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CLINICAL GUIDES IN ONCOLOGY

# SEOM–SOGUG clinical guideline for urothelial cancer (2025)

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**Abstract**
This clinical guideline provides evidence-based recommendations for the diagnosis, staging, and management of bladder cancer across all disease stages. In these guidelines (updated in 2025), we summarize current evidence and available therapies for the medical management of urothelial cancer.

**Keywords** Bladder cancer · Muscle-invasive · Non-muscle invasive · Upper tract tumor · Urothelial

## Introduction

Urothelial carcinomas (UC), also known as transitional cell carcinomas, originate from the urothelium. The majority (90%) are located in the bladder, followed by the renal pelvis (upper tract urothelial carcinoma [UTUC], 8%), ureter, and urethra (2%). UC is four times more common in males than in females, with the incidence increasing with age and peaking in the seventh and eighth decades of life. Overall, 90% of bladder UC are localized at diagnosis, with 75% confined to the mucosa or submucosa, as non-muscle-invasive bladder cancer (NMIBC), and 25% infiltrating the detrusor muscle, qualifying as muscle-invasive bladder cancer (MIBC). Up to 10% of patients present with clinically evident metastases at

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diagnosis, and approximately one-third of those with localized MIBC will develop metastases following primary tumor treatment [1].

## Methodology

Development of the initial Spanish Society of Medical Oncology (SEOM)–Spanish Group Association of Genitourinary Oncology (SOGUG) guideline was based on a systematic review of relevant published studies and clinical guidelines, complemented by multidisciplinary expert consensus. The utilized methodological framework adhered to the principles established by the Infectious Diseases Society of America–United States (US) Public Health Service Grading System for ranking recommendations. The updated recommendations in these guidelines reflect the results of clinical trials released since the publication of the previous version of these guidelines in 2022 [2], plus some minor corrections to the wording of the original guidelines. The updated version of these guidelines has been approved by all the authors.

A comprehensive review of peer-reviewed articles, clinical trials, meta-analyses, and guidelines published up to 2025 was conducted, with an emphasis on high-quality evidence, including randomized controlled trials (level I evidence) and well-conducted meta-analyses. A panel comprising ten Spanish expert oncologists from affiliated cooperative oncology research groups participated in the guidelines' development. The grading of recommendations followed the Infectious Diseases Society of America framework classifying levels of evidence from I to V, where I represents evidence from large, randomized trials and V represents expert opinion. Similarly, grades of recommendation range from A to E, where A reflects strong evidence for substantial clinical benefit (Table 1). The final recommendations were formulated through multiple rounds of discussion to achieve consensus among authors. Notably, local regulatory status and procedural guidelines should be considered when interpreting the recommendations. The final version was reviewed externally and approved by SEOM to ensure accuracy, clarity, and clinical applicability.

## Epidemiology and risk factors

Bladder cancer is a major global public health concern and remains one of the most prevalent malignancies of the urinary tract. In 2022, an estimated 613,791 new cases and 220,349 deaths were attributed to bladder cancer worldwide, ranking it as the ninth most common cancer globally. The disease shows significant geographical variation, with Europe, particularly Spain, exhibiting some of the highest incidence rates. According to the latest Spanish Network of Cancer Registries (REDECAN) projections, bladder cancer will be the fifth most diagnosed cancer in Spain in 2025, with an estimated 22,435 new cases and 4499 deaths in 2023 [3, 4].

The primary etiological factor for bladder cancer is exposure to environmental carcinogens, with tobacco smoking being the most significant risk factor; approximately 50% of tumors in both sexes are attributed to smoking. Other major risk factors include occupational exposure to aromatic amines, polycyclic hydrocarbons and benzidines, which are widely used in the dye, rubber, leather, and chemical industries. Additional recognized risk factors include pelvic radiation therapy, cumulative doses of cyclophosphamide and schistosomiasis infection (endemic in Africa, Asia, and South America) [5]. While a family history of bladder cancer may suggest a genetic predisposition, specific hereditary

**Table 1** Levels of evidence/grades of recommendation

| | |
|---|---|
| *Levels of evidence* | |
| I | Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity |
| II | Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case–control studies |
| V | Studies without control group, case reports, experts' opinion |
| *Grades of recommendation* | |
| A | Strong evidence for efficacy with a substantial clinical benefit; strongly recommended |
| B | Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended |
| C | Insufficient evidence for efficacy or benefit; does not outweigh risk or disadvantages (adverse events, costs, etc.); optional |
| D | Moderate evidence against efficacy or for adverse outcome; generally not recommended |
| E | Strong evidence against efficacy or for adverse outcome; never recommended |

syndromes are uncommon. However, patients with Lynch syndrome have a significantly increased risk of developing urothelial tumors, particularly those arising in the upper urinary tract [6].

## Pathological and molecular subtypes of urothelial bladder cancer

Urothelial tumors are broadly classified into non-invasive urothelial neoplasms and invasive UC. The former follows as a four-tiered classification based on architectural and cytological abnormalities, and includes entities such as urothelial papilloma and carcinoma in situ (CIS). The 2022 World Health Organization (WHO) classification redefined low-grade tumors with < 5% high-grade fraction as ''low-grade tumors with < 5% high-grade component", rather than classifying them as high grade as in previous editions. Invasive UC is predominantly high grade; however, since low-grade invasive UC may occasionally occur with more favorable prognosis, it is now recognized in the 2022 WHO classification, which also recommends grading all invasive UC cases. Invasive UC can present with diverse morphological patterns, most commonly as UC with divergent differentiation, including squamous and/or glandular differentiation, and less frequently, neuroendocrine, trophoblastic, or Müllerian lineage differentiation. The classification also introduces an expanding list of histologic subtypes (previously termed variants, a terminology that has been abandoned in the most recent WHO classification). Notably, the 2022 WHO classification added two new subtypes: large nested carcinoma and tubular carcinomas. Finally, non-urothelial tumors of the bladder (NUC) include pure squamous cell carcinomas (SCC) and adenocarcinomas (AC), among others (Table 2) [7].

Histopathologically, T stage and lymph node status remain the most important prognostic factors following radical cystectomy (RC) for MIBC. Additional features associated with a worse prognosis include tumor location in the trigone or bladder neck, prostatic urethral involvement, lymphovascular invasion or concurrent CIS in organ-confined disease [8].

NMIBC and MIBC have distinct pathogenic pathways with commonly mutated genes including *FGFR3*, *TERT*, *TP53*, *PIK3CA*, and genes involved in chromatin remodeling. Advances in molecular pathology have led to several RNA expression-based classifications, reflecting the heterogeneous biological behavior of the disease in both NMIBC and MIBC. For MIBC, six molecular classifications have been proposed using non-overlapping datasets. To unify research efforts, a team of multidisciplinary experts developed the ''Consensus Molecular Classification of Muscle-invasive Bladder Cancer'' [9]. This classification defines six transcriptomic subtypes: luminal papillary (24%), luminal non-specified (8%), luminal unstable (15%), stroma-rich (15%), basal/squamous (35%), and neuroendocrine-like (3%). Each molecular subtype exhibits unique differentiation patterns, oncogenic mechanisms, tumor microenvironments and histopathological features, which correlate with clinical outcomes. From a clinical perspective, this classification may have a prognostic role (neuroendocrine-like tumors have been linked with poor survival, while luminal papillary tumors have improved outcomes), with potential therapeutic implications. For example, luminal papillary tumors are enriched for fibroblast growth factor receptor 3 (FGFR3) signaling, making them a potential candidate for FGFR inhibitors. Other studies suggest that transcriptomic clustering could serve as predictive biomarkers of response to therapy, including intravesical Bacillus Calmette-Guérin (BCG), neoadjuvant chemotherapy (NACT), or immune checkpoint inhibitors (CPIs); however, prospective validation is lacking. Molecular clustering of NMIBC has been less studied. Disease aggressiveness in NMIBC has been linked with genomic alterations, transcriptomic classes, and immune cell infiltration. Although molecular subtyping has the potential to improve the traditional clinical risk-classification systems, its role in guiding treatment decisions remains unproven [10].

From a genomic perspective, *FGFR3* alterations are more frequent in NMIBC (up to 60% in high-grade Ta tumors without CIS, and around 75% of low-grade Ta tumors) [11]. This knowledge has driven the development of novel intravesical devices that deliver FGFR3 inhibitors, which are currently being tested in clinical trials for NMIBC. In metastatic UC, where *FGFR3* alterations are found in only 15–20% of cases, FGFR-targeted therapies have been successfully developed. Other potential biomarkers (e.g., programmed cell death-ligand 1 [PD-L1], tumor mutation burden, transforming growth factor β), remain challenging to implement in clinical practice, with inconsistent evidence supporting their routine use.

## Clinical presentation and staging workup

Hematuria is the most common presenting symptom, occurring in approximately 85% of patients. It is typically painless and may be either macroscopic or microscopic. Additionally, patients may report irritative urinary symptoms, such as dysuria, urinary frequency, urgency, or nocturia. Pelvic pain is less common but may suggest advanced or MIBC. In advanced stages, patients may present with weight loss, fatigue, or bone pain, which could indicate metastatic disease.

