Original Article

The volume of low-dose thoracic irradiation influences systemic inflammation-immunity status after chemoradiation in esophageal cancer

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Background: Definitive chemoradiation is an essential treatment for non-operative thoracic esophageal cancer. However, it may trigger radiation-induced lymphopenia, impacting survival outcomes. The neutrophil-lymphocyte ratio (NLR) is an indicator of inflammatory status and survival outcomes. Here, we determined the association of clinical and dosimetric parameters with changes in hematological variables.

Methods: We recruited 93 thoracic esophageal squamous-cell cancer patients who have completed definitive concurrent chemoradiotherapy (CCRT) between 2010 and 2015. Clinical, dosimetric, and hematological data, including absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and NLR, were analyzed at baseline and during CCRT. Cox regression model and Kaplan-Meier analyses were used to analyze different survival outcomes. Associations between clinical, hematological, and dosimetric variables were determined using Spearman's rank or Pearson correlation coefficients, and a multivariable logistic regression was used to verify identified correlations.

Results: Patients (mean age =58.6 y) were predominantly males (94%), 27% of which were stage II (n=25) and 73% were stage III (n=68), with a median overall survival (OS) of 13 months [95% confidence interval (CI): 10.304–15.696]. Baseline NLR (NLR-b) and highest NLR during CCRT (NLR-h) was significantly correlated with OS, progression-free survival (PFS), disease-specific survival (DSS), and freedom from distant metastasis (FFDM). Dichotomized NLR-b, >3.68 or ≤3.68, was also correlated with survival. Primary esophageal tumor length (Spearman's r=0.324, P=0.011) and baseline body weight (Spearman's r=–0.251, P=0.019) were significantly correlated with NLR-b >3.68. In multivariable logistic regression, primary esophageal tumor length (OR =1.345, P=0.021) was associated with a higher NLR-b. Lung V5 (Pearson r=0.254, P=0.014) and V10 (Pearson r=0.317, P=0.002) were significantly correlated with NLR-h. Lung V5 (Pearson r=0.299, P=0.005) and heart V10 (Pearson r=0.273, P=0.011) were significantly correlated with the decrease in ALC during CCRT.

Conclusions: Status of inflammation is correlated with survival outcomes and tumor size, and low-dose thoracic irradiation affects inflammation-immunity dynamics. A novel approach that decreases unnecessary exposures to radiation may further improve survival outcomes in esophageal cancer treated with CCRT.

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Keywords: Inflammation; lung dose; cardiac dose; esophageal cancer; chemoradiation

Received: 07 December 2020; Accepted: 07 May 2021; Published: 30 June 2021.
doi: 10.21037/tro-20-62
View this article at: http://dx.doi.org/10.21037/tro-20-62

Introduction

For inoperable locally advanced disease, concurrent chemoradiotherapy (CCRT) used according to the Radiation Therapy Oncology Group 85-01 protocol is the standard therapy (1). Although ionizing radiation or radiation therapy (RT) is mandatory for local control, the lung and heart are two critical organs that are impacted during thoracic radiation. A majority of the thoracic volume is irradiated especially during intensity-modulated radiotherapy, although techniques involving the use of multiple fields during RT expose the lungs and heart to a low dose of radiation (2). Radiation dose-volume effects in the lung, such as radiation pneumonitis, are well known (3,4), and radiation dose-volume may also independently impact survival outcomes (5-7). Cardiac irradiation is also correlated with heart disease, especially ischemic events, and may occur earlier than historically understood (8-11). There is also evidence correlating the dosage of cardiac irradiation with survival (12,13). In addition to affecting the gross tumor and organs, radiation also impacts the adjacent microenvironment (14,15); immune cells surrounding the gross tumor, stromal cells, and adjacent vasculature are also affected by different doses of RT (16).

Lymphopenia and prognosis have been established to have a clinical correlation (17). A model has been proposed to estimate the effective dose of RT experienced by circulating immune cells after administration of CCRT for esophageal cancer, and it also provides the mean lung dose, mean heart dose, mean liver dose, and integral dose of the scanned body region. It demonstrated the correlation between a higher effective dose and grade 4 lymphopenia (18). Although lymphopenia is also triggered by cytotoxic chemotherapy, it is commonly seen after the administration of RT and is associated with the recurrence of and mortality in several solid tumors (19). Although the dose of cardiac irradiation is associated with immunosuppression and even poor survival in patients with lung cancer (12), the exact correlation between different doses and pathological changes in each organ, especially the lung, which is the largest thoracic organ, and the heart, which circulates the entire blood volume, during administration of CCRT for esophageal cancer has not been reported.

