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: 2020-B-205 Nivolumab

Stand: September 2020

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

Nivolumab
[zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion]

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	*Es liegen keine Beschlüsse vor.*
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>Zu prüfendes 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.
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: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-205 (Nivolumab)

Auftrag von:	Abteilung Arzneimittel
Bearbeitet von:	Abteilung Fachberatung Medizin
Datum:	26. August 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouacil
A	Doxorubicin
ACH	Adjuvant Chemotherapy
AMED	Allied & Complementary Medicine
AM-RL	Arzneimittel-Richtlinie
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Bladder Cancer
BCG	Bacillus-Calmette Guérin
C	Cisplatin
CAP	Cyclophosphamid, Doxorubicin und Cisplatin
CDR	Clinical Decision Rule
CEBM	Centre for Evidence-Based Medicine
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CM	Cisplatin und Methorexat
CMV	Cisplatin, Methotrexat und Vinblastin
CPS	Combined Positive Score
CT	Computed Tomography
CTU	Computed Tomography Urography
df	Degress of Freedom
DKG	Deutsche Krebsgesellschaft
DKH	Deutsche Krebshilfe
E	Etoposid
EAU	European Association of Urology
ECRI	ECRI Guidelines Trust
Embase	Excerpta Medica
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
G	Gemcitabin

GC	Gemcitabin und Cisplatin
GCP	Gemcitabin, Cisplatin und Paclitaxel
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
Gy	Gray, Einheit für ionisierende Strahlung
HCP	Healthcare Professional
HR	Hazard Ratio
IGRT	Image-Guided Radiotherapy
IQR	Interquartil Range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IMRT	Intensitiy-Modulated Radiotherapy
ITT	Intention-to-treat
IV	Inverse Variance
LA	Lymphadenektomie
LE	Level of Evidence
LND	Lymph Node Dissection
LoE	Level of Evidence
M	Methotrexat
MIBC	Muscle-invasive Bladder Cancer
MRI	Magnetic Resonance Imaging
MVAC	Methotrexat, Vinblastin, Doxorubicin und Cisplatin
MVEC	Methotrexat, Vinblastin, Epirubicin und Cisplatin
NA	Not Available
NAC	Neoadjuvant Chemotherapy
NICE	National Institute for Health and Care Excellence
NMBIC	Non-muscle-invasive Bladder Cancer
OS	Overall Survival
PFS	Progression-Free Survival
PD-L1	Programmed Cell Death-Ligand 1
PLND	Pelvic Lymph Node Dissection
RC	Radical Cystectomy
RCT	Randomized Controlled Trial

RNU	Radical Nephroureterectomy
RT	Radiotherapy
SCC	Squamous Cell Carcinoma
SCI-EXPANDED	Science Citation Index Expanded
SE	Standard Error
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SSCI	Social Sciences Citation Index
SUO	Society of Urologic Oncology
TRIP	Turn Research into Practice Database
TUR	Transurethrale Resektion
TUR-B	Transurethrale Resektion der Blase
TURBT	Transurethral Resection of Bladder Tumor
UC	Urothelial Carcinoma
UTUC	Upper Urinary Tract Urothelial Cacinoma
UUT	Upper Urinary Tract
V	Vinblastin
WHO	World Health Organization

1 Indikation

Zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Urothelkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 05.08.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1356 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen 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 15 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Gemeinsamer Bundesausschuss (G-BA), 2018 [4].

Beschluss des Gemeinsamen Bundesausschusses über die Erteilung von Aufträgen an die Expertengruppen nach § 35 c Abs. 1 SGB V (Expertengruppen Off-Label): Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patienten mit inoperablem lokal-fortgeschrittenen oder metastasiertem Urothelkarzinom nach Versagen einer Chemotherapie oder wenn eine Cisplatin-Therapie nicht infrage kommt

Vom 19. April 2008

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 19. April 2018 beschlossen, die Expertengruppen Off-Label mit wissenschaftlichen Erkenntnissen zu beauftragen:

Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patienten mit inoperablem lokal-fortgeschrittenen oder metastasiertem Urothelkarzinom nach Versagen einer Chemotherapie oder wenn eine Cisplatin-Therapie nicht infrage kommt

Gemeinsamer Bundesausschuss (G-BA), 2019 [5].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung zum Beschluss vom 20. Juni 2019 – Atezolizumab (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse: Urothelkarzinom)

Anwendungsgebiet

Neues Anwendungsgebiet (laut Zulassung vom 2. Juli 2018):

Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC)

- nach vorheriger platinhaltiger Chemotherapie oder
- die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen.

Hinweis:

Der Beschluss vom 20. Juni 2019 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Atezolizumab in der Teilpopulation: a) Urothelkarzinom; Patienten, die nicht für eine Behandlung mit Cisplatin geeignet sind und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen (Erstlinie).

a) <u>Urothelkarzinom; Patienten, die nicht für eine Behandlung mit Cisplatin geeignet sind und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen (Erstlinie)</u>

Zweckmäßige Vergleichstherapie

Eine Chemotherapie nach Maßgabe des Arztes

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Patienten mit vorheriger Platin-basierter Therapie

Zweckmäßige Vergleichstherapie

a) Für Patienten mit einem Frührezidiv (≤ 6 Monate)
   Vinflunin

b) Für Patienten mit einem Spätrezidiv (> 6 – 12 Monate)
   Vinflunin
   oder
   Eine erneute Cisplatin-basierte Chemotherapie (für Patienten die, abhängig von Krankheitsverlauf, Allgemeinzustand und Verträglichkeit der Erstlinientherapie, für eine solche in Frage kommen)

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen.

Gemeinsamer Bundesausschuss (G-BA), 2019 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung zum Beschluss vom 20. Juni 2019 – Pembrolizumab (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse: Urothelkarzinom)

Anwendungsgebiet

Neues Anwendungsgebiet (laut Zulassung vom 6. Juli 2018):

Keytruda ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt.

Keytruda ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms nach vorheriger Platin-basierter Therapie bei Erwachsenen angezeigt.

Hinweis:

Der Beschluss vom 20. Juni 2019 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Pembrolizumab in der Teilpopulation: a) Urothelkarzinom; Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren (Erstlinie).

a) Urothelkarzinom; Patienten, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren (Erstlinie)

Zweckmäßige Vergleichstherapie

Eine Chemotherapie nach Maßgabe des Arztes

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Patienten mit vorheriger Platin-basierter Therapie

Zweckmäßige Vergleichstherapie

c) Für Patienten mit einem Frührezidiv (≤ 6 Monate)

Vinflunin

d) Für Patienten mit einem Spätrezidiv (> 6 – 12 Monate)

Vinflunin

oder

Eine erneute Cisplatin-basierte Chemotherapie (für Patienten die, abhängig von Krankheitsverlauf, Allgemeinzustand und Verträglichkeit der Erstlinientherapie, für eine solche in Frage kommen)

Fazit / Ausmaß des Zusatznutzens

Hinweis auf einen beträchtlichen Zusatznutzen.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Kim DK et al., 2019 [7].

Role of adjuvant cisplatin-based chemotherapy following radical cystectomy in locally advanced muscle-invasive bladder cancer: systematic review and meta-analysis of randomized trials

Zielsetzung

[…] to examine the effects of ACH on improvement of survival outcomes in patients with locally advanced MIBC following RC.

Methodik

Population:

patients with locally advanced MIBC who underwent RC

Intervention:

ACH

Komparator:

RC only

Primärer Endpunkt:

PFS

Sekundärer Endpunkt:

Overall Survival

Recherche/Suchzeitraum:

[…] computerized bibliographic search of PubMed/MEDLINE, Embase, and Cochrane library databases in February 2018.

Qualitätsbewertung der Studien:

Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien: (⇨ Anhang Tabellen 1 und 2)

- Four RCTs with a total of 490 patients were included in this study.
- The chemotherapy regimens used varied between studies. Three or four cycles of ACH were used in most of the trials.

Charakteristika der Population:

- One study was performed in Europe [15], two studies were performed in the United States [14,26], and one study was a multicenter RCT that included patients from Europe and Canada [18].
- Four trials enrolled patients with locally advanced MIBC (pT3-4 and/or pN+ and M0).

Qualität der Studien:

- There were two main sources of bias. The first source was unblinded study design, which would cause bias in the results towards ACH. The second source was early trial termination. The reasons for early discontinuation was showing ACH effect to be greater.
- Early discontinuation of a trial was included as other bias.