The initial diagnostic workup includes a physical examination, complete blood count, and biochemistry tests, as

**Table 2** The 2022 WHO classification of urinary tract tumors [7]

| | |
|---|---|
| Non-invasive urothelial neoplasms | Urothelial papilloma<br>Urothelial papilloma, inverted<br>Papillary urothelial neoplasm of low malignant potential<br>*Inverted papillary urothelial neoplasm of low malignant potential*<br>Non-invasive papillary urothelial carcinoma, low grade<br>*Low-grade papillary urothelial carcinoma with an inverted growth pattern*<br>Non-invasive papillary urothelial carcinoma, high grade<br>*Non-invasive high-grade papillary urothelial carcinoma with an inverted growth pattern*<br>Urothelial carcinoma in situ |
| Invasive urothelial neoplasms | Invasive urothelial carcinoma<br>Conventional urothelial carcinoma<br>Urothelial carcinoma with squamous differentiation<br>Urothelial carcinoma with glandular differentiation<br>Urothelial carcinoma with trophoblastic differentiation<br>Nested urothelial carcinoma<br>Large nested urothelial carcinoma<br>Tubular and microcystic urothelial carcinomas<br>Micropapillary urothelial carcinoma<br>Lymphoepithelioma-like urothelial carcinoma<br>Plasmacytoid urothelial carcinoma<br>Giant cell urothelial carcinoma<br>Lipid-rich urothelial carcinoma<br>Clear cell (glycogen-rich) urothelial carcinoma<br>Sarcomatoid urothelial carcinoma<br>Poorly differentiated urothelial carcinoma |
| *Squamous cell neoplasms of the urinary tract* | |
| Squamous papilloma | |
| *Squamous cell carcinomas of the urinary tract* | Verrucous carcinoma<br>Pure squamous carcinoma of the urothelial tract |
| *Glandular neoplasms* | |
| Adenomas | Villous adenoma<br>Tubular adenoma<br>Tubulovillous adenoma |
| Adenocarcinomas | Adenocarcinoma, NOS<br>Enteric adenocarcinoma<br>Mucinous adenocarcinoma<br>Mixed adenocarcinoma<br>Signet ring cell adenocarcinoma<br>Adenocarcinoma in situ |
| Urachal and diverticular neoplasms | Urachal carcinoma<br>Invasive urothelial carcinoma |
| *Urethral neoplasms* | |
| Urethral accessory gland carcinomas | Carcinoma of Littré glands<br>Carcinoma of Skene glands<br>Carcinoma of Cowper glands |
| Tumors of Müllerian type | Clear cell carcinoma<br>Endometrioid carcinoma |

*NOS* not otherwise specified

well as urinary cytology, upper urinary tract imaging, and cystoscopy. Cystoscopy is the gold standard for the initial diagnosis, allowing direct visualization of the bladder mucosa and enabling biopsy of suspicious lesions. Transurethral resection of bladder tumor (TURBT) provides tissue for histopathological analysis, confirming the diagnosis, and assessing the depth of invasion (NMIBC versus MIBC). Histological diagnosis should follow the WHO classification [7].

Staging workup should include a chest, abdomen, and pelvis computed tomography (CT) scan. CT urography is the preferred imaging modality to evaluate the upper urinary tract (kidneys and ureters) and assess for extravesical (outside the bladder) extension of the disease. Magnetic resonance imaging is particularly helpful for assessing the local extent of the disease, and is an option in selected cases. A bone scan is indicated if bone metastases are suspected. 18-fluorodeoxyglucose positron emission tomography/CT has limited value and is not recommended for routine staging [8]. Staging should follow the guidelines outlined in the American Joint Committee on Cancer Staging Manual, 8th edition (Table 3) [12].

## Treatment of non-muscle-invasive bladder cancer

TURBT is the cornerstone surgical intervention for NMIBC. The primary goal of complete TURBT is to remove all visible tumor areas and obtain adequate tissue for pathological assessment, ensuring accurate staging and risk stratification. A second TURBT within 6 weeks is recommended in high-risk patients or when the initial resection is incomplete. Based on European Association of Urology (EAU) risk stratifications (Table 4) [13], intravesical therapy instillations are recommended following TURBT.

For patients with low-risk NMIBC, as well as those with a small, low-grade Ta recurrence detected more than one year after previous TURBT, a single immediate post-operative intravesical chemotherapy instillation with mitomycin C, epirubicin, or gemcitabine is recommended. A large systematic review and meta-analysis including 2278 patients, demonstrated that immediate intravesical chemotherapy instillation reduced the 5-year recurrence rate by 14%, from 59 to 45% compared with TURBT alone [14].

For intermediate- and high-risk NMIBC, intravesical administration of BCG therapy is recommended to reduce

**Table 3** TNM staging system for urothelial carcinoma of the bladder [12]

| | |
|---|---|
| *T. primary tumor* | |
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Ta | Non-invasive papillary carcinoma |
| Tis | Carcinoma in situ: "flat tumor" |
| T1 | Tumor invades subepithelial connective tissue |
| T2 | Tumor invades muscle |
| T2a | Tumor invades superficial muscle (inner half) |
| T2b | Tumor invades deep muscle (outer half) |
| T3 | Tumor invades perivesical tissue: |
| T3a | Microscopically |
| T3b | Macroscopically (extravesical mass) |
| T4 | Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall |
| T4a | Tumor invades prostate stroma, seminal vesicles, uterus, or vagina |
| T4b | Tumor invades pelvic wall or abdominal wall |
| *N. regional lymph nodes* | |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral) |
| N2 | Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral) |
| N3 | Metastasis in a common iliac lymph node(s) |
| *M. distant metastasis* | |
| M0 | No distant metastasis |
| M1a | Non-regional lymph nodes |
| M1b | Other distant metastasis |

**Table 4** EAU guidelines on NMIBC prognostic factor risk groups [13]

| Risk group | |
|---|---|
| Low risk | A primary, single TaT1 LG/G1 tumor < 3 cm in diameter without CIS in a patient ≤ 70 years<br>A primary Ta LG/G1 tumor without CIS with at most 1 of the additional clinical risk factors |
| Intermediate risk | Patients without CIS who are not included in either the low-, high-, or very high-risk groups |
| High risk | All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group<br>All CIS patients, EXCEPT those included in the very high-risk group<br>Stage, grade with additional clinical risk factors:<br>Ta LG/G2 or T1G1, no CIS with all 3 risk factors<br>Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors<br>T1G2 no CIS with at least 1 risk factor |
| Very high risk | Stage, grade with additional clinical risk factors:<br>Ta HG/G3 and CIS with all 3 risk factors<br>T1G2 and CIS with at least 2 risk factors<br>T1 HG/G3 and CIS with at least 1 risk factor<br>T1 HG/G3 no CIS with all 3 risk factors |

*CIS* carcinoma in situ; *EAU* European Association of Urology; *G* grade; *HG* high grade; *LG* low grade; *NMIBC* non muscle-invasive bladder cancer; *T* tumor

the risk of recurrence. Several meta-analyses have demonstrated that intravesical BCG after TURBT is superior to TURBT alone or TURB plus intravesical chemotherapy for preventing recurrence of NMIBC [15]. The standard BCG schedule includes an induction phase of 6-weekly instillations, followed by a maintenance phase of up to 1–3 years from the start of the induction cycle. For high-risk NMIBC (including multiple or large tumors, high-grade tumors, or CIS, three years of maintenance therapy are strongly recommended [16].

Patients with very high-risk NMIBC face a substantial risk of progression to muscle-invasive disease and, therefore, immediate RC is the preferred treatment option. In cases where the patient is considered unfit or rejects RC, a complete schedule of intravesical BCG for 1–3 years is recommended.

Recurrences after intravesical therapy are managed based on the tumor risk classification and the prior administered therapy. Patients with NMIBC who relapse during or after intravesical chemotherapy can be treated with BCG instillations. For patients with NMIBC who experience recurrence during or after intravesical BCG, several categories of BCG failure have been proposed, including:

- *BCG-relapsing tumor:* recurrence of high-grade/G3 tumor after completion of BCG maintenance, despite an initial response.
- *BCG-refractory tumor:*

  1. If T1 high-grade/G3 tumor is present at 3 months.
  2. If Ta high-grade/G3 tumor is present after 3 months and/or at 6 months, after either re-induction or the first course of maintenance therapy.
  3. If CIS (without concomitant papillary tumor) is present at 3 months and persists at 6 months after either re-induction or the first course of maintenance therapy. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases.
  4. If high-grade tumor appears during BCG maintenance therapy.

- *BCG-unresponsive tumor:* includes all BCG-refractory tumors and those who develop T1/Ta high-grade recurrence within 6 months of completion of adequate BCG exposure, or those who develop CIS within 12 months of completion of adequate BCG exposure.

Patients with high-grade NMIBC who relapse after BCG, but do not meet the criteria for BCG-unresponsive disease, may still benefit from additional BCG therapy. Patients with BCG-unresponsive NMIBC are unlikely to respond to further BCG therapy and RC is the preferred treatment option. Patients with BCG-unresponsive disease, who are ineligible for RC may undergo bladder-preserving alternative therapies including intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, or intravesical or systemic immunotherapy like pembrolizumab (currently not approved by the European Medicines Agency [EMA]) [17], ideally within a clinical trial. It is important to note that all these alternative treatments for BCG-unresponsive disease remain exploratory and are considered oncologically inferior to RC.

## Management of locoregional disease

### Radical cystectomy

RC with regional lymphadenectomy (LND) and urinary diversion is the standard surgical treatment for MIBC cT2-T4aN0M0 [18]. In men, RC includes removal of the bladder, distal ureters, and regional lymph nodes as well as the prostate and seminal vesicles. In women, the urethra, uterus, distal ureters, and part of the vagina should also be resected. RC can be performed via open, laparoscopic, or robot-assisted surgery. Standard LND includes removal of the distal common, internal and external iliac nodes, the obturator, and hypogastric lymph nodes. Although extended LND has been investigated, prospective trials have not demonstrated a significant benefit in recurrence-free survival or overall survival (OS) [19].

