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Clinical outcomes and prognostic factors of volumetric modulated arc therapy (VMAT) of esophageal cancer

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Abstract

Background: The objective was to evaluate the efficacy and safety of radiotherapy and the prognostic factors in patients with esophageal cancer who received definitive radiotherapy, using volumetric modulated arc therapy (VMAT).

Materials and methods: Forty-seven patients who received definitive radiotherapy using VMAT between September 2017 and December 2020 were enrolled. Prescription doses were 60 Gy in 30 fractions to the PTV primary and 48 Gy in 30 fractions to the PTV subclinical.

Overall survival (OS), progression free survival (PFS), and toxicity were analyzed, and univariate and multivariate analyses were used to investigate the prognostic factors.

Results: Median follow up time was 10 months. Most of the patients had an advanced disease stage (stage I, 12.8%; II, 8.5%; III, 27.7%; IV, 51.0%) patients (38.3%) had a T4 tumor. The median survival time was 14 months (range: 0–56 months). The 2-year OS and PFS were 31.3% and 20.4%, respectively. Acute adverse events (≥ Grade 3) were observed in 25 patients (53.2%), and the most frequent types were dysphagia, hematological toxicities including leukopenia, and febrile neutropenia in 14 (29.8%), 10 (21%), and 10 (21%) patients, respectively. Late adverse events (Grade 3 or higher) were observed in eight patients (17.0%), and the most frequent types were pneumonitis in four patients (8.5%), and Grade 5 in one patient (2.1%; esophageal fistula). In multivariate analysis, neutrophil-to-lymphocyte ratio (NLR) > 3 ($p = 0.026$) was significantly associated with poor survival.

Conclusion: Definitive radiotherapy of 60Gy with VMAT is feasible and safe for patients with esophageal cancer. Pre-treatment NLR >3 was an independent prognostic factor for OS.

Key words: esophageal cancer; volumetric modulated arc therapy; neutrophil-to-lymphocyte ratio

Introduction

Esophageal cancer is one of the most aggressive gastrointestinal cancers, with a global 5-year survival rate of 15–25% [1]. Radiation therapy is considered to be the standard treatment for patients with early stage esophageal cancer with endoscopically unresectable tumors or a high risk of developing lymph node metastasis after endoscopic resection [2, 3], and for patients with advanced esophageal cancer who wish to preserve the esophagus, have an unresectable tumor, or are in poor general condition [4–7].

Three-dimensional conformal radiation therapy (3D-CRT) is the current standard radiation technique used to treat esophageal cancer. However, 3D-CRT for esophageal cancer

is often unable to meet dose constraints for organs at risk, such as the spinal cord, lungs, and heart, while delivering a sufficient dose to the planning target volume (PTV). Consequently, volumetric modulated arc therapy (VMAT), which modulates gantry rotation speed, multi-leaf collimator, and dose rate, has become the main treatment modality because of its higher conformity, lower dose to normal tissues compared to 3D-CRT, and a shorter treatment time in addition to these factors when compared with fixed intensity modulated radiation therapy (IMRT) [8 ,9]. Radiation pneumonitis and pericardial effusion are associated with lung volume receiving a radiation dose of ≥ 20 Gy (V20), mean lung dose (MLD) [10, 11], and cardiac V30 [12, 13]. VMAT can reduce lung V20, V30, and cardiac V30 doses compared with 3D-CRT, whereas low doses in lung V5 and V10 tend to be increased [14] and may be associated with increased cardiopulmonary adverse events.

Therefore, this study aimed to determine the efficacy and safety of definitive radiation therapy, using VMAT, and the prognosis of patients with esophageal cancer undergoing this treatment at our institution.

Materials and methods

Patients and treatment characteristics

This study was approved by the Institutional Review Board of our institution (22R156) and was conducted under the Declaration of Helsinki. The need for written informed consent was waived because of the retrospective nature of the study.

We retrospectively analyzed 62 patients with esophageal cancer who underwent definitive radiation therapy using VMAT between September 2017 and December 2020. Patients with stages I–IVA esophageal cancer that were treated with definitive chemoradiotherapy, or radiotherapy were included. For patients with stage II–III, definitive radiotherapy was selected for those who requested esophagus preservation, had no suitable surgical indications due to their general condition, or initially had neoadjuvant chemotherapy not receiving

subsequent surgery due to progression or other reasons. Treatment interrupted cases were also included. However, patients undergoing postoperative treatment, postoperative recurrence treatment, palliative treatment, and concurrent synchronous cancer treatment were excluded. In total, 15 patients were excluded and 47 were analyzed.

