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Modeling 1-year Relapse-free Survival After Neoadjuvant Chemotherapy and Radical Cystectomy in Patients with Clinical T2–4N0M0 Urothelial Bladder Carcinoma: Endpoints for Phase 2 Trials

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Abstract

Background: Several ongoing phase 2 trials are evaluating new neoadjuvant therapy regimens in patients with muscle-invasive bladder cancer (MIBC). The 1-yr recurrence-free survival (RFS) after radical cystectomy (RC), with or without perioperative chemotherapy, can be used to model statistical assumptions and interpret outcomes from these studies.

Objective: To provide a benchmark for predicting 1-yr RFS in patients with cT2–4N0 MIBC.

Design, setting, and participants: We identified 950 patients with clinical stage T2–4N0 MIBC undergoing RC at 27 centers between 1990 and 2016. We assessed 1-yr RFS rates for patients managed with no perioperative chemotherapy, neoadjuvant chemotherapy (NAC), adjuvant chemotherapy (AC), or NAC followed by AC. Cox regression analyses tested for 1-yr postsurgical RFS predictors. A Cox-based nomogram was developed to estimate 1-yr RFS and its accuracy was assessed in terms of Harrell's c-index, a calibration plot, and decision curve analysis. We report 1-yr RFS rates across the nomogram tertiles.

Results and limitations: The 1-yr RFS rates were 67.9% (95% confidence interval [CI] 64–72) after no perioperative chemotherapy, 76.9% (95% CI 72–83%) after NAC, 77.8% (95% CI 71–85%) after AC, and 57% (95% CI 37–87) after NAC + AC. On multivariable analysis, positive surgical margins ($p = 0.002$), pT stage ($p < 0.0001$), and pN stage (p<.0001) were significantly associated with RFS, while NAC was not ($p = 0.6$). The model including all these factors yielded a c-index of 0.76 (95% CI 0.72–0.79), good calibration, and a high net benefit. The 1-yr RFS rates across nomogram tertiles were 90.5% (95% CI 87–94%), 73.4% (95% CI 68–79%), and 51.1% (95% CI 45–58%), respectively. The results lack external validation.

Conclusions: Benchmark 1-yr RFS estimates for phase 2 design of new neoadjuvant trials are proposed and can be used for statistical assumptions, pending external validation.

Patient summary: Our prognostic model predicting 1-yr survival free from recurrence of bladder cancer after radical cystectomy, with or without standard chemotherapy, could provide an improvement to the quality of phase 2 clinical trial designs and interpretation of their results.

Keywords

Urothelial carcinoma; Bladder cancer; Perioperative chemotherapy; Nomogram; Relapse-free survival

1. Introduction

Over the last three decades, perioperative cisplatin-based chemotherapy, added to radical cystectomy (RC), represented the recommended therapeutic option for patients with muscle-invasive urothelial bladder cancer (MIBC) owing to the possibility of better relapse-free survival (RFS) and overall survival (OS) compared to surgery alone [1–5]. Nevertheless,

patients treated with platinum-based neoadjuvant therapies and RC exhibit suboptimal disease control. The small benefit perceived by the urologic oncology community for standard chemotherapy has been responsible for low rates of chemotherapy administration worldwide [6–8]. Meanwhile, the proven efficacy of immune checkpoint inhibitors in patients with locally advanced or metastatic urothelial carcinoma [9] has supported the evaluation of these drugs in the perioperative setting, alone or in combination with platinum-based chemotherapy. To date, several ongoing phase 2 trials are testing neoadjuvant immunotherapy agents in MIBC patients who are candidates for RC. The same situation applies to the use of targeted agents in patients with molecularly selected tumors, in particular for agents targeting the FGFR pathway.

Results from these studies are largely pending. However, there are several uncertainties surrounding the activity of neoadjuvant therapy with checkpoint inhibitors. Primarily, identification of novel agent activity may be impaired (or inflated) by the use of pathologic response as the primary endpoint for such trials. In fact, the proportion of patients who might achieve a complete response after transurethral resection of the bladder (TURB) alone may vary substantially, and this issue has remained widely unaddressed in the literature. Despite the availability of multiple postcystectomy nomograms to predict OS in patients according to pathological findings, very limited information is available regarding RFS prediction in the short term (ie, 1 yr). Formulating such data with a specific focus on patients with cT2–4N0M0 disease may help in the design of single-arm phase 2 trials with novel agents and in comparison of findings across studies [10–12]. If available, a prognostic model predicting 1-yr RFS after RC, with or without standard chemotherapy, could aid in improving the quality of these study designs and interpretation of the results. To address this issue, we analyzed a large multi-institutional patient population.

