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ORIGINAL ARTICLE

Perioperative therapy in muscle-invasive bladder cancer: real-world evidence from the MINOTAURO study

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Background: Radical cystectomy with neoadjuvant and/or adjuvant therapy is the standard treatment of muscle-invasive urothelial cancer (MIUC). Although perioperative immunotherapy use has expanded, real-world data remain limited. The MINOTAURO study evaluated perioperative treatment patterns and outcomes in Spain.

Patients and methods: This retrospective, multicenter study included adults with MIUC treated at 17 hospitals in Northern and Eastern Spain (April 2022-June 2024). Clinical data were extracted from electronic health records. Outcomes included perioperative treatment patterns, pathological response, safety, recurrence, and survival. Overall survival and disease-free survival were estimated using Kaplan—Meier methods.

Results: A total of 629 patients were analyzed (median age 71 years; 79.5% male). Most tumors originated in the bladder/urethra (95.0%) and were urothelial (92.8%); 70.4% were clinical stage II. Cisplatin-based neoadjuvant chemotherapy (NAC) was administered to 40% of patients, primarily cisplatin—gemcitabine. The main reasons for not receiving NAC were creatinine clearance $<$60 mL/min (40.8%), Eastern Cooperative Oncology Group performance status $\geq$2 (18.4%), and cardiovascular disease (18%). Among NAC-treated patients, 41.3% achieved a pathologically documented complete response, and 50% achieved downstaging. Surgery was carried out in 77% of patients, mainly radical cystectomy. Adjuvant chemotherapy was given to 10.7%, and 46.2% of eligible patients received adjuvant immunotherapy, predominantly nivolumab. Recurrence occurred in 28.9% of patients. At a median follow-up of 18.5 months, 75% were alive and 69.7% were recurrence-free.

Conclusions: MINOTAURO demonstrates evolving real-world perioperative management of MIUC, with notable use of perioperative immunotherapy in routine clinical practice and outcomes that appear favorable in comparison with historical data, although no formal comparative analysis was carried out.

Key words: adjuvant immunotherapy, muscle-invasive urothelial carcinoma, neoadjuvant chemotherapy, nivolumab, perioperative therapy, real-world evidence

INTRODUCTION

Bladder cancer remains a major public health burden, with ~614 000 incident cases and ~221 000 deaths worldwide in 2022, underscoring persistent outcome gaps across regions. In Europe, Spain stands out for its elevated bladder cancer incidence, with an estimated 22 435 new cases in 2025 and among the highest incidences globally, with an age-standardized rate of 19.3 per 100 000 (men ~32.4 per 100 000).[1-3] Approximately one in four patients (25%-30%)

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present with muscle-invasive disease (MIBC) (≥T2) at diagnosis, and among those with nonmuscle-invasive (NMIBC) tumors, 10% to 20% will progress to MIBC over time (higher—up to 40%-50%—in the highest-risk NMIBC groups). The historical standard of care for MIBC has centered on cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy with pelvic lymph-node dissection, which improves overall survival (OS) compared with surgery alone.[4] Nevertheless, applicability is often limited by cisplatin eligibility, comorbidities, concerns about surgical delays, and potential impact on perioperative morbidity.[5] In the adjuvant setting, the phase III CheckMate 274 trial established nivolumab versus placebo as an option for patients who could not receive NAC or who, despite completing NAC, were still at high risk of recurrence. Nivolumab demonstrated a disease-free survival (DFS) benefit, although there has been no statistically significant impact on OS yet.[6] With extended follow-up, durable efficacy and safety signals have reinforced its adoption into clinical practice.[7] More recently, the phase III NIAGARA trial confirmed that perioperative durvalumab (durvalumab plus cisplatin-based NAC followed by adjuvant durvalumab) significantly improves both event-free survival (EFS) and OS compared with NAC alone in cisplatin-eligible patients, setting a new benchmark for perioperative immunotherapy.[8] In parallel, the AMBASSADOR/Alliance A031501 trial reported a significant DFS advantage for adjuvant pembrolizumab over observation after radical surgery, broadening the adjuvant immunotherapy landscape.[9] A recent meta-analysis also demonstrated that the addition of immune checkpoint inhibitors to NAC significantly increases pathologically documented complete response (pathological CR) rates compared with chemotherapy alone, supporting intensified neoadjuvant strategies.[10]

Recent large registry analyses and real-world studies underline a persistent challenge in the management of MIBC: the underutilization of NAC, which historically has been administered to <20% of eligible patients despite level 1 evidence supporting its benefit.[11,12] Despite the rapid evolution of perioperative treatment strategies, important gaps remain between clinical trial evidence and real-world implementation.[13] Although most evidence in this field derives from studies in MIBC, urothelial carcinoma may also arise from the upper urinary tract, including the renal pelvis and ureter. Although differences exist in epidemiology, surgical management, and patterns of recurrence, perioperative systemic treatment strategies are largely extrapolated from MIBC and applied to muscle-invasive urothelial cancers (MIUCs) in clinical practice. Therefore, the term MIUC is increasingly used to encompass both bladder and non-bladder primary sites in contemporary real-world studies.

