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Urothelial Carcinoma (Bladder Cancer)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

SSMO SSOM SGMO

SGH+SSH

Publisher

DGHO Deutsche Gesellschaft für Hämatologie und
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www.onkopedia-guidelines.info

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Urothelial Carcinoma (Bladder Cancer)

ICD-10: C67.-
Date of document: November 2024

Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Urothelial carcinoma is one of the most common malignant tumors. Men are affected three times more often than women, and the average age of onset is over 70 years. Bladder carcinomas account for over 90% of all urothelial carcinomas. A distinction is made between urothelial carcinomas of the lower and upper urinary tract. The most common form of manifestation is superficial, non-muscle-invasive urothelial carcinoma of the bladder. Local recurrences and the development of a more advanced stage indicate a higher-risk situation. In muscle-invasive localized urothelial carcinoma of the urinary bladder, treatment is multimodal with optimal, patient-oriented cystectomy and the option of perioperative systemic therapy or trimodal therapy. Postoperative immunotherapy with checkpoint inhibitors is a new option for resectable muscle-invasive urothelial carcinomas.

Systemic tumor therapy is indicated for metastatic disease. The current standard of systemic treatment is the option of immunotherapy with a checkpoint inhibitor and antibody-drug conjugate in the first line.

Urothelial carcinomas of the upper urinary tract (UTUC) are discussed separately due to their special therapeutic features.

Non-urothelial bladder carcinomas are not covered by this guideline.

2 Basics

2.1 Definition and basic information

Carcinoma of the urinary bladder is a common tumor in elderly people. Histologically, urothelial carcinoma predominates. Squamous cell carcinomas of the urinary bladder are rarities in Central Europe. They occur more frequently in regions with higher incidences of schistosomiasis and are not addressed in this guideline.

2.2 Epidemiology

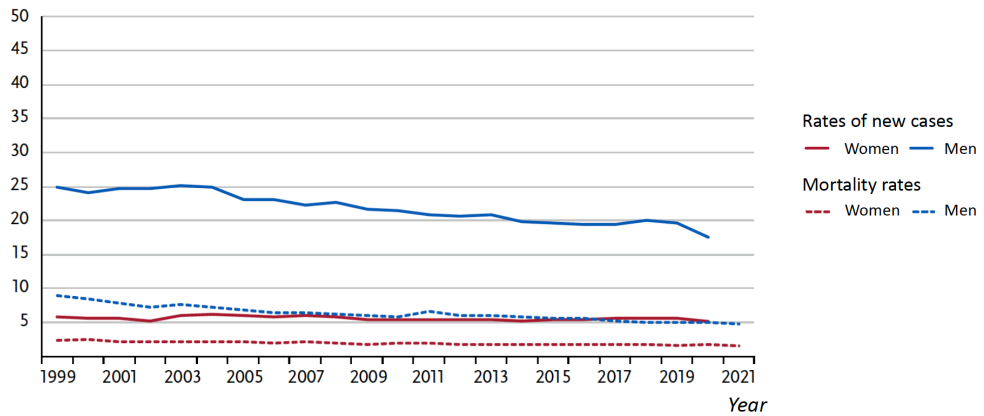
In Germany, around 32,000 people are newly diagnosed with urothelial carcinoma of the urinary bladder every year, with around three quarters of all new cases occurring in men. This makes bladder cancer the fourth most common tumor in men and the ninth most common in women [1]. When recording urinary bladder tumors in the cancer registries, in contrast to other localizations, the first occurring urinary bladder tumor is counted as incidence-relevant, regardless of the behavioral pattern (in situ, malignant). Subsequent changes in behavior have not yet been documented.

Table 1: Overview of the most important epidemiological measures for urinary bladder cancer (ICD-10 C67) for Germany

Incidence	2019		2020			
	Women	Men	Women	Men		
New cases[5]	4,930 (7,790)	13,690 (24,410)	4,630 (7,540)	12,500 (23,270)		
Crude rate of new cases[1,5]	11.7 (18.5)	33.4 (59.5)	11.0 (17.9)	30.5 (56.7)		
Standardized new disease rate[1,2,5]	5.6 (9.3)	19.6 (35.4)	5.2 (8.9)	17.6 (33.2)		
Middle age at onset[3,5]	77 (75)	75 (74)	77 (76)	75 (74)		
Mortality	**2019**		**2020**		**2021**	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
Deaths	1,814	3,824	1,935	3,942	1,852	3,891
Crude mortality rate[1]	4.3	9.3	4.6	9.6	4.4	9.5
Standardized mortality rate[1,2]	1.6	5	1.7	4.9	1.7	4.8
Age at death[3]	82	80	83	81	82	81
Prevalence and survival rates	**5 years**		**10 years**		**25 years**	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
Prevalence	12,200	40,300	19,100	63,800	30,400	97,500
Absolute survival rate (2019-2020)[4]	37 (31-48)	45 (42-54)	27 (23-32)	29 (26-38)		
Relative survival rate (2019-2020)[4]	46 (38-58)	58 (53-67)	43 (35-50)	50 (44-62)		

Legend:
[1] per 100,000 persons, in percent;
[2] age-standardized by age of the European population;
[3] median;
[4] in percent (lowest and highest value of the German federal states in parenthesis);
[5] values in parenthesis: incl. in situ tumors and neoplasms of uncertain or unknown behavior (D09.0, D41.4)
Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c67_harnblase

Figure 1: Rates of new cases and mortality (per 100,000, old European standard) in Germany over time; ICD-10 C67, Germany 1999-2020/2021



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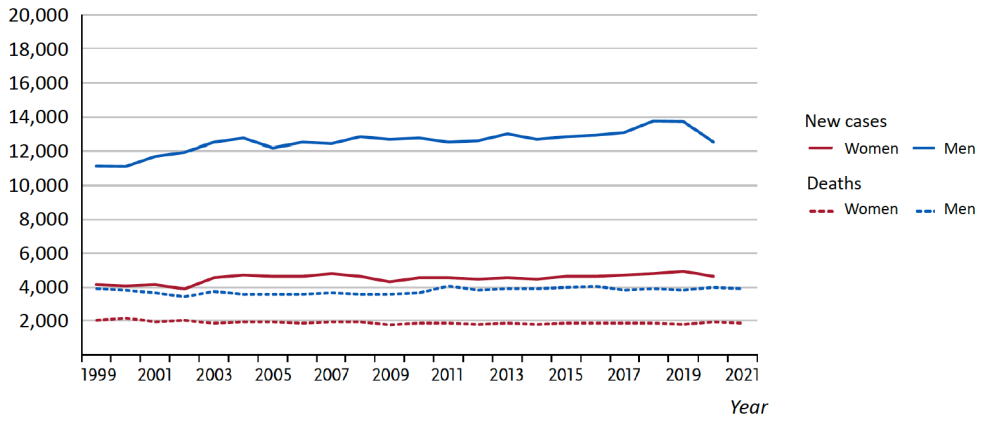
Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c67_harnblase

Both the incidence rate and the mortality rate for men are declining significantly (Figure 1). Nevertheless, the number of cases is increasing due to demographic changes (Figure 2). In women, constant case numbers as well as incidence and mortality rates have been observed for some time.

Figure 2: Absolute number of new cases and deaths by gender, bladder cancer (ICD-10 C67), Germany 1999-2020/2021



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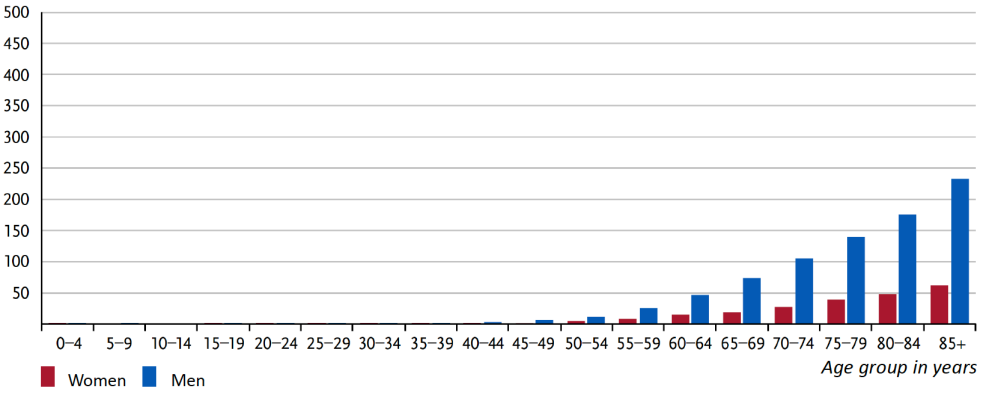
The median age at onset in Germany is 77 years for women and 75 years for men. The higher incidence in men is evident in all age groups, although the divergence between the sexes increases considerably with age, see Figure 3.

Figure 3: Age-specific new case rates by gender per 100,000 for urinary bladder cancer (CD-10 C67), Germany 2019-2020



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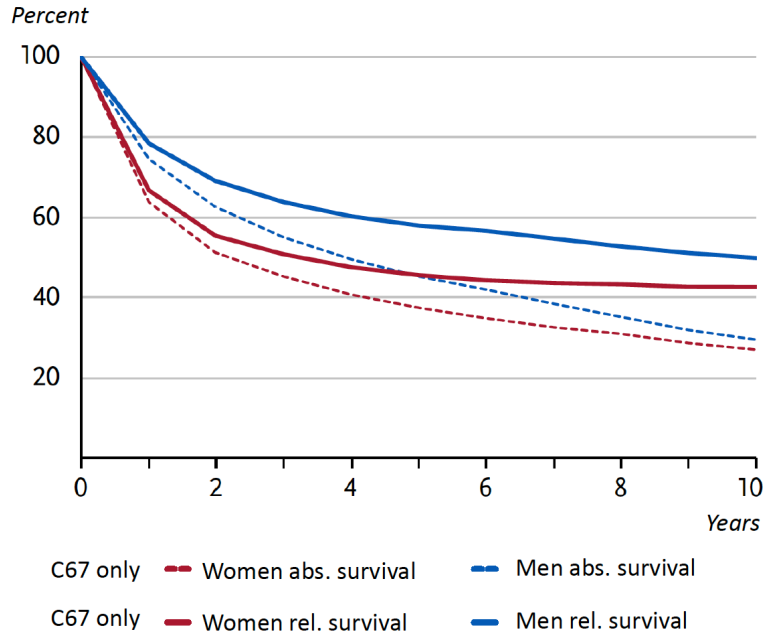
Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c67_harnblase

The absolute 5-year survival rate of patients with malignant neoplasms of the urinary bladder (ICD-10 C67) is 45% (men) and 37% (women), with less than 30% of patients alive 10 years after diagnosis. Due to the relatively high age at onset and thus also a high mortality rate in the general population, the difference between absolute and relative survival is considerable. The relative 5-year survival rate is 58% (men) and 46% (women) (Figure 4). When looking at the relative 5-year survival rates by tumor stage, the expected picture of a significantly better prognosis in *UICC* stage I (> 70%) and poor prognosis in stage IV (< 15%) arises, with the majority of patients being diagnosed in stage I or II (Figure 5).