Pre-treatment endoscopic pathological diagnosis, computed tomography (CT) images, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) images were obtained for all patients. The eighth edition of Union for International Cancer Control TNM Classification was used for staging. The following pretreatment patient demographic characteristics were collected: age, sex, Eastern Cooperative Oncology Group Performance Status, body mass index (BMI), the presence or absence of dysphagia, and laboratory data (neutrophil, lymphocyte, monocyte, and platelet ($\times 10^4/\mu L$) counts and albumin, C-reactive protein (CRP) levels). Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (PNI), and modified Glasgow prognostic score (mGPS), as a systemic inflammation-based marker, were calculated.

Radiotherapy

Before treatment planning, surgical clips were placed endoscopically at the proximal and distal ends of the esophageal tumor. All patients underwent contrast enhanced CT (SOMATOM Definition AS, Siemens Healthcare, Forchheim, Germany) in the supine position with a vacuum pillow; CT images, 2 mm thick, were obtained. Primary gross tumor volume (GTVp) was defined as the volume of the primary tumor identified by upper gastrointestinal endoscopy or contrast-enhanced CT. Nodal gross tumor volume (GTVn) was defined as the volume of the metastatic lymph nodes enlarged to a total length of at least 10 mm and a short diameter of at least 5 mm on CT and PET-CT with reference to FDG-PET

uptake findings. Primary clinical target volume (CTVp) was the GTVp along with 2 cm of the esophagus in the cephalocaudal direction and 0.5 cm in the lateral direction. Nodal clinical target volume (CTVn) was the GTVn in addition to 5 mm in all directions. Elective node areas (CTV subclinical) included the cervical and superior mediastinal lymph node areas in case of cervical esophageal cancer, supraclavicular and superior mediastinal lymph node areas in upper thoracic esophageal cancer, superior and inferior mediastinal and intraperitoneal lymph node areas in middle thoracic esophageal cancer, and inferior mediastinal and intraperitoneal lymph node areas in lower thoracic esophageal cancer. Peri-gastric and celiac lymph nodes were omitted when they were far from the primary lesion. A PTV margin was added 5 mm from the CTV. The prescription doses were 60 Gy in 30 fractions to the PTV primary and 48 Gy in 30 fractions to the PTV subclinical. All plans were normalized such that 95% of the PTV (PTV D95) was covered by 100% of the prescription dose. The dose constraints for Organs at risk (OAR) are as follow: spinal cord, maximum dose < 45Gy, lung, V20 ≤ 25□, V10 ≤ 50%, V5≤ 60%, mean lung dose ≤ 20Gy and heart, mean heart dose ≤ 40Gy. Therapy for all patients was planned using VMAT. The geometrical approach consisted of 1 to 2 full arcs and was delivered by a linear accelerator (Varian Medical Systems, California, USA) with photons of 6–15 MV energy. On day 1 of radiation therapy, cone beam CT (CBCT) was performed to verify the actual tumor position. Prior to each daily radiation fraction, CBCT or orthogonal two-dimensional kilo-voltage images were acquired from an on-board kilo-voltage imaging system (Varian Medical Systems, California, USA). In daily verification, the orthogonal kV images were used for the patient setup with bone matching. Once a week, CBCT was performed with soft-tissue matching to ensure that setup errors did not exceed 5 mm in any direction. When setup errors exceeded 5mm, or the relationship between the PTV and adjacent organs at risk changed significantly, re-planning with an update CT was performed. Dose distribution of the treatment plan for middle thoracic

esophageal cancer is shown (Supplementary File — Fig. S1).

Chemotherapy

Typically, patients underwent induction chemotherapy followed by concurrent chemoradiotherapy.

Patients with stage II–III received chemotherapy for preoperative treatment, and those with unresectable disease received induction chemotherapy. Patients with renal dysfunction and those in poor general condition did not receive chemotherapy, and radiation therapy alone was administered.

Induction chemotherapy consisted of continuous intravenous 5-fluorouracil (5-FU) (800 mg/m^2 per day from days 1 to 5) and intravenous cisplatin (80 mg/m^2 on day 1) (FP) or intravenous docetaxel (70 mg/m^2 on day 1) and intravenous cisplatin (70 mg/m^2 on day 1) and continuous intravenous 5-FU (750 mg/m^2 per day from days 1 to 5) (DCF). Concurrent chemotherapy consisted of two cycles of FP (continuous intravenous 5-FU [700 mg/m^2 per day from days 1 to 4] and intravenous cisplatin [70 mg/m^2 on day 1] every 4 weeks). Two courses of FP were administered as additional chemotherapy. The course was adapted according to patient's general condition.