Abbildung 1: Risk of bias assessment

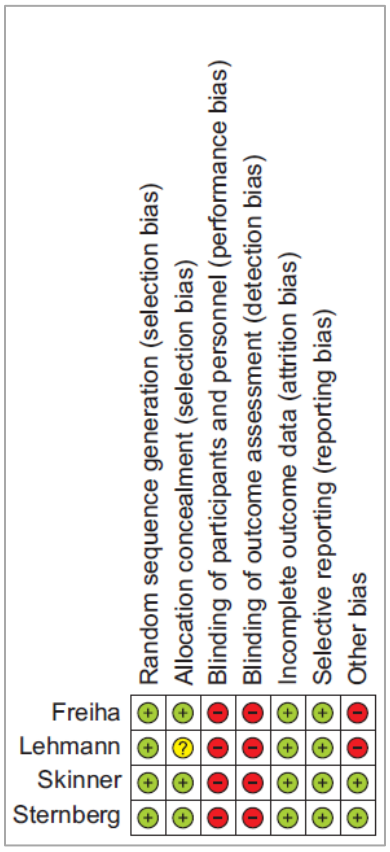
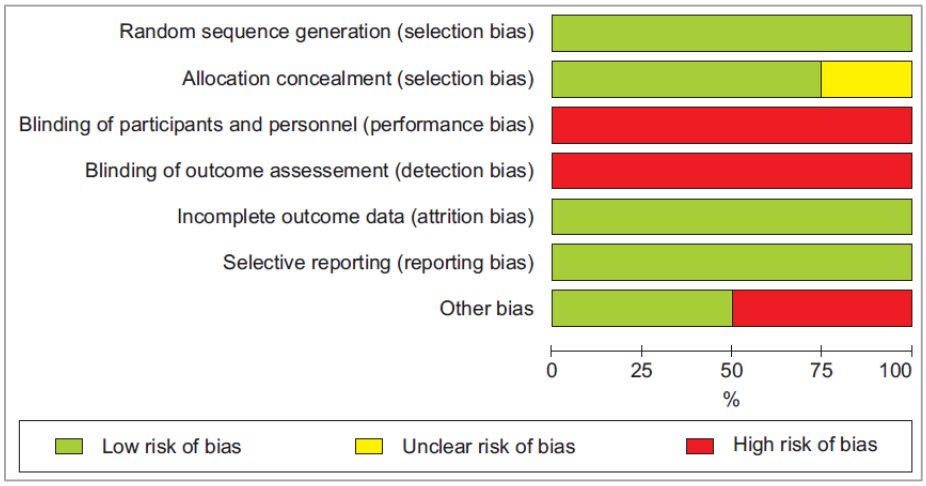


Abbildung 2: Risk of bias graph

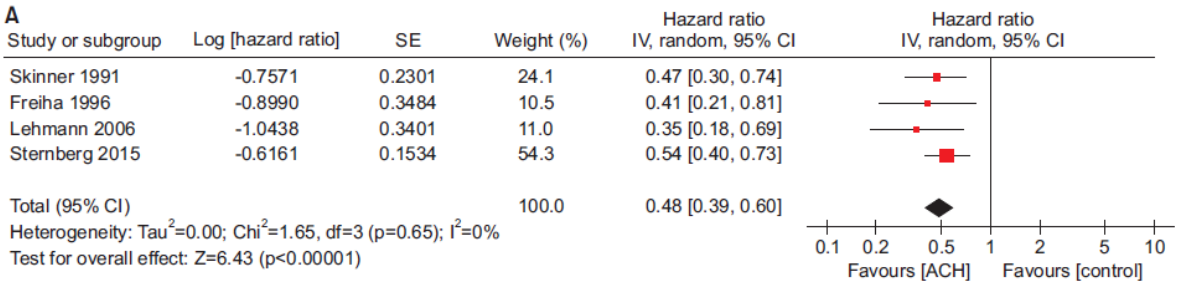


Studienergebnisse:

Primary endpoint: PFS

Meta.-analysis of the included trials revealed an overall HR of 0.48 for PFS for ACH (p<0.00001; 95% CI, 0.39-0.60). Results indicated that the among-study heterogeneity was [not] statistically significant (Cochran Q statistic, p=0.65; I^2 statistic, 0%). The absolute increases in PFS for all trials was 17%, respectively (i.e., equivalent to numbers needed to treat of 5.9, respectively).

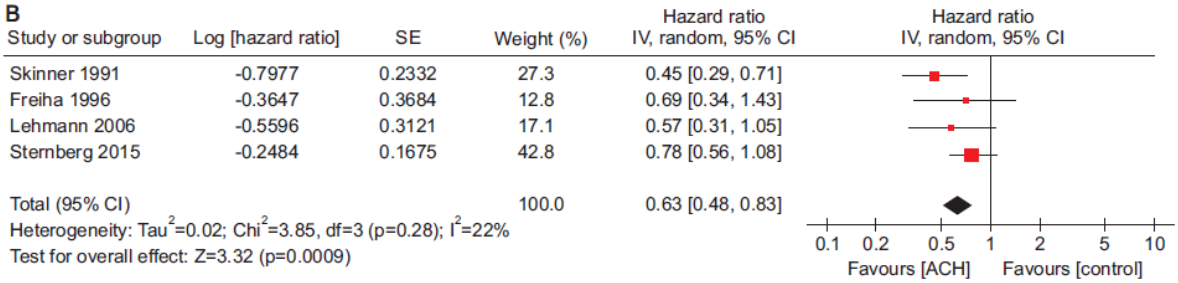
Abbildung 3: Forest plot of PFS in locally advanced MIBC (pT3-4 and/or pN+ and M0)



Secondary endpoint: Overall survival

Analysis of the random-effects model revealed that pooled HR across all studies was 0.63 (p=0.0009; 95% CI, 0.48-0.83); among-study heterogeneity was not statistically significant (Cochran Q statistic, p=0.28; I^2 statistic, 22%). The absolute increase in OS for all trials was 10%, respectively (i.e., equivalent to numbers needed to treat of 10, respectively).

Abbildung 4: Forest plot of OS in locally advanced MIBC (pT3-4 and/or pN+ and M0)



Sensitivity analyses

Sensitivity analysis was performed using sequential exclusion of studies to evaluate the effect of each study on overall meta-analysis results. Trial by Sternberg et al. [18] had the greatest negative effects on both PFS and OS HRs. Study by Lehmann et al. [15] had the largest positive effects on PFS, and Skinner et al. [26] showed the largest positive effects on OS HRs, respectively. Exclusion of any one study did not result in any statistically significant changes in the results. Results were statistically reliable.

Anmerkung/Fazit der Autoren

Our meta-analysis of four RCTs found that ACH may provide benefits for PFS and OS in patients with locally advanced MIBC who received ACH after RC, compared to those who underwent surgery alone. Our results […] suggest that beneficial effects of ACH may be greater in patients with locally advanced MIBC patients than in those with MIBC.

Kommentare zum Review

Die Wirkstoffe Cyclophosphamid und Epirubicin sind im Anwendungsgebiet nicht zugelassen.

Referenzen

14. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996;155:495-499.

15. Lehmann J, Franzaring L, Thüroff J, Wellek S, Stöckle M. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int 2006;97:42-47.

18. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Ageraek M, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015;16:76-86.

26. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991;145:459-464.

Kim HS et al., 2017 [8].

Adjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and network meta-analysis of randomized clinical trials

Zielsetzung

[…] to evaluate the efficacy of ACH and determine the optimal ACH regimen associated with significant improvement in survival outcomes in MIBC patients who underwent RC.

Methodik

Population:

patients with MIBC

Intervention:

various cisplatin-based ACH regimens

Komparator:

RC alone

Primärer Endpunkt:

PFS

Sekundärer Endpunkt:

OS

Recherche/Suchzeitraum:

A literature search was conducted […] until December 2016, using the Pubmed, Embase, and Cochrane Library databases.

Qualitätsbewertung der Studien:

[…] estimated the methodological quality of each included study in accordance with the Repoting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines [29]. Six items were assigned a score of 0 or 1, thus the final quality scale ranged from 0 (lowest) to 6 (highest).

Ergebnisse

Anzahl eingeschlossener Studien: (⇨ Anhang Tabellen 3 und 4)

- […] a total of 11 RCTs conducted between 1991 and 2015 were ultimately included in the current meta-analysis.
- The recruitment period of patients ranged from 1980 to 2008.
- The distribution of patients to control and case (ACH) groups utilized a nearly 1:1 randomization in each study, ranging from 23 to 143 subjects per group.
- Assessed chemotherapy regimens consisted of the following: a cisplatin-based combination, including cisplatin, Adriamycin (doxorubicin), and cyclophosphamide (CAP) [17]; cisplatin and methotrexate (CM) [19]; cisplatin, methotrexate, and vinblastine (CMV) [9]; methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) [13,15]; methotrexate, vinblastine, epirubicin, and cisplatin (MVEC) [11,12,20]; gemcitabine, cisplatin, and paclitaxel (GCP) [21]; and gemcitabine and cisplatin (GC) [14,15]. Only one trial investigated adjuvant cisplatin monotherapy [18].
- The dosages of each chemotherapeutic agent were similar when specific ACH regimens (MVAC, MVEC, and GC) were used. The number of cycles of ACH ranged from 3 to 4 in most studies.

Charakteristika der Population:

- Seven studies were performed in Europe [11,12,14,18-21], three studies were conducted in the United States [9,13,17], and the remaining study was multinational from Europe and Canada [15].
- The pathologic stages in most trials included muscle-invasive or locally advanced (pN+) disease without distant metastases.

Qualität der Studien:

- […] most of the studies investigated in this review satisfied all of the evaluation criteria.
- The quality scale ranged from 4 to 6, and 7 of the 11 studies showed a quality scale of 6, implying that most of the included studies were well-designed and of high quality.