### Bladder-preservation strategies

Although RC is considered the gold standard for localized MIBC, bladder-preserving therapy is a reasonable alternative for patients medically unfit for surgery or who wish to avoid it. Ideal candidates for bladder preservation include those who, after maximal TURBT, meet the following criteria: have a unifocal tumor < 5 cm of urothelial histology, absence of CIS, clinical stage T2–T3a, no hydronephrosis, and good bladder function and capacity [20]. The preferred strategy is trimodal therapy (TMT), which consists of maximal TURBT followed by concurrent chemoradiotherapy. If residual disease is present at response evaluation, salvage cystectomy is recommended. A multidisciplinary approach including urologists, medical oncologists, and radiation oncologists is essential. The two commonly used radiotherapy dose regimens include conventional fractionation regimen (2 Gy per fraction, 64 Gy over 6 weeks) and a hypofractionated regimen (2.75 Gy per fraction, 55 Gy over 4 weeks). A meta-analysis of individual patient data from trials where both dose regimens were permitted, showed superior locoregional control with hypofractionation and comparable toxicity rates [21]. The benefit of adding concurrent chemotherapy to radiotherapy over radiotherapy alone has been confirmed in two randomized trials: the first one with cisplatin, demonstrating a reduction in the incidence of first pelvic recurrence, and the second one with combination of 5-fluorouracil (5-FU) and mitomycin, improving 2-year locoregional disease-free survival (DFS) and 5-year OS [22, 23]. Alternative regimens are cisplatin plus 5-FU, cisplatin plus paclitaxel, and low-dose gemcitabine [24, 25]. However, there is no consensus on the optimal chemotherapy agent and treatment selection varies in practice based on patient-specific factors, chemotherapy agent availability, and clinician preference. Response to TMT is prognostic and patients with favorable pathological response have better OS. No randomized trials directly compare bladder-preserving strategies with RC; propensity score-matched and -weighted analysis of data from retrospective studies suggests OS rates equivalent to RC series at 5 years [26]. Meta-analyses have not found significant differences in progression-free survival (PFS), metastasis-free survival, or OS between the two strategies [27, 28].

### Perioperative systemic therapies

#### Neoadjuvant treatment

Cisplatin-based NACT improves OS and DFS in patients with localized non-metastatic MIBC (T2–T4aN0M0), and this benefit has been demonstrated in several randomized trials. The BA06 30894 study compared neoadjuvant cisplatin/methotrexate/vinblastine versus RC or full-dose external-beam radiotherapy. With a median follow-up of 8 years, NACT resulted in a 16% reduction in the risk of death (hazard ratio [HR] 0.84; 95% confidence interval [CI] 0.72–0.99), corresponding to an increase in the 10-year OS rate from 30 to 36% and in the median OS from 37 to 44 months in favor of NACT [29]. Also, a Southwest Oncology Group study, SWOG-8710, confirmed the benefit of NACT compared with surgery alone, with median OS of 46 versus 77 months. In both treatment groups, the absence of residual cancer in the cystectomy specimen (i.e., pathological complete response [pCR]) was associated with improved OS compared with patients with residual disease at surgery, with 85% of patients with pCR alive at 5 years. Patients receiving NACT had a significantly higher proportion of pCR than those who underwent RC alone (38% vs 15%). Patients treated with NACT did not have an increased risk of death or surgical complications [30].

Three meta-analyses have further demonstrated the benefit of NACT in MIBC. The first included ten trials and found a relative reduction in the risk of death of 9% with NACT versus RC, with an absolute 5-year OS benefit of 5% with platinum-based combinations [31]. A second meta-analysis with 11 trials (8 of them with cisplatin-based NACT), found an absolute survival benefit of 6% with NACT, and only 1% chemotherapy-related mortality [32]. The results of the latest meta-analysis also support the use of NACT, with a 5% absolute improvement in OS at 5 years [33].

Despite these findings, the optimal cisplatin-based neoadjuvant regimen is not clearly defined. An academic phase 3 trial aimed to address this question by comparing six cycles of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) with four cycles of

cisplatin–gemcitabine (CG). Among the study population, 88% of patients received NACT while 11% received adjuvant chemotherapy. The study failed to demonstrate a significant increase in three-year PFS with ddMVAC versus CG (66% vs 56%; HR 0.77; 95% CI 0.57–1.02), although pCR rates were higher with ddMVAC than with CG (42% vs 36%). However, ddMVAC was associated with a higher incidence of adverse events. At five years, there was no evidence of improved OS with ddMVAC compared with CG in the intent-to-treat (ITT) population (64% vs 56%; HR 0.79, 95% CI 0.59–1.05) [34, 35]. Cisplatin-free regimens are not recommended due to their poor pCR rates [36] so, in patients who are ineligible for optimal doses of cisplatin, it is recommended to proceed directly to RC. Additionally, there is no consensus regarding the optimal number of cycles of NACT. While most regimens currently administer four cycles of NACT, six cycles may be considered in patients with pelvic lymph node involvement (a subgroup associated with poor prognosis and underrepresented in most studies) [37].

Recent studies have also explored the role of immunotherapy in the neoadjuvant setting. The phase 3 Niagara trial randomized 1063 cisplatin-eligible patients to receive neoadjuvant CG with or without durvalumab for 4 cycles, followed by RC. In the experimental arm, patients also received adjuvant durvalumab for eight additional cycles. Event-free survival in the ITT population at 2 years was 67.8% in the durvalumab group and 59.8% in the comparator group (HR 0.68; 95% CI 0.56–0.82); estimated 24-month OS rates were 82.2% and 75.2%, respectively (HR 0.75; 95% CI 0.59–0.93). While the planned formal analysis for pCR did not reach statistical significance, the experimental arm showed numerically higher pCR rates with durvalumab versus without (33.8% vs 25.8%) [38].

Given the positive results obtained with the perioperative approach in the NIAGARA trial, this strategy is currently considered the preferred option in cisplatin-eligible patients with localized MIBC (Fig. 1). In contrast, the use of ddMVAC in combination with CPIs is under active investigation, but there is currently insufficient evidence to support its routine clinical use.

## Adjuvant treatment

The role of adjuvant chemotherapy (ACT) in high-risk MIBC after RC remains controversial, particularly in patients who did not receive neoadjuvant therapy. To date, only one randomized trial has demonstrated a significant OS benefit. This study, conducted by SOGUG, was closed early due to low accrual but showed a significant difference in 5-year OS, favoring the chemotherapy arm with cisplatin–gemcitabine–paclitaxel over observation (60% vs 31%; HR 0.39) [39]. A meta-analysis of ten randomized trials, including individual patient data from 1183 patients, further evaluated the role of cisplatin-based ACT and demonstrated

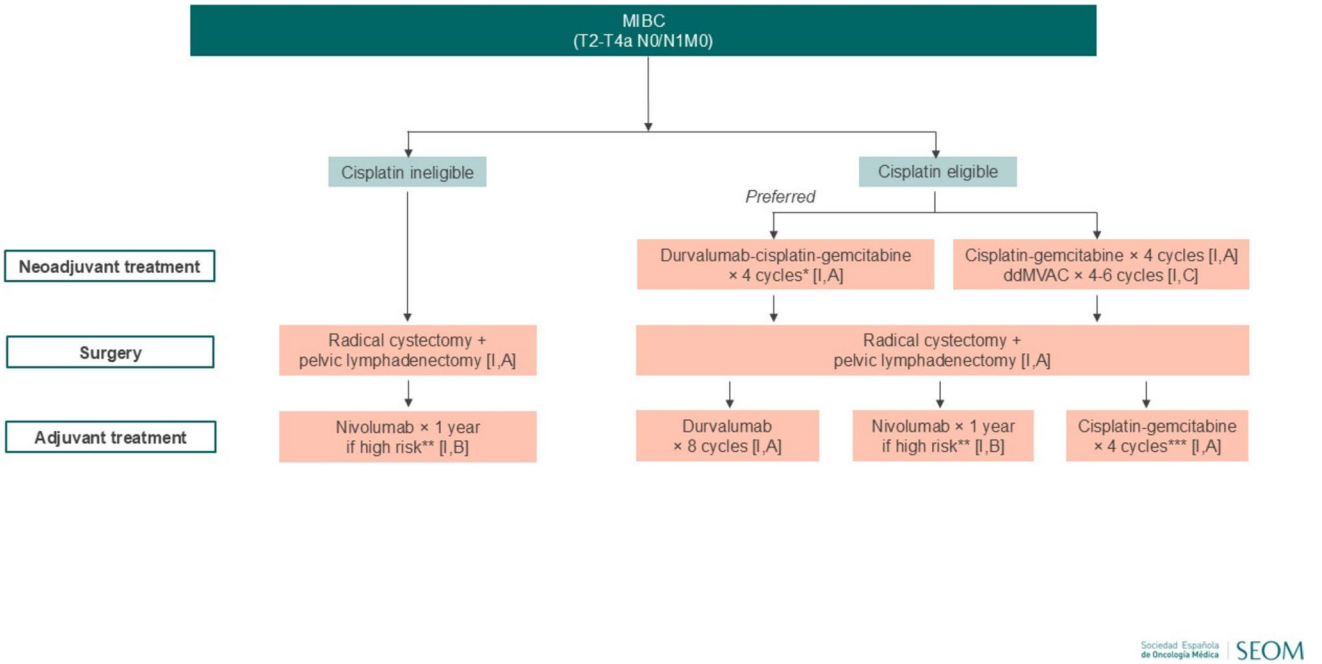


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**Fig. 1** Management of patients with muscle-invasive bladder cancer. ddMVAC: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EMA: European Medicines Agency; MIBC: muscle-invasive bladder cancer; PD-L1: programmed cell death-ligand 1. *Approved by the EMA, not reimbursed in Spain. **ypT ≥ 2 and/or ypN+ and PD-L1+. In patients without prior chemotherapy, ypT ≥ 3 and or pN+, and PD-L1+. ***For patients without prior neoadjuvant chemotherapy

a significant OS benefit (HR 0.82; 95% CI 0.70–0.96), with an absolute improvement of 6% in five-year OS [40]. However, the use of adjuvant chemotherapy in cisplatin-unfit patients is not recommended due to the lack of sufficient evidence supporting its efficacy.