The MINOTAURO multicenter, retrospective study was designed to address this gap by analyzing perioperative treatment patterns, adherence, toxicity, recurrence management (including maintenance avelumab in advanced disease), and survival outcomes of patients with MIUC in Northern Spain. By anchoring contemporary evidence to routine clinical practice, this study aims to clarify real-world outcomes and highlight opportunities to optimize MIUC care.

PATIENTS AND METHODS

Study design and population

The MINOTAURO study is a retrospective, observational, multicenter analysis conducted in 17 hospitals in Northern Spain. Eligible patients were adults (aged ≥18 years) diagnosed with MIUC between 1 April 2022 and 30 June 2024. Patients were excluded if they were presented with advanced or metastatic disease at diagnosis (M1) or if their diagnosis was made outside the predefined study period.

Study aims

The primary objective was to analyze real-world data on the use of perioperative treatments in patients with MIUC, including neoadjuvant and adjuvant chemotherapy, surgery, radiotherapy (RT), and immunotherapy. Secondary objectives included the evaluation of treatment patterns, with a specific focus on the sequencing of therapies and clinical decision making across the perioperative setting, as well as the assessment of pathological response, relapse rates, survival outcomes, and treatment-related toxicities.

Data collection

Clinical data were obtained retrospectively from electronic health records at each participating institution. The following variables were systematically collected: (i) *Epidemiological and demographic characteristics*: age, sex, body mass index, smoking and alcohol history, comorbidities, cisplatin eligibility (primarily assessed according to Galsky criteria), and additional investigator-reported contraindications not strictly captured by Galsky criteria (e.g. advanced age and peripheral vasculopathy), and relevant occupational exposures; (ii) *Disease characteristics:* primary tumor location, presence of carcinoma *in situ*, histological subtype, clinical and pathological stage, and programmed death-ligand 1 (PD-L1) expression when available, categorized as <1% or ≥1%. For patients with upper tract urothelial carcinoma, the date of diagnosis was defined as the date of definitive pathological confirmation from the surgical specimen, which may occur after surgical intervention; (iii) *Treatment information:* NAC regimens, number of cycles, radiologic response, and timing relative to surgery; surgical details including type of procedure, outcomes, and pathological downstaging; adjuvant chemotherapy regimens, duration, and reasons for discontinuation; adjuvant immunotherapy eligibility (according to CheckMate 274 criteria),[6] use of immunotherapy, type of agent administered, treatment duration, cycles received, toxicities, and progression events; RT use and indications (trimodal therapy, adjuvant, or palliative), RT schedules, concomitant chemotherapy, and posttreatment outcomes; (iv) *Outcomes:* pathological response, relapse and progression rates, OS and DFS; and (v) *Safety:* treatment-related adverse

