–2 urothelial BC following RC, although this approach has been evaluated in only a limited number of studies without conclusive data demonstrating improvements in OS. Radiation fields should encompass areas at risk for harbouring residual microscopic disease based on pathologic findings at surgery and may include the cystectomy bed and pelvic LNs. Doses in the range of 45 to 50.4 Gy may be considered. A phase II trial with 72 patients showed that a dose of 50.4 of radiotherapy Gy can be used with acceptable toxicity and a high rate of local control [311]. A small retrospective study of 25 patients (median age 64 years) evaluated acute and late toxicity of moderate doses of pelvic RT (range, 45–50.4 Gy). After a median follow-up of 10.4 months the authors concluded that orthotopic ileal neobladders can tolerate moderate radiation doses without

significant induced morbidity. Most of the acute GI toxicity seen was grade 1, four patients developed acute grade 2 toxicity; three of whom had been treated by NAC [312]. For patients not treated with NAC, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy. The safety and efficacy of concurrent radiosensitising chemotherapy in the adjuvant setting needs further study.

Referenzen

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311. Fonteyne, V., et al. Adjuvant Radiotherapy After Radical Cystectomy for Patients with High-risk Muscle-invasive Bladder Cancer: Results of a Multicentric Phase II Trial. Eur Urol Focus, 2022. 8: 1238. https://www.ncbi.nlm.nih.gov/pubmed/34893458
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7.6 Adjuvant therapy

Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting in patients with high-risk MIBC who have or have not received NAC have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

Hintergrund

7.6.1 Role of adjuvant platinum-based chemotherapy

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) 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 micrometastases is avoided;
- 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;
- delay of or intolerability to chemotherapy, due to post-operative morbidity [463].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [464-469]. An individual patient data meta-analysis [470] of survival data from six RCTs of adjuvant chemotherapy [471-473] included 491 patients (unpublished data from Otto et

al., were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases) [464]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin with methotrexate (CM) were used [474], and one trial used cisplatin monotherapy [475]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [467-469] resulting in the inclusion of 945 patients from nine trials [466]. None of the trials had fully accrued and individual patient data were not used in the analysis [466]. For one trial only an abstract was available at the time of the meta-analysis [468] and none of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine/cisplatin) [467, 468]. The HR for OS was 0.77 (95% CI: 0.59–0.99, p = 0.049) and for DFS 0.66 (95% CI: 0.45–0.91, p = 0.014) with a stronger impact on DFS in case of nodal positivity. Recently, a systematic review and meta-analysis of individual patient data from RCTs in patients treated with adjuvant cisplatin-based chemotherapy for MIBC was conducted [476]. In an analysis of 10 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 5 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). Adjuvant chemotherapy was also shown to improve RFS (HR: 0.71, 95% CI: 0.60-0.83, p < 0.001), locoregional RFS (HR: 0.68, 95% CI: 0.55–0.85, p < 0.001), and MFS (HR: 0.79, 95% CI: 0.65–0.95, p = 0.01), with absolute benefits of 11%, 11%, and 8%, respectively.

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) [477]. A publication of the largest RCT (European Organisation for Research and Treatment of Cancer [EORTC] 30994), although not fully accrued, showed a significant improvement of PFS for immediate, compared with deferred, cisplatin- based chemotherapy (HR: 0.54, 95% CI: 0.4–0.73, p < 0.0001), but there was no significant OS benefit [478].

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 vs. observation. Twenty-three percent of patients received adjuvant chemotherapy with a 5-year OS of 37% for the adjuvant arm vs. 29.1% (HR: 0.70, 95% CI: 0.64–0.76) in the observation group [479]. Another large retrospective analysis based on the U.S. National Cancer Database including 15,397 patients with locally-advanced (pT3/4) or LN-positive disease also demonstrated an OS benefit in patients with UC histology [480]. 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.

7.6.2 Role of adjuvant immunotherapy

To determine the benefit of PD-1/PD-L1 checkpoint inhibitors, three phase III RCTs have evaluated checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC. The CheckMate 274 phase III multi-centre, double-blind, RCT of adjuvant nivolumab vs. placebo for up to 1 year in 709 patients with muscle-invasive UC with a high risk of recurrence (pathological stage pT3, pT4a, or pN+) (neoadjuvant cisplatin-based chemotherapy was allowed before trial entry) 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 6 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% (tumor 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) [481]. In an analysis using both PD-L1 TC score and combined positive score (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 [482]. There was no clinically meaningful deterioration in health-related quality of life with adjuvant nivolumab compared to placebo [483].

The primary endpoint of DFS was not achieved in a multi-centre RCT of adjuvant atezolizumab vs. observation in patients with ypT2–4a or ypN+ tumours following NAC or pT3–4a or pN+ tumours if no NAC was received (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: 0.74–1.08, p = 0.24) [484]. A similarly designed trial of pembrolizumab in the adjuvant setting has completed accrual with results awaited.

The FDA has approved nivolumab for adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing surgery [485] whereas the EMA has approved adjuvant nivolumab for the treatment of adults with muscle-invasive UC (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at

high risk of recurrence after undergoing radical resection of MIUC. A promising report (see Marker section) has suggested a potential role for ctDNA to guide the use of adjuvant IO for UC [486].