2. Patients and methods

2.1. Study design

The study was approved by the institutional review boards of the 27 participating institutions. The analysis population included the cystectomy database of the Urological Research Institute (URI) of San Raffaele Hospital in Milan (n = 1067), and the Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC) database (n = 3024). This contemporary database includes data gathered between 1990 and 2016 from hospitals in the USA, Europe, Israel, and Canada. Criteria for patient selection included: pure or predominant urothelial carcinoma (UC) histology, cT2–4N0M0 stage, and radical cystectomy treatment. For patients who received chemotherapy, administration of at least two cycles of any chemotherapy course in either the neoadjuvant or adjuvant setting was required. Administration of any new drug, either alone or combined with chemotherapy, was an exclusion criterion. Concomitant or sequential delivery of radiotherapy was also an exclusion criterion. The study flow chart, with patient numbers and reasons for patient exclusions, is provided in Supplementary Figure 1.

2.2. Study outcomes

Descriptive statistics included the frequency and proportion for categorical variables, and the median and interquartile range (IQR) for continuous variables. The statistical significance of differences in medians and proportions was determined using Kruskal-Wallis and χ^2 tests, respectively. The primary endpoint of the analyses was 1-yr RFS. Recurrence after RC was defined as any radiologic evidence of pelvic recurrences or distant metastases (cases with newly diagnosed upper-tract tumors were excluded). The Kaplan-Meier method was used to estimate RFS and OS, both defined as the period of survival from RC.

2.3. Statistical analyses

The analyses consisted of five steps. First, we assessed 1-yr RFS rates in the overall population, as well as according to the use of perioperative chemotherapy: no perioperative chemotherapy ($n = 545$) versus neoadjuvant chemotherapy (NAC; $n = 242$) versus adjuvant chemotherapy (AC; $n = 146$) versus NAC followed by AC ($n = 17$). Second, univariable and multivariable Cox regression models [13] were applied to test for predictors of recurrence and predictors of death from any cause after RC. Third, to reject the hypothesis of an immortal time bias, we used a 3-mo landmark analysis and refitted the multivariable Cox regression analysis testing for death from any cause. Fourth, we developed a Cox-based nomogram for prediction of 1-yr RFS, including variables that were significantly associated with RFS after RC on multivariable analysis; we decided a priori to include NAC given its univariable significance and to more finely estimate the outcomes according to precystectomy chemotherapy administration. The performance of the model was assessed in terms of discrimination (Harrell's c-index) and calibration (calibration plots). Furthermore, decision curve analysis (DCA) [14] was applied to assess the net benefit related to nomogram use, and validation (2000 bootstrap resamples) was internally tested. Finally, we examined 1-yr RFS rates across nomogram-derived tertiles. All statistical tests were two-sided, with the level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

Between 1990 and 2016, 950 patients with cT2–4N0M0 MIBC were suitable for the study purposes (Table 1). The median age at diagnosis was 68 yr (IQR 60–74). Most patients were Caucasian (89.5%), former (36.9%) or current smokers (22.6%), and had a Charlson comorbidity index of ≥1 (59.7%). Overall, 567 patients (59.7%) harbored cT2N0 MIBC, while 223 (23.5%) had cT3–4N0 tumors. NAC was administered in 259 patients (27.3%). Cisplatin-based combination chemotherapy was the regimen most commonly administered (82.6%). Pathological examination revealed that 350 (36.8%), 294 (30.9%), and 278 patients (29.3%) harbored ≤pT2N0, pT3–4N0, and pTanyN+ MIBC, respectively. In addition, 28 patients (3%) had pT0–4NX disease. After RC, AC was administered in 163 patients (17.2%), with cisplatin-based regimens accounting for 50.9% of this group.

3.2. RFS outcomes

After median follow-up of 26 mo (IQR 12–49 mo), there were 548 recurrence and 371 death events. Of these events, 288 were attributable to MIBC. Overall, the 1-yr RFS was 71.5% (95% confidence interval [CI] 69–75%). After stratification according to use of perioperative chemotherapy, 1-yr RFS rates were 67.9% (95% CI 64–72%) for no perioperative chemotherapy, 76.9% (95% CI 72–83%) for NAC, 77.8% (95% CI 71–85%) for AC, and 57% (95% CI 37–87%) for NAC + AC patients, respectively. Of note, patients with residual muscle-invasive disease after NAC, and in particular those with high-risk residual disease (pT3–4 and/or pN+) had inferior RFS compared to those without perioperative therapy or adjuvant therapy, as already reported (Table 2). Conversely, patients with downstaging to pT<2 stage after NAC had higher RFS than patients with pT<2 without NAC at 12 mo (94.2% vs 90.6%), 24 mo (88.5% vs 84.9%), and 36 mo (81.1% vs 74.9%) after RC (Supplementary Fig. 2).

