IN VIVO *39*: 3381-3393 (2025)
doi: 10.21873/invivo.14135

A Snapshot from the Italian Clinical Practice Regarding Efficacy and Utility Rate of Perioperative Chemotherapy in Muscle-invasive Bladder Cancer: The RealBLADDER Study

ELISABETTA GAMBALE[1,2], ROBERTA GIORGIONE[1], UMBERTO BASSO[3], LUCA GALLI[4], GIUSEPPE FORNARINI[5], FRANCESCO ATZORI[6], SARAH SCAGLIARINI[7], CRISTINA MASINI[8], VALENTINA BALDAZZI[9], FEDERICO SCOLARI[10], MARINELLA MICOL MELA[1], MARCO MARUZZO[3], ISMAELA ANNA VASCOTTO[1], VIRGINIA ROSSI[1], DANIELE ROSSINI[1,2], GIANDOMENICO ROVIELLO[11], DANIELE LAVACCHI[1], SERGIO SERNI[12,13], ANDREA MINERVINI[12,14], SERENA PILLOZZI[10] and LORENZO ANTONUZZO[1,2]

[1]Careggi University Hospital, Oncology Unit, Florence, Italy;
[2]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;
[3]Oncology Unit 1, Istituto Oncologico Veneto, IOV- IRCCS, Padua, Italy;
[4]Azienda Ospedaliero-Universitaria Pisana, Medical Oncology Unit 2, Pisa, Italy;
[5]U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy;
[6]A.O.U. di Cagliari-Presidio Policlinico Duilio Casula, Cagliari, Italy;
[7]UOC di Oncologia, Azienda Ospedaliera di Rilievo Nazionale Cardarelli di Napoli, Naples, Italy;
[8]Medical Oncology Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy;
[9]Department of Medical Oncology, Santa Maria Annunziata Hospital, Florence, Italy;
[10]Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence, Florence, Italy;
[11]Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Florence, Italy;
[12]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;
[13]Unit of Urology and Renal Transplantation, Oncology Department, Careggi University Hospital, Florence, Italy;
[14]Unit of Urology and Andrology, Oncology Department, Careggi University Hospital, Florence, Italy

Abstract

Background/Aim: The standard of care for patients with muscle-invasive bladder cancer (MIBC) is treatment with radical cystectomy (RC) and perioperative platinum-based chemotherapy (neoadjuvant or adjuvant). Perioperative treatment can improve overall survival (OS), and the most robust evidence favors neoadjuvant chemotherapy (NAC). The RealBLADDER study assessed the efficacy and safety of perioperative chemotherapy in patients with MIBC in an Italian real-world setting.

continued

Lorenzo Antonuzzo, Department of Experimental and Clinical Medicine, University of Florence, Viale Morgagni 63, 50134 Florence, Italy. E-mail: lorenzo.antonuzzo@unifi.it

Received August 9, 2025 | Revised August 29, 2025 | Accepted September 2, 2025

Patients and Methods: RealBLADDER enrolled patients with MIBC treated with perioperative chemotherapy from June 2018 to June 2023. The primary endpoint was the rate of non-invasive downstaging (NID) (ypT0/pTis/pTaN0 or <ypT1N0) and complete pathological response (pCR) (yp0N0), defined as the absence of residual tumor cells in the bladder and lymph nodes at the pathological examination after NAC. Secondary endpoints were disease-free survival (DFS), OS and surgical outcomes.

Results: A total of 173 eligible patients were identified. One hundred and thirty-seven patients (79.2%) received NAC and 36 (20.8%) received adjuvant chemotherapy (AC). The NID rate was 36.8%, and pCR achieved in 33.6% of patients treated with NAC. The rate of surgical morbidity and mortality were 20.9% and 0%, respectively. The 12-month DFS was 73.7% [95% confidence interval (CI)=0.672-0.808]. The 12-month OS rate in the entire population was 92.1% (95%CI=0.880-0.963). Compared to AC, DFS was improved in patients treated with NAC (p=0.019).

Conclusion: NAC is associated with an improved DFS compared to AC, a high rate of NID and pCR and low rate of surgical morbidity and mortality, supporting NAC as the preferred perioperative strategy for MIBC in clinical practice.

Keywords: Muscle-invasive bladder cancer, perioperative chemotherapy, Italian clinical practice, pathological downstaging, survival.

Introduction

Bladder cancer (BC) is the 10th most common cancer type worldwide and the second most common malignancy of the genitourinary tract following prostate cancer. Urothelial carcinoma (UC)represents the main histological subtype, accounting for 90% of all BCs (1). BC accounts for 7% of all cancer diagnoses in Italy. In 2023, 29,700 new cases of BC were observed (23,700 in men and 600 in women), with over 8.300 deaths. Among urothelial tumors, 30% are diagnosed as muscle-invasive bladder cancer (MIBC) at the time of the initial diagnosis (2). The treatment of MIBC represents a challenge for the clinician. Although radical surgery (*i.e.*, radical cystectomy and bilateral pelvic lymph node dissection) can be curative in approximately half of the patients with MIBC, approximately 50% of patients will develop distant metastases within two years and the vast majority of these cases will die from BC (3). Perioperative chemotherapy (CT) has been developed to eradicate micro metastatic disease and offer a benefit in reducing the risk of relapse and improving survival outcomes. Several trials exploring the impact of adjuvant CT (AC) have yielded inconclusive results. Indeed, these studies were limited due to small sample size, slow and difficult recruitment, and suboptimal chemotherapeutic regimens (4-8). In recent years, neoadjuvant CT (NAC) has been considered the preferred strategy in order to improve survival outcomes compared with AC. Several randomized studies conducted in this patient population revealed an improvement in survival compared to loco-regional treatments alone (cystectomy or radiotherapy). Neoadjuvant cisplatin-based CT has been shown to reduce the risk of relapse and improve overall survival (OS) in clinical trials and meta-analyses (9-12). The Advanced Bladder Cancer (ABC) Meta-analysis Collaboration included 11 clinical trials for a total of 3005 patients. The platinum-based regimens have been shown to offer a 5% increase in 5-year OS [hazard ratio (HR)=0.86, 95% confidence interval (CI)=0.77-0.95, p=0.003] and 9% increase in 5-year disease-free survival (DFS) (HR=0.78, 95%CI=0.71-0.86, p<0.0001) (10). According to the literature, GC (gemcitabine, cisplatin) and MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) are considered the standard neoadjuvant regimens in patients with MIBC (9-12). Consistent with the positive results obtained with the dense-dose MVAC regimen (ddMVAC) in the advanced setting, a phase II study including 44 patients with operable MIBC confirmed an encouraging rate of pCR (38%) with a favorable safety profile and no toxic death (13).