Systemic inflammation-immunity, evaluated in terms of the neutrophil-lymphocyte ratio (NLR), has been correlated with prognosis in esophageal cancer (20-22). NLR is an easy tool to understand inflammation-immunity dynamics at various time periods. We hypothesized that the volume of the two largest organs irradiated during thoracic irradiation contributes to changes in general inflammation-immunity conditions. The heart also circulates the entire volume of blood, and therefore, circulating immune cells are also irradiated during treatment. Lymphocytes are most vulnerable to irradiation (23,24) and are critical anti-tumor immune cells (25,26); therefore, we hypothesized that the volume of irradiated heart may affect lymphocyte counts during treatment. In this study, we investigate the association between survival outcomes and inflammation and determine the possible correlation between patient characteristics, during the pretreatment and the treatment period, and relevant dosimetric parameters. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tro-20-62).

Methods

Patient characteristics and study design

We retrospectively selected 93 patients from the Changhua Christian Hospital with non-metastatic thoracic esophageal cancer, who were treated with non-surgical treatments including definitive RT with or without induction, concurrent, and adjuvant chemotherapy. All patients were diagnosed between January 2010 and December 2015. Patients who had received a complete course of RT, with a median total radiation dose of 59.4 (range: 48.6–72) Gy and standard daily fractionation (1.8–2.0 Gy per fraction), were included in the study, and they had undergone complete blood count (CBC) tests during different periods of interest. All patients had esophagogastroduodenoscopy

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(EGD) biopsy-proven squamous-cell carcinoma, and we directly measured the gross tumor size under the scope. We used the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM classification system for staging using chest CT scans. Bronchoscopy was optionally used to evaluate the trachea if there was any suspicion of direct invasion based on the chest CT scan. A metastatic survey with whole-body F-18 fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT), Tc99m methylene diphosphonate bone scan, or abdominal sonography was also used, if it was part of the initial or further follow-up workup based on the physician's decision. Patients with any other cancer that was diagnosed or treated before this cancer, and those with synchronous cancer, were excluded. The age-adjusted Charlson comorbidity index (ACCI) score (27,28) was calculated (current esophageal cancer diagnosis not included) to estimate the 10-year pre-treatment risk of mortality. Treatment-related toxicities were graded using the Common Terminology Criteria for Adverse Events, version 4.0. After treatment, we used chest CT scans and EGD every 3–6 months to evaluate local, regional, and distant recurrences, in combination with the study of any other metastatic disease if needed.

Patient follow-up was updated and censored on February 29, 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Changhua Christian Hospital (CCH IRB No. 180310), and individual consent for this retrospective analysis was waived because the research presented no more than minimal risk.

Radiation treatment and dosimetric analysis

The target volume for RT consisted of the primary tumor, lymphadenopathy, and an additional 1-centimeter circumferential margin and a 3- to 5-centimeter longitudinal margin. Elective nodal irradiation is also be included in the target volume based on the physician's discretion. The target volume and critical organ at risk, such as the heart and lungs, were reviewed and recontoured (if needed) without adding a margin to each organ. Further dosimetric analysis was performed by a dosimetrist and reviewed by a physician. The analysis was performed on all patients, with available RT plans on the pinnacle treatment planning system (Pinnacle Treatment Planning/Philips Radiation Oncology Systems, Fitchburg, WI, USA). The dose-volume histogram parameter was identified as Vx (%) because the heart and lungs received a dose of RT relative to their percent volume for at least x (Gy). The mean dose was also evaluated.

Chemotherapy regimen

Patients received induction, sequential, or concurrent chemotherapy with radiotherapy based on the patients' general condition and physician's discretion. Concurrent chemotherapy was strongly recommended, and patients were provided sequential chemotherapy only if they exhibited poor performance with concurrent chemotherapy. The chemotherapy regimen involved intravenous administration of 75 mg/m^2 of cisplatin on the first day followed by the continuous infusion of fluorouracil, 1,000 mg/m^2 in the next four days in each session. Chemotherapy was repeated every 4 weeks for four cycles, and if patients exhibited a creatinine clearance rate <60 mL/min, carboplatin was used instead of cisplatin. CCRT with weekly cisplatin was only performed if the patient could not tolerate the above regimen. One to two cycles of induction chemotherapy, consisting of the same regimen as the concurrent chemotherapy, was used to reduce disease burden before initiation of radiation.

