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ORIGINAL RESEARCH

Does Neutrophil-to-Lymphocyte Ratio (NLR) Predict Pathologic Response to Neoadjuvant Chemoradiotherapy in Patients with Esophageal Squamous Cell Carcinoma?

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Abstract

Background Neoadjuvant chemoradiotherapy (nCRT), followed by surgery, is the current standard of care for patients with locally advanced esophageal squamous cell carcinoma. However, up to 30% of the patients do not respond to nCRT. Hence, a simple, cost-effective marker to predict response before initiation of nCRT is needed. Neutrophil-to-lymphocyte ratio (NLR) has been reported as a prognostic marker in various cancers. However, its role as a predictive marker in patients with esophageal SCC planned for nCRT has not been prospectively analyzed.

Materials and Methods All consecutive patients with locally advanced (T1N1 and T2–T4a with or without nodal involvement) SCC planned for nCRT (CROSS protocol) followed by esophagectomy with total two field lymphadenectomy between December 2013 and December 2019 were included in this prospective analytical cohort study. NLR was calculated 1 week before starting the nCRT and was correlated with the histopathological response [Mandard tumor regression grade (TRG)].

Results Of the 216 patients with esophageal cancer evaluated during the study period, 57 patients with SCC who fulfilled the inclusion criteria were included. A good pathologic response (TRG 1 and 2) to nCRT was seen in 28 (49.1%) patients. Using a ROC curve, the optimal cutoff value of pretherapy NLR for predicting good pathologic response was 2.33. With an NLR cutoff value of 2.33, 53.3% of patients had a good pathologic response to nCRT compared with 47.6% patients with NLR ≥ 2.33 (P = 0.77).

Conclusion In patients with locally advanced esophageal SCC, NLR is not a useful marker to predict pathologic response to nCRT.

Keywords Neutrophil-to-lymphocyte ratio · Esophageal cancer · Neoadjuvant therapy · Squamous cell carcinoma

Introduction

Multimodality treatment involving neoadjuvant therapy followed by surgery is the preferred approach for locally advanced esophageal cancer to reduce locoregional recurrence and distant metastasis [1]. However, nearly one-third of eligible patients do not respond to neoadjuvant therapy. These subsets of patients have a poor long-term outcome [1, 2]. Predicting response before initiation of neoadjuvant therapy can spare nonresponders from treatment-related toxicity and unnecessary delay in surgery. While multiple predictive biomarkers are evaluated, the majority require complex assay and not suitable for routine clinical practice [3, 4]. Hence, a simple, cost-effective marker to predict response before initiation of neoadjuvant therapy is needed.

Interaction between cancer and inflammatory cells is increasingly reported and neutrophil-to-lymphocyte ratio (NLR) is the widely evaluated inflammatory marker that has prognostic value in various cancer [5–8]. As neutrophil is a primary source of vascular endothelial growth factor (VEGF), neutrophilic infiltration of the tumor and an elevated NLR has been postulated to promote tumor growth and distant metastasis [9]. Recent meta-analyses have reported that high NLR was associated with poor overall survival in patients with esophageal carcinoma [10, 11]. However, its role in predicting

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response to neoadjuvant therapy has not been well studied. A few studies that have analyzed the significance of NLR in predicting response to neoadjuvant therapy have limitations like retrospective study design, use of only chemotherapy as the neoadjuvant therapy regimen, and inclusion of both adenocarcinoma and squamous cell carcinoma (SCC) [12–14]. Since the publication of CROSS trial, neoadjuvant chemoradiotherapy (nCRT) has been regarded as the standard treatment of esophageal cancer, especially SCC of the esophagus [15]. Also, recent studies have shown that neutrophil is not a homogeneous population of cells; its subpopulation can have both protumor and antitumor activity [16, 17]. These subpopulations can show transition and their function is determined by chemokines in the tumor microenvironment. As the predictive value of NLR has not been prospectively evaluated in esophageal SCC, this study was conducted to determine whether the pretreatment NLR is a predictive marker for the pathologic response to nCRT.