The role of immunotherapy with CPIs has been evaluated in three phase III trials in two clinical scenarios: (1) patients who had not received prior NACT and were cisplatin ineligible or refused ACT, presenting pathological stage pT3/pT4 and/or pN +; and (2) patients with high-risk pathological features in the RC specimen after NACT, specifically ypT2 to ypT4a or ypN +.

The Checkmate 274 trial was a phase III study that randomized 709 patients with MIBC meeting these criteria to receive adjuvant nivolumab or placebo. The study reported a significant improvement in DFS with adjuvant nivolumab, both in the ITT population (median 20.8 vs 10.8 months; HR 0.70; 95% CI 0.55–0.90) and in patients with PD-L1 ≥ 1%, where the benefit was even more pronounced. A recent update with an extended 36.1 month follow-up has confirmed this DFS benefit. While final OS data (a secondary endpoint) have not yet been published, interim analyses continue to show a trend favoring adjuvant nivolumab over placebo. In the ITT population, the 36-month OS rate was 64.2% with nivolumab compared with 53.7% with placebo (HR 0.70; 95% CI 0.55–0.90). In the PD-L1 ≥ 1% population, the 36-month OS rate was 71.8% with nivolumab versus 52% with placebo (HR 0.48; 95% CI 0.29–0.77) [41–43]. The AMBASSADOR phase III trial evaluated 702 patients who were randomly assigned to receive pembrolizumab for one year or undergo observation. With a median of follow-up of 44.8 months, median DFS was 29.6 months with pembrolizumab compared with 14.2 months with observation (HR 0.73; 95% CI 0.59–0.9); OS data are still immature [44]. Contrastingly, the IMvigor010 trial, which investigated adjuvant atezolizumab versus observation, failed to show a significant difference in either DFS or OS, suggesting that not all CPIs may provide the same level of benefit in the adjuvant setting [45].

### Follow-up strategies for localized bladder cancer

Follow-up strategies should be tailored based on the probability, timing, and most frequent sites of recurrence, as well as on the available salvage options. Nearly 90% of local or systemic recurrences in MIBC occur within 36 months following local treatment of the primary tumor. The risk of local or pelvic recurrence ranges between 5 and 15%, depending on advanced tumor stages, nodal involvement, or positive surgical margins. Secondary urethral urothelial carcinoma is diagnosed in 1.5–6.0% of men with a history of BC, typically developing within 13.5–39.0 months post-treatment. New UTUC occurs in 1.8–6.0% of patients, representing the most common site of late recurrence, particularly in patients with multifocal disease, NMIBC with CIS or positive ureteral margins. Diagnosis is based on symptoms in more than half of patients, urine cytology in 7%, and imaging in 30% of cases. Overall, 50% of patients with MIBC will develop distant metastases, but the percentage is higher in patients with pT3–4 or nodal involvement. The most frequent metastatic sites are lymph nodes, lungs, liver, and bone. The frequency and duration of follow-up after MIBC should be individualized according to age, comorbidities, and disease stage. Some follow-up schedules, such as the EAU guideline, includes a CT scan every 6 months until the third year, followed by annual imaging thereafter; however, closer follow-up, especially during the first three years, may be necessary in patients with high-risk disease. In patients with bladder preservation, cystoscopy and random biopsies should be additionally performed. In patients with multifocal disease, NMIBC with CIS or positive ureteral margins, upper tract monitoring is mandatory during follow-up [46].

## Management of advanced/metastatic disease

### First-line systemic treatment and prognostic classifications

Cisplatin-based chemotherapy has been the standard first-line treatment for metastatic UC (mUC) for decades in patients eligible to receive cisplatin. Several regimens (i.e., MVAC, ddMVAC, and CG) are considered standard first-line therapy based on results of randomized trials, all providing OS of 12–15 months [47–49]. Due to comorbidities and poor renal function, around 50% of patients are ineligible for cisplatin [50]. In these patients, carboplatin–gemcitabine is a safer alternative, but with a lower efficacy (median OS of 9–10 months) [51]. However, durable responses with only chemotherapy are rare. The JAVELIN Bladder 100 trial compared avelumab plus best supportive care (BSC) versus BSC alone in patients with mUC who were progression-free after 4–6 cycles of first-line platinum-based chemotherapy. This phase III trial showed that switching to avelumab maintenance significantly prolonged OS in both the overall population (median 21.4 vs 14.3 months; HR 0.69; 95% CI 0.56–0.86) and in the PD-L1-positive subgroup of patients (median not reached vs 17.1 months; HR 0.56; 95% CI 0.40–0.79). The OS benefit was consistent across all prespecified subgroups, regardless of the type of treatment received (cisplatin or carboplatin) or the number of previous cycles. PFS was also significantly improved with avelumab (HR 0.62; 95% CI 0.52–0.75). After an updated median follow-up of 38 months, maintenance avelumab continued

to demonstrate significant OS improvement compared with BSC alone (36% vs 29.8%) [52, 53].

Attempts to optimize the therapeutic activity of CPIs by leveraging their synergy when combined with chemotherapy have been widely explored. However, several phase III trials testing this approach yielded discouraging results [54–56]. To date, nivolumab is the only CPI that has shown a survival benefit when added to first-line cisplatin-based chemotherapy. In the phase III CheckMate 901 trial, 608 cisplatin-eligible patients with untreated mUC were randomly assigned to nivolumab plus CG for up to six cycles followed by maintenance nivolumab for a maximum of 2 years, versus six cycles of CG alone. Avelumab or pembrolizumab was subsequently administered before disease progression in 2.0% of patients in the nivolumab-combination group and in 14.5% of those in the CG group. At a median follow-up of 33.6 months, median OS was 21.7 months in the nivolumab plus CG group and 18.9 months in the CG alone group (HR 0.78; 95% CI 0.63–0.96), and PFS was comparable between the two groups. Notably, 21.7% of patients receiving nivolumab achieved a complete response (CR) [57].

A major milestone in first-line therapy for mUC has been the combination of the nectin-4-directed antibody–drug conjugate (ADC) enfortumab vedotin (EV) with pembrolizumab. The phase III EV-302/KEYNOTE-A39 study randomized 886 treatment-naïve patients with mUC to either EV–pembrolizumab (the latter up to 35 cycles) or 6 cycles of platinum-based chemotherapy for up to 6 cycles. With a median follow-up of 17.2 months, EV–pembrolizumab was associated with a twofold improvement in PFS (12.5 vs 6.3 months; HR 0.45; 95% CI 0.38–0.54) and OS (31.5 vs 16.1 months; HR 0.47; 95% CI 0.38–0.58) compared with chemotherapy. The benefit was observed in all subgroups regardless of cisplatin-eligibility, PD-L1 expression, metastatic disease site, or tumor location. The overall response rate (ORR) was 67.7% with EV–pembrolizumab, including a CR rate of 29.1% [58]. The benefit of EV–pembrolizumab versus chemotherapy was subsequently confirmed in a recent update (median follow-up 29.1 months), with 24-month PFS of 37.1% vs 12.6% (HR 0.48; 95% CI 0.41–0.57) and OS of 60.1% vs 35.4% (HR 0.51; 95% CI 0.43–0.61). The response to EV–pembrolizumab was durable, with a median duration of response of nearly 2 years [59]. Thus, given the available evidence, the combination of EV–pembrolizumab is considered the preferred first-line treatment option for mUC. The significantly greater benefit with EV-pembrolizumab versus chemotherapy across all subgroups of the EV-302/KEYNOTE-A39 study are considered more notable since 30% of patients in the chemotherapy arm received maintenance avelumab. This highlights the robustness of the EV–pembrolizumab combination, and reinforces its role as the preferred first-line standard of care for mUC.

Single-agent CPIs may be an option for platinum-ineligible patients with PD-L1-positive disease. These treatments are reserved for frail patients who are unable to complete combination therapy, and preferably with low tumor volume. Approvals were based on data from two single-arm trials, IMvigor210 (cohort 1) with atezolizumab and KEYNOTE-052 with pembrolizumab, which demonstrated ORRs of 23.5% and 28.6%, respectively, with acceptable toxicity profiles [60, 61]. Moreover, subcutaneous atezolizumab represents an alternative to intravenous administration, reducing time of administration (Fig. 2).

## Therapeutic sequence after the first line of treatment

CPIs are approved as second-line therapy for patients with platinum-refractory mUC based on results of two phase 3 trials. Pembrolizumab was compared with second-line chemotherapy (taxanes or vinflunine) in the phase III KEYNOTE-045 trial and demonstrated an OS benefit (median 10.1 vs 7.2 months; HR 0.71; 95% CI 0.59–0.86) with a median follow-up of more than 5 years. ORR was also higher with pembrolizumab than with chemotherapy (21% vs 11%) [62]. In the IMVigor211 trial of atezolizumab versus second-line chemotherapy, although the trial was negative for the primary endpoint of OS in the PD-L1-positive population (defined as immunohistochemistry [IHC] 2/3), this results was likely due to the hierarchical study design that precluded further statistical analysis [63]. Updated 30-month OS data in the ITT population favored atezolizumab over chemotherapy, with 24-month OS rates of 23% versus 13% [64].