The VESPER (French Genito-Urinary Tumor Group and French Association of Urology V05) trial reported improved 5- year PFS and OS with dd-MVAC *versus* GC in patients who received NAC, but not in the overall perioperative setting (14). In the absence of randomized studies with a direct comparison between the two standard regimens GC and MVAC, a systematic review and meta-analysis has been recently conducted (15). It identified studies including patients with MIBC who received neoadjuvant GC compared to ddMVAC from PubMed, Web of Science, and EMBASE. Ten studies were identified (four OS, two PFS, and six pCR clinical endpoints). Neoadjuvant ddMVAC improved OS (HR=0.71, 95%CI= 0.56-0.90), PFS (HR=0.76, 95%CI= 0.60-0.97), and pathological downstaging (odds ratio=1.34, 95%CI=1.01-1.78) as compared to GC. There was no significant difference between regimens for pCR rates (odds ratio= 1.38, 95%CI=0.90-2.12). In conclusion, the optimal perioperative CT for patients with MIBC is not defined, and ddMVAC and GC remain both the standard of care. ddMVAC should be probably preferred over GC for patients with MIBC who can tolerate its greater toxicity. However, outside clinical trials, little is known about the treatment strategies of real-world patients, who usually present with unfavorable clinical features.

RealBLADDER is an observational study with a descriptive intent. Considering the previously detailed literature, the RealBLADDER study aimed to describe the use of perioperative CT for patients with cT1-T4a N0-2 MIBC in an Italian real-world setting.

Patients and Methods

Study design. RealBLADDER is an Italian, multicentric (n=7), observational, retrospective and prospective study, which enrolled all eligible patients with MIBC treated with perioperative CT from June 2018 to June 2023.

Study population. The study population included all eligible patients affected by MIBC treated with perioperative CT in each study center from June 2018 to June 2023. The treatment was performed according to clinical practice and national and international guidelines, regardless of the inclusion in the study. Patient demographics, tumor characteristics, and treatment information were collected *via* Internal Review Board (IRB)-approved retrospective review of electronic medical records at all institutions.

Inclusion criteria. Main inclusion criteria were age >18 years, histological or cytological evidence of MIBC, treated with perioperative CT (NAC or AC).

Exclusion criteria. Main exclusion criteria were metastatic disease or extravesical tumor that invades pelvic wall or abdominal wall (cT4b).

Endpoints. The primary objectives were the evaluation of the rate of patients treated with NAC who achieved a non-invasive downstaging (NID) (ypT0/pTis/pTaN0 or <ypt1N0) and the rate of those who achieved a pCR (ypT0N0) defined as the absence of residual tumor cells in bladder and nodes at the pathological examination.

Secondary endpoints were the rates of <ypT2N0 response, DFS- defined as the time from the start of treatment to disease progression, relapse or death-, OS- defined as the time from the start of treatment to death from any cause-, of patients who annually undergo radical cystectomy after diagnosis of cT1-4a N0-3 bladder cancer, as well as the rates of surgical morbidity and mortality.

Statistical analysis. Demographic and clinical data, disease and treatment characteristics, treatment exposure, and surgical issues/outcomes were reported using descriptive statistics. Continuous variables were reported as median and range, while categorical variables were reported as absolute number and percentage. Primary endpoints were NID and pCR rate. Time-to-event endpoints were described using the Kaplan-Meier method. Survival distribution differences between specific subgroups of patients (age ≤75 *vs*. age >75, adjuvant *vs*. neoadjuvant, cN+ *vs*. cN0, ypT ≥1 *vs*. ypT<1, cT1-2 *vs*. cT3-4) were tested with a two-sided log-rank test. A p-value of 0.05 or lower was considered statistically significant.

Results

Baseline patient characteristics. A total of 213 patients who underwent radical cystectomy at seven Italian referral centers between June 2018 and June 2023 were identified. Patients who had undergone perioperative combinatorial treatment with CT and immunotherapy within clinical trials were excluded. In total, 173 patients were eligible for the analysis. Baseline characteristics of the overall cohort are shown in Table I, Table II, Table III, and Table IV. Median age was 67 (29-82) years and 85.5% were male. Of these patients, 137 (79.2%) received NAC and 36 (20.8%) received AC. GC for four cycles was the most frequently used NAC regimen. Among 137 patients treated with NAC, only three patients received ddMVAC. At the time of analysis, the median follow-up was 26.3 months (19.7-34.9).

Disease-free survival and overall survival. The 12-month DFS was 73.7% (95%CI=0.672-0.808) in the entire population (Figure 1A). DFS was significantly improved in patients treated with NAC compared to AC (p=0.019) (Figure 1B). The DFS was significantly better in patients aged under 75 years old (p=0.043) (Figure 1C). No significantly longer 12-months OS was reported between patients treated with NAC and those treated with AC (p=0.33) (Figure 2A). No differences in median OS were reported according to clinical T and/or N at baseline (Figure 2B and C). DFS and OS were significantly high in NAC treated patients that achieved a complete pCR (Figure 3A and B).

Pathological response. The rate of NID (ypT0/pTis/pTaN0 or <ypT1) in patients that underwent NAC was 36.8%, with 33.6% of pCR (ypT0N0). A pathological downstaging (<ypT2N0) was achieved in 54 patients (43.2%) treated with NAC (Table III).

Rate of radical cystectomy and surgical morbidity. The rate of RC among the entire population was 40.9%. Of the 137 patients receiving NAC, 123 underwent RC, with a surgical morbidity rate of 19.5% and no surgery-related deaths.

Table I. *Descriptive statistics for the entire cohort of evaluable patients (N=173). Categorical variables are reported as the absolute number and percentage; continuous variables are reported as median and range.*

Characteristics		N=173
Age	Median [range]	67 [29-82]
Sex	Male	148 (85.5%)
	Female	25 (14.5%)
cT	2	119 (68.8%)
	3	35 (20.2%)
	4	7 (4%)
	X	12 (6.9%)
cN	0	119 (68.8%)
	1	13 (7.5%)
	2	16 (9.2%)
	X	25 (14.5%)
Stage at diagnosis	II	97 (61.8%)
	III	60 (38.2%)
	NA	16
ECOG PS	0	158 (91.3%)
	1	14 (8.1%)
	2	1 (0.6%)
RC	No	14 (8.1%)
	Yes	159 (91.9%)
Chemotherapy	NAC	137 (79.2%)
	AC	36 (20.8%)
NAC Regimen	GC	134
	ddMVAC	3
Progression	No	112 (64.7%)
	Yes	61 (35.3%)
Death	No	131 (75.7%)
	Yes	42 (24.3%)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; RC: radical cystectomy; NAC: neoadjuvant chemotherapy; AC: adjuvant chemotherapy; GC: gemcitabine-cisplatin; ddMVAC: dose dense methotrexate, vinblastine, doxorubicin, and cisplatin; NA: not available.

Subgroup analysis of patients with variant histology. Of the 213 patients enrolled, 23 (10.8%) had variant histology (VH). The median age was 66 years (range=45-80 years), and 82.6% were male. Fifteen patients (65.2%) received NAC, while eight (34.8%) received AC. Twenty-two patients (95.7%) underwent radical cystectomy and one patient progressed during NAC (Table V). Main VHs are summarized in Table V.

