# Impact of the controlling nutritional status (CONUT) score on perioperative morbidity and oncological outcomes in patients with bladder cancer treated with radical cystectomy

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## Abstract

**Introduction and objectives:** To evaluate the impact of the Controlling Nutritional Status (CONUT) score on perioperative morbidity and oncological outcomes of bladder cancer (BC) patients treated with radical cystectomy (RC).

**Materials and Methods:** We retrospectively analyzed a multi-institutional cohort of 347 patients treated with RC for clinical-localized BC between 2005 and 2019. The CONUT-score was defined as an algorithm including serum albumin, total lymphocyte count, and cholesterol. Multivariable logistic regression analyses were performed to evaluate the ability of the CONUT-score to predict any-grade complications, major complications and 30 days readmission. Multivariable Cox' regression models were performed to evaluate the prognostic effect of the CONUT-score on recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS).

**Results:** A cut-off value to discriminate between low and high CONUT-score was determined by calculating the receiver operating characteristic (ROC) curve. The area under the curve was 0.72 hence high CONUT-score was defined as ≥3 points. Overall, 112 (32.3%) patients had a high CONUT. At multivariable logistic regression analyses, high CONUT was associated with any-grade complications (OR 3.58, $P = 0.001$), major complications (OR 2.56, $P = 0.003$) and 30 days readmission (OR 2.39, $P = 0.01$). On multivariable Cox' regression analyses, high CONUT remained associated with worse RFS (HR 2.57, $P < 0.001$), OS (HR 2.37, $P < 0.001$) and CSS (HR 3.52, $P < 0.001$).

**Conclusions:** Poor nutritional status measured by the CONUT-score is independently associated with a poorer postoperative course after RC and is predictive of worse RFS, OS, and CSS. This simple index could serve as a comprehensive personalized risk-stratification tool identifying patients who may benefit from an intensified regimen of supportive cares. 

*Keywords:* Biomarkers; Morbidity; Nutrition assessment; Postoperative complications; Radical cystectomy; Survival; Urinary bladder neoplasms

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## 1. Introduction

Radical cystectomy (RC) and pelvic lymph-node dissection (PLND) with or without neoadjuvant chemotherapy (NAC) represents the current standard-of-care treatment for both muscle-invasive bladder cancer (MIBC) and high-risk as well Bacillus Calmette-Guerin (BCG) unresponsive non-muscle-invasive bladder cancer (NMIBC) [1,2]. RC and urinary diversion (UD) is a complex surgical procedure with a recognized high perioperative morbidity due to patient, disease and surgical determinants [3]. Despite several improvements in surgical technique and perioperative management, both morbidity profile and survival following RC have remained largely optimizable [4−7].

Bearing this in mind for a predominantly elderly and comorbid population, preoperative risk-stratification tools are urgently needed to guide individualized treatment strategies. To date, our ability to predict perioperative complications is limited and the accuracy of current prognostic nomograms remains suboptimal [8].

Being a central part of the enhanced recovery after surgery (ERAS) protocols and a potentially reversible condition, nutrition has gained interest in BC patients [9]. The Controlling Nutritional Status (CONUT) score is a validated nutritional assessment system that comprehensively evaluates host's anabolism and immuno-competence and is widely used to select patients for nutritional support [10]. High CONUT-score has been identified as a prognostic biomarker of poor survival among cancer patients undergoing radical surgery [11]. Previous reports have validated the prognostic impact of malnutrition evaluated by the CONUT-score in patients with urological malignancies [12−14].

In this context, the objective of our study was to comprehensively evaluate the impact of preoperative nutritional-risk assessment provided by the CONUT-score on perioperative morbidity and survival outcomes using a multi-institutional cohort of BC patients undergoing RC. We hypothesized that impaired nutritional status described by the CONUT score would be associated with a higher rate of postoperative complications, unplanned readmission, and worse survival.

## 2. Materials and Methods

### 2.1. Patients' selection

Demographic, clinicopathological, perioperative and long-term outcomes data of 347 non-consecutive patients who underwent RC, PNLD, and UD for cT1-4aN0M0 BC between January 2005 and December 2019 were retrospectively collected. Procedures were performed at five European tertiary care referral centers (Figure S1). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was centrally approved by the ethical institutional review board (ID 113/2021).

Before surgery, all patients underwent standard laboratory tests, and were staged with computed tomography of the abdomen and/or pelvis and chest. Patients with an acute infection or any other acute or chronic systemic inflammatory conditions, hepatic dysfunction, and other malignancies at time of surgery were excluded from the analysis. Patients with end-stage or severe chronic kidney disease were also excluded from the study. Variables collected include age, gender, Charlson comorbidity index (CCI), body mass index (BMI), American Society of Anesthesiologists (ASA) score, NAC administration, length of stay (LOS), perioperative complications, 30 days readmission, pathological tumor (pT) and nodal (pN) stage, tumor grade, presence of concomitant carcinoma-in-situ (CIS), lymphovascular invasion (LVI), positive surgical margins (PSMs), type of UD, and adjuvant chemotherapy (AC) administration.

Clinical and radiological follow-up regimens were conducted according to the European Association of Urology Guidelines [1]. Stage was based on the Tumor Nodes Metastasis (TNM) classification system (2017 classification, 8th edition), while tumor grade was based on the 2004/2016 World Health Organization system.

### 2.2. Endpoints

Primary endpoints comprised postoperative complications and unplanned 30-days readmission. Complications were reported according to the Clavien-Dindo classification [15], and further divided into any-grade (grade 1-5) and major complications (grade 3−5). Any event occurring within the in-hospital stay was considered. Readmission was defined as any subsequent and unplanned inpatient admission occurring within 30 days from the day of discharge of the index hospitalization. Recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS) after RC were set as secondary endpoints of the current analysis. RFS was defined as the time from RC to the first locoregional recurrence and/or distant metastasis on radiological imaging. CSS and OS were defined as the time from RC to cancer-related death or any-cause death, respectively. Cause of death was abstracted from the medical charts and/or from death certificates.