Materials and Methods

A prospective study of patients with locally advanced SCC of the esophagus eligible for nCRT followed by esophagectomy with a total two-field lymphadenectomy during the study period from December 2013 to December 2019 (Table 1). The study was approved by the institute scientific advisory and ethics committee. In patients with endoscopic biopsy-proven SCC, the preoperative staging was done with contrast-enhanced computed tomography (CT) neck, thorax, and abdomen. Till December 2018, positron emission tomography (PET) was selectively performed in patients with T3/T4a tumor and extensive regional lymphadenopathy. Since January 2019, PET was performed in all patients planned for nCRT. Endoscopic ultrasound was not used for staging. In patients who fulfilled the inclusion criteria, three sets of blood samples on three consecutive days were withdrawn 1 week before initiation of nCRT to determine the pretreatment absolute neutrophil and lymphocyte count. The NLR was calculated by dividing the average neutrophil and the lymphocyte count obtained from three samples. nCRT was given as per CROSS protocol that includes 5 cycles of weekly administration of carboplatin and paclitaxel and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) [15]. The clinical response to nCRT was assessed by improvement in dysphagia (Takita's dysphagia grade) [18]. Response assessment CT was done after 4–6 weeks and surgery was done 6–12 weeks after completion of nCRT. The radiological response was evaluated using response evaluation criteria in solid tumors (RECIST) version 1.1 [19]. Demographic characteristics, clinical features, endoscopic, and radiological findings of the patients were noted at baseline and following nCRT.

Table 1 Eligibility criteria for inclusion in the study

Inclusion criteria

Patients with locally advanced (T1N1 and T2–T4a with or without nodal involvement) squamous cell carcinoma planned for nCRT followed by esophagectomy with total two-field lymphadenectomy with the following:

Age 18 years or older and less than 75

Adequate hematological, renal, hepatic, and pulmonary functions as defined by the following:

- Absolute neutrophil count (ANC) more than 1.5×10^9/L
- Platelet count > 100×10^9/L
- Total bilirubin less than1.5 × upper normal (< 1.8 mg/dL)
- Alanine aminotransferase (ALT) less than 2.5 × upper normal limits (< 125 IU/L)
- Pulmonary: FeV1 > 1 l
- Renal (serum creatinine < 1.5 mg/dL or creatinine clearance > 60 mL/min)

An ECOG performance status score of 2 or less

Exclusion criteria

- Patients with upper border of tumor within 5 cm from upper esophageal sphincter
- Patients with adenocarcinoma
- Patients with active infection or treated for infection in the last 2 weeks
- Patients with autoimmune disorders
- Patients on steroids
- Women who are pregnant or lactating
- Previous radiotherapy to the area to be treated
- Previous chemotherapy
- Contraindication to nCRT treatment protocol
- Underwent non curative (R1 or R2) resection
- Patients with clinical evidence of metastatic disease

The minimally invasive approach was used in all patients included in the study. We have previously reported our technique of minimally invasive esophagectomy and the lymph node stations removed in total two-field lymphadenectomy [20]. Thoracic duct excision was selectively performed in patients with bulky anterior thoracic paraaortic (112aoA), left recurrent laryngeal nerve (106 rec), and middle thoracic (108) paraesophageal nodes as previously reported by us to ensure total mediastinal lymphadenectomy [21]. The stomach was used as a conduit in all patients and was pulled up through posterior mediastinum for single stapled cervical esophagogastric anastomosis. For histopathological examination, multiple (minimum ten) sections were examined from the tumor area in patients without obvious residual tumor and complete tumor tissue was studied in patients with residual tumor. Pathologic response was assessed according to Mandard tumor regression grade (TRG) [22]. TRG 1 (complete regression) suggests complete pathologic response (no residual tumor cells); TRG 2 was characterized by the rare residual cancer cells scattered through the fibrosis; TRG 3

