

# The optimal number of induction chemotherapy cycles in clinically lymph node-positive bladder cancer

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See Appendix 1 for the CLIPOLY Study Group Collaborators.

## Objective

To investigate the optimal number of induction chemotherapy cycles needed to achieve a pathological response in patients with clinically lymph node-positive (cN+) bladder cancer (BCa) who received three or four cycles of induction chemotherapy followed by consolidative radical cystectomy (RC) with pelvic lymph node dissection.

## Patients and Methods

We included 388 patients who received three or four cycles of cisplatin/gemcitabine or (dose-dense) methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), followed by consolidative RC for cTanyN1–3M0 BCa. We compared pathological complete (pCR = ypT0N0) and objective response (pOR = yp ≤ T1N0) between treatment groups. Predictors of pCR and/or pOR were assessed using uni- and multivariable logistic regression analysis. The secondary endpoints were overall (OS) and cancer-specific survival (CSS). We evaluated the association between the number of induction chemotherapy cycles administered and survival outcomes on multivariable Cox regression.

## Results

Overall, 101 and 287 patients received three or four cycles of induction chemotherapy, respectively. Of these, 72 (19%) and 128 (33%) achieved pCR and pOR response, respectively. The pCR (20%, 18%) and pOR (40%, 31%) rates did not differ

significantly between patients receiving three or four cycles ( $P > 0.05$ ). The number of cycles was not associated with pCR or pOR on multivariable logistic regression analyses. The 2-year OS estimates were 63% (95% confidence interval [CI] 0.53–0.74) and 63% (95% CI 0.58–0.7) for patients receiving three or four cycles, respectively. Receiving three vs four cycles was not associated with OS and CSS on uni- or multivariable Cox regression analyses.

## Conclusion

Pathological response and survival outcomes did not differ between administering three or four induction chemotherapy cycles in patients with cN+ BCa. A fewer cycles (minimum three) may be oncologically sufficient in patients with cN+ BCa, while decreasing the wait for definitive local therapy in those patients who end up without a response to chemotherapy. This warrants further validation.

## Keywords

cN+, induction chemotherapy, urinary bladder neoplasms, pathology, survival

## Introduction

The management of clinically lymph node-positive (cN+) bladder cancer (BCa) remains controversial due to the lack of evidence to provide guidance [1,2]. The most widely used strategy is systemic induction chemotherapy as primary treatment followed by consolidative local treatment if patients respond to the chemotherapy. While there is high-level evidence regarding the benefits of neoadjuvant cisplatin-based combined chemotherapy for node-negative muscle-invasive urothelial carcinoma of the urinary bladder [3,4], the same is not proven in patients with cN+ BCa. These patients were excluded from clinical trials of neoadjuvant chemotherapy (NAC) [5]. Nevertheless, retrospective studies have suggested a superiority in survival outcomes for multimodal treatment approaches compared to systemic or local therapy alone in patients with cN+ BCa [6–8]. Indeed, patients that experience a pathological complete response (pCR) after induction chemotherapy may achieve disease-free status with long-term survival rates of ~60% [9,10].

Previous retrospective studies have shown that up to 60% of patients with cN+ BCa undergoing systemic induction chemotherapy followed by consolidative radical cystectomy (RC) were found to be ypN0 at final pathology report [6,9–11]. Yet, the optimal number of induction chemotherapy cycles to maximise pathological response in patients with cN+ BCa has not been previously assessed. In the early NAC trials, three cycles of cisplatin-based chemotherapy were commonly administered, whereas six cycles of cisplatin-based chemotherapy are historically the standard of care in locally advanced or metastatic BCa [3,12,13]. Secondary analyses from recent studies in the metastatic setting have suggested no difference in survival rates between four to six cycles of platinum-based chemotherapy when followed by maintenance avelumab [14]. However, an increasing number of chemotherapy cycles has been associated with more adverse events. If the number of cycles can be decreased based on

non-inferior oncological outcomes, then it should be considered.

To address this knowledge gap, we assessed pathological response and survival outcomes in patients with cN+ BCa who received three or four cycles of induction chemotherapy followed by consolidative RC with pelvic lymph node dissection (PLND). We evaluated whether there was a difference in pathological and survival outcomes based on the number of chemotherapy cycles.