### 2.3. Preoperative CONUT-score

Routine blood samples were usually obtained within 30 days before surgery. The CONUT-score was calculated from albumin, lymphocytes, and total cholesterol, as listed in Table 1. The optimal CONUT cut-off value was defined by creating a time-dependent receiver operating characteristic (ROC) curve with CSS as the endpoint to yield the highest Youden-index. Patients with preoperative CONUT lower than the cut-off value were defined as the "low" CONUT group, while the remaining patients were assigned to the "high" CONUT group.

Table 1
Nutrition assessment according to the CONUT score.

| Parameter | NormalNutrition | LightMalnutrition | ModerateMalnutrition | SevereMalnutrition |
|---|---|---|---|---|
| Albumin (g/dl) | 3.50 or Greater | 3.00 - 3.49 | 2.50 - 2.99 | Less than 2.50 |
| Score | 0 | 2 | 4 | 6 |
| Lymphocyte count (/mm$^3$) | 1600 or Greater | 1200 - 1599 | 800 - 1199 | Less than 800 |
| Score | 0 | 1 | 2 | 3 |
| Total cholesterol (mg/dl) | 180 or Greater | 140 - 179 | 100 - 139 | Less than 100 |
| Score | 0 | 1 | 2 | 3 |
| Total score | 0 - 1 | 2 - 4 | 5 - 8 | 9 - 12 |

CONUT = Controlling Nutritional Status.

### *2.4. Statistical analysis*

Descriptive analysis included frequencies and proportions for categorical variables. Medians and interquartile range (IQR) were reported for continuous coded variables. The Mann-Whitney U test was used for comparison of the continuous data and the Chi-square or Fisher's exact test for categorical data. All tests were two-sided with a level of significance set at $P < 0.05$. The Kaplan-Meier method was used to estimate RFS, OS, and CSS stratified by CONUT group, and the log-rank method was used to determine significance. Multivariable binomial logistic regression analyses were performed to assess the odds ratio (OR) with 95% confidence intervals (CI) testing the ability of the CONUT-score to predict postoperative complications (any-grade and major complications) and 30 days readmission, after adjusting for all possible predictors. The area under the curve (AUC) was calculated to determine the discrimination of the logistic regression models. DeLong's test was used to test for statistical significance between different AUCs. Multivariable Cox' regression models were used to assess the hazard ratio (HR) with 95% CI testing the prognostic effect of the CONUT-score on RFS, OS and CSS. The discriminatory ability of these models and the additional information provided by the CONUT-score were tested using Harrell's concordance index (C-index). Likelihood-ratio test was used to test for statistical significance. Statistical analyses were performed using R v.3.6.3.

## 3. Results

### *3.1. ROC curve analysis and cut-off value for the CONUT-score*

The ROC analysis for the CONUT-score showed that the AUC predicting CSS was 0.72 (95% CI, 0.66−0.78) (Fig. 1). According to the maximum Youden-index, the cut-off for the CONUT-score was set at 3. Therefore, 235 (67.7%) patients were classified into the low CONUT group (CONUT-score 0, 1, 2), whereas the remaining 112 (32.3%) patients were classified into the high CONUT group (CONUT-score ≥3).

### *3.2. Patients' characteristics*

The clinicopathological characteristics of the 347 patients stratified by CONUT group are displayed in Table 2. Median age at RC was 72 years (IQR, 68−74). Surgery was performed with an open approach in the majority of cases (78.4%), whereas in 75 (21.6%) patients with a minimally-invasive technique either laparoscopic (10.9%) or robot-assisted (10.7%). A total of 20 (5.8%) patients received NAC and 6 of them also received AC. No significant differences were found between the two groups considering NAC or AC administration. High CONUT-score was significantly correlated with older age, higher rates of ASA score ≥3 points, and features of tumor aggressiveness such as advanced pT and pN stage, presence of high-grade BC and PSMs at final pathological report (all $P < 0.05$). Supplementary Table 1 described the frequency of each CONUT score.

### *3.3. Prediction of postoperative morbidity and 30 days readmission*

In total, 269 (77.5%) patients experienced complications after RC. Of these, 193 (55.6%) patients had minor complications (grade 1−2) while 76 (21.9%) experienced major complications (grade ≥3). Median LOS was 19 days (IQR, 15−26) (Table 2). On multivariable analysis, high CONUT was associated with significantly increased odds of both any-grade (OR 3.58, 95% CI 1.71−8.18, $P = 0.001$) and major complications (OR 2.56, 95% CI 1.37-4.79, $P = 0.003$), respectively. The addition of the CONUT-score to the reference models improved the discriminating ability for prediction of any-grade (+4.0%, $P = 0.03$) and major complications (+4.0%, $P = 0.04$), respectively (Table 3).

A total of 68 (19.6%) patients were readmitted after discharge. Multivariable analysis identified high CCI (≥2) (OR 1.25, 95% CI 1.10−2.62, $P = 0.02$), open approach (OR 17.0, 95% CI 3.33−31.6, $P = 0.01$), and high preoperative CONUT-score (OR 2.39, 95% CI 1.19−4.89, $P = 0.01$)