Figure 4: Absolute and relative survival rates up to 10 years after first diagnosis of bladder cancer, by gender, ICD-10 C67, Germany 2019-2020



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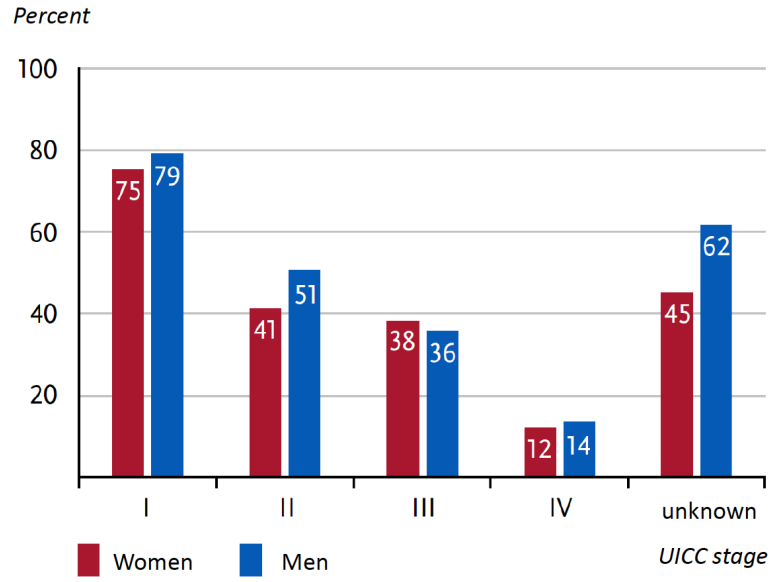
Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c67_harnblase

Figure 5: Relative 5-year survival by UICC stage (7th and 8th edition TNM) and gender, ICD-10 C67, Germany 2019-2020



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Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c67_harnblase

2.3 Pathogenesis

The pathomechanisms of urothelial carcinoma are complex. One of the oncogenic pathways is associated with genetic alterations in the *FGFR3* and *HRAS genes*, which activate the *RAS/MEK/ERK* signaling pathway [2]. The tumors grow towards the bladder lumen, are not muscle-invasive, are often histologically classified as papillary, have a high risk of recurrence, but a good prognosis in terms of survival time.

Invasive urothelial carcinomas arise from severe dysplasia or carcinoma *in situ*. Molecular genetics often reveal inactivating mutations in the tumor suppressor genes *TP53*, *RB1* or *PTEN*. The risk of metastasis in these muscle-invasive carcinomas is around 30%. Further mutations in *PI3K, TSC1, PTCH, CDKN2A* and *DBC1* can be detected in both invasive and non-invasive carcinomas. At least 5 prognostically relevant subgroups can be distinguished on the basis of their mutational signatures [3]. In addition, germline alterations in gene loci associated with hereditary tumor diseases and DNA mismatch repair were found in 20% of patients with advanced urothelial carcinoma.

The immune system plays an important role in the pathogenesis of urothelial carcinoma in terms of pro- and anti-tumor effects [4].

2.4 Risk factors

The risk of developing bladder cancer is increased by the following factors:

- Genetic
  - Lynch syndrome, especially with *MSH2* mutation [5, 6]
- Acquired
  - Cigarette smoking [7]
  - Aromatic amines (recognized as an occupational disease) => aniline [8, 9]
  - Cyclophosphamide, chlornaphazine (previous chemotherapeutic agent for Hodgkin's lymphoma and polycythaemia vera)
  - Phenacetin, aristolochic acid (both off the market)
    - However, aristolochic acid is contained in Chinese herbs, the corresponding molecular signature is detectable in up to three quarters of liver cancer in China/Taiwan [10]
  - Radiotherapy [11]
  - Chronic inflammation, e.g., in schistosomiasis or from long-term indwelling catheters
  - High-fat and low-fruit diet (questionable) [12]

Aromatic amines are recognized as occupational diseases (German Occupational Diseases Ordinance [8]). A precise occupational history is therefore necessary for patients with urothelial carcinomas, taking into account the long latency period (mean, over 30 years).

The amount of fluid consumed appears to correlate inversely with the risk of developing bladder cancer [13]. A link between a high-fat and low-fruit diet and the development of urothelial carcinoma has been noted [12].

3 Prophylaxis and early detection

Avoiding known occupational noxious substances is recommended for prophylaxis [14], but avoiding cigarette smoking is by far most relevant epidemiologically. Sufficient fluid intake could play a preventive role in women [12, 13], but in another study this was not confirmed for men, although the ingredients of tap water played a decisive role [15].

Data from 1987 through 1992 showed an increased rate of early detection in men by regular screening of urine for microhematuria [16], from which, however, no corresponding program for early detection was derived. A study on systematic screening in a high-risk group of patients with aristolochic acid-induced nephropathy showed a high rate (52%) of consecutive bladder

cancer. No screening program is available for the general population, given that cigarette smoking is by far the most important risk factor [17].

4 Clinical characteristics

4.1 Symptoms

The main symptom is hematuria in terms of micro- or painless macrohematuria. However, non-specific irritation symptoms such as pollakisuria or dysuria may also be indicative. In the metastatic stage, the typical symptoms of a consuming malignancy are to be expected.

5 Diagnosis

5.1 Diagnostic criteria

The diagnostic criteria for differentiating urothelial carcinoma from other malignancies such as renal cell carcinoma or CUP (Cancer of unknown primary; see Onkopedia guideline CUP) are explained below. In particular, the detection of *GATA3* in immunohistochemistry may indicate urothelial carcinoma. In differential diagnostic problem cases, a more detailed molecular pathological examination [18] may be indicated.

5.2 Diagnostic procedures

5.2.1 Initial diagnosis

The first step is to confirm the suspected clinical or sonographic diagnosis, see Table 1, starting with urine sediment and an attempt to confirm the suspected clinical diagnosis by means of positive urine cytology from fresh urine, whereby the sensitivity depends on the examiner [19]. The sensitivity of cytology correlates with the degree of differentiation of the tumors; for highly differentiated tumors (G1), the sensitivity is low, so that cytology is not suitable for exclusion diagnostics under any circumstances. Other markers in the urine have not been validated. Ultrasound of the complete urinary tract including bladder excludes urinary retention or stones as the cause of hematuria. Occasionally, an exophytic bladder tumor can also be visualized sonographically when the bladder is filled. The bladder is examined using white light or fluorescence-assisted cystoscopy with subsequent transurethral resection (TUR-B) to obtain tissue for histology or simultaneous treatment of non-muscle-invasive tumors. Fluorescence-assisted diagnosis is particularly useful in case of multifocal or high-grade tumors in patient history or in the case of a positive urine cytology.

Table 2: Diagnostic procedures for new-onset symptoms [20]

Procedure	Remark
Urine sediment and cytology	Depends on examiner and tumor grading
Ultrasound of the bladder and complete urinary tract	Exclusion of urinary retention, urolithiasis
White light or fluorescence-based cystoscopy if indicated	Flexible or rigid endoscope (flexible is more comfortable)
Endoscopy with transurethral resection to obtain histology	Impact on stage definition

An investigation of the upper urinary tract is particularly important in the case of hematuria without a bladder tumor or without any other cause (see chapter 7).

Routine laboratory tests (blood counts, coagulation tests, thyroid-stimulating hormone, liver and renal function tests) including the determination of serum lactate dehydrogenase as well

as computed tomography of the thorax, abdomen and pelvis in case of a muscle-invasive disease complete the diagnosis. An imaging examination of the head and skeletal scintigraphy are only recommended if clinical symptoms are present. An 18F-FDG positron emission tomography with computed tomography may be helpful as part of the primary diagnosis, particularly in cases of suspected (oligo)metastasis [21]. It should not be used for precise anatomical assessment or for the diagnosis of non-muscle-invasive urothelial carcinoma of the urinary bladder.

Table 3: Diagnosis of spread in muscle-invasive urothelial carcinoma of the urinary bladder, in non-muscle-invasive stage high grade, relapse, multifocal or trigonum involvement

Investigation	Remark
Clinical chemistry (serum)	Blood counts, coagulation tests, thyroid-stimulating hormone, liver and renal function tests
CT urography[1]	Especially for visualization of the upper urogenital tract
MRI[2] of the abdomen and pelvis with contrast medium	Alternative to CT urography; in individual cases on the question of resectability
CT thorax, abdomen and pelvis with CT urography	Only for muscle-invasive bladder cancer
CCT/MRI[3] or bone scintigraphy	Only in case of symptoms
PET-CT[4]	In case of primary suspicion of (oligo)metastasis

Legend:
[1] CT - computed tomography; [2] MRI - magnetic resonance imaging; [3] CCT – cerebral computed tomography; [4] PET-CT - positron emission tomography with computed tomography

5.3 Classification

5.3.1 Histology

The histopathological classification of bladder tumors is based on the *WHO* classification for bladder tumors of 2022 [22]. For the non-muscle-invasive stages, the *EORTC* risk calculator is used with the classification into low, intermediate and high risk, see Table 6 and Table 7. For invasive tumors, the three-stage grading with G1-G4 follows the 1973 WHO classification or the *WHO* 2004/2022 with a combination of the WHO1973 and the *WHO* 2004/2016 classification in PUNLMP (papillary urothelial neoplasm of low malignant potential), non-invasive papillary carcinoma low grade (LG) and high grade (HG) in the WHO 2004/2022 classification with the subcategories LG G1 (low risk), LG G2 (intermediate risk), HG G2 (high risk), HG G3 (highest risk)

Urothelial carcinomas are characterized by often multifocal growth. Ideally, each lesion should be assessed separately. In mixed tumors, the proportion of individual subtypes should be listed. The separate focal tumors can be monoclonal or originate from different clones [23].

Muscle-invasive urothelial carcinomas (tumors from pT2 with invasion of the muscle layer of the bladder wall, possibly also of surrounding tissue) are divided into the following subtypes in the WHO classification 2022 [22, 24], all of which are classified as "high-grade" (Table 4):

Table 4: Histopathological subtypes of muscle-invasive urothelial carcinoma according to WHO 2022 [22, 24]

• Invasive urothelial carcinoma ◦ with squamous differentiation ◦ with glandular differentiation ◦ with trophoblastic differentiation
• "Nested" urothelial carcinoma, including "large nested"
• Tubular and microcystic urothelial carcinoma
• Micropapillary urothelial carcinoma
• Lymphoepithelioma-like urothelial carcinoma
• Plasmacytoid urothelial carcinoma /
• Signet ring cell urothelial carcinoma /
• Diffuse urothelial carcinoma
• Giant cell urothelial carcinoma
• Lipid-rich urothelial carcinoma
• Clear cell (glycogen-rich) urothelial carcinoma
• Sarcomatoid urothelial carcinoma
• Poorly differentiated urothelial carcinoma

The number of lymph nodes, the localization and the maximum size should be described in the histopathology, as well as extracapsular spread.