## Patients and Methods

### Patient Selection

This was a retrospective, multicentre study by the Clinically Positive Lymph Nodes (CLIPOLY) study group of patients who received three or four cycles of cisplatin-based induction chemotherapy followed by RC with PLND for cTanyN1–3M0 BCa between 1991 and 2022. The decision to deliver three or four cycles was at the discretion of the treating physician, guided by the available evidence and guideline recommendations at the time of treatment. We excluded primary distant metastatic patients (cM+) and those who did not undergo RC. Only gemcitabine/cisplatin and (dose-dense) methotrexate, vinblastine, doxorubicin, and cisplatin ([dd] MVAC) were allowed as induction chemotherapy regimens (Fig. S1). No patients received perioperative radiotherapy. Six patients with incomplete follow-up status were included in the analysis of pathological response to induction chemotherapy but excluded from survival analysis. Local ethics committees approved the study at all participating institutions as well as data collection at the leading site (reference number 1480/2022).

### Baseline Characteristics

Baseline characteristics included induction chemotherapy regimen, sex, age at RC, imaging modality prior to induction

chemotherapy, chronic kidney disease (CKD) stage according to the National Kidney Foundation, cT and cN stage. Pathological characteristics comprised ypT and ypN stage, the total lymph node count and number of positive lymph nodes removed, soft tissue surgical margin (STSM) status [15], variant histology at RC [16], and receipt of adjuvant treatment. cN-status was assessed via preoperative CT, MRI, or positron emission tomography (PET)-CT. To evaluate clinical response to induction chemotherapy, re-staging was performed during and/or after induction chemotherapy using conventional imaging or PET-CT.

### Pathological Response and Survival Endpoints

The primary objective was to assess pathological response to induction chemotherapy in patients with cN+ BCa who subsequently underwent RC. We defined pCR as presence of ypT0N0 and pathological objective response (pOR) as presence of yp  $\leq$  T1N0 at final pathological examination. Survival endpoints consisted of overall survival (OS), defined as time from RC to death of any cause, and cancer-specific survival (CSS), defined as time from RC to death from BCa. Cause of death was determined by the treating physician, meticulous chart review, telephone interviews with family members, or death certificates [17]. Patients were censored at their last follow-up or death.

### Statistical Analysis

We stratified our cohort according to number of induction chemotherapy cycles received. First, we calculated point estimates and 95% CIs using exact binomial distribution for pCR and pOR at the time of RC and identified predictors of pCR and/or pOR on uni- and multivariable logistic regression analysis. Multivariable analyses were adjusted for the effects of induction chemotherapy regimen, age at RC, sex, the imaging modality prior to induction chemotherapy, and cT and cN stage.

We employed the Kaplan–Meier method to assess survival curves for OS and CSS. Survival curves were compared with the log-rank test. We evaluated the association between the number of induction chemotherapy cycles administered and survival outcomes on multivariable Cox regression. We adjusted multivariable models for the effects of confounders, including the induction chemotherapy regimen, age at surgery, sex, CKD stage, ypT and ypN stage, STSM status, and variant histology at RC.

All statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The reported *P* values were two-sided, and a *P* < 0.05 was considered statistically significant.

## Results

### Baseline Characteristics

A total of 388 patients following induction chemotherapy who underwent RC were available for analysis of treatment response and 382 for survival analysis. The vast majority of patients (287/388 [74%]) received four cycles of chemotherapy, regardless of whether they received gemcitabine/cisplatin or ddMVAC (Table 1). Overall, 234 (60%) and 128 (33%) patients presented with cN1 or cN2 stage on clinical imaging, respectively, with a higher proportion of cN2/3 patients among those receiving four cycles of induction chemotherapy. Gemcitabine/cisplatin was the most commonly used regimen (*n* = 269 [69%]). The majority of patients had  $\geq$ cT2 disease (*n* = 366 [94%]). A detailed resolution of the cN and pN stage distribution is displayed in Table S1.

Data regarding toxicity-related treatment modifications were available in 273 (70%) patients. Of these, 21 patients (7.7%) stopped induction chemotherapy due to adverse events (13 patients), disease progression (four), both (one), patient preference (one), or unknown reasons (two) during the third (16) or the fourth (five) induction chemotherapy cycle. The median (interquartile range [IQR]) time to re-staging during chemotherapy was 2 (1–3) months. Of those patients for whom data on re-staging during/after chemotherapy was available (*n* = 268 [69%]), 16 patients (6%) underwent RC despite an upstaging in ycN stage (Table S2). In total, 149 patients (55%) exhibited ycN0 after induction chemotherapy.