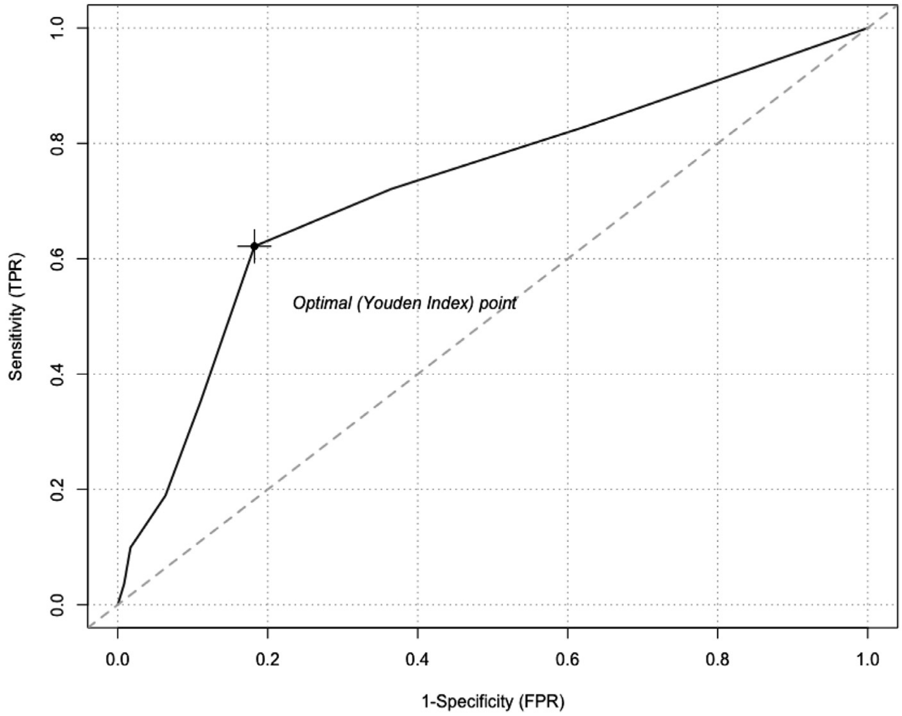


Fig. 1. ROC curve for preoperative prediction of CSS in 347 patients with clinical-localized non-metastatic BC treated with RC and PLND. Sensitivity, specificity, and accuracy were 0.62 (95% CI 0.54−0.72), 0.82 (95% CI 0.76−0.87) and 0.76 (95% CI 0.71−0.80), respectively. BC = bladder cancer; CSS = cancer-specific survival; CI = confidence interval; PLND = pelvic lymph node dissection; ROC: receiver operating characteristic; RC = radical cystectomy.

as independent predictors for unplanned readmission within 30 days. The addition of the CONUT-score to the reference model improved the discriminating ability for prediction of 30 days readmission (+5.0%, $P = 0.02$) (Table 3).

### 3.4. *Association of CONUT-score with survival outcomes*

The median follow-up was 26 months (IQR 12−60). Kaplan-Meier curves for RFS, OS and CSS are shown in Fig. 2. During this time-interval, 150 (43.2%) patients experienced disease recurrence, 167 (48.1%) patients died, and 111 (32.0%) patients died of BC. At 2 years, high CONUT was significantly associated with worse RFS (27.8% vs. 73.4%, HR 4.08, $P < 0.001$), OS (42.1% vs. 75.1%, HR 3.39, $P < 0.001$) and CSS (47.9% vs. 84.3%, HR 5.16, $P < 0.001$) (Fig. 2). High preoperative CONUT-score was independently associated with worse RFS (HR 2.57, 95% CI 1.75−3.78, $P < 0.001$), OS (HR 2.37, 95% CI 1.68−3.35, $P < 0.001$), and CSS (HR 3.52, 95% CI 2.29−5.42, $P < 0.001$) at multivariable Cox' regression analyses adjusted for the effect of all standard clinicopathological prognosticators (Table 4). The addition of the CONUT-score significantly improved the C-indices of the reference models considering RFS (+2.0%), OS (+2.0%), and CSS (+4.0%).

## 4. Discussion

In this retrospective multi-institutional analysis, we evaluated the role of the preoperative CONUT-score in a cohort of BC patients undergoing RC. We found that high CONUT-score was strongly associated with a poorer postoperative course and worse oncological outcomes. These findings highlight the clinical relevance of nutritional-risk assessment described by the CONUT-score as a comprehensive, personalized risk-stratification tool for patients' counseling prior RC.

Identifying novel and patient-specific predictors of postsurgical outcomes to potentially inform treatment decision-making and perioperative care is an unmet clinical need. Blood-based and molecular biomarkers have been proposed to improve risk stratification before RC [16−18]. However, their implementation into clinical practice remains hindered due to the lack of properly designed external validations hampering a patient-centered approach [16,18]. As a potentially reversible risk-factor, nutritional status is a particularly attractive target to reduce morbidity and costs surrounding RC. However, low reliability of conventional tools has been described [19]. Several reports highlighted the limitations of albumin as surrogate marker of nutritional status [9]. Thus, different combinations between albumin and other parameters for prediction of post-RC outcomes have been explored [16,19,20]. In this context, the CONUT-score is a validated nutritional-assessment tool that may better reflect the balance between the host immuno-nutritional status and the degree of cancer-related inflammation than single-factor markers [11].

We found that almost 1 out of 3 patients undergoing RC was malnourished according to the CONUT assessment. It

Table 2
Descriptive baseline characteristics, clinicopathological data and postoperative outcomes of 347 patients with clinical localized BC treated with RC and PLND according to the CONUT group.