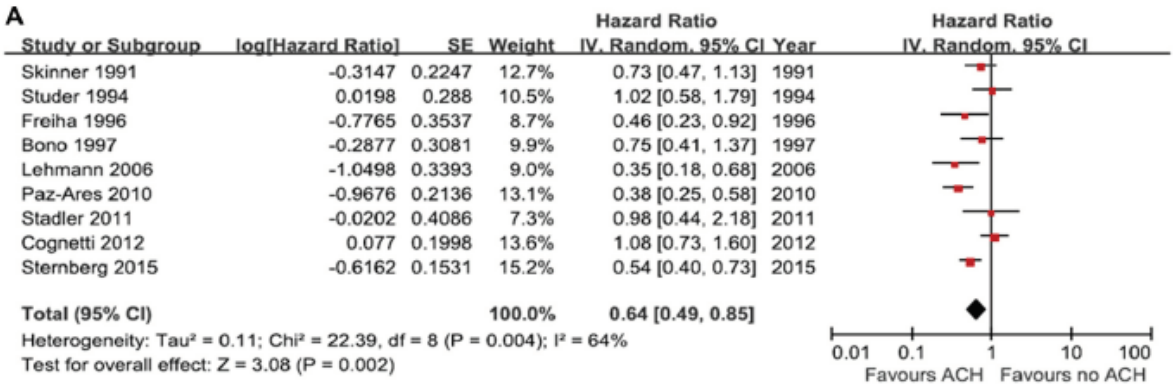
Studienergebnisse:

Direkte Vergleiche

Primary endpoint: PFS

A total of 9 studies including 1,1111 patients, were available for the meta-analysis of progression-free survival (PFS). The pooled analysis of PFS indicated that ACH was significantly associated with better PFS outcomes than controls (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.49-0.85). Significant heterogeneity among the included studies for PFS was observed (p=0.004; I^2=64%).

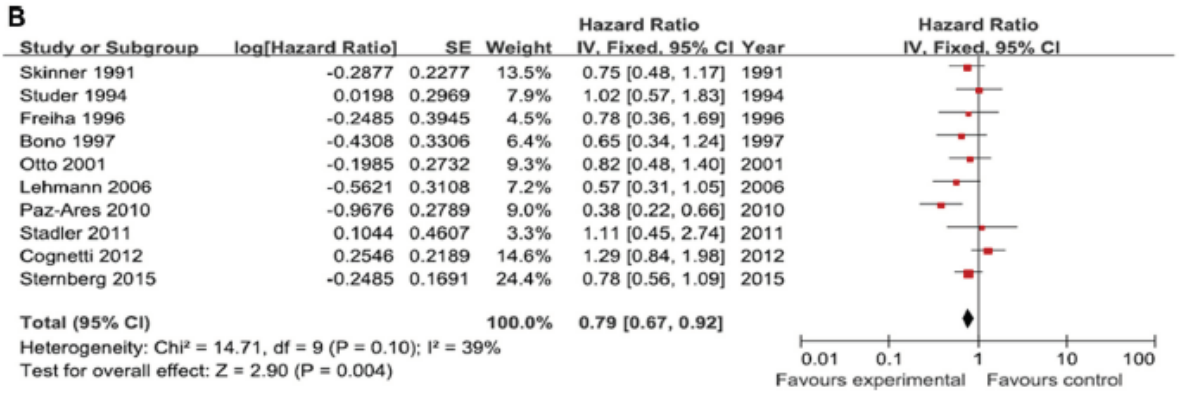
Abbildung 5: Forest plot of prognosis with adjuvant chemotherapy (A) progression-free survival



Secondary endpoint: PFS

The pooled analysis of OS was based on ten publications involving 1,219 patients. The pooled HR (95% CI) was 0.79 (0.67-0.92), which suggested favorable OS outcomes for patients who received ACH compared to controls. There was no significant heterogeneity among included studies for OS (p=0.10; i²=39%).

Abbildung 6: Forest plot of prognosis with adjuvant chemotherapy (B) overall survival



Sensitivity analyses

Sensitivity analysis was conducted to evaluate the influence of individual studies on the overall meta-analysis results by omitting one study at a time. Omission of any study made no significant difference, demonstrating that […] results were statistically reliable (data not shown).

Indirekte Vergleiche

Die Ergebnisse aus indirekten Vergleichen werden nicht berichtet, da die grundlegenden Annahmen von Netzwerk-Metaanalysen nicht adäquat überprüft wurden.

Anmerkung/Fazit der Autoren

Based on the pairwise meta-analysis, the use of ACH showed significantly better PFS […] and OS […] than RC alone. ACH following RC for MIBC may therefore contribute to improved PFS

and OS. […] Additional well-designed, large scale, prospective, randomized trials are still required to establish the optimal ACH regimen in MIBC patients.

Kommentare zum Review

Die Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) Checkliste [29] besteht aus 20 Items. Es handelt sich um Publikationsstandards zu prognostischen Markern in der Onkologie. Es bleibt unklar, welche Items zur Bewertung des Verzerrungspotenzials einer Studie herangezogen wurden.

Die Wirkstoffe Cyclophosphamid, Epirubicin und Paclitaxel sind im Anwendungsgebiet nicht zugelassen.

Referenzen

9. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996;155:495-499.

11. Lehmann J, Retz M, Wiemers C, Beck J, Thüroff J, Weining C, et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). J Clin Oncol 2005;23:4963-4974.

12. Lehmann J, Franzaring L, Thüroff J, Wellek S, Stöckle M. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int 2006;97:42-47.

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3.4 Leitlinien

Leitlinienprogramm Onkologie, 2020 [9].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Deutsche Krebsgesellschaft (DKG) und Stiftung Deutsche Krebshilfe (DKH)

S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms

Zielsetzung

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

Methodik

Grundlage der Leitlinie

- 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

Es erfolgte eine systematische, jedoch selektive Literaturrecherche in der Datenbank Medline via PubMed (Suchdatum 30.12.2017)

LoE

Tabelle 1: Schema der Evidenzgraduierung nach SIGN

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

Grad	Beschreibung
4	Expertenmeinung

GoR

Tabelle 2: Schema der Empfehlungsgraduierung

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

Tabelle 3: Konsensusstärke

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

Empfehlungen

7.2. Radikale Zystektomie bei Harnblasenkarzinompatienten

7.6.	Konsensbasierte Empfehlung
EK	Bei der radikalen Zystektomie sollen in der Regel die gesamte Blase und unmittelbare Nachbarorgane, beim Mann Prostata und Samenblasen, bei der Frau Uterus, Adnexe und Anteile der vorderen Vaginalwand, entfernt werden.
	Konsens

7.7.	Konsensbasierte Empfehlung
EK	Bei Patienten mit muskelinvasivem Harnblasenkarzinom (≥pT2) soll eine radikale Zystektomie angeboten werden.
	Konsens

7.8.	Konsensbasierte Empfehlung
EK	Bei der Frau kann in Abhängigkeit von der Tumorlokalisation und Ausdehnung auf die Entfernung der vorderen Vaginalwand verzichtet werden, bzw. in Abhängigkeit vom Menopausenstatus auf die Entfernung der Adnexe.
	Starker Konsens

7.9.	Konsensbasierte Empfehlung
EK	Patienten mit muskelinvasivem Harnblasenkarzinom (≥pT2) kann eine laparoskopische (konventionell oder roboterassistiert) radikale Zystektomie angeboten werden.
	Starker Konsens

7.10.	Konsensbasiertes Statement
EK	Die Schonung autonomer sympathischer und parasympathischer Nervenfasern kann zum Erhalt der Sexualität und der Sphinkterfunktion beitragen.
	Starker Konsens

7.3. Partielle Zystektomie bei Harnblasenkarzinompatienten

7.11.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Eine partielle Zystektomie soll aufgrund nicht nachgewiesener Gleichwertigkeit nicht als Standardtherapie empfohlen werden.
Level of Evidence **2+**	Primärrecherche: [630, 631]
	Konsens

7.5. Einfluss der Lymphadenektomie im Rahmen der radikalen Zystektomie auf das progressionsfreie Überleben und das Gesamtüberleben

7.19.	Evidenzbasiertes Statement
Level of Evidence **2-**	Eine pelvine Lymphadenektomie im Rahmen einer radikalen Zystektomie kann das progressionsfreie, das tumorspezifische und das Gesamtüberleben verbessern.
	Primärrecherche: [682-689]
	Konsens

7.20.	Evidenzbasiertes Statement
Level of Evidence **2-**	Durch eine extendierte pelvine Lymphadenektomie werden – verglichen mit einer limitierten pelvinen Lymphadenektomie – signifikant mehr Lymphknoten entfernt sowie eine signifikant höhere Zahl an Lymphknotenmetastasen gefunden.
	Primärrecherche: [568, 690-693]
	Konsens

7.21.	Evidenzbasiertes Statement
Level of Evidence **2-**	Eine extendierte pelvine Lymphadenektomie werden – verglichen mit einer limitierten pelvinen Lymphadenektomie – das tumorfreie Überleben vermutlich verbessern. Daten aus prospektiven randomisierten Studien stehen aus. Das Ausmaß der extendierten LA ist bislang noch nicht definiert.
	Primärrecherche: [568, 683, 685, 693-698]
	Konsens