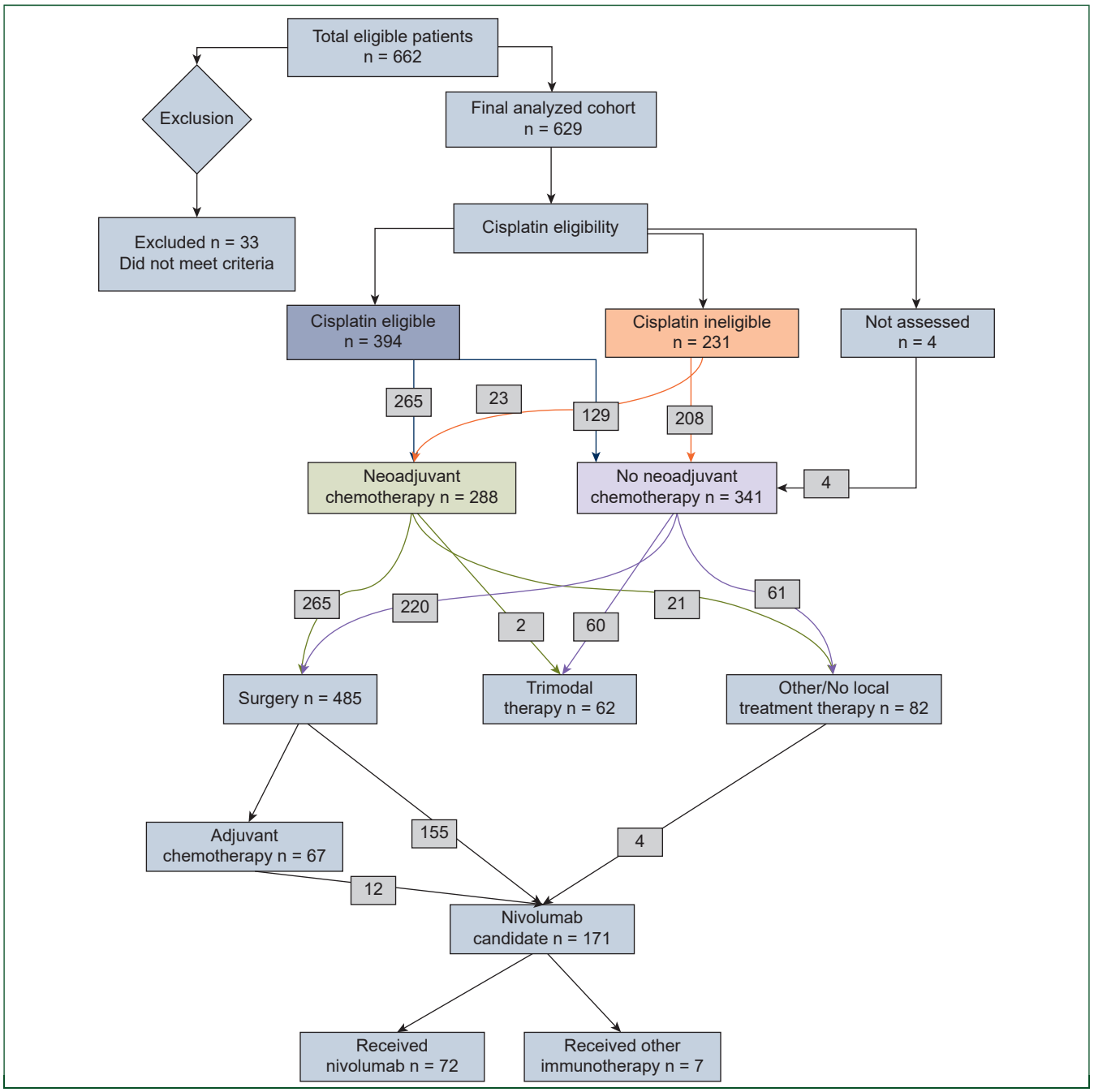

Figure 1. **Patient flow and perioperative treatment pathways in the MINOTAURO cohort.**

events (AEs), toxicities leading to treatment interruption or discontinuation, and treatment-related mortality.

Statistical analysis

Descriptive statistics were applied for categorical and continuous variables. Frequencies and percentages were reported for categorical data, while medians, means, standard deviations, and interquartile ranges were used for continuous variables. Survival analyses were carried out using the Kaplan—Meier method to estimate OS and DFS, and landmark survival rates were reported at predefined follow-up time points. All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics of the population

A total of 629 patients with MIUC were included after excluding 33 screening failures. The overall patient flow and perioperative treatment pathways, including cisplatin eligibility, the use of NAC, and subsequent management strategies, are summarized in Figure 1. The median follow-up was 18.5 months (range, 0.4-37.7). The median age was 71 years, and almost 80% of patients were male. Most tumors

Table 1. Baseline demographic, clinical, and disease characteristics

Characteristic	Value
Median age at diagnosis, years (range)	71 (41-95)
Sex	
Male	499 (79.5%)
Female	129 (20.5%)
BMI, mean, kg/m^2	27
Smoking status	
Never smoker	107 (17.0%)
Current smoker	159 (25.5%)
Former smoker	305 (48.1%)
Alcohol use	
Never	263 (41.8%)
Current	178 (28.3%)
Former	35 (5.6%)
Occupational exposure	31 (4.9%)
Hypertension	327 (52.0%)
Type 2 diabetes mellitus	149 (23.7%)
Autoimmune disease	17 (2.7%)
Primary tumor site	
Bladder	595 (94.6%)
Urethra	3 (0.5%)
Ureter	9 (1.4%)
Renal pelvis	22 (3.5%)
Carcinoma *in situ* present	
Yes	138 (21.9%)
No	491 (78.1%)
Histology	
Urothelial	584 (92.8%)
Squamous	16 (2.5%)
Adenocarcinoma/glandular	2 (0.3%)
Micropapillary	2 (0.3%)
Small cell/neuroendocrine	8 (1.3%)
Sarcomatoid	9 (1.4%)
Other	8 (1.3%)
Stage at diagnosis	
II	443 (70.4%)
IIIA	159 (25.3%)
IIIB	4 (0.6%)
IVA	3 (0.5%)
PD-L1 status	
Not available	428 (68%)
Available	178 (32%)
PD-L1 <1%	125 (70.2%)
PD-L1 ≥1%	53 (29.8%)

Values are *n* (%) unless otherwise specified.
PD-L1, programmed death-ligand 1.

originated in the lower urinary tract, and the predominant histology was urothelial carcinoma. At diagnosis, most patients presented with stage II disease. Detailed demographic, clinical, and disease characteristics are summarized in Table 1.

Neoadjuvant treatment

Approximately two-thirds of the patients (62.6%; $n = 394$) were considered cisplatin-eligible according to Galsky criteria, 36.7% ($n = 231$) were deemed ineligible, and the information was not available for four patients (0.6%). As shown in Table 2, a total of 288 patients (46.0%) received any form of neoadjuvant therapy. Among cisplatin-eligible patients, 64.2% underwent cisplatin-based regimens, representing 40.2% of the overall population. The most frequently used regimen was cisplatin—gemcitabine (65.7%), followed by dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) (22.2%), with fewer

Table 2. Neoadjuvant treatment regimens and pathological response in patients with muscle-invasive urothelial carcinoma

Regimen or response	*n* (%)
Patients receiving neoadjuvant therapy	288 (46.0%)
Regimens	
Cisplatin—gemcitabine	189 (65.7%)
DD-MVAC	64 (22.2%)
Carboplatin—gemcitabine	14 (4.9%)
Cisplatin—etoposide	4 (1.4%)
EV + pembrolizumab	4 (1.4%)
TAR-200 + cetrelimab	4 (1.4%)
Durvalumab + tremelimumab + EV	3 (1.0%)
Durvalumab + EV	2 (0.7%)
Other regimens	4 (1.3%)
Radiologic response to cisplatin-based NAC	
CR	30 (11.8%)
PR	91 (36.0%)
Stable disease	59 (23.3%)
Progression	18 (7.1%)
Not available	55 (21.8%)
Pathological response after cisplatin-based NAC and surgery ($n = 235$)	
Downstaging (ypT0-T1/Tis)	118 (50.2%)
ypT0	97 (41.3%)
ypT2-T4 or ypN+	117 (49.8%)