| Variables | Overall | low CONUT | high CONUT | *P* |
|---|---|---|---|---|
| Patients, *n* (%) | 347 (100.0) | 235 (67.7) | 112 (32.3) | |
| Age (years), median (IQR) | 72 (68-74) | 71 (63-77) | 73 (68-79) | 0.003 |
| Gender, *n* (%) | | | | 0.68 |
| Male | 239 (68.9) | 164 (69.8) | 75 (67.0) | |
| Female | 108 (31.1) | 71 (30.2) | 37 (33.0) | |
| BMI, median (IQR) | 25.5 (23-28.3) | 25.6 (23.1-28.1) | 25.4 (23-28.6) | 0.8 |
| CCI, *n* (%) | | | | 0.73 |
| 0 | 44 (12.7) | 30 (12.8) | 14 (12.5) | |
| 1 | 34 (9.8) | 25 (10.6) | 9 (8.0) | |
| ≥ 2 | 269 (77.5) | 180 (76.6) | 89 (79.5) | |
| ASA score | | | | <0.001 |
| 1, 2 | 179 (51.6) | 140 (59.6) | 39 (34.8) | |
| 3, 4 | 168 (48.4) | 95 (40.4) | 73 (65.2) | |
| Neoadjuvant chemotherapy, *n* (%) | 20 (5.8) | 14 (6.0) | 6 (5.4) | 0.82 |
| pT-stage, *n* (%) | | | | 0.01 |
| pT0 | 23 (6.6) | 17 (7.2) | 6 (5.4) | |
| NMIBC (pTa/is/1) | 37 (10.7) | 32 (13.6) | 5 (4.5) | |
| pT2 | 101 (29.1) | 78 (33.2) | 23 (20.5) | |
| pT3 | 110 (31.7) | 72 (30.6) | 38 (33.9) | |
| pT4 | 76 (21.9) | 36 (15.3) | 40 (35.7) | |
| pN-stage, *n* (%) | | | | 0.01 |
| pN0 | 245 (70.6) | 178 (75.7) | 67 (59.8) | |
| pN1 | 34 (9.8) | 21 (8.9) | 13 (11.6) | |
| pN2 | 51 (14.7) | 29 (12.3) | 22 (19.6) | |
| pN3 | 17 (2.0) | 7 (3.1) | 10 (8.9) | |
| Concomitant CIS, *n* (%) | 89 (25.6) | 63 (26.8) | 26 (23.2) | 0.56 |
| Tumor Grade, *n* (%) | | | | 0.03 |
| Low Grade | 31 (8.9) | 27 (11.5) | 4 (3.6) | |
| High Grade | 316 (91.1) | 208 (88.5) | 108 (96.4) | |
| LVI, *n* (%) | 154 (44.4) | 96 (40.9) | 58 (51.8) | 0.07 |
| PSMs, *n* (%) | 36 (10.4) | 16 (6.8) | 20 (17.9) | 0.03 |
| Surgical approach, *n* (%) | | | | 0.004 |
| Open | 272 (78.4) | 174 (74.0) | 98 (87.5) | |
| Minimally-Invasive | 75 (21.6) | 61 (26.0) | 14 (12.5) | |
| Urinary Diversion, *n* (%) | | | | 0.04 |
| Ileal Conduit | 231 (66.6) | 154 (65.5) | 77 (68.7) | |
| Orthotopic Neobladder | 43 (12.4) | 36 (15.3) | 7 (6.3) | |
| Ureterocutaneostomy | 73 (21.0) | 45 (19.1) | 28 (25.0) | |
| Clavien complication grade, *n* (%) | | | | <0.001 |
| None | 78 (22.5) | 68 (28.9) | 10 (8.9) | |
| 1 - 2 | 193 (55.6) | 134 (57.0) | 59 (52.7) | |
| 3 (a, b) | 52 (15.0) | 24 (10.2) | 28 (25.0) | |
| 4 (a, b) | 17 (4.9) | 7 (3.0) | 10 (8.9) | |
| 5 | 7 (2.0) | 2 (0.9) | 5 (4.5) | |
| Length of stay (days), median (IQR) | 19 (15-26) | 18 (14-25) | 21 (16-28) | 0.002 |
| 30-days readmission, *n* (%) | 68 (19.6) | 34 (14.5) | 34 (30.4) | <0.001 |
| Adjuvant chemotherapy, *n* (%) | 106 (30.5) | 67 (28.5) | 39 (34.8) | 0.29 |
| Recurrent disease, *n* (%) | 150 (43.2) | 65 (27.7) | 85 (75.9) | <0.001 |
| Cancer-related deaths, *n* (%) | 111 (32.0) | 42 (17.9) | 69 (61.6) | <0.001 |
| Any-cause deaths, *n* (%) | 167 (48.1) | 82 (34.9) | 85 (75.9) | <0.001 |
| Follow-up (months), median (IQR) | 26 (12-60) | 32 (14-71) | 14 (8-33) | <0.001 |
| Follow-up of survivors (months), median (IQR) | 44 (23-77) | 49 (24-82) | 29 (12-47) | 0.004 |

ASA = American Society of Anesthesiologists; BC = bladder cancer; BMI = body mass index; CCI = Charlson comorbidity index; CONUT = Controlling Nutritional Status; CIS = carcinoma in situ; IQR = interquartile range; LVI = lymphovascular invasion; PLND = pelvic lymph node dissection; pT-stage = pathological tumor stage; pN-stage = pathological nodal stage; PSMs = positive surgical margins; RC = radical cystectomy.

Table 3
Multivariable logistic regression analysis for prediction of overall postoperative complications, major postoperative complications and 30 days readmission among 347 patients with clinical localized BC treated with RC and PLND.