Hematological parameters

We estimated baseline absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) before the commencement of any treatment, including induction chemotherapy or CCRT. The ALC nadir was determined to be the lowest ALC recorded during RT. NLR refers to the ratio of ANC to ALC, and this was recorded prior to the commencement of treatment, as the baseline NLR (NLR-b), and for the highest NLR during CCRT (NLR-h), i.e., the day with the lowest ALC during RT.

Statistical analysis

Data continuously recorded are presented as median and range, whereas categorical data are presented as numbers and percentages. Clinical endpoints consisted of overall survival (OS), progression-free survival (PFS), disease-specific survival (DSS), freedom from distant metastasis (FFDM), and freedom from locoregional recurrence (FFLR). Follow-up time and time of recording clinical endpoints were calculated from the date of diagnosis. OS is defined as the time until death. PFS is defined as time until

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the patient is clinically or radiologically suspected to have encountered locoregional recurrence or distant metastasis or death, whichever came first. DSS is defined as death from tumor progression or related complications. FFDM or FFLR is defined as the time until distant metastasis or locoregional recurrence, respectively. Patients who did not experience locoregional recurrence or distant metastasis were censored at the date of the last follow-up.

A Cox regression model was used to analyze the relationship between NLR-b with OS and NLR-h with OS. The median NLR-b (3.68) was chosen as the threshold to dichotomize continuous numerical data and to increase specificity. OS, PFS, DSS, FFDM, and FFLR rates were estimated using Kaplan-Meier analyses by log-rank test to calculate the significance of survival estimate differences. To test the possible relationships between the NLR-b and clinical variables, we used Spearman's rank correlation coefficient. A multivariate logistic regression model was used to analyze the correlations between variables, identified using Spearman's rank correlation, and NLR-b. In addition, we used the Pearson correlation coefficient to find a possible correlation of NLR-h and decreased ALC percentage with dosimetric parameters of the normal organ. A P value of ≤0.05 was considered significant. Hazard ratios and odds ratios were reported with a 95% confidence interval (CI). All tests were performed using IBM® SPSS®, version 26 (SPSS IBM, Armonk, NY, USA).

Results

Treatment modalities, patient outcome, and cause of death

Patient and tumor characteristics are summarized in *Table 1*, and the treatment modalities are summarized in *Table 2*. Most patients underwent a PET/CT (74%) as part of their initial staging and workup. All patients were diagnosed with squamous-cell carcinoma, and majority of them had grade II squamous-cell carcinoma (69%). Various radiation techniques were used, consisting of either three-dimensional conformal RT (3D-CRT) (23.7%), intensity-modulated RT (IMRT) (43%), or volumetric-modulated arc therapy (33.3%). More than one-quarter (27.9%) of patients also received online cone-beam CT-based imaging correction, such as image-guided RT, before treatment. The median prescribed dose was 59.4 (range: 48.6–72) Gy.

Almost all patients (97.9%) received concurrent chemotherapy with RT, and only two patients received chemotherapy and RT sequentially. More than half (52.7%) of the patients received induction chemotherapy before CCRT. The chemotherapy regimen comprised triweekly administration of cisplatin and fluorouracil (96%). Patients received induction chemotherapy (range: 0–2 cycle, median: 1 cycle) and concurrent chemotherapy with radiotherapy (range: 0–2 cycle, median: 1 cycle), based on their tolerance and the chosen chemotherapy regimen. The median cumulative cisplatin dose during and before completion of CCRT was 75 (range: 0–225) mg/m^2 and 135 (range: 0–300) mg/m^2, respectively.

During CCRT, the most acute toxicity of grade ≥3 was hematological toxicity, which was exhibited separately, from the other grade 3 toxicities, including dysphagia (6%), mucositis (2%), anorexia (1%), and fatigue (1%), and there was no reported grade ≥4 toxicity.

