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Long term oncologic outcome in patients with bladder cancer after radical cystectomy: Impact of carcinoma in situ in the era of neoadjuvant chemotherapy

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Abstract

Purpose To assess the impact of carcinoma in situ (CIS) on oncologic outcomes in patients who underwent radical cystectomy, with a focus on those who received neoadjuvant chemotherapy (NAC) including patients with down-staging to ≤pT1cancer after chemotherapy.

Materials and methods All patients who underwent radical cystectomy for urothelial cancer with curative intent from 1985 to 2011 were included. The impact of CIS on recurrence free and overall survival (OS) was assessed in the whole cohort and a subgroup who received NAC as well as those with response to chemotherapy and down-staging to ≤pT1.

Results A total of 2518 patients with a median follow-up period of 9 years were included. Among all, 1397 (55.5%) had concomitant CIS on final pathology. CIS was associated with high risk pathologic features including high-grade disease, multifocality, and nodal involvement as well as worse recurrence free survival (RFS) with no impact on OS. We did not find a significant association between CIS and oncologic outcomes in a subset of patients who received NAC including those with down-staging to ≤pT1 disease. In multivariate analysis, CIS had no association with either recurrence free or OS.

Conclusions Concomitant CIS in radical cystectomy specimens is associated with decreased RFS; however, in multivariate analysis, it was not an independent predicting factor of oncologic outcomes. Moreover, the impact of CIS on oncologic outcomes in a subset of patients who received NAC was insignificant.

Keywords Carcinoma in situ · Cystectomy · Neoadjuvant therapy · Survival · Urinary bladder neoplasms

Introduction

Urothelial bladder cancer is a relatively common malignancy and according to American Society of Cancer, 81,190 new cases of bladder cancer and 17,240 deaths are anticipated in 2018 [1]. Radical cystectomy and pelvic lymph node dissection has remained the gold standard treatment for muscle invasive and high risk non-muscle invasive bladder cancer (MIBC). Appropriately selected patients with MIBC may benefit from bladder-sparing trimodal therapy [2]; however, conflicting evidence exists to support the use of this approach [3]. Neoadjuvant chemotherapy (NAC) prior to radical cystectomy has also been shown to be associated with improved survival compared to cystectomy alone and implementation of NAC is gradually and steadily increasing [4]. Despite all improvements, almost half of patients experience disease recurrence within 5 years following surgery and the majority of these patients succumb to disease [5]. Improved understanding of risk factors could help in outcome prognostication, patient counselling, and individualized allocation to adjuvant treatments. Several studies have evaluated risk factors associated with disease recurrence and worse outcomes in patients undergoing radical cystectomy.

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Carcinoma in situ (CIS) has been shown to be associated with higher risk of disease recurrence and progression in patients with non-MIBC [6]. Concomitant CIS in cystectomy specimens is also relatively common and has been proposed to be associated with increased risk of urethral involvement [7] and decreased complete response rate to NAC [8]. However, few studies have evaluated the impact of concomitant CIS at the time of cystectomy on long-term oncologic outcomes. Prognostic value of concomitant CIS in cystectomy patients who receive NAC has also remained relatively unknown. We conducted this study to evaluate the impact of CIS on oncologic outcomes in a large population of patients who underwent radical cystectomy with curative intent. Moreover, we determined oncologic outcomes in a subgroup of patients who received NAC and assessed the prognostic value of CIS in this subgroup of patients as well as those with appropriate response to NAC and downstaging to non-MIBC.

Materials and methods

Our institution prospectively maintains demographic, clinical, and pathologic data for all patients undergoing radical cystectomy for bladder cancer under Institutional Review Board approval. Patients who underwent radical cystectomy with curative intent for primary urothelial bladder cancer between 1985 and 2011 were included in this study. Patients who underwent salvage cystectomy, those with primary bladder CIS, and non-urothelial cancers were excluded from enrollment. Radical cystectomy was performed with pelvic lymph node dissection extending to at least the aortic bifurcation. Pathologic staging was reported based on the 2010 AJCC (American Joint Committee on Cancer) Cancer Staging Manual. The final pathologic report was reviewed for pathologic stage, tumor multifocality, concomitant CIS, lymphovascular Invasion (LVI), and nodal disease. Dedicated genitourinary pathologists at our institution review and determine the final pathology, including concomitant CIS. The same genitourinary pathologists were present at our institution during the study timespan, and there were no changes in the diagnostic criteria for CIS during the study period. Clinical characteristics including age, sex, body mass index, Charlson Comorbidity Index, clinical stage, adjuvant chemotherapy or radiotherapy, and type of NAC were also reviewed. Recurrence and survival times are recorded prospectively. Data through the most recent follow up were used at the time of analysis.