CR, complete response; DD-MVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EV, enfortumab vedotin; NAC, neoadjuvant therapy; PR, partial response.

patients receiving carboplatin—gemcitabine (4.9%) or experimental regimens within clinical trials (9%). The median time from diagnosis of MIUC to initiation of neoadjuvant treatment was 45 days, with a median treatment duration of 63 days. Most patients (63.6%) received four cycles of systemic treatment. In patients with radiologically evaluable disease at diagnosis ($n = 225$), radiologic assessment after cisplatin-based chemotherapy showed a CR in 14.2%, partial response in 45.4%, and stable disease in 29.3%; 8.4% of patients had progressive disease, whereas 2.7% had unavailable results.

Surgical strategy and perioperative outcomes

A total of 485 patients (77.1%) underwent surgery. Among the 141 patients who did not, 2 were still pending evaluation, and 62 received trimodal therapy. The main reasons for not undergoing surgery were poor performance status or substantial comorbidities. The median time from completion of NAC to surgery was 50 days (range, 10-307). For patients who did not receive neoadjuvant therapy, the median interval between diagnosis and surgery was 66 days. Most procedures were radical cystectomy with lymphadenectomy (Bricker diversion, 84.8%; orthotopic neobladder, 4.7%), followed by nephroureterectomy (6.0%). Other procedures, including partial cystectomy and palliative cystectomy, were less frequent. Pathological assessment demonstrated that among patients treated with cisplatin-based NAC and surgery ($n = 235$), 50% achieved downstaging (≤pT1)[14] and 41.3% achieved complete pathological response (ypT0 ypN0). PD-L1 expression was available in 178 surgical specimens, with 70.2% showing PD-L1 expression ≥1%. Details of surgical procedures,

Table 3. Surgical procedures and perioperative outcomes

Variable	*n* (%)
Patients undergoing surgery	485 (77.1%)
Type of surgery	
Radical cystectomy + lymphadenectomy (Bricker diversion)	411 (84.8%)
Radical cystectomy + lymphadenectomy (orthotopic neobladder)	23 (4.7%)
Radical cystectomy (palliative)	12 (2.5%)
Partial cystectomy	3 (0.6%)
Nephroureterectomy	29 (6.0%)
Other procedures	7 (1.4%)
Median time to surgery, days (range)	
After NAC	50 (10-307)
Without NAC (diagnosis to surgery)	66 (−31 to 379)
Pathological response (cisplatin-based NAC + surgery, $n = 235$)	
Downstaging (ypT0−T1/Tis)	118 (50.2%)
ypT0 ypN0	97 (41.3%)
ypT2−T4 or ypN+	117 (49.8%)

Time from diagnosis to surgery may appear as a negative value in a small subset of patients with upper tract urothelial carcinoma, as the date of diagnosis corresponds to the pathological confirmation obtained after surgery.
NAC, neoadjuvant chemotherapy.

timing, and pathological outcomes are summarized in Table 3.

Adjuvant treatment with chemotherapy and immunotherapy

Details of adjuvant chemotherapy and immunotherapy, including adherence and toxicity, are summarized in Table 4.

Chemotherapy. A total of 67 patients (10.7%) received adjuvant chemotherapy, most frequently cisplatin−gemcitabine (88.1%), followed by carboplatin−gemcitabine (11.9%). The median time from surgery to initiation of chemotherapy was 56.5 days, and the median treatment duration was 65 days. Most patients (71.6%) completed planned treatment, and the majority received four cycles. In those who discontinued adjuvant treatment (28.4%), toxicity was the most common reason for discontinuation (57.9%), followed by progression (10.5%) or death (10.5%). Reported toxicities leading to discontinuation included febrile neutropenia, anemia, renal impairment, and sepsis.

Immunotherapy. According to CheckMate 274 criteria,[5] 171 patients were candidates for adjuvant immunotherapy, and 79 (46.2%) received this type of treatment, with nivolumab (91.1%) as the most common agent used. The median time from surgery to initiation of immunotherapy was 70 days, with treatment delivered every 14 or 28 days. Adherence to adjuvant immunotherapy was moderate, as more than half of the candidates did not initiate therapy. Of the 171 patients considered eligible, 92 (53.8%) did not ultimately receive adjuvant immunotherapy. The reasons for not proceeding with treatment included administrative or access barriers in 32 patients (34.8%), poor performance status or comorbidities in 16 (17.4%), and persistent postsurgical complications in 11 (12.0%). Additional reasons included medical contraindications such as pre-existing autoimmune disease ($n = 4$) or histological factors ($n = 1$), lack of referral to Medical Oncology ($n = 6$), patient refusal ($n = 5$), physician decision ($n = 2$), and loss to follow-up ($n = 2$). Although the study period commenced after European Medicines Agency approval of adjuvant nivolumab, its effective availability across participating centers was not uniform. This was due to the typical delay between regulatory approval and reimbursement implementation within the Spanish National Health System, as well as regional and institutional variability in access. As a result, a subset of eligible patients did not receive adjuvant immunotherapy due to these administrative and funding-related constraints. Toxicity was observed in 45.6% of patients receiving immunotherapy. The most frequent AEs included dermatologic events (18.3%), colitis (16.7%), thyroid disorders (11.7%), and renal toxicity (8.3%). Less common but clinically significant AEs included pneumonitis, hepatitis, and adrenal insufficiency. At the data cut-off, 20.2% had completed therapy, 40.5% remained on treatment, and 36.7% had discontinued, most commonly due to toxicity.