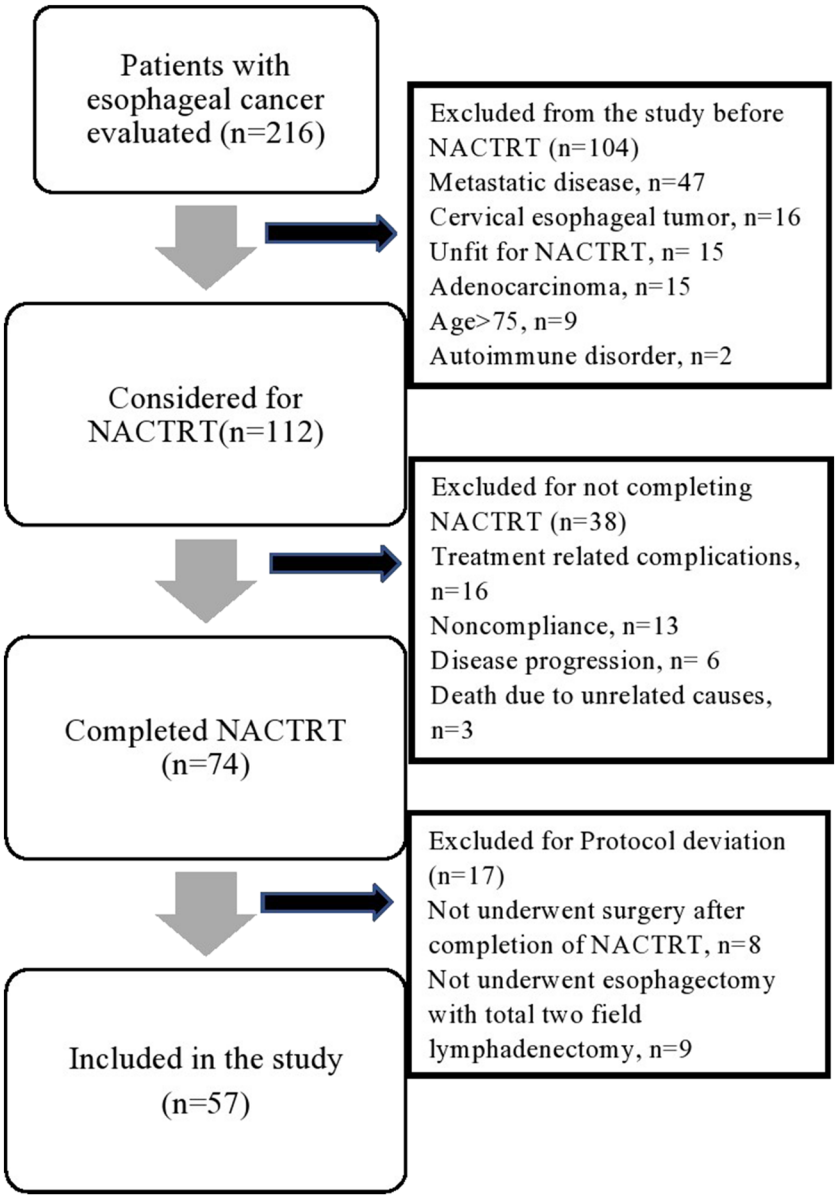

Fig. 1 Flowchart of patient allocation in the study

was characterized by an increase in the number of residual cancer cells, but fibrosis still predominated; TRG 4 showed residual cancer outgrowing fibrosis; and TRG 5 was characterized by absence of regressive changes. For analysis, TRG 1 and 2 are categorized as a good response (responders) and TRG 3 to 5 is classified as a poor response (nonresponders). The tumor was staged according to the eighth edition of TNM classification (AJCC staging) [23]. Patients included in the study before the publication of the eighth edition was restaged as per the current classification.

The data was entered and analyzed in Statistical Package for the Social Sciences (SPSS) version 19 (IBM, Armonk, New York, USA). Normality of the data was assessed by Shapiro-Wilk test. Quantitative variables were expressed as mean ± standard deviation. Categorical variables were summarized as proportions. A receiver operating characteristic (ROC) curve was plotted to determine the optimal cutoff value of preoperative NLR that predicts a pathologic response to nCRT. The association of NLR to pathologic response was assessed by the McNemar test. Analyses involving quantitative variables were done with student's *t* test. Categorical variables were compared using chi-square test. All statistical analysis was carried out at 5% level of significance and *P* value < 0.05 was considered as significant.