The distribution of categorical demographic and clinical characteristics between patients with and without concomitant CIS were compared with the Pearson's Chi square or Fisher's exact test. Kaplan–Meier analyses were used to estimate the probabilities of recurrence free (RFS) and overall survival (OS) based on presence or absence of concomitant CIS. Log-rank tests were used to compare the differences in RFS and OS between the groups. A subset analysis was also performed in patients who received NAC. Through stepwise selection, Cox proportional hazard models were used to identify independent prognostic factors in a multivariable setting. All analyses were performed with SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

Results

A total of 2518 patients with mean age of 67.9 ± 10.6 and median follow up period of 9 years (range 0.1–28.8) underwent radical cystectomy with curative intent during the study period (1985–2011). The study population was divided into two groups based on presence of concomitant CIS in cystectomy specimen. Baseline characteristics including age, body mass index, and Charlson comorbidity index were comparable between the study groups. Rate of clinically locally advanced disease (> T2) and treatment with NAC were lower in patients with CIS; however, pathologic node positive disease was detected more frequently in patients with CIS and none of them had pT0 disease. In addition, rate of high grade urothelial cancer and tumor multifocality was higher in patients with CIS (Table 1).

During a median follow up period of 9 years, we noted higher recurrence rates in patients with CIS, whereas OS did not differ significantly (Fig. 1). In a second analysis, patients were stratified according to NAC status. Overall, 364 patients (14.5%) received NAC and downstaging to non-muscle invasive disease was identified in 169 patients (46%). Chemotherapy protocol was MVAC (Methotrexate, Vinblastine, Adriamycin, Cisplatin) or dose-dense MVAC in 103 patients (28%) and GC (Gemcitabine plus Cisplatin) in 195 patients (53.6%). The remaining 66 patients received miscellaneous chemotherapy regimens. Receiving NAC was not limited to the recent years; however, chemotherapy regimen has been a combination of therapies including cisplatin-based (if eligible) and/or taxol/5-FU and other regimens. Following Grossman study in 2003 [9], the regimens have been more standardized, mostly with platinum-based therapies. We did not find worse RFS and OS in patients with CIS who treated with NAC; however, CIS was associated with worse 5-year RFS among patients who did not receive chemotherapy (Table 2). We also could not show any association between CIS and oncologic outcomes in patients with appropriate response to NAC and down-staging to non-MIBC as well as those with ≥ pT2 disease. Figure 2 shows survival curves in NAC responders (non-MIBC) and those with no response to NAC (≥ pT2 disease) based on presence or absence of concomitant CIS.

Table 1 Patients' demographic and disease characteristics in study subgroups

	No CIS ($n=1121$, 44.5%)	CIS ($n=1397$, 55.5%)	P-value
Sex (%)			
Male	877 (78.2)	1131 (81.0)	0.091
Female	244 (21.8)	266 (19.0)	
Age	67.7 ± 10.6	68.1 ± 10.6	0.415
Body mass index	27.3 ± 5.1	27.5 ± 5.1	0.619
Charlson comorbidity index (%)			
0	551 (50.8)	680 (50.9)	0.832
1	236 (21.8)	302 (22.6)	
≥ 2	297 (27.4)	354 (26.5)	
Clinical stage (%)			
≤ T2	967 (86.3)	1254 (89.8)	0.007
> T2	154 (13.7)	143 (10.2)	
NAC			
No	916 (81.7)	1238 (88.6)	< 0.001
Yes	205 (18.3)	159 (11.4)	
Pathological stage (%)			
T0	271(24.2)	0 (0)	< 0.001
Ta-1	221 (19.7)	591 (42.3)	
T2	218 (19.4)	296 (21.2)	
T3–4	411 (36.7)	510 (36.5)	
Lymph node involvement (%)	228 (20.3)	348 (24.9)	0.007
Grade (%)			
Low/no tumor	531 (47.4)	381 (27.3)	< 0.001
High	590 (52.6)	1016 (72.7)	
Soft tissue margin (%)			
Negative	1107 (98.7)	1383 (99.0)	0.557
Positive	14 (1.3)	14 (1.0)	
LVI (%)			
Absent	841 (75.0)	942 (67.4)	< 0.001
Present	280 (25.0)	455 (32.6)	
Multifocal tumors (%)			
Absent	1023 (91.3)	695 (49.8)	< 0.001
Present	98 (8.7)	702 (50.2)	
Adjuvant chemotherapy (%)	169 (15.1)	288 (20.6)	< 0.001
Adjuvant radiation (%)	4 (0.36)	7 (0.50)	0.585