Among VH patients treated with NAC, the <ypT1N0 response rate was 57.1% (8 pts), with pCR (ypT0N0) achieved in five patients (35.7%). At 18 months, DFS was 59.5%, with no significant differences between NAC and AC [median not reported (NR) *vs*. 8.6, p=0.41]. At 18

Table II. *Descriptive statistics for the subset of patients who underwent cystectomy (N=159). Categorical variables are reported as the absolute number and percentage; continuous variables are reported as median and range.*

Characteristics		N=159
Surgery technique	Laparoscopy	13 (10.7%)
	Open	59 (48.8%)
	Robotic	49 (40.5%)
	NA	38
Comorbidity	No	125 (80.1%)
	Yes	31 (19.9%)
	NA	3

Table III. *Descriptive statistics for patients who received neoadjuvant chemotherapy (N=137). Categorical variables are reported as the absolute number and percentage; continuous variables are reported as median and range.*

Characteristics		N=137
Radiological response after NAC	CR	22 (17.9%)
	SD	55 (44.7%)
	PD	7 (5.7%)
	PR	39 (31.7%)
	NA	14
ypT	ypT0	42 (33.6%)
	ypT1	8 (7.4%)
	ypT2	0
	ypT3	23 (21.3%)
	ypT4	38 (30.4%)
	ypTis, ypTa	4 (3.2%)
	NA	22
ypN	ypN0	101 (80.8%)
	ypN1	8 (6.4%)
	ypN2	12 (9.6%)
	ypN3	1 (0.8%)
	ypNx	3 (2.4%)
	NA	12
Pathological response after NAC	ypT0N0	42 (33.6%)
	<ypT1N0	46 (36.8%)
	<ypT2N0	54 (43.2%)
Comorbidity after RC	No	99 (80.5%)
	Yes	24 (19.5%)

NAC: Neoadjuvant chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not available; RC: radical cystectomy.

months OS was 78.3%, with no significant differences between NAC and AC (median NR *vs*. 33.8, p=0.2). The rate of surgical morbidity was 13% (3 pts), with no deaths related to surgery. Three patients (13%) experienced grade 3 toxicities related to chemotherapy.

Table IV. *Descriptive statistics for patients who received adjuvant chemotherapy (N=37). Categorical variables are reported as the absolute number and percentage; continuous variables are reported as median and range. NA: Not available.*

Characteristics		N=36
pT	pT1	2 (6.2%)
	pT2	3 (9.4%)
	pT3	19 (59.4%)
	pT4	8 (25.0%)
	NA	4
pN	pN0	8 (23.5%)
	pN1	6 (17.6%)
	pN2	19 (52.9%)
	pNX	2 (5.9)
	NA	3
Pathologic stage	IIIA	14 (42.4%)
	IIIB	18 (54.5%)
	IVA	1 (3.0%)
	NA	3

Discussion

Curing MIBC is an aspiration for oncologists. Delivering maximum advantages to patients is essential, and optimal treatment should be provided. Numerous trials have reported the efficacy of perioperative CTs, illustrating an enhancement in survival when compared to loco-regional treatments alone (*i.e.*, cystectomy or radiotherapy). NAC prior to RC for MIBC is a conventional method, yet real-world data indicates it is underutilized. The percentage of patients receiving NAC in the RealBLADDER study (79.2%) surpasses that stated in more recent studies, which report rates between 16% to 44% (16-20). Concerns regarding the heightened risk of perioperative complications and mortality have been proposed as a possible rationale for the lack of NAC administration. A recent study published by Proietti et al. examined the effects of NAC on the incidence of adverse perioperative outcomes in MIBC patients undergoing RC. A total of 317 patients receiving RC for MIBC (T2-4a N0 M0) from 2016 to 2022 were identified. Additionally, a 1:1 propensity score matching (PSM) was utilized to compare RC alone with RC plus NAC, aiming to evaluate the relationship between NAC status and perioperative results. Among the

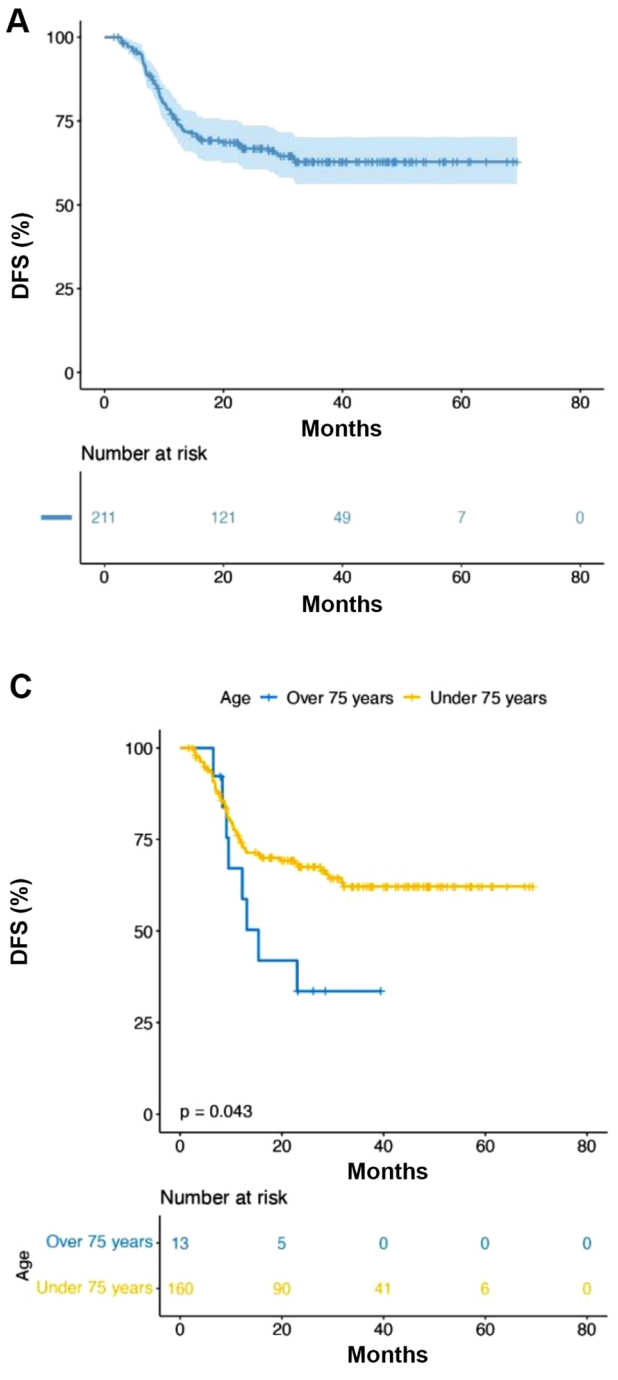

Figure 1. *Disease-free survival (DFS) in patients with muscle-invasive bladder cancer treated with perioperative chemotherapy: overall population and subgroup analyses. (A) Disease-free survival (DFS) of the entire population after perioperative chemotherapy and radical cystectomy. (B) DFS of patients according to the chemotherapy setting: neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC). (C) DFS of patients according to the age: over 75 years and under 75 years.*

317 patients treated with RC for confirmed MIBC, 98 (31%) received NAC. After PSM, no differences were observed in the considered outcomes, leading the authors to conclude that NAC is not linked to an elevated rate of perioperative complications (21). In line with this evidence, we herein reported a rate of surgical morbidity of 19.5 %, and no deaths related to surgery.