7.22.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Bei einem invasiven Harnblasenkarzinom soll im Rahmen der radikalen Zystektomie zeitgleich eine beidseitige pelvine Lymphadenektomie erfolgen.
Level of Evidence **2-**	Primärrecherche: [568, 682, 683, 685-688, 699-701]
	Konsens

7.23.	Evidenzbasiertes Statement
Level of Evidence **3**	Eine suffiziente beidseitige pelvine Lymphadenektomie umfasst die Entnahme und Beurteilung von mind. 10-16 Lymphknoten.
	Primärrecherche: [568, 683, 685, 694, 695, 702-704]
	Konsens

7.6. Indikation zur Urethrektomie

7.6.1. Urethrektomie bei Frauen (modifiziert)

7.24.	Evidenzbasiertes Statement
Level of Evidence **3**	Tumorbefall des Blasenhalses ist ein unabhängiger Risikofaktor für das gleichzeitige Vorliegen eines Tumorbefalls der Urethra.
	Primärrecherche: [586, 735-737]
	Konsens

7.25.	Evidenzbasiertes Statement
Level of Evidence **3**	Tumorbefall der Vaginalvorderwand ist ein unabhängiger Risikofaktor für das gleichzeitige Vorliegen eines Tumorbefalls der Urethra.
	Primärrecherche: [586, 735, 738]
	Konsens

7.27.	Evidenzbasiertes Statement
Level of Evidence **3**	Die intraoperative Schnellschnittuntersuchung des Harnröhrenabsetzungsrandes der Frau bietet mit einer Sensitivität von 97-100% eine hohe Sicherheit, da eine sehr hohe Korrelation zur endgültigen Histologie besteht.
	Primärrecherche: [216, 579, 735, 739, 740]
	Starker Konsens

7.29.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Bei Tumornachweis im urethralen Absetzungsrand im Rahmen der intraoperativen Schnellschnittdiagnostik soll eine Urethrektomie erfolgen.
Level of Evidence **3**	Primärrecherche: [579, 735]
	Starker Konsens

7.6.2. Urethrektomie bei Männern (modifiziert)

7.35.	Konsensbasierte Empfehlung
EK	Im Rahmen der radikalen Zystektomie des Mannes soll ein Schnellschnitt des urethralen Absetzungsrandes durchgeführt werden.
	Konsens

7.36.	Konsensbasierte Empfehlung
EK	Auf eine Urethrektomie im Rahmen der Zystektomie kann verzichtet werden, wenn die Urethra im Absetzungsbereich nicht direkt vom Tumor befallen ist.
	Konsens

7.8. Transurethrale Resektion gefolgt von Radiochemotherapie als Alternative zur radikalen Zystektomie bei Patienten mit muskelinvasivem Urothelkarzinom der Harnblase

7.40.	Konsensbasiertes Statement
EK	Die multimodale, primär organerhaltende Therapie (TUR gefolgt von Radiochemotherapie, Salvage-Zystektomie bei invasivem Rest- oder Rezidivtumor stellt eine Alternative zur radikalen Zystektomie mit kurativer Zielsetzung für Patienten mit muskelinvasivem Urothelkarzinom dar.
	Konsens

7.41.	Konsensbasierte Empfehlung
EK	Die multimodale, primär organerhaltende Therapie sollte bei Patienten mit lokal begrenztem, muskelinvasivem Urothelkarzinom (cT2-4 cN0/NX M0) angeboten werden, die sich nicht für eine radikale Zystektomie eignen oder die eine Alternative zur radikalen Operation anstreben. Besonders geeignet sind solche mit frühen Tumoren (cT2N0) ohne Hydronephrose oder assoziiertem Carcinoma in situ, bei denen die initial transurethrale Resektion zur möglichst kompletten Tumorentfernung führt.
	Starker Konsens

7.9. Durchführung der TUR-B vor geplanter Radiotherapie/Radiochemotherapie (modifiziert)

7.42.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Bei Patienten mit muskelinvasivem Blasenkarzinom, die ein organerhaltendes Vorgehen wünschen, soll eine komplette transurethrale Tumorresektion angestrebt werden. Eine Perforation der Blasenwand soll aber vermieden werden.
Level of Evidence **3**	Primärrecherche: [796, 804-808]
	Starker Konsens

7.10. Etablierte Behandlungskonzepte und simultane Chemotherapeutika für die Radiotherapie/Radiochemotherapie beim muskelinvasiven Urothelkarzinom

7.45.	Konsensbasierte Empfehlung
EK	Im Rahmen eines blasenerhaltenden Vorgehens mit kurativer Intention soll eine simultane Radiochemotherapie durchgeführt werden.
	Konsens

7.46.	Konsensbasierte Empfehlung
EK	Die Radiosensibilisierung im Rahmen der simultanen Radiochemotherapie sollte mit einer Cisplatin-basierten Chemotherapie oder mit einer Kombination von 5-Fluorouracil und Mitomycin C erfolgen.
	Starker Konsens

9. Neoadjuvante/adjuvante Therapie

9.1.	Konsensbasierte Empfehlung
EK	Patienten mit muskelinvasivem Harnblasenkarzinom (≥T2) sollen über die Möglichkeiten einer neoadjuvanten oder adjuvanten

	Chemotherapie unter Berücksichtigung ihrer individuellen Situation aufgeklärt werden.
	Konsens

9.1. Neoadjuvante Chemotherapie

9.2.	Konsensbasierte Empfehlung
EK	Bei Patienten mit muskelinvasivem Harnblasenkarzinom (≥T2) soll das Therapiekonzept multidisziplinär vor Therapiebeginn festgelegt werden.
	Konsens

9.3.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Eine neoadjuvante Chemotherapie sollte 3-4 Zyklen einer cisplatinhaltigen Kombinationschemotherapie beinhalten.
Level of Evidence 1++ Quality of Evidence nach GRADE **moderat**	Quellen: [881]

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

9.2. Adjuvante Chemotherapie

9.5.	Konsensbasierte Empfehlung
EK	Bei Patienten mit organüberschreitendem, muskelinvasiven Harnblasenkarzinom (≥pT3) und/oder pN+ soll eine multidisziplinäre Abstimmung zur weiteren Therapieplanung erfolgen.
	Konsens

9.6.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Die adjuvante Kombinationschemotherapie (3-4 Zyklen) nach Zystektomie soll cisplatinbasiert sein.
Level of Evidence **1++** Quality of Evidence nach GRADE **moderat**	Quellen: [881]
	Konsens

9.4. Postoperative Radiotherapie / Radiochemotherapie nach radikaler Zystektomie

9.8	Evidenzbasiertes Statement
Level of Evidence **1-**	Es besteht keine Indikation zur adjuvanten Radiotherapie / Radiochemotherapie nach radikaler Zystektomie mit R0-Resektion.
	Literatur: [917,918] Starker Konsens

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Gakis G et al., 2020 [3].

European Association of Urology (EAU)

EAU guidelines on primary urethral carcinoma

siehe auch: Gakis G et al., 2020 [2].

Zielsetzung

The aim of these guidelines is to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma. 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.

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Verfahren zur Konsensfindung nicht beschrieben, externes Begutachtungsverfahren (vor Veröffentlichung im Jahr 2015) dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert[1].

Recherche/Suchzeitraum:

An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the prior search, covering a time frame between June 30th, 2018 and July 3rd, 2019. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

LoE/GoR

[…] the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence (⇨ Anhang Tabelle 5).

The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between diserable and undiserable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

[1] European Association of Urology (EAU). EAU Handbook for Guidelines Development [online]. Arnhem (NED): EAU; 2017. [Zugriff: 25.08.2020]. URL: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Production-Handbook-July-17.pdf.

Empfehlungen
(⇨ Anhang Abbildung 1)

7. Disease management

7.1. Treatment of localised primary urethral carcinoma in males

7.1.1. Summary of evidence and guidelines for the treatment of localised primary urethral carcinoma in males

Summary of evidence	LE
In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence.	3

Recommendations	LE	Strength rating
Offer distal urethrectomy as an alternative to penile amputation in localised distal urethral tumours, if surgical margins are negative.	3	Weak
Ensure complete circumferential assessment of the proximal urethral margin if penis-preserving surgery is intended.	3	Strong

Referenzen

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7.2. Treatment of localised primary urethral carcinoma in females

7.2.3. Summary of evidence and guidelines for the treatment of localised primary urethral carcinoma in females

Summary of evidence	LE
In distal tumours, urethra-sparing surgery and local RT represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

Recommendations	LE	Strength rating
Offer urethra-sparing surgery, as an alternative to primary urethrectomy, to women with distal urethral tumours, if negative surgical margins can be achieved intraoperatively.	3	Weak
Offer local radiotherapy, as an alternative to urethral surgery, to women with localized urethral tumours, but discuss local toxicity.	3	Weak

Referenzen

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7.3. Multimodal treatment in locally advanced urethral carcinoma in both genders

7.3.6. Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both genders

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

Recommendations	LE	Strength rating
Discuss treatment of patients with locally advanced urethral carcinoma within a multidisciplinary team of urologists, radio-oncologists and oncologists.	3	Strong
In locally advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	3	Weak
In locally advanced squamous cell carcinoma of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	3	Weak
Offer salvage surgery or RCT to patients with urethral recurrence after primary treatment.	3	Weak

Referenzen

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Rouprêt M et al., 2020 [13].