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European Association of Urology (EAU)

EAU guidelines on upper urinary tract urothelial carcinoma

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- The 2024 UTUC Guidelines presents an update of the 2023 version. For the 2024 UTUC Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines.
- For the 2023 UTUC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between May 4th 2022 and May 1st 2023. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

Anmerkung: Es sind keine Angaben zur Recherche und Suchzeitraum für das „structured assessment of the literature“ des updates der Leitlinie aus 2024 dargelegt. Die beschriebenen Änderungen der Version von 2024 betreffen nicht die Indikation dieser Synopse.

LoE

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

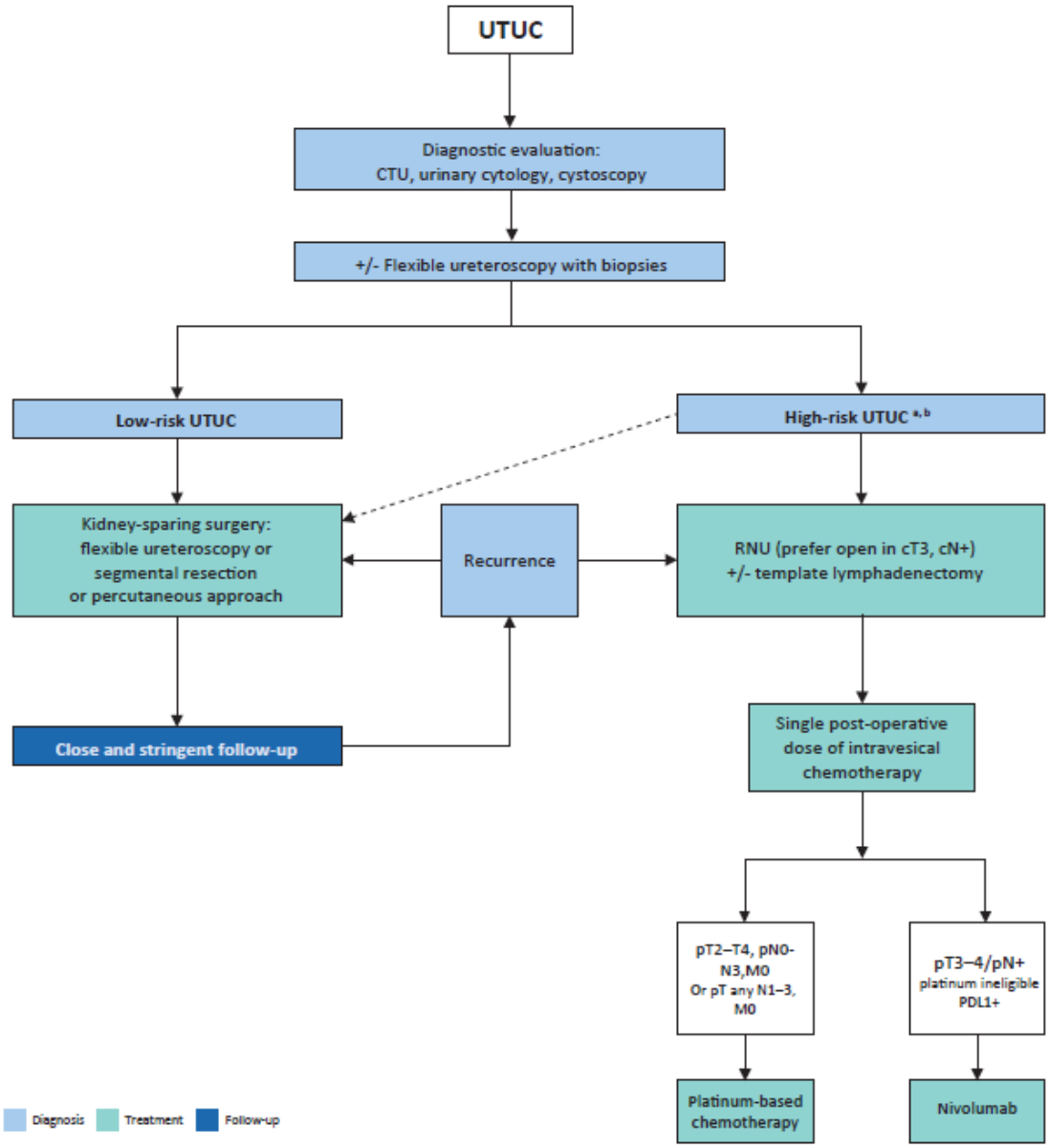
GoR

- 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

Empfehlungen

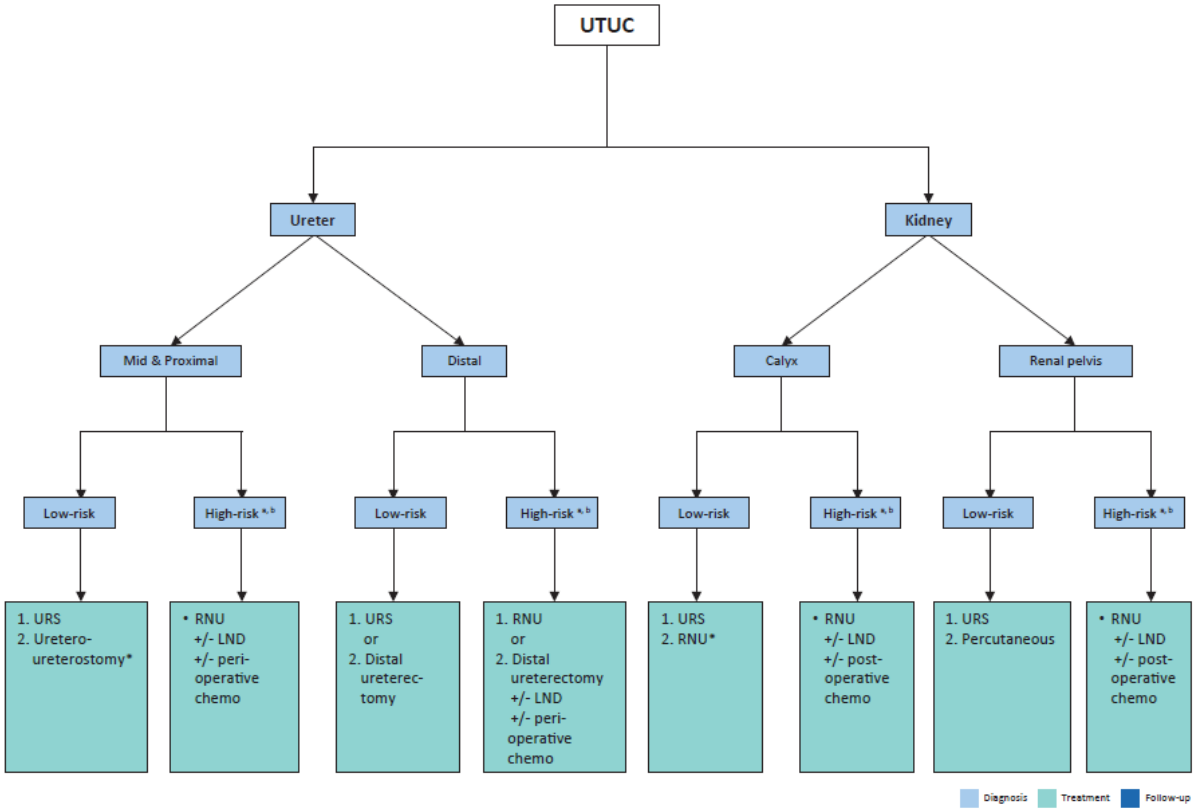
7. DISEASE MANAGEMENT

Figure 7.1: Proposed flowchart for the management of UTUC



a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
CTU = computed tomography urography; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

Figure 7.2: Surgical treatment according to location and risk status



a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

7.1 Localised low-risk disease

Recommendation	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong

⇨ Keine Empfehlungen für adjuvante Therapie aus der Evidenz abgeleitet

Hintergrund

7.1.6 Adjuvant instillations

7.1.6.1 Upper urinary tract