### Pathological Response

Overall, 72 (19%; 95% CI 15–23%) and 128 (33%; 95% CI 28–38%) patients achieved pCR and pOR response at RC, respectively. Among the patients who received three or four cycles of induction chemotherapy, 20 (20%; 95% CI 13–29) and 52 (18%; 95% CI 14–23) experienced pCR and 40 (40%; 95% CI 30–50) and 88 (31%; 95% CI 25–36) experienced pOR, respectively (Fig. 1). No statistically significant differences in pathological response rates were observed between treatment groups (all *P*  $\geq$  0.1). On multivariable logistic regression, the number of induction chemotherapy cycles administered was not associated with pCR and pOR (Table 2). Patients with cN2 stage had a significantly lower likelihood of experiencing pOR (odds ratio 0.42, 95% CI 0.23–0.73; *P* = 0.002) compared to patients with cN1 stage.

### The OS and CSS

Of 382 patients, 167 (44%) died, with 144 (38%) dying from BCa. The median (IQR) follow-up of patients who were alive

**Table 1** Baseline characteristics of 388 patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by RC for cTanyN1–3M0 BCa cancer.

Characteristic	Overall N = 388	3 cycles N = 101 (26%)	4 cycles N = 287 (74%)	P
Induction chemotherapy regimen, n/N (%)				<b>0.011</b>
Gemcitabine/cisplatin	269/388 (69)	82/101 (81)	187/287 (65)	
ddMVAC	76/388 (20)	12/101 (12)	64/287 (22)	
MVAC	43/388 (11)	7/101 (6.9)	36/287 (13)	
Sex, n/N (%)				0.4
Female	92/388 (24)	27/101 (27)	65/287 (23)	
Male	296/388 (76)	74/101 (73)	222/287 (77)	
Age at RC (continuous), years, median (IQR)	65.0 (13.0)	65.0 (10.2)	65.0 (15.0)	0.2
Imaging prior to induction chemotherapy, n/N (%)				0.009
Conventional (CT or MRI)	266/342 (78)	74/84 (88)	192/258 (74)	
PET	76/342 (22)	10/84 (12)	66/258 (26)	
CKD stage according to the NKF, n/N (%)				0.6
Stage 1–2, eGFR ≥60 mL/min/1.73 m <sup>2</sup>	310/379 (82)	81/97 (84)	229/282 (81)	
Stage 3–5, eGFR <60 mL/min/1.73 m <sup>2</sup>	69/379 (18)	16/97 (16)	53/282 (19)	
Clinical T stage, n/N (%)				0.2
≤cT1	22/388 (5.7)	8/101 (7.9)	14/287 (4.9)	
cT2	179/388 (46)	52/101 (51)	127/287 (44)	
≥cT3	187/388 (48)	41/101 (41)	146/287 (51)	
Clinical N stage, n/N (%)				<b>0.012</b>
cN1	234/388 (60)	73/101 (72)	161/287 (56)	
cN2	128/388 (33)	25/101 (25)	103/287 (36)	
cN3	26/388 (6.7)	3/101 (3.0)	23/287 (8.0)	
Pathological T stage, n/N (%)				0.039
ypT0	93/388 (24)	23/101 (23)	70/287 (24)	
ypTa/ypTis/ypT1	89/388 (23)	31/101 (31)	58/287 (20)	
ypT2	88/388 (23)	26/101 (26)	62/287 (22)	
≥ypT3	118/388 (30)	21/101 (21)	97/287 (34)	
Pathological N stage, n/N (%)				0.2
ypN0	216/388 (56)	65/101 (64)	151/287 (53)	
ypN1	69/388 (18)	12/101 (12)	57/287 (20)	
ypN2	79/388 (20)	18/101 (18)	61/287 (21)	
ypN3	24/388 (6.2)	6/101 (5.9)	18/287 (6.3)	
Number of lymph nodes removed, median (IQR)	20.0 (17.0)	23.5 (15.2)	18.0 (16.0)	<b>0.004</b>
Unknown, n	19	1	18	
Number of positive lymph nodes, median (IQR)	0.0 (2.0)	0.0 (1.0)	0.0 (2.0)	0.1
Unknown, n	15	2	13	
STSM, n/N (%)				0.7
Negative	352/386 (91)	91/101 (90)	261/285 (92)	
Positive	34/386 (8.8)	10/101 (9.9)	24/285 (8.4)	
Variant histology at RC, n/N (%)	71/328 (22)	18/94 (19)	53/234 (23)	<b>0.028</b>
Adjuvant treatment, n/N (%)	36/387 (9.3)	15/100 (15)	21/287 (7.3)	<b>0.023</b>

Fisher's exact test; Pearson's chi-squared test; Wilcoxon rank-sum test. Bold values statistically significant at  $P < 0.05$ . eGFR, estimated GFR; NKF, National Kidney Foundation.

was 28 (11.5–64) months. Detailed 2- and 3-year OS and CSS rates are shown in Table S3. On univariable Cox analyses, compared to three cycles, receiving four cycles of induction chemotherapy was associated with neither OS (hazard ratio [HR] 0.99, 95% CI 0.69–1.41;  $P > 0.9$ ) nor CSS (HR 0.95, 95% CI 0.65–1.39;  $P = 0.8$ ) (Fig. 2). On multivariable Cox regression analyses, receiving four induction chemotherapy cycles was not associated with longer OS (HR 0.81, 95% CI 0.54–1.22;  $P = 0.3$ ) or CSS (HR 0.73, 95% CI 0.47–1.12;  $P = 0.2$ ) (Table 3).