3.3. Cox regression models predicting RFS and OS

In multivariable Cox regression models, positive surgical margins (hazard ratio [HR] 1.66, 95% CI 1.21–2.30; $p = 0.002$), pT stage (overall $p < 0.0001$), and pN stage (overall $p < 0.0001$) were associated with high recurrence rates (Table 3). The bootstrapped (2000 samples) c-index of the model, including NAC, was 0.76 (95% CI 0.72–0.79). Of note, AC was not univariably associated with RFS ($p = 0.6$), whereas NAC was univariably significantly associated with RFS (HR 0.74, 95% CI 0.59–0.94; $p = 0.013$) but the significance was lost on multivariable analyses ($p = 0.6$). As noted above, NAC resulted in a detrimental HR compared to no NAC (HR 1.08, 95% CI 0.83–1.39). Sensitivity analyses were run excluding non-cisplatin regimens and the results were similar (c-index 0.76, 95% bootstrapped CI 0.73–0.78).

Similarly, in multivariable Cox regression models for OS, positive surgical margins (HR 1.74, 95% CI 1.24–2.45; $p = 0.002$), pT stage ($p = 0.002$), and pN stage ($p < 0.0001$) were the only significant predictors (Supplementary Table 1). After applying a 3-mo landmark analysis the results were comparable. The c-index of the model, including NAC and landmark analysis, was 0.70 (95% bootstrapped CI 0.74–0.78).

3.4. Nomogram prediction of 1-yr RFS and 1-yr RFS rates across nomogram-derived tertiles

To provide 1-yr RFS estimates, we internally developed and validated a Cox-based nomogram predicting 1-yr RFS after RC (Fig. 1). The calibration plot and DCA are shown in Figure 2. According to nomogram-derived tertiles, for patients in the first, second, and third tertile the 1-yr RFS estimates were 90.5%, 73.4%, and 51.1%, respectively (Fig. 3).

4. Discussion

Cisplatin-based NAC represents the standard of care for patients with MIBC and its use is supported by European Association of Urology, National Comprehensive Cancer Network, and European Society of Medical Oncology guidelines for patients with clinical stage T2–4N0M0 MIBC (level 1 evidence) [1,15,16]. Nevertheless, a minority of patients ultimately

receive chemotherapy before surgery. This is one of the reasons why several ongoing phase 2 trials are planned to evaluate immune checkpoint inhibitors or targeted agents as neoadjuvant therapy in MIBC patients before RC. Results from these studies are largely unavailable, with the exception of preliminary results from the PURE-01 study (NCT02736266) [17]. In this ongoing study, pembrolizumab is administered as single-agent therapy in a short course of three doses every 3 wk before RC. Preliminary data for 36 patients after RC revealed a pT0 rate of 38.9% (95% CI 23.1–56.5%) in the intention-to-treat population. Indeed, it is likely that results from many similar studies will be available in the near future and that chemotherapy-free regimens may represent a viable alternative. Interpreting the findings from similar noncomparative studies will be of paramount importance to drive the development of new agents versus standard chemotherapy.

Indeed, the primary endpoint used by the majority of these studies is pathologic response, represented either by pT0 or by downstaging to non–muscle-invasive residual tumor [18] primarily on the basis that pT0 response is associated with a 55% decrease in the risk of death according to a recent meta-analysis [19]. pT0 is a difficult target to use in clinical studies of MIBC. In fact, the unavoidable bias of TURB impact on pT0 results at RC is an unsolved issue for any neoadjuvant study, and this bias largely affects the results reported for standard chemotherapy. This is exemplified by the study by Brant et al [20], who found that 38% of pathologic responses could have been attributed to TURB, suggesting that TURB must also be considered in evaluating the pT0 endpoint. Moreover, it could also be argued that immune-checkpoint inhibitors will not induce high rates of pathologic complete responses. However, patients benefiting from a pT0 response may experience sustained durability compared to standard chemotherapy. As a consequence, time-based outcomes, such as 1-yr RFS, may be more useful endpoints.

Importantly, we focused on the population of patients with MIBC, clinical lymph node–negative staging, and at least predominant UC component. These patients truly represent the cleanest model for testing any new drugs given in the neoadjuvant RC setting. Data on 1-yr RFS probabilities for these patients are scarce in the literature, mostly because the prognostic models and nomograms available typically analyzed a heterogeneous population of RC patients, without selecting them according to pre-RC characteristics [12]. As a result, patients undergoing RC for non–muscle-invasive bladder cancer or presenting with enlarged lymph nodes or predominant non-urothelial carcinoma histology were included.

The clinical investigation benefits arising from the proposed model may be twofold. First, the model provides a possibility of fine tuning the design and statistical assumptions of small phase 2, open-label, single-arm studies of new neoadjuvant therapies in MIBC; in this case, use of the lower nomogram tertile (1-yr RFS of 51.1%) may be recommended as the null hypothesis for statistical assumptions. Second, the model will allow retrospective comparisons of estimated versus observed 1-yr RFS in phase 2 trials in the absence of a randomized design.

