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Original article

The prognostic value of derived neutrophil to lymphocyte ratio in oesophageal cancer treated with definitive chemoradiotherapy

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ABSTRACT

Background and purpose: The derived neutrophil–lymphocyte ratio (dNLR) is a validated prognostic biomarker for cancer survival but has not been extensively studied in locally-advanced oesophageal cancer treated with definitive chemoradiotherapy (dCRT). We aimed to identify the prognostic value of dNLR in patients recruited to the SCOPE1 trial.

Materials and methods: 258 patients were randomised to receive dCRT ± cetuximab. Kaplan–Meier's curves and both univariable and multivariable Cox regression models were calculated for overall survival (OS), progression free survival (PFS), local PFS inside the radiation volume (LPFSi), local PFS outside the radiation volume (LPFSo), and distant PFS (DPFS).

Results: An elevated pre-treatment dNLR ≥ 2 was significantly associated with decreased OS in univariable (HR 1.74 [95% CI 1.29–2.35], $p < 0.001$) and multivariable analyses (HR 1.64 [1.17–2.29], $p = 0.004$). Median OS was 36 months (95% CI 27.8–42.4) if dNLR < 2 and 18.4 months (95% CI 14.1–24.9) if dNLR ≥ 2. All measures of PFS were also significantly reduced with an elevated dNLR. dNLR was prognostic for OS in cases of squamous cell carcinoma with a non-significant trend for adenocarcinoma/undifferentiated tumours.

Conclusions: An elevated pre-treatment dNLR may be an independent prognostic biomarker for OS and PFS in oesophageal cancer patients treated with definitive CRT. dNLR is a simple, inexpensive and readily available tool for risk-stratification and should be considered for use in future oesophageal cancer clinical trials.

The SCOPE1 trial was an International Standard Randomised Controlled Trial [number 47718479].

Oesophageal cancer is the 13th most common cancer in the UK with approximately 8800 new diagnoses each year [1]. Despite steady improvements in treatment outcomes over the last four decades, the majority of patients present with advanced disease and 5-year survival rates remain low at round 15% [1].

The SCOPE1 (Study of Chemoradiotherapy in OesoPhageal Cancer with or without Erbitux) trial has standardised radiotherapy treatment protocols within the UK [2]. The trial was closed at the phase II stage due to higher rates of toxicity and poorer survival outcomes in patients randomised to CRT with cetuximab [3]. However the long-term outcomes have demonstrated survival rates similar to surgical studies, with a median overall survival of 34.5 months (95% CI 24.7–42.3 months) for patients treated with cisplatin/capecitabine-based CRT [4]. This has added to the growing evidence that definitive chemoradiotherapy (dCRT) is a comparable curative treatment option in selected patient groups, particularly in cases of locally advanced squamous cell carcinoma or if surgery is unfeasible due to extent of disease or patient co-morbidities [5–7].

In an era of personalised medicine, the use of robust prognostic factors is being investigated to further improve outcomes as risk-stratification at the point of diagnosis could allow an appropriate treatment strategy to be selected for the individual patient [8]. Systemic inflammation is a recognised characteristic of malignancy [9]

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and a number of inflammatory markers have been investigated as prognostic indicators in cancer patients [10,11].

One such biomarker, the neutrophil–lymphocyte ratio (NLR), has been associated with reduced survival in many solid tumours [12,13]. As the differential white cell count is regularly performed in the management of cancer patients, NLR is a relatively simple and inexpensive biomarker to implement in routine clinical practice. However it is a usual practice to only record total white blood cell (WBC) count and absolute neutrophil count (ANC) in trial databases, which may restrict the wider use of NLR in the clinical trial setting. As a result a modified version, the derived NLR (dNLR), has been developed using WBC and ANC parameters and is reported to have a similar prognostic value to NLR, using an optimal cut-off value $\geq$ 2:1 [14].

In this study, we investigated the prognostic value of dNLR on progression-free survival (PFS) and overall survival (OS) in oesophageal cancer patients treated with dCRT in the SCOPE1 (Study of Chemoradiotherapy in OesoPhageal Cancer with or without Erbitux) trial. We also aimed to identify the optimal dNLR cut-off value in this patient group.

Materials and methods

Study design and setting

The primary objective of the randomised (1:1) phase 2/3 SCOPE1 study was to compare the effect of CRT with and without cetuximab on survival in patients with oesophageal cancer deemed unsuitable for surgery. 258 patients were recruited from 36 centres in the UK between February 2008 and January 2012. The CRT regimen consisted of 2 cycles of induction cisplatin–capecitabine chemotherapy followed by a further 2 cycles given concurrently with conformal external beam radiotherapy (50 Gy in 25 fractions over 5 weeks) with or without 12 weeks of cetuximab. The SCOPE1 adhered to the rules of CONSORT; the trial design, eligibility criteria and results have been reported previously [3,15]. Written informed consent was obtained from all recruited patients. A blood sample was taken in the week prior to starting treatment in all patients enroled to the trial; WBC and ANC were documented on the case report form.