## Discussion

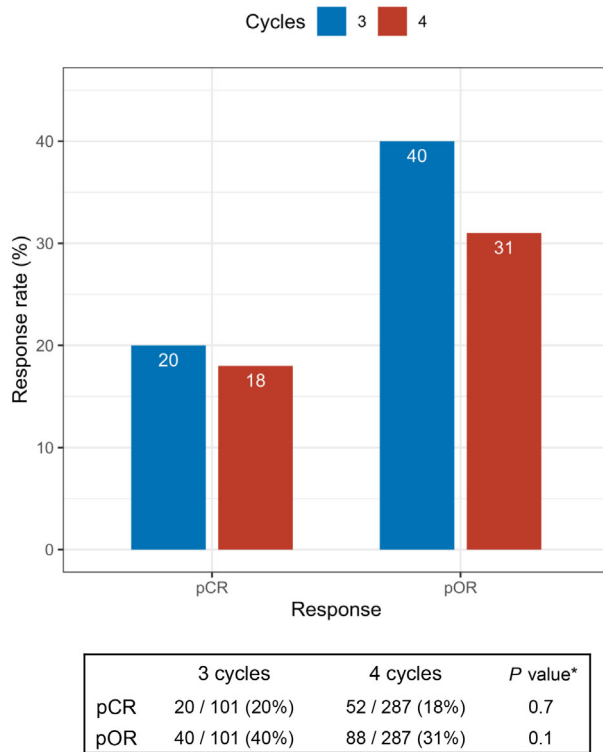
In this study, assessing the optimal number of induction chemotherapy cycles in the unique population of cN+ BCa,

we found no difference in pCR and pOR as well as the 2- and 3-year OS and CSS rates after treatment with three or four cycles of induction chemotherapy followed by RC with PLND.

Response rates to preoperative chemotherapy in BCa differ across the literature. We found that 19% and 33% of all patients achieved pCR and pOR response, respectively. Moreover, in the present study, the number of cycles was not associated with pathological response in multivariable logistic regression analyses. The recent VESPER trial (ClinicalTrials.gov identifier: NCT01812369) compared four cycles of perioperative gemcitabine/cisplatin with six cycles of ddMVAC in cT2–4aN0M0 BCa. In the neoadjuvant group of the VESPER trial, 36% and 42% of patients experienced



**Fig. 1** The pCR and pOR rates in 388 patients receiving three or four cycles of cisplatin-based induction chemotherapy followed by consolidative RC for cTanyN1–3M0 BCa. \*Wilcoxon rank-sum test.



pCR, respectively, whereas 50% and 63% experienced pOR, respectively [4]. In contrast, in the cN+ setting, pathological response rates to preoperative chemotherapy at RC are lower than in the neoadjuvant setting. Indeed, after a median of

four induction chemotherapy cycles administered, a multi-institutional series including 248 patients with cN+ BCa reported a pCR rate of 14.5% and a pOR rate of 27%, respectively [10]. While the authors did not provide the exact number of cycles per induction chemotherapy regimen, 44 (14%) patients received more than four cycles, which was not associated with pCR or pOR in multivariable analyses [10]. In another single-centre cohort, 27% of patients with cT1–4N1–3M1 BCa experienced pCR after a median of four induction chemotherapy cycles [18]. Interestingly, despite allowing carboplatin-based induction chemotherapy and including M1 patients, pCR was higher compared to our study, highlighting the apparent challenges related to treatment and patient selection in cN+ BCa. Given that we included only cisplatin-based induction chemotherapy and that pathological response rates differed marginally between patients receiving three and four cycles, a more restrictive use of induction chemotherapy with fewer cycles and timelier RC may be sufficient to achieve acceptable response rates in cN+ BCa.

