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Prognostic value of neutrophil-to-lymphocyte ratio in patients treated with concurrent chemoradiotherapy for locally advanced oesophageal cancer

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ABSTRACT

Background: We performed a retrospective analysis of Asian patients with locally advanced oesophageal cancer to test the hypothesis that an elevated neutrophil-to-lymphocyte ratio is associated with a poor survival rate after definitive concurrent chemoradiotherapy.
Methods: In total, 138 patients diagnosed with locally advanced oesophageal cancer (TNM classification of malignant tumours stage II or III) who were treated with definitive concurrent chemoradiotherapy between January 2005 and December 2010 were retrospectively analysed. Definitive concurrent chemoradiotherapy was performed using two different chemotherapy regimens.
Results: The median follow-up duration was 39.5 months (range 1.1–93.4). The median progression-free survival was 14.0 months, and the median overall survival was 19.9 months. Compared with the low (<2.0) neutrophil-to-lymphocyte ratio group ($n = 43$, 31.2%), the high (≥2.0) neutrophil-to-lymphocyte ratio group ($n = 95$, 68.8%) exhibited significant decreases in the durations of both progression-free survival and overall survival. Using multivariate analysis, an elevated neutrophil-to-lymphocyte ratio was also significantly associated with decreased progression-free survival (HR 1.799; 95% CI, 1.050–3.083; $P = 0.032$) and overall survival duration (HR 2.115; 95% CI, 1.193–3.749; $P = 0.010$).
Conclusions: The pretreatment neutrophil-to-lymphocyte ratio is a useful prognostic marker in patients with locally advanced oesophageal cancer treated with definitive concurrent chemoradiotherapy.

1. Introduction

Surgical resection is considered a curative aim for early stage oesophageal cancer (EC). However, over 60% of cases exhibit unresectable disease at presentation [1]. For these patients, definitive concurrent chemoradiotherapy (CCRT) has been suggested as an option for both prolonging survival and relieving symptoms. In randomised trials, the addition of cisplatin-based chemotherapy to radiotherapy (RT) significantly improves survival over RT alone [2–4]. Despite the relatively prolonged median and overall survival times conferred by CCRT, marked heterogeneity still exists between the survival duration of patients with locally advanced EC [5–7]. Thus, prognostic factors have been sought that will enable more precise patient stratification and improve decision-making by clinicians. Demographic factors such as weight loss or performance status have been suggested to be related to treatment response and survival in previous studies of inoperable oesophago-gastric cancer [8,9]. However, the use of these demographic factors as prognostic touchstones remains problematic, since they are often not accurately defined and are subject to bias. Both tumour- and treatment-related factors such as tumour length, T-stage, N-stage, histopathological grade, radiotherapy dose, and CCRT have been reported to be associated with disease progression and survival [10]. However, data are still lacking regarding prognostic factors associated with overall survival duration or treatment response for Asian EC patients treated with definitive CCRT.

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Recently, various studies have proposed measurements and/or scoring systems to simplify and standardise the measurement of systemic inflammatory response in clinical practice [11,12]. These parameters include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the modified Glasgow Prognostic Score (mGPS) in gastrointestinal tract cancer. For example, the NLR represents a non-specific measurement of systemic inflammation; furthermore, an elevated NLR has been shown to be associated with poor prognosis in patients with cardiovascular disease, colorectal cancer, renal cell carcinoma, ovarian cancer, and EC [13,14]. It has been reported as part of the systemic inflammatory response, associated with compromised immune function and host anti-tumour immune responses regardless of ethnicity [15]. However, with regard to EC, the NLR has only been investigated in pre-operative or neoadjuvant settings, and its predictive abilities have not been assessed in locally advanced cases, indicated for definitive CCRT [16–19].

We therefore performed a retrospective analysis of data from Asian patients with locally advanced EC. Our primary hypothesis was that elevated pre-CCRT NLRs are associated with poor survival results or treatment responses after definitive CCRT. We also assessed the appropriate cut-off value for defining an elevated NLR, and examined the value of other factors for predicting survival outcomes associated with definitive CCRT.