Interestingly, supporting NAC over upfront surgery, multiple studies have revealed that general anesthesia, surgical stress, and pneumoperitoneum can promote cancer advancement (22-25). Hence, NAC can facilitate en-bloc radical resection before the dissemination of tumor cells.

We observed that 43.2% of the patients treated with NAC achieved pathologic downstaging to <pT2N0, which aligns with the rates of 36-63% reported in previous phase II studies and several population-based studies (26-30). Regarding the RealBLADDER pCR rate of 33.8%, it is consistent with previous studies that indicated pCR rates between 13% and 38% (11, 31). Survival following NAC is profoundly influenced by whether pathological downstaging is achieved, supporting pCR and major pathological

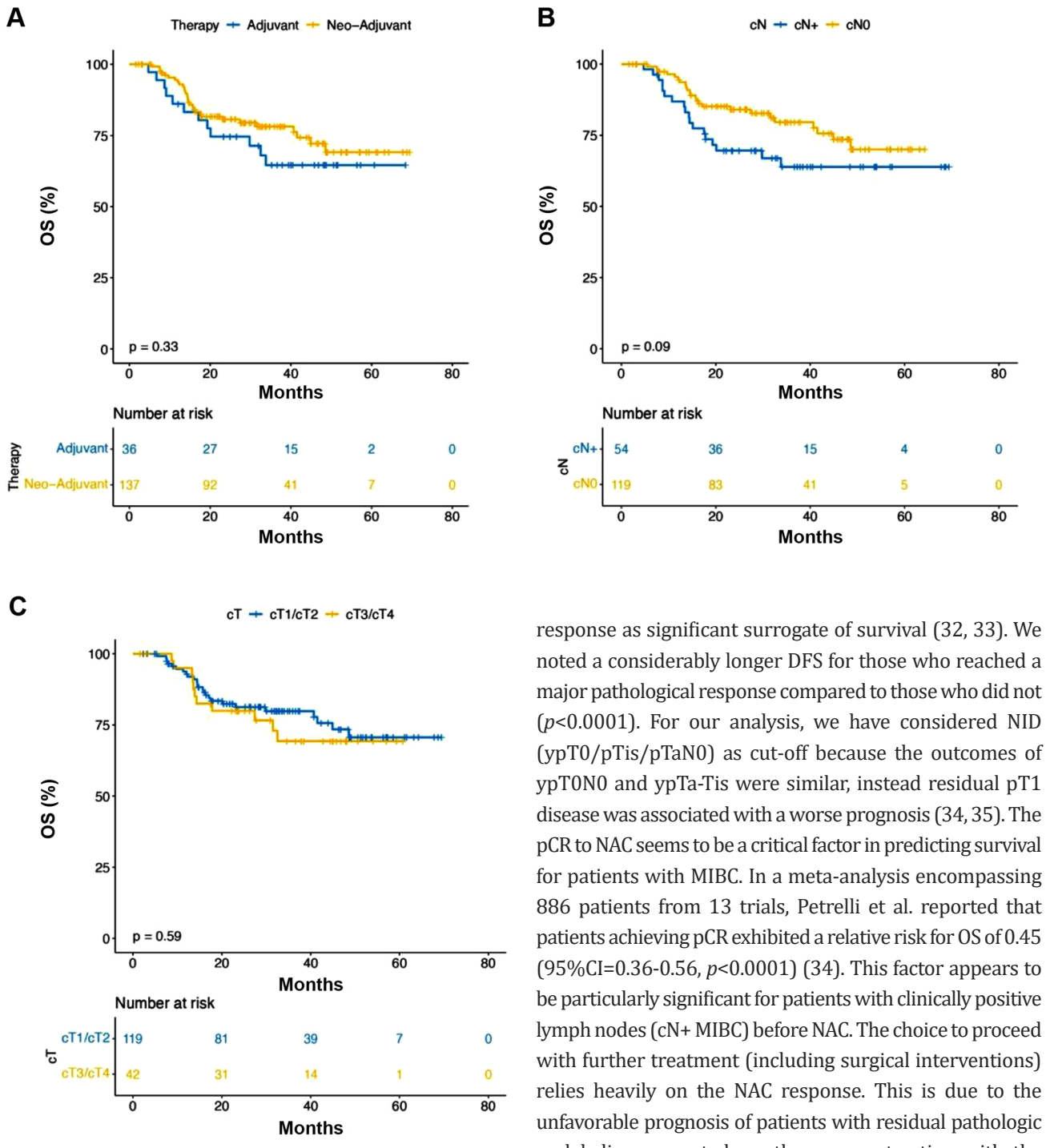

Figure 2. *Overall survival in patients with muscle-invasive bladder cancer according to the chemotherapy setting. (A) Overall survival (OS) of patients according to the chemotherapy setting: neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC). (B) OS according baseline T. (C) OS according baseline N.*

response as significant surrogate of survival (32, 33). We noted a considerably longer DFS for those who reached a major pathological response compared to those who did not (p<0.0001). For our analysis, we have considered NID (ypT0/pTis/pTaN0) as cut-off because the outcomes of ypT0N0 and ypTa-Tis were similar, instead residual pT1 disease was associated with a worse prognosis (34, 35). The pCR to NAC seems to be a critical factor in predicting survival for patients with MIBC. In a meta-analysis encompassing 886 patients from 13 trials, Petrelli et al. reported that patients achieving pCR exhibited a relative risk for OS of 0.45 (95%CI=0.36-0.56, p<0.0001) (34). This factor appears to be particularly significant for patients with clinically positive lymph nodes (cN+ MIBC) before NAC. The choice to proceed with further treatment (including surgical interventions) relies heavily on the NAC response. This is due to the unfavorable prognosis of patients with residual pathologic nodal disease post-chemotherapy, contrasting with the comparatively positive outcomes in patients who reached pCR (36). Regarding patients with clinically positive lymph nodes (cN+), current guidelines are vague and vary in their