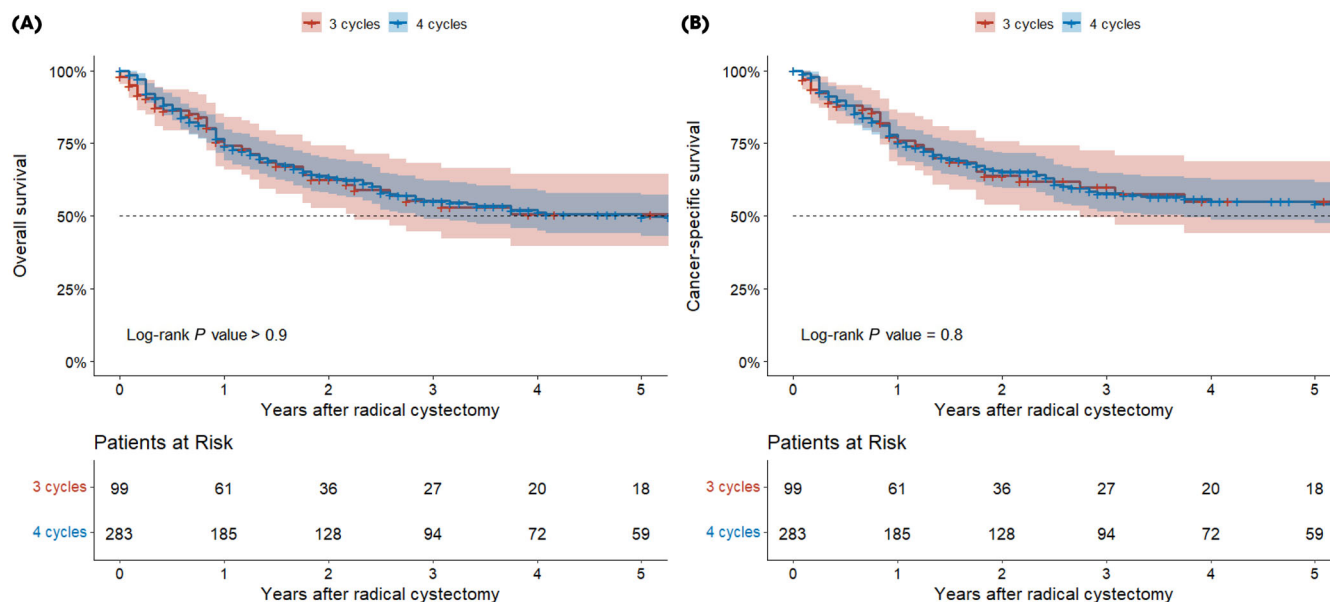
In our study, the number of induction chemotherapy cycles was not associated with survival on uni- and multivariable analyses. This indirectly supports the results of a retrospective study performed in advanced urothelial cancer that reported a 2-year OS of 46.1% after three to five cycles and 47% after six to nine cycles, respectively [19]. The authors concluded that four cycles of platinum-based first-line chemotherapy were adequate. It is noteworthy that 18% of the study population had upper tract urothelial cancer [19]. In contrast, in patients with cN-negative BCa (cT2–4N0M0), two recent studies evaluated the optimal number of NAC cycles. While the results from one study favoured four cycles of NAC [20], Patel et al. [21] concluded that completing three cycles of

**Table 2** Multivariable logistic regression analysis predicting pCR and pOR in 388 patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by RC for cTanyN1–3M0 BCa.

	pCR		pOR	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Number of cycles (ref: 3)				
4	0.83 (0.43–1.64)	0.6	0.83 (0.47–1.49)	0.5
Regimen (ref: gemcitabine/cisplatin)				
ddMVAC	0.95 (0.40–2.12)	>0.9	0.61 (0.29–1.21)	0.2
MVAC	1.55 (0.62–3.68)	0.3	0.79 (0.35–1.74)	0.6
Age at RC	1.04 (1.01–1.08)	<b>0.020</b>	1.03 (1.00–1.06)	<b>0.042</b>
Sex (ref: female)				
Male	2.34 (1.13–5.38)	<b>0.031</b>	2.11 (1.16–3.97)	<b>0.017</b>
Imaging prior to induction chemotherapy (ref: conventional CT or MRI)				
PET	2.34 (1.19–4.56)	<b>0.013</b>	1.27 (0.69–2.32)	0.4
Clinical T stage (ref: ≤cT1)				
cT2	1.96 (0.63–7.55)	0.3	1.89 (0.71–5.53)	0.2
≥cT3	1.21 (0.39–4.62)	0.8	0.89 (0.33–2.59)	0.8
Clinical N stage (ref: cN1)				
cN2	0.61 (0.31–1.15)	0.14	0.42 (0.24–0.73)	<b>0.002</b>
cN3	1.45 (0.47–4.04)	0.5	0.87 (0.32–2.26)	0.8

Bold values statistically significant at  $P < 0.05$ .