European Association of Urology (EAU)

EAU guidelines on upper urinary tract urothelial carcinoma

siehe auch: Rouprêt M et al., 2020 [12].

Zielsetzung

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of upper urinary tract urothelial carcinoma (UTUC).

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Verfahren zur Konsensfindung nicht beschrieben, externes Begutachtungsverfahren (vor Veröffentlichung im Jahr 2016) dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert[2].

Recherche/Suchzeitraum

The search was restricted to articles published between June 20th (Cochrane)/June 26th 2018 (Embase) and May 31st 2019. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

LoE/GoR

[…] the overall quality of the evidence which exists for the recommendation references used in this text are graded according to the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence. For the Disease Management […] chapters a system modified from the 2009 CEBM LEs has been used.

The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between diserable and undiserable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

[2] European Association of Urology (EAU). EAU Handbook for Guidelines Development [online]. Arnhem (NED): EAU; 2017. [Zugriff: 25.08.2020]. URL: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Production-Handbook-July-17.pdf.

Empfehlungen

(⇨ Anhang Abbildung 2)

7.1.2. Management of high-risk non-metastatic UTUC

7.1.6. Summary of evidence and guidelines 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.	2
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Peri-operative chemotherapy may improve survival.	3
Single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.	1

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
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer peri-operative chemotherapy to patients with muscle-invasive UTUC.	Weak
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

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Witjes JA et al., 2020 [15].

European Association of Urology (EAU)

EAU guidelines on muscle-invasive and metastatic bladder cancer

siehe auch: Witjes JA et al., 2020 [14].

Zielsetzung

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Formale Konsensusprozesse und externes Begutachtungsverfahren (nach Veröffentlichung im Jahr 2018 durch Patientinnen und Patienten) dargelegt,

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert[3].

Recherche/Suchzeitraum

Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 1st, 2018 and May 10th, 2019.

LoE/GoR

[…] the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between diserable and undiserable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Empfehlungen
(⇨ Anhang Abbildung 3)

7.2. Neoadjuvant therapy

7.2.5 Summary of evidence and guidelines for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (8% at five years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently immunotherapy with checkpoint inhibitors as monotherapy, or in different combinations, is being tested in phase II and III trials. Initial results are promising.	
There are still no tools available to select patients who have a higher probability of benefitting from NAC. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.	
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients with a clinical trial setting.	Strong

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7.3. Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

7.3.3. Summary of evidence and guidelines for pre- and post-operative radiotherapy

Summary of evidence	LE
No data exist to support that pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer (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 high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after radical cystectomy.	3

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy with urinary diversion is planned.	Strong

7.3.4. EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).

* Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).

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7.4. Radical surgery (modifiziert)

7.4.10. Summary of evidence and guidelines for radical cystectomy

Summary of evidence	LE
For MIBC, radical cystectomy (RC) is the curative treatment of choice.	3
Higher hospital volume likely improves quality of care and reduction in peri-operative mortality and morbidity.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended lymph node dissection (LND) (vs. standard or limited LND) improves survival after RC.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution […].	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open RC.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

Recommendations	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Offer RC in T2-T4a, N0M0, and high-risk non-muscle-invasive BC.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

7.4.11. EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral healthcare professional such as a specialist nurse.
Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.

* Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).

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7.6. Bladder-sparing treatments for localised disease

7.6.1.1. Guideline for transurethral resection of bladder tumour

Recommendations	Strength rating
Do not offer transurethral resection of bladder tumour alone as curative treatment option as most patients will not benefit.	Strong

7.6.1.2. EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma in situ.
An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).

* Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).

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7.6.2. External beam radiotherapy

7.6.2.1. Summary of evidence and guideline for external beam radiotherapy

Summary of evidence	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or as part of a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendations	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong

7.6.2.2. EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*

Consensus statement
Radiotherapy alone (single block) is not the preferred radiotherapeutic schedule.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended.

* Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).

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7.7. Adjuvant therapy

7.7.3. Guidelines for adjuvant therapy

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
Only offer immunotherapy with a checkpoint inhibitor in a clinical trial setting.	Strong

7.7.4. EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer*

Consensus statement
When adjuvant chemotherapy is offered, patients should be selected based on the result of PLND (if done).

* Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).

Referenzen

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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

Zielsetzung

This multidisciplinary, evidence-based guideline for clinically nonmetastatic muscle-invasive bladder cancer focuses on the evaluation, treatment and surveillance of muscle-invasive bladder cancer guided toward curative intent.

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Formale Konsensusprozesse dargelegt, externes Begutachtungsverfahren erwähnt, aber nicht detailliert beschrieben,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum

A research librarian […] searched in Ovid MEDLINE® (January 1990 to October 2014), the Cochrane Central Register of Controlled Trials (through September 2014), the Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessments (through Third Quarter 2014), the National Health Sciences Economic Evaluation Database (through Third Quarter 2014), and the Database of Abstracts of Reviews of Effects (through Third Quarter 2014) […]. A supplemental search of Ovid Medline and Cochrane Central Register of Controlled Trials was conducted to capture additional published literature through February 2, 2016.

LoE

Tabelle 4: Determination of Evidence Strength

Grade A	Well-conducted and highly-generalizable 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

[…] Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.

GoR ⇨ Anhang Tabelle 6

Empfehlungen

Treatment

Neoadjuvant/Adjuvant Chemotherapy

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

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. (Expert Opinion)

Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from NAC. (Expert Opinion)

Eligible patients who have not received cisplatin-based NAC and have non-organ confined (pT3/T4 and/or N+) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy. (Moderate Recommendation, Evidence Level: Grade C)

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Radical Cystectomy

Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) MIBC. (Strong Recommendation, Evidence Level: Grade B)

When performing a standard radical cystectomy, clinicians should remove the bladder, prostate and seminal vesicles in males, and should remove the bladder, uterus, fallopian tubes, ovaries and anterior vaginal wall in females. (Clinical Principle)

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)

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Pelvic Lymphadenectomy

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

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

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Bladder Preserving Approaches

For patients with newly diagnosed non-metastatic MIBC who desire to retain their bladder and for those with significant comorbidities for whom radical cystectomy is not a treatment option, clinicians should offer bladder preserving therapy when clinically appropriate. (Clinical Principle)

In patients under consideration for bladder preserving therapy, maximal debulking TURBT and assessment of multifocal disease/carcinoma in situ should be performed. (Strong Recommendation, Evidence Level: Grade C)

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Maximal TURBT and Partial Cystectomy

Patients with MIBC who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal TURBT as primary curative therapy. (Moderate Recommendation, Evidence Level: Grade C)

Referenzen

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Primary Radiation Therapy

For patients with MIBC, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation, Evidence Level: Grade C)

Referenzen

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Multi-modal Bladder Preserving Therapy

For patients with MIBC who have elected multimodal bladder preserving therapy, clinicians should offer maximal TURBT, chemotherapy combined with external beam radiation therapy and planned cystoscopic reevaluation. (Strong Recommendation, Evidence Level: Grade B)

Radiation sensitizing chemotherapy regimens should include cisplatin or 5-fluorouracil and mitomycin C. (Strong Recommendation, Evidence Level: Grade B)

Following completion of bladder preserving therapy, the clinician should perform regular surveillance with CT scans, cystoscopy and urine cytology. (Strong Recommendation, Evidence Level: Grade C)

Referenzen

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National Institute for Health and Care Excellence (NICE), 2015 [10].

Bladder cancer: diagnosis and management

siehe auch: National Institute for Health and Care Excellence (NICE), 2019 [11].

Zielsetzung

This guideline does not include recommendations covering every detail of the diagnosis and treatment of bladder cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of of high quality evidence; or (iv) where NICE guidelines are likely to have most impact.

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 following databases were included in the literature search: The Cochrane Library, Medline and Premedline 1946 onwards, Excerpta Medica (Embase) 1974 onwards, Web of Science [specifically Science Citation Index Expanded (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards], Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards, Allied & Complementary Medicine (AMED) 1985 onwards, Psycinfo 1806 onwards. [...] June 2014 should be considered the starting point for searching for new evidence.

LoE/GoR

Tabelle 5: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made.

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm
- 'Do not offer' – the intervention will not be of benefit for most patients
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have an intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Sonstige methodische Hinweise

NICE's surveillance team checked whether recommendations in bladder cancer: diagnosis and management (NICE guideline NG2) remain up to date [11]. After considering all evidence and other intelligence and the impact on current recommendations, [...] decided that no update is necessary.

Empfehlungen

5 Managing muscle-invasive bladder cancer

5.1 The role of chemotherapy in treatment of organ confined muscle-invasive bladder cancer

5.1.1 Neoadjuvant chemotherapy

Which patients with bladder cancer should be offered neoadjuvant chemotherapy?

Offer neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable. Ensure that they have an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

Referenzen

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5.1.2 Adjuvant chemotherapy

Which patients with bladder cancer should be offered adjuvant chemotherapy?