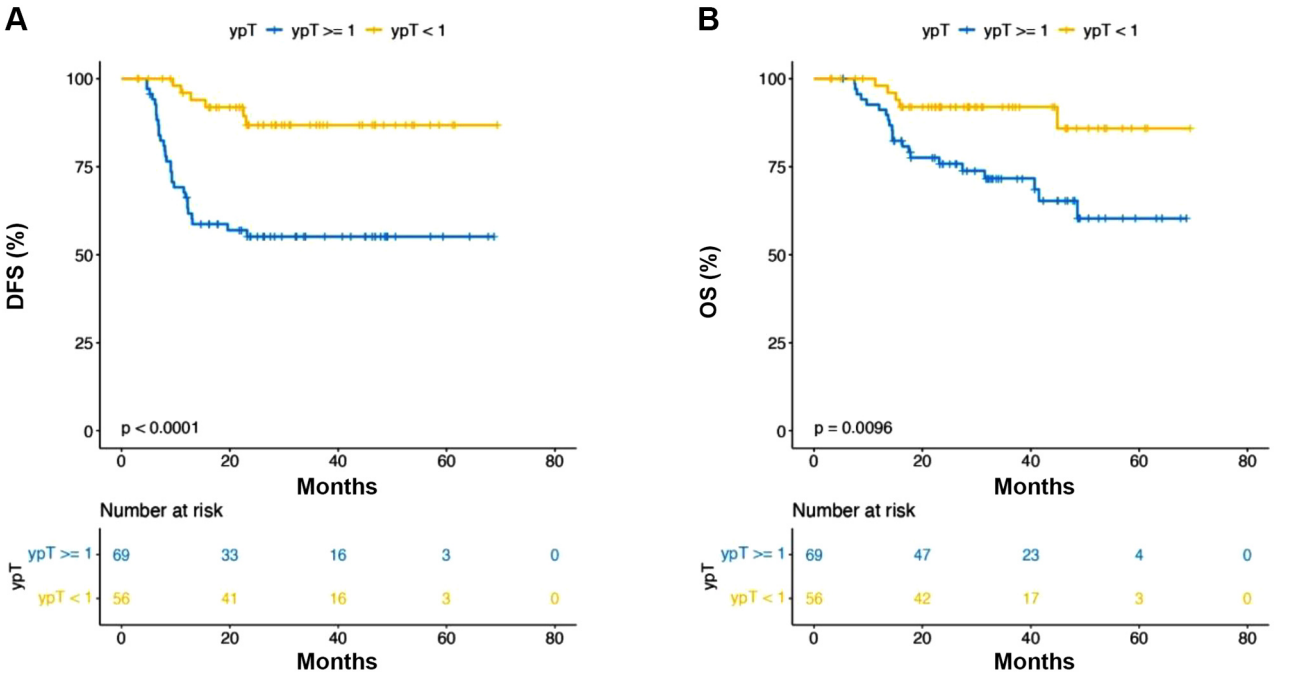

Figure 3. *Impact of non-invasive downstaging on disease-free (DFS) and overall survival (OS) in patients receiving neoadjuvant chemotherapy. (A) DFS of patients undergoing neoadjuvant chemotherapy according to achievement or not of non-invasive downstaging (NID), <ypt1 and ≥ypT1. (B) OS of patients undergoing neoadjuvant chemotherapy according to achievement or not of NID, <ypt1 and ≥ypT1, respectively.*

recommendations. The management of patients with cN+ MIBC remains uncertain in many respects. From diagnostics to surgical intervention and culminating in systemic therapy, there is a notable deficiency in high-quality clinical research. Nonetheless, existing data permit some crucial conclusions. Multimodal treatment incorporating NAC and RC yields the best prognosis for patients with cN+ BC (37). Furthermore, although they are underrepresented in perioperative chemo-immunotherapy trials like NIAGARA (38), that randomized patients with MIBC (1:1) to receive neoadjuvant programmed death-ligand -1 (PD-L1) inhibitor durvalumab combined with NAC (GC) followed by RC and then adjuvant durvalumab monotherapy, node-positive patients may derive particular benefits from a perioperative chemo-immunotherapy strategy due to high relapse rates. The NIAGARA trial recently reported that the addition of durvalumab to standard therapy proved effective in extending both event free survival (EFS) and OS in both pCR (EFS HR=0.58; OS HR=0.72) and non-pCR (EFS HR=0.77; OS HR=0.84) populations (39). In the CheckMate-901 trial, patients with previously untreated unresectable or metastatic urothelial carcinoma were randomized either to receive the programmed death 1 (PD-1) inhibitor nivolumab plus GC for up to six cycles, followed by nivolumab for a maximum of two years, or to receive GC alone for up to six cycles, patients with lymph node-only metastases exhibited remarkably higher response rates (81.5% *vs.* 64.3%), extended median PFS (30.5 *vs.* 8.8 months; HR=0.38), and improved OS (46.3 *vs.* 24.9 months; HR=0.58) when treated with GC plus nivolumab (40). Data from the NIAGARA and CheckMate-901 trials, taken together, could encourage the use of perioperative immunotherapy in the MIBC setting. Furthermore, emerging evidence indicates that the results of AC are comparable to those of NAC; however, there remains a lack of definitive studies. Ultimately, the response to NAC is critical as a prognostic indicator for patients with cN+, and AC should be administered to those who did not receive NAC. Given the high percentage of MIBC patients

ineligible for NAC, the importance of neoadjuvant and adjuvant immunotherapy is increasingly recognized in clinical practice. Recently, the Checkmate 274 trial revealed a DFS advantage with the application of nivolumab for high-risk patients with MIBC (at least pT3, ypT2, or N+) post-RC. In this trial, only 43% of patients received NAC. Notably, subgroup analyses have indicated that patients with cN+ disease and those who received NAC demonstrated greater benefits from nivolumab compared to those with cN0 or without NAC (41).

Ultimately, it remains uncertain whether patients with VH will also benefit from NAC. We have noted some degree of efficacy in terms of pathological downstaging; however, no advantages in DFS or OS were recorded. A retrospective analysis indicated that patients with neuroendocrine tumors experienced improved OS and lower rates of non-organ-confined disease when treated with neoadjuvant cisplatin/etoposide CT. In cases of micropapillary differentiation, sarcomatoid differentiation, and adeno-carcinoma, lower incidences of non-organ confined disease were observed, yet without statistically significant effects on OS. Patients with squamous cell carcinoma did not benefit from NAC (16). A systematic review conducted in 2019 demonstrated advantages of NAC for patients with micropapillary, plasmacytoid, sarcomatoid, and mixed variants, particularly emphasizing patients with neuroendocrine tumors (42). A study from the U.S. National Cancer Database assessing potential associations between the administration of NAC, pathological downstaging, and OS for patients with different histological subtypes of MIBC indicated that NAC was linked to pathological downstaging across all MIBC histological subtypes (UC; sarcomatoid UC; micropapillary UC; squamous cell carcinoma; neuroendocrine carcinoma; and adenocarcinoma), with improved OS noted in patients with UC, sarcomatoid variant UC, and neuroendocrine carcinoma (43). An analysis of the VESPER trial showed that histological subtypes had no significant impact on the effectiveness of NAC, except for squamous cell carcinoma and micropapillary subtypes, which seemed to show poorer outcomes (44).