The median follow-up duration was 13 (range: 3–104) months in all patients and 61 (range: 53–104) months in survivors. In all patients, the estimated median OS was 13 (95% CI: 10.38–15.63) months, DSS was 14 (95% CI: 11.60–16.40) months, and PFS was 9 (95% CI: 7.70–10.30) months. The estimated 2-year FFDM and FFLR were 37.1% and 40.3%, respectively.

By the last follow-up, 83 patients (89%) died, wherein most patients (92%) died owing to disease progression or subsequent complications, while others died because of second primary cancer (5%), tuberculosis infection (1%), or due to unknown etiology (2%). Cardiac complications along with acute myocardial infarction or life-threatening arrhythmia were noted in four of the expired patients (5%), and no survivors reported newly diagnosed cardiac disease.

Hematological parameters and toxicity

Based on pre-treatment CBCs (baseline) of 87 patients, the median number of days between baseline CBC and initiation of RT was 18 days (range: 2–81). Median baseline ANC, ALC, and NLR were 5,384 (range: 1,716–14,309) cells/mm^3, 1,635 (range: 512–4,127) cells/mm^3, and 3.68 (range: 0.77–13.92), respectively. Thirteen out of 87 (14%) patients exhibited a low baseline ALC, wherein eight patients had grade 1 lymphopenia and five patients had grade 2 lymphopenia.

The day of ALC nadir and NLR-h was available for all patients. We found that ALC nadir and NLR-h occurred on the median day of 28 (range: 7–74 and 1–74, respectively) after initiation of RT, although 24 patients showed different days of ALC nadir and NLR-h. The median nadir ALC and NLR-h was 212 (range: 16–742.1) cells/mm^3 and 16.8

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Table 1 Patient and tumor characteristics

Patient and tumor characteristics (n=93)	Median	Range or %
Sex		
Man	87	93.5
Woman	6	6.5
Age (years)	58.6	37.9–87.7
Pre-treatment body weight (kg)	57.4	36–91
Smoker		
No (never smoked)	9	9.7
Yes (current smoker or quitted)	73	78.5
Unknown	11	11.8
Alcohol consumption		
No (never or not regular)	6	6.5
Yes (current use or ever regular use)	74	79.6
Unknown	13	14.0
Betel-nuts chewer		
No (never or not regular)	23	24.7
Yes (current use or ever regularly use)	54	58.1
Unknown	16	17.2
ECOG PS, n (%)		
0 & 1	85	91.4
2	8	8.6
ACCI, excluding esophageal cancer	2	0–6
Esophageal tumor length (cm)	5.5	2–25
Location, n (%)		
Upper esophagus	21	22.6
Milddle esophagus	38	40.9
Lower esophagus	34	36.6
Histologic grade, n (%)		
Grade 1	2	2.2
Grade 2	64	68.8
Grade 3	8	8.6
Unknown	19	20.4
Clinical T stage, n (%)		
T1	2	2.2
T2	33	35.5
T3	43	46.2
T4	15	16.1
T4a	2	2.2
T4b	13	14.0
Clinical N stage, n (%)		
N0	11	11.8
N1	28	30.1
N2	35	37.6
N3	19	20.4
cTNM stage, n (%)		
IIA	4	4.3
IIB	21	22.6
IIIA	23	24.7
IIIB	15	16.1
IIIC	30	32.3

ECOG PS Eastern Cooperative Oncology Group performance status; ACCI, age adjusted Charlson's comorbidity index.

(range: 2.64–155), respectively. Ten out of 93 patients (10.8%) had grade 2 lymphopenia, 41 out of 93 patients (44.1%) had grade 3 lymphopenia, and 42 out of 93 patients (45.1%) had grade 4 lymphopenia. The median decreased ALC percentage (%) from baseline to nadir was 86.18 (range: 53.25–98.76).

High NLR-b and NLR-h during CCRT are associated with worse OS

The Cox regression model was used to analyze the impact of NLR-b and NLR-h on OS. When NLR is regarded as a continuous variable, a higher NLR-b (HR: 1.109, 95% CI: 1.016–1.210, P=0.02) and NLR-h (HR: 1.007, 95% CI: 1.000–1.014, P=0.037) were significantly associated with worse OS. In addition, both higher NLR-b and NLR-h were significantly associated with worse PFS, DSS, and FFDM, but not FFLR (*Table 3*).

