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ORIGINAL ARTICLE

# Concomitant CIS on TURBT does not impact oncological outcomes in patients treated with neoadjuvant or induction chemotherapy followed by radical cystectomy

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## Abstract

**Background** Cisplatin-based neoadjuvant chemotherapy (NAC) for muscle invasive bladder cancer improves all-cause and cancer specific survival. We aimed to evaluate whether the detection of carcinoma in situ (CIS) at the time of initial transurethral resection of bladder tumor (TURBT) has an oncological impact on the response to NAC prior to radical cystectomy.

**Patients and methods** Patients were identified retrospectively from 19 centers who received at least three cycles of NAC or induction chemotherapy for cT2-T4aN0-3M0 urothelial carcinoma of the bladder followed by radical cystectomy between 2000 and 2013. The primary and secondary outcomes were pathological response and overall survival, respectively. Multivariable analysis was performed to determine the independent predictive value of CIS on these outcomes.

**Results** Of 1213 patients included in the analysis, 21.8% had concomitant CIS. Baseline clinical and pathologic characteristics of the 'CIS' versus 'no-CIS' groups were similar. The pathological response did not differ between the two arms when response was defined as pT0N0 (17.9% with CIS vs 21.9% without CIS; $p=0.16$) which may indicate that patients with CIS may be less sensitive to NAC or ≤ pT1N0 (42.8% with CIS vs 37.8% without CIS; $p=0.15$). On Cox regression model for overall survival for the cN0 cohort, the presence of CIS was not associated with survival (HR 0.86 (95% CI 0.63–1.18; $p=0.35$). The presence of LVI (HR 1.41, 95% CI 1.01–1.96; $p=0.04$), hydronephrosis (HR 1.63, 95% CI 1.23–2.16; $p=0.001$) and use of chemotherapy other than ddMVAC (HR 0.57, 95% CI 0.34–0.94; $p=0.03$) were associated with shorter overall survival. For the whole cohort, the presence of CIS was also not associated with survival (HR 1.05 (95% CI 0.82–1.35; $p=0.70$).

**Conclusion** In this multicenter, real-world cohort, CIS status at TURBT did not affect pathologic response to neoadjuvant or induction chemotherapy. This study is limited by its retrospective nature as well as variability in chemotherapy regimens and surveillance regimens.

**Keywords** Neoadjuvant chemotherapy · Carcinoma insitu · Bladder cancer · Radical cystectomy

## Introduction

Cisplatin-based neoadjuvant chemotherapy (NAC), followed by radical cystectomy (RC) and bilateral pelvic lymph node dissection is considered the standard of care for patients with muscle invasive bladder cancer (MIBC) who are eligible to receive this multimodal therapy. This approach has been shown to improve all-cause and cancer-specific mortality compared to RC alone [1, 2]. The pathologic response,

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defined as either no residual carcinoma (pT0N0) or no residual MIBC (≤ pT1N0), is considered a surrogate end point for overall survival [3]. Patients with residual MIBC have a high risk of recurrence and subsequent death from bladder cancer [2].

In current clinical practice, it is sometimes suggested that NAC may have less effect on CIS, which could lead patients with concomitant CIS to have a higher rate of residual disease after NAC [14, 15]. There is little evidence in the literature regarding the oncological response of patients with CIS to NAC. We hypothesized that there is no difference in outcome in patients diagnosed with CIS on initial TURBT who subsequently receive NAC prior to RC. We tested this hypothesis in a large international consortium.

## Patients and methods

### Study population

From 2000 to 2013, patients with MIBC (cT2-T4aN0-3M0) who were managed with pre-operative systemic chemotherapy followed by RC were retrospectively identified at 19 centers across Europe, Canada and the USA. These centers collectively agreed to share data and this was approved by the respective Institutional Review Boards at each center. The term neoadjuvant chemotherapy (NAC) is conventionally used only for patients with cN0M0 bladder cancer. Here, we also included patients receiving induction chemotherapy for cN1-3M0 disease under the term NAC.