Table V. *Descriptive statistics for patients with variant histology (N=23). Categorical variables are reported as the absolute number and percentage; continuous variables are reported as median and range.*

Characteristics		N=23
Age	Median [range]	66 [45-80]
Sex	Male	19 (82.6%)
	Female	4 (17.4%)
cT	2	8 (34.8%)
	3	8 (34.8%)
	4	3 (13%)
	X	4 (17.4%)
cN	0	16 (69.6%)
	1	1 (4.3%)
	2	2 (8.7%)
	X	4 (17.4%)
VH	Nested	6 (26%)
	Plasmacytoid	3 (13%)
	Neuroendocrine	3 (13%)
	Sarcomatoid	2 (8.7%)
	Squamous	2 (8.7%)
	Signet ring cells	1 (4.3%)
	Poorly differentiated carcinoma	1 (4.3%)
	Two or more variants	5 (21.7%)
Stage at diagnosis	II	8 (42.1%)
	IIIA	9 (47.4%)
	IIIB	2 (10.5%)
	NA	4
ECOG PS	0	22 (95.7%)
	1	1 (4.3%)
RC	No	1 (4.3%)
	Yes	22 (95.7%)
Surgery technique	Robotic	7 (50%)
	Open	7 (50%)
	NA	8
Comorbidity after RC	No	19 (86.4%)
	Yes	3 (13.6%)
	NA	0
Comorbidity after RC	No	19 (86.4%)
	Yes	3 (13.6%)
	NA	0
Chemotherapy	NAC	15 (65.2%)
	AC	8 (34.8%)
Radiological response after NAC	CR	3 (20%)
	SD	6 (40%)
	PD	1 (6.7%)
	PR	3 (20%)
	NA	2
Pathological response after NAC	ypT0N0	5 (35.7%)
	<ypT1N0	8 (57.1%)
	<ypT2N0	8 (57.1%)
Progression	Yes	12 (52,2%)
	No	11 (47.8%)
Death	Yes	16 (69.6%)
	No	7 (30.4%)

VH: Variant histology; ECOG PS: Eastern Cooperative Oncology Group Performance Status; RC: radical cystectomy; NAC: neoadjuvant chemotherapy; AC: adjuvant chemotherapy; NA: not available; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not available.

In our present study, although conducted retrospectively, we affirmed the efficacy and the safety of NAC in patients with MIBC. Therefore, a more comprehensive treatment approach involving NAC+RC could be proposed as a sensible strategy for patients with high- or locally advanced MIBC.

Study limitations. First, it was retrospective with a relatively brief follow-up period. Second, while it represents the largest scale study of perioperative chemotherapy for MIBC in Italian clinical practice, a larger cohort may be necessary. Third, the lack of complete standardization in follow-up protocols resulted in discrepancies in the types and frequencies of examinations.

Conclusion

The RealBLADDER study has confirmed the greater effectiveness of NAC over AC in MIBC settings. The reported NAC utility rate at 79.2% was high, and NAC was not associated with any increased rate of postoperative complications. Survival after NAC is strongly influenced by whether a pathologic downstaging is achieved, and there is a large need for predictive biomarkers to select patients who will benefit from NAC, as well as new treatment options for non-responders. Our data offer an opportunity to reflect on therapeutic strategies for MIBC in a real-life setting, underlining the importance of a multimodal treatment to achieve better oncological outcome. Further research needs to be performed, particularly regarding immune checkpoint inhibitors, in order to offer more treatment options for patients with MIBC.

Conflicts of Interest

LA has received honoraria or consultation fees for speaker, consultancy, or advisory roles from Amgen, Bayer, Eisai, Merck Serono, Pierre Fabre, Roche, Servier, Incyte, Ipsen, and MSD; has also received travel grants from AstraZeneca, MSD, Merck Serono, and Ipsen; research funding was provided to LA's institution by Novartis and AstraZeneca. FB has received consulting fees or speaker bureau honoraria from Eli Lilly, MSD, Eisai, Bristol Myers Squibb, AstraZeneca, Pierre Fabre, Servier, and AAA Novartis. DM has participated in advisory boards for Roche, MSD, and Merck. The other Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contributions

Elisabetta Gambale: Data curation, Writing – original draft, Visualization, Writing – review & editing. Roberta Giorgione: Data curation. Umberto Basso: Data curation. Marco Maruzzo: Data curation. Luca Galli: Data curation. Giuseppe Fornarini: Data curation. Francesco Atzori: Data curation. Sarah Scagliarini: Data curation. Cristina Masini: Data curation. Valentina Baldazzi: Data curation. Federico Scolari: Data curation. Marinella Micol Mela: Data curation. Ismaela Anna Vascotto: Data curation. Virginia Rossi: Data curation. Daniele Rossini: Review & editing. Giandomenico Roviello: Review & editing. Daniele Lavacchi: Conceptualization, Methodology, Formal analysis, Validation, Writing – review & editing. Serena Pillozzi: Conceptualization, Methodology, Formal analysis, Validation, Writing – review & editing. Lorenzo Antonuzzo: Conceptualization, Methodology, Supervision.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A: Epidemiology of Bladder Cancer. Med Sci (Basel) 8(1): 15, 2020. DOI: 10.3390/medsci8010015

2 Associazione Italiana Registri Tumori - AIRTUM - Fondazione AIOM. I numeri del cancro in Italia 2023. Available at: https://www.aiom.it/wp-content/uploads/2023/12/2023_AIOM_NDC-web.pdf [Last accessed on September 1, 2025]

3 Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan

D, Skinner DG: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 19(3): 666-675, 2001. DOI: 10.1200/JCO.2001.19.3.666

4 Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Krailo M, Groshen S: Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. Semin Urol 8(4): 279-284, 1990.

5 Stöckle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, Thüroff JW, Huber C, Hohenfellner R: Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J Urol 153(1): 47-52, 1995. DOI: 10.1097/00005392-199501000-00019

6 Studer UE, Bacchi M, Biedermann C, Jaeger P, Kraft R, Mazzucchelli L, Markwalder R, Senn E, Sonntag RW: Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 152(1): 81-84, 1994. DOI: 10.1016/s0022-5347(17)32822-7

7 Cognetti F, Ruggeri EM, Felici A, Gallucci M, Muto G, Pollera CF, Massidda B, Rubagotti A, Giannarelli D, Boccardo F, Study Group(†): Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol 23(3): 695-700, 2012. DOI: 10.1093/annonc/mdr354

8 Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, Dumez H, de Santis M, Théodore C, Leahy MG, Chester JD, Verbaeys A, Daugaard G, Wood L, Witjes JA, de Wit R, Geoffrois L, Sengelov L, Thalmann G, Charpentier D, Rolland F, Mignot L, Sundar S, Symonds P, Graham J, Joly F, Marreaud S, Collette L, Sylvester R, European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group, Groupe d'Etude des Tumeurs Urogénitales, National Cancer Research Institute Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, German Association of Urologic Oncology: Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 16(1): 76-86, 2015. DOI: 10.1016/S1470-2045(14)71160-X

9 Hall R: Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy for muscle-invasive bladder cancer (abstract 710). Proc Am Soc Clin Oncol 21: 178a, 2002.