| | Any-grade complications | | Major complications | | 30-days readmission | |
|---|---|---|---|---|---|---|
| Variable | OR 95% CI | *P* | OR 95% CI | *P* | OR 95% CI | *P* |
| Age (as cont.) | 1.03 (1.00-1.07) | 0.07 | 0.99 (0.95-1.02) | 0.5 | 1.00 (0.96-1.03) | 0.9 |
| Sex | | | | | | |
| Female | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Male | 0.90 (0.44-1.80) | 0.8 | 0.94 (0.49-1.86) | 0.9 | 0.59 (0.30-1.23) | 0.2 |
| BMI (as cont.) | 1.02 (0.95-1.10) | 0.6 | 1.03 (0.96-1.10) | 0.4 | 1.02 (0.95-1.09) | 0.6 |
| CCI | | | | | | |
| 0 | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| 1 | 2.56 (0.64-11.7) | 0.2 | 2.16 (0.52-10.0) | 0.3 | 0.72 (0.21-2.45) | 0.6 |
| ≥ 2 | 1.46 (0.56-3.58) | 0.4 | 2.10 (0.72-7.73) | 0.2 | 1.25 (1.10-2.62) | 0.02 |
| ASA score | | | | | | |
| 1, 2 | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| 3, 4 | 1.05 (0.56-2.02) | 0.9 | 2.48 (1.31-4.81) | 0.01 | 1.91 (0.93-4.03) | 0.08 |
| NAC | | | | | | |
| No | 1.00 (Ref) | - | 1.00 (Ref) | - | 1.00 (Ref) | - |
| Yes | 1.05 (0.29-4.21) | 0.9 | 1.31 (0.24-5.68) | 0.7 | 2.41 (0.53-9.77) | 0.2 |
| Surgical Approach | | | | | | |
| Open | 4.63 (2.48-8.78) | - | 5.65 (2.12-19.7) | - | 17.0 (3.33-31.6) | - |
| Minimally-Invasive | 0.22 (0.11-0.40) | < 0.001 | 0.18 (0.05-0.47) | 0.002 | 0.26 (0.39-0.78) | 0.01 |
| pT-stage | | | | | | |
| Organ-Confined (≤ pT2) | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Locally-advanced (pT3-4) | 0.81 (0.42-1.53) | 0.5 | 0.80 (0.41-1.56) | 0.5 | 0.96 (0.46-2.00) | 0.9 |
| pN-stage | | | | | | |
| Negative | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Positive | 0.71 (0.36-1.42) | 0.3 | 1.07 (0.52-2.17) | 0.9 | 0.71 (0.31-1.59) | 0.4 |
| Urinary Diversion | | | | | | |
| Ureterocuteneostomy | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Ileal Conduit | 0.88 (0.39-1.95) | 0.8 | 1.04 (0.50-2.21) | 0.9 | 1.77 (0.77-4.39) | 0.2 |
| Orthotopic Neobladder | 1.27 (0.39-4.21) | 0.7 | 0.75 (0.18-2.76) | 0.7 | 1.31 (0.31-5.22) | 0.5 |
| CONUT | | | | | | |
| Low | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| High | 3.58 (1.71-8.18) | 0.001 | 2.56 (1.37-4.79) | 0.003 | 2.39 (1.19-4.89) | 0.01 |
| Accuracy (AUC) | | [a]0.03 | | [a]0.04 | | [a]0.02 |
| Reference Model | 0.72 (0.65-0.78) | | 0.71 (0.65-0.77) | | 0.59 (0.53-0.66) | |
| Model with CONUT | 0.76 (0.70-0.81) | | 0.75 (0.69-0.81) | | 0.64 (0.59- 0.71) | |

ASA = American Society of Anaesthesiologists; AUC = area under the curve; BC = bladder cancer; CI = confidence interval; BMI = body mass index; CCI = Charlson comorbidity index; CONUT = Controlling Nutritional Status; NAC = neoadjuvant chemotherapy; OR = odds ratio; PLND = pelvic lymph node dissection; pT-stage = pathological tumor stage; pN-stage = pathological nodal stage; RC = radical cystectomy.
[a] De Long's test was used to test for statistical significance.

is estimated that approximately 16%−41% of BC individuals undergoing RC are malnourished [6]. Here, high CONUT patients were significantly correlated with increasing age and higher ASA score. Conversely, no differences were found regarding median BMI. Inconsistency in the observations regarding BMI as predictor of post-RC outcomes have been reported [6,19]. Our data confirm that BMI cannot rule out the presence of malnutrition since its lack of specificity in characterizing the true body composition.

An important finding of our study is the strong link of high CONUT-score with any-grade and major complications. In the context of nutritional determinants, Mayr et al. reported sarcopenia defined as Skeletal Muscle Index in 33% of patients undergoing RC. Sarcopenia was an independent predictor of major complications and 90 days mortality [21]. A significant correlation between sarcopenia and high CONUT was demonstrated in patients with upper tract urothelial carcinoma (UTUC) undergoing radical surgery [12]. If viewed as a whole, this highlights the complex interplay between malnutrition defined by the CONUT-score and sarcopenia.

The overall readmission rate in this study was 19.6%. Hospital LOS and unplanned readmission are two metrics which are sensitive to the RC morbidity profile and patients' characteristics [19]. We found that both high CONUT-score and open approach were significantly associated with an increased risk of unplanned 30 days readmission. However, readmission rate after RC continues to be high up to 29% even in contemporary series, which benefit from the stable adoption of minimally-invasive approach [22]. Here, a recent multicenter prospective comparative-effectiveness study found no differences in terms on 90 days unplanned readmission between open and robot-assisted RC [23]. Thus, controversy exist regarding which patients benefit the most from the minimally-invasive approach. Moreover, previous reports have shown a decrease in OS among patients who were readmitted [24]. Therefore, identification of preoperative risk-factors for unplanned readmission is of paramount importance for the adoption of tailored prevention strategies.

All together these findings suggest that individuals with high CONUT-score have fewer resources to recover after RC. Indeed, the addiction of this metric to the reference models significantly improved the discriminatory ability for prediction of any-grade complications (+4.0%), major complications (+4.0%) and unplanned 30 days readmission (+5.0%).

Nutrition interventions are critical and current evidence show that outcomes after RC may be partly attributable to poor nutritional status [25]. However, controversy remains surrounding the costs, timing and target group for immunonutrition protocols [26−28]. Moreover, since the one-size-fits all approach is not associated with significant benefits, an objective assessment system for patients' nutritional status is highly desirable. In this context, the CONUT-score could serve as screening tool to identify RC candidates who may potentially benefit from an intensified regimen of supportive and nutritional cares.

Regarding oncological outcomes, Miyake et al. found that high CONUT-score was not associated with worse CSS among RC patients. However, this study was limited by the single-center design, the small sample size and a cut-off set at 1 point for CONUT that could biased the results [14]. Comprising a small cohort of RC patients and a cut-off of 3-points, Nemoto et al. showed results that mirrored ours: within a median follow-up of 21 months, they found that high CONUT-score was independently associated with worse OS, RFS and CSS [29]. Suzuki et al. reported that high CONUT-score (0-1 vs. 2−3 vs. ≥4) was an independent prognostic biomarker in patients with advanced urothelial carcinoma treated with first-line platinum-based chemotherapy [30]. Considering UTUC and the same cut-off, Ishihara et al. demonstrated that high CONUT was independently associated with worse OS and CSS [12]. Although rates of adverse pathological features such as worse pT and pN stages, high-grade disease, and presence of PSMs were significantly different among the two groups, we performed multivariable analyses to overcome such