Statistical analysis

Overall survival (OS) was defined as the time from the start of radiation therapy to the last follow-up or death, and progression free survival (PFS) was defined as the time from the start of radiation therapy to disease progression or death. OS and PFS were calculated using the Kaplan–Meier method, and the log-rank test was used to compare survival between groups. Multivariate analysis was performed using Cox regression analysis. The selection criteria for the explanatory variables in the multivariate analysis were variables that were significantly different in the univariate analysis. For all tests, $P < 0.05$ was considered statistically

significant.

Results

Patient characteristics are summarized in Table 1. A total of 47 patients with esophageal cancer were evaluated. Their median age was 72 years (range: 33–91 years) and 39 patients (83%) were male. All patients had squamous cell carcinoma. Twenty-one (41%) and 13 (26%) patients had tumors in the middle and upper thoracic esophagus, respectively. Thirteen (27.7%) and 24 (51%) patients had stage Ⅲ and IV disease, respectively. Eighteen (38.3%) patients had a T4 tumor, and 16 (34%) patients had a T3 tumor. The median BMI was 19.5 (range: 14.5–29.2), and 13 (38%) patients had dysphagia at the beginning of the treatment. Eight (12.8%) patients underwent induction chemotherapy, 34 (72.3%) patients underwent concurrent chemoradiotherapy, and seven (14.9%) patients underwent radiotherapy alone. ENI was performed in 45 (95.7%) patients; two patients were omitted due to poor cardiopulmonary function and prior radiotherapy to the superior mediastinum.

PTV dose parameters are shown in Supplementary File — Table S2. The median value of PTV primary D2, D98, and D50 were 66.5 Gy (63.9–69.8), 58.5 Gy (53.9–59.5) and 63.7 Gy (61.1–65.7), respectively, for cervical esophagus (Ce) — upper thoracic esophagus (Ut) and 64.3 Gy (53.3–68.1), 41.3 Gy (4.15–51.1), 62.0Gy (50.4–69.6), respectively, for middle (Mt) — lower thoracic esophagus (Lt).

The results of dosimetry are shown in Supplementary File — Table S3. The median lung V5, V10, V20 and the MLD were 52.0%, 38.6%, 18.2 %, and 10.5 Gy, respectively, for Ce-Ut esophageal cancer and 78.2%, 46.6%, 21.2%, and 13.5 Gy, respectively, for Mt-Lt esophageal cancer. The median heart V30 and V40 and the MLD were 7.1%, 4.2%, and 6.1 Gy,

respectively, for Ce-Ut esophageal cancer and 53 Gy, 25.1 Gy, and 31.5 Gy, respectively, for Mt-Lt esophageal cancer.

The median OS and PFS times were 14 months (range: 0–56 months) and 8 months (range: 0–56 months), respectively. The 2-year OS and PFS rates were 31.3% and 20.4%, respectively. The 2-year OS rates for stage I, II, III, and IV disease were 87.5%, 50%, 21.7%, and 13.7%, respectively. The 2-year PFS rates for stage I, II, III, and IV disease were 75%, 25%, 16%, and 5%, respectively. The rate of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 21.6%, 29.4%, 25.5%, and 3.9%, respectively. The treatment was discontinued in six patients (10.6%) due to heart failure (two [4%] patients), febrile neutropenia (one [2%] patient), poor general condition (one [2%] patient), esophagitis and grade 3 radiation pneumonitis (one [2%] patient), and sudden death (one [2%] patient).

Overall, 27 of 47 patients (57%) died during the study period. The main cause of death was primary cancer, seen in 20 (43%) patients. Other causes of death were massive hematemesis or hemorrhagic shock in three (6%) patients, aspiration pneumonia, heart failure possibly related to chemotherapy, combined heart failure and pneumonia, and sudden death (cause unknown), in one patient each (2% each).

Recurrence was observed in 27 of 47 patients (57%); of them, 14 (29.7%) had primary recurrences, 8 (17%) had regional lymph node recurrences, and 14 (29.7%) had distant metastases (Supplementary File — Tab. S4).

