Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Prognostic significance of red cell distribution width in esophageal squamous cell carcinoma

Noriyuki Hirahara, Ph, MD, Yoshitsugu Tajima, Ph, MD, Yusuke Fujii, MD, Ryoji Hyakudomi, MD, Tetsu Yamamoto, Ph, MD, Kazunari Ishitobi, MD, Takahito Taniura, MD, and Yasunari Kawabata, Ph, MD*

Department of Digestive and General Surgery, Shimane University Faculty of Medicine, Izumo, Shimane, Japan

ARTICLE INFO

Article history:
Received 31 May 2017
Received in revised form
11 April 2018
Accepted 19 April 2018
Available online xxx

Keywords:
Esophageal squamous cell carcinoma
Red cell distribution width
Prognosis

ABSTRACT

Background: Red cell distribution width (RDW) is routinely assessed as part of the complete blood count (CBC) to gather information on the heterogeneity in the size of circulating erythrocytes. RDW is a more sensitive screening marker for anemia, inflammation, and nutritional deficiencies. The purpose of this study was to explore the prognostic value of RDW in esophageal squamous cell carcinoma (ESCC) patients.

Methods: We conducted a retrospective study of data from 148 ESCC consecutive patients who underwent potentially curative esophagectomy and analyzed the correlation of RDW with various clinicopathological factors.

Results: Multivariate analyses identified a high RDW (HR, 2.061; $P = 0.0286$) as a significant risk factor for cancer-specific survival (CSS). Kaplan–Meier analysis and the log-rank test demonstrated that patients with a high RDW had a significantly worse prognosis in terms of CSS than those with a low RDW ($P = 0.0011$). In multivariate analysis, there was no significant relationship between RDW and CSS in pathological tumor node metastasis stage I or II patients. However, a high RDW (HR, 2.386; $P = 0.0471$) was confirmed to be an independent worse prognostic factor for CSS in pathological tumor node metastasis stage III cancer patients. Kaplan–Meier analysis and the log-rank test showed a significant relationship between RDW and CSS in patients with pathological tumor node metastasis stage III ($P = 0.0175$).

Conclusions: The RDW was a significant and independent predictor of poor survival in ESCC patients after curative esophagectomy. RDW may aid clinicians in detecting signs of recurrence very early and effectively customize treatment regimens. RDW is thus a convenient, cost-effective, and readily available biomarker to predict survival in ESCC.

Introduction

It is widely recognized that disease progression and survival outcomes of patients with cancer are not determined by tumor characteristics alone and that patient-related factors such as age, performance status, and nutritional status play an important role. Cancer-associated systemic inflammation is a well-known key determinant of patient prognosis in various cancer types.[1] While underlying inflammation has been known to promote disease progression, it is increasingly being accepted that markers of systemic inflammation can also accurately reflect tumor volume.[2-4]

* *Corresponding author*. Shimane University Faculty of Medicine, Department of Digestive and General Surgery 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan. Tel.: +81 853 20 2232; fax: +81 853 20 2229.
E-mail address: norinorihirahara@yahoo.co.jp (N. Hirahara).
0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2018.04.051

Red cell distribution width (RDW), which is based on the width of the red blood cell (RBC) volume distribution curve, reflects the variability in size of circulating RBCs. Alterations in RDW are related to changes in RBC survival patterns and signify derailment of erythropoiesis.[5,6] Recently, studies have revealed that RDW is elevated in patients with active inflammation and correlates well with impaired cardiometabolic function, hypertension, and chronic obstructive pulmonary disease.[7-9] It is well accepted that cancers trigger chronic inflammation and inflammatory responses and involve the release of a wide variety of cytokines, such as tumor necrosis factor-alpha and interleukin-6.[10,11] It has also been proposed that a high RDW value reflects poor nutritional status, and that the nutritional status of cancer patients is compromised due to disease progression. It can thus be hypothesized that the RDW value can help in the assessment of patient prognosis in cancer. However, RDW has not been explored adequately for its application in the area of oncology. In addition, there have been very few studies with specific emphasis on the relationship of RDW with disease progression and patient survival in esophageal cancer.