The study population was divided into patients with and without CIS at TURBT. All patients had urothelial carcinoma of the bladder. Mixed histology with squamous and/or glandular differentiation was allowed, but no other variant histology. All patients received at least three cycles of NAC prior to RC.

Information regarding demographics, clinical staging, chemotherapy regimen and other treatment parameters was obtained. Additionally, the pathological outcome after cystectomy was retrieved. All centers used the American Joint Committee on Cancer (AJCC) criteria for pathologic assessment, but there was no central review.

### Statistical analysis

Clinical and pathologic data were compared between groups. For variables with non-normal distribution, data were presented as median and interquartile range (IQR), and the respective groups were compared using the Mann–Whitney $U$ test. Categorical variables were compared using the $\chi^2$ test. Multivariable logistic regression analysis of selected variables (age, cT stage, gender and type of chemotherapy regimen) was used to define factors predicting pCR (pathological complete response) and pPR (pathological partial response). For comparison of adjusted pathologic response rates, the odds ratio (OR) was reported, and the 95% confidence interval (CI) was calculated with bootstrapping. The multivariable Cox proportional hazards regression model for survival was used to assess hazard ratios (HRs) for variables of interest selected based on univariable analysis as well as clinical relevance (gender, type of chemotherapy regimen, surgical margin, extent of lymph node dissection and presence of pPR). Significance was set at $p$ value $< 0.05$. Analyses were performed using SPSS v.21 software (IBM SPSS Statistics; IBM Corp, Armonk, NY, USA). The primary outcome was pathologic response defined as either pT0N0 or ≤ pT1N0 in RC specimens. Multivariate analysis was performed to identify factors predictive of either outcome. Multivariable binary regression models were created, first including all cN stages and then only for patients with cN0 disease. The same was also repeated only in patients who received cisplatin-based chemotherapy. A multivariable Cox regression model for overall survival was also generated. Significance was set at $p$ value $< 0.05$.

## Results

After applying our selection criteria from the total of 1865 patients, 1253 met our criteria. The presence of CIS was not annotated in 40 patients and they were excluded from the analysis. Overall, 1213 patients met criteria, including 823 patients who were cN0, 117 cNx and 273 cN1-3. Concomitant CIS was reported in 21.8% of the patients. Table 1 shows the clinical and pathological features in both the "CIS" and "no-CIS" cohorts. The "no-CIS" patients had higher baseline risk with respect to cT stage, cN stage and hydronephrosis, whereas the rate of lymphovascular invasion (LVI) was higher in the "CIS" patients.

The NAC regimens employed were gemcitabine–cisplatin (GC) in 608 (50.1%), methotrexate–vinblastine–adriamycin–cisplatin (MVAC) or dose-dense MVAC in 401 (33.1%) and other in 196 (16.2%) (Table 2). The NAC regimen was not specified for the remaining patients (0.6%). There was no difference between groups with respect to NAC regimens. The time from NAC to cystectomy was significantly longer in patients with CIS (17 weeks) versus those without CIS (16 weeks; $p = 0.006$). The median follow-up was 1.6 years (range 0.5–3.5 years).

The pathological response for all patients regardless of cN status showed no significant difference according to CIS status (Table 2). However, if only cN0 patients were considered, the downstaging to ≤ pT1N0 occurred more frequently in the CIS group (53.0%) than in the non-CIS group (41.7%; $p = 0.007$). Downstaging to pT0N0 did not differ according to CIS status.