Local recurrence, regional lymph node recurrence, and distant metastasis were observed in 7 (30.9%), 3 (13.0%), and 4 (17.4%) patients, respectively, in the resectable group, and 7 (29.2%), 5 (20.8%), and 10 (41.7%) patients, respectively, in the unresectable group. Lymph node recurrence within the elective nodal irradiation field was observed in

only 5 of 47 patients (10.6%); 2 of 23 patients (8.7%) in the resectable group and 3 of 24 patients (12.5%) in the unresectable group, most of whom presented with progressive disease (concurrent distant metastasis in 3 [6%] and concurrent local recurrence in 1 [2%] patient) and regional lymph node recurrence only occurred in 1 patient (2%). Recurrence outside the irradiated field was observed in 2 of 47 patients (4%): in the esophagus in one (2%) patient and peri gastric lymph node in another (2%). Further, 4 of 47 patients (9%) underwent salvage surgery after recurrence; of them, 2 (4%) patients underwent R0 resection. Recurrence was treated with systemic chemotherapy in seven patients and immune check point inhibitor in two patients.

Adverse events are listed in Table 2. Acute adverse events ≥ grade 3 were observed in 25 (53.2%) patients. The most frequent types of ≥ grade 3 acute adverse events were dysphagia in 14 (29.8%) patients, hematological toxicities including leukopenia in 10 (21%), febrile neutropenia in 10 (21%), and thrombocytopenia in 2 (4.3%) patients. Grade 4 acute adverse events observed were leukopenia in four (8%) patients and febrile neutropenia in five (10.6%) patients. The most frequent types of ≥ grade 3 late adverse events were pneumonia in four (8.5%) patients, esophageal fistula in two (4.2%) patients, and esophageal perforation in two (4.2%) patients. Grade 5 was adverse event was observed in one patient (2.1%); esophageal fistula occurred after CRT followed by esophageal stent insertion.

The univariate analysis showed female sex ($p = 0.009$), T4 disease ($p = 0.031$), dysphagia ($p = 0.001$), BMI < 18.5 ($p = 0.048$), NLR > 3 ($p = 0.00003$), PLR > 207 ($p = 0.001$), mGPS 2 ($p = 0.006$), and PNI < 40 ($p = 0.02$) to be significantly associated with poor OS (Supplementary Table 5). In multivariate analysis, NLR > 3 (hazard ratio [HR]: 6.869; 95% confidence interval [CI]: 1.675–28.398; $p = 0.007$) was significantly associated with poor OS (Tab. 6).

Discussion

In the present study, the MST was 14 months, and the 2-year OS and PFS were 31.3% and 20.4%, respectively. Our results are consistent with those previously reported, except for the poor 2-year PFS despite good PTV coverage. Patients with esophageal cancer reportedly have a poor prognosis. The INT 0123 study reported a median survival of 18.1 months, a 2-year survival of 40%, and a locoregional recurrence of 52% in patients with esophageal cancer who received concurrent chemoradiotherapy [7]. Previous studies have reported that the 3- and 5-year OS rates in patients with stage Ⅰ disease were 94.7% and 86.5% in the surgery arm and 93.1% and 85.5% in the CRT arm, respectively [15]. In those with stage II-III and stage IV disease who received chemoradiotherapy, the 3-year OS has been reported as 44.2–74.2% [4, 16, 17] and 30% [4, 6], respectively. The dose escalation trial with VMAT in stages I–IV [18], set at 58.8–66 Gy (BED10 71–80.5 Gy, EQD2 59.3–67.1) for GTV primary, demonstrated 3y locoregional progression free survival (LRPFS) 73% but no benefit over standard therapy. The reason for the poor 2-year PFS in the present results even though the doses were nearly the equivalent of dose escalation could be that 18 of 47 patients (38.3%) in our study had T4 disease and 24 (51%) had stage IV disease. Furthermore, salvage surgery was performed only in four patients (8.5%). Therefore, approximately half of the patients in our study were included in the “poor prognosis” group. In contrast, in the INT0123 study [7], only nine patients had T4 disease, and in the JCOG 0909 study, salvage surgery was performed in approximately 30% of the patients. To determine the efficacy of induction chemotherapy with DCF [19] followed by radical surgery or definitive chemoradiotherapy compared with that observed with standard definitive chemoradiotherapy for patients with locally advanced unresectable squamous cell carcinoma of the thoracic esophagus, a phase III randomized trial is currently underway [20].