Table 4. Adjuvant chemotherapy and immunotherapy: regimens, adherence, and toxicity

Variable	*n* (%)
Adjuvant chemotherapy	67 (10.7%)
Cisplatin−gemcitabine	59 (88.1%)
Carboplatin−gemcitabine	8 (11.9%)
Median time to chemotherapy (from surgery), days	56.5
Median treatment duration, days	65
Discontinuation	19 (28.4%)
Due to toxicity	11 (57.9%)
Due to progression	2 (10.5%)
Due to death	2 (10.5%)
Adjuvant immunotherapy candidates	171
Received treatment	79 (46.2%)
Nivolumab	72 (91.1%)
Other agents (e.g. durvalumab, atezolizumab)	7 (8.9%)
Median time to immunotherapy (from surgery), days	70
Median treatment duration (completed patients), days (range)	164 (1-373)
Toxicity during immunotherapy	36 (45.6%)
Dermatologic	11 (18.3%)
Colitis	10 (16.7%)
Thyroid disorders	7 (11.7%)
Renal	5 (8.3%)
Pneumonitis	3 (5.0%)
Hepatic	3 (5.0%)
Adrenal/pituitary	3 (5.0%)
Other/unspecified	5 (8.3%)

Radiotherapy

Radiotherapy was administered in 12.1% of patients ($n = 76$). The predominant indication was its incorporation into trimodal therapy (84.0%), while a smaller proportion received adjuvant (5.3%) or other forms, including palliative intent (10.7%). Concomitant chemotherapy as part of trimodal treatment was reported in 88% of cases, most frequently utilizing weekly gemcitabine (32.8%) or cisplatin (28.4%). Mitomycin C−fluorouracil was used in 15% of the cases as a radiosensitizer. Only one patient proceeded to surgery after RT.

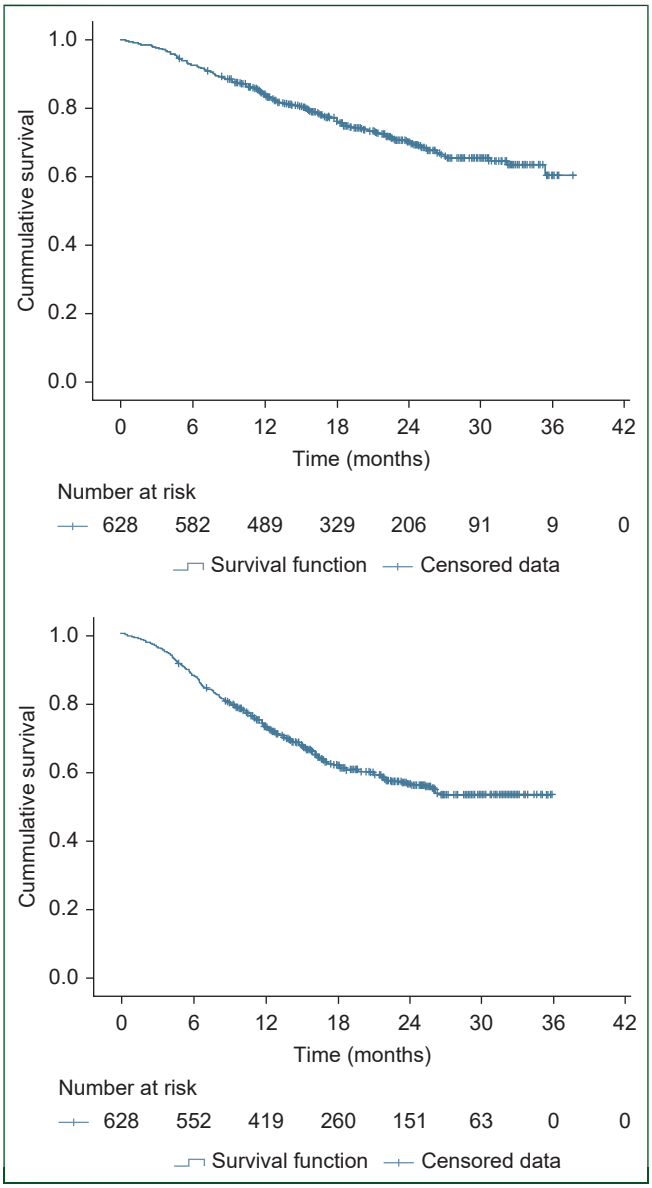

Figure 2. Kaplan—Meier estimates of overall survival and disease-free survival in the MINOTAURO cohort.