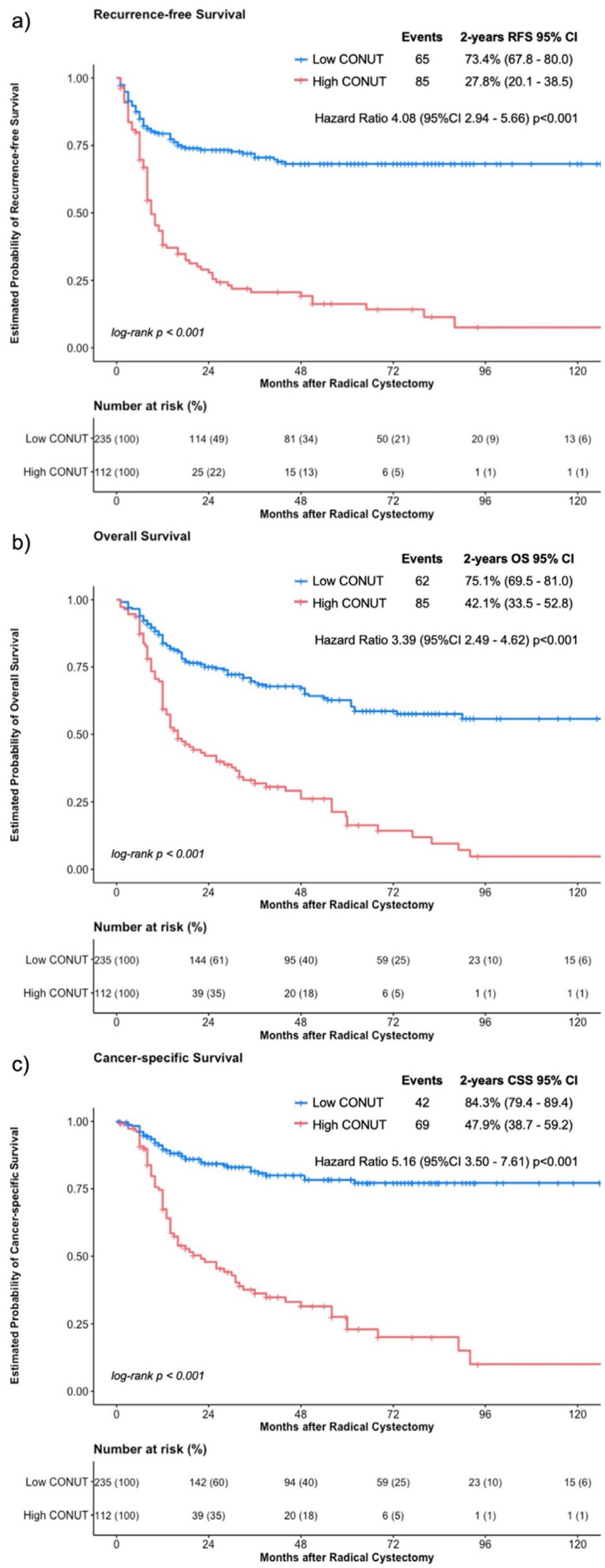


Fig. 2. Kaplan-Meier survival curves of RFS (2A), OS (2B), and CSS (2C) (all log-rank, $P < 0.001$) stratified by preoperative CONUT-score among 347 patients with clinical-localized non-metastatic BC undergoing RC and PLND are shown. Univariable Cox's regression analysis assessed the HRs with their 95%CI considering low CONUT as reference. For RFS high CONUT (HR 4.08, 95% CI 2.94−5.66, $P < 0.001$). For OS high CONUT (HR 3.39, 95% CI 2.49−4.62, $P < 0.001$). For CSS high CONUT (HR 5.16, 95% CI 3.50−7.61, $P < 0.001$). BC = bladder cancer; CSS = cancer-specific survival; CONUT = Controlling Nutritional Status; CI = confidence interval; HR = hazard ratio; OS = overall survival; PLND = pelvic lymph node dissection; RFS = recurrence-free survival; RC = radical cystectomy.

Table 4
Multivariable Cox' regression analysis for prediction of RFS, OS, and CSS among 347 patients with clinical localized BC treated with RC and PLND.