In this study, we found that VMAT for treating patients with esophageal cancer did

not increase pulmonary toxicity. Grade 3 pneumonitis was noted in 4 (8.5%) patients, similar to the findings of previous studies (Supplementary File — Tab. S6). For the IMRT of esophageal cancer, the current recommended dose constraints for the total lung include V20 < 30–35%, V5 < 65%, and MLD < 20 Gy according to the National Comprehensive Cancer Network guideline [21]. Asakura et al. reported that the optimal threshold of lung V20 to predict symptomatic radiation pneumonitis was 30.5% [22]. A previous study reported that the rates of grade 3 and grade 5 pneumonitis in patients with esophageal cancer who received VMAT were 2.3–6% [23, 24] and 2% [25], respectively. A systematic review of IMRT radiation pneumonitis by Tonison et al. found that V20 > 23% was strongly associated with Grade 2 or higher radiation pneumonitis; hence, they recommended that V20 reduction should be prioritized over V5 reduction [26]. Consequently, in our study, we attempted to preferentially reduce lung V20, MLD, and lung V5 as much as possible. Although the Mt-Lt group had a relatively higher median lung V5 of 78% due to anatomical reasons, they had a low median lung V20 of 21%.

Furthermore, even though patients had a relatively higher median MHD (31.9 Gy in all cases and Mt-Lt median 31.5 Gy) in the present study, pericardial effusion, heart failure, and sudden death occurred in only one (2.1%) patient each. Heart V30 is recommended to be maintained between < 30–46% and MHD between < 26–30 Gy to reduce the risk of cardiac toxicity. Previous studies that investigated patients with esophageal cancer who received chemoradiotherapy reported that pericardial effusions occurred in 14–52.2% individuals [14] [27–29]. Severe pericarditis occurred in 10%, chronic heart failure in 3%, acute myocardial infarction, which was not necessarily treatment-related, occurred in 2.7% [30], and sudden death occurred in 1.4–3.4% patients [31–33]. Comparatively, most of our patients had advanced disease and died early after treatment, which may have contributed to the relatively low rates of cardiac adverse events. Recently, cardiac radiology has been proposed, and

cardiology intervention is expected to improve noncancer mortality rates through cardiovascular adverse event management.

In the multivariate analysis, we found that NLR > 3 was an independent factor for poor prognosis. Previous studies have reported that a higher T and N stages [25, 34–36], radiotherapy alone [25, 37], and a larger GTV (> 60 Gy, > 80 Gy) [34, 36] were significantly associated with poor prognosis in patients with esophageal cancer. Inflammation is a feature of the tumor microenvironment and induces an increase in neutrophils and the production of cytokines such as tumor necrosis factor (TNF), interleukins (IL): IL-1, IL-6, and IL-8 [38], which promotes tumor growth potential, invasiveness, and angiogenesis; thus, inflammation and tumor progression are closely related systemic inflammation-based markers. NLR and PLR, as well as mGPS and PNI, are recognized prognostic indicators in various types of tumors. NLR is a marker of aggressive tumor activity in advanced cancer [39], and NLR > 2.2–4.0 is reported to be a prognostic factor in esophageal cancer [40, 41]. In this study, wherein most patients had advanced disease, NLR > 3 was an independent prognostic factor and could be a potential useful biomarker regarding the disease status of advanced cancer. In practice, it is suggested that the optimal treatment strategy should consider the stage of disease and general condition of the patient, as well as the disease status by following systemic inflammation-based markers.

In this study, ENI field recurrence was 8.6% (2/23) in the resectable group with a relatively long prognosis and regional lymph node recurrence in only 1 case (2%), suggesting that ENI is effective. Furthermore, cancer cell invasion into the deepest submucosal layer of the esophagus increases the incidence of lymph node metastasis to 46% [42]. Akutsu et al. investigated the sites and frequencies of overall and initial lymph node metastases in 211 patients with clinical T1N0 esophageal cancer [43] and reported that 57 of 211 patients (27%) with clinical N0 disease had pathological lymph node metastases and that in patients with

middle thoracic esophageal cancer, lymph node metastases were observed in the neck, mediastinal, and abdominal regions. Therefore, the authors recommended that sentinel lymph node metastasis should be surveyed in all three fields. In patients with esophageal cancer, regional lymph node dissection was performed in two or three areas to improve prognosis. ENI reduced recurrence from the prophylactic area to 1.0% in the CR cohort [44]. Additionally out of field lymph node recurrence was more frequently involved in field radiation therapy (IFRT), ranging from 13.8–15.9% [45, 46]. On the contrary, some believe that ENI in combination with chemotherapy is unnecessary [47] or that IFRT reduces esophageal toxicity without increasing lymph node recurrence: LRPFS and OS have been reported to be superior [48]. Furthermore, local recurrence is the most common form of recurrence after CRT for esophageal cancer. Additionally, ENI is not related to disease-specific survival (DSS) and PFS. In this study, the long-term efficacy of ENI could not be verified due to the poor CR rate and short survival time. Thus, the indication of ENI should carefully be considered in patients with advanced disease or a poor general condition. It may be avoided in patients who have advanced disease with NLR > 3 because the prognosis of these patients is particularly poor.