Our model showed high accuracy, good calibration, and a high net benefit on DCA, with a fairly wide range of decision thresholds, after internal validation. Moreover, the model will also be valuable in predicting OS with good accuracy. The incremental complexity of

hypothesis testing with multiple adjustment levels and landmark analysis meant that the null hypothesis of no association between the selected variables and the primary-endpoint (1-yr RFS) was incorrectly rejected.

The availability of the proposed endpoint may avoid the critical use of pathological response (which will remain the primary goal in testing the activity of any new drug at histological and molecular levels) for translational purposes [21–24].

In addition, our results strengthen evidence of the poor prognostic impact of invasive residual disease after NAC [25]. In fact, 1-yr RFS rates after NAC were lower (<85.9% vs. 97.2%) in patients with residual disease (>pT0N0) compared with results for RC alone or RC followed by AC. On the other hand, patients with pathologic major response, represented by downstaging to pT<2 residual tumor, exhibited longer RFS post-NAC (+6.2% at 36 mo). These RFS curves will serve for comparison with RFS results obtained after a major pathologic response with new agents.

Another intriguing issue that could be evaluated using our nomogram is whether patients with residual high-risk disease after neoadjuvant immune-checkpoint inhibition have poor outcomes comparable to those reported after chemotherapy; such information could guide post-RC management of patients who received prior immune-checkpoint inhibitors.

RFS estimates for patients receiving AC are likely to be biased by unaccountable patient selection factors that typically affect retrospective studies, as AC was not significantly associated with RFS on univariable analysis.

Some limitations of the study should be acknowledged. First, despite high accuracy, good calibration, and a high net benefit on DCA, our model lacks external validation, which would have strengthened our findings. Second, a small but significant proportion of patients (n = 28, 3%) did not receive guideline-recommended lymphadenectomy at the time of RC. However, our data are in agreement with a recent publication showing that lymphadenectomy is currently avoided in approximately 18.1% of RC cases [26]. As a consequence, the decision to include those individuals stems from the intent to better reflect a real-world population, in which lymphadenectomy might be avoided for some cases because of technical problems or patient preferences. The same considerations apply to the NAC and AC regimens administered, which included non-cisplatin regimens in a minority of patients, although the sensitivity analyses that excluded non-cisplatin regimens led to similar results (comparable c-index). Third, the criteria for choosing AC instead of NAC were probably heterogeneous, being based on either clinical judgment or the policy in use at each center. Finally, an advantage of using pathologic response is the small number of patients needed to test the null hypothesis in phase 2 studies. In our nomogram, the lowest tertile still has 1-yr RFS of50%, so it might not represent a useful tool for single-center studies.

5. Conclusions

Identification of novel active agents in the neoadjuvant MIBC setting may be impaired by use of pathologic response as the primary endpoint in phase 2 trials. Use of 1-yr RFS as the endpoint for single-arm phase 2 studies and application of the proposed nomogram to set the

null hypothesis and analyze outcomes may represent a useful tool to enhance the quality of results reported for new agents given preoperatively in MIBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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To overcome the limitations of pathologic complete response as the endpoint for phase 2 trials of neoadjuvant new drugs for T2–4N0M0 muscle-invasive bladder cancer we developed a model for prediction of 1-yr recurrence-free survival. The model could help in the design of single-arm phase 2 trials of novel agents and in comparison of findings across studies.