5.3.2 Molecular pathology

Recommendations for molecular pathological diagnostics were published in 2019 by the International Society of Uropathology, which define molecular markers to confirm the differential diagnosis and to identify subgroups of urothelial carcinoma [18]. Beyond this, determination of PD-L1 expression is recommended for all urothelial carcinomas, as well as testing for alterations in the fibroblast growth factor receptors 2 and 3 (*FGFR2* and *FGFR3*) for urothelial carcinomas that cannot be cured by local means, as drugs are available for targeted therapy in this setting (see below). To date, there is no indication for extensive genome sequencing procedures outside of studies [25]. *HER2/HER3* typing for targeted therapies is likely to become more important in the future.

Sequencing methods from circulating tumor DNA (ctDNA) are used for primary genomic characterization [26], for possible selection for postoperative systemic therapy [27] and for monitoring the response to immune checkpoint blockade [28] in the context of studies, but are not yet recommended for standard diagnostics [29].

5.3.3 Stages and staging

The classification of the extent of the primary tumor and metastasis is based on the *UICC*-TNM criteria. The current classification is summarized in Table 5 and the staging in Table 6.

Table 5: UICC-TNM classification - Tumors of the urothelium (2022) [22].

Classification	Tumor
T	**Primary tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
• T2a	• Tumor infiltrates superficial muscularis propria (inner half)
• T2b	• Tumor infiltrates deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue:
• T3a	• microscopically
• T3b	• macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic or abdominal wall
• T4a	• Tumor invades prostatic stroma or seminal vesicles or uterus or vagina
• T4b	• Tumor invades pelvic or abdominal wall
N	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a lymph node of the true pelvis (a hypogastric, obturator or presacral lymph node or a lymph node from the area of the external iliac artery)
N2	Metastases in several lymph nodes of the true pelvis (one hypogastric, obturator or presacral lymph node or one lymph node from the area of the external iliac artery)
N3	Metastasis in common iliac lymph node(s)
M	**Distant metastases**
M0	No distant metastases
M1a	Distant metastases in non-regional lymph nodes
M1b	Other distant metastases

The stages pTis, pTa and pT1 are referred to as non-muscle-invasive bladder carcinomas, all carcinomas ≥pT2 as muscle-invasive bladder carcinomas.

Table 6: Staging - Tumors of the urothelium (2022) [22]

Stage	Classification		
0a	Ta	N0	M0
0is	Tis	N0	M0
I	T1	N0	M0
II	T2a-b	N0	M0
IIIa	T3a to 4a	N0	M0
IIIb	T1 to 4a	N1	M0
IVa	Each T	Each N	M1a
IVb	Each T	Each N	M1b

5.4 Prognostic factors

The probability of relapse and progression of non-muscle-invasive bladder cancer is calculated according to an *EORTC* point score (http://www.eortc.be/tools/bladdercalculator/download.asp), see Table 7 and Table 8.

Table 7: Probability of relapse and progression of non-muscle-invasive urothelial carcinoma of the urinary bladder according to the EORTC risk classification score [30]

Factor	Recurrence (points score)	Progression (points score)
Number of tumors		
1	0	0
2-7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary tumor	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Degree		
G1	0	0
G2	1	0
G3	2	5
Total	**0-17**	**0-23**

Table 8: EORTC risk scoring for non-muscle-invasive bladder cancer [30]

Factor	Risk group
0	Low risk
1-4	Intermediate risk
5-9	Intermediate risk
10-17	High risk

5.5 Differential diagnosis

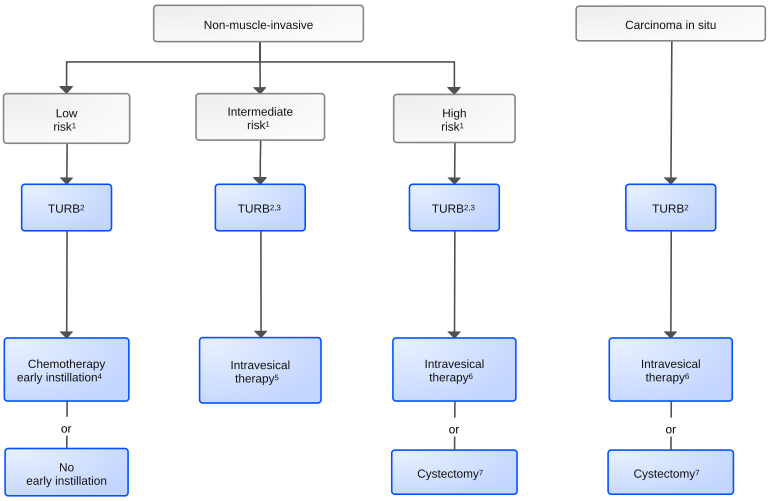
More than 90% of bladder cancers are urothelial carcinomas. Of the non-urothelial tumors, around 90% are of epithelial origin, i.e., squamous cell carcinomas, adenocarcinomas or neuroendocrine neoplasms. Sarcomas, lymphomas and melanomas are very rare.

6 Therapy

6.1 Treatment structure

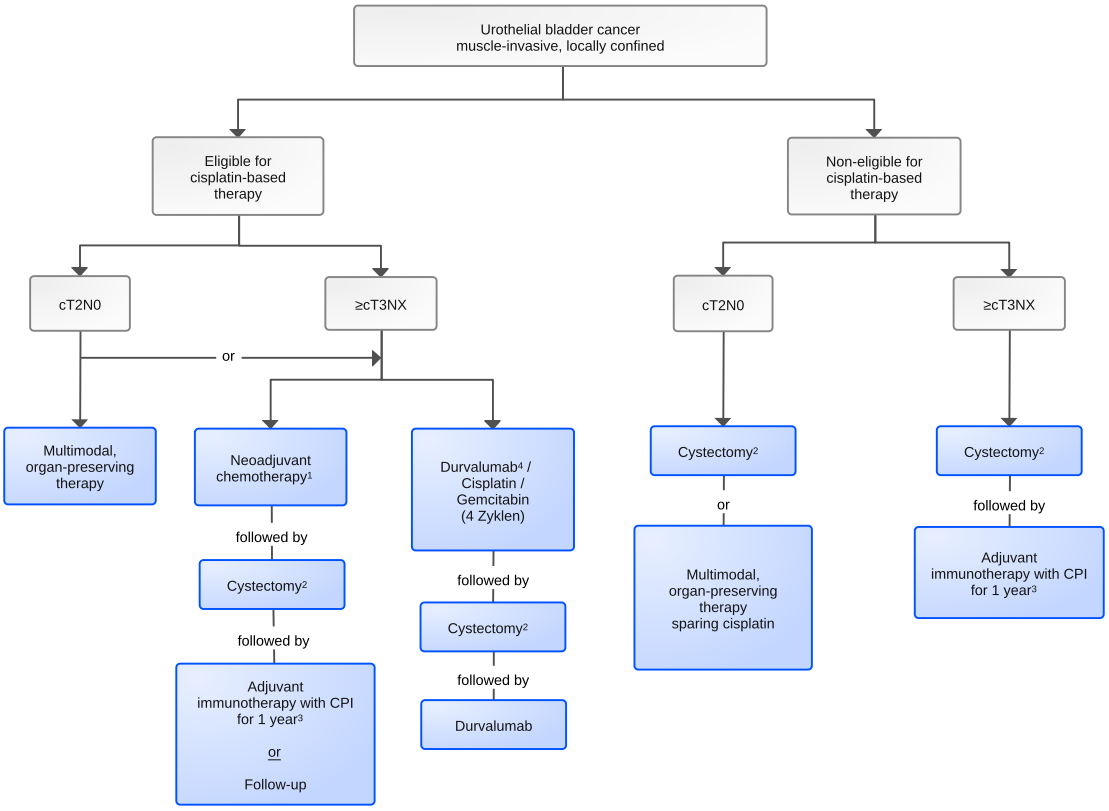
Treatment depends on the histology, stage and other risk factors, see Figure 6 to Figure 9.

Figure 6: First-line treatment of non-muscle-invasive urothelial carcinoma of the urinary bladder and carcinoma in situ



Legend:
curative intention
[1] see Tables 7 and Table 8
[2] TURB - transurethral bladder resection
[3] Follow-up with option for transurethral re-resection for high-risk tumors, also to be considered for intermediate risk
[4] Early chemotherapy instillation - once during TURB with mitomycin C, alternatively also with doxorubicin/epirubicin
[5] Intravesical therapy with BCG (Bacillus Calmette-Guérin) or mitomycin C for 1-3 years; if BCG is not available, primarily mitomycin C
[6] Intravesical therapy with BCG for 1-3 years; if BCG is not available, mitomycin C or gemcitabine intravesically if indicated
[7] plus bilateral pelvic lymphadenectomy

Figure 7: First-line treatment of localized muscle-invasive urothelial carcinoma of the bladder



Legend:
curative intention
[1] neoadjuvant therapy = ddMVAC or gemcitabine/cisplatin
[2] plus bilateral pelvic lymphadenectomy
[3] for PD-L1 ≥ 1 (nivolumab approved); pembrolizumab not yet approved
[4] not yet approved
ICI = immune checkpoint inhibitor

6.1.1 Non-muscle-invasive urothelial carcinoma of the urinary bladder

75% of all urothelial carcinomas of the urinary bladder are non-muscle-invasive bladder carcinomas confined to the mucosa or submucosa. Disease-specific mortality is low, but they can recur and therefore require regular follow-up [31].

6.1.1.1 Transurethral bladder resection (TURB)

Non-muscle-invasive urothelial carcinoma of the urinary bladder is removed by transurethral sling resection, if possible, in toto; if required, a repeat resection is performed to ensure complete removal. This is indicated for

- incomplete TUR
- lack of muscle tissue in the histopathological specimen (except pTa, low risk)
- pT1 tumors
- high risk, except pTis (carcinoma in situ).

6.1.1.2 Instillation therapy

Chemotherapy instillation can be carried out as early instillation in the case of uncomplicated TURB. Alternatively, intravesical therapy, which can consist of instillation with BCG (Bacillus

Calmette-Guérin) or mitomycin C, is only advisable in cases of intermediate or high risk. Therapy consists of induction with BCG followed by regular maintenance over 1-3 years. Induction is initially carried out once a week for 6 weeks, then at longer intervals up to 1 year. High-risk tumors should be treated with BCG. In view of the BCG shortage for several years, discussions are being held internationally about possible alternatives of equal therapeutic value [29].

6.1.1.3 Relapse/refractoriness after intravesical therapy

In the event of relapse or refractoriness, patients from the intermediate risk group are then treated as a high-risk group and receive a new TURB, optionally followed by intravesical BCG, if mitomycin C has previously been used. If refractoriness persists, a cystectomy is indicated.