It has been reported that VMAT plan has a significantly higher conformity index (CI) for PTV, a significantly lower lung V20, lung V30, and MU, and a significantly shorter treatment time compared to conventional IMRT plan [49]. Clinical outcomes are reported to be comparable between VMAT and conventional IMRT (2-year OS of 60.6% vs 55.6% [p = 0.965] and FFS of 60.1% vs. 56.7% [p = 0.998], respectively) [50]. Although VMAT plan has a higher lung V5, V10, and V13 than conventional IMRT plan, the rates of radiation pneumonitis and other late effects are comparable between VMAT and conventional IMRT. Therefore, we consider that VMAT may be a more preferable treatment option than conventional IMRT.

Despite its findings, this single institution and retrospective study has some limitations. Our cohort was small, and the follow-up period was not long enough to reach a convincing conclusion. In addition, 40% of the patients included in our study had primary cervical esophageal and upper esophageal cancer; therefore, lung and cardiovascular toxicity were decreased.

Conclusions

We found that definitive radiotherapy of 60 Gy with VMAT is feasible and safe for treating patients with esophageal cancer without increasing cardiopulmonary toxicity. We also found that patients with advanced esophageal cancer with NLR >3 have particularly poor prognosis.

Conflict of interest

Authors declare no conflict of interests.

Presentation at a conference

None.

Clinical Trial Registration number

Not required

Author contributions

All authors participated in the preparation of this research. All authors have approved the final article.

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Table 1. Characteristics of patients

	N (%)
Age [y]	
Median (range)	72 (33-91)
Sex	
Male	39 (83.0%)
Female	8 (17%)
PS (ECOG)	
0–1	39 (78.0%
2–3	8 (16%)
Location	
Ce	9 (18%)
Ut	13 (26%)
Mt	21 (41%)
Lt	8 (16%)

Pathological type	
Squamous cell carcinoma	51 (100%)
T (UICC 8Th)	
1	8 (17.0%)
2	5 (10.6%)
3	16 (34%)
4	18 (38.3%)
N (UICC 8Th)	
0	13 (27.6%)
1	7 (14.9%)
2	21 (44.7%)
3	6 (12.8%)
Stage (UICC 8Th)	
Ⅰ	6 (12.8%)
Ⅱ	4 (8.5%)
Ⅲ	13 (27.7%)
Ⅳ	24 (51.0%)
Elective nodal irradiation	
Yes	45 (95.7%)
No	2 (4.2%)
Chemotherapy	
ICT	8 (12.8%)
CRT	34 (72.3%)
None	7 (14.9%)
Dysphagia	
No	34(72.3%)
Yes	13(27.6%)
BMI	

Median (range)	19.5 (14.5-29.2)
GTV p volume	
Median (range)	38.4 (3.27-655.9)
NLR	
Median (range)	3.30 (0.8-9.88)
LMR	
Median (range)	3.15 (1.38-7.8)
PLR	
Median (range)	206.9 (42.1-1059)
mGPS	
Median (range)	1(0-1)
PNI	
Median (range)	40.9 (7.34-57.6)

PS — perfomance status; EGOG — Eastern Cooperative Oncology Group; UICC — Union International Cancer Control; Ce — cervical esophagus; Ut — upper thoracic esophagus; Mt — middle thoracic esophagus; Lt — lower thoracic esophagus; ICT — induction chemotherapy; CRT — chemoradiation therapy; BMI — body mass index; GTV p — primary gross tumor volume; NLR — neutrophil-to-lymphocyte ratio; LMR — lymphocyte-to-monocyte ratio; PLR — platelet-to-lymphocyte ratio; mGPS — modified glasgow prognostic score; PNI — prognostic nutrition index