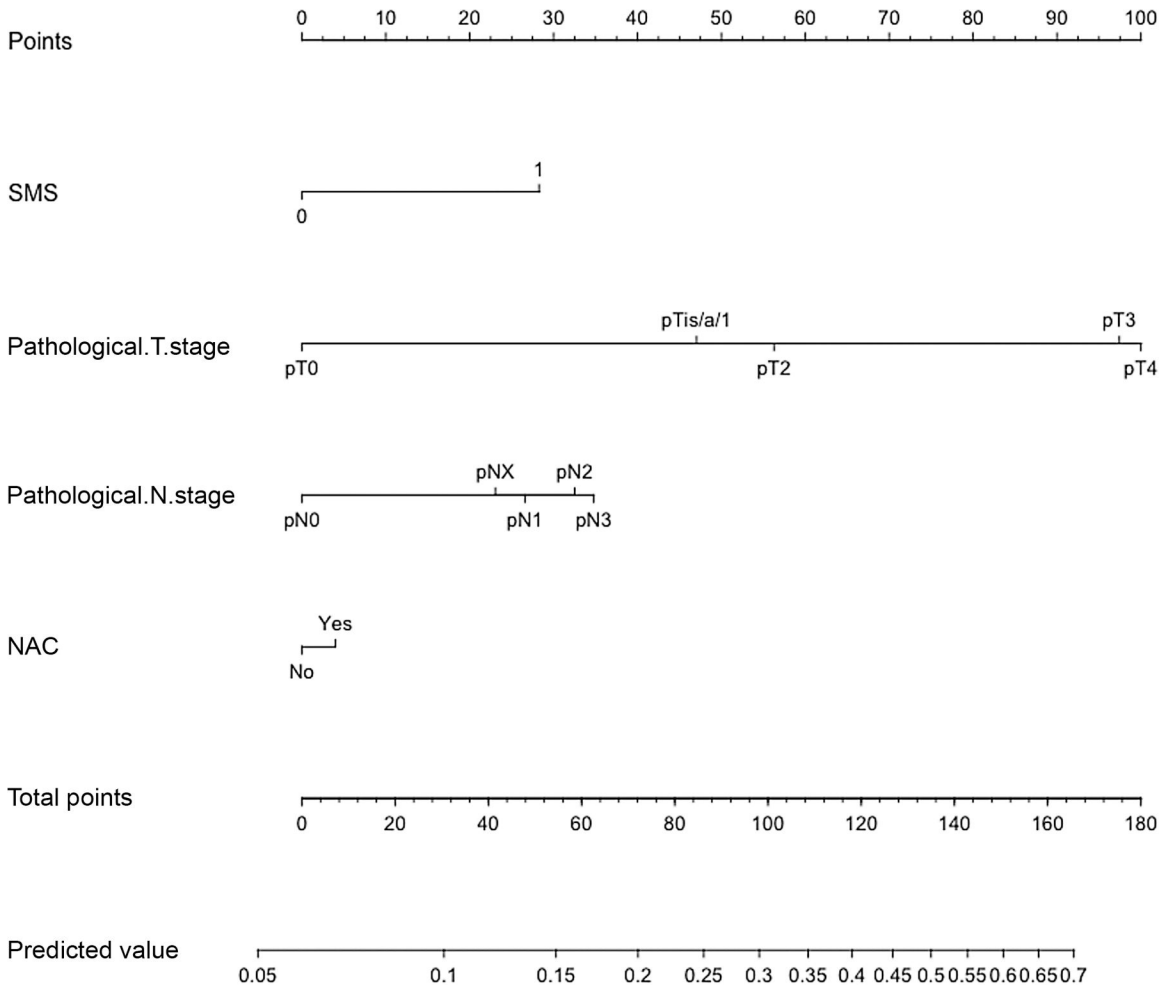

Fig. 1 –.

Nomogram for prediction of disease recurrence after radical cystectomy in patients with T2–4N0M0 urothelial carcinoma of the bladder. SMS = surgical margin status; NAC = neoadjuvant chemotherapy.

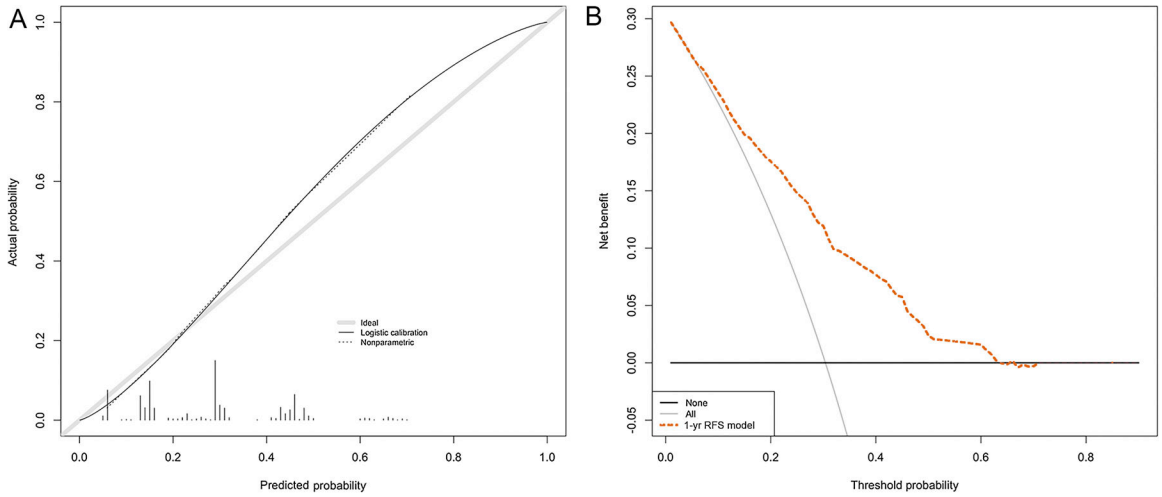

Fig. 2 –.

Calibration plot and decision curve analysis for the Cox-based nomogram for prediction of 1-yr recurrence-free survival (RFS). (A) Average predicted probability (nomogram-predicted 1-yr RFS) versus Kaplan-Meier estimate (observed 1-yr RFS) with 95% confidence interval for the Kaplan-Meier estimate. The grey line indicates the reference, where an ideal nomogram would lie. (B) Net benefit of a strategy involving treating all patients (grey line), no patients (black line), or according to the nomogram predictions (dotted line). The plot shows that model-based decisions are supported for a threshold probability range of approximately 10–60% at 12 mo.