10 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 48(2): 202-205, 2005. DOI: 10.1016/j.eururo.2005.04.006

11 Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, Crawford ED: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349(9): 859-866, 2003. DOI: 10.1056/NEJMoa022148

12 Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, Kaag M, Fransen van de Putte EE, Horenblas S, Drabick JJ: Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and two-step meta-analysis. Oncologist 21(6): 708-715, 2016. DOI: 10.1634/theoncologist.2015-0440

13 Galsky MD, Pal SK, Chowdhury S, Harshman LC, Crabb SJ, Wong YN, Yu EY, Powles T, Moshier EL, Ladoire S, Hussain SA, Agarwal N, Vaishampayan UN, Recine F, Berthold D, Necchi A, Theodore C, Milowsky MI, Bellmunt J, Rosenberg JE, Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators: Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. Cancer 121(15): 2586-2593, 2015. DOI: 10.1002/cncr.29387

14 Pfister C, Gravis G, Flechon A, Chevreau C, Mahammedi H, Laguerre B, Guillot A, Joly F, Soulie M, Allory Y, Harter V, Culine S, VESPER Trial Investigators: 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 25(2): 255-264, 2024. DOI: 10.1016/S1470-2045(23)00587-9

15 Eule CJ, Warren A, Molina Kuna E, Callihan EB, Kim SP, Flaig TW: Neoadjuvant cisplatin-based chemotherapy in nonmetastatic muscle-invasive bladder cancer: a systematic review and pooled meta-analysis to determine the preferred regimen. Urology 188: 118-124, 2024. DOI: 10.1016/j.urology.2024.04.034

16 Alfred Witjes J, Max Bruins H, Carrión A, Cathomas R, Compérat E, Efstathiou JA, Fietkau R, Gakis G, Lorch A, Martini A, Mertens LS, Meijer RP, Milowsky MI, Neuzillet Y, Panebianco V, Redlef J, Rink M, Rouanne M, Thalmann GN, Sæbjørnsen S, Veskimäe E, van der Heijden AG: European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2023 Guidelines. Eur Urol 85(1): 17-31, 2024. DOI: 10.1016/j.eururo.2023.08.016

17 Anceschi U, Brassetti A, Tuderti G, Ferriero MC, Costantini M, Bove AM, Calabrò F, Carlini P, Vari S, Mastroianni R, Gallucci M, Simone G: Impact of clinical response to neoadjuvant chemotherapy in the era of robot assisted radical cystectomy: results of a single-center experience. J Clin Med 9(9): 2736, 2020. DOI: 10.3390/jcm9092736

18 Reardon ZD, Patel SG, Zaid HB, Stimson CJ, Resnick MJ, Keegan KA, Barocas DA, Chang SS, Cookson MS: Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol 67(1): 165-170, 2015. DOI: 10.1016/j.eururo.2014.01.009

19 Zaid HB, Patel SG, Stimson CJ, Resnick MJ, Cookson MS, Barocas DA, Chang SS: Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder

cancer: Results from the National Cancer Database. Urology 83(1): 75-80, 2014. DOI: 10.1016/j.urology.2013.07.072

20 Booth CM, Karim S, Brennan K, Siemens DR, Peng Y, Mackillop WJ: Perioperative chemotherapy for bladder cancer in the general population: Are practice patterns finally changing? Urol Oncol 36(3): 89.e13-89.e20, 2018. DOI: 10.1016/j.urolonc.2017.11.015

21 Proietti F, Flammia RS, Licari LC, Bologna E, Bove AM, Brassetti A, Tuderti G, Mastroianni R, Tufano A, Simone G, Leonardo C: Impacts of neoadjuvant chemotherapy on perioperative outcomes in patients with bladder cancer treated with radical cystectomy: a single high-volume center experience. J Pers Med 14(2): 212, 2024. DOI: 10.3390/jpm14020212

22 Li R, Mukherjee MB, Jin Z, Liu H, Lin K, Liu Q, Dilger JP, Lin J: The potential effect of general anesthetics in cancer surgery: meta-analysis of postoperative metastasis and inflammatory cytokines. Cancers (Basel) 15(10): 2759, 2023. DOI: 10.3390/cancers15102759

23 Chen Z, Zhang P, Xu Y, Yan J, Liu Z, Lau WB, Lau B, Li Y, Zhao X, Wei Y, Zhou S: Surgical stress and cancer progression: the twisted tango. Mol Cancer 18(1): 132, 2019. DOI: 10.1186/s12943-019-1058-3

24 Ni S, Tao W, Chen Q, Liu L, Jiang H, Hu H, Han R, Wang C: Laparoscopic versus open nephroureterectomy for the treatment of upper urinary tract urothelial carcinoma: a systematic review and cumulative analysis of comparative studies. Eur Urol 61(6): 1142-1153, 2012. DOI: 10.1016/j.eururo.2012.02.019

25 Rouprêt M, Smyth G, Irani J, Guy L, Davin JL, Saint F, Pfister C, Wallerand H, Rozet F: Oncological risk of laparoscopic surgery in urothelial carcinomas. World J Urol 27(1): 81-88, 2009. DOI: 10.1007/s00345-008-0349-x

26 Iyer G, Balar AV, Milowsky MI, Bochner BH, Dalbagni G, Donat SM, Herr HW, Huang WC, Taneja SS, Woods M, Ostrovnaya I, Al-Ahmadie H, Arcila ME, Riches JC, Meier A, Bourque C, Shady M, Won H, Rose TL, Kim WY, Kania BE, Boyd ME, Cipolla CK, Regazzi AM, Delbeau D, McCoy AS, Vargas HA, Berger MF, Solit DB, Rosenberg JE, Bajorin DF: Multicenter prospective phase II trial of neoadjuvant dose-dense gemcitabine plus cisplatin in patients with muscle-invasive bladder cancer. J Clin Oncol 36(19): 1949-1956, 2018. DOI: 10.1200/JCO.2017.75.0158

27 Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, Bubley GJ, Stack EC, Signoretti S, Walsh M, Steele G, Hirsch M, Sweeney CJ, Taplin ME, Kibel AS, Krajewski KM, Kantoff PW, Ross RW, Rosenberg JE: Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. J Clin Oncol 32(18): 1889-1894, 2014. DOI: 10.1200/JCO.2013.52.4785

28 Plimack ER, Hoffman-Censits JH, Viterbo R, Trabulsi EJ, Ross EA, Greenberg RE, Chen DY, Lallas CD, Wong YN, Lin J, Kutikov A, Dotan E, Brennan TA, Palma N, Dulaimi E, Mehrazin R, Boorjian SA, Kelly WK, Uzzo RG, Hudes GR: Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol 32(18): 1895-1901, 2014. DOI: 10.1200/JCO.2013.53.2465