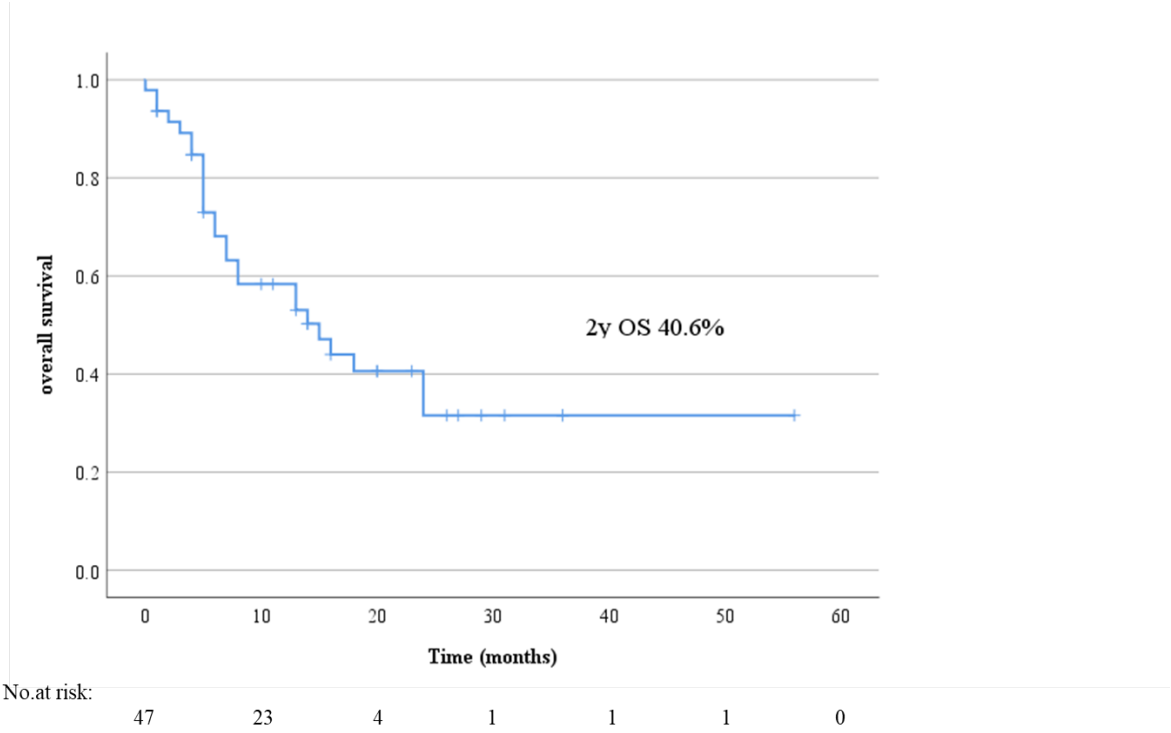
Table 2. Treatment -related adverse events

Adverse events	**Common Terminology Criteriafor Adverse Events Version5.0**			
	Grade2	**Grade3**	**Grade4**	**Grade5**
	No (%)	**No (%)**	**No (%)**	**No (%)**
Acute				

Esophagitis	19 (40.4)	4 (8.5)	-	-
Dermatitis	13 (27.7)	-	-	-
Mucositis	7 (14.9)	1(2.1)	-	-
Dysphagia	6 (12.8)	14 (29.8)	-	-
Leucopenia	19 (38.0)	10 (20)	4 (8.0)	-
Febrile neutropenia	6 (12.0)	5(10.6)	5(10.6)	-
Thrombocytopenia	1 (2.1)	2 (4.3)	-	-
Creatinine increased	-	-	-	-
Diarrhea	1 (2.1)	-	-	-
Late				
Pneumonitis	1 (2.1)	4 (8.5)	-	-
Heart failure	1 (2.1)	-	-	-
Pericardial effusion	1 (2.1)	-	-	-
Pleural effusion	1 (2.1)	1 (2.1)	-	-
Esophageal fistula	-		1 (2.1)	1 (2.1)
Esophageal perforation	-	-	2 (4.2)	-

Figure 1. A. Overall survival; **B.** Progression free survival. OS — overall survival; PFS — progression free survival

(a)



(b)