Also, in cases of primary non-response despite re-TURB, prompt cystectomy is currently still recommended.

As an alternative, multimodal therapy with the aim of preserving the bladder is being considered [32]. In this case, treatment should be offered as part of a clinical trial, e.g., for the use of immune checkpoint inhibition [33]. The *FDA* has approved the administration of pembrolizumab as monotherapy with 200 mg every 3 weeks for a maximum of 24 months if intravesical therapy with BCG has been ineffective. Approval has not yet been granted in Europe.

6.1.2 Muscle-invasive urothelial carcinoma of the urinary bladder

6.1.2.1 Localized

Following the diagnosis of muscle-invasive urothelial carcinoma of the urinary bladder, the complete treatment concept should be discussed on a multidisciplinary basis including urology, medical oncology, radiation oncology and other specialist disciplines involved. Surgery alone is indicated for patients who are not suitable for cisplatin chemotherapy but are operable [34].

Another treatment option may be multimodal, primarily organ-preserving therapy starting with a transurethral resection followed by combined radiochemotherapy.

6.1.2.1.1 Neoadjuvant and adjuvant systemic therapy

In localized muscle-invasive urothelial carcinoma of the urinary bladder, the prognosis is improved by additional neoadjuvant or adjuvant cisplatin-containing systemic therapy, so that these treatment options must be discussed with all patients with tumor stages ≥cT2N0. Results of head-to-head comparative studies of pre- versus postoperative chemotherapy with the endpoints disease-free survival or overall survival are not available. Early studies (e.g. [35]) were examined in a meta-analysis [36]. Further studies on neoadjuvant chemotherapy [37] showed superiority over primary cystectomy. A more recent meta-analysis also showed a significant advantage in progression-free survival and overall survival for neoadjuvant therapy [20]. Arguments in favor of neoadjuvant therapy are the higher number of patients investigated in studies and the better general performance of patients before cystectomy. Arguments in favor of adjuvant chemotherapy are the more precise staging through histopathological examination of the cystectomy specimen. Neoadjuvant therapy has now become established, after having long been discussed controversially.

6.1.2.1.1.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) leads to an improvement in the overall survival rate by 5-8% after 10 years and represents the current standard for cisplatin-eligible patients [36]. It usually consists of cisplatin-containing combination chemotherapy. MVAC (methotrexate, vinblastine, doxorubicine, cisplatin) was most frequently investigated. In comparison between gemcitabine/cisplatin (GC) and MVAC, both protocols (3 cycles each) were found to be equivalent in terms of feasibility, histopathological response and survival [38]. A randomized comparison between perioperatively administered 6 cycles of dose-dense MVAC (ddMVAC) and 4 cycles of GC did not show a significant survival benefit in the overall population (a small proportion of the randomized patients received chemotherapy as adjuvant therapy) for dose-dense MVAC [39], but progression-free survival (primary endpoint) was significantly better after neoadjuvant therapy, so that ddMVAC is primarily recommended for "fit" patients without serious comorbidity. For the less fit patients, treatment with cisplatin and gemcitabine remains the standard [40].

Monitoring including imaging procedures is required during neoadjuvant chemotherapy to ensure that eventual progression will not be missed. The subsequent cystectomy should be performed within 4 weeks after NAC and should early be planned appropriately.

6.1.2.1.1.2 Neoadjuvant immunotherapy or chemoimmunotherapy

The inclusion of immune checkpoint inhibitors (ICI) such as durvalumab, nivolumab or pembrolizumab in neoadjuvant or bladder-preserving multimodal concepts has been investigated almost exclusively in phase II studies. Preoperative monotherapy with 3 cycles of pembrolizumab monotherapy resulted in downstaging to pT0 in 42% of patients [41], while the combination of pembrolizumab with gemcitabine and dose-modified ("split-dose") cisplatin resulted in pT0 in 36% of patients [42]. After combining nivolumab with gemcitabine/cisplatin, a complete remission was clinically diagnosed in 43% of patients. In 8 of 32 patients who opted for organ preservation, local recurrence occurred during a follow-up period of 18-44 months, and metastasis occurred in one patient [43]. After neoadjuvant administration of durvalumab in combination with gemcitabine/cisplatin, a histopathological complete remission was documented in 33% of 52 patients undergoing subsequent radical cystectomy [44]. Since September 2024, phase 3 data have been available for perioperative therapy with 4 cycles of cisplatin/gemcitabine and durvalumab followed by 8 courses of durvalumab maintenance therapy [45]. There was an 8% difference in event-fee survival (EFS) in favor of the ICI arm with 67.8% (95% CI 63.6-71.7) with durvalumab vs 59.8% (55.4 -64.0) in the comparator arm. In overall survival at 24 months, the difference was 7% with 82.2% (95% CI 78.7-85.2) in the durvalumab arm vs 75.2% (95%CI 71.3-78.8) in the comparator arm. The value of ICI alone or in combination in this indication cannot yet be definitely assessed.

6.1.2.1.1.3 Adjuvant chemotherapy

While the standard procedure is neoadjuvant therapy, primary cystectomy may have to be performed due to urgent necessity. In these cases, adjuvant chemotherapy with 3-4 cycles of cisplatin-based chemotherapy - usually cisplatin/gemcitabine - can then be given within 12-14 weeks postoperatively if the patients are capable of chemotherapy with cisplatin, from a stage ≥pT3 and or pN+ [46].

6.1.2.1.1.4 Adjuvant immunotherapy

At present, nivolumab is the only adjuvant immunotherapy approved after neoadjuvant chemotherapy or in patients unsuitable for cisplatin, since it has been shown to significantly prolong progression-free survival after 2-3 years, although data on overall survival are still lacking [47]. There was a median disease-free survival of 22.0 months with nivolumab versus 10.9 months with placebo in the ITT population and 52.6 months with nivolumab versus 8.4 months with placebo in patients with PD-L1 ≥1% [48]. Initial evaluations of overall survival also show an advantage for nivolumab, particularly in tumors with a PD-L1 ≥1% (by CPS/TC), but also in the overall population in the ITT analysis [48]. This treatment is particularly indicated when

there are larger tumor residuals in terms of ypT3 or ypN+ of a PD-L1-positive urothelial carcinoma [49].

Data on pembrolizumab for adjuvant therapy in locally advanced urothelial carcinoma were also presented in 2024 [50]. Compared to postoperative observation only, there was a significant advantage in disease-free survival (29.6 months vs. 14.2 months in the observation arm with a hazard ratio of 0.73), but so far, no difference in overall survival (3-year survival 60.8% with pembrolizumab vs. 61.9% in the observation group) has been observed.

The PD-L1 checkpoint inhibitor atezolizumab has shown no benefit in disease-free or overall survival in this setting and should not be used [51].

6.1.2.1.2 Local surgery

6.1.2.1.2.1 Radical cystectomy and lymph node dissection

Cystectomy is an obligatory component of a curative concept for localized, muscle-invasive bladder carcinoma. Before a planned cystectomy, there should be a careful discussion with the patient about the various forms of urinary drainage. Incontinent urinary diversions with a ureteral skin fistula, an ileum or colonic conduit are possible. Alternatively, there is a continent urinary diversion using a catheterizable pouch, a neobladder (orthotopic bladder replacement) or a transrectal urinary diversion. Preoperative consultation about the position of the stoma is also part of the information provided.

After radical cystectomy, usually with bilateral pelvic lymphadenectomy, the most important prognostic parameters for recurrence-free and disease-specific survival are the pT and pN stage as well as tumor-free resection margins showing completeness of tumor resection (pathological complete response, pCR) [52]. The extent of lymphadenectomy (limited to the region up to the bifurcation of the common iliac artery or at least up to the inferior mesenteric artery) is the subject of controversial debate. In a pooled evaluation [53] of two randomized clinical trials [54, 55], no advantage of the more extensive lymphadenectomy was found. Nomograms with better predictive accuracy are also being evaluated, but these are not predictive of further therapeutic measures [56]. Molecular markers have not yet played a role.

6.1.2.1.2.2 Partial cystectomy with bladder preservation

The equivalence of a partial cystectomy to a radical cystectomy has not yet been proven [57]; nevertheless, a partial cystectomy may be useful in individual cases if a lifelong follow-up with cystoscopy can be performed.

6.1.2.1.3 Multimodal primary organ-preserving therapy

Good data are available from a retrospective matched pair study (n=722 patients with T2-T4N0M0 muscle-invasive urothelial carcinoma of the bladder) on multimodal therapy, which includes tumor resection with TUR, as completely as possible, and pursues a curative approach with subsequent simultaneous radiochemotherapy [58]. The clinical-oncological outcome was equivalent to primary radical cystectomy, and salvage cystectomy after trimodal therapy was only required in 13% of patients. In a non-randomized study of 415 patients with localized bladder carcinoma after transurethral tumor resection conducted between 1982 and 2000, complete clinical remission after radio(chemo)therapy was achieved in 72% of patients and bladder preservation after 10 years in 62% of patients, with distant metastasis occurring in 35% [59]. A randomized study comparing primary radical cystectomy and neoadjuvant chemotherapy had to be discontinued after 45 patients due to lack of recruitment and did not yield clinically useful

results [60]. There are several monocenter, observational studies providing long-term results that describe complete remission rates after TURB and simultaneous radiochemotherapy of 60-90% with long-term survival after 5 years of between 45 and 75% with 80% bladder preservation [61, 62]. Cisplatin-based therapy or 5-fluorouracil (5-FU) plus mitomycin C are used as chemotherapy for simultaneous radiochemotherapy, both of which improve the results compared with radiotherapy alone [63, 64]. In the *BC2001* trial [64], a randomized comparison between radiotherapy and radiochemotherapy, predominantly after complete transurethral tumor resection, showed a significant advantage of radiochemotherapy with regard to the risk of local recurrence, but not for overall survival. Salvage cystectomy was required in 11.4% versus 16.8% of patients (p = 0.07). Gemcitabine plus cisplatin [65] or capecitabine alone [66] or in combination with mitomycin C [67] can also be considered as alternatives to the chemotherapeutic agents mentioned. Gemcitabine as monotherapy in small doses was also investigated in a phase I study [68].

Multimodal concepts are particularly suitable for patients suffering from localized muscle-invasive bladder cancer who are not suitable for a cystectomy or who refuse a cystectomy. Accordingly, cT2cN0 tumors are particularly suitable for this purpose. Unfavorable prognostic factors are multifocal tumors, hydronephrosis and synchronous carcinoma in situ.

6-12 weeks after the end of therapy, the success of the therapy should be checked by means of cystoscopy and biopsies so that further therapy with TURB, intravesical therapy or cystectomy can follow if necessary.

6.1.2.1.4 Postoperative radiotherapy or radiochemotherapy

Postoperative radio- or radiochemotherapy is not indicated after an R0 resection, but various case series have reported a positive effect in cases of R1 resection, poorly differentiated tumors, extravesical growth or pelvic lymph nodes.