| | RFS | | OS | | CSS | |
|---|---|---|---|---|---|---|
| Variable | HR 95% CI | *P* | HR 95% CI | *P* | HR 95% CI | *P* |
| Age (as cont.) | 1.03 (1.01-1.05) | 0.01 | 1.03 (1.00-1.05) | 0.002 | 1.04 (1.02-1.07) | 0.001 |
| Sex | | | | | | |
| Female | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Male | 0.79 (0.53-1.19) | 0.3 | 0.96 (0.67-1.39) | 0.7 | 0.84 (0.53-1.32) | 0.4 |
| BMI (as cont.) | 0.98 (0.94-1.03) | 0.4 | 0.97 (0.93-1.01) | 0.12 | 0.98 (0.92-1.03) | 0.4 |
| CCI | | | | | | |
| 0 | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| 1 | 0.87 (0.39-1.94) | 0.7 | 0.65 (0.29-1.47) | 0.3 | 0.79 (0.27-2.28) | 0.7 |
| ≥ 2 | 0.72 (0.40-1.28) | 0.3 | 0.85 (0.48-1.48) | 0.6 | 1.21 (0.60-2.46) | 0.6 |
| ASA score | | | | | | |
| 1, 2 | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| 3, 4 | 1.19 (0.81-1.75) | 0.04 | 1.27 (0.89-1.82) | 0.2 | 1.02 (0.65-1.61) | 0.9 |
| NAC | | | | | | |
| No | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Yes | 2.76 (1.07-7.15) | 0.04 | 3.62 (1.41-9.29) | 0.01 | 6.34 (2.11-19.1) | 0.001 |
| pT-stage | | | | | | |
| Organ-Confined (≤ pT2) | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| ≥ pT3 | 2.28 (1.37-3.79) | 0.001 | 1.63 (1.05-2.54) | 0.03 | 1.84 (1.02-3.31) | 0.042 |
| pN-stage | | | | | | |
| Negative | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Positive | 3.38 (2.44-4.67) | <0.001 | 1.22 (0.98-1.91) | 0.06 | 2.59 (1.46-3.22) | 0.001 |
| Tumor Grade | | | | | | |
| Low Grade | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| High Grade | 1.89 (0.57-6.25) | 0.3 | 1.12 (0.52-2.42) | 0.8 | 4.43 (0.59-33.1) | 0.15 |
| LVI | | | | | | |
| Absence | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Presence | 1.27 (0.79-2.04) | 0.3 | 1.61 (1.05-2.47) | 0.03 | 1.57 (0.90-2.74) | 0.11 |
| PSMs | | | | | | |
| Absence | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Presence | 2.51 (1.55-4.08) | <0.001 | 2.11 (1.29-3.44) | 0.003 | 2.14 (1.23-3.75) | 0.01 |
| Concomitant CIS | | | | | | |
| Absence | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Presence | 0.94 (0.61-1.45) | 0.8 | 0.95 (0.63-1.44) | 0.8 | 0.84 (0.50-1.43) | 0.5 |
| AC | | | | | | |
| No | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| Yes | 1.59 (1.04-2.42) | 0.03 | 0.96 (0.64-1.46) | 0.9 | 1.42 (0.86-2.34) | 0.2 |
| CONUT | | | | | | |
| Low | 1.00 (Ref.) | - | 1.00 (Ref.) | - | 1.00 (Ref.) | - |
| High | 2.57 (1.75-3.78) | <0.001 | 2.37 (1.68-3.35) | <0.001 | 3.52 (2.29-5.42) | <0.001 |
| C-index | | [a]<0.001 | | [a]<0.001 | | [a]<0.001 |
| Reference Model | 0.77 (0.73-0.81) | | 0.72 (0.68-0.76) | | 0.77 (0.73-0.82) | |
| Model with CONUT | 0.79 (0.76-0.83) | | 0.74 (0.70-0.78) | | 0.81 (0.77-0.84) | |

ASA = American Society of Anesthesiologists; BC = bladder cancer; BMI = body mass index; CCI = Charlson comorbidity index; CI = confidence interval; CSS = cancer-specific survival; CONUT = Controlling Nutritional Status; HR = hazard ratio; NAC = neoadjuvant chemotherapy; OS = overall survival; PLND = pelvic lymph node dissection; pT-stage = pathological tumor stage; pN-stage = pathological nodal stage; RC = radical cystectomy; RFS = recurrence-free survival.

[a] Likelihood ratio test was used to test for statistical significance.

influences demonstrating the independent ability of the CONUT-score to predict RFS, OS, and CSS.

Our study is not devoid of limitations which are mainly inherent to its retrospective design. Data about smoking status were not available. Only 5.8% of patients received the standard-of-care NAC and this relatively small sample size may have biased the multivariable models. Confounding conditions such as drug-interaction including the statin adoption may have affected the CONUT assessment leading to systematic bias. The CONUT-score was analyzed as a categorical variable with a predefined cut-off value. Although we obtained a 3-points cut-off as Youden-index, the same threshold has been proposed in a systematic review as an acceptable trade-off between sensitivity and specificity among cancer patients [11]. During the study period different temporal practice patterns may have existed, thus standardized ERAS protocols that were implemented in more recent patients were not captured. Pending further external validations, especially in the context of an integrated-biomarker assessment, this is the first multi-institutional experience evaluating the comprehensive impact of preoperative CONUT-score in patients undergoing RC.

## 5. Conclusions

Preoperative high CONUT-score was an independent predictor for a worse postoperative course and was associated with poor oncological outcomes. Being simple and inexpensive, its preoperative assessment could be part of a more refined risk-stratification. Since the CONUT-score reflects both nutritional-status and the degree of tumor-derived chronic inflammation, targeted-intervention strategies may improve outcomes by reversing these conditions before RC.

## Author contributions

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## Declaration of Competing Interest

The authors declare that there are no conflict of interest.

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## Supplementary materials

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## References

[1] 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. https://doi.org/10.1016/j.eururo.2020.03.055.

[2] Babjuk M, Burger M, Compérat EM, et al. European association of urology guidelines on non-muscle-invasive bladder cancer (TaT1 and Carcinoma In Situ) - 2019 update. Eur Urol 2019:1–19. https://doi.org/10.1016/j.eururo.2019.08.016.

[3] Satkunasivam R, Tallman CT, Taylor JM, Miles BJ, Klaassen Z, Wallis CJD. Robot-assisted radical cystectomy versus open radical cystectomy: a meta-analysis of oncologic, perioperative, and complication-related outcomes. Eur Urol Oncol 2019;2:443–7. https://doi.org/10.1016/j.euo.2018.10.008.

[4] Wessels F, Lenhart M, Kowalewski KF, et al. Early recovery after surgery for radical cystectomy: comprehensive assessment and meta-analysis of existing protocols. World J Urol 2020;38:3139–53. https://doi.org/10.1007/s00345-020-03133-y.

[5] Zehnder P, Studer UE, Skinner EC, et al. Unaltered oncological outcomes of radical cystectomy with extended lymphadenectomy over three decades. BJU Int 2013;112. https://doi.org/10.1111/bju.12215.

[6] Psutka SP, Barocas DA, Catto JWF, et al. Staging the host: personalizing risk assessment for radical cystectomy patients. Eur Urol Oncol 2018;1:292–304. https://doi.org/10.1016/j.euo.2018.05.010.

[7] Leow JJ, Fay AP, Mullane SA, Bellmunt J. Perioperative therapy for muscle invasive bladder cancer. Hematol Oncol Clin North Am 2015;29:301–18. https://doi.org/10.1016/j.hoc.2014.11.002.

[8] Mori K, Janisch F, Mostafaei H, et al. Prognostic value of preoperative blood-based biomarkers in upper tract urothelial carcinoma treated with nephroureterectomy: A systematic review and meta-analysis. Urol Oncol Semin Orig Investig 2020;38:315–33. https://doi.org/10.1016/j.urolonc.2020.01.015.