On multivariable analysis, as shown in Table 3, RFS and OS were significantly affected by pathologic stage, grade, nodal disease, LVI, and receiving NAC. Age and Charlson comorbidity index had significant reverse association with OS but not RFS. Presence of concomitant CIS had no significant association with either RFS (HR 1.136, 95%CI 0.969–1.333, $P=0.116$) or OS (HR 1.015, 95%CI 0.899–1.146, $P=0.809$).

Discussion

In the present study, we showed that higher proportions of patients with concomitant CIS at cystectomy specimens have clinically organ confined disease; however, CIS was associated with higher rate of pathologic nodal

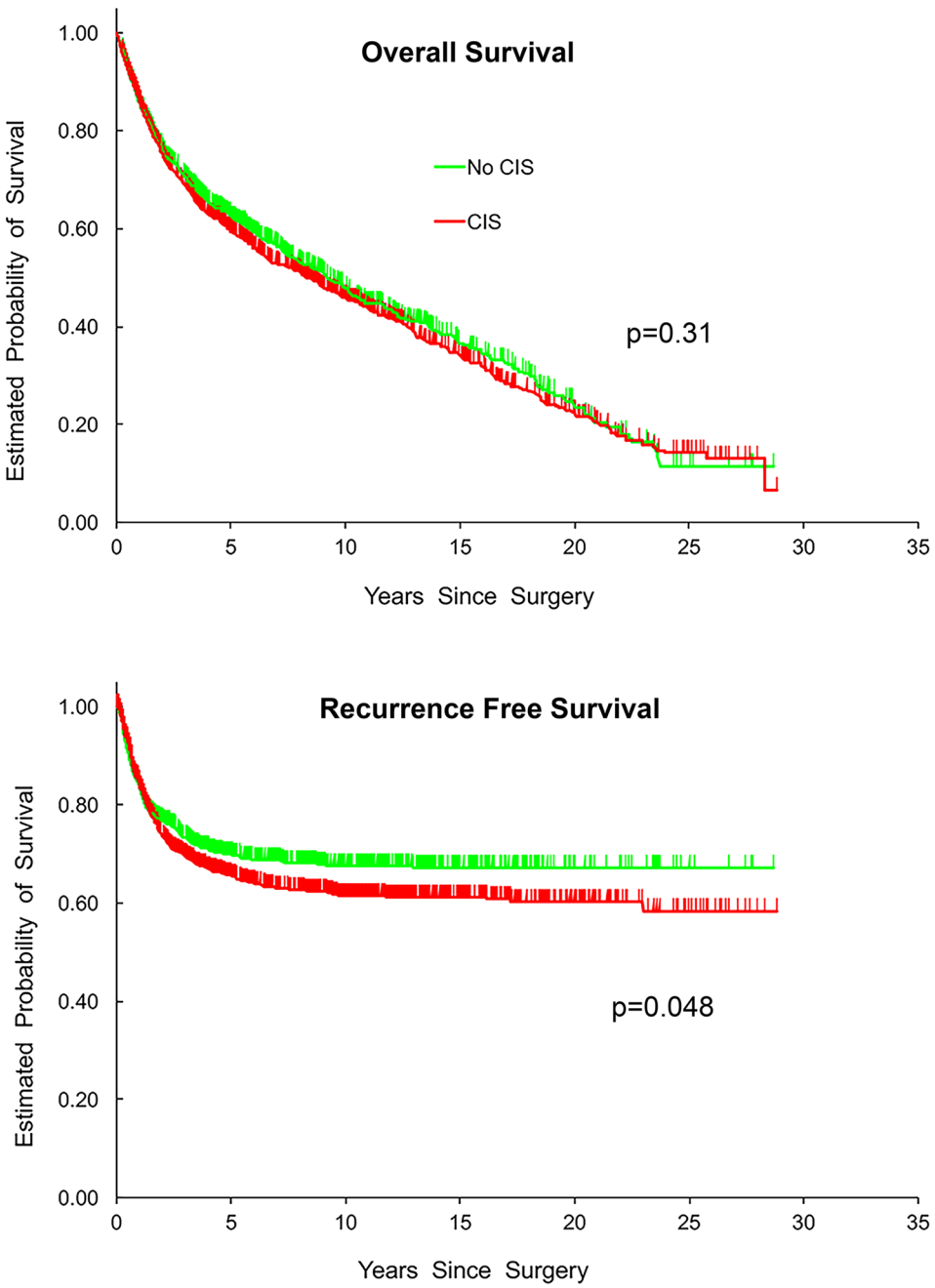

Fig. 1 Kaplan Meier curves for RFS and OS in the whole study cohort stratified according to presence or absence of concomitant CIS

involvement, tumor multifocality, and disease recurrence. In a subgroup of patients who received NAC, including those with downstaging to non-MIBC, CIS was not associated with worse outcomes. Moreover, CIS was not an independent predictor of RFS and OS in multivariate analysis.