**Table 1** Baseline demographic and clinicopathological findings at initial TURBT

| | CIS 265 | No CIS 948 | *p* |
|---|---|---|---|
| Age, median (IQR) years | 64 (57,71) | 64 (57, 71) | 0.75 |
| Male gender, *N* (%) | 199 (75.1) | 722 (76.1) | 0.91 |
| Never smoked, *N* (%) | 65 (28.1) | 246 (30.3) | 0.89 |
| Clinical T stage, *N* (%) | | | 0.06 |
| T2 | 161 (60.8) | 499 (52.6) | |
| T3 | 72 (27.2) | 309 (32.6) | |
| T4a | 32 (12.1) | 140 (14.8) | |
| Clinical N stage, *N* (%) | | | 0.05 |
| N0 | 188 (70.9) | 635 (67.0) | |
| N+ | 46 (17.4) | 227 (23.9) | |
| Nx | 31 (11.7) | 86 (9.1) | |
| Hydronephrosis, *N* (%) | | | 0.03 |
| Present | 63 (23.8) | 305 (32.2) | |
| Absent | 139 (52.5) | 450 (47.5) | |
| Status unknown | 63 (23.8) | 193 (20.4) | |
| LVI, *N* (%) | | | 0.04 |
| Yes | 59 (22.3) | 163 (17.2) | |
| No | 99 (37.4) | 432 (45.6) | |
| Unavailable data | 107(40.4) | 353 (37.2) | |
| Primary pathology TURBT, *N* (%) | | | 0.94 |
| Urothelial cancer | 236 (89.1) | 839 (88.5) | |
| Urothelial cancer with squamous differentiation | 22 (8.3) | 85 (9.0) | |
| Urothelial cancer with glandular differentiation | 7 (2.6) | 24 (2.5) | |

*IQR* interquartile range, *LVI* lymphovascular invasion, *TURBT* transurethral resection of bladder tumour

Table 3 summarizes the multivariable analysis assessing potential risk factors for pathologic downstaging in all patients (cN0-3). cN1-3 status was an independent predictor of lower pT0N0 (compared to cN0; OR 0.48, 95% CI 0.32–0.72; $p < 0.001$) and ≤ pT1N0 rates (compared to cN0; 0.44, 95% CI 0.31–0.61; $p < 0.001$). Table 4 summarizes the multivariable analysis assessing potential risk factors for pathologic down-staging for patients with N0 disease.

On Cox regression model for overall survival for the cN0 cohort using clinicopathological data (Table 5), the presence of CIS was not associated with survival (HR 0.87 (95% CI 0.64–1.89; $p = 0.38$). The presence of LVI (HR 1.44, 95% CI 1.04–2.00; $p = 0.03$), hydronephrosis (HR 1.58, 95% CI 1.18–2.11; $p = 0.002$) and use of a chemotherapy regimen other than ddMVAC (HR 0.58, 95% CI 0.35–0.96; $p = 0.03$) were associated with worse survival outcomes.

Assessing overall survival for the entire cohort (Table 6), cN + status, the presence of hydronephrosis and the use of a chemotherapy regimen other than ddMVAC predicted worse overall survival. The presence of CIS was not associated with overall survival (HR 1.06 (95% CI 0.83–1.36; $p = 0.65$). When the same analyses were performed for either cN0-3 or cN0 patients who received only cisplatin-based chemotherapy, the results did not change significantly (data not shown).

## Discussion

Risk stratification to guide optimal management of patients with MIBC is limited to that obtained from bimanual examination, imaging and pathologic data from TURBT samples. The use of cisplatin-based NAC offers an overall survival advantage, but some patients do not respond and likely experience only adverse effects with no clinical benefit. It is therefore important to identify patients who are less likely to respond and/or more likely to progress during NAC [1–3]. Potential clinical factors that may be associated with lower response to NAC include tumor location at the bladder neck, presence of hydronephrosis and variant histology such as sarcomatoid, small cell, plasmacytoid or micropapillary carcinoma [4]. Furthermore, research has revealed that genomic markers such as DNA damage repair gene (ERCC2, Rb1, FANCC, ATM) mutations, ErbB2 alterations, molecular subtyping based on gene expression and the Co-expression Extrapolation (COXEN) model for analysis of gene expression signatures may predict response to cisplatin-based NAC [5–10]. Ongoing clinical trials are evaluating the clinical utility of such molecular biomarkers (e.g., NCT02177695, NCT02710734) [4, 10].