[9] Mir MC, Izquierdo L. Nutrition for cystectomy with pelvic lymph nodes dissection: Perioperative considerations. Minerva Urol e Nefrol 2016;68:150–60.

[10] Ignacio De Ulíbarri J, González-Madroño A, De Villar NGP, et al. CONUT: A tool for Controlling Nutritional Status. First validation in a hospital population. Nutr. Hosp. 2005;20:38–45. https://doi.org/10.3305/nutr.

[11] Kheirouri S, Alizadeh M. Prognostic potential of the Preoperative Controlling Nutritional Status (CONUT) score in predicting survival of patients with cancer: A systematic review. Adv Nutr 2021;12:234–50. https://doi.org/10.1093/advances/nmaa102.

[12] Ishihara H, Kondo T, Yoshida K, et al. Preoperative controlling nutritional status (CONUT) score as a novel predictive biomarker of survival in patients with localized urothelial carcinoma of the upper urinary tract treated with radical nephroureterectomy. Urol Oncol Semin Orig Investig 2017;35:539.e9–16. https://doi.org/10.1016/j.urolonc.2017.04.012.

[13] Suzuki H, Ito M, Takemura K, et al. Prognostic significance of the controlling nutritional status (CONUT) score in advanced urothelial

carcinoma patients. Urol Oncol Semin Orig Investig 2020;38:76.e11–17. https://doi.org/10.1016/j.urolonc.2019.10.014.
[14] Miyake M, Morizawa Y, Hori S, et al. Integrative assessment of pretreatment inflammation-, nutrition-, and muscle-based prognostic markers in patients with muscle-invasive bladder cancer undergoing radical cystectomy. Oncol 2017;93:259–69. https://doi.org/10.1159/000477405.
[15] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
[16] Schuettfort VM, D'Andrea D, Quhal F, et al. Impact of preoperative serum albumin-globulin ratio on disease outcome after radical cystectomy for urothelial carcinoma of the bladder. Urol Oncol Semin Orig Investig 2021;39:235.e5–14. https://doi.org/10.1016/j.urolonc.2020.11.005.
[17] Mertens LS, Claps F, Mayr R, et al. Prognostic markers in invasive bladder cancer: FGFR3 mutation status versus P53 and KI-67 expression: a multi-center, multi-laboratory analysis in 1058 radical cystectomy patients. Urol Oncol 2022;40:110.e1–9. https://doi.org/10.1016/J.UROLONC.2021.10.010.
[18] Claps F, Mir MC, Zargar H. Molecular markers of systemic therapy response in urothelial carcinoma. Asian J Urol 2021;8:376–90. https://doi.org/10.1016/J.AJUR.2021.05.001.
[19] Ornaghi PI, Afferi L, Antonelli A, et al. The impact of preoperative nutritional status on post-surgical complication and mortality rates in patients undergoing radical cystectomy for bladder cancer: a systematic review of the literature. World J Urol 2020. https://doi.org/10.1007/s00345-020-03291-z.
[20] Claps F, Rai S, Mir MC, et al. Prognostic value of preoperative albumin-to-fibrinogen ratio (AFR) in patients with bladder cancer treated with radical cystectomy. Urol Oncol 2021;39:835.e9–17. https://doi.org/10.1016/J.UROLONC.2021.04.026.
[21] Mayr R, Fritsche HM, Zeman F, et al. Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. World J Urol 2018;36:1201–7. https://doi.org/10.1007/s00345-018-2259-x.
[22] Cacciamani GE, Medina L, Lin-Brande M, et al. Timing, Patterns and Predictors of 90-Day Readmission Rate after Robotic Radical Cystectomy. J Urol 2021;205:491–9. https://doi.org/10.1097/JU.0000000000001387.
[23] Wijburg CJ, Michels CTJ, Hannink G, et al. Robot-assisted radical cystectomy versus open radical cystectomy in bladder cancer patients: a multicentre comparative effectiveness study [formula presented]. Eur Urol 2021;79:609–18. https://doi.org/10.1016/j.eururo.2020.12.023.
[24] Borza T, Jacobs BL, Montgomery JS, et al. No differences in population-based readmissions after open and robotic-assisted radical cystectomy: implications for post-discharge care. Urology 2017;104:77–83. https://doi.org/10.1016/j.urology.2017.01.042.
[25] Munbauhal G, Drouin SJ, Mozer P, et al. Malnourishment in bladder cancer and the role of immunonutrition at the time of cystectomy: An overview for urologists. BJU Int 2014;114:177–84. https://doi.org/10.1111/bju.12529.
[26] Hamilton-Reeves JM, Bechtel MD, Hand LK, et al. Effects of immunonutrition for cystectomy on immune response and infection rates: a pilot randomized controlled clinical trial. Eur Urol 2016;69:389–92. https://doi.org/10.1016/j.eururo.2015.11.019.
[27] Ritch CR, Cookson MS, Clark PE, et al. Perioperative oral nutrition supplementation reduces prevalence of sarcopenia following radical cystectomy: Results of a prospective randomized controlled trial. J Urol 2019;201:470–7. https://doi.org/10.1016/j.juro.2018.10.010.
[28] Lyon TD, Turner RM, McBride D, et al. Preoperative immunonutrition prior to radical cystectomy: A pilot study. Can J Urol 2017;24:8895–901.
[29] Nemoto Y, Kondo T, Ishihara H, et al. The controlling nutritional status CONUT score in patients with advanced bladder cancer after radical cystectomy. In Vivo 2021;35:999–1006. https://doi.org/10.21873/INVIVO.12343.
[30] Suzuki H, Ito M, Takemura K, et al. The controlling nutritional status (CONUT) score is a prognostic biomarker in advanced urothelial carcinoma patients treated with first-line platinum-based chemotherapy. Bl Cancer 2021;7:13–21. https://doi.org/10.3233/BLC-200354.