Urothelial CIS is characterized by flat lesions with cytologically malignant cells. The degree of anaplasia in these cells is identical to high-grade urothelial carcinomas. In contrast to the in situ lesions in other organs (i.e., prostatic and testicular intraepithelial neoplasia) that are precursors of malignancy, bladder CIS is a high risk and serious disorder. Several investigations have shown that a high proportions of patients with CIS have gene mutations similar to MIBC [10]. Presence of CIS in patients with non-MIBC increases the rate of progression and has been associated with worse survival. Due to its oncological impact, most guidelines and authors debate the risk and benefit of aggressive intervention for such cases [6, 11, 12].

CIS is widely present in cystectomy series, ranging from 23 to 44% [8, 13–15]. Much of this variability is attributed to whether CIS is reported in pre or post cystectomy pathological evaluation. In our series, 55.5% (1397/2518) of patients

Table 2 Five-year RFS and OS rates in study subgroups

	5-year RFS rate (%)		*P*-value	5-year OS rate (%)		*P*-value
	Without concomitant CIS	with concomitant CIS		Without concomitant CIS	with concomitant CIS	
Patients treated with NAC	58.9 ± 4.1	53.1 ± 4.4	0.218	57.1 ± 4.3	51.1 ± 4.9	0.832
Patients did not receive NAC	73.1 ± 1.6	67.7 ± 1.5	0.031	62.8 ± 1.8	60.0 ± 1.5	0.174