Results

During the study period, 216 patients with esophageal cancer were evaluated. Of them, 57 patients who fulfilled the

Table 2 Demographic, clinical, and pathological features of patients with squamous cell carcinoma included in the study ($n = 57$)

Parameter	Value
Age (mean ± SD), years	53.6± 11.5
Sex (male: female)	1.3:1
BMI (mean ± SD), Kg/m^2	17.3± 3.9
Symptoms at presentation, *n* (%)	
Dysphagia	57 (100)
Loss of appetite	40 (70)
Loss of weight	49 (86)
Cough	10 (18)
Chronic smoking, *n* (%)	19 (33.3)
Chronic alcohol intake, *n* (%)	23 (40.4)
ECOG* performance status, *n* (%)	
One	34 (59.6)
Two	23 (40.4)
Location of tumor, *n* (%)	
Upper thoracic	8 (14.0)
Middle thoracic	24 (42.1)
Lower thoracic	25 (43.9)
Clinical TNM stage, *n* (%)	
Stage II	13 (22.8)
Stage III	42 (73.7)
Stage IVa	2 (3.5)
Grade of tumor, *n* (%)	
Well differentiated (G1)	9 (15.8)
Moderately differentiated (G2)	35 (61.4)
Poorly differentiated (G3)	13 (22.8)
Postneoadjuvant therapy (ypTNM) stage, *n* (%)	
T0N0M0 (stage I)	20 (35.1)
T1N0M0 (stage I)	8 (14.0)
T2N0M0 (stage I)	3 (5.3)
T3N0M0 (stage II)	4 (7.0)
T0N1M0 (stage IIIA)	8 (14.0)
T1N1M0 (stage IIIA)	1 (1.8)
T2N1M0 (stage IIIA)	2 (3.5)
T3N1M0 (stage IIIB)	7 (12.3)
T2N2M0 (stage IIIB)	2 (3.5)
T3N2M0 (stage IIIB)	1 (1.8)
T4N2M0 (stage IVa)	1 (1.8)

*ECOG—Eastern Co-operative Oncology Group

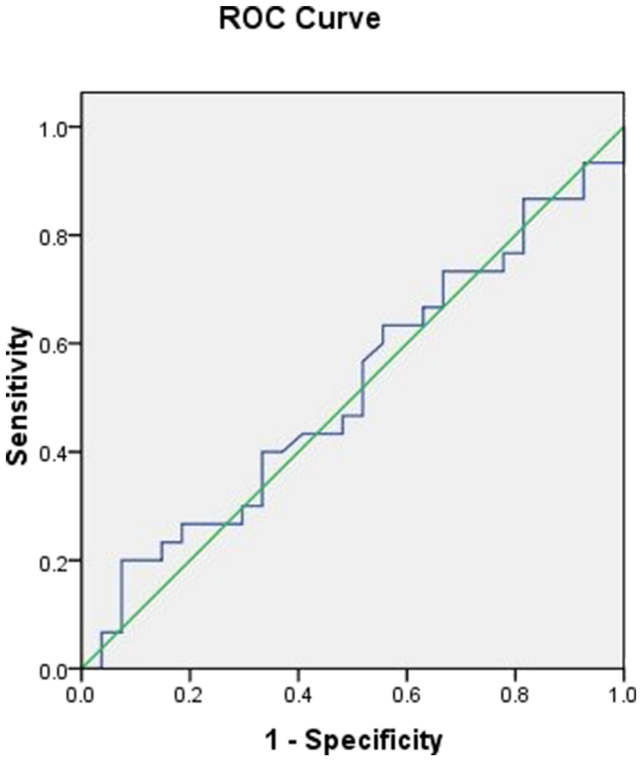

Fig. 2 Receiver operating characteristic (ROC) curve identified an optimal neutrophil-to-lymphocyte ratio (NLR) cutoff value of 2.33 for predicting pathologic response with a sensitivity of 78% and specificity of 37.5%. Area under curve = 0.515

inclusion criteria were included in the study (Fig. 1). Chemotherapy related complications precluded completion of nCRT in 16 patients and three patients died of chemotherapy-related toxicity. Thirteen patients could not complete nCRT due to lack of family support (noncompliance), and six patients had disease progression due to delay in the initiation of nCRT. Eight patients refused to undergo definitive surgery due to significant symptom relief. The demographic profile and clinicopathological features of 57 patients included in the study are summarized in Table 2. Ten patients who had signs of lower respiratory tract infection were treated with antibiotics and blood samples for determination of NLR were taken after the resolution of symptoms. The mean (± SD) total leukocyte count of patients before initiation of nCRT was 8560.18 (3123) cells/mm^3. The mean (± SD) baseline lymphocyte count was 1978 (748.63) cells/mm^3. Only one patient had lymphocytopenia of less than 1000 cells/mm^3. The mean (± SD) pretherapy NLR was 3.02 (1.15) and ranged between 1.44 and 7.87.