Consider adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy). Ensure that the person has an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer.

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5.2 Treatment of organ confined muscle-invasive bladder cancer

5.2.1 Radical cystectomy versus radical radiotherapy

In which patient groups with muscle invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and in which groups would radical radiotherapy produce better outcomes?

Ensure that a specialist urology multidisciplinary team reviews all cases of muscle-invasive bladder cancer, including adenocarcinoma, squamous cell carcinoma and neuroendocrine carcinoma, and that the review includes histopathology, imaging and discussion of treatment options.

Offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the

choice is based on a full discussion between the person and a urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Include in the discussion:

- the prognosis with or without treatment
- the limited evidence about whether surgery or radiotherapy with a radiosensitiser is the most effective cancer treatment
- the benefits and risks of surgery and radiotherapy with a radiosensitiser, including the impact on sexual and bowel function and the risk of death as a result of the treatment.

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5.2.2 Optimal radical radiotherapy regimen

What is the optimal radiotherapy regimen (including chemoradiotherapy) for patients offered radical radiotherapy for bladder cancer?

Use a radiosensitiser (such as mitomycin in combination with fluorouracil [5-FU][a] or carbogen in combination with nicotinamide[b]) when giving radical radiotherapy (for example, 64 Gy in 32 fractions over 6.5 weeks or 55 Gy in 20 fractions over 4 weeks) for muscle-invasive urothelial bladder cancer.

[a] At the time of publication (February 2015), mitomycin in combination with fluorouracil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented […].

[b] Although this use is common in UK clinical practice, at the time of publication (February 2015), carbogen in combination with nicotinamide did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. […].

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 8 of 12, August 2020) am 04.08.2020

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
2	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
3	(urotheli* OR transitional OR bladder):ti,ab,kw
4	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma*):ti,ab,kw
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from Aug 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 04.08.2020

#	Suchfrage
1	((("carcinoma, transitional cell/drug therapy"[mh]) OR "carcinoma, transitional cell/radiotherapy"[mh]) OR "carcinoma, transitional cell/surgery"[mh]) OR "carcinoma, transitional cell/therapy"[mh]
2	((("urinary bladder neoplasms/drug therapy"[mh]) OR "urinary bladder neoplasms/radiotherapy"[mh]) OR "urinary bladder neoplasms/surgery"[mh]) OR "urinary bladder neoplasms/therapy"[mh]
3	((urotheli*[tiab]) OR transitional[tiab]) OR bladder[tiab]
4	((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR cancer*[tiab]
5	(#3) AND #4
6	(#5) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
7	#1 OR #2 OR #6
8	(#7) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR

	Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
9	(#8) AND ("2015/08/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 04.08.2020

#	**Suchfrage**
1	"carcinoma, transitional cell"[MeSH Major Topic]
2	"urinary bladder neoplasms"[MeSH Major Topic]
3	((urotheli*[ti]) OR transitional[ti]) OR bladder[ti]
4	((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR cancer*[tiab]
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2015/08/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Tabelle 1: Characteristics of eligible studies (Kim DK et al., 2019 [7].)

Trial	Year	Country	ACH regimens	ACH dose (mg/m²)	No. of planned cycles	Recruitment period	Pathologic stage	Total patients (ITT)		Median follow-up (IQR)
								Control (RC only)	Treatment (RC + ACH)	
Skinner et al. [26]	1991	USA	CAP	C 100, A 60, P 600	4	1980-1988	T3-4, Nany, M0	52	50	Overall: 160 mo
Freiha et al. [14]	1996	USA	CMV	C 100, M 30, V 4	4	1986-1993	T3b-4, Nany, M0	28	27	Overall: 62 mo (26-94)
Lehmann et al. [15]	2006	Germany	MVAC or MVEC	M 30, V 3, A 40, C 70 M 30, V 3, E 45, C 70	3	1987-1990	T3-4a, Nany, M0	23	26	Control: 57 mo Treatment: 54 mo
Sternberg et al. [18]	2015	Europe and Canada	MVAC or GC	M 30, V 3, A 30, C 70 G 1000, C 70	4	2002-2008	T3-4, Nany, M0	143	141	Control: 7.2 yr (5.6-8.7) Treatment: 7 yr (5.2-8.7)

Tabelle 2: Treatment characteristics of included studies (Kim DK et al., 2019 [7].)

Trial	Median age, range (y)	Interval between RC and ACH	Number of surgeon	Surgical type of RC	ACH regimens	ACH dose (mg/m²)	No. of planned cycles
Skinner et al. [26]	Control: 62, 30-73 ACH: 61, 22-75	6 wk	3	Open	CAP	C 100, A 60, P 600	4
Freiha et al. [14]	Control: 64 (mean), 49-78 ACH: 59 (mean), 40-76	6 wk	NA	NA	CMV	C 100, M 30, V 4	4
Lehmann et al. [15]	Control: 62.7 ACH: 58.8	NA	NA	NA	MVAC or MVEC	M 30, V 3, A 40, C 70 M 30, V 3, E 45, C 70	3
Sternberg et al. [18]	Control: 61, 37-76 ACH: 61, 35-82	90 d	NA	NA	MVAC or GC	M 30, V 3, A 30, C 70 G 1000, C 70	4

Tabelle 3: Study characteristics of the eligible studies (Kim HS et al., 2017 [8].)

Study	Year	Country	Recruitment period	Total patients (ITT)	Median age, range (years)	No. of gender (male/female)	Quality scale
Skinner [17]	1991	USA	1980-1988	Control: 52 ACH: 50	Control: 62, 30-73 ACH: 61, 22-75	Control: 35/12 ACH: 34/10	6
Studer [18]	1994	Switzerland	1984-1989	Control: 45 ACH: 46	Control: 61, 41-65 ACH: 64, 54-73	Control: 27/13 ACH: 30/7	6
Freiha [9]	1996	USA	1986-1993	Control: 28 ACH: 27	Control: 64 (mean), 49-78 ACH: 59 (mean), 40-76	Control: 23/2 ACH: 22/3	6
Bono [19]	1997	Italy	1984-1987	Control: 47 ACH: 43	NA	NA	4
Otto [20]	2001	Germany	1993-1999	Control: 53 ACH: 55	NA	NA	4
Lehmann [11]	2005	Germany	1994-2000	CM: 163 MVEC: 164	CM: 60.2 MVEC: 60.7	CM: 123/40 MVEC: 134/30	6
Lehmann [12]	2006	Germany	1987-1990	Control: 23 ACH: 26	Control: 62.7 ACH: 58.8	Control: 19/4 ACH: 22/4	6
Paz-Ares [21]	2010	Spain	2000-2007	Control: 74 ACH: 68	63 overall	NA	5
Stadler [13]	2011	USA	1997-2006	Control: 56 ACH: 58	NA	Control: 47/9 ACH: 51/7	5
Cognetti [14]	2012	Italy	2001-2007	Control: 92 ACH: 102	Control: 63, 36-75 ACH: 64, 38-75	Control: 75/11 ACH: 90/7	6
Sternberg [15]	2015	Europe and Canada	2002-2008	Control: 143 ACH: 141	Control: 61, 37-76 ACH: 61, 35-82	Control: 112/27 ACH: 114/27	6

Tabelle 4: Treatment characteristics of the eligible studies (Kim HS et al., 2017 [8].)

Study	Pathologic stage	Chemotherapy regimens	Chemotherapy dosage (mg/m²)	No. of planned cycles	Median follow-up, range (months)
Skinner [17]	T3-4, Nany, M0	CAP	C 100, A 60, P 600	4	168 overall
Studer [18]	T1-4a, M0	C	C 90	3	69 overall
Freiha [9]	T3b-4, Nany, M0	CMV	C 100, M 30, V 4	4	62, 26-94 overall
Bono [19]	T2-4a, N0, M0	CM	C 70, M 40	4	69 overall
Otto [20]	T3, N1-2, M0	MVEC	M 30, V 3, E 45, C 70	3	3.62 yr overall
Lehmann [11]	T3-4a, Nany, M0	CM vs MVEC	C 70, M 40 M 30, V 3, E 45, C 70	3	42 overall
Lehmann [12]	T3-4a, Nany, M0	MVAC or MVEC	M 30, V 3, A 40, C 70 M 30, V 3, E 45, C 70	3	Control: 57 ACH: 54
Paz-Ares [21]	T3-4, Nany, M0	GCP	G 1000, C 70, P 80	4	30, 1-95 overall
Stadler [13]	T1-2, N0, M0	MVAC	NA	3	5.4 yr overall
Cognetti [14]	T2-4, Nany, M0	GC	G 1000, C 70	4	35, 15-57 (IQR) overall
Sternberg [15]	T3-4, Nany, M0	(high dose) MVAC or GC	M 30, V 3, A 30, C 70 G 1000, C 70	4	Control: 7.2 yr, 5.6-8.7 yr (IQR) ACH: 7 yr, 5.2-8.7 yr (IQR)

Tabelle 5: Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009) (Gakis G et al., 2020 [3].)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Referenz