2. Methods

2.1. Patient eligibility

Eligible cases consisted of 903 patients diagnosed with EC at Severance Hospital, Yonsei University College of Medicine (Seoul, Korea) between January 2005 and December 2010. Among them, patients meeting one or more of the following exclusion criteria were omitted from further study: (1) any malignancy except EC during the study period; (2) previous surgery, with either a curative or a palliative aim; (3) previous radiotherapy or chemotherapy only; (4) previous palliative or supportive care only; and (5) any other serious medical co-morbidities or lost to follow-up stage (Fig. 1). Upon application of these criteria, 216 EC patients treated with CCRT without surgery were selected. Next, patients with either early stage EC (TNM classification of malignant tumours (TNM) stage I) or metastatic EC (TNM stage IV) were excluded. Finally, 138 patients with locally advanced EC (TNM stage II or III) treated with definitive CCRT were analysed in this study (Fig. 1). Patient demographic and clinical information, as well as tumour characteristics and patient follow-up, were assessed in a prospective fashion. A standardised questionnaire was used to collect comprehensive information on demographic characteristics and substance use *via* a personal interview with participants within 1 week of cancer diagnosis. This study was approved by the Institutional Review Board of the Severance Hospital.

2.2. Diagnostic and staging procedures and clinical data collection

Tumour stage was assessed based on the American Joint Committee on Cancer (AJCC) 6th edition staging manual [20]. Pre-treatment clinical staging was based on an endoscopy, an endoscopic ultrasound (EUS), a barium swallow test, a computed tomography (CT) scan of the abdomen and thorax, and a positron emission tomography (PET) scan. Routine laboratory tests, including a complete blood cell count (CBC), a serum chemistry profile, and a C-reactive protein (CRP) test, were carried out within 1 week of commencing CCRT. In addition, a complete history was taken, a physical examination was completed, and the Eastern Cooperative Oncology Group (ECOG) performance was assessed. To evaluate the patients' comorbidity disease status, Charlson's comorbidity index was also calculated [21].

The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The mGPS was determined as previously described [22]. Patients who had elevated CRP levels (>10 mg/L) were assigned an mGPS score of 1, and those who exhibited both elevated CRP levels and hypoalbuminaemia (<35 g/L) were assigned a score of 2. Patients with none of these abnormalities were assigned a score of 0.

3. Treatment protocol

3.1. Radiotherapy

Radiotherapy was performed once daily, 5 times a week, except for weekends and public holidays. Daily doses of 1.8 Gy were administered. Linac accelerators, with 10–15 MeV photons and a multiple field technique, were used for treatment. Portal images were obtained at least once a week. The total dose administered to planning target volume (PTV)-2 and PTV-1 patients was 50.4 and 63 Gy. Dose heterogeneities within the target volume were less than 5%.

3.2. Target volume definition

PTV-1 included the primary tumour volume and the volumes of the macroscopically involved lymph nodes. PTV-2 consisted of a 5-cm superior–inferior volume and a 2.5-cm lateral safety margin beyond the volume of PTV-1. In cases of oesophago-gastric junction tumours, coeliac lymph nodes were included in the PTV-2 measurement. In cases of tumours located in the upper oesophagus, supraclavicular nodes were included in the PTV-2 measurement.

3.3. Chemotherapy

In our study, two kinds of chemotherapy regimens were adjusted for in the study population. The first regimen included cisplatin and 5-fluorouracil (5-FU)-based chemotherapy. CCRT included two identical courses, each extending over 4 weeks. Cisplatin was administered at a dose of 80 mg/m^2 per day on days 1 and 29, and 5-FU was administered at a dose of 800 mg/m^2 continuously on days 1–4 and 29–33 throughout the entire CCRT course.

The second regimen encompassed chemotherapy in combination with a novel fluoropyrimidine, S-1, and a cisplatin course. This regimen included two identical courses, each consisting of 2 weeks of CCRT separated by a 1-week rest period. Treatment courses comprised oral S-1, at a dose of 70 mg/m^2 per day for 2 weeks from day 1, and cisplatin infusion for 24 h at a dose of 75 mg/m^2 on day 8.

For patients who demonstrated a favourable response to CCRT, an additional two or four cycles of chemotherapy, consisting of either 5-FU/cisplatin or S-1/cisplatin, were also administered after CCRT. All patients were given supportive management, including antiemetic treatment, nutritional support, and IV hydration. Additional dose reduction of chemotherapy was considered if either haematological grade 4 toxicity or non-haematological grade 3 toxicity occurred.

3.4. Adverse events and response evaluation

During CCRT, routine CBC counts and serum chemistry profiles were assessed twice weekly. Body weight, performance status, related symptoms, and ability to swallow were checked daily. Treatment toxicity was evaluated according to the National