The antegrade **instillation of BCG or mitomycin C** in the upper urinary tract via percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [186, 222]. Retrograde instillation through a single-J open-ended ureteric stent is also used. Before both the antegrade and retrograde approach a nephro-ureterogram needs to rule out ureteric obstruction or leakage, asses that there is no infection and ensure a low pressure system to avoid pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used but **this approach is suboptimal** because the drug often does not reach the renal pelvis [223-226].

A systematic review and meta-analysis assessing the oncologic outcomes of patients with papillary UTUC or CIS of the upper tract treated with kidney-sparing surgery and **adjuvant endocavitary treatment** analysed the effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after kidneysparing surgery for papillary non-invasive (Ta–T1) UTUCs and BCG for the treatment of upper tract CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS; however, all included studies were underpowered and highly heterogeneous. Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [227]. **The analyses were based on retrospective small studies suffering from publication and reporting bias.**

Recent evidence suggests that early **single adjuvant intracavitary upper tract instillation of mitomycin C** in patients with low-grade UTUC might reduce the risk of local recurrence [228]. The authors report limited complications related to the instillations but propose a retrograde pyelography before instillations are commenced to exclude contrast extravasation. **This concept will need further evaluation in a randomised context [228].**

7.1.6.2 Bladder

There are currently **no data to support the use of bladder instillation of chemotherapy after kidney-sparing surgery** as available RCTs included only patients who received RNU.