6.1.3 Locally advanced or metastatic muscle-invasive urothelial carcinoma of the urinary bladder (stage IV)

The primary treatment of metastatic urothelial carcinoma of the urinary bladder is preferably based on immunotherapy and molecularly targeted therapy (antibody drug conjugate), alternatively on a combination of cisplatin with gemcitabine and immunotherapy with nivolumab. In clinical practice, a relevant proportion of (generally older) patients are not suitable for cisplatin therapy. Contraindications to platinum-containing therapy are summarized in Table 9.

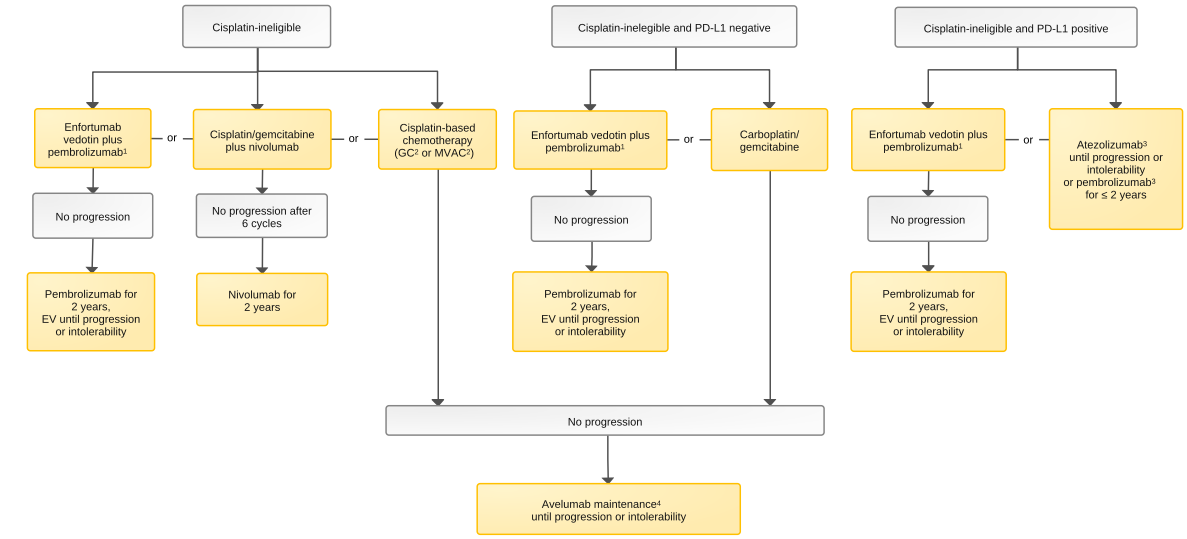
Table 9: Criteria for cisplatin-ineligibility [69]

Parameters	Specification	Remark
General condition	*Karnofsky* performance score ≤60 and/or ECOG performance status ≥2	
Creatinine clearance	≤ 40 ml/min	This recommendation differs from the prescribing information, in which a creatinine clearance ≤60 ml/min is listed as a contraindication; a dose adjustment or a change in the application regimen (e.g., split-dose cisplatin) is required for a creatinine clearance of 40-60 ml/min.
Hearing loss	CTCAE grade 2 or higher	
Peripheral polyneuropathy	CTCAE grade 2 or higher	
Heart failure	NYHA class 3 or 4	

6.1.3.1 Systemic treatment

Treatment decisions are based on patient general condition, comorbidity, treatment goal and availability of effective medication, see Figure 8.

Figure 8: First-line systemic therapy for metastatic or locally non-curable urothelial carcinoma of the urinary bladder



Legend:
non-curative intention
[1] *Preferred first-line standard*
[2] *GC: gemcitabine/cisplatin; MVAC: methotrexate/vinblastine/doxorubicin/cisplatin*
[3] *Atezolizumab approval for PD-L1 ≥5%; pembrolizumab approved for PD-L1 (CPS) ≥10*
[4] *particularly in case of PD-L1 positivity*

6.1.3.1.1 First-line therapy for metastatic or locally non-curable disease*

**See* Figure 8

In addition to a poor general condition, measured as *Karnofsky* Performance Status <80%, visceral metastases including bone metastases are considered to be prognostically unfavorable factors in terms of overall survival [70].

The new preferred first-line therapy is the combination of pembrolizumab with the immunotoxin conjugate enfortumab vedotin (EV), which is directed against *nectin-4*. In a randomized comparison with first-line chemotherapy, this combination led to a significant increase in median overall survival from 16.1 to 31.5 months in the *KEYNOTE-A39/EV-302* trial [71].

The combination of nivolumab with cisplatin/gemcitabine (C/G) chemotherapy also led to a significant increase in median overall survival from 18.9 to 21.7 months in a randomized comparison with C/G chemotherapy alone in the *CheckMate-901* study [72].

In contrast, the combination of atezolizumab with cis-/carboplatin plus gemcitabine showed an advantage in progression-free survival for immuno-chemotherapy compared to chemotherapy alone, but no significant difference in overall survival [73].

In patients who were cisplatin-eligible, the option of combining pembrolizumab with a platinum-based first-line therapy was also tested in a randomized comparison with platinum-based chemotherapy alone. In the *KEYNOTE-361* study, no significant improvement in progression-

free or overall survival was achieved with the combination of immunotherapy and chemotherapy in a total of 1,010 randomized patients [74].

If both EV plus pembrolizumab and the combination of C/G with nivolumab cannot be considered due to individual contraindications, the classic combined chemotherapy with C/G or methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) is primarily used. MVAC, dose-dense MVAC and C/G are approximately equally effective. C/G is less toxic than MVAC. A higher dose intensity of C/G or a triple combination, e.g., with paclitaxel, leads to higher remission rates and higher toxicity, but does not prolong survival [75].

In patients with a good general condition but impaired renal function with a creatinine clearance between 50 and 60 ml/min, it should be discussed whether to give cisplatin in split doses, e.g., on days 1 and 8 or days 1 and 2.

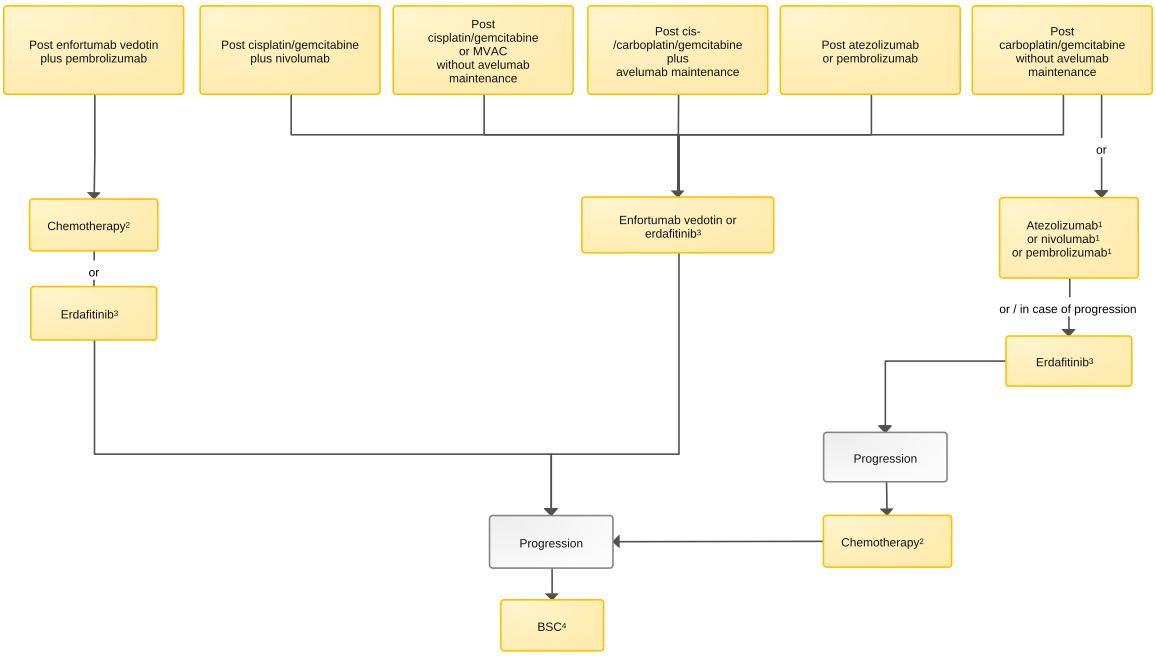
If treatment with cisplatin is not possible, it can be replaced by carboplatin, but a significant loss of efficacy has to be taken into account [20, 25, 76, 77].

One treatment option for patients who are not suitable for cisplatin-based chemotherapy is immunotherapy with the PD1 inhibitor pembrolizumab or with the PD-L1 inhibitor atezolizumab. In a non-randomized phase II study, a response rate of 29% and a median survival of 11 months were reported for pembrolizumab monotherapy in 370 patients [78, 79], with overall survival and duration of response in patients with tumors with high PD-L1 expression. The overall survival and duration of response in patients with tumors with high PD-L1 expression (combined positive score CPS ≥ 10) was significantly better than with an expression < 10. In a non-randomized phase II study in 123 patients, atezolizumab led to a remission rate of 23%, a median progression-free survival of 2.7 months and a median overall survival of 15.9 months [80]. In a randomized comparison between atezolizumab and platinum-based chemotherapy, there was no difference in overall survival [81]. Data from clinical trials (*KEYNOTE-361* and *IMvigor130*) tended to show a survival disadvantage with pembrolizumab/atezolizumab monotherapy compared to standard chemotherapy if the tumors had an expression of PD-L1 <10% (CPS). Atezolizumab and pembrolizumab are therefore only approved for cisplatin-ineligible patients with positive PD-L1 expression (pembrolizumab CPS ≥10%; atezolizumab PD-L1 ≥5%) [82]. However, predictive biomarkers for treatment response have not yet been prospectively validated.

Before the results of *KEYNOTE-A39/EV-302* and *CheckMate-901* were reported, another first-line treatment option has been the combination of 4-6 cycles of first-line chemotherapy with cis- or carboplatin plus gemcitabine followed by maintenance treatment with the PD-L1 inhibitor avelumab in all patients who have shown no progression after chemotherapy [83]. In the overall cohort of 700 evaluable patients and in the 358 patients with PD-L1-positive tumors (≥ 1% in the "*Ventana Assay*"), the addition of avelumab to the best supportive therapy resulted in a significant advantage in progression-free and overall survival compared to best supportive therapy alone. Patients with PD-L1-negative tumors did not show an overall survival benefit. Study results were confirmed with a median follow-up of 38 and 40 months, respectively [84].