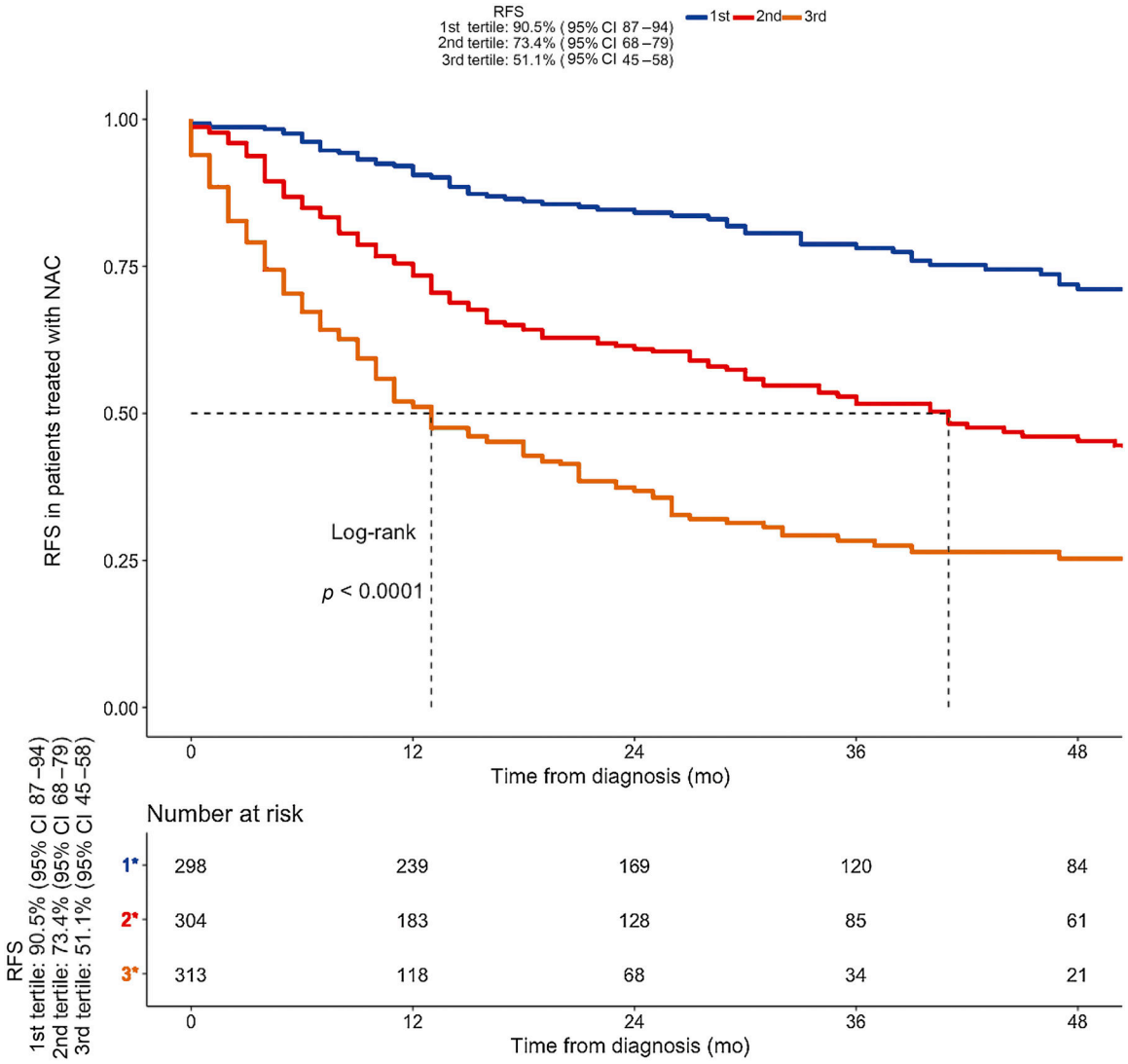

Fig. 3 –.

Kaplan-Meier curves of recurrence-free survival (RFS) for 950 patients with muscle-invasive bladder cancer after stratification according to nomogram-derived tertiles. NAC = neoadjuvant chemotherapy; CI = confidence interval.