Two agents are approved after progression with platinum-based chemotherapy and CPIs. The phase III EV-301 trial, demonstrated a significant OS benefit with EV compared with chemotherapy (i.e., taxane or vinflunine), with median OS of 12.88 versus 8.97 months (HR 0.70; 95% CI 0.56–0.89). The ORR was also higher in the EV arm (40.6% vs 17.9%) [65]. With an updated median follow-up of 2 years, the OS benefit with EV was maintained [66]. Also, in the phase III THOR study, erdafitinib, a FGFR pan-inhibitor, demonstrated improved OS versus docetaxel or vinflunine (median 12.1 vs 7.8 months; HR 0.64; 95% CI 0.47–0.88) and ORR (45.6% vs 11.5%) in tumors with *FGFR3/2* mutations or fusions after progression on one or two lines of treatment that included an anti–programmed cell death protein 1 (PD-1) or anti–PD-L1 [67]. There is currently no clear evidence regarding the optimal sequencing of erdafitinib and EV in patients with *FGFR3/2* alterations progressing after platinum-based chemotherapy and a CPI. Later lines with vinflunine or taxanes could be used in

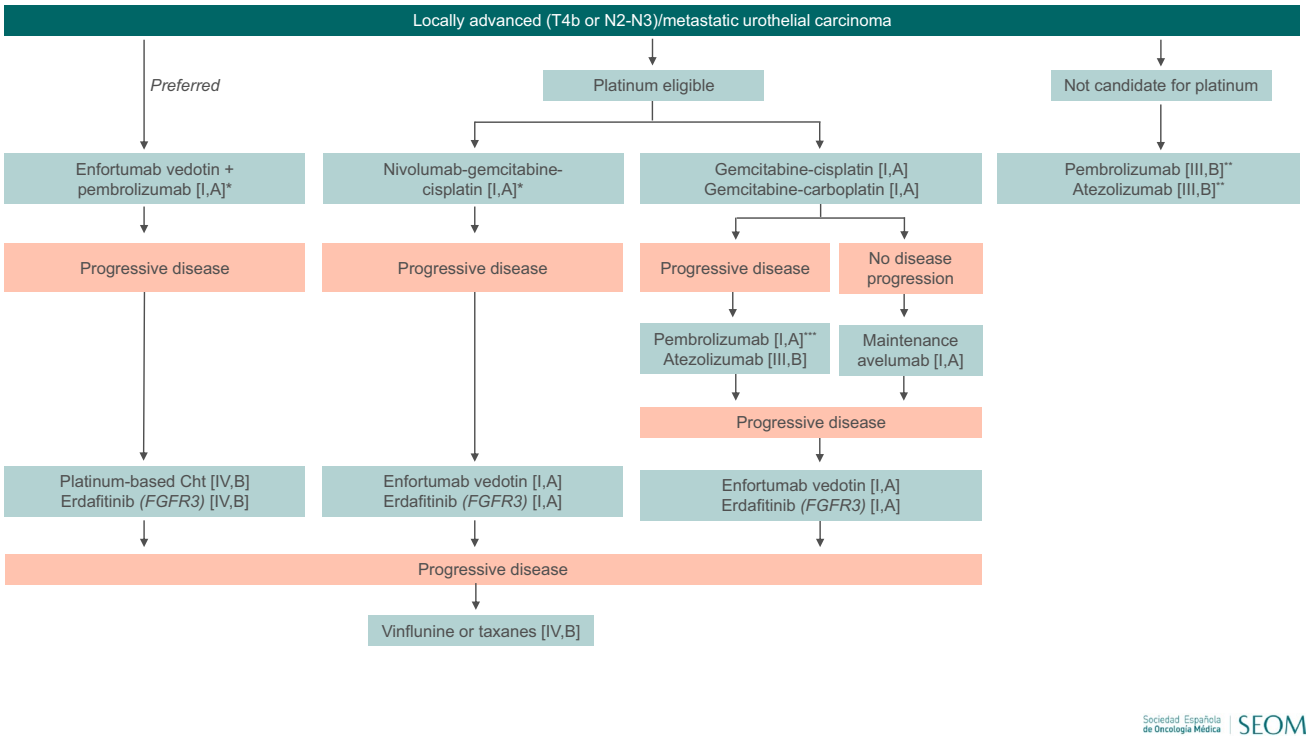


**Fig. 2** Management of patients with locally advanced/metastatic urothelial carcinoma. Cht: chemotherapy; FGFR3: fibroblast growth factor receptor 3; EMA: European Medicines Agency; PD-L1: programmed cell death-ligand 1. *EMA approved, awaiting reimbursement in Spain. **EMA approved for cisplatin-ineligible patients with PD-L1 + tumors, not reimbursed in Spain. ***EMA approved, not reimbursed in Spain

selected patients, although there is insufficient evidence to recommend it routinely.

Other ADCs, such as those directed against human epidermal growth factor 2 (HER2), are under investigation. Trastuzumab deruxtecan (T-Dxd), an ADC targeting HER2, demonstrated durable responses in multiple tumor types in the phase II DESTINY-PanTumor02 study. Among 41 patients with bladder cancer, 65.9% had received two or more prior treatments including a CPI, with an ORR of 44.4% in pretreated patients with HER2 IHC 3 + and 2 + expression [68]. The US Food and Drug Administration has granted T-Dxd accelerated approval following a priority review designation, but it is not approved in Europe.

Currently, there is no evidence regarding second-line treatment after first-line EV–pembrolizumab. In these cases, platinum-based chemotherapy without avelumab maintenance is considered the best option. For patients with *FGFR2/3* alterations, erdafitinib may also be a reasonable choice.

## Upper tract urothelial carcinoma

UTUC account for only 8% of UCs [69]. The most common histological subtype is UC, although variants are present in up to 25% of the cases [70]. The diagnosis of UTUC may be incidental; however, the most common symptoms are hematuria (70–80% of patients) and flank pain (10–20%) [71]. The diagnostic workup for UTUC includes CT urography and diagnostic ureteroscopy. An in-situ cytology sample of the upper tract should be collected during ureteroscopy, although cytology is less sensitive for UTUC than for bladder UC [72].

Hereditary UTUCs are associated with hereditary nonpolyposis colorectal carcinoma (HNPCC), and patients should be screened during the initial consultation. Those identified at risk for HNPCC should be referred to a specialist genetic counsellor [73]. Nonetheless, given the limited diagnostic performance of clinical criteria, patients with UTUC without suspicion for genetic predisposing factors could be tested for microsatellite instability or mismatch repair deficiency using polymerase chain reaction or IHC, respectively. In case of clinical suspicion of hereditary UTUC, those with a positive instability test should also undergo germline DNA sequencing and family counselling.

UTUCs are stratified into two risk categories, low- and high-risk tumors. Low-risk tumors include unifocal tumors of < 1 cm, low-grade disease on cytology/biopsy, and no invasive features on CT urography. High-risk tumors are > 2 cm, associated with possible hydronephrosis, high-grade disease on cytology/biopsy, multifocal disease, variant

histology, or a history of RC for bladder cancer [7]. At initial diagnosis, 60% of UTUCs are invasive, compared with only 15–25% of bladder tumors. Invasive UTUCs typically have a poor prognosis, with a 5-year cancer-specific survival rate of < 50% for patients with pT2/pT3 tumors and < 10% for those with pT4 disease [74].

Kidney-sparing management, such as endoscopic laser ablation, should be offered as the primary treatment option for patients with low-risk UTUC. High-risk UTUC patients should undergo open or laparoscopic radical nephroureterectomy with bladder cuff excision, regardless of tumor location [75].

Studies evaluating systemic therapy in UTUC are limited, and most clinical decision-making is extrapolated from bladder cancer evidence or small, single-center UTUC studies. For adjuvant therapy, the phase III Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer (POUT) trial demonstrated improve DFS with perioperative chemotherapy versus surveillance (HR 0.45; 95% CI 0.30–0.68) in patients with locally advanced UTUC (pT2–T4 pN0–N3 M0 or pT any N1–3 M0) [76]. The final analysis confirmed the DFS benefit at 5 years (62% vs 45%; HR 0.55; 95% CI 0.38–0.80) and demonstrated 5-year OS rates of 66% versus 57% (univariable HR 0.68; 95% CI 0.46–1.00; p = 0.049) [77]. Although the study was not sufficiently powered for subgroup analysis, patients receiving cisplatin appeared to derive a significant benefit, while carboplatin-treated patients did not; therefore, optimizing cisplatin-based administration is recommended for these patients. The role of adjuvant CPIs in UTUC remains controversial. Although underrepresented, patients with UTUC included in the CheckMate 274 and AMBASSADOR trials appeared to benefit less from adjuvant nivolumab than patients with bladder cancer [42, 44]. Since the benefit in PD-L1-positive tumors is unclear, and OS data currently remain immature, adjuvant nivolumab cannot be strongly recommended for patients with UTUC.

For advanced disease, systemic therapy should follow bladder cancer treatment recommendations. Notably, UTUC is enriched with *FGFR* mutations compared with bladder UC [78].

## Special issues in non-urothelial bladder carcinomas

The 2022 WHO classification of urinary tract tumors includes a list of NUC subtypes (previously referred to as variants of UC). Although significantly less common than pure UC (approximately 10% of bladder tumors), some of these tumors are associated with worse outcomes. These pathological entities include mixed histology, pure SCC, AC, small cell bladder cancer (SCBC), urachal AC (UrAC), or primary bladder sarcoma [7]. Prospective data for managing these pure NUC subtypes are limited because they are often excluded or underrepresented in clinical trials. A comprehensive understanding of the molecular characteristics, biology, and response to modern UC therapies remain an unmet need.

In general, patients with invasive NUC are treated with cystectomy. However, those with certain urachal tumors require complete urachal resection (en-bloc resection of the urachal ligament with the umbilicus) or may be appropriately managed with partial cystectomy [79]. For localized SCC, surgery is recommended, with postoperative radiation therapy considered in case of positive margins. Bladder preservation is rarely considered an equivalent option to surgery in NUC. For localized SCBC, initial platinum-based chemotherapy followed by local consolidation (surgery or radiotherapy) is generally accepted.

