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# Neutrophil-to-lymphocyte ratio as a detection marker of tumor recurrence in patients with muscle-invasive bladder cancer after radical cystectomy

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## Abstract

**Purpose:** High–neutrophil to lymphocyte ratio (NLR) values have been shown to be associated with a poor prognosis in many human malignant tumors. We evaluated the correlation of the NLR with other variables in patients with muscle-invasive bladder cancer after radical cystectomy (RC); in particular, we evaluated chronological changes in the postoperative NLR.

**Methods:** We included the data from a total of 110 patients who underwent RC for muscle-invasive bladder cancer. The NLR was calculated using complete blood counts determined before RC. Kaplan-Meier and Cox proportional regression analyses of recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were performed to identify significant prognostic variables.

**Results:** The median patient age was 72 years (41–91 years). In univariate analysis, the pretreatment NLR ($\geq 2.6$ vs. $< 2.6$) was associated with RFS (hazard ratio [HR] = 2.41, $P = 0.008$), CSS (HR = 2.89, $P = 0.006$), and OS (HR = 2.73, $P = 0.002$). In multivariate analysis, an NLR $\geq 2.6$ and an infiltrative growth pattern at the tumor invasion front were significantly associated with RFS (HR = 2.61, $P = 0.023$), CSS (HR = 2.58, $P = 0.08$), and OS (HR = 2.77, $P = 0.004$). Postoperative chronological analysis revealed that the NLR of 68 patients without recurrence remained low during follow-up, whereas the NLR of the remaining 42 patients with recurrence increased significantly in the last visit before recurrence was detected radiographically ($P < 0.01$).

**Conclusions:** The NLR and tumor growth pattern were strong predictors of prognosis for patients undergoing RC. Our results suggest that an increase in the NLR during follow-up after RC is a potential marker for the early detection of recurrence. © 2016 Elsevier Inc. All rights reserved.

*Keywords:* NLR; Muscle-invasive bladder cancer; Tumor growth pattern; Recurrence

## 1. Introduction

Radical cystectomy (RC) remains the gold standard for the treatment of muscle-invasive bladder cancer (MIBC). However, survival outcomes following RC have not changed over decades [1]. Despite curative treatment, tumor recurrence rate remains high (5-year recurrence-free survival [RFS] = 63.9%) [2]. Many patients experience recurrence after surgery, probably from micrometastasis present at RC. RC in combination with neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC) has been shown to improve cancer outcomes [3,4]. Hautmann et al. [5] reported that early RC in patients with high-risk non-MIBC improved cancer outcomes. However, because of the side effects of these aggressive treatments, it may be excessive to treat all patients in this manner. Many poor prognostic factors have been documented in patients with bladder cancer undergoing RC, such as age, gender performance status, preoperative low hemoglobin (Hb),

pathological T stage, lymph node (LN) metastasis, and lymphovascular invasion (LVI) [6–10]. However, risk stratification based on a patient's background and clinicopathological data is unlikely to be sufficient to determine treatment options. Thus, novel prognostic biomarkers are needed to improve outcomes.

Grivennikov et al. [11] suggest that oncological outcome is influenced not only by tumor behavior but also by host response through systemic inflammation. Some researchers have reported that patients with an elevated preoperative C-reactive protein (CRP) level were more likely to experience subsequent disease recurrence and lower rates of cancer-specific survival (CSS) following RC [9,10]. The neutrophil-to-lymphocyte ratio (NLR) is another marker reflecting a systemic inflammatory response. In recent years, several studies have shown that a high NLR correlates with advanced stage and poor prognosis in a variety of human malignant tumors [12–14]. The preoperative NLR may be a prognostic biomarker for patients undergoing RC for urothelial bladder carcinoma [15,16]. However, the clinical significance of preoperative and postoperative NLR remains inconclusive. To our knowledge, there have been no studies addressing postoperative NLR changes as a prognostic parameter of tumor progression or recurrence after RC.

Thus, we attempted to conclusively demonstrate the clinical significance of preoperative and postoperative systemic inflammatory markers, such as the NLR and CRP level, in patients with MIBC. In addition, we evaluated whether postoperative NLR changes would be a useful parameter for predicting outcome in patients after RC.

## 2. Methods

### 2.1. Patients and data collection

This is a retrospective study of 127 cases with urothelial carcinoma of bladder without evidence of distant metastasis undergoing RC from 2002 to 2013 at the Department of Urology, Nara Medical University, Nara, Japan. overall, 14 cases were excluded because of non–muscle invasive bladder cancer such as T1 high grade and Tis and 3 cases were excluded because differential leukocyte counts were not available, leaving 110 cases. In all, 7 patients have past history of other malignancies. We are sure that the other malignancies could not influence preoperative NLR data and prognosis of MIBC because they are stable without recurrence in other cancers. The histopathology of the primary tumors and LNs was confirmed by the Department of Pathology. We collected the following data: age, sex, body mass index (BMI), performance status according to the Eastern Cooperative Oncology Group scale, preoperative comorbidity (Charlson comorbidity index), pretreatment laboratory parameters (NLR, Hb, albumin, CRP, and sodium), preoperative hydronephrosis, NAC, clinical T stage, pathological T stage, histological subtypes, number of resected nodes, LN metastasis, LVI, and infiltrative growth pattern at the tumor invasion front (tumor growth pattern). The tumor growth pattern is characterized by single cell infiltration of stromal tissues, possibly because of a loss of cell cohesion. Invasive bladder cancers are categorized into the following 3 groups: "nodular" (composed mostly of well-delineated, round nests of tumor cells), "trabecular" (composed of broad trabeculae that have anastomosed with each other), and "infiltrative" (composed of infiltrating narrow cords or single cells). For T1 high grade bladder cancer it has been reported that infiltrative growth pattern is an important factor significantly associated with worse outcome [17,18]. We compared 2 groups of "infiltrative" with "nodular" and "nodular". Pretreatment laboratory parameters for each patient were defined as the date of initiation of RC. In those who received NAC pretreatment laboratory parameters were defined the date of initiation of NAC because neutropenia is a known side effect that may have affected our results. In addition, patients who have bleeding diathesis, hematological malignancies, and acute inflammatory diseases were excluded.

Owing to the retrospective study, postoperative follow-up was not standardized. However, at our institution, follow-up after RC is generally recommended quarterly for the first 2 years postoperatively, semiannually for the next 3 years, and annually thereafter for patients without evidence of recurrent disease. Oncological evaluation includes history, physical examination, blood tests, urine cytology, and imaging of the chest, abdomen, and pelvis. We evaluated postoperative NLR changes at 3 months after RC, the last visit before recurrence, time of the recurrence, the visit before latest visit and the latest visit. Because the NLR is elevated in early postoperative period, we evaluated at 3 months after RC.

This study was approved by the Medical Ethics Committee of Nara Medical University (NMU-900), which waived the requirement for informed patient consent because of the retrospective nature of the analysis.

### 2.2. Statistical analyses

The outcome measures were RFS, CSS, and overall survival (OS) measured in months from the date of RC. The cutoff date of the last follow-up was December 31, 2014. Receiver operating characteristic (ROC) curve analysis was used to investigate whether the NLR could distinguish between patients with recurrence and those without recurrence (area under the ROC curve). The NLR value with the best accuracy (the greatest sensitivity and specificity) was selected as the NLR cutoff value. Univariate and multivariate analyses were performed using the Cox proportional