Table 1 –

General characteristics of the study patients

Characteristic	Overall	No NAC or AC	NAC	AC	NAC + AC
Median age at surgery, yr (range)	68 (60.2–74)	71 (63–77)	64 (57–70)	65 (56–70)	62 (55–68)
Median LNs removed, *n* (range)	15 (9–22)	15 (9–22)	16 (10–22)	16 (10–24)	20.5 (14–26.5)
Race, *n* (%)					
Caucasian	850 (89.5)	479 (87.9)	229 (94.6)	128 (87.7)	14 (82.4)
Hispanic or Latino	69 (7.3)	51 (9.4)	1 (0.4)	16 (11)	1 (5.9)
Black	22 (2.3)	9 (1.7)	9 (3.7)	2 (1.4)	2 (11.8)
Other or mixed	9 (0.9)	6 (1.1)	3 (1.2)	0 (0)	0 (0)
Smoking status, *n* (%)					
Never smoker	192 (20.2)	111 (20.4)	55 (22.7)	22 (15.1)	4 (23.5)
Current smoker	215 (22.6)	110 (20.2)	62 (25.6)	39 (26.7)	4 (23.5)
Former smoker	351 (36.9)	179 (32.8)	108 (44.6)	57 (39)	7 (41.2)
Unknown	192 (20.2)	145 (26.6)	17 (7)	28 (19.2)	2 (11.8)
CCI, *n* (%)					
0	288 (30.3)	133 (24.4)	100 (41.3)	47 (32.2)	8 (47.1)
≥1	567 (59.7)	377 (69.2)	89 (36.8)	92 (63)	9 (52.9)
Unknown	95 (10)	35 (6.4)	53 (21.9)	7 (4.8)	0 (0)
Histology, *n* (%)					
Pure UC	826 (86.9)	474 (87)	206 (85.1)	129 (88.4)	17 (100)
UC with divergent histology	124 (13.1)	71 (13)	36 (14.9)	17 (11.6)	0 (0)
cT stage, *n* (%)					
cT2	567 (59.7)	319 (58.5)	145 (59.9)	91 (62.3)	12 (70.6)
cT3–4	223 (23.5)	100 (18.3)	91 (37.6)	29 (19.9)	3 (17.6)
Unknown	160 (16.8)	126 (23.1)	6 (2.5)	26 (17.8)	2 (11.8)
pT stage, *n* (%)					
pT0	96 (10.1)	17 (3.1)	79 (32.6)	0 (0)	0 (0)
pT1	63 (6.6)	43 (7.9)	16 (6.6)	3 (2.1)	1 (5.9)
pT2	189 (19.9)	121 (22.2)	42 (17.4)	21 (14.4)	5 (29.4)
pT3	389 (40.9)	232 (42.6)	65 (26.9)	84 (57.5)	8 (47.1)
pT4	154 (16.2)	94 (17.2)	20 (8.3)	37 (25.3)	3 (17.6)
pTa/pTis	59 (6.2)	38 (7)	20 (8.3)	1 (0.7)	0 (0)
pN stage, *n* (%)					
pN0	644 (67.8)	379 (69.5)	197 (81.4)	61 (41.8)	7 (41.2)
pN1	102 (10.7)	50 (9.2)	20 (8.3)	31 (21.2)	1 (5.9)
pN2	160 (16.8)	89 (16.3)	21 (8.7)	43 (29.5)	7 (41.2)
pN3	16 (1.7)	7 (1.3)	1 (0.4)	6 (4.1)	2 (11.8)
pNX	28 (2.9)	20 (3.7)	3 (1.2)	5 (3.4)	0 (0)
Margin status, *n* (%)					
Negative	850 (89.5)	490 (89.9)	216 (89.3)	132 (90.4)	12 (70.6)
Positive	84 (8.8)	48 (8.8)	20 (8.3)	12 (8.2)	4 (23.5)

Characteristic	Overall	No NAC or AC	NAC	AC	NAC + AC
NAC, *n* (%)					
No	691 (72.7)	545 (100)	0 (0)	146 (100)	0 (0)
Yes	259 (27.3)	–	242 (100)	–	17 (100)
NAC platinum regimen, *n* (%) [a]					
Carboplatin	22 (2.3)	–	20 (8.3)	–	2 (11.8)
Cisplatin	214 (22.5)	–	203 (83.9)	–	11 (64.7)
Unknown	23 (2.4)	–	19 (7.9)	–	4 (23.5)
Median NAC cycles, *n* (range)	3 (2–6)	–	3 (2–6)	–	3 (2–4)
AC, *n* (%)					
No	787 (82.8)	545 (100)	242 (100)	0 (0)	0 (0)
Yes	163 (17.2)	0 (0)	0 (0)	146 (100)	17 (100)
AC platinum regimen, *n* (%) [b]					
Carboplatin	20 (2.1)	0 (0)	0 (0)	18 (12.3)	2 (11.8)
Cisplatin	83 (8.7)	0 (0)	0 (0)	73 (50)	10 (58.8)
Unknown	60 (6.3)	0 (0)	0 (0)	55 (37.7)	5 (29.4)
Median AC cycles, *n* (range)	4 (2–6)	–	–	4 (2–6)	4 (2–4)
Outcomes		–	–		
RFS, *n* (%)					
No	551 (58)	313 (57.4)	160 (66.1)	71 (48.6)	7 (41.2)
Yes	399 (42)	232 (42.6)	82 (33.9)	75 (51.4)	10 (58.8)
Site of relapse, *n* (%)					
Distant	334 (35.2)	192 (35.2)	68 (28.1)	67 (45.9)	7 (41.2)
Local	63 (6.6)	38 (7)	13 (5.4)	9 (6.2)	3 (17.6)
Not specified	3 (0.3)	2 (0.4)	1 (0.4)	0 (0)	0 (0)
Unknown	550 (57.9)	313 (57.4)	160 (66.1)	70 (47.9)	7 (41.2)
Status at last follow-up, *n* (%)					
Alive	575 (60.5)	306 (56.1)	176 (72.7)	83 (56.8)	10 (58.8)
Died of disease	288 (30.3)	177 (32.5)	50 (20.7)	55 (37.7)	6 (35.3)
Died of other causes	83 (8.7)	58 (10.6)	16 (6.6)	8 (5.5)	1 (5.9)