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7.2 Localised high-risk disease

7.2.4 Peri-operative chemotherapy

7.2.4.2 Adjuvant treatments

7.2.5 ***Summary of evidence and recommendations for the management of high-risk non-metastatic UTUC***

Summary of evidence	LE
Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location.	2a
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2a
Failure to completely remove the bladder cuff increases the risk of BC recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Post-operative platinum-based adjuvant chemotherapy improves disease-free survival.	1b
Single post-operative intravesical instillation of chemotherapy lowers the BC recurrence rate.	1b

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Weak
Offer adjuvant platinum-based chemotherapy after RNU to eligible patients with pT2–T4 and/or pN+ disease.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate in patients without a history of BC.	Strong
Discuss adjuvant nivolumab with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for > pT3 and/or pN+ disease after previous RNU alone or > ypT2 and/or ypN+ disease after previous neoadjuvant chemotherapy, followed by RNU.	Weak
Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter.	Weak
Discuss kidney-sparing management to high-risk patients with imperative indication on a case- by-case basis, in a shared-decision making process with the patient despite the higher risk of disease progression.	Strong

Hintergrund

7.2.4.2.1 Bladder instillations

The rate of bladder recurrence after RNU for UTUC is 22–47% [189, 246]. Two prospective randomised trials [271, 272] and two meta-analyses [273, 274] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2–10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU in patients without a history of BC. Prior to instillation, a cystogram can be considered in case of concerns about drug extravasation. All studies showed a very low risk of adverse events. Intravesical chemotherapy has also been safely given at the time of RNU prior to

bladder cuff opening, removing the need for a post- operative cystogram, but with low level data for efficacy [275].
Based on current evidence it is unlikely that additional instillations beyond one peri-operative instillation of chemotherapy further substantially reduce the risk of intravesical recurrence [276]. Whilst there is no direct evidence supporting the use of intravesical chemotherapy instillation of chemotherapy after kidney-sparing surgery, single- dose chemotherapy might also be effective in that setting as well. Management is outlined in Figures 7.1 and 7.2. One low-level evidence study suggested that bladder irrigation might reduce the risk of bladder recurrence after RNU [277].

7.2.4.2.2 Systemic Chemotherapy

A phase III multicentre prospective RCT (n = 261) evaluating the benefit of four cycles of adjuvant gemcitabine-platinume combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival (DFS) in patients with pT2–pT4, N (any) or positive (pT any, N1–3) M0 UTUC (3 year DFS 71% vs 50%; 5 year DFS 63% vs 46%. HR 0.54 ; CI 0.36-0.79; 3 & 5 year MFS 19 % improvement HR 0.55 CI 0.0.36-0.77) [278]. Patients were stratified to gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy based on GFR alone with benefit seen irrespective of chemotherapy type. There was a non-significant trend towards improved OS (12% at 3 years) but as the study had met its primary endpoint of 3 year DFS, it closed early, leaving it underpowered for the secondary endpoint of OS. The main potential limitation of using adjuvant chemotherapy is the concern that renal function may deteriorate after RNU precluding cisplatin use in patients who could benefit from this [279, 280]. A review of peri-operative predictors of decline in renal function after RNU showed three month GFR levels of around 50 mls/min [281]. With split dose and hydration cisplatin may be considered in patients with a GFR down to 45 mL/min. Table 2 outlines the eligibility criteria for platinum chemotherapy.
In a retrospective study histological subtypes of UTUC exhibit different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [282]. However, whilst histological subtypes of UTUC exhibit different survival rates in retrospective studies, adjuvant chemotherapy should be considered where UC is the dominant pathology.

Table 2: Definitions of platinum-eligibility for systemic treatment of urothelial carcinoma. [2]

Platinum-eligible		Platinum-ineligible
Cisplatin-eligible	**Carboplatin*-eligible**	
ECOG PS 0-1 ***and*** GFR > 50–60 mL/min ***and*** Audiometric hearing loss grade < 2 ***and*** Peripheral neuropathy grade < 2 ***and*** Cardiac insufficiency NYHA class < III	ECOG PS 2 *or* GFR 30–60 mL/min ***or*** not fulfilling other cisplatin-eligibility criteria	Any of the following: • GFR < 30mL/min • ECOG PS > 2 • ECOG PS 2 *and* GFR < 60mL/min • Comorbidites > Grade 2

**** Carboplatin is not indicated for neoadjuvant treatment***

7.2.4.2.3 Immunotherapy

In a phase III, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery (pT3, pT4a, or pN+), adjuvant nivolumab improved DFS compared to placebo in the intention-to-treat population (20.8 vs. 10.8 months) and among patients with a programmed death-ligand 1 (PDL1) expression level of 1% or more [283]. The patient population predominantly consisted of BC patients postradical cystectomy, with an additional smaller cohort of patients with UTUC post-RNU. The median recurrence-free survival outside the urothelial tract in the entire intention-to-treat population was 22.9 months for nivolumab and 13.7 months for placebo. Treatment-related adverse events > grade 3 occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. **On subgroup analysis, patients with UTUC included in this study did not seem to benefit from adjuvant nivolumab, which requires further follow-up and analysis. Nonetheless, the European Medicines Agency (EMA) approved nivolumab as monotherapy for the adjuvant treatment of patients with muscle-invasive UC with tumour cell PD-L1 expression > 1%, who are at high risk of recurrence after radical surgery and who decline or are unfit for adjuvant chemotherapy [284].**
A network meta-analysis suggests superior oncological benefit for adjuvant platinum-based chemotherapy over immune checkpoint inhibitors in patients treated with radical surgery for UTUC [285].

7.2.4.2.4 Radiotherapy

Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [286-289]. Moreover, its added value to chemotherapy remains questionable [288].

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Neuzillett Y et al., 2024 [7].