**Fig. 2** The OS (A) and CSS (B) in 382 patients receiving three or four cycles of cisplatin-based induction chemotherapy followed by consolidative RC for cTanyN1–3M0 BCa.



**Table 3** Multivariable Cox regression models predicting OS and CSS in 382 patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by RC for cTanyN1–3M0 BCa.

	OS		CSS	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Number of cycles (ref: 3)				
4	0.81 (0.54–1.22)	0.3	0.73 (0.47–1.12)	0.2
Regimen (ref: gemcitabine/cisplatin)				
ddMVAC	1.87 (1.22–2.86)	<b>0.004</b>	1.79 (1.12–2.85)	<b>0.014</b>
MVAC	1.07 (0.59–1.94)	0.8	1.25 (0.67–2.34)	0.5
Age at RC	1.02 (1.00–1.05)	<b>0.027</b>	1.01 (0.99–1.04)	0.2
Sex (ref: female)				
Male	0.68 (0.46–1.00)	<b>0.048</b>	0.69 (0.45–1.04)	0.074
CKD stage according to the NKF (ref: stage 1–2 eGFR ≥60 mL/min/1.73 m <sup>2</sup> )	1.76 (1.04–2.98)	<b>0.035</b>	1.80 (1.01–3.19)	<b>0.045</b>
Pathological T stage (ref: ypT0)				
ypTa/ypTis/ypT1	0.76 (0.38–1.53)	0.4	0.64 (0.29–1.42)	0.3
ypT2	1.15 (0.58–2.28)	0.7	1.25 (0.59–2.64)	0.6
≥ypT3	2.10 (1.09–4.04)	<b>0.026</b>	2.39 (1.17–4.85)	<b>0.016</b>
Pathological N stage (ref: ypN0)				
ypN1	2.35 (1.47–3.75)	<b>&lt;0.001</b>	2.50 (1.49–4.17)	<b>&lt;0.001</b>
ypN2	2.77 (1.79–4.27)	<b>&lt;0.001</b>	3.05 (1.90–4.89)	<b>&lt;0.001</b>
ypN3	3.31 (1.79–6.13)	<b>&lt;0.001</b>	3.97 (2.10–7.51)	<b>&lt;0.001</b>
STSM (ref: negative)				
Positive	2.01 (1.19–3.42)	<b>0.009</b>	2.06 (1.17–3.60)	<b>0.012</b>
Variant histology at RC (ref: no)				
Yes	1.44 (0.95–2.18)	0.087	1.34 (0.86–2.10)	0.2

eGFR, estimated GFR; NKF, National Kidney Foundation. Bold values statistically significant at *P* < 0.05.

cisplatin-based NAC seems sufficient. Moreover, the 2-year (69% and 81%) and 3-year (76% and 73%) OS estimates after three or four cycles of NAC displayed an inconclusive picture regarding the additional benefit of a fourth NAC cycle [20,21].

In cN+ disease, given the absence of prospective trials and only a limited number of retrospective studies, comparison of survival outcomes concerning the number of chemotherapy cycles remains difficult. The differences in results across studies may be attributed to variations in patient populations,

treatment protocols, and response evaluation methodologies. A population-based study found a 2-year OS rate of 52% in cTanyN1–3M0 patients with urothelial carcinoma of the bladder but did not report the induction chemotherapy regimen nor the number of cycles administered [22]. In our study, the 2-year OS rates were 63% and 63% for patients receiving three or four cisplatin-based induction chemotherapy cycles, respectively. In the VESPER trial, six NAC cycles of ddMVAC resulted in significantly longer progression-free survival compared to four cycles of gemcitabine/cisplatin [4]. However, whether this difference in survival was related to the number of cycles administered or the difference in the regimens remains uncertain. In that regard, excluding patients with other than three or four chemotherapy cycles constitutes a selection bias towards chemo-sensitive patients with a favourable response to induction chemotherapy. Yet, a previous study in patients with cN+ BCa found that administering more than three induction chemotherapy cycles was not associated with longer OS in multivariable regression analysis [10].

Our study contributes to the concept of chemotherapy de-escalation in BCa, which aims to minimise the side-effects and adverse events associated with aggressive chemotherapy while achieving similar oncological outcomes. It is noteworthy, that the concept of chemotherapy de-escalation is an area of ongoing research, as the treatment landscape of metastatic BCa evolves [23]. The advent in molecular profiling of tumours may also contribute to the identification of subgroups of patients who may respond particularly well to fewer cycles of chemotherapy, allowing for a more personalised approach to chemotherapy.