Kaplan-Meier analysis was used for evaluating the effect of dichotomized NLR-b values on OS. The median OS was stratified to 9 and 15 months when NLR-b >3.68 and ≤3.68, respectively (P=0.007, *Figure 1A*). The estimated 2-year OS rates was stratified to 11.6% and 31.8% when NLR-b >3.68 and ≤3.68, respectively. NLR-b values >3.68 are

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Table 2 Treatment modalities

Treatment modalities (n=93)	Median	Range or %
RT technique		
3D-CRT	22	23.7
IMRT	40	43
VMAT	31	33.3
Radiation dose (Gy)	59.4	48.6–72
Number of fractions	30	25–35
Mean heart dose (cGy)	2,119	104–3,174
Dose-volume of heart (%)		
V10 Gy	92	0–100
V20 Gy	50	0–98
V30 Gy	18	0–53
V40 Gy	5	0–23
Mean lung dose (cGy)	1,538	580–2,232
Dose-volume of lung (%)		
V5 Gy	92	29–100
V10 Gy	71	21–96
V20 Gy	22	6–48
Radiotherapy and chemotherapy sequence, n (%)		
Induction chemo, CCRT, and ± adjuvant chemo	49	52.7
CCRT and ± adjuvant chemo	42	45.2
Sequential RT and chemo	2	2.2
CCRT chemotherapy regimen		
Cisplatin and fluorouracil (PF)	87	93.5
Carboplatin and fluorouracil	2	2.2
Weekly cisplatin	2	2.2
Sequential PF and RT	2	2.2

Vx (%), relative percent of volumes for at least x (Gy); RT, radiation therapy; 3D-CRT, three-dimensional conformal RT; IMRT, intensity-modulated RT; VMAT, volumetric modulated arc therapy; CCRT, concurrent chemoradiation.

also associated with worse PFS (P=0.010), DSS (P=0.008), and FFDM (P=0.005), but not with FFLR (P=0.432, *Figure 1B,C,D*).

Patient characteristics associated with higher NLR-b

We used the Spearman's rank correlation coefficient of NLR-b to test possible relationships between NLR-b and clinical variables (*Table 4*). Baseline body weight (Spearman's correlation coefficient r=–0.251, P=0.019), primary esophageal tumor length (Spearman's correlation coefficient r=0.324, P=0.011), and advanced clinical T stage (Spearman's correlation coefficient r=0.230, P=0.032) were found to be significantly correlated with NLR-b >3.68. Using multivariate logistic regression, we found that primary esophageal tumor length (OR =1.345, P=0.021) was associated with a higher NLR-b (*Table 5*).

Dosimetric parameters are associated with NLR-h and percentage of decreased ALC (%) at ALC nadir

The relationship between NLR-h and continuous normal organ dosimetric parameters during CCRT is summarized in *Table 5*. The volume of low lung dose, such as lung V5 (Pearson correlation coefficient, r=0.254, P=0.014) and lung V10 (Pearson correlation coefficient, r=0.317, P=0.002), was found to be correlated with NLR-h (*Table 6*).

The percentage of ALC decrease at ALC nadir during CCRT was found to be significantly correlated with heart V10 (Pearson correlation coefficient, r=0.273, P=0.011) and lung V5 (Pearson correlation coefficient, r=0.299, P=0.005) (*Table 7*).

Discussion

In this retrospective study on thoracic esophageal cancer, we report that systemic inflammation at baseline and during RT were predictive of FFDM, DSS, PFS, and OS. Our findings suggest that gross tumor length is correlated with baseline systematic inflammation. In addition to irradiation

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Table 3 Univariate Cox regression model of NLR-b and NLR-h associated with different survival outcomes

Survival outcomes	NLR-b	NLR-h
OS	HR: 1.109, 95% CI: 1.016–1.210, P=0.020	HR: 1.007, 95% CI: 1.000–1.014, P=0.037
PFS	HR: 1.123, 95% CI: 1.027–1.229, P=0.011	HR: 1.009, 95% CI: 1.002–1.016, P=0.008
DSS	HR: 1.112, 95% CI: 1.017–1.216, P=0.020	HR: 1.008, 95% CI: 1.001–1.015, P=0.023
FFLR	HR: 1.020, 95% CI: 0.890–1.169, P=0.774	HR: 0.999, 95% CI: 0.988–1.011, P=0.925
FFDM	HR: 1.170, 95% CI: 1.056–1.295, P=0.003	HR: 1.012, 95% CI: 1.005–1.019, P=0.001

NLR-b, baseline NLR; NLR-h, highest NLR during CCRT; NLR, neutrophil-lymphocyte ratio; CCRT, concurrent chemoradiation; OS, overall survival; PFS, progression free survival; DSS, disease specific survival; FFLR, freedom from locoregional recurrence; FFDM, freedom from distant metastasis; HR, hazard ratio; CI, confidence interval.