Recurrence, management of advanced disease, and maintenance with avelumab

Of the 629 patients included in the study, 182 (28.9%) developed disease recurrence during follow-up. Recurrences were most commonly observed in lymph nodes (39%), followed by visceral sites including lung (37%), liver (22%), and bone (20%).

First-line systemic therapy was administered to 131 patients (72% of those with recurrence), most frequently platinum-based chemotherapy. Atezolizumab monotherapy was used in a subset of patients, particularly those previously exposed to perioperative platinum.

Among patients who achieved disease control after platinum-based chemotherapy, 29 received maintenance avelumab. At the time of data cut-off, 58.6% had completed treatment and 41.4% remained on therapy.

Subsequent lines of therapy were administered in a smaller proportion of patients, with limited clinical benefit observed. A more detailed description of the management of recurrent and metastatic disease, including treatment patterns, outcomes, and safety data, is provided in the Supplementary Appendix (Supplementary Table S1, available at https://doi.org/10.1016/j.esmorw.2026.100732).

Survival analysis

With a median follow-up of 18.5 months (range, 0.4-37.7), OS and DFS were evaluated for the entire study population ($n = 629$). The estimated OS rate was 75% at the median follow-up of 18.5 months, 65.5% at 30 months, and 60.4% at 37 months; however, estimates at later time points were based on a limited number of patients at risk and should be interpreted with caution. The proportion of patients who were disease-free was 60.7% at 18.5 months, 52.8% at 30 months, and 52.8% at 37 months. Survival data are illustrated in the corresponding Kaplan—Meier curves (Figure 2).

DISCUSSION

The MINOTAURO study provides one of the largest real-world assessments of perioperative treatment in MIUC, conducted in Spain. Nearly half of patients received any form of neoadjuvant therapy, most frequently cisplatin—gemcitabine, with a pathological CR rate of ∼41% among cisplatin-treated patients. These findings are consistent with prospective randomized trials demonstrating the benefit of cisplatin-based NAC, such as SWOG-8710, which reported significant improvements in OS compared with surgery alone.[15] Subsequent studies have confirmed the efficacy of both gemcitabine—cisplatin and dose-dense MVAC regimens, each demonstrating substantial pathological CR rates in the neoadjuvant setting.[16,17] In the VESPER trial, pathological CR rates were ∼42% with dose-dense MVAC and 36% with gemcitabine—cisplatin, which are comparable to the ∼41% pathological CR rate observed in our cohort. These findings further support the external validity of our results in the context of contemporary neoadjuvant treatment strategies.[18] Only a subset of all patients in MINOTAURO received NAC, highlighting persistent barriers such as comorbidity burden and renal function. However, when restricting the analysis to cisplatin-eligible patients, more than two-thirds ultimately received cisplatin-based NAC, demonstrating a substantially higher uptake than historical real-world series and underscoring meaningful progress in guideline-concordant care. Real-world studies from North America and Europe have documented the persistent underutilization of NAC in MIBC, with uptake rates typically ranging between ∼20% and 40% depending on patient fitness and institutional practice.[11,19] In a recent Norwegian population-based study, increasing use of NAC was associated with improved survival outcomes, highlighting the potential impact of broader implementation of guideline-based therapy.[12] This aligns with findings from a nationwide Finnish registry study, which reported NAC utilization in

∼29% of patients, with high rates of pathological CR and encouraging survival outcomes in routine clinical practice.[20]

Although only 46.2% of eligible patients received adjuvant immunotherapy in our cohort, suggesting potential underutilization, emerging data from biomarker-driven studies such as TOMBOLA and IMvigor011 indicate that a universal approach may not be necessary, as circulating tumor DNA (ctDNA)-guided strategies could help identify patients most likely to benefit from adjuvant treatment. In the adjuvant setting, fewer than half of eligible patients received immunotherapy, contrasting with the reported benefit in DFS in CheckMate 274.[6,7] Updated 5-year results presented at the European Society for Medical Oncology (ESMO) Congress 2025 demonstrated sustained DFS advantages and a continued trend toward improved OS, with no new safety signals, reinforcing the durability of nivolumab benefit in high-risk MIUC.[21] More recently, the NIAGARA trial demonstrated that perioperative durvalumab combined with NAC followed by adjuvant therapy improves EFS and OS compared with NAC alone, establishing a new benchmark for perioperative therapy.[8] The AMBASSADOR/Alliance A031501 study also confirmed improved DFS with adjuvant pembrolizumab compared with observation.[8] Emerging perioperative trials (KEYNOTE-866 and KEYNOTE-905/EV-303) suggest that pembrolizumab in combination with enfortumab vedotin may expand the role of immunotherapy in earlier disease settings.[22] Results from the EV-303 trial in cisplatin-ineligible patients, recently presented at ESMO 2025, showed that the combination of enfortumab vedotin and pembrolizumab achieved pathological CR rates approaching 60% and significantly improved EFS and OS, albeit with increased toxicity, leading to recent US Food and Drug Administration approval.[23]