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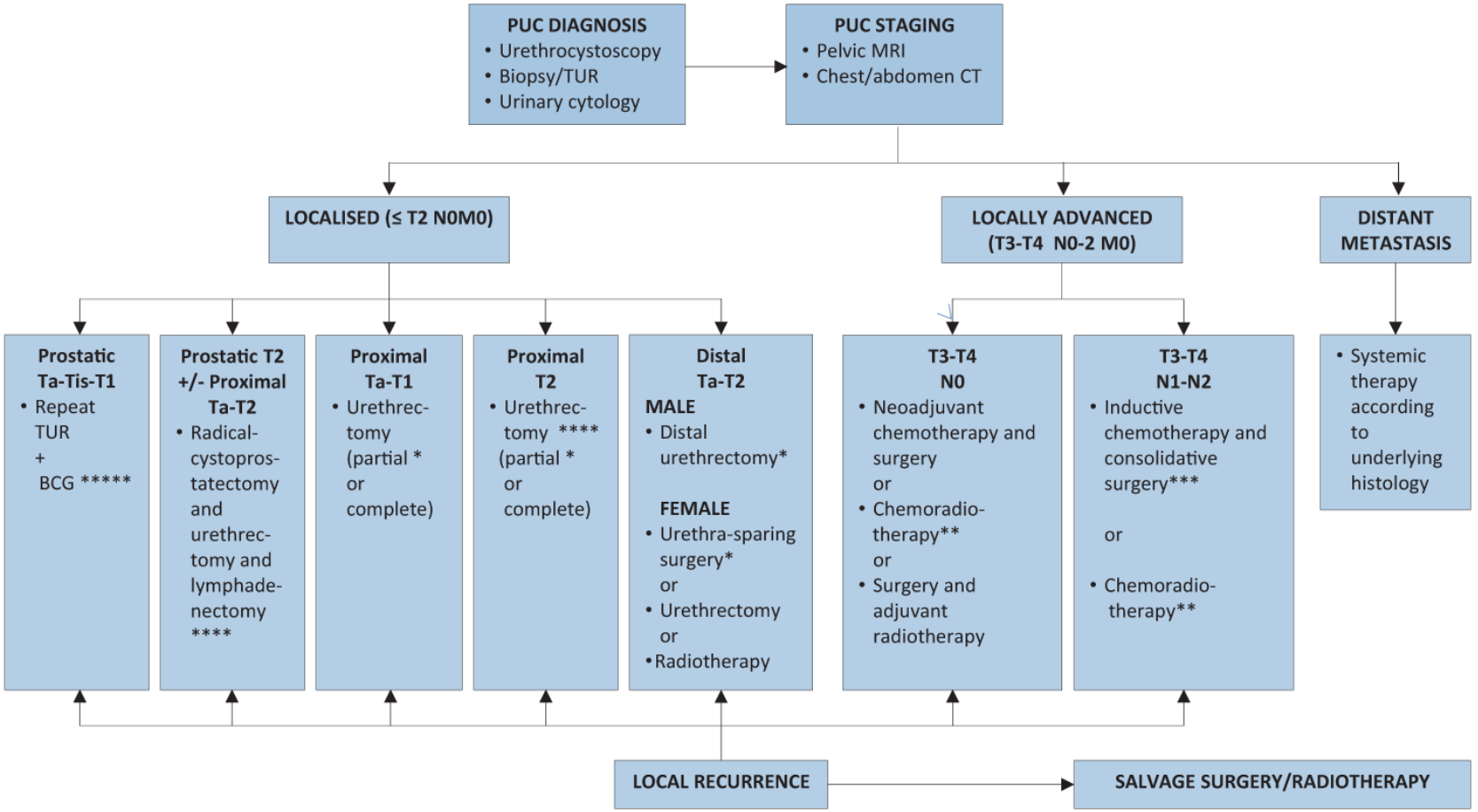
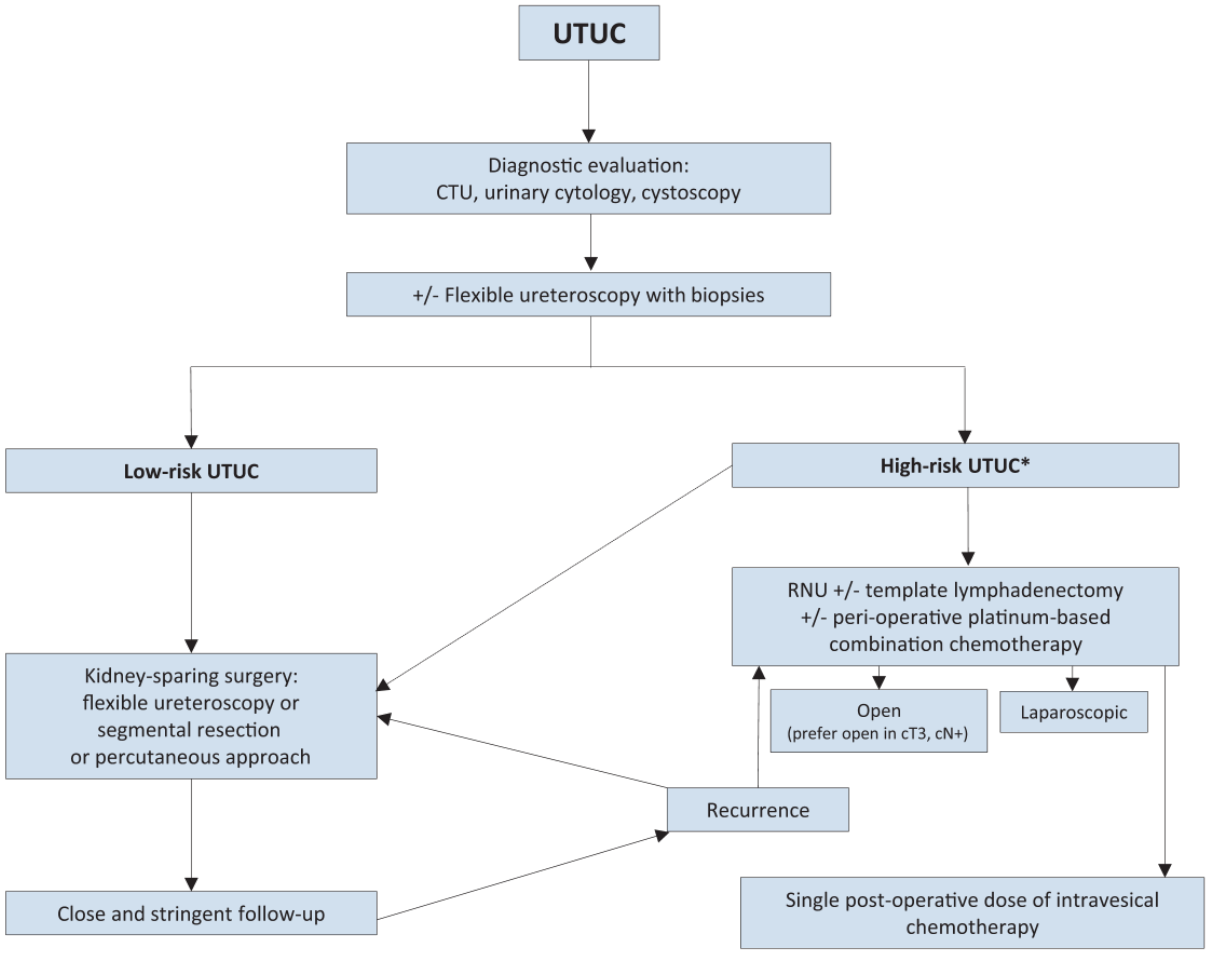
Abbildung 1: Management of primary urethal carcinoma (Gakis G et al., 2020 [3].)



* Ensure complete circumferential assessment if penis-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.

Abbildung 2: Proposed flowchart for the management of UTUC (Rouprêt M et al., 2020 [13].)



* In patients with solitary kidney, consider a more conservative approach.

Abbildung 3: Flow chart for the management of T2-T4a N0M0 urothelial bladder carcinoma (Witjes JA et al., 2020 [15].)