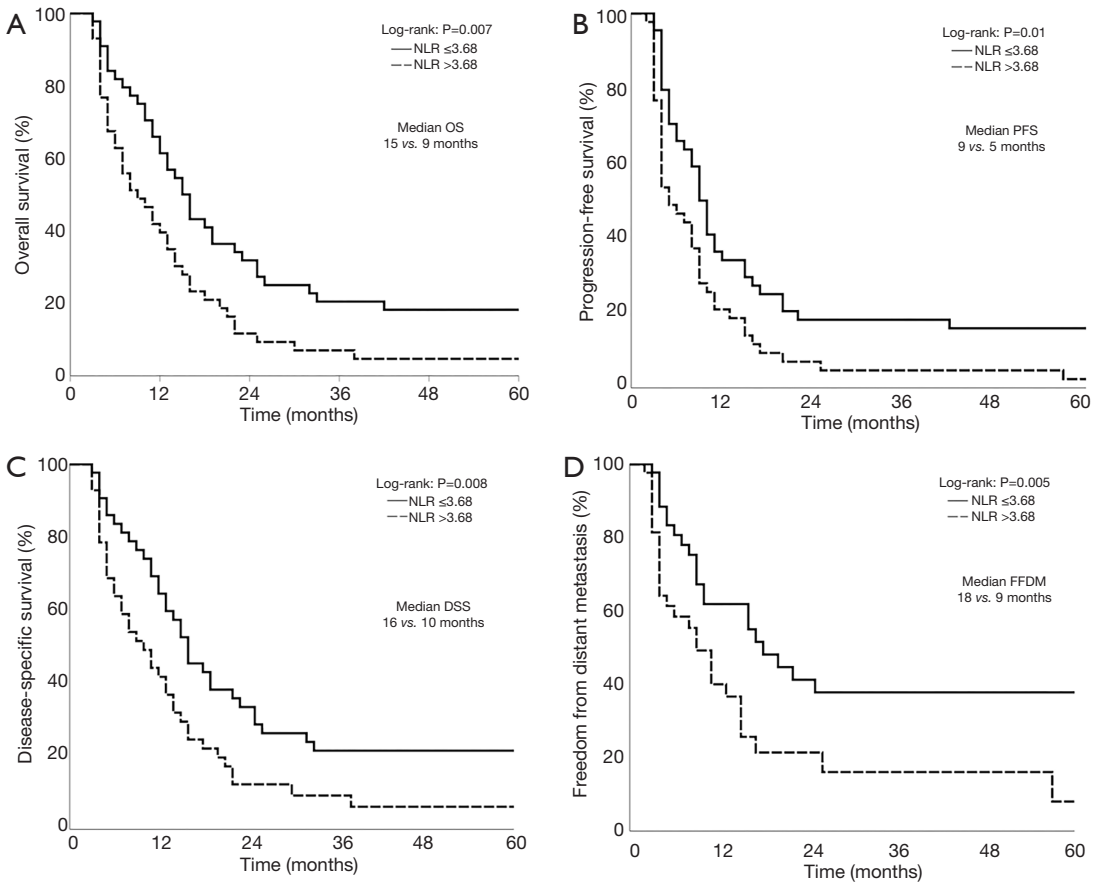

Figure 1 Kaplan-Meier's curves for different survival outcomes, and patients are stratified by NLR-b >3.68 (dotted line) or ≤3.68 (solid line): (A) OS; (B) PFS; (C) DSS; (D) FFDM. NLR-b, baseline NLR; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; DSS, disease-specific survival; FFDM, freedom from distant metastasis.

of the gross tumor, the volume of the lungs that receives a low dose of radiation may further contribute to systemic inflammation. We also correlated the cardiac and lung volume exposed to low doses of irradiation with the extent of decrease in ALC during RT.