European Association of Urology (EAU)

EAU guidelines on primary urethral carcinoma

Zielsetzung/Fragestellung

This overview represents the updated European Association of Urology (EAU) Guidelines for primary urethral carcinoma. The aim is to provide practical recommendations on the clinical management of Primary Urethral Carcinoma with a focus on clinical presentation. When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary urethral carcinoma, in contrast to secondary urethral carcinoma, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary urethral carcinoma is reported after radical cystectomy for bladder cancer.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- The literature for the complete document has been assessed and updated for the 2024 print, resulting in a text update in section 3.3 on histopathology and genomic profiling.
- For the 2023 Primary Urethral Carcinoma Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the prior search, covering a time frame between August 9th 2022 and May 1st 2023. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 68 unique records were identified, retrieved, and screened for relevance. Only one reference was updated in this 2023 publication.

Anmerkung: Es sind keine Angaben zur Recherche und Suchzeitraum für das „assessment“ des updates der Leitlinie aus 2024 dargelegt. Die beschriebenen Änderungen der Version von 2024 betreffen nicht die Indikation dieser Synopse.

LoE

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

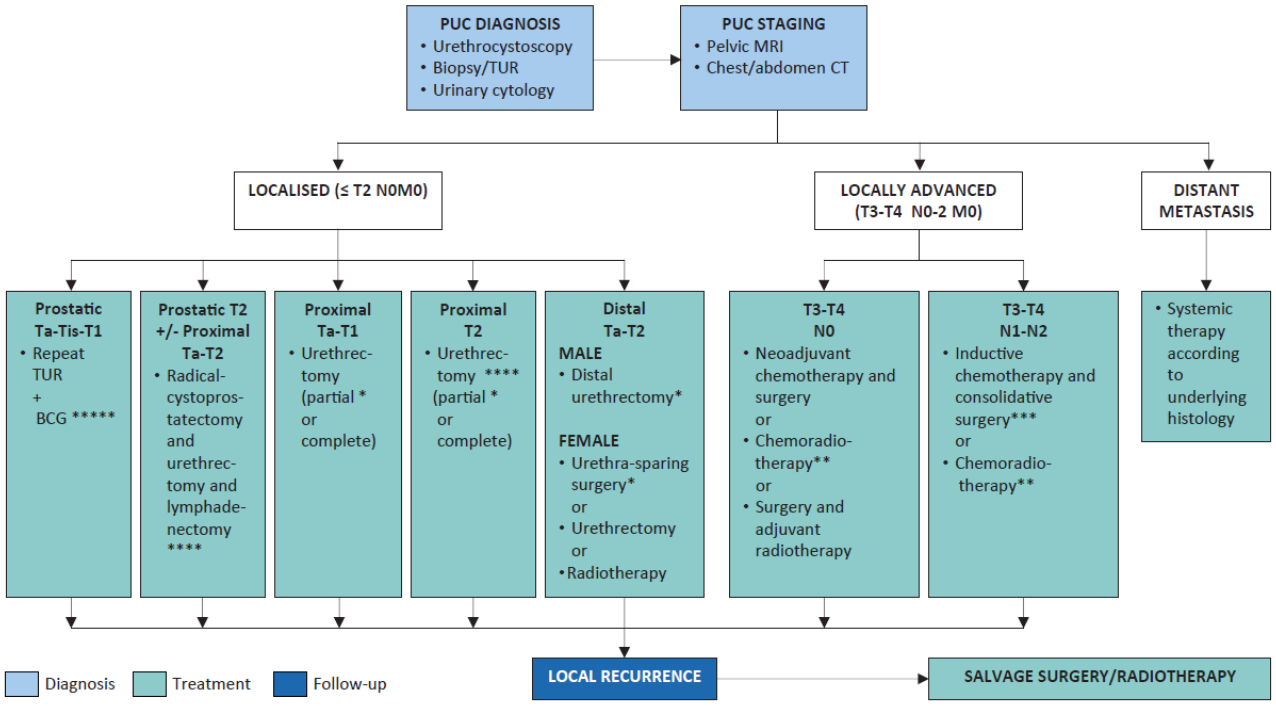
GoR

- 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

Empfehlungen

7. DISEASE MANAGEMENT

Figure 7.1: Management of primary urethral carcinoma



* *Ensure complete circumferential assessment if penile-preserving/urethra-sparing surgery or partial urethrectomy is intended.*

** *Squamous cell carcinoma.*

*** *Regional lymphadenectomy should be considered in clinically enlarged lymph nodes.*

**** *Consider neoadjuvant chemotherapy.*

***** *In extensive or BCG-unresponsive disease: consider (primary) cystoprostatectomy +/- urethrectomy + lymphadenectomy.*

BCG = bacillus Calmette-Guérin; CT = computed tomography; MRI = magnetic resonance imaging; PUC = primary urethral carcinoma; TUR = transurethral resection.