Real-world studies have begun to confirm the external validity of CheckMate 274. A recent US community-based cohort reported that adjuvant nivolumab achieved survival outcomes comparable to those observed in the pivotal trial, even among patients not fully represented in the original study population.[13] Additional real-world analyses evaluating the implementation of adjuvant nivolumab after radical surgery have reported encouraging outcomes and highlighted the gradual adoption of adjuvant immunotherapy in routine clinical practice following regulatory approval.[24] Although RT was used in only a minority of patients in our cohort, its incorporation into trimodal therapy yielded pathological CRs in a relevant subset. These findings align with recent evidence demonstrating that bladder-preserving trimodal approaches—including maximal transurethral resection of bladder tumor, concurrent chemoradiotherapy, and radiation alone—can achieve oncologic outcomes comparable to radical cystectomy in well-selected patients.[25] Moreover, systematic reviews emphasize the appropriateness of chemoradiotherapy in elderly populations, highlighting its tolerability and effectiveness even beyond conventionally fit candidates.[26] Still, our findings underscore the limited adoption of bladder preservation in Spain, despite guideline-recognized bladder-sparing options being increasingly supported by contemporary literature.[25]

PD-L1 testing influenced adjuvant immunotherapy use in our cohort, yet many patients lacked biomarker results or were excluded due to PD-L1 negativity. This underscores ongoing challenges in applying PD-L1 status to guide treatment, given its limited predictive utility and the biomarker-independent benefit seen in CheckMate 274.[6] Meanwhile, biomarker-driven strategies using ctDNA are gaining traction. Preliminary results from the TOMBOLA trial suggest that serial ctDNA monitoring after cystectomy can identify patients at high risk of relapse and may support early initiation of immunotherapy.[11] The IMvigor011 trial demonstrated that ctDNA-guided adjuvant atezolizumab significantly reduced recurrence risk and improved DFS among patients with detectable ctDNA after cystectomy, supporting the use of ctDNA as a tool for molecular risk stratification and treatment selection in MIBC.[27] Multiple reviews and clinical studies have reinforced ctDNA as a reliable prognostic marker of minimal residual disease, with the potential to guide escalation or de-escalation of perioperative therapy.[21,28,29] Therefore, although only 46.2% of eligible patients received adjuvant immunotherapy in our cohort, suggesting potential underutilization, emerging biomarker-driven strategies indicate that a universal approach may not be necessary, as ctDNA-guided approaches could help identify patients most likely to benefit from adjuvant treatment.

Recurrence patterns in MINOTAURO were consistent with those of prior studies, with lymph nodes, lung, liver, and bone as the predominant metastatic sites. Avelumab maintenance was administered to patients achieving disease control after platinum-based chemotherapy, with generally good adherence, although treatment discontinuation occurred in ∼30% of patients due to progression, toxicity, or intercurrent illness. These findings align with international guideline recommendations supporting maintenance immunotherapy in advanced urothelial carcinoma.[5] Overall, survival outcomes in MINOTAURO compared favorably with both pivotal trial benchmarks and other real-world series of perioperative therapy, particularly among patients who received cisplatin-based NAC or adjuvant immunotherapy.[12,13] These data reinforce the clinical benefit and tolerability of perioperative systemic therapy in routine practice, but also reveal significant gaps in its implementation.

The study has several limitations inherent to its retrospective and observational design. Firstly, clinical data were extracted from electronic health records, which may introduce variability in reporting and missing information, particularly regarding radiologic response and toxicity grading. In addition, radiographic responses were determined using conventional imaging according to routine clinical practice at each participating institution and were investigator-assessed based on RECIST criteria. The timing of response assessments was not standardized and could vary across centers according to local protocols, further

contributing to heterogeneity. Secondly, heterogeneity in clinical practice across participating centers could influence treatment selection and timing, limiting comparability. Thirdly, although follow-up was relatively mature, longer observation is needed to fully assess OS outcomes, particularly for patients receiving adjuvant immunotherapy. Finally, the study was conducted mostly in Northern Spain, and results may not be generalizable to other regions with different health care systems, patient populations, or access to novel therapies. These limitations are consistent with those reported in other real-world series evaluating perioperative therapy in urothelial cancer.[11,12] In addition, no multivariable analyses were carried out, as the retrospective design and heterogeneity in data completeness across centers could limit the robustness and interpretability of adjusted models. Despite these limitations, the large sample size and multicenter design provide valuable real-world evidence to complement findings from pivotal clinical trials.

In conclusion, the MINOTAURO study underscores the importance of perioperative therapy in MIUC and highlights variability in its real-world implementation. The uptake of cisplatin-based NAC in cisplatin-eligible patients is remarkable in this series, representing a meaningful improvement over historical real-world benchmarks. Our findings confirm that adjuvant nivolumab is both effective and safe in daily practice, consistent with trial findings; however, its translation to the clinic is modest. Efforts should focus on reducing barriers to NAC and immunotherapy, expanding biomarker-independent access, and optimizing treatment delivery timelines. Strengthening adherence to guideline-based recommendations will be critical to improving outcomes for patients with MIUC.

ETHICAL APPROVAL AND INFORMED CONSENT

The study was approved by the Institutional Review Board and Ethics Committee of all participating centers and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained whenever required by Spanish law.