**Table 2** Chemotherapy regimens and final pathological results

| | CIS *N* (%) | No CIS *N* (%) | *p* value |
|---|---|---|---|
| Number of patients | 265 (21.8) | 948 (72.2) | |
| Chemo regimen | | | 0.18 |
| ddMVAC, *N* (%) | 50 (18.9) | 211 (22.3) | |
| MVAC, *N* (%) | 31 (11.7) | 109 (11.5) | |
| GC, *N* (%) | 133 (50.2) | 475 (50.1) | |
| Other, *N* (%) | 49 (18.5) | 147 (15.5) | |
| Unavailable data | 2 (0.8) | 6 (0.6) | |
| Number of Cycles | | | |
| 3 cycles, *N* (%) | 122 (46.0) | 371 (39.1) | 0.07 |
| 4 cycles, *N* (%) | 111 (41.9) | 494 (52.2) | |
| > 4 cycles, *N* (%) | 32 (12.1) | 83 (8.8) | |
| Time between TURBT and NAC**, median (IQR) weeks | 6 (2.8) | 5 (2.10) | 0.13 |
| Duration of NAC, median (IQR) weeks | 9 (6.12) | 9 (5.12) | 0.35 |
| Time between NAC and cystectomy, median (IQR) weeks | 17 (14. 24) | 16 (12.21) | 0.006 |
| Pathological outcome | | | |
| All cNstage, *N* (%) | 46 (17.9) | 204 (21.9) | 0.16 |
| pT0N0 | 110 (42.8) | 352 (37.8) | 0.15 |
| ≤pT1N0 | | | |
| cN0, N (%) | 42 (23.0) | 152 (24.5) | 0.67 |
| pT0N0 | 97 (53.0) | 259 (41.7) | 0.007 |
| ≤pT1N0 | | | |
| CIS on final pathology, *N* (%) | 116 (43.8) | 248 (26.2) | < 0.001 |
| Number of nodes removed, median (IQR) | 18 (12–27) | 18 (10–27) | 0.58 |
| Number of positive nodes, median (range) | 0 (0–21) | 0 (0–50) | 0.22 |
| Positive surgical margin, *N* (%) | 22 (8.4) | 102 (10.9) | 0.31 |
| Follow up time, median years | 1.2 (0.5,2.3) | 1.4 (0.5,2.9) | 0.11 |

** Time between TURBT and start of NAC

**Table 3** Predictors of pT0N0 and ≤ ypT1N0 for the entire cohort (pT2-4, N0-3; $n = 1213$)

| Variables | ≤ypT1N0 OR (95%CI) | *p* | ypT0N0 OR (95%CI) | *p* |
|---|---|---|---|---|
| Gender* | | | | |
| Female | 1 | | 1 | |
| Male | 0.75 (0.66, 1.04) | 0.08 | 0.77 (0.38, 1.55) | 0.46 |
| cT stage | | | | |
| cT2 | 1 | | 1 | |
| cT3-4 | 0.83 (0.64, 1.08) | 0.17 | 0.85 (0.63, 1.16) | 0.31 |
| NAC regimen | | | | |
| MVAC | 1 | | 1 | |
| ddMVAC | 1.49 (0.93, 2.38) | 0.09 | 1.70 (0.95, 3.03) | 0.07 |
| GC | 1.39 (0.90, 2.15) | 0.13 | 1.46 (0.84, 2.51) | 0.17 |
| Other | 1.19 (0.72, 1.97) | 0.49 | 1.54 (0.83, 2.84) | 0.17 |
| cN stage | | | | |
| N0 | 1 | | 1 | |
| N+ | 0.44 (0.31, 0.61) | < 0.001 | 0.48 (0.32, 0.72) | < 0.001 |
| Nx | 0.74 (0.47, 1.16) | 0.19 | 0.66 (0.37, 1.15) | 0.14 |
| CIS | | | | |
| No | 1 | | 1 | |
| Yes | 0.93 (0.67, 1.27) | 0.64 | 0.66 (0.45, 0.98) | 0.04 |

* Addition of this variable did not alter the performance of the other variables and this was not included in the final model