6.1.3.1.2 Second- and third-line therapy

Figure 9: Second- and third-line systemic treatment for metastatic or locally non-curable urothelial carcinoma of the bladder



Legend:
non-curative intention
[1] *Atezolizumab, nivolumab and pembrolizumab are approved in this indication regardless of PD-L1 expression*
[2] *After EV + pembrolizumab: platinum-based combination chemotherapy as third-line therapy; mono-chemotherapy. vinflunine, carboplatin, docetaxel, gemcitabine, paclitaxel*
[3] *If a susceptible FGFR3 mutation is detected (approved since August 2024)*
[4] *Best supportive care*

6.1.3.1.2.1 Molecularly targeted therapy and immunotherapy

As an option for subsequent therapy in patients with urothelial carcinoma with *FGFR3* mutation or *FGFR2/FGFR3* fusion, the oral *FGFR* inhibitor erdafitinib showed a response rate of 40% and a median overall survival of 11.3 months [85]. In a randomized comparison with salvage chemotherapy with docetaxel or vinflunine, erdafitinib led to a significant improvement in overall survival from 7.8 to 12.1 months in 266 patients in the *THOR* study [86]. In the same study, a randomized comparison of erdafitinib with pembrolizumab in 351 patients showed no difference in overall survival (10.9 vs 11.1 months) [87]. Before or after failure of erdafitinib or in the absence of evidence of *FGFR* alteration, EV can be used as monotherapy if it has not been given before. European approval by the EMA was granted in August 2024.

The antibody-toxin conjugate EV, which is directed against *nectin-4*, was randomized against relapse chemotherapy with paclitaxel, docetacel or vinflunine in 608 patients in relapse after platinum-based first-line therapy or checkpoint inhibitor therapy. This resulted in a significant increase in median overall survival from 8.97 to 12.88 months [74]. In 89 platinum-naïve patients in relapse after first-line therapy with an immune checkpoint inhibitor, relapse therapy with EV resulted in a response rate of 52% and a median overall survival of 12.4 months [88]. The detection of *nectin-4* amplification (in up to 26% of metastatic urothelial carcinomas) appears to be predictive of response to EV [89]. EV can also be used after failure of erdafitinib if it has not been given before.

The current data on treatment options in relapse/progression can be summarized as follows:

- In a randomized phase III study, pembrolizumab after platinum-containing chemotherapy alone led to a prolongation of overall survival (hazard ratio 0.71; median 10.1 vs. 7.2 months) compared to monochemotherapy (taxane, vinflunine), but not to a prolongation of progression-free survival [90, 91].
- Atezolizumab led to a remission rate of 15% and a median overall survival time of 7.4 months in 315 patients in a single-arm phase II study [92]. Data from a confirmatory, randomized phase III study showed no significant advantage in progression-free and overall survival compared to monochemotherapy (taxane, vinflunine). The evaluation of the *Imvigor211* study comparing atezolizumab with chemotherapy (paclitaxel, docetaxel or vinflunine) in relapse therapy showed a median follow-up time of 33 months, in contrast to the primary publication [93], both for the overall cohort (n = 467 vs. 464) as well as for the PD-L1-negative cohort (n = 151 vs 155), each showed a significant advantage in overall survival (HR = 0.82 and HR = 0.76 respectively) [94].
- Nivolumab led to a remission rate of 20% in 270 patients in a non-randomized phase II study [95].
- Durvalumab led to an objective response rate of 31% in a phase I/II study [78].
- Avelumab led to an objective response rate of 16-17% in phase I trials [96, 97].

The rate of severe side effects of CTCAE grade 3 or 4 is low, and lower than with chemotherapy. Atezolizumab, pembrolizumab and nivolumab are approved for this indication.

The antibody-toxin conjugate sacituzumab govitecan (SG) directed against *trophoblast cell surface antigen-2* (*TROP2*) as monotherapy or in combination with pembrolizumab is expected to be a future second-line treatment option for metastatic disease. In the phase II study *TROPHY-U-01*, SG monotherapy led to an overall response rate of 27% in 113 patients [98], while the combination with pembrolizumab led to an overall response rate of 41% in 41 patients [99]. Trastuzumab-deruxtecan as an antibody-drug conjugate in combination with nivolumab was evaluated in a small number of patients [100].

6.1.3.1.2.2 Chemotherapy

If a relapse/progression occurs after primary therapy with EV plus pembrolizumab, platinum-based combination chemotherapy is an option in the relapse. EV is a treatment option for patients who have been in remission for more than six months after primary therapy with cisplatin or after (immuno)chemotherapy alone.

Vinflunine can also be considered as a secondary option in relapse chemotherapy. It is approved in Europe for the second-line treatment of bladder cancer after previous platinum-containing therapy, as it showed a survival advantage over supportive care alone (hazard ratio 0.78; median 2.6 months). Without disease-related risk factors, the median overall survival was 14.2 months, as compared with 1.7 months in case of more than 2 risk factors.

In another patient cohort, paclitaxel/gemcitabine were used in combination, the risk factors were confirmed and an overall survival without risk factor of 11.8 months vs. 3.2 months with more than 2 risk factors was achieved [101].

In refractory relapse after failure of chemo-/immunotherapy and erdafitinib, monotherapy with vinflunine, paclitaxel or docetaxel may be considered in addition to best supportive care.

6.1.3.2 Surgery

6.1.3.2.1 Palliative cystectomy

A cystectomy with palliative intent is rarely necessary, but it can be useful for symptom control such as bleeding, fecaluria, urinary retention and pain, if there is no other treatment option.

6.1.3.2.2 Surgical resection of metastases

Resection of metastases with curative intent is no treatment standard. It may be recommended in single patients with primary urothelial carcinoma of the urinary bladder by a multidisciplinary board.

Surgical resection can also be recommended without curative intent if metastases are symptomatic and these symptoms may be resolved by the resection, e.g., in the case of acute paraplegia caused by vertebral body metastasis.

6.1.3.3 Radiotherapy

Radiotherapy is an effective option for local symptoms, e.g., for pain that cannot be manageable with medication, or hemostyptic radiation, for treatment of cerebral metastases or after vertebral body surgery for symptomatic spinal cord compression [102].

7 Treatment principles for urothelial carcinoma of the upper urogenital tract

Urothelial carcinomas of the upper urinary tract, i.e., the ureter and renal pelvis ("upper tract urothelial cancer, UTUC"), account for approx. 5% of all urothelial carcinomas [103]. Of these, 10-20% are multifocal [104] and in 17% of cases there is also a synchronous urothelial carcinoma of the urinary bladder [105]. Urothelial carcinomas of the urinary bladder can also occur in the history or during the course of UTUC [106].

A detailed guideline on the diagnosis and treatment of urothelial carcinoma of the upper urinary tract was updated by the *European Association of Urology (EAU)* in 2023 [31].

In summary, the recommendations for this Onkopedia guideline are as follows:

- The upper urinary tract should always be included in the primary diagnostic procedures in patients with urothelial carcinomas (CT, urine cytology, cystoscopy, ureteroscopy if necessary)
- Depending on the individual risk constellation, primary treatment consists of a radical nephroureterectomy ± lymphadenectomy or an organ-preserving partial resection [31]
- For patients with locally advanced, non-metastatic UTUC, the benefit of adjuvant platinum-based chemotherapy (cisplatin or carboplatin/gemcitabine) for disease-free and overall survival has been proven [107, 108]. Adjuvant immunotherapy is not indicated.
- Robust data recommending neoadjuvant systemic tumor therapy for patients with UTUC are not yet available.

These recommendations are also in line with the 2022 ESMO guideline [25].

8 Systemic tumor therapy

8.1 Drugs for systemic tumor therapy (alphabetical)

8.1.1 Atezolizumab

Atezolizumab is a humanized IgG1 antibody directed against PD-L1 and belongs to the class of immune checkpoint inhibitors. It is approved for the treatment of urothelial carcinoma [73] and a broad spectrum of other malignant neoplasms. Proven PD-L1 expression of ≥5% is required for first-line therapy in patients unsuitable for cisplatin, but not for relapse treatment after initial platinum-based therapy. As with other immune checkpoint inhibitors directed against PD1 or PD-L1, immune-mediated side effects such as hepatitis, pneumonitis, colitis, endocrinopathies or skin reactions have been documented in clinical studies, as well as pronounced fatigue in some cases. There is a risk of exacerbation of a pre-existing autoimmune disease. Clinically significant pharmacological interactions with other active substances have not been described, although the efficacy of atezolizumab is expected to be impaired if immunosuppressive drugs are administered at the same time.

8.1.2 Avelumab

Avelumab is a human monoclonal IgG1 antibody and belongs to the class of immune checkpoint inhibitors. Approved indications are cutaneous Merkel cell carcinoma, renal cell carcinoma and maintenance treatment of urothelial carcinoma. The most common side effects documented in studies on the treatment of urothelial carcinoma [83, 84] were fatigue, diarrhea, hypertension, nausea, weight loss, constipation and immune-mediated side effects. The prescribing information points to side effects such as pneumonitis, colitis, endocrinopathies, skin reactions, hepatitis, pancreatitis and others. There is a risk of exacerbation of pre-existing autoimmune diseases. Clinically relevant pharmacological interactions with other active substances have not been described. Concomitant administration of immunosuppressive drugs is expected to impair the efficacy of avelumab.

8.1.3 BCG (Bacillus Calmette-Guérin)

BCG is a live vaccine containing bacteria derived from *Mycobacterium bovis*. It is approved for intravesical use in non-muscle-invasive urothelial carcinoma and carcinoma in situ of the urinary bladder. Its efficacy is weakened by the simultaneous administration of antimicrobial agents active against mycobacteria such as fluoroquinolones, doxycycline, gentamicin and tuberculostatic drugs (rifampicin, ethambutol, streptomycin, isoniazid, etc.). Side effects described in the prescribing information include (mainly local) infections, fever reactions, local discomfort such as pain and gastrointestinal reactions such as nausea and diarrhea. The possibility of clinically overt tuberculosis caused by intravesical BCG application cannot be ruled out. As the intravesical administration of BCG can lead to a positive skin test for tuberculosis, it is recommended that such a skin test be carried out before BCG application (prescribing information).

8.1.4 Carboplatin

Carboplatin is a platinum derivative that is primarily used in patients with urothelial carcinoma if they cannot be treated with cisplatin, typically in combination with gemcitabine [76, 107, 108]. Approval exists for the treatment of ovarian carcinoma, cervical carcinoma, head and neck squamous cell carcinoma and small cell lung cancer (varying between prescrib-

ing informations provided by the various suppliers). Neutropenia, nausea, vomiting, alopecia, diarrhea or constipation have been reported as frequent side effects. Rarely, neurotoxicity may also occur. Yellow fever vaccination during carboplatin therapy is contraindicated and the use of live attenuated vaccines should be avoided if possible. A relevant pharmacological interaction is described for phenytoin. Simultaneous treatment with immunosuppressants such as cyclosporine or tacrolimus leads to a more pronounced immunosuppression.