In the metastatic setting, histologic classification may guide treatment selection. A prospective study of ifosfamide, paclitaxel, and cisplatin demonstrated a median OS of 8.9 months in patients with metastatic SCC [80]. Bladder AC and UrAC are rare entities and recent molecular studies have shown that genomic alterations typically characteristic of colorectal AC are common in UrAC [81]. Combination chemotherapy with a 5-FU-based regimen (such as FOLFOX6 with or without bevacizumab) should be considered, based on multiple retrospective case reports [82]. Optimal management of SCBC remains poorly defined. Metastatic SCBC is associated with significantly worse outcomes than UC. These tumors are initially very responsive to platinum-based chemotherapy, although responses usually last less than a year, with median OS ranging 10.3–13.3 months [83].

There is some evidence (mainly in the platinum-refractory setting) suggesting CPIs may play a role in treating UC subtypes and NUC. Various series have demonstrated comparable ORR, PFS, and OS with pure and other histologic subtypes treated with CPIs, although those with neuroendocrine features had worse outcomes [84]. No efficacy data are available for targeted therapies or ADCs in UC subtypes beyond case series. Nectin-4 expression seems to be lower in UC variants [85], and retrospective series suggest that, although active, the efficacy of EV is lower in UC variants and that pure NUC tumors (SCC, AC, and SCBC) may not benefit from EV [86]. Inclusive clinical trials are crucial to developing therapies based on actionable targets for these rare cancers.

## Conclusions

These updated clinical guidelines provide evidence-based recommendations for the diagnosis, staging, and medical management of urothelial cancer across all disease stages. Current recommendations are summarized in Table 5.

**Table 5** SEOM–SOGUG recommendations for localized muscle-invasive and advanced urothelial bladder cancer

| | LoE; GoR |
|---|---|
| *Non-muscle-invasive bladder cancer* | |
| A complete TURBT aims to resect all visible tumor areas and obtain adequate tissue for pathological assessment to ensure accurate staging and risk grading | IA |
| In patients with low-risk NMIBC and in those with a small low-grade Ta recurrence detected more than 1 year after previous TURBT, a single post-operative immediate intravesical chemotherapy instillation is recommended | IA |
| For intermediate- and high-risk NMIBC, intravesical administration of BCG therapy is recommended to reduce the risk of relapse | IA |
| For optimal efficacy, a complete intravesical BCG schedule must be given, including a maintenance phase up to 1–3 years from the start of the induction cycle | IA |
| For high-risk NMIBC, which includes multiple or large tumors, high-grade tumors, or CIS, 3-year maintenance therapy is strongly recommended | |
| Patients with intermediate-risk NMIBC can be treated with a shorter maintenance phase of 1 year | |
| For very high-risk NMIBC, immediate RC is the preferred treatment option | IA |
| Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; therefore, RC is the recommended preferred option | IA |
| Patients with BCG-unresponsive tumors, who are ineligible for RC due to comorbidities, or who refuse it, can be treated with bladder-preserving alternative strategies | IIIB |
| Locoregional disease | |
| *Radical cystectomy* | |
| RC with pelvic LND is the standard treatment of MIBC cT2–T4aN0M0 | IA |
| Removal of ≥ 10 lymph nodes is recommended for correct evaluation of lymph node status | IVA |
| Extended lymph node dissection is not recommended | IA |
| *Bladder-preserving strategies* | |
| In experienced centers bladder-preserving TMT for MIBC is a reasonable alternative to cystectomy for selected patients who wish to avoid, or are unlikely to tolerate, RC | IIB |
| A hypofractionated radiotherapy regimen is preferred over conventionally fractionated radiotherapy due to a superior locoregional control and comparable toxicity rates | IA |
| Radiosensitizing regimens, such as cisplatin or the combination of 5-FU + mitomycin C are generally recommended | IIB |
| Other regimens, such as cisplatin + 5-FU, cisplatin + paclitaxel, and low-dose gemcitabine are established alternatives | IIB |
| Other approaches such as TURBT alone, TURBT followed by chemotherapy or TURBT followed by radiotherapy are options for patients who cannot tolerate TMT | IIB |
| *Neoadjuvant treatment* | |
| Neoadjuvant cisplatin-based chemotherapy regimens are recommended for patients with T2–T4a N0–N1 bladder cancer | IA |
| Neoadjuvant CG combined with durvalumab, followed by durvalumab for 8 cycles after RC is preferred for patients with T2–T4a N0–N1 bladder cancer* | IA |
| *Adjuvant treatment* | |
| Adjuvant cisplatin-based chemotherapy is recommended in patients with pT3/4 and or pN+ disease after RC if no neoadjuvant chemotherapy has been given and who have no contraindication for cisplatin | IA |
| Adjuvant nivolumab is recommended after NACT in patients ypT2-4 and/or ypN + tumor after RC, or pT3–4 and/or pN + without previous NACT if they are not fit for cisplatin-based adjuvant therapy[†] | IB |
| *Follow-up* | |
| Follow-up for MIBC should be individualized and adapted to the risk of recurrence. CT scans should be done every 3–6 months for ≥ 3 years and annually thereafter, with urethral washing and cystoscopy in selected cases, and adequate monitoring of the urothelial upper tract | VA |
| Advanced/metastatic disease | |
| *First-line systemic treatment* | |
| EV + pembrolizumab is a standard-of-care preferred treatment for most patients with mUC. The degree of benefit makes this combination a first-choice option[‡] | IA |
| CG + nivolumab is a valid alternative for patients who are cisplatin-eligible[‡] | IA |
| Avelumab remains a standard maintenance option for patients who do not progress after 4–6 cycles of platinum-based chemotherapy (CG or CaG) | IA |
| A cisplatin-based chemotherapy combination is considered the standard option for first-line mUC in those patients receiving chemotherapy. CG is preferred over MVAC or ddMVAC due to its better safety profile | IA |
| For unfit patients receiving chemotherapy, CaG should be the preferred first-line treatment option | IA |

**Table 5** (continued)

| | LoE; GoR |
|---|---|
| Pembrolizumab or atezolizumab could be an option in platinum-ineligible patients[§] | IIIB |
| *Therapeutic sequence after the first line of treatment* | |
| After progression with a first-line platinum-based therapy, PD-1/PD-L1 inhibitors are standard options:<br>Pembrolizumab[¶]<br>Atezolizumab | IA<br>IIIB |
| EV is standard therapy in patients after progression with chemotherapy + CPI in unselected patients | IA |
| Erdafitinib is standard after progression with chemotherapy + CPI in patients with *FGFR3* alterations[‡] | IA |
| After progression with EV–pembrolizumab:<br>Platinum-based chemotherapy is a preferred option<br>Erdafitinib could be an option in patients with *FGFR3* alterations[‡] | IVB<br>IVB |
| Treatment with chemotherapy (vinflunine or taxane) in patients who have progressed with all prior therapies could be an option | IVB |
| *Upper-tract urothelial carcinoma* | |
| Radical nephroureterectomy with bladder cuff excision should be offered for high-risk UTUC. For those patients with low-risk UTUC, kidney-sparing treatment should be the first treatment option | IIB |
| There is evidence to support the use of adjuvant platinum-based chemotherapy based on the POUT trial data | IIB |
| Adjuvant treatment with nivolumab could be considered in selected patients[†] | VC |
| Systemic therapy recommendations for advanced UTUC should follow those for advanced bladder cancer | IVB |

*5-FU* 5-fluorouracil; *BCG* Bacillus Calmette-Guérin; *CG* cisplatin–gemcitabine; *CaG* carboplatin–gemcitabine; *CIS* carcinoma in situ; *CPI* checkpoint inhibitor; *CT* computed tomography; *ddMVAC* dose dense methotrexate, vinblastine, doxorubicin, and cisplatin; *EMA* European Medicines Agency; *EV* enfortumab vedotin; *FGFR3* fibroblast growth factor receptor 3; *GoR*, grade of recommendation; *LoE* level of evidence; *LND* lymphadenectomy; *MIBC* muscle-invasive bladder cancer; *mUC* metastatic urothelial cancer; *MVAC* methotrexate, vinblastine, doxorubicin, and cisplatin; *NACT* neoadjuvant chemotherapy; *NMIBC* non-muscle-invasive bladder cancer; *PD-1* programmed cell death protein 1; *PD-L1* programmed cell death-ligand 1; *POUT* Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer; *RC* radical cystectomy; *SEOM* Spanish Society of Medical Oncology; *SOGUG* Spanish Group Association of Genitourinary Oncology; *TMT* trimodal therapy; *TURBT* transurethral resection of bladder tumor; *UTUC* upper tract urothelial carcinoma

[*]Not approved by the EMA, no reimbursement in Spain

[†]EMA approved only in PD-L1 + tumors

[‡]EMA approved, awaiting reimbursement in Spain

[§]EMA approved for cisplatin-ineligible patients with PD-L1 + tumors; not reimbursed in Spain