7.3.6 ***Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both males and females***

Summary of evidence	LE
In locally-advanced urethral carcinoma, cisplatin-based chemotherapy with curative intent prior to surgery might improve survival compared to chemotherapy alone, or surgery followed by chemotherapy.	3
In locally-advanced SCC of the urethra, treatment with chemoradiotherapy might be an alternative to surgery.	3
In locally-advanced urothelial- and SCC of the urethra, treatment in academic centres improves OS.	3

Recommendations	Strength rating
Refer patients with advanced urethral carcinoma to academic centres.	Strong
Discuss treatment of patients with locally-advanced urethral carcinoma within a multidisciplinary team of urologists, radiation-oncologists, and oncologists.	Strong
In locally-advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	Weak
In locally-advanced squamous cell carcinoma (SCC) of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	Weak
Offer inguinal lymph node (LN) dissection to patients with limited LN-positive urethral SCC.	Weak

Hintergrund

7.3 Multimodal treatment in locally-advanced urethral carcinoma in both males and females

7.3.1 Introduction

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with additional RT [76]. Multimodal therapy was often underutilised as shown by Cahn and colleagues in locally-advanced disease (only 16%) notwithstanding promising results [76-79]. In a recent study monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex, and year of treatment ($p = 0.017$). Its use has decreased over time [80]. Treatment in academic centres was reported to result in higher utilisation of neoadjuvant- and multimodal treatment and improved OS in patients with locally- advanced urothelial- and SCC primary urethral carcinoma [65].

7.3.2 Preoperative cisplatin-based chemotherapy

Retrospective studies reported that modern cisplatin-based combination chemotherapy regimens can be effective in advanced primary urethral carcinoma providing prolonged survival even in LN-positive disease. Moreover, they emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally-advanced urethral carcinoma. In a study using the National Cancer Database in men with primary urothelial carcinoma, NAC was reported to decrease the risk of all-cause mortality, while AC was not associated with an OS benefit, as compared to no chemotherapy in men, with primary urothelial carcinoma neoadjuvant chemotherapy (NAC) was reported to exhibit improved OS compared with adjuvant chemotherapy [81].

In a series of 124 patients, 39 (31%) were treated with peri-operative platinum-based chemotherapy for advanced primary urethral carcinoma (twelve patients received NAC, six received neoadjuvant chemoradiotherapy and 21 adjuvant chemotherapy). Patients who received NAC or chemoradiotherapy for locally-advanced primary urethral carcinoma (> cT3 and/or cN+) appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy [82]. Another retrospective series including 44 patients with advanced primary urethral carcinoma, reported outcomes on 21 patients who had preoperatively received cisplatin-based combination chemotherapy according to the underlying histologic subtype. The overall response rate for the various regimens was 72% and the median OS 32 months [51].

7.3.3 Chemoradiotherapy in locally-advanced squamous cell carcinoma of the urethra

The clinical feasibility of local RT with concurrent chemotherapy as an alternative to surgery in locally-advanced SCC has been reported in several series. This approach offers a potential for genital preservation [83-87]. The largest, and recently updated, retrospective series reported outcomes in 25 patients with primary locally- advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent EBRT. A complete clinical response was observed in ~80% of patients. The 5-year OS and disease-specific survival was 52% and 68%, respectively. In this updated series, salvage surgery, initiated only in non-responders or in case of local failure, was not reported to be associated with improved survival

[83]. A large retrospective cohort study in patients with locally-advanced urethral carcinoma treated with **adjuvant RT and surgery** vs. surgery alone demonstrated that the addition of RT improved OS [88].

7.3.4 Salvage treatment in recurrent primary urethral carcinoma after surgery for primary treatment

A multicentre study reported that patients who were treated with surgery as primary therapy and underwent surgery or RT-based salvage treatment for recurrent solitary or concomitant urethral disease, demonstrated similar survival rates compared to patients who never developed recurrence after primary treatment [66].

7.3.5 Treatment of regional lymphnodes

Nodal control in urethral carcinoma can be achieved either by regional lymph node (LN) dissection [36], RT [74] or chemotherapy [51]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/ or pelvic LND in all patients with urethral carcinoma [53]. However, in patients with clinically enlarged inguinal/ pelvic LNs or invasive tumours, regional LND should be considered as initial treatment since cure might still be achievable with limited disease [36]. It was recently shown that in patients with invasive urethral SCC and cN1–2 al LND conferred an OS benefit [53].

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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

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

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

Neoadjuvant/**Adjuvant Chemotherapy**

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 cisplatin-based chemotherapy and have pT2-4 and/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, meta-analyses 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-cisplatin-eligible, 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 pT3-pT4 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]

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Coleman JA et al., 2023 [3].

American Urological Association (AUA)/Society of Urologic Oncology (SUO)

Diagnosis and management of non-metastatic upper tract urothelial carcinoma: AUA/SUO guideline (2023)

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
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Recherche/Suchzeitraum:

- Searches in Ovid MEDLINE (1946 to March 3rd, 2022), Cochrane Central Register of Controlled Trials (through January 2022), and Cochrane Database of Systematic Reviews (through January 2022). The searches were updated August 2022 and January 2023.

LoE

- Grade A (well-conducted and highly-generalizable randomized control trial (RCTs) or exceptionally strong observational studies with consistent findings)
- Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings)
- Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).