The purpose of this study was to explore whether RDW has prognostic value, independent of other conventional clinicopathological risk factors, in esophageal squamous cell carcinoma (ESCC) patients who underwent potentially radical resection for ESCC.

Material and methods

Patients

We retrospectively reviewed a database containing data of 148 consecutive patients who underwent potentially radical esophagectomy with curative resection for histologically verified ESCC at our institute between January 2006 and December 2014. Video-assisted or thoracoscopic subtotal esophagectomy with three-field lymph node dissection was performed for all patients. The patients' clinical characteristics, laboratory data, treatment regimen, and pathological data were obtained from their medical records. Patients who underwent neoadjuvant therapy were excluded because of concern that systemic chemotherapy and radiotherapy could affect systemic inflammation. The pathological tumor node metastasis (pTNM) stages of the primary tumors were determined according to the TNM classification system (seventh edition).[12]

We evaluated cancer-specific survival (CSS), defined as the interval from the date of surgery to cancer-specific death. The cause of death was determined from the case notes or computerized records. The observation period started from the day of the operation until death, loss to follow-up, or withdrawal of consent, which ever occurred first.

This retrospective study was approved by the ethical board of our institution and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of this study.

Blood sample analysis data

Preoperative complete blood count (CBC) was retrospectively extracted from patient medical records. Blood sample analysis data were obtained within 1 wk before surgery. The records showed that CBC and hematological marker levels were measured using an automated hematology analyzer XE-5000 (TOA Medical Electronics, Japan). We extracted RDW values directly from the CBC test reports.

Red cell distribution width

The RDW is a measurement derived from the RBC distribution curves that contain RDW coefficient of variation (RDW-CV) and RDW standard deviation (RDW-SD) value, and it reflects the size heterogeneity of RBCs. The RDW-CV is a calculation based on both the width of the distribution curve and the mean cell size. The RDW-CV is calculated with the following formula: RDW = (One SD of red cell volume/mean cell volume) $\times$ 100 and is reported as a %. The reference ranges for RDW-CV is approximately 11.0%-15.0%. On the other hand, the RDW-SD is an actual measurement of the width of the red cell distribution curve in femtoliters. The width of the distribution curve is measured at the point that is 20% above the baseline. Because the RDW-SD is an actual measurement, it is not influenced by the mean corpuscular volume and more accurately reflects the red cell size variance. Therefore, we treated RDW-SD as a prognostic value of RDW and analyzed these data. The normal RDW-SD range for adults is 40.0-55.0 fL, but reference ranges may vary depending on the individual laboratory and patient's age.[6] The routine reference cutoff value for RDW used in our hospital laboratory was <50.

Statistical analysis

The means and SDs were calculated, and the differences were analyzed using the student's *t*-test. Differences between categories of each clinicopathological feature were analyzed using the chi-square test. The CSS was analyzed using Kaplan–Meier statistics and log-rank test.

A Cox proportional hazards model was used for univariate and multivariate analyses to determine the variables associated with CSS. The potential prognostic factors assessed were age (<70 *versus* ≥70 y), sex (female *versus* male), pathological TNM stage (pTNM stage; I/II *versus* III), tumor size (<3 cm *versus* ≥3 cm), operative time (<600 min *versus* ≥600 min), intraoperative blood loss (<500 mL *versus* ≥500 mL), SCC antigen value (<1.5 *versus* ≥1.5), C-reactive protein (<0.14 *versus* ≥0.14), blood transfusion (no/yes), adjuvant chemotherapy (no/yes), and RDW (<50 *versus* ≥50).

All statistical analyses were performed using the statistical software JMP (version 11 for Windows; SAS Institute, Cary, NC), and *P* values <0.05 were considered statistically significant.

Results

Relationship between RDW and clinicopathological features

The correlation between RDW values and clinical parameters of 148 patients enrolled in the present study is summarized in Table 1. The preoperative mean value of RDW in this study was 48.7 ± 6.9, ranging from 39.1 to 76.1. Patients were categorized into two groups according to their RDW values. A cutoff value of