We acknowledge several limitations inherent to our retrospective study design. First, our investigation centred on patients who were subjected to either three or four chemotherapy cycles followed by RC with PLND. We did not provide evidence of whether receiving five or six cycles followed by RC with PLND would result in an oncological benefit, our cohort lacked the requisite patient volume to perform this analysis. Furthermore, we acknowledge that with increasing cN stage the likelihood of a patient to receive four induction chemotherapy cycles increases due to the detected extent of the metastatic spread. This could potentially account for the higher proportion of patients with cN2/3 disease among those who received four chemotherapy cycles.

Second, we provided limited information on toxicities related to the delivery of induction chemotherapy, did not report detailed dose-reduction rates, and we did not provide differences between the intended and administered number of cycles. Third, we included only cN+ patients, a BCa subgroup acknowledged for its inherent heterogeneity and bias, whose classification is based on error-prone staging

methods [24,25]. Indeed, using PET/CT may lead to upstaging in some patients, questioning the reliability of available conventional staging methods [26,27]. To account for differences between modern staging technologies and conventional imaging, we adjusted our multivariable models for the effects of the staging modality. Fourth, the existence of disparities in clinical practices among institutions, despite prevailing guideline recommendations, represents another limitation. Given our study's multicentre design, chemotherapy administration was not standardised or randomised, which may result in a selection bias. Last, in general, only patients who responded to induction chemotherapy underwent RC and were available for pathological response assessment, skewing our cohort towards chemo-sensitive patients with favourable outcomes. Therefore, our patient population may not be fully representative of the broader cN+ BCa population [28].

## Conclusion

In this study, patients with cN+ BCa did not have significantly worse outcomes after three cycles of cisplatin-based induction chemotherapy followed by RC with PLND compared with patients receiving four cycles followed by RC with PLND. Prospective validation of these findings is needed. Ultimately, fewer cycles may reduce the risk of adverse events, cumulative toxicity, and shorten the transition to definitive local therapy.

## Disclosure of Interests

Philippe E. Spiess reports that he serves as a vice-chair of the National Comprehensive Cancer Network (NCCN) guidelines for bladder and penile cancer panel. Shahrokh F. Shariat received follows: Honoraria: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Roche, Takeda; Consulting or Advisory Role: Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Takeda; Speakers Bureau: Astellas, AstraZeneca, Bayer, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Richard Wolf, Roche, Takeda. The other authors have no conflicts of interest to declare.

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## References

- Witjes JA, Bruins HM, Cathomas R et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. *Eur Urol* 2021; 79: 82–104