AC = adjuvant chemotherapy; CCI = Charlson comorbidity index; CMV = cisplatin, methotrexate, vinblastine; DD = dose-dense; LN = lymph node; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NAC = neoadjuvant chemotherapy; RFS = relapse-free survival; UC = urothelial carcinoma.

[a] NAC regimens: CMV, *n* = 5; DD-MVAC, *n* = 36; MVAC, *n* = 11; gemcitabine-cisplatin, *n* = 162; gemcitabine-carboplatin, *n* = 22; unknown regimen (23)

[b] AC regimens: DD-MVAC, *n* = 5; MVAC, *n* = 15; gemcitabine-cisplatin, *n* = 63; gemcitabine-carboplatin, *n* = 20.

Table 2 –

The 1-yr recurrence-free survival rates according to use of perioperative chemotherapy

pT stage	Recurrence-free survival, % (95% confidence interval)				
	Overall (*n* = 950)	**No NAC or AC (*n* = 545)**	**NAC (n=242)**	**AC (n=146)**	**NAC + AC (n=17)**
Overall	71.5 (69–75)	67.9 (64–72)	76.9 (72–83)	77.8 (71–85)	57.0 (37–87)
pT0N0 (*n* = 91)	97.6 (94–100)	NE.	97.2 (94–99)	NE	NE
pTis/a/1N0 (*n* = 108)	88.3 (82–95)	88.8 (81–97)	85.9 (74–99)	NE	NE
pT2N0 (*n* = 151)	85.8 (80–92)	87.9 (81–95)	82.3 (70–96)	NE	NE
pT3–4N0 (*n* = 294)	65.7 (60–72)	61.4 (54–70)	55.1 (42–73)	79.2 (69–91)	NE
pTanyN+ (*n* = 278)	54.3 (48–61)	46.2 (38–57)	40.3 (27–60)	74.8 (63–86)	45.7 (22–93)

AC = Adjuvant chemotherapy; NAC = neoadjuvant chemotherapy; NE = not evaluable because of small numbers.

Table 3 –

Univariable and multivariable Cox regression models predicting recurrence after radical cystectomy in 950 MIBC patients

Covariate	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Male (reference female)	0.99 (0.77–1.27)	0.9	–	–
UC with divergent histology (reference UC)	1.23 (0.92–1.65)	0.2	–	–
Margin status (reference negative)	2.69 (2.01–3.60)	<0.0001	1.66 (1.21–2.30)	0.002
Race				
Caucasian	Reference	0.08	–	-
Hispanic or Latino	1.15 (0.81–1.65)		–	-
Black	2.39 (1.45–3.95)		–	-
Other or mixed	1.17 (0.44–3.14)		–	-
pT stage				
pT0	Reference	<0.0001	Reference	<0.0001
pTa/is/1	2.26 (1.16–4.40)		2.34 (1.16–4.74)	
pT2	1.72 (1.17–2.53)		2.77 (1.42–5.39)	
pT3	3.84 (2.77–5.33)		5.80 (3.07–11.0)	
pT4	4.92 (3.41–7.09)		6.08 (3.10–11.93)	
pN stage				
pN0	Reference	<0.0001	Reference	<0.0001
pN1	2.15 (1.61–2.88)		1.61 (1.20–2.18)	
pN2	2.73 (2.13–3.50)		1.80 (1.38–2.34)	
pN3	3.25 (1.60–6.60)		1.87 (0.91–3.84)	
pNX	1.71 (1.00–2.94)		1.52 (0.88–2.61)	
NAC (reference no NAC)	0.74 (0.59–0.94)	0.0126	1.08 (0.83–1.39)	0.6
AC (reference AC)	1.08 (0.85–1.37)	0.6	–	–

AC = adjuvant chemotherapy; CI = confidence interval; HR = hazard ratio; NAC = neoadjuvant chemotherapy; UC = urothelial carcinoma.