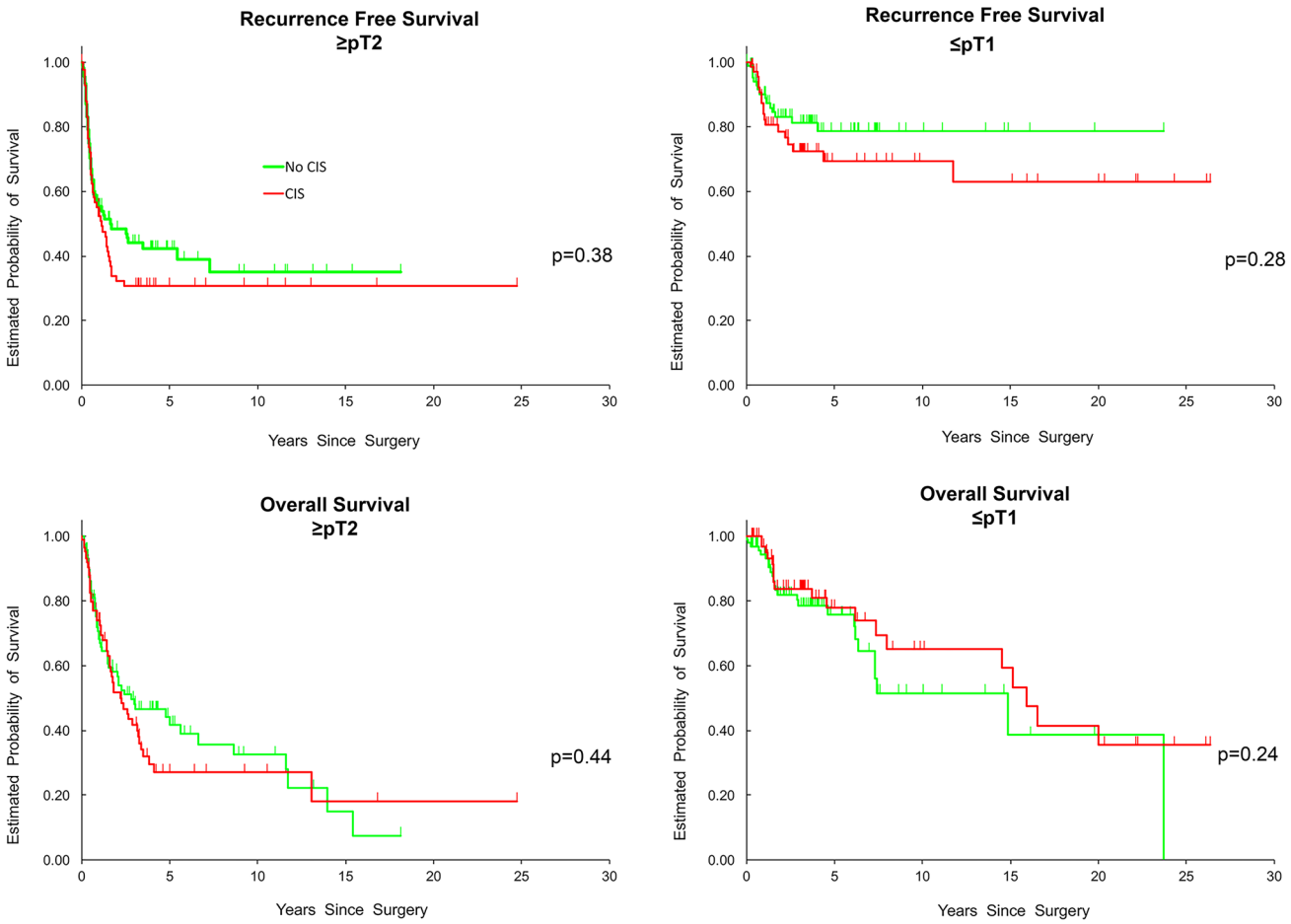

Fig. 2 Kaplan Meier survival curves in NAC responders (non-MIBC) and those with no response to NAC (≥pT2 disease) based on presence or absence of concomitant CIS

had concomitant CIS in pathologic staging. Similar to our findings, other studies have also demonstrated concomitant CIS is associated with lower stage, higher grade, and LVI as well as tumor multifocality [13, 14].

Few studies have evaluated the impact of concomitant CIS on oncologic outcomes in patients undergoing radical cystectomy; however, most of these studies have been restricted with limited sample size and follow up duration [8] and they date back to the era that NAC was under-used [14].

Prognostic effects of concomitant CIS in patients undergoing radical cystectomy also seem to be stage specific;

Table 3 Cox proportional hazards of factors associated with RFS and OS after radical cystectomy for bladder cancer (2518 patients)

Prognostic factors	RFS		OS	
	HR [95% CI]	*P* value	HR [95% CI]	*P* value
Age	1.001 [0.993–1.009]	0.848	1.032 [1.025–1.038]	< 0.001
Charlson comorbidity index				
1 vs. 0	1.031 [0.849–1.253]	0.757	1.274 [1.097–1.480]	0.002
≥ 2 vs. 0	1.030 [0.850–1.248]	0.765	1.399 [1.216–1.610]	< 0.001
CIS (present vs. absent)	1.136 [0.969–1.333]	0.116	1.015[0.899–1.146]	0.809
Pathologic stage (≥ pT2 vs. <pT2)	2.166 [1.728–2.715]	< 0.001	1.439 [1.236–1.675]	< 0.001
Pathologic grade	1.268 [1.031–1.559]	0.025	1.468 [1.245–1.731]	< 0.001
Nodal disease (pN+)	2.870 [2.345–3.513]	< 0.001	2.350 [2.000-2.763]	< 0.001
LVI	1.599 [1.328–1.926]	< 0.001	1.256 [1.088–1.449]	< 0.002
NAC	2.199 [1.796–2.691]	< 0.001	1.381 [1.148–1.662]	0.001