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
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GoR

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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

Kidney Sparing Management

14. Tumor ablation may be the initial management option offered to patients with LR unfavorable UTUC and select patients with HR favorable disease who have low-volume tumors or cannot undergo RNU. (Conditional Recommendation; Evidence Level: Grade C)

16. Following ablation of UTUC tumors and after confirming there is no perforation of the bladder or upper tract, clinicians **may instill adjuvant pelvicalyceal chemotherapy** (Conditional Recommendation; Evidence Level: Grade C) **or intravesical chemotherapy** (Expert Opinion) to decrease the risk of urothelial cancer recurrence.

Hintergrund

There is ample evidence supporting the use of an immediate instillation of intravesical chemotherapy at the time of transurethral resection of a bladder tumor for urothelial carcinoma for the purpose of reducing the rate of intravesical tumor recurrence.[96, 97] **The principle of an immediate instillation of intravesical or pyelocaliceal (upper tract) chemotherapy at the time of endoscopic tumor ablation for UTUC is undertaken by extrapolation of the data supporting this practice in the management of urothelial carcinoma of the lower tract.** At present, this is considered an optional part of routine practice. The available reported clinical experience reported in the upper tract is less compelling. A small, prospective, non-randomized single center cohort study by Gallioli et al., showed a strong trend in improving urothelial recurrence free survival (URFS) for patients treated with a single upper tract instillation of Mitomycin C after endoscopic ablation. Mean URFS was 29 months for the treated group compared to 19 months in patients who did not receive treatment (log-rank p = 0.067).[98] Though a small study including only 51 patients, there were controls for several potential confounding variables and low ROB was identified. A larger study (n=73) by Cutress et al. did not control for confounding variables and failed to identify a difference in RFS with adjuvant intraluminal chemotherapy.[99] In the Gallioli study, the majority of recurrences were observed in the bladder.98 More recent work has explored the role of an adjuvant dose of upper tract mitomycin gel following endoscopic ablation with a report of 63% ipsilateral disease-free rate at 6.8 months following instillation, albeit with a 19% ureteral stenosis rate and no comparator group.[100] While acceptable, there are limited direct supporting data for this common practice in upper tract applications at this time.

TECHNICAL CONSIDERATIONS

The optimal administration technique is not fully elucidated. Both ex vivo and in vivo porcine models suggest higher rates of topical therapy delivery to the pyelocaliceal system with retrograde administration by ureteral catheter.[101-104] However, the Panel considers each of the following delivery approaches to be acceptable: 1) antegrade perfusion by nephrostomy tube, 2) retrograde perfusion via ureteral catheter, and 3) bladder instillation by transurethral catheter with reflux via a double J ureteral stent. In the third scenario, it is recommended to perform a cystogram and demonstrate adequate reflux of contrast into the pyelocaliceal system. Finally, while bacillus Calmette-Guerin (BCG) is the mainstay of topical therapies for UTUC, the following agents have been described: mitomycin c, gemcitabine, docetaxel, epirubicin, adriamycin, thiotepa, and BCG with interfero[105, 106]

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Neoadjuvant/**Adjuvant Chemotherapy and Immunotherapy**

27. Clinicians should offer platinum-based adjuvant chemotherapy to patients with advanced pathological stage (pT2–T4 pN0–N3 M0 or pTany N1–3 M0) UTUC after RNU or ureterectomy who have not received neoadjuvant platinum-based therapy. (Strong Recommendation; Evidence Level: Grade A)

Hintergrund

Adjuvant platinum-based chemotherapy for select patients with UTUC post-RNU is a standard based on results from the randomized phase III POUT trial.[135] In this study, 261 chemotherapy-naïve patients were identified and enrolled post-RNU, with HR patients selected based on postoperative stage in non-metastatic patients of pT2–T4 pN0–N3 M0 or pTany N1–3. In this trial, patients were randomized to platinum chemotherapy day 1 based on eligibility (cisplatin, or carboplatin for glomerular filtration rate <50 mL/min) with gemcitabine days 1 and 8 for four planned adjuvant cycles to start within 90 days of RNU. The trial was designed to show improved disease-free survival (DFS) in the chemotherapy versus the observation arm, and after meeting an early efficacy point, accrual was halted. At a median follow-up of 30.3 months, subjects in the adjuvant chemotherapy arm had improved DFS (HR: 0.45; 95% CI: 0.30 to 0.68; p=0.0001) compared with those on observation. Subjects on the chemotherapy arm had a significantly lower risk of metastases or death compared to observation (HR: 0.48; 95% CI: 0.31 to 0.74; log-rank p=0.0007). Side effects of platinum chemotherapy were as expected with no grade 5 events. The completion rate of four adjuvant cisplatin cycles was low in this dataset at 58%, including 21% of patients who started with cisplatin but switched to carboplatin for post allocation decline in GFR.

A subgroup analysis demonstrated that outcomes for patients with lymph node involvement and those treated with carboplatin chemotherapy were worse than those without positive nodes or treated with cisplatin chemotherapy.[136] As the primary endpoint was powered based on the intent to treat population, speculation about these subgroups, the potential utilization of six versus four cycles for metastatic N+ disease or the impact of carboplatin in this setting are hypothesis generating discussions. Based on these data, carboplatin remains a reasonable choice for HR cisplatin-ineligible patients post-RNU if NAC was not given.