Of the 42 patients with high-grade dysphagia (Takita's grades III–VI), 24 patients had symptomatic improvement (Takita's grades I–II) after nCRT. Radiological response (complete and partial) was observed in 41 (71.9%) patients. The mean (± SD) interval between completion of nCRT and esophagectomy was 62 (31) days. Of the 57 patients, 28 (49.1%) patients had a good pathologic response to nCRT. Using a ROC curve, the optimal cutoff value of pretherapy NLR for predicting good pathologic response was 2.33 (Fig. 2). With the NLR cutoff value of 2.33, 53.3% of patients had a good pathologic response to nCRT compared with 47.6% patients with NLR ≥ 2.33 (Table 3). On univariate analysis, age, gender, differentiation, location of the tumor, total leukocyte count, NLR, and post-nCRT duration did not

Table 3 Prediction of the pathologic response using the pretreatment neutrophil-lymphocyte ratio (NLR)

NLR	Number of patients, *n*	Responders, *n* (%)	Nonresponders, *n* (%)	*P* value
NLR < 2.33	15	8 (53.3)	7 (46.7)	0.77
NLR ≥ 2.33	42	20 (47.6)	22 (52.4)	

show any statistically significant difference between pathologic responders and nonresponders (Table 4). However, early clinical stage tumors had a statistically significant better response rate when compared with the advanced-stage tumor.

Discussion

The results of the present study suggest that NLR does not predict pathologic response to nCRT in patients with locally advanced SCC of the esophagus. In the CROSS trial, the pathologic response rate was more in SCC compared with adenocarcinoma [15]. Also, the clinical response does not correlate with the pathologic response rate [20]. Hence, nCRT, followed by surgery, has been regarded as a standard of care even in patients with apparent complete clinical response. However, one-third of eligible patients have a poor response to nCRT. In the present series, 78% of patients had clinical stage III/IV tumors. In post-nCRT, 38% of patients had stage III/IV tumors. In this subset of patients with poor response, nCRT is detrimental due to its toxicity and undue delay in surgery. Despite the better safety profile of the CROSS regimen, 16 out of 112 eligible patients experienced severe nCRT-related complications underscoring the need for appropriate patient selection. Hence, numerous clinical, biochemical, and molecular predictive markers have been evaluated to tailor therapy in an individual patient with esophageal cancer [3, 4]. Molecular markers, although promising, require an expensive and labor-intensive analysis. Hence, there is a need to identify a simple marker that can be derived from routine preoperative investigations.

Inflammatory markers are known to influence tumor progression and NLR is the widely studied inflammatory marker [16, 17]. High NLR is associated with poor overall survival in various cancers like colorectal cancer, gastric cancer, ovarian cancer, and breast cancer [5–8]. Two recent meta-analyses in esophageal cancer reported that elevated NLR is a poor prognostic factor adversely affecting overall and disease-free survival [10, 11]. The protumor effects of neutrophilic activation are due to the production of VEGF and cytokines like IL-6 and TNF that promote tumor growth and metastasis [9]. Also, neutrophilic infiltration of the tumor is known to interfere with T cell activation and function of natural killer cell by the production of reactive oxygen species and enzymes such as arginase 1 [17].

In contrast to its prognostic role, the role of NLR in predicting response to nCRT has not been well studied. Miyata et al. retrospectively analyzed 152 patients with esophageal cancer who underwent surgery after neoadjuvant chemotherapy [12]. There was no significant relationship between response to chemotherapy and NLR. However, Sato et al., in their retrospective study, observed 56% pathologic response in patients with an NLR of < 2.2, compared with 21% in patients with an NLR ≥ 2.2 ($P = 0.001$) [13]. Recently, Powell et al. reported that esophageal adenocarcinoma patients with NLR > 2.25 had poor pathologic response [14]. The conflicting results in the published studies could be due to retrospective study design, the inclusion of patients with SCC and adenocarcinoma, heterogeneity in the neoadjuvant treatment regimen, and the surgical approach. As neutrophils and lymphocytes are easily influenced by infections and inflammation, it is challenging to control these confounding

Table 4 Univariate analysis of variables for the pathologic response to nCRT in patients with locally advanced SCC of the esophagus ($n = 57$)