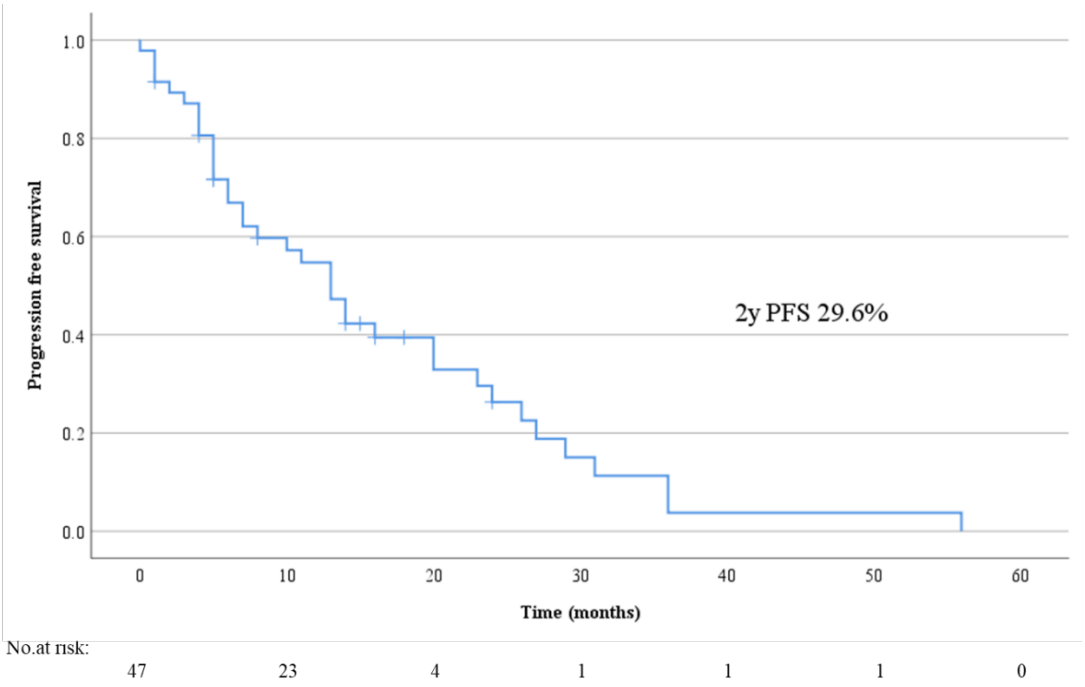
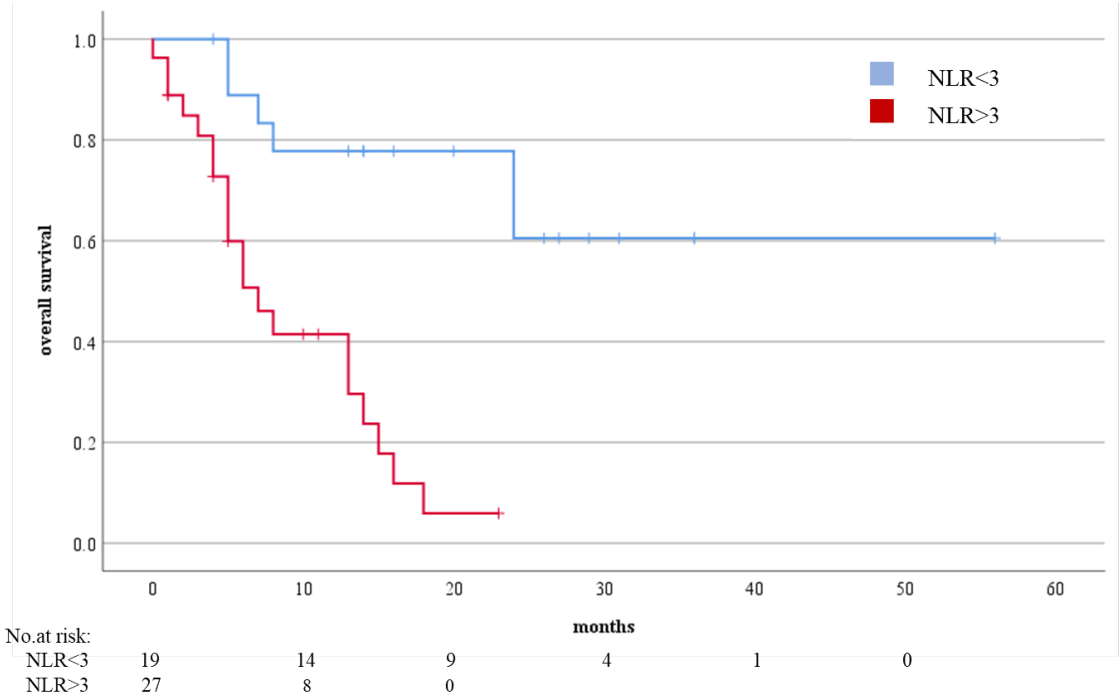


Figure 2. Kaplan–Meier estimates of overall survival (OS) for neutrophil-to-leukocyte ratio (NLR) < 3 vs. NLR > 3. The OS was significantly longer in patients with NLR < 3 (p =

0.026). The1-year OS rates for the NLR < 3 and NLR 3 were 78% and 42%, respectively



Supplementary File

Figure S1. Dose distribution of > 10 Gy for esophageal cancer patients treated with volumetric modulated arch therapy (VMAT). Red line; primary gross tumor volume (GTVp): green line; primary clinical target volume (CTVp): magenta; primary planning target volume: light green; subclinical clinical target volume (CTV subclinical): pink; subclinical planning target volume (PTV subclinical)