The interaction between tumor, host, and microenvironment has been reported to have a significant effect on immunotherapy outcomes (29). Neutrophils

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Table 4 Spearman's rank correlation coefficient of patient characteristics associated with high NLR-b (>3.68)

Patient characteristics	Spearman's correlation coefficient (r)
Sex	0.003, P=0.981
Age (years)	0.051, P=0.640
Baseline body weight (kg)	–0.251, P=0.019
Smoking or not	0.046, P=0.696
Alcohol drinking or not	0.006, P=0.956
Betel-nuts chewer or not	–0.117, P=0.326
ECOG PS, 0/1 *vs.* 2	0.083, P=0.443
ACCI, excluding esophageal cancer	0.057, P=0.600
Esophageal tumor length (cm)	0.324, P=0.011
Location U/3 *vs.* M & L/3	–0.006, P=0.957
Histologic grade Gr. 1 & 2 *vs.* 3	–0.128, P=0.295
Clinical T stage T1 & T2 *vs.* T3 & T4	0.230, P=0.032
Clinical N stage N0 & N1 *vs.* N2 & N3	0.106, P=0.327
cTNM stage II *vs.* III	0.199, P=0.065

NLR-b, baseline NLR; NLR, neutrophil-lymphocyte ratio; ECOG PS Eastern Cooperative Oncology Group performance status; ACCI, age-adjusted Charlson comorbidity index.

Table 5 Multivariable logistic regression of patient characteristics associated with high NLR-b (>3.68)

Patient characteristics	Odds ratio (95% CI)
Pre-treatment body weight (kg)	0.965 (0.920–1.012), P=0.138
Esophageal tumor length (cm)	1.345 (1.047–1.727), P=0.021
Clinical T stage T1 & T2 *vs.* T3 & T4	2.098 (0.659–6.677), P=0.210

NLR-b, baseline NLR; NLR, neutrophil-lymphocyte ratio; CI, confidence interval.

potentially promote cancer progression (30), and lymphocytes play a key role in mediating tumoricidal effects (26). NLR has been used as valuable biomarker to predict the survival outcomes of patients with esophageal cancer, regardless of whether they were treated surgically or with RT (20-22,31,32). We determined the OS correlation with NLR-b and NLR-h, and found the optimal cut-off value for NLR-b is 3.68. Interestingly, only FFLR was not correlated to NLR-b, indicating that NLR-b is more reflective of the systemic disease status. We also found that the initial tumor size is an indicator of a higher NLR-b, and the primary tumor size contributes to inflammatory-immunity dynamics. Therefore, a larger tumor size will further elicit a stronger inflammatory reaction and suppression of patient immunity. This correlation has also been demonstrated in thyroid cancer (33) and should be further investigated for a translational significance.

Dynamic changes in NLR during treatment are also potentially associated with survival outcomes and may be more informative than static baseline values (34,35). RT may turn so-called "cold" tumors "hot" via the release of pro-inflammatory mediators and increase in tumor-infiltrating immune cells (36). Thus, changes in NLR during treatment may serve as an early biomarker to reflect the treatment response and guide further treatment. We also demonstrate that the volume of lungs, such as V5 and V10, that receives low-dose irradiation is correlated with NLR-h, although cardiac volume receiving low dose irradiation is not correlated to NLR-h. This suggests that a

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Table 6 Pearson correlation coefficient of highest NLR-h with dosimetric parameters

Dosimetric parameters	Pearson correlation coefficient r
Heart mean dose	0.079, P=0.457
Heart V10 Gy	0.189, P=0.073
Heart V20 Gy	–0.017, P=0.875
Heart V30 Gy	–0.021, P=0.844
Heart V40 Gy	0.066, P=0.536
Lung mean dose	0.202, P=0.052
Lung V5 Gy	0.254, P=0.014
Lung V10 Gy	0.317, P=0.002
Lung V20 Gy	0.046, P=0.660

NLR-h, highest NLR during CCRT; NLR, neutrophil-lymphocyte ratio; CCRT, concurrent chemoradiation.