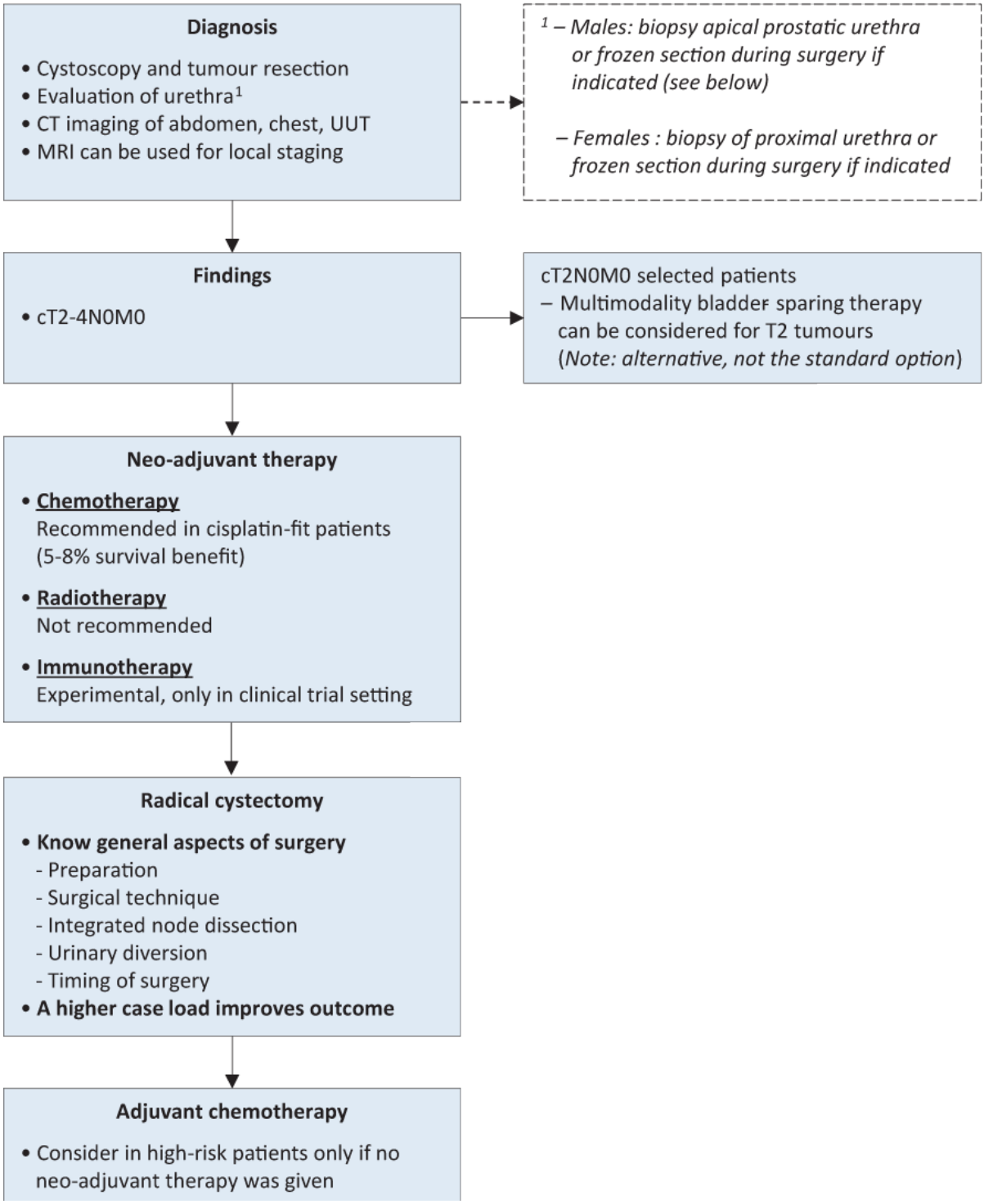


Tabelle 6: AUA nomenclature linking statement type to level of certainty, magnitude of benefit or risk/burden, and body of evidence strength (Chang SS et al., 2017 [1].)

	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 (No apparent net benefit or harm)	• Benefits = Risks/Burdens • Best action depends on individual patient circumstances • Future research 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 • 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 is no evidence.		

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

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Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

Bei Erwachsenen zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei *Erwachsenen zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion*? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Die radikale Zystektomie gilt als Standardtherapie des **muskelinvasiven Urothelkarzinoms der Harnblase**. Während nach vollständiger Resektion organbegrenzte (≤ pT2b pN0 cM0) Tumoren hohe Heilungsraten aufweisen, sind organüberschreitende Tumoren mit bzw. ohne begleitende Lymphknotenmetastasen mit einem hohen Rezidivrisiko von bis zu 80% vergesellschaftet. Insofern soll im Stadium ≥pT3 und/oder pN+ eine multidisziplinäre Abstimmung zur weiteren Therapieplanung im Hinblick auf eine evtl. adjuvante Chemotherapie erfolgen. In dieser klinischen Situation weist das beschriebene therapeutische Vorgehen einen Gesamtüberlebensvorteil im Vergleich zur alleinigen Zystektomie auf. Es kommt in einem systematischen Review zur Reduktion der Gesamtmortalität von 26% (95%CI 1-45%) während einer medianen Nachbeobachtungszeit von 2,5 bis 7,5 Jahren [1]. Hierbei wurden neun Arbeiten und Daten von 945 Patienten einbezogen. Unter Einbeziehung der nach der Arbeit von Leow publizierten EORTC Studie zeigt sich in der Analyse aller verfügbaren Studien unter Einbeziehung von nun 1229 Patienten keine Änderung für die Gesamtmortalität [2].

Eine adjuvante Polychemotherapie des **Urothelkarzinoms der Harnblase** ist immer Cisplatin-basiert, so dass nur Patienten mit guter Nierenfunktion (GFR > 60 ml/min/1.73 qmKO) und mit gutem Allgemeinzustand (ECOG 0-1) in Frage kommen. In Deutschland gilt als De Facto Standard Gemcitabin + Cisplatin, üblich ist die Verabreichung von 3-4 Zyklen.

Bei **muskelinvasiven Urothelkarzinomen des oberen Harntraktes** ist die Nephroureterektomie der Therapiestandard; für Tumoren des distalen Ureters kommt auch eine Ureterteilresektion mit Blasenmanschette und Ureteroneozystostomie in Betracht. Auch hier weisen Tumoren im Stadium ≥pT3 und/oder pN+ ein hohes Rezidivrisiko auf. Eine aktuelle randomisierte Phase 3 Studie zeigt hier einen signifikanten Vorteil im krankheitsfreien Überleben für eine adjuvante Chemotherapie mit entweder Gemcitabin/Cisplatin oder bei einer GFR <50 ml/Min. Gemcitabin/Carboplatin [3]. Die Ergebnisse dieser Studie haben bisher keinen Eingang in die aktuelle Leitlinie der EAU gefunden [4, 5](S3-Leitlinie im Antragsstadium).

In der „Versorgungspraxis“ werden Cisplatin-geeignete Patienten mit hohem Rezidivrisiko nach kurativ intendierter radikaler Zystektomie und Lymphknotenmetastasen häufig 3-4 Zyklen Gemcitabin/Cisplatin

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erhalten. Eine Behandlung von Patienten mit organ-überschreitenden Tumoren ohne Lymphknotenmetastasen (≥pT3 pN0 cM0) ist eher selten. Die Situation bei Tumoren des oberen Harntraktes ist vergleichbar, eine adjuvante Chemotherapie mit Gemcitabin/Carboplatin wie in der POUT-Studie ist aktuell noch die Ausnahme.

Insgesamt gibt es einen beträchtlichen Anteil an Patienten, die nach kurativ intendierter Operation eine adjuvante Polychemotherapie ablehnen oder aufgrund anderer Faktoren (Multimorbidität, eingeschränkte Nierenfunktion etc.) nicht erhalten.

Tabelle 1: Vorschlag zur ZVT

Indikation	Vorschlag ZVT
Erwachsene zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion, **Cisplatin ungeeignet**	**Tumornachsorge, Therapie bei Rezidiv**
Erwachsene zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko **aufgrund von Lymphknotenmetastasen (pN+)** nach vollständiger Resektion, **Cisplatin geeignet**	**Gemcitabin/Cisplatin, 3-4 Zyklen**
Erwachsene zur adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko **aufgrund von organüberschreitendem Wachstum (≥pT3 pN0 cM0)** nach vollständiger Resektion, **Cisplatin geeignet**	**Gemcitabin/Cisplatin, 3-4 Zyklen** **oder** **Tumornachsorge, Therapie bei Rezidiv**

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen *bei der adjuvanten Behandlung des muskelinvasiven Urothelkarzinoms mit hohem Rezidivrisiko nach vollständiger Resektion bei*

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***Erwachsenen*, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Zum aktuellen Zeitpunkt können keine klinischen oder molekularen Marker identifiziert werden, die es im klinischen Alltag zuverlässig ermöglichen, diejenigen Patienten zu ermitteln, die von einer adjuvanten Chemotherapie profitieren. Ebenso stehen keine entsprechenden Marker zur Verfügung, die ein Versagen einer adjuvanten Chemotherapie mit ausreichender Sicherheit vorhersagen.

Entsprechend der aktuellen Empfehlung zur Therapie eines metastasierten Urothelkarzinoms sollten auch Patienten in der adjuvanten Situation mit zumindest einem der folgenden 5 Parameter nicht mit Cisplatin-basierter Chemotherapie behandelt werden [5, 6]

- WHO oder ECOG Performance Status (PS) von ≥ 2 oder Karnofsky PS ≤ 70
- Hörverlust in der Audiometrie (≥ Grad 2 CTCAE Version 4)
- Periphere Neuropathie (≥ Grad 2 CTCAE Version 4)
- NYHA Klasse > III Herzinsuffizienz
- Kreatinin Clearance (gerechnet oder gemessen) ≤ 60 ml/min (bei reduzierter Kreatinin Clearance von 40-60 ml/min kann eine Dosisanpassung von Cisplatin stattfinden; dann im adjuvanten Setting besonders kritische Abwägung von Nutzen und Risiko).

Cisplatin-ungeeignete Patienten mit hohem Rezidivrisiko werden gemäß Leitlinienempfehlung engmaschig nachgesorgt und im Falle eines Tumorrezidivs behandelt.

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