- 2 Chang SS, Bochner BH, Chou R *et al.* Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J Urol* 2017; 198: 552–9
- 3 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: 859–66
- 4 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: 2013–22
- 5 Reitblat C, Bellmunt J, Gershman B. Management of clinically regional node-positive urothelial carcinoma of the bladder. *Curr Oncol Rep* 2021; 23: 24
- 6 Hermans TJN, Fransen van de Putte EE, Horenblas S *et al.* Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer—results of a nationwide population-based study. *Eur J Cancer* 2016; 69: 1–8
- 7 Galsky MD, Stensland K, Sfakianos JP *et al.* Comparative effectiveness of treatment strategies for bladder cancer with clinical evidence of regional lymph node involvement. *J Clin Oncol* 2016; 34: 2627–35
- 8 Afferi L, Zamboni S, Karnes RJ *et al.* The impact of treatment modality on survival in patients with clinical node-positive bladder cancer: results from a multicenter collaboration. *World J Urol* 2021; 39: 443–51
- 9 Ho PL, Willis DL, Patil J *et al.* Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: the M.D. Anderson cancer center experience. *Urol Oncol Semin Orig Investig* 2016; 34: 59.e1–8
- 10 Zargar-Shoshtari K, Zargar H, Lotan Y *et al.* A multi-institutional analysis of outcomes of patients with clinically node positive urothelial bladder cancer treated with induction chemotherapy and radical cystectomy. *J Urol* 2016; 195: 53–9
- 11 Ghadjari P, Burkhard FC, Gautschi O, Thalmann GN, Studer UE. Induction chemotherapy for unresectable urothelial carcinoma of the bladder. *BJU Int* 2010; 107: 894–7
- 12 Plimack ER, Hoffman-Censits JH, Viterbo R *et al.* 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* 2014; 32: 1895–902
- 13 von der Maase H, Hansen SW, Roberts JT *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; 17: 3068–77
- 14 Powles T, Park SH, Voog E *et al.* Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med* 2020; 383: 1218–30
- 15 Novara G, Svatek RS, Karakiewicz PI *et al.* Soft tissue surgical margin status is a powerful predictor of outcomes after radical cystectomy: a multicenter study of more than 4,400 patients. *J Urol* 2010; 183: 2165–70
- 16 Moschini M, D'Andrea D, Korn S *et al.* Characteristics and clinical significance of histological variants of bladder cancer. *Nat Rev Urol* 2017; 14: 651–68
- 17 Rink M, Fajkovic H, Cha EK *et al.* Death certificates are valid for the determination of cause of death in patients with upper and lower tract urothelial carcinoma. *Eur Urol* 2012; 61: 854–5
- 18 Meijer RP, Mertens LS, Van Rhijn BW *et al.* Induction chemotherapy followed by surgery in node positive bladder cancer. *Urology* 2014; 83: 134–9
- 19 Sonpavde GP, Mariani L, Lo Vullo S *et al.* Impact of the number of cycles of platinum based first line chemotherapy for advanced urothelial carcinoma. *J Urol* 2018; 200: 1207–14
- 20 D'Andrea D, Black PC, Zargar H *et al.* Identifying the optimal number of neoadjuvant chemotherapy cycles in patients with muscle invasive bladder cancer identifying the optimal number of neoadjuvant chemotherapy cycles in patients with muscle invasive bladder cancer. *J Urol* 2022; 207: 70–6
- 21 Patel HD, Patel SH, Blanco-Martinez E *et al.* Four versus 3 cycles of neoadjuvant chemotherapy for muscle-invasive bladder cancer: implications for pathological response and survival. *J Urol* 2022; 207: 77–85
- 22 Al-Alao O, Mueller-Leonhard C, Kim SP *et al.* Clinically node-positive (cN+) urothelial carcinoma of the bladder treated with chemotherapy and radical cystectomy: clinical outcomes and development of a postoperative risk stratification model. *Urol Oncol Semin Orig Investig* 2020; 38: 76.e19–28
- 23 van der Heijden MS, Sonpavde G, Powles T *et al.* Nivolumab plus gemcitabine–cisplatin in advanced urothelial carcinoma. *N Engl J Med* 2023; 389: 1778–89
- 24 Hensley PJ, Panebianco V, Pietzak E *et al.* Contemporary staging for muscle-invasive bladder cancer: accuracy and limitations. *Eur Urol Oncol* 2022; 5: 403–11
- 25 von Deimling M, Furrer M, Mertens LS *et al.* Impact of the extent of lymph node dissection on survival outcomes in clinically lymph node-positive bladder cancer. *BJU Int* 2024; 133: 341–50
- 26 Voskuilen CS, van Gennep EJ, Einerhand SMH *et al.* Staging (18)F-fluorodeoxyglucose positron emission tomography/computed tomography changes treatment recommendation in invasive bladder cancer. *Eur Urol Oncol* 2022; 5: 366–9
- 27 Richters A, van Ginkel N, Meijer RP *et al.* Staging fluorodeoxyglucose positron emission tomography/computed tomography for muscle-invasive bladder cancer: a nationwide population-based study. *BJU Int* 2023; 420–7: 420–7
- 28 Swinton M, Mariam NBG, Tan JL *et al.* Bladder-sparing treatment with radical dose radiotherapy is an effective alternative to radical cystectomy in patients with clinically node-positive nonmetastatic bladder cancer. *J Clin Oncol* 2023; 41: 4406–15

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Abbreviations: BCa, bladder cancer; CKD, chronic kidney disease; cN+, clinically lymph node-positive; CSS, cancer-specific survival; (dd)MVAC, (dose-dense) methotrexate, vinblastine, doxorubicin, and cisplatin; HR, hazard ratio; NAC, neoadjuvant chemotherapy; OS, overall survival; pCR, pathological complete response; PET, positron emission tomography; PLND, pelvic lymph node dissection; pOR, pathological objective response; RC, radical cystectomy; STSM, soft tissue surgical margin.

## Appendix 1

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Fig. S1** Flowchart showing selection of patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by consolidative RC for cTanyN1–3M0 BCa.

**Table S1** Distribution of clinical and pathological N stage in 388 patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by RC for cTanyN1–3M0 BCa.

**Table S2** Staging modality and outcomes before and during/after induction chemotherapy in 388 patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by RC for cTanyN1–3M0 BCa.

**Table S3** The 2- and 3-year survival probabilities for OS and CSS in 328 patients treated with three or four cycles of cisplatin-based induction chemotherapy followed by RC for cTanyN1–3M0 BCa.