29 Grassauer J, Schmidt J, Cowan A, Gilbert SM, Chakiryan NH: Downstaging and survival associated with neoadjuvant immunotherapy before radical cystectomy for muscle-invasive bladder cancer. Eur Urol Oncol 7(1): 139-146, 2024. DOI: 10.1016/j.euo.2023.06.005

30 Hermans TJN, Voskuilen CS, Deelen M, Mertens LS, Horenblas S, Meijer RP, Boormans JL, Aben KK, van der Heijden MS, Pos FJ, de Wit R, Beerepoot LV, Verhoeven RHA, van Rhijn BWG: Superior efficacy of neoadjuvant chemotherapy and radical cystectomy in cT3-4aN0M0 compared to cT2N0M0 bladder cancer. Int J Cancer 144(6): 1453-1459, 2019. DOI: 10.1002/ijc.31833

31 Hanna N, Trinh QD, Seisen T, Vetterlein MW, Sammon J, Preston MA, Lipsitz SR, Bellmunt J, Menon M, Choueiri TK, Abdollah F: Effectiveness of neoadjuvant chemotherapy for muscle-invasive bladder cancer in the current real world setting in the USA. Eur Urol Oncol 1(1): 83-90, 2018. DOI: 10.1016/j.euo.2018.03.001

32 Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullén A, Nilsson S, Malmström PU, Nordic Urothelial Cancer Group: Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol 61(6): 1229-1238, 2012. DOI: 10.1016/j.eururo.2011.12.010

33 Ikarashi D, Kitano S, Tsuyukubo T, Yamashita M, Matsuura T, Maekawa S, Kato R, Kato Y, Kanehira M, Takata R, Sugai T, Obara W: Pathological complete response to neoadjuvant chemotherapy may improve antitumor immune response via reduction of regulatory T cells in muscle-invasive bladder cancer. Sci Rep 14(1): 1442, 2024. DOI: 10.1038/s41598-024-51273-7

34 Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S: Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. Eur Urol 65(2): 350-357, 2014. DOI: 10.1016/j.eururo.2013.06.049

35 Sonpavde G, Goldman BH, Speights VO, Lerner SP, Wood DP, Vogelzang NJ, Trump DL, Natale RB, Grossman HB, Crawford ED: Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. Cancer 115(18): 4104-4109, 2009. DOI: 10.1002/cncr.24466

36 Voskuilen CS, Oo HZ, Genitsch V, Smit LA, Vidal A, Meneses M, Necchi A, Colecchia M, Xylinas E, Fontugne J, Sibony M, Rouprêt M, Lenfant L, Côté JF, Buser L, Saba K, Furrer MA, van der Heijden MS, Daugaard M, Black PC, van Rhijn BWG,

Hendricksen K, Poyet C, Seiler R: Multicenter validation of histopathologic tumor regression grade after neoadjuvant chemotherapy in muscle-invasive bladder carcinoma. Am J Surg Pathol 43(12): 1600-1610, 2019. DOI: 10.1097/PAS.0000000000001371

37 Małkiewicz B, Gurwin A, Karwacki J, Nagi K, Knecht-Gurwin K, Hober K, Łyko M, Kowalczyk K, Krajewski W, Kołodziej A, Szydełko T: Management of bladder cancer patients with clinical evidence of lymph node invasion (cN+). Cancers (Basel) 14(21): 5286, 2022. DOI: 10.3390/cancers14215286

38 Powles T, Catto JWF, Galsky MD, Al-Ahmadie H, Meeks JJ, Nishiyama H, Vu TQ, Antonuzzo L, Wiechno P, Atduev V, Kann AG, Kim TH, Suárez C, Chang CH, Roghmann F, Özgüroğlu M, Eigl BJ, Oliveira N, Buchler T, Gadot M, Zakharia Y, Armstrong J, Gupta A, Hois S, van der Heijden MS, NIAGARA Investigators: Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. N Engl J Med 391(19): 1773-1786, 2024. DOI: 10.1056/NEJMoa2408154

39 Galsky MD, Van Der Heijden MS, Catto JWF, Al-Ahmadie H, Meeks JJ, Nishiyama H, Drakaki A, Vu TQ, Antonuzzo L, Atduev V, Galapo Kann A, Kim TH, Font Pous A, Chang CH, De Wit R, Wojtukiewicz MZ, Xin W, Donegan SE, Hois S, Powles T: Additional efficacy and safety outcomes and an exploratory analysis of the impact of pathological complete response (pCR) on long-term outcomes from NIAGARA. JCO 43(5_suppl): 659-659, 2025. DOI: 10.1200/JCO.2025.43.5_suppl.659

40 van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, Sade JP, Bamias A, Beuzeboc P, Bedke J, Oldenburg J, Chatta G, Ürün Y, Ye D, He Z, Valderrama BP, Ku JH, Tomita Y, Filian J, Wang L, Purcea D, Patel MY, Nasroulah F, Galsky MD, CheckMate 901 Trial Investigators: Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med 389(19): 1778-1789, 2023. DOI: 10.1056/NEJMoa2309863

41 Galsky MD, Witjes JA, Gschwend JE, Milowsky MI, Schenker M, Valderrama BP, Tomita Y, Bamias A, Lebret T, Shariat SF, Park SH, Agerbaek M, Jha G, Stenner F, Ye D, Giudici F, Dutta S, Askelson M, Nasroulah F, Zhang J, Brophy L, Bajorin DF: Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: expanded efficacy from CheckMate 274. J Clin Oncol 43(1): 15-21, 2025. DOI: 10.1200/JCO.24.00340

42 Vetterlein MW, Wankowicz SAM, Seisen T, Lander R, Löppenberg B, Chun FK, Menon M, Sun M, Barletta JA, Choueiri TK, Bellmunt J, Trinh QD, Preston MA: Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer 123(22): 4346-4355, 2017. DOI: 10.1002/cncr.30907

43 Chakiryan NH, Jiang DD, Gillis KA, Green E, Hajiran A, Hugar L, Zemp L, Zhang J, Jain R, Chahoud J, Poch M, Manley BJ, Li R, Sexton W, Gilbert SM: Pathological downstaging and survival outcomes associated with neoadjuvant chemotherapy for variant histology muscle invasive bladder cancer. J Urol 206(4): 924-932, 2021. DOI: 10.1097/JU.0000000000001855

44 Groeneveld CS, Pfister C, Culine S, Harter V, Krucker C, Fontugne J, Dixon V, Sirab N, Bernard-Pierrot I, de Reyniès A, Radvanyi F, Allory Y, VESPER trial investigators: Basal/squamous and mixed subtype bladder cancers present poor outcomes after neoadjuvant chemotherapy in the VESPER trial. Ann Oncol 36(1): 89-98, 2025. DOI: 10.1016/j.annonc.2024.09.008