Statistical methods

All statistical analyses were pre-planned and conducted using Stata SE 14. We calculated % of total dose (actual total dose divided by protocol total dose) and % dose intensity (actual dose intensity [dose per unit time] divided by protocol dose intensity) for each protocol drug as measures of compliance. As has been done elsewhere, patients who progressed or died during the treatment period had denominators calculated up to the point where they progressed or died [16]. Likewise for radiotherapy we calculated % of full protocol dose received by each patient and for those who progressed or died during the treatment period the denominator was calculated up to the point where they progressed or died.

A derived neutrophil to lymphocyte ratio was calculated using the formula [14]:

$$\text{dNLR} = \frac{\text{ANC}}{\text{WBC} - \text{ANC}}$$

dNLR was redefined as a binary variable by finding the value from a receiver-operating characteristic (ROC) curve that maximised the percentage correctly classified for predicting survival at 24 months (the median OS found in the first analysis of SCOPE1 [3]). The balance of this binary dNLR variable across prognostic characteristics of the SCOPE1 patients was assessed using chi square tests. Kaplan–Meier's curves were used to display the prognostic value of the binary dNLR variable for different types of survival measure: overall survival (OS), progression free survival (PFS), local progression free survival inside the radiation volume (LPFSi), local progression free survival outside the radiation volume (LPFSo), and distant progression free survival (DPFS). We calculated survival from date of randomisation to when an event occurred i.e. progression or any death for PFS, and any death for overall survival. Patients who were event free were censored at the time they were last known to be event free. Univariable (the binary dNLR) and multivariable Cox regression models were used to assess the prognostic effect of dNLR on the different types of survival at two time points – pre-treatment (baseline) and following two cycles of induction chemotherapy prior to dCRT. The multivariable models included, in addition to the binary dNLR, SCOPE1 trial arm, age, reason for not receiving surgery, sex, WHO performance status at baseline, disease stage, tumour type, radiation compliance, cisplatin compliance, capecitabine compliance, and total disease length as covariates, and treating centre as a shared frailty. Additionally, a Cox model with a treatment–dNLR level interaction was used to assess whether the treatment effect differed between the two dNLR groups. In each case, the validity of the proportional hazards assumption was checked using Cox–Snell's residuals and Schoenfeld's global test.

Results

Of the 258 patients recruited into the SCOPE1 trial between February 2008 and February 2012, 257 had both pre-treatment WBC and ANC results collected and were used in these analyses. The median follow-up (IQR) was 46.2 (35.9–48.3) months for surviving patients. The distribution of dNLR was positively skewed with a median of 1.86 (IQR: 1.46–2.43, range: 0.75–26.00). The ROC analysis of the sensitivity and specificity of dNLR in predicting death within 24 months after randomisation was performed on 250 (97.2%) patients (1 patient did not have a pre-treatment dNLR available and a further 7 were lost to follow-up prior to 24 months) (Supplemental material, Fig. S1). Using ROC curve analysis, the optimal dNLR cut-off value was calculated as 2.029 (sensitivity = 55.75%, specificity = 70.07%) (Supplemental material, Fig. S1).

Patient and tumour baseline characteristics according to dNLR (<2 vs. ≥ 2) are shown in Table 1. Of the clinicopathological features analysed, sex, performance status, and total disease length were significantly associated with pre-treatment dNLR. However, if using a Bonferroni correction ($p = 0.05/11 = 0.005$), only sex was significantly associated with dNLR.

Kaplan–Meier's curves according to the pre-treatment dNLR demonstrated a survival advantage for patients with dNLR <2 (Fig. 1). Median OS was 36 months (95% CI 27.8–42.4) for patients with dNLR <2 and 18.4 months (95% CI 14.1–24.9) for patients with dNLR ≥ 2. An elevated dNLR ≥ 2 was significantly associated with a decreased OS in both univariable analysis (HR 1.74 [95% CI 1.29–2.35], $p < 0.001$) and multivariable analysis (HR 1.64 [1.17–2.29], $p = 0.004$) (Table 2). In subgroup analysis, dNLR ≥ 2 was an independent prognostic factor for poor OS in patients with squamous cell carcinoma (HR = 2.06, 95% CIs: 1.25–3.41, $p = 0.005$) but the evidence was weaker for adenocarcinoma/undifferentiated tumours (HR = 2.52, 95% CIs: 0.88–7.23, $p = 0.085$) for whom the sample size was smaller (Supplemental material, Table S1). PFS, LPFSi, LPFSo and DPFS were all significantly reduced in patients with dNLR ≥ 2 in both univariable and multivariable analyses (Fig. 1; Supplemental material Table S1).

In the analysis of OS according to arm allocation within the SCOPE1 trial, dNLR was not predictive for treatment effect (Fig. 2, Table 3). The addition of cetuximab to CRT was not associated with

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