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28. Adjuvant nivolumab therapy may be offered to patients who received neoadjuvant platinum-based chemotherapy (ypT2–T4 or ypN+) or who are ineligible for or refuse perioperative cisplatin (pT3, pT4a, or pN+). (Conditional Recommendation; Evidence Level: Grade B)

Hintergrund

Two completed RCTs compared adjuvant checkpoint inhibitor therapy versus observation (IMvigor 010) or placebo (CheckMate 274) following surgery in patients with HR non-metastatic urothelial carcinoma (Appendix V).[137, 138] Although the majority of patients in these studies underwent radical cystectomy for bladder primaries, 20% of patients in CheckMate 274 and 7% of IMvigor 010 patients underwent surgery for UTUC, with endpoints based on the intention to treat population. Inclusion criteria for both studies were patients with HR urothelial cancer defined as pT3, pT4a, or pN+ for patients who had not received neoadjuvant cisplatin-based chemotherapy and ypT2 to ypT4a or ypN+ for patients who had received neoadjuvant cisplatin.

In the IMvigor 010 trial, (n=406; 29 with UTUC) planned one year of adjuvant atezolizumab did not meet the primary endpoint of improved DFS compared to observation (19.4 months versus 16.6 months; HR: 0.89; 95% CI: 0.74 to 1.08).[139] Another study, the phase III randomized adjuvant study of pembrolizumab in muscle invasive and locally advanced urothelial carcinoma including UTUC patients (AMBASSADOR) versus observation trial, has completed accrual and is maturing with data yet to be presented.[140]

The CheckMate 274 (n=709; 149 with UTUC) study of one year of planned adjuvant nivolumab did meet its co-primary endpoints, with improved DFS (definition per-protocol included within and outside of the

urothelial tract) of 20.8 months (95% CI: 16.5 to 27.6) with nivolumab versus 10.8 months (95% CI: 8.3 to 13.9) with placebo in the intention to treat population.138 The 6-month DFS benefit of 74.5% with nivolumab and 55.7% with placebo (HR: 0.55; 98.72% CI: 0.35 to 0.85; P<0.001) was even more striking in patients whose tumors expressed PD-L1 (>1%).

Additionally, non-urothelial tract RFS (77.0% versus 62.7%; HR: 0.72; 95% CI: 0.59 to 0.89), and distant metastasis free survival (MFS, 82.5% versus 69.8%; HR: 0.75; 95% CI: 0.59 to 0.94) were also improved. In a subgroup analysis of patients with UTUC, there was no difference in DFS for renal pelvic cancers (HR: 1.23; 95% CI: 0.67 to 2.23) or the ureter (HR: 1.56; 95% CI: 0.70 to 3.48) in either arm. The small sample size limits the statistical power to detect a difference, and thus the results from this subgroup analysis in UTUC are hypothesis generating only. Based on the strength of the overall evidence, adjuvant nivolumab was approved for UTUC and urothelial carcinoma of the bladder in patients with advanced disease identified from post-surgical pathology findings.

With respect to harms, nivolumab was well tolerated and similar to placebo with respect to overall AEs (98.9% versus 95.4%) and grade 3 or higher AEs (42.7% versus 36.8%).107 However, nivolumab was associated with increased likelihood of treatment-related AEs (77.5% versus 55.5%) and grade 3 or higher treatment-related AEs (17.9% versus 7.2%). The most common toxicities in the nivolumab group were pruritus (23.1%), fatigue (17.4%), and diarrhea (16.8%); and the most common grade 3 or higher AEs were elevations in serum lipase (5.1%) and amylase (3.7%) levels, diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%). Treatment-related death occurred in three patients treated with nivolumab (two due to pneumonitis and one due to bowel perforation). Toxicity-related treatment discontinuation was also higher from nivolumab compared to placebo (12.8% versus 2.0%); most frequently from pneumonitis (1.7%), rash (1.1%), colitis (0.9%), and increased alanine aminotransferase level (0.9%). These toxicities are similar to other checkpoint inhibitor studies with no new safety signals noted. No adjuvant studies have compared nivolumab to platinum-based chemotherapy regimens.

Based on the relative strengths of the available data, the Panel recommends the use of adjuvant platinum-chemotherapy over adjuvant nivolumab for eligible patients who did not receive NAC. Scenarios for use of adjuvant nivolumab include: 1) patients with contraindications to platinum-based chemotherapy (e.g., poor renal function, performance status, sensorineural hearing loss, neuropathy or congestive heart failure, allergy), 2) patients with HR pathology after NAC, 3) patients who refuse standard forms of adjuvant chemotherapy after appropriate counseling.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2025) am 04.02.2025

#	Suchschritt
1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
2	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
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 Feb 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 04.02.2025

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 15.01.2025.

#	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 ("2020/02/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
164	**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]
12	bladder[tiab] OR urotheli*[tiab] OR transitional[tiab]

#	Suchschritt
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"[mh] 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 ("2020/02/01"[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)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 05.02.2025

- 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)
- 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

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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