Variable	Responders ($n = 28$)	Nonresponders ($n = 29$)	*P* value
Age, mean ± SD	51.2 ± 11.46	56.3 ± 9.36	0.12
Gender (male/female), *n*	16/12	16/13	1.00
Level of growth (upper/middle/lower thoracic), *n*	3/10/15	5/14/10	0.34
Pre-nCRT serum albumin (gm/dL), mean ± SD	3.5 ± 0.18	3.4 ± 0.52	0.74
Pre-nCRT white blood cell count (cells/mm^3), mean ± SD	8505 ± 2861	8768 ± 3440	0.71
Pre-nCRT neutrophil-lymphocyte ratio (NLR), mean ± SD	2.9 ± 1.1	3.1± 1.3	0.52
Clinical stage (II/III/IVa), *n*	10/18/0	3/24/2	0.02
Grade of tumor (G1/G2/G3), *n*	4/18/6	5/17/7	0.90
Interval between completion of nCRT and esophagectomy (days), mean ± SD	56.5 ± 20.1	67.1± 25.5	0.16

factors in a retrospective study. In the present series, 18% of patients had evidence of respiratory tract infection at presentation and only blood samples taken after control of active infection were included for the analysis. Also, in contrast to the present series, timing of blood samples for NLR determination in relation to nCRT was not uniform in the previously reported studies. Only patients who underwent esophagectomy with a total two-field lymphadenectomy were included in the analysis to determine true pathologic complete response. As previously reported, patients with a complete response of the primary tumor can still have lymph node metastasis and prognosis in these patients is poor compared with patients with true complete pathologic response [20]. Hence, in the present AJCC tumor staging patients with ypT0N1 tumor is classified as stage III disease [23]. As the recurrent laryngeal group of lymph nodes is an important site of metastasis in patients with SCC, its dissection is essential for accurate staging and determination of true pathologic response [24].

The conflicting results of the studies correlating NLR to the response to neoadjuvant therapy in patients with esophageal cancer could be explained by recent research, which suggests that neutrophils play both pro- and antitumor role in the cancer microenvironment [17]. The neutrophils can be divided into N1 antitumor and N2 protumor subpopulation. Antitumor effects are mediated by Granzyme B and MET signaling [25, 26]. These subpopulations can show transition and their function is determined by chemokines in the tumor microenvironment. Also, whether serum levels of neutrophils and lymphocytes reflect their levels in the tumor microenvironment is not clear. Hence, the role of the systemic inflammatory response and inflammatory markers like NLR in determining response to nCRT requires further research.