[¶]EMA approved, not reimbursed in Spain

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**Conflict of interest** *Javier Puente* has received speaker fees and attended advisory boards for Astellas, MSD, Janssen, Roche, Eisai, Bayer, AstraZeneca, and Ipsen; has received grants and attended an advisory board for Merck; has received speaker fees from BMS; and has received speaker fees and grants, and attended advisory boards for Gilead and Novartis. *Alejo Rodríguez-Vida* has received speaker fees and attended advisory boards for Astellas, MSD, BMS, and Merck. *Sergio Vázquez Estévez* has received speaker fees and attended advisory boards for Astellas, BMS, Merck, MSD, and Roche. *Carlos Álvarez Fernández* has received speaker fees and attended advisory boards for Pfizer and Bayer; and has received speaker fees from AstraZeneca, Merck/Pfizer, BMS, and MSD. *Miguel Ángel Climent* has received speaker fees from AstraZeneca and BMS; has attended advisory boards for Astellas and MSD; has received speaker fees and attended an advisory board for Merck; and has received a grant from Janssen. *Ovidio Fernández* has attended an advisory board for Pfizer; has received speaker fees from Astellas, Bayer, BMS, AstraZeneca, MSD, and Regeneron; and has received speaker fees and attended advisory boards for Janssen, AAA-Novartis, and Pierre Fabre. *Alfonso Gómez de Liaño* has received non-financial support and other fees and attended advisory boards for AstraZeneca and MSD; has received speaker fees and attended an advisory board for Astellas; has received speaker fees and a grant from BMS; has received other fees from Gilead; has received speaker and other fees and attended an advisory board for Johnson & Johnson; has received non-financial support from Merck; and has received non-financial support and attended an advisory board for Roche. *Begoña Pérez Valderrama* has received speaker and other fees and attended advisory boards for Bristol-Myers Squibb, Pfizer, Astellas, Merck, MSD, and AstraZeneca; has received speaker fees and attended advisory boards for Bayer and AAA HealthCare; has at-

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## References

1. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63:234–41. https://doi.org/10.1016/j.eururo.2012.07.033.
2. Valderrama BP, González-Del-Alba A, Morales-Barrera R, Peláez Fernández I, Vázquez S, Caballero Díaz C, et al. SEOM-SOGUG clinical guideline for localized muscle invasive and advanced bladder cancer (2021). Clin Transl Oncol. 2022;24:613–24. https://doi.org/10.1007/s12094-022-02815-w.
3. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63. https://doi.org/10.3322/caac.21834.
4. Sociedad Española de Oncología Médica (SEOM). Las cifras del cáncer en España 2025. https://seom.org/publicaciones/el-cancer-en-españa.com. Accessed 17 Jun 2025.
5. Jubber I, Ong S, Bukavina L, Black PC, Compérat E, Kamat AM, et al. Epidemiology of bladder cancer in 2023: a systematic review of risk factors. Eur Urol. 2023;84:176–90. https://doi.org/10.1016/j.eururo.2023.03.029.
6. Chandran EBA, Iannantuono GM, Atiq SO, Akbulut D, Sinaii N, Simon NI, et al. Mismatch repair deficiency and microsatellite instability in urothelial carcinoma: a systematic review and meta-analysis. BMJ Oncol. 2024;3:e000335. https://doi.org/10.1136/bmjonc-2024-000335.
7. Netto GJ, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization classification of tumors of the urinary system and male genital organs-part B: prostate and urinary tract tumors. Eur Urol. 2022;82:469–82. https://doi.org/10.1016/j.eururo.2022.07.002.
8. Alfred Witjes J, Max Bruins H, Carrión A, Cathomas R, Compérat E, Efstathiou JA, et al. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2023 guidelines. Eur Urol. 2024;85:17–31. https://doi.org/10.1016/j.eururo.2023.08.016.
9. Kamoun A, de Reyniès A, Allory Y, Sjödahl G, Robertson AG, Seiler R, et al. A consensus molecular classification of muscle-invasive bladder cancer. Eur Urol. 2020;77:420–33. https://doi.org/10.1016/j.eururo.2019.09.006.
10. Lindskrog SV, Prip F, Lamy P, Taber A, Groeneveld CS, Birkenkamp-Demtröder K, et al. An integrated multi-omics analysis identifies prognostic molecular subtypes of non-muscle-invasive bladder cancer. Nat Commun. 2021;12:2301. https://doi.org/10.1038/s41467-021-22465-w.
11. di Martino E, Tomlinson DC, Williams SV, Knowles MA. A place for precision medicine in bladder cancer: targeting the FGFRs. Future Oncol. 2016;12:2243–63. https://doi.org/10.2217/fon-2016-0042.
12. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
13. Gontero P, Birtle A, Compérat E, Dominguez Escrig JL, Liedberg F, Mariappan P, et al. EAU guidelines on non-muscle-invasive bladder cancer (TaT1 and CIS). 2025. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Non-muscle-invasive-Bladder-Cancer-2025.pdf. Accessed 23 Jun 2025.
14. Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: which patients benefit from the instillation? Eur Urol. 2016;69:231–44. https://doi.org/10.1016/j.eururo.2015.05.050.
15. Malmström PU, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56:247–56. https://doi.org/10.1016/j.eururo.2009.04.038.
16. Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. 2013;63:462–72. https://doi.org/10.1016/j.eururo.2012.10.039.
17. Balar AV, Kamat AM, Kulkarni GS, Uchio EM, Boormans JL, Roumiguié M, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol. 2021;22:919–30. https://doi.org/10.1016/S1470-2045(21)00147-9.
18. Lee RK, Abol-Enein H, Artibani W, Bochner B, Dalbagni G, Daneshmand S, et al. Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes. BJU Int. 2014;113:11–23. https://doi.org/10.1111/bju.12121.
19. Lerner SP, Tangen C, Svatek RS, Daneshmand S, Pohar KS, Skinner E, et al. Standard or extended lymphadenectomy for muscle-invasive bladder cancer. N Engl J Med. 2024;391:1206–16. https://doi.org/10.1056/NEJMoa2401497.
20. Bladder cancer: diagnosis and clinical management 1st ed. Lerner SP, Schoenberg MP, Sternberg CN, editors. Hoboken: Wiley-Blackwell; 2015.
21. Choudhury A, Porta N, Hall E, Song YP, Owen R, MacKay R, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. Lancet Oncol. 2021;22:246–55. https://doi.org/10.1016/S1470-2045(20)30607-0.

22. Coppin CM, Gospodarowicz MK, James K, Tannock IF, Zee B, Carson J, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1996;14:2901–7. https://doi.org/10.1200/JCO.1996.14.11.2901.
23. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med. 2012;366:1477–88. https://doi.org/10.1056/NEJMoa1106106.
24. Mitin T, Hunt D, Shipley WU, Kaufman DS, Uzzo R, Wu CL, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. Lancet Oncol. 2013;14:863–72. https://doi.org/10.1016/S1470-2045(13)70255-9.
25. Coen JJ, Zhang P, Saylor PJ, Lee CT, Wu CL, Parker W, et al. Bladder preservation with twice-a-day radiation plus fluorouracil/cisplatin or once daily radiation plus gemcitabine for muscle-invasive bladder cancer: NRG/RTOG 0712-a randomized phase II trial. J Clin Oncol. 2019;37:44–51. https://doi.org/10.1200/JCO.18.00537.
26. Zlotta AR, Ballas LK, Niemierko A, Lajkosz K, Kuk C, Miranda G, et al. Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis. Lancet Oncol. 2023;24:669–81. https://doi.org/10.1016/S1470-2045(23)00170-5.
27. Ditonno F, Veccia A, Montanaro F, Pettenuzzo G, Franco A, Manfredi C, et al. Trimodal therapy vs radical cystectomy in patients with muscle-invasive bladder cancer: a systematic review and meta-analysis of comparative studies. BJU Int. 2024;134:684–95. https://doi.org/10.1111/bju.16366.
28. Vashistha V, Wang H, Mazzone A, Liss MA, Svatek RS, Schleicher M, et al. Radical cystectomy compared to combined modality treatment for muscle-invasive bladder cancer: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2017;97:1002–20. https://doi.org/10.1016/j.ijrobp.2016.11.056.
29. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK, International Collaboration of Trialists, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011;29:2171–7. https://doi.org/10.1200/JCO.2010.32.3139.
30. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349:859–66. https://doi.org/10.1056/NEJMoa022148.
31. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003;361:1927–34. https://doi.org/10.1016/s0140-6736(03)13580-5.
32. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H, Genitourinary Cancer Disease Site Group, et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol. 2004;171:561–9. https://doi.org/10.1097/01.ju.0000090967.08622.33.
33. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48:202–5. https://doi.org/10.1016/j.eururo.2005.04.006.
34. Pfister C, Gravis G, Flechon A, Chevreau CM, Mahammedi H, Laguerre B, et al. 652O Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for patients with muscle-invasive bladder cancer (MIBC): results of the GETUG/AFU VESPER V05 phase III trial [ESMO abstract]. Ann Oncol. 2021;32:S678. https://doi.org/10.1016/j.annonc.2021.08.048.
35. Pfister C, Gravis G, Flechon A, Chevreau C, Mahammedi H, Laguerre B, et al. Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER): survival endpoints at 5 years in an open-label, randomised, phase 3 study. Lancet Oncol. 2024;25:255–64. https://doi.org/10.1016/S1470-2045(23)00587-9.
36. Peyton CC, Tang D, Reich RR, Azizi M, Chipollini J, Pow-Sang JM, et al. Downstaging and survival outcomes associated with neoadjuvant chemotherapy regimens among patients treated with cystectomy for muscle-invasive bladder cancer. JAMA Oncol. 2018;4:1535–42. https://doi.org/10.1001/jamaoncol.2018.3542.
37. Sternberg CN, Apolo AB. Everything old is new again! Neoadjuvant chemotherapy in the treatment of muscle-invasive bladder cancer. J Clin Oncol. 2014;32:1868–70. https://doi.org/10.1200/JCO.2014.55.4055.
38. Powles T, Catto JWF, Galsky MD, Al-Ahmadie H, Meeks JJ, Nishiyama H, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. N Engl J Med. 2024;391:1773–86. https://doi.org/10.1056/NEJMoa2408154.
39. Paz-Ares LG, Solsona E, Esteban E, Saez A, Gonzalez-Larriba J, Anton A, et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study [ASCO abstract]. J Clin Oncol. 2010;28:LBA4518. https://doi.org/10.1200/jco.2010.28.18_suppl.lba4518.
40. Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and meta-analysis of individual participant data from randomised controlled trials. Eur Urol. 2022;81:50–61. https://doi.org/10.1016/j.eururo.2021.09.028.
41. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med. 2021;384:2102–14. https://doi.org/10.1056/NEJMoa2034442.
42. Galsky MD, Witjes JA, Gschwend JE, Milowsky MI, Schenker M, Valderrama BP, et al. Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: expanded efficacy from CheckMate 274. J Clin Oncol. 2025;43:15–21. https://doi.org/10.1200/JCO.24.00340.
43. Milowsky MI, Galsky MD, Witjes JA, Gschwend JE, Schenker M, Perez Valderrama B, et al. Adjuvant nivolumab (NIVO) vs placebo (PBO) for high-risk muscle-invasive urothelial carcinoma (MIUC): additional efficacy outcomes including overall survival (OS) in patients (pts) with muscle-invasive bladder cancer (MIBC) from CheckMate 274 [ASCO abstract]. J Clin Oncol. 2025;43:658. https://doi.org/10.1200/JCO.2025.43.5_suppl.658.
44. Apolo AB, Ballman KV, Sonpavde G, Berg S, Kim WY, Parikh R, et al. Adjuvant pembrolizumab versus observation in muscle-invasive urothelial carcinoma. N Engl J Med. 2025;392:45–55. https://doi.org/10.1056/NEJMoa2401726.
45. Bellmunt J, Hussain M, Gschwend JE, Albers P, Oudard S, Castellano D, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22:525–37. https://doi.org/10.1016/S1470-2045(21)00004-8.
46. van der Heijden AG, Bruins HM, Carrion A, Cathomas R, Compérat EM, Dimitropoulos K, et al. EAU guidelines on