Table 7 Pearson correlation coefficient of percentage of decreased ALC (%) at ALC nadir with dosimetric parameters

Dosimetric parameters	Pearson correlation coefficient (r)
Heart mean dose	0.097, P=0.375
Heart V10 Gy	0.273, P=0.011
Heart V20 Gy	–0.028, P=0.802
Heart V30 Gy	–0.075, P=0.494
Heart V40 Gy	–0.016, P=0.887
Lung mean dose	0.175, P=0.105
Lung V5 Gy	0.299, P=0.005
Lung V10 Gy	0.207, P=0.054
Lung V20 Gy	0.052, P=0.632

ALC, absolute lymphocyte count.

larger volume of lung irradiated with low-dose RT induces a greater degree of systemic inflammation and suppression of immunity. Thus, strategies aimed to reduce NLR-h should be investigated further.

Recently, radiation-induced lymphopenia has also drawn attention, as survival outcomes have been correlated with lymphocyte nadir (17), and there is emerging evidence linking thoracic radiation dose to lymphopenia and survival outcomes (12,18,37,38). Although lymphotoxic chemotherapeutic agents exist, lymphocytes remain the most radiosensitive cell type in the body and are the only non-dividing cells killed by small doses of X-rays (23,24), and thus, radiation can exert immunosuppressive effects. Prior *in vitro* assays revealed that even a single small dose of 1 Gy can deplete and induce lymphoid cell death, while 2 Gy dose reduces the population of lymphocytes by 50% (39-41). Unintentional irradiation of the circulating lymphocyte pool causes lymphopenia (18). We found that the heart V10 and the lung V5 correlated with a decreased percentage of ALC at ALC nadir, and this is compatible with findings of the previous studies (37,42). We speculate that this is caused by a prolonged exposure of thoracic organs, especially the heart, and the circulating pool of blood to low-dose RT contributes to the ALC nadir. Irradiation of large vascular volumes causes lymphopenia, and the decrease in lymphocyte counts was directly proportional to the strength of irradiation (19). Although there exists a robust model to predict lymphopenia (18), here, we correlated the decrease in lymphocyte counts with low-dose thoracic irradiation simply by examining the two most relevant organs in the thorax. It is a convenient way for clinicians to evaluate treatment plans and predict the possibility of radiation-induced lymphopenia. Retrospective studies have reported a correlation between proton therapy and less severe treatment-related lymphopenia compared with photon therapy (43,44).

Our single-institute retrospective study has some limitations. We examined a small number of patients, who did not exhibit expression of other inflammatory markers, such as lactate dehydrogenase or C-reactive protein. Although we analyzed the pretreatment and nadir parameters during CCRT, the influence of different chemotherapy regimens on lymphocyte count was not completely elucidated. We only demonstrated a few correlations between the dosimetric variables and some clinical variables, whereas dosimetric variables constitutionally interact with each other and with most clinical variables. In addition, our findings focus on the volume of low-dose radiation because we hypothesize it to be more clinically relevant, and future studies are needed to validate our findings.

In conclusion, our study showed that a higher NLR-b and NLR-h predicted adverse survival outcomes, despite the absence of any correlation between NLR and FFLR. NLR is thus a promising indicator of systemic inflammation and disease status, at different time points. Tumor size constitutes systemic inflammation and is related to NLR, and the target volume of low- dose radiation in both lungs and heart impact inflammation-immunity during treatment. RT dosage experienced by the lungs is correlated

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with NLR, and by the heart to the extent of decrease in lymphocyte counts. We suggest that both heart and lung doses should be optimized and minimized during radiation treatment, with an emphasis on low-dose volume. The use of advanced techniques, such as proton therapy, may serve as a fundamental strategy to reduce unnecessary exposure to radiation.

Acknowledgments

We would like to thank all members of the Department of Radiation Oncology, Division of Medical Physics, and Division of Hematology/Oncology and those who had collaborated to the patient treatments in this study. We also thank the editor and series editor for constructive criticisms of an earlier version of this chapter. This study was performed in accordance with ethical standards.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tro-20-62

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tro-20-62). JCL serves as an unpaid editorial board member of *Therapeutic Radiology and Oncology* from May 2020 to Apr 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Changhua Christian Hospital (CCH IRB No. 180310) and individual consent for this retrospective analysis was waived.

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doi: 10.21037/tro-20-62
Cite this article as: Ho YC, Lai YC, Lin HY, Ko MH, Wang SH, Yang SJ, Lin PJ, Chou TW, Hung LC, Huang CC, Chang TH, Lin JC, Lin JB. The volume of low-dose thoracic irradiation influences systemic inflammation-immunity status after chemoradiation in esophageal cancer. Ther Radiol Oncol 2021;5:9.

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