**Table 4** Predictors of pT0N0 and ≤ypT1N0 for cT2-4, N0 patients ($n = 823$)

| Variables | ≤ypT1N0 OR (95%CI) | *p* | ypT0N0 OR (95%CI) | *p* |
|---|---|---|---|---|
| Gender* | | | | |
| Female | 1 | | 1 | |
| Male | 0.73 (0.49, 1.09) | 0.13 | 0.88 (0.56, 1.38) | 0.58 |
| cT stage | | | | |
| cT2 | 1 | | 1 | |
| cT3-4 | 0.66 (0.48, 0.91) | 0.01 | 0.71 (0.49, 1.03) | 0.07 |
| NAC regimen | | | | |
| MVAC | 1 | | 1 | |
| ddMVAC | 1.32 (0.72, 2.44) | 0.36 | 1.23 (0.62, 2.46) | 0.54 |
| GC | 1.17 (0.66, 2.08) | 0.56 | 1.03 (0.53, 1.98) | 0.93 |
| Other | 0.88 (0.45, 1.74) | 0.72 | 0.97 (0.45, 2.11) | 0.94 |
| CIS | | | | |
| No | 1 | | 1 | |
| Yes | 1.18 (0.81, 1.72) | 0.38 | 0.79 (0.51, 1.23) | 0.30 |

* Addition of this variable did not alter the performance of the other variables and this was not included in the final model

**Table 5** Cox regression model for OS for cT2-4,N0 cohort using pre-cystectomy data

| Variables | OS HR (95% CI) | *p* |
|---|---|---|
| Age | 1.00 (0.99, 1.01) | 0.40 |
| cT stage | | |
| cT2 | 1 | |
| cT3-4 | 1.14 (0.88, 1.48) | 0.31 |
| NAC regimen | | |
| MVAC | 1 | |
| ddMVAC | 0.58 (0.35, 0.96) | 0.03 |
| GC | 1.00 (0.65, 1.55) | 0.98 |
| Other | 1.11 (0.68, 1.80) | 0.68 |
| LVI | | |
| No | 1 | |
| Yes | 1.44 (1.04, 2.00) | 0.03 |
| Unknown | 1.13 (0.83, 1.54) | 0.44 |
| Hydronephrosis | | |
| No | 1 | |
| Yes | 1.58 (1.18, 2.11) | 0.002 |
| Unknown | 1.33 (0.93, 1.92) | 0.11 |
| CIS | | |
| No | 1 | |
| Yes | 0.87 (0.64, 1.89) | 0.38 |

It is notable that CIS might have distinct molecular features compared to papillary urothelial tumors [11, 14]. CIS alone is regarded as high-risk non-MIBC because it is estimated that > 50% of cases will progress to MIBC over time if left untreated [13, 14] Concomitant CIS in patients with papillary NMIBC increases the risk of progression.

**Table 6** Cox regression model for OS for the entire cohort using pre-cystectomy data

| Variables | OS HR (95% CI) | *p* |
|---|---|---|
| Age | 1.00 (0.99, 1.01) | 0.23 |
| cT stage | | |
| cT2 | 1 | |
| cT3-4 | 1.23 (0.99, 1.51) | 0.06 |
| cN stage | | |
| N0 | 1 | |
| N+ | 1.54 (1.23, 1.92) | <0.001 |
| Nx | 0.91 (0.54, 1.54) | 0.73 |
| NAC regimen | | |
| MVAC | 1 | |
| ddMVAC | 0.66 (0.46, 0.94) | 0.02 |
| GC | 0.93 (0.67, 1.29) | 0.66 |
| Other | 0.99 (0.68, 1.43) | 0.95 |
| LVI | | |
| No | 1 | |
| Yes | 1.25 (0.96, 1.65) | 0.10 |
| Unknown | 1.13 (0.89, 1.45) | 0.30 |
| Hydronephrosis | | |
| No | 1 | |
| Yes | 1.35 (1.07, 1.71) | 0.01 |
| Unknown | 1.32 (0.98, 1.77) | 0.06 |
| CIS | | |
| No | 1 | |
| Yes | 1.06 (0.83, 1.36) | 0.65 |

If patients with CIS proceed to cystectomy, upstaging can occur in up to 55% of cases compared to 6% of cases without CIS [12]. In patients diagnosed with CIS on initial TURBT, the published literature varies on whether or not CIS itself may predict lower response rates to NAC [14, 15].