The limitation of the present study is the small sample size. Despite the limitation, this is the first study to prospectively analyze the role of NLR in predicting response to nCRT in patients with locally advanced SCC of the esophagus. The strengths of the study are standardized sample collection for calculation of NLR, use of uniform nCRT protocol, the inclusion of single histological type (SCC), uniform surgical approach, and extent of lymphadenectomy. Although NLR is proposed as an exciting and inexpensive predictive marker, the results of the present study suggest that it is not a reliable marker to predict pathologic response to nCRT in patients with SCC of the esophagus. The results of the present study highlight the importance of prospective study design in determining the role of NLR in patients with esophageal cancer.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen M, Wijnhoven BPL, van Laarhoven H, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, ten Kate F, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen M, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij C, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, CROSS study group; CROSS study group (2015). Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 16:1090–1098.
2. Sjoquist KM, Burmeister BH, Smithers BM, et al; Australasian Gastro-Intestinal Trials Group. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12:681–92.
3. Chiam K, Mayne GC, Watson DI, Woodman RJ, Bright TF, Michael MZ, et al. Identification of microRNA biomarkers of response to neoadjuvant chemoradiotherapy in esophageal adenocarcinoma using next generation sequencing. Ann Surg Oncol. 2018;25:2731–8.
4. Wong C, Law S. Predictive factors in the evaluation of treatment response to neoadjuvant chemoradiotherapy in patients with advanced esophageal squamous cell cancer. J Thorac Dis. 2017;9:S773–80.
5. Carruthers R, Tho LM, Brown J, Kakumanu S, McCartney E, McDonald AC. Systemic inflammatory response is a predictor of outcome in patients undergoing preoperative chemoradiation for locally advanced rectal cancer. Color Dis. 2012;14:e701–7.
6. Kim YJ, Lee I, Chung YS, Nam EJ, Kim S, Kim SW, et al. Pretreatment neutrophil-to-lymphocyte ratio and its dynamic change during neoadjuvant chemotherapy as poor prognostic factors in advanced ovarian cancer. Obstet Gynecol Sci. 2018;61:227–34.
7. Liu D, Huang Y, Li L, Song J, Zhang L, Li W. High neutrophil-to-lymphocyte ratios confer poor prognoses in patients with small cell lung cancer. BMC Cancer. 2017;17:882.
8. Clarke KV, Amir E, Berman HK, Maganti M, Sridhar SS. Association between pretreatment neutrophil to lymphocyte ratio (NLR) and complete pathological response (pCR) in breast cancer patients treated with neoadjuvant chemotherapy (NACT). J Clin Oncol. 2015;33:e11588.
9. Kusumanto YH, Dam WA, Hospers GA, et al. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis. 2003;6:283–7.
10. Pirozzolo G, Gisbertz SS, Castoro C, van Berge Henegouwen MI, Scarpa M. Neutrophil-to-lymphocyte ratio as prognostic marker in esophageal cancer: a systematic review and meta-analysis. J Thorac Dis. 2019;11:3136–45.
11. Zhang X, Jiang Y, Wang Y, Wang Z, Zhao L, Xue X, et al. Prognostic role of neutrophil-lymphocyte ratio in esophageal cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2018;97:e13585.
12. Miyata H, Yamasaki M, Kurokawa Y, et al. Prognostic value of an inflammation-based score in patients undergoing pre-operative chemotherapy followed by surgery for esophageal cancer. Exp Ther Med. 2011;2:879–85.
13. Sato H, Yasuhiro T, Kawano T. Correlation between the pretherapeutic neutrophil to lymphocyte ratio and the pathologic response to neoadjuvant chemotherapy in patients with advanced esophageal cancer. World J Surg. 2012;36:617–22.
14. Powell AGMT, Chin C, Coxon AH, Chalishazar A, Christian A, Roberts SA, et al. Neutrophil to lymphocyte ratio as a predictor of

response to neoadjuvant chemotherapy and survival in oesophageal adenocarcinoma. BJS Open. [Epub ahead of print]. 2020;4:416–23.
15. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen M, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.
16. Sagiv JY, Michaeli J, Assi S, Mishalian I, Kisos H, Levy L, et al. Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. Cell Rep. 2015;10:562–73.
17. Giese MA, Hind LE, Huttenlocher A. Neutrophil plasticity in the tumor microenvironment. Blood. 2019;133:2159–67.
18. Peters JH, Meester TR, Stein HJ. Surgical therapy for cancer of the esophagus and cardia (1995). In: Castell DO; Ed. The Esophagus, 2nd ed. New York: Little, Brown. p.293–335.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
20. Sasikumar K, Kalayarasan R, Gnanasekaran S, et al (2020). Minimally invasive oesophagectomy with a total two-field lymphadenectomy after neoadjuvant chemoradiotherapy for locally advanced squamous cell carcinoma of the oesophagus: a prospective study. J minim access Surg Jan 9 [Epub ahead of print].
21. Anand S, Kalayarasan R, Chandrasekar S, Gnanasekaran S, Pottakkat B. Minimally invasive esophagectomy with thoracic duct resection post neoadjuvant chemoradiotherapy for carcinoma esophagus-impact on lymph node yield and hemodynamic parameters. J Gastrointest Cancer. 2019;50:230–5.
22. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic Correlations Cancer. 1994;73:2680–6.
23. Amin MB, Edge S, Greene F, et al. (Eds.). AJCC cancer staging manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017.
24. Miyata H, Sugimura K, Yamasaki M, Makino T, Tanaka K, Morii E, et al. Clinical impact of the location of lymph node metastases after neoadjuvant chemotherapy for middle and lower thoracic esophageal cancer. Ann Surg Oncol. 2019;26:200–8.
25. Martin A, Seignez C, Racoeur C, Isambert N, Mabrouk N, Scagliarini A, et al. Tumor-derived granzyme B-expressing neutrophils acquire antitumor potential after lipid a treatment. Oncotarget. 2018;9:28364–78.
26. Finisguerra V, Di Conza G, Di Matteo M, et al. MET is required for the recruitment of anti-tumoural neutrophils. Nature. 2015;522:349–53.