patients with lower stage disease associated with CIS have poorer outcome. This could be due to important value of pathologic stage for survival outcome that advanced stage supersedes potential survival impact of concomitant CIS [5]. Masood et al. evaluating outcome of radical cystectomy in patients with clinical T1G3 bladder cancer showed that concomitant CIS is associated with higher probability of disease upstaging and worse cancer specific survival [16]. Similarly, in a study of 713 cystectomy patients with a median follow-up of 36.4 months, Shariat et al. showed that concomitant CIS was associated with higher likelihood of recurrence [14]. The difference in disease recurrence rates between patients with and without concomitant CIS was highest in lower stages. The study cited a 7-year recurrence-free estimate of 57% versus 84% in patients with organ confined disease with or without concomitant CIS, respectively. In patients with non-organ confined disease, concomitant CIS was neither an independent predictor of bladder cancer recurrence nor of disease specific survival. However, patients receiving NAC were excluded from enrollment in their study [14]. In contrast, Nuhn and colleagues [13] in a series of more than 3000 cases showed that presence of concomitant CIS is associated with higher recurrence rate and worse cancer-specific survival in a subgroup of patients with pT3 disease [13]. However, the increased risk in patients with pT3 disease and concomitant CIS did not retain significance after adjustment for the effect of pathological stage, surgical margin status, LVI, and lymph node metastasis. In their study, overall probabilities of 10-year recurrence were 52% and 56% in patients with and without concomitant CIS, respectively. In the present study, we noted that impact of CIS on oncologic outcome is not stage specific. Presence of concomitant CIS was not associated with worse RFS and OS, when study population was dichotomized based on response to NAC into ≥ pT2 and < PT2 groups.

In recent years, NAC has been shown to offer survival advantages, especially in those who pathologically downstage [9, 17, 18]. Petrelli and colleagues have shown in a meta-analysis that patients with complete response to NAC have improved survival after RC [19]. Also, Zargar and colleagues in a multi-institutional study demonstrated no differences between the survival of patients with pathological complete response and residual non-MIBC after NAC [20]. Recent trends have shown increasing utilization of NAC, and in most academic institutions, it has become standard of care for MIBC or locally advanced disease [4, 21]. Similarly, the utilization of NAC at our institution has followed the trend and is currently routinely offered to patients where clinically indicated in the absence of any contraindication. Due to the change in the treatment paradigm, the prognostic value and significance of concomitant CIS following NAC needs to be investigated. In 2015, Parker and colleagues showed that presence of CIS is associated with significantly less pathological response to NAC; however, there was no effect on survival outcomes [8]. One of the main limitations of their study was that the presence of CIS was assessed based on the pre-cystectomy pathology (clinical staging) and hence subject to potential sampling error as well as underdiagnosis of pathologic CIS. The assessment of CIS on final pathology is more clinically relevant to urologists as a number of studies have shown that final pathologic stage is the most important prognostic factor for oncologic outcomes in these patients [22, 23]. Finally, the median follow up of 23 months in the study by Parker et al. may not have been long enough to ascertain survival benefit. Shariat and colleagues noted that separation of the survival curves occurs after four years postoperatively, though most recurrences occur within 2 years [4]. In present study, assessing more than 2500 patients with a median follow-up of 9 years, we showed that concomitant CIS is associated with higher recurrence rate in univariate analysis. However, this association did not stay significant in multivariate analysis, nor in a subgroup of patients who received NAC.

The main limitation of our study is its retrospective nature, relatively small sample size in NAC group as well as the variability of NAC agents used, number of cycles,

and dose. Furthermore, our data may be subject to some heterogeneity secondary to the long timespan reviewed and absence of pathology re-review. However, the same group of genitourinary pathologists at our institution determined the final pathology, and there were no changes in the pathologic diagnostic criteria for CIS during this time. In addition, the present study is one of the largest studies to date with the longest follow up assessing the impact of concomitant CIS on oncologic outcomes in cystectomy patients. The time frame of study up to 2011 was also determined to have a long and robust follow-up oncologic outcomes. Present study also addresses the prognostic significance of CIS in patients receiving NAC, including those with downstaging to non-MIBC.