In our study, we evaluated the pathologic and clinical outcomes in patients diagnosed with or without CIS on the initial TURBT prior to NAC followed by RC. We found no statistically or clinically significant difference in the pathologic response rates between the two groups when response was defined either as pT0N0 or ≤ pT1N0. On Cox regression model for overall survival for the cN0 cohort using clinicopathological data, the presence of CIS was not associated with overall survival. The presence of LVI at TURBT, hydronephrosis and use of chemotherapy regimens other than ddMVAC were associated with shorter overall survival. In our series, we accept that all CIS may not have been captured on initial TURBT, but this has had no bearing on data capture. This reflects higher CIS being diagnosed on final RC specimen analysis. This reflects real-world experiences with CIS reporting on initial TURBT. For the whole cohort, the presence of CIS was not associated with overall survival.

Our study is consistent with two prior smaller reports in the literature. Thomas et al. described the impact of CIS on the pathologic response to NAC, as well as on progression-free survival (PFS) and OS after NAC and RC [13]. Of 137 patients in this single institutional series, 30.7% had CIS prior to treatment. While the pT0N0 rate in the bladder after NAC and RC was lower in patients with pre-treatment CIS (23.2% vs 9.5%), this was predominantly due to pTisN0 and had no negative impact on PFS or OS. Both survival outcomes were similar to patients with pT0N0 disease in this series. Parker et al. reported very similar findings in a series of 189 patients from two centers [15]. There was a lower rate of pT0N0 disease (26.3% vs 10.7%), but no difference in PFS or OS was observed. Some of the patients from this latter series are also captured in our series.

Our study is limited by its retrospective nature. There is variability in the use of NAC regimens, dose schedules and number of cycles administered, as well as surveillance regimens. As a multi-institutional study without central review, it lacks consistency with respect to surgical technique in TURBT and RC, and histopathological reporting. Essentially all patients in this study underwent white light cystoscopy, although this was not captured explicitly (vs blue light). The rate of CIS detection would likely be higher if patients had been evaluated with blue light cystoscopy [16–21], which would have allowed for a more complete analysis of the impact of CIS in the context of NAC. A key strength of the study is its large sample size.

## Conclusion

Our multicenter retrospective study demonstrated that concomitant CIS of the bladder at the time of TURBT did not impact pathologic response or overall survival after neoadjuvant or induction chemotherapy and RC in patients with MIBC. These results suggest that concomitant CIS should have no bearing on the treatment decision-making process in patients with MIBC being considered for NAC and RC.

**Author contributions** NV: protocol/project development, data collection/management, manuscript writing/editing; HZ: data collection/management, data analysis, manuscript writing/editing; JPN: data collection, manuscript writing/editing; RV: data collection, manuscript review; ASF: data collection, manuscript review; LSM: data collection, manuscript review; CPD: data collection, manuscript review; MCM: data collection, manuscript review; LMK: data collection, manuscript review; MSC: data collection, manuscript review; NEJ: data collection, manuscript review; NMG: data collection, manuscript review; JG: data collection, manuscript review; JSM: data collection, manuscript review; EYY: data collection, manuscript review; EX: data collection, manuscript review; NJC: data collection, manuscript review; WK: data collection, manuscript review; MAD: data collection, manuscript review; JAS: data collection, manuscript review; CEE: data collection, manuscript review; SH: data collection, manuscript review; SSS: data collection, manuscript review; JSM: data collection, manuscript review; JA: data collection, manuscript review; SFS: data collection, manuscript review; JLW: data collection, manuscript review; TMM: data collection, manuscript review; TJB: data collection, manuscript review; SN: data collection, manuscript review; DAB: data collection, manuscript review; YL: data collection, manuscript review; PG: data collection, manuscript review; AJS: data collection, manuscript review; JBS: data collection, manuscript review; BWR: data collection, manuscript review; SD: data collection, manuscript review; PES: data collection, manuscript review; JMH: data collection, manuscript review; AT: manuscript writing/editing; PCB: manuscript writing/editing.

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Research involving human participants and animals** For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study where applicable.

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