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DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at https://gco.iarc.who.int/today. Accessed December 29, 2025.
2. Red Española de Registros de Cáncer (REDECAN). *Estimaciones De La Incidencia Del Cáncer En España*. [Estimates of Cancer Incidence in Spain, 2025]. Available at https://redecan.org/storage/documentation/442e1d1a-4040-4674-81cf-5e6a67af6458.pdf. Accessed December 29, 2025.
3. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10-45.
4. Yin M, Joshi M, Meijer RP, et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and two-step meta-analysis. *Oncologist*. 2016;21(6):708-715.
5. van der Heijden AG, Bruins HM, Carrion A, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2025 guidelines. *Eur Urol*. 2025;87(5):582-600.
6. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med*. 2021;384(22):2102-2114.
7. Galsky MD, Powles T, Necchi A, et al. Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: updated efficacy and safety from CheckMate 274. *J Clin Oncol*. 2025;43(suppl 7):4500.
8. Powles T, Catto JWF, Galsky MD, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. *N Engl J Med*. 2024;391:1773-1786.
9. Apolo AB, Ballman KV, Sonpavde GP, et al. AMBASSADOR Alliance A031501: phase III randomized adjuvant study of pembrolizumab in muscle-invasive and locally advanced urothelial carcinoma (MIUC) vs observation. *J Clin Oncol*. 2024;42(4 suppl):LBA531.
10. Menegat ALRS, Menegat BLRS, Braz LDG, Piccoli MVF, Rebelo TG, de Moraes FCA. Neoadjuvant immune checkpoint inhibitors for muscle-invasive urothelial carcinoma: a systematic review and meta-analysis. *Immunotherapy*. 2026;18:139-155.
11. Zaid HB, Patel SG, Stimson CJ, et al. Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. *Urology*. 2014;83(1):75-80.
12. Haugnes HS, Kjaeve H, Bjerkaas E, Hellesnes R, Hjelle L, Larsen M. Real-world data on utilization of neoadjuvant chemotherapy for muscle invasive bladder cancer: impact on surgical complications and oncological efficacy. *Acta Oncol*. 2025;64:13-21.
13. García-Rayo C, Juste-Álvarez S, Gómez-Cañizo C, et al. The dynamic field of perioperative treatment for localized muscle-invasive bladder cancer: a review of the current research landscape. *J Clin Med*. 2025;14(16):5653.
14. Amin MB, Greene FL, Edge SB, et al. *AJCC Cancer Staging Manual*.. 8th ed. New York, NY: Springer; 2017.
15. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349(9):859-866.
16. Dash A, Pettus JA 4th, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer*. 2008;113(9):2471-2477.
17. Choueiri TK, Jacobus S, Bellmunt J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol*. 2014;32(18):1889-1894.
18. Pfister C, Gravis G, Fléchon A, et al. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: results of the GETUG-AFU V05 VESPER trial. *J Clin Oncol*. 2022;40(18):2013-2022.
19. Møller CT, Støer NC, Blindheim A, et al. Downstaging and survival after Neoadjuvant chemotherapy for bladder cancer in Norway; a population-based study. *BMC Cancer*. 2022;22(1):1301.
20. Nikulainen I, Salminen AP, Högerman M, Seikkula H, Boström PJ, The Finnish National Cystectomy Database Research Group. Neoadjuvant chemotherapy in muscle-invasive bladder cancer: a nationwide analysis of eligibility, utilization, and outcomes. *Cancers (Basel)*. 2025;17(3):505.
21. Galsky MD, Gschwend JE, Milowsky MI, et al. Adjuvant nivolumab versus placebo for high-risk muscle-invasive urothelial carcinoma: 5-year efficacy and ctDNA results from CheckMate 274. *Ann Oncol*. 2026;37(1):69-78.
22. Vulsteke C, Adra N, Danchaivijitr P, et al. Perioperative enfortumab vedotin and pembrolizumab in bladder cancer. *N Engl J Med*. 2026;394(13):1257-1269.
23. Barragán-Carrillo R, Ebrahimi H, John WS, et al. Clinical outcomes in patients with muscle-invasive urothelial carcinoma treated with nivolumab. *JAMA Netw Open*. 2025;8(6):e2514427.

24. Guilbert A, Lebret T, Oudard S, et al. Real-world evaluation of nivolumab utilization in adjuvant treatment of localized muscle-invasive urothelial carcinoma. *Fr J Urol*. 2024;34(13):102744.
25. Gupta S, Hensley PJ, Li R, et al. Bladder preservation strategies in muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *Eur Urol*. 2026;89(1):18-28.
26. Sakaguchi M, Maebayashi T, Sekino Y, Ishikawa H. Efficacy of curative radiotherapy for the treatment of elderly patients with muscle-invasive bladder cancer: a systematic review. *BMC Urol*. 2025; 25(1):26.
27. Powles T, Kann AG, Castellano D, et al. ctDNA-guided adjuvant atezolizumab in muscle-invasive bladder cancer. *N Engl J Med*. 2025;393(24): 2395-2408.
28. Crupi E, de Padua TC, Marandino L, et al. Circulating tumor DNA as a predictive and prognostic biomarker in the perioperative treatment of muscle-invasive bladder cancer: a systematic review. *Eur Urol Oncol*. 2024;7(1):44-52.
29. Harrs CF, Pusala S, Cheng L, Jazayeri B, Li R. Recent advances in liquid biopsy for genitourinary cancers: a narrative review. *Histopathology*. 2026;88(1):338-352.