8.1.5 Cisplatin

Cisplatin is a platinum derivative that is used as standard therapy for urothelial carcinoma, typically in combination with gemcitabine ± nivolumab or with methotrexate/vinblastine/doxorubicin in the MVAC protocol. It is approved for the treatment of bladder cancer and a broad spectrum of other malignant neoplasms. Major side effects reported include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte imbalances, cardiotoxicity and diarrhea. Vaccination with live vaccines (e.g., yellow fever) is contraindicated. The prescribing information point to relevant pharmacological interactions with other active substances such as ototoxic or nephrotoxic substances, anticoagulants, anticonvulsants or phenytoin as well as more pronounced effects when combined with paclitaxel, docetaxel, bleomycin, vinorelbine or cyclosporine.

8.1.6 Docetaxel

Docetaxel is a taxane. It can be used as a palliative monotherapy for urothelial carcinoma. It is approved for the treatment of breast carcinoma, adenocarcinoma of the stomach, non-small cell lung cancer, prostate cancer and head and neck cancer. Severe grade 3 or 4 side effects include infections, nail changes, stomatitis and diarrhea, while grade 2 side effects include alopecia. Polyneuropathy, sometimes irreversible, is particularly burdensome. Common side effects such as nausea/vomiting and allergic reactions can be prevented by adequate pre-/comedication.

8.1.7 Doxorubicin

Doxorubicin (synonym: Adriamycin) is a cytotoxic chemotherapeutic agent from the class of anthracyclines. It is used for urothelial carcinomas in combination with vinblastine, methotrexate and cisplatin (MVAC protocol) [38]. It is approved for urinary bladder carcinoma and a broad spectrum of malignant neoplasms (breast cancer, lung cancer, ovarian carcinoma, endometrial carcinoma, sarcomas, Wilms' tumor, thyroid carcinoma, neuroblastoma, Hodgkin's and non-Hodgkin's lymphomas, acute leukemias, myeloma). In addition to cardiotoxicity (maximum cumulative total dose in adults 550 mg/m2), particular attention should be paid to hematotoxicity.

Doxorubicin is a substrate of *CYP3A4* and *CYP2D6* and is transported by *P-glycoprotein*. *CYP3A4* inducers and inhibitors of *CYP3A4, CYP2D6* and *P-glycoprotein* can influence the pharmacokinetics and effect of doxorubicin. The simultaneous use of inhibitors or inducers of *CYP* enzymes or *P-glycoprotein* should be avoided if possible. In combination with other cardioactive agents such as calcium antagonists or with other QT-prolonging drugs, electrocardiographic monitoring is necessary. A combination of doxorubicin with taxanes or cyclophosphamide increases cardiotoxicity. In combination with ciclosporin A, *P-glycoprotein* inhibition leads to altered pharmacokinetics with increased plasma levels, possibly resulting in seizures and increased hematotoxicity. In combination with mercaptopurine, doxorubicin increases the mercaptopurine-induced hepatotoxicity. With combined administration of allopurinol and doxorubicin, blood count changes occur more frequently than with administration of either drug alone. Doxorubicin

can reduce the oral bioavailability of digoxin and reduce the absorption of certain antiepileptic drugs (e.g., phenytoin, carbamazepine) with reduced plasma levels of these drugs.

Cardiac function, blood count, liver function, uric acid, potassium, calcium, phosphate and creatinine levels should be monitored before and during treatment. Doxorubicin should be administered via a safe venous access due to its tissue-damaging effect.

8.1.8 Durvalumab

Durvalumab is a monoclonal antibody directed against PD-L1 and belongs to the immune checkpoint inhibitors. It is approved for the treatment of small cell and non-small cell lung cancer, hepatocellular and biliary carcinomas. In advanced urothelial carcinoma, durvalumab has been used as monotherapy [109] and tested in studies for neoadjuvant therapy. As with other immune checkpoint inhibitors, the use of durvalumab is associated with immune-mediated side effects such as pneumonitis, colitis, endocrinopathies, skin reactions, hepatitis, pancreatitis and others, and there is a risk of exacerbation of pre-existing autoimmune diseases. In addition, fatigue and gastrointestinal side effects are frequently described. Clinically relevant pharmacological interactions with other active substances have not been identified, but concomitant administration of immunosuppressive drugs is expected to impair the efficacy of durvalumab.

8.1.9 Enfortumab Vedotin

Enfortumab vedotin is a fully humanized IgG1 antibody directed against *nectin-4* and coupled with the cytotoxic agent MMAE. It is approved for first-line therapy in combination with pembrolizumab and as monotherapy for pre-treated urothelial carcinoma. The most common side effects include fatigue, anemia, peripheral polyneuropathy, alopecia, gastrointestinal complaints and, in some cases, severe skin reactions including toxic epidermiolysis and *Stevens-Johnson* syndrome. The prescribing information also points to hyperglycemia, ophthalmopathy and interstitial pneumonitis as possible side effects. Close monitoring for signs of toxicity is recommended during concomitant treatment with strong *CYP3A4* inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole). Administration of strong *CYP3A4* inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin, St. John's wort) may attenuate the effect of MMAE.

8.1.10 Erdafitinib

Erdafitinib is an orally administered tyrosine kinase inhibitor directed against *fibroblast growth factor receptor (FGFR)* classes 1-4, which is approved in the EU for second-line treatment of urothelial carcinoma with *FGFR3* alterations, after immunotherapy has failed. Clinically relevant side effects most frequently described in clinical studies (e.g., [86]) include hyperphosphatemia, diarrhea and other gastrointestinal complaints, stomatitis and skin/nail disorders. The prescribing information also emphasizes the risk of severe retinopathies. Pharmacological interactions include inhibitors of *CYP2C9* and *CYP3A4*, inducers of *CYP3A4* and substrates of *P-glycoprotein*.

8.1.11 Gemcitabine

Gemcitabine is a nucleoside analog. It is phosphorylated intracellularly and incorporated into the DNA instead of cytidine. Gemcitabine is approved for the treatment of advanced bladder carcinoma (in combination with cisplatin) and various other solid tumors (non-small cell lung cancer, pancreatic carcinoma, ovarian carcinoma, breast cancer). Severe side effects (grade 3

or 4), which occurred in more than 5% of patients in the large randomized phase 3 studies, are neutropenia (10-30%), thrombocytopenia (5-10%), fatigue (5-20%), anemia (5-10%), nausea/vomiting (5%) and laboratory hepatotoxicity with elevation of bilirubin and/or transaminases (5%). Gemcitabine is administered intravenously. Clinically relevant pharmacological interactions have not been described. The use of live vaccines such as yellow fever is cautioned against.

8.1.12 Methotrexate (MTX)

MTX is an antimetabolite which, as a folic acid antagonist, inhibits the conversion of folic acid into folinic acid by dihydrofolate reductase. In the treatment of advanced urothelial carcinoma, it is used in combination with vinblastine/doxorubicin/cisplatin (MVAC protocol). The main side effects are hematotoxicity, gastrointestinal, cardiovascular and renal toxicity. Methotrexate is eliminated renally by tubular secretion. Penicillins and sulfonamides, non-steroidal anti-inflammatory drugs and other drugs can reduce the renal clearance of methotrexate. The simultaneous intake of vitamin preparations containing folic acid or its derivatives can reduce the efficacy of methotrexate. The clearance of other drugs such as oxaliplatin or vancomycin may be decreased in combination with methotrexate. When combined with certain antivirals (e.g., adefovir, cidofovir), radiologic contrast agents or cisplatin, nephrotoxicity increases. Some antivirals, tyrosine kinase inhibitors and antibiotics increase the hepatotoxicity of methotrexate. In combination with TNF blockers and other immunosuppressants or cytostatic drugs, the risk of infections increases. Serious infections or thromboembolism can occur with the simultaneous use of immunosuppressive or myelosuppressive drugs or thalidomide.

Concomitant treatment with immunosuppressants, retinoids, cotrimoxazole and trimethoprim is not recommended. Renal function should be monitored closely. The dosage of methotrexate must be reduced in the case of hepatic or renal insufficiency.

8.1.13 Mitomycin C

Mitomycin belongs to the group of alkylating antibiotics with an antiproliferative effect. It is used as an alternative to BCG for intravesical instillation in non-muscle-invasive urothelial carcinomas of the urinary bladder, for which it is approved. In the presence of bladder perforation or cystitis, its use is contraindicated according to the prescribing information. Allergic skin reactions and treatment-related cystitis are described as possible side effects after intravesical application. Systemic side effects, on the other hand, are very rare.

8.1.14 Nivolumab

Nivolumab is a monoclonal anti-PD1 antibody and belongs to the substance class of immune checkpoint inhibitors. It has been approved as a monotherapy and combination therapy for the treatment of a broad spectrum of malignant neoplasms including urothelial carcinomas. In patients undergoing palliative nivolumab monotherapy for urothelial carcinoma, fatigue, diarrhea and skin reactions have been observed. In addition, anemia, hypoalbuminemia, hyperkalemia, liver enzyme elevations, heart failure, serum amylase elevation, hyponatremia, creatine phosphokinase elevation and renal dysfunction have been reported. Other possible side effects include severe pyrexia and interstitial pneumonia (immune-mediated pneumonitis) as well as immune-mediated intestinal, liver or kidney inflammation and endocrinopathies. Reactivation of a pre-existing autoimmune disease is also possible. In first-line therapy with the combination of nivolumab and cisplatin/gemcitabine (approved in 2024), the side effects and interactions listed under these active substances must be taken into account.

Clinically relevant pharmacological interactions with other active substances are not expected. Concomitant administration of immunosuppressive drugs is expected to impair the efficacy of nivolumab.

8.1.15 Paclitaxel

Like docetaxel, paclitaxel is a cytotoxic chemotherapeutic agent from the taxane class. It is approved for the treatment of breast cancer, ovarian carcinoma, non-small cell lung cancer and AIDS-associated Kaposi's sarcoma. Severe side effects may include infections, stomatitis and diarrhea as well as allergic reactions to the solvent cremophor. Premedication with glucocorticoids, H2 receptor antagonists and antihistamines is mandatory. Alopecia is one of the most troublesome side effects, and polyneuropathy, which can be irreversible, is particularly serious.

The metabolism of paclitaxel is catalyzed in part by the *cytochrome P450* isoenzymes *CYP2C8* and *CYP3A4*. Therefore, special caution is required when paclitaxel is used together with other drugs that inhibit either *CYP2C8* or *CYP3A4* (e.g., azole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir and nelfinavir), as the toxicity of paclitaxel may be increased due to higher paclitaxel exposure. The use of paclitaxel together with other medicinal products that induce either *CYP2C8* or *CYP3A4* (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended as efficacy may be impaired due to lower paclitaxel exposure.

8.1.16 Pembrolizumab

Pembrolizumab is a fully humanized IgG4 monoclonal antibody directed against PD1, that belongs to the class of immune checkpoint inhibitors. It is approved for the treatment of a broad spectrum of malignant neoplasms including urothelial carcinomas as monotherapy and for first-line therapy in combination with enfortumab vedotin. As with other immune checkpoint inhibitors, there is a risk of immune-mediated, sometimes severe side effects such as pneumonitis, endocrinopathy, nephritis, hepatitis, colitis or skin reactions as well as reactivation of pre-existing autoimmune diseases.