Conclusions

Concomitant CIS at radical cystectomy is associated with higher grade, LVI, and tumor multifocality. It does not impact oncologic outcome per pathologic stage. In patients who received NAC, pathologic stage, grade, and LVI are independent predictors of oncologic outcomes, but CIS is not.

Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interests.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

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

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68:7
2. Kulkarni GS, Hermanns T, Wei Y et al (2017) Propensity score analysis of radical cystectomy versus bladder-sparing trimodal therapy in the setting of a multidisciplinary bladder cancer clinic. J Clin Oncol 35:2299
3. Williams SB, Shan Y, Jazzar U et al (2018) Comparing survival outcomes and costs associated with radical cystectomy and trimodal therapy for older adults with muscle-invasive bladder cancer. JAMA Surg 153:881
4. Reardon ZD, Patel SG, Zaid HB et al (2015) Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol 67:165
5. Stein JP, Lieskovsky G, Cote R et al (2001) Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 19:666
6. Smits G, Schaafsma E, Kiemeney L et al (1998) Microstaging of pT1 transitional cell carcinoma of the bladder: identification of subgroups with distinct risks of progression. Urology 52:1009
7. Shariat SF, Karakiewicz PI, Palapattu GS et al (2006) Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol 176:2414
8. Parker WP, Ho PL, Melquist JJ et al (2015) The effect of concomitant carcinoma in situ on neoadjuvant chemotherapy for urothelial cell carcinoma of the bladder: inferior pathological outcomes but no effect on survival. J Urol 193:1494
9. Grossman HB, Natale RB, Tangen CM et al (2003) Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349:859
10. Dyrskjot L, Kruhoffer M, Thykjaer T et al (2004) Gene expression in the urinary bladder: a common carcinoma in situ gene expression signature exists disregarding histopathological classification. Cancer Res 64:4040
11. Vicente J, Laguna MP, Duarte D et al (1991) Carcinoma in situ as a prognostic factor for G3pT1 bladder tumours. Br J Urol 68:380
12. Sylvester RJ, van der Meijden AP, Oosterlinck W et al (2006) Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49:466
13. Nuhn P, Bastian PJ, Novara G et al (2011) Concomitant carcinoma in situ in cystectomy specimens is not associated with clinical outcomes after surgery. Urol Int 87:42
14. Shariat SF, Palapattu GS, Karakiewicz PI et al (2007) Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ-confined TCC at radical cystectomy. Eur Urol 51:152
15. Yafi FA, Aprikian AG, Chin JL et al (2014) Impact of concomitant carcinoma in situ on upstaging and outcome following radical cystectomy for bladder cancer. World J Urol 32:1295
16. Masood S, Sriprasad S, Palmer JH et al (2004) T1G3 bladder cancer–indications for early cystectomy. Int Urol Nephrol 36:41
17. International Collaboration of T, Medical Research Council Advanced Bladder Cancer Working P, European Organisation for R, et al (2011) International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 29:2171
18. Meeks JJ, Bellmunt J, Bochner BH et al (2012) A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol 62:523
19. Petrelli F, Coinu A, Cabiddu M et al (2014) Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. Eur Urol 65:350
20. Zargar H, Zargar-Shoshtari K, Lotan Y et al (2015) Final Pathologic stage after neoadjuvant chemotherapy and radical cystectomy for bladder cancer: does pT0 predict better survival than pTa/Tis/T1? J Urol 195(4):886–893
21. Cowan NG, Chen Y, Downs TM et al (2014) Neoadjuvant chemotherapy use in bladder cancer: a survey of current practice and opinions. Adv Urol https://doi.org/10.1155/2014/746298
22. Bostrom PJ, van Rhijn BWG, Fleshner N et al (2010) Staging and staging errors in bladder cancer. Eur Urol Suppl 9:2–9
23. Saadat SH, Al-Tawil MO (2011) Risk factors for disconcordance between pre and post radical cystectomy stages. Urol J 8:291