muscle-invasive and metastatic bladder cancer. 2023. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Muscle-Invasive-Bladder-Cancer-2025.pdf. Accessed 23 Jun 2025.
47. Loehrer PJ Sr., Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1992;10:1066–73. https://doi.org/10.1200/JCO.1992.10.7.1066.
48. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23:4602–8. https://doi.org/10.1200/JCO.2005.07.757.
49. Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer. 2006;42:50–4. https://doi.org/10.1016/j.ejca.2005.08.032.
50. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011;12:211–4. https://doi.org/10.1016/S1470-2045(10)70275-8.
51. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30:191–9. https://doi.org/10.1200/JCO.2011.37.3571.
52. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383:1218–30. https://doi.org/10.1056/NEJMoa2002788.
53. Powles T, Park SH, Caserta C, Valderrama BP, Gurney H, Ullén A, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN bladder 100 trial after ≥2 years of follow-up. J Clin Oncol. 2023;41:3486–92. https://doi.org/10.1200/JCO.22.01792.
54. Galsky MD, Arija JÁA, Bamias A, Davis ID, De Santis M, Kikuchi E, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395:1547–57. https://doi.org/10.1016/S0140-6736(20)30230-0.
55. Powles T, Csőszi T, Özgüroğlu M, Matsubara N, Géczi L, Cheng SY, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:931–45. https://doi.org/10.1016/S1470-2045(21)00152-2.
56. Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2020;21:1574–88. https://doi.org/10.1016/S1470-2045(20)30541-6.
57. van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med. 2023;389:1778–89. https://doi.org/10.1056/NEJMoa2309863.
58. Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024;390:875–88. https://doi.org/10.1056/NEJMoa2312117.
59. Powles T, Van Der Heijden MS, Loriot Y, Bedke J, Valderrama BP, Iyer G, et al. EV-302: Updated analysis from the phase 3 global study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC). J Clin Oncol. 2025;43(5_suppl):664. https://doi.org/10.1200/JCO.2025.43.5_suppl.664.
60. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389:67–76. https://doi.org/10.1016/S0140-6736(16)32455-2.
61. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18:1483–92. https://doi.org/10.1016/S1470-2045(17)30616-2.
62. Balar AV, Castellano DE, Grivas P, Vaughn DJ, Powles T, Vuky J, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. Ann Oncol. 2023;34:289–99. https://doi.org/10.1016/j.annonc.2022.11.012.
63. Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391:748–57. https://doi.org/10.1016/S0140-6736(17)33297-X.
64. van der Heijden MS, Loriot Y, Durán I, Ravaud A, Retz M, Vogelzang NJ, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: a long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. Eur Urol. 2021;80:7–11. https://doi.org/10.1016/j.eururo.2021.03.024.
65. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med. 2021;384:1125–35. https://doi.org/10.1056/NEJMoa2035807.
66. Rosenberg JE, Powles T, Sonpavde GP, Loriot Y, Duran I, Lee JL, et al. EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. Ann Oncol. 2023;34:1047–54. https://doi.org/10.1016/j.annonc.2023.08.016.
67. Loriot Y, Matsubara N, Park SH, Huddart RA, Burgess EF, Houede N, et al. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. N Engl J Med. 2023;389:1961–71. https://doi.org/10.1056/NEJMoa2308849.
68. Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, González-Martín A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol. 2024;42:47–58. https://doi.org/10.1200/JCO.23.02005.
69. Soria F, Shariat SF, Lerner SP, Fritsche HM, Rink M, Kassouf W, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol. 2017;35:379–87. https://doi.org/10.1007/s00345-016-1928-x.

70. Rink M, Robinson BD, Green DA, Cha EK, Hansen J, Comploj E, et al. Impact of histological variants on clinical outcomes of patients with upper urinary tract urothelial carcinoma. J Urol. 2012;188:398–404. https://doi.org/10.1016/j.juro.2012.04.009.
71. Inman BA, Tran VT, Fradet Y, Lacombe L. Carcinoma of the upper urinary tract: predictors of survival and competing causes of mortality. Cancer. 2009;115:2853–62. https://doi.org/10.1002/cncr.24339.
72. Rouprêt M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, et al. European association of urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. Eur Urol. 2018;73:111–22. https://doi.org/10.1016/j.eururo.2017.07.036.
73. Rouprêt M, Yates DR, Comperat E, Cussenot O. Upper urinary tract urothelial cell carcinomas and other urological malignancies involved in the hereditary nonpolyposis colorectal cancer (lynch syndrome) tumor spectrum. Eur Urol. 2008;54:1226–36. https://doi.org/10.1016/j.eururo.2008.08.008.
74. Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol. 2012;62:100–14. https://doi.org/10.1016/j.eururo.2012.02.030.
75. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009;115:1224–33. https://doi.org/10.1002/cncr.24135.
76. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020;395:1268–77. https://doi.org/10.1016/S0140-6736(20)30415-3.
77. Birtle AJ, Jones R, Chester J, Lewis R, Biscombe K, Johnson M, et al. Improved disease-free survival with adjuvant chemotherapy after nephroureterectomy for upper tract urothelial cancer: final results of the POUT trial. J Clin Oncol. 2024;42:1466–71. https://doi.org/10.1200/JCO.23.01659.
78. Sfakianos JP, Gul Z, Shariat SF, Matin SF, Daneshmand S, Plimack E, et al. Genetic differences between bladder and upper urinary tract carcinoma: implications for therapy. Eur Urol Oncol. 2021;4:170–9. https://doi.org/10.1016/j.euo.2020.12.007.
79. Taktak S, El-Taji O, Hanchanale V. Modern methods in managing urachal adenocarcinoma. Curr Urol. 2023;17:188–92. https://doi.org/10.1097/CU9.0000000000000189.
80. Galsky MD, Iasonos A, Mironov S, Scattergood J, Donat SM, Bochner BH, et al. Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. Urology. 2007;69:255–9. https://doi.org/10.1016/j.urology.2006.10.029.
81. Cigliola A, Basnet A, Jacob JM, Mercinelli C, Tateo V, Patanè DA, et al. Urachal and nonurachal adenocarcinomas of the urinary bladder: a comprehensive genomic profiling study. JCO Precis Oncol. 2024;8:e2400200. https://doi.org/10.1200/PO.24.00200.
82. Teo M, Swan NC, McDermott RS. Sustained response of adenocarcinoma of the urinary bladder to FOLFOX plus bevacizumab. Nat Rev Urol. 2011;8:282–5. https://doi.org/10.1038/nrurol.2011.48.
83. Teo MY, Guercio BJ, Arora A, Hao X, Regazzi AM, Donahue T, et al. Long-term outcomes of local and metastatic small cell carcinoma of the urinary bladder and genomic analysis of patients treated with neoadjuvant chemotherapy. Clin Genitourin Cancer. 2022;20:431–41. https://doi.org/10.1016/j.clgc.2022.05.005.
84. Miller NJ, Khaki AR, Diamantopoulos LN, Bilen MA, Santos V, Agarwal N, et al. Histological subtypes and response to PD-1/PD-L1 blockade in advanced urothelial cancer: a retrospective study. J Urol. 2020;204:63–70. https://doi.org/10.1097/JU.0000000000000761.
85. Case K, Martini DJ, Dababneh M, Nazha B, Brown JT, Joshi SS, et al. Expression of Nectin-4 and PD-L1 in bladder cancer with variant histology [ASCO genitourinary cancers symposium abstract]. J Clin Oncol. 2022;40:529. https://doi.org/10.1200/JCO.2022.40.6_suppl.529.
86. Jindal T, Jiang CY, Alhalabi O, Nguyen CB, Nizam A, Basu A, et al. Outcomes with enfortumab vedotin in patients with advanced urothelial carcinoma and histology variants: analysis of the UNITE study [ASCO genitourinary cancers symposium abstract]. J Clin Oncol. 2024;42:652. https://doi.org/10.1200/JCO.2024.42.4_suppl.652.