Relevant pharmacological interactions have not been described. Concomitant administration of immunosuppressive drugs is expected to impair the efficacy of pembrolizumab.

8.1.17 Sacituzumab Govitecan

Sacituzumab Govitecan is a humanized monoclonal antibody against *TROP2* (*trophoblast cell surface antigen 2*), which is coupled with the cytotoxic topoisomerase inhibitor SN-38. It is approved for the treatment of breast cancer. From studies on treatment of patients with urothelial carcinoma, mainly hematotoxicity (anemia, neutropenia, thrombocytopenia) and gastrointestinal side effects (mainly diarrhea, but also nausea and vomiting) have been reported. Hematotoxicity appears to be particularly pronounced in patients with reduced *UGT1A1* activity.

No systematic studies are available on pharmacological interactions with other active substances. Concomitant administration of *UGT1A1* inhibitors (e.g., propofol, ketoconazole, *EGFR* tyrosine kinase inhibitors) could lead to increased toxicity due to SN-38. Accordingly, the concomitant administration of *UGT1A1* inducers (e.g., carbamazepine, phenytoin, rifampicin, ritonavir, tipranavir) may lead to an attenuation of the efficacy of sacituzumab govitecan.

8.1.18 Vinblastine

Vinblastine is a chemotherapeutic agent from the vinca alkaloid drug class and inhibits mitosis by inhibiting the formation of microtubules. It is approved for the treatment of malignant lymphomas, breast and testicular carcinomas and Langerhans cell histiocytosis. For the treatment of urothelial carcinoma, it is used in combination with cisplatin/methotrexate/doxorubicin (MVAC). The side effects documented among them are accordingly attributable to the combination of these agents. Specific vinblastine-associated side effects include hematotoxicity (leukopenia, thrombocytopenia, anemia), neurotoxicity (peripheral polyneuropathy), nausea/vomiting and constipation.

The prescribing information points out that the use of vinblastine sulfate in patients who are simultaneously receiving drugs with an inhibitory effect on the metabolization of drugs via isoenzymes of the hepatic cytochrome *CYP3A*, as well as in patients with liver dysfunction, may lead to earlier occurrence and/or increased severity of side effects. Concomitant administration with digitoxin may lead to reduced digitoxin blood levels. The simultaneous use of phenytoin with vinblastine sulfate may cause reduced phenytoin levels in the blood.

8.1.19 Vinflunine

Vinflunine is a fluorinated derivative of vinorelbine and, as a vinca alkaloid, belongs to the active substance class of mitosis inhibitors whose cytotoxicity is based on inhibition of the microtubules. It has been approved for the palliative monotherapy of urothelial carcinoma [82]. The main side effects are hematotoxicity (neutropenia, thrombocytopenia, anemia), gastrointestinal disorders (constipation, loss of appetite, nausea, vomiting, diarrhea), stomatitis/mucositis and fatigue. Vinflunine can also cause sensory peripheral neuropathy, but only very rarely to a severe degree (grade 3 or 4) according to the prescribing information.

No strong *CYP3A4* inhibitors (e.g., ritonavir, ketoconazole, itraconazole or grapefruit juice) or strong *CYP3A4* inducers (e.g., rifampin or *St. John's wort*) should be taken together with vinflunine. Concomitant use of drugs that can prolong the QT time should be avoided.

9 Rehabilitation

Patients with bladder cancer require follow-up care after cystectomy and urinary diversion that is adapted to their specific needs. After neoadjuvant therapy, rehabilitation can begin as soon as possible postoperatively. In the case of adjuvant chemotherapy, it should only take place after this has been completed. Patients in a severely reduced general condition postoperatively may require somatic and psychological consolidation to ensure the feasibility of the planned adjuvant therapy.

In rehabilitation, postoperative functional disorders are treated in a multidisciplinary setting with the necessary therapeutic spectrum. In particular, the focus is on urinary incontinence, bladder emptying disorders, sexual dysfunction and, if necessary, dealing with urostomy. In the case of multimorbidity of the (mostly elderly) patients, treatment strategies are individually adapted to their mental and physical capacity. In employed patients, information on participation in professional and social life and the offer of specific assistance in returning to work is an additional task.

9.1 Urinary diversion

Patients with neobladder after cystectomy require a multimodal concept with physiotherapy, education, drug therapy and, if necessary, biofeedback sphincter training with video-assisted

cystoscopy to overcome postoperative urinary incontinence. In contrast, patients with a urostomy require training in independent care with psycho-oncological support to improve acceptance of the altered body image.

Patients are also trained to pay attention to possible acidosis, mucus development in the intestinal replacement bladder, urinary tract infections or obstructions and digestive problems. Adequate fluid intake is always a problem [110].

9.2 Sexual dysfunction

There is little data available on sexual dysfunction in women, while erectile dysfunction in men can be treated with established aids. These include medication with phosphodiesterase inhibitors following neurobehavioral surgical techniques. If their use alone is ineffective, vacuum erection assist systems, intracavernous injections or intraurethral prostaglandin applications are available.

9.3 Lymphedema

Lymphedema of the legs should be treated with compression using stockings or elastic wrapping. Manual lymphatic drainage is also useful after thrombosis has been ruled out and a lymphocele has been excluded.

9.4 Rehabilitation after chemotherapy

After neoadjuvant or adjuvant chemotherapy as part of the primary treatment of bladder cancer, the typical chemotherapy-induced side effects such as cisplatin-induced polyneuropathy or fatigue are also treated.

10 Monitoring and follow-up

10.1 Monitoring

The regular recording of quality of life, distress and symptom burden as "PROs" (Patient-Reported Outcomes) is desirable. This can be easily integrated into regular patient care using the "Distress Thermometer". More extensive scores such as the *EORTC* quality of life questionnaires or fatigue questionnaires are also possible, but are considerably more complex.

10.2 Follow-up

The aims of follow-up are the early diagnosis of a relapse with the aim of extending survival time / increasing the chance of recovery, the detection of side effects of therapy and prevention.

10.2.1 Non-muscle-invasive bladder carcinoma

For non-muscle-invasive bladder cancers, divided into low-, intermediate- and high-risk cancers according to the EORTC risk classification, follow-up according to assigned risk group is carried out according to NICE guideline [111], see Table 10.

Table 10: Follow-up for non-muscle-invasive bladder cancer

	Time after primary therapy in months												
Procedure	3	6	9	12	15	18	21	24	30	36	48	60	Annually
Low risk													
Cystoscopy	X			X				X		X	X	X	
Intermediate risk													
Cystoscopy	X	X	X	X		X		X	X	X	X	X	
Urine cytology	X	X	X	X		X		X	X	X	X	X	
Thin-layer CT urography or MRI				X				X		X	X	X	
High risk													
Cystoscopy	X	X	X	X	X	X	X	X	X	X	X	X	
Urine cytology	X	X	X	X	X	X	X	X	X	X	X	X	
Thin-layer CT urography or MRI				X				X		X	X	X	

10.2.2 Muscle-invasive bladder carcinoma

Follow-up is adapted to the primary curative therapy in various forms**.** The recommendations follow the adaptation of the *NICE* guideline by the German S3 guideline of the *AWMF* [20]. It is unclear whether the early diagnosis of metastasis with a correspondingly early start of salvage treatment leads to an increase in survival time or whether this is merely due to the "lead-time bias effect".

10.2.2.1 Radical cystectomy and urinary diversion

Localized urinary bladder tumors ≤pT2pN0 are checked for the first time after 3-6 months by CT thorax and abdomen, ureteroscopy, lavage cytology and urine cytology for the upper urinary tract, then for 2 years at 6-month intervals, in the 3rd-5th follow-up years every 12 months, and from the 6th year onwards imaging is only performed in case of positive urine cytology or new hydronephrosis.

For locally advanced bladder cancer (≥pT3 and/or pN1), follow-up imaging begins after 3-6 months up to the 3rd year, in the following 3 years it is indicated every 12 months and from the 6th year only in case of new hydronephrosis or positive urine cytology.

Due to a possible vitamin B12 deficiency, the vitamin B12 level is checked annually from the 3rd year onwards. Functional disorders of the urinary tract should be checked at the same intervals; long-term continuation at annual intervals is also recommended from the 6th year onwards (Tables 11 and 12).

Table 11: Follow-up after cystectomy for ≤pT2pN0

Procedures	Time after cystectomy in months											
	3	6	12	18	24	30	36	42	48	54	60	Annually
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Blood gas analysis	X	X	X	X	X	X	X	X	X	X	X	X
Urine culture	X	X	X	X	X	X	X	X	X	X	X	X
Urine cytology		X	X	X		X		X		X		X
Lavage cytology (defunctionalized urethra)			X		X		X		X		X	
Vitamin B12							X		X		X	X
Ultrasound	X	X	X	X	X	X	X	X	X	X	X	X
CT thorax/abdomen incl. urography	(X)	X	X	X	X		X		X		X	suspected relapse
Stoma control	X	X	X	X	X	X	X	X	X	X	X	X
History of continence and sexual function	X	X	X	X	X	X	X	X	X	X	X	X
Psycho-oncological social status	X	X	X	X	X	X	X	X	X	X	X	X

Table 12: Follow-up after cystectomy for ≥pT3 and/or pN+, or after multimodal therapy

Diagnostics	Time after cystectomy in months											
	3	6	12	18	24	30	36	42	48	54	60	Annualy
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Blood gas analysis	X	X	X	X	X	X	X	X	X	X	X	X
Urine culture	X	X	X	X	X	X	X	X	X	X	X	X
Urine cytology		X	X	X		X		X		X		X
Lavage cytology (defunctionalized urethra)		X	X	X	X	X	X	X	X		X	
Vitamin B12							X		X		X	X
Sonography	X	X	X	X	X	X	X	X	X	X	X	X
CT thorax/abdomen incl. urography	(X)	X	X	X	X		X		X		X	suspected relapse
Stoma control	X	X	X	X	X	X	X	X	X	X	X	X
History of continence and sexual function	X	X	X	X	X	X	X	X	X	X	X	X
Psycho-oncological social status	X	X	X	X	X	X	X	X	X	X	X	X

10.2.2.2 Follow-up after multimodal therapy

Patients who are in complete remission require lifelong regular follow-up by cystoscopy and urine cytology, which should take place at 3-monthly intervals in the first 3 years, every 6 months in the 4th and 5th year and annually from the 5th year onwards. In case of suspicious findings, biopsies and an early diagnostic check may be necessary. The remaining imaging corresponds to the follow-up after cystectomy.

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15 Links

Occupational exposure http://www.thieme-connect.de/ejournals/html/10.1055/s-0029-1243897

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17 Disclosures

according to the rules of the responsible Medical Societies.

17 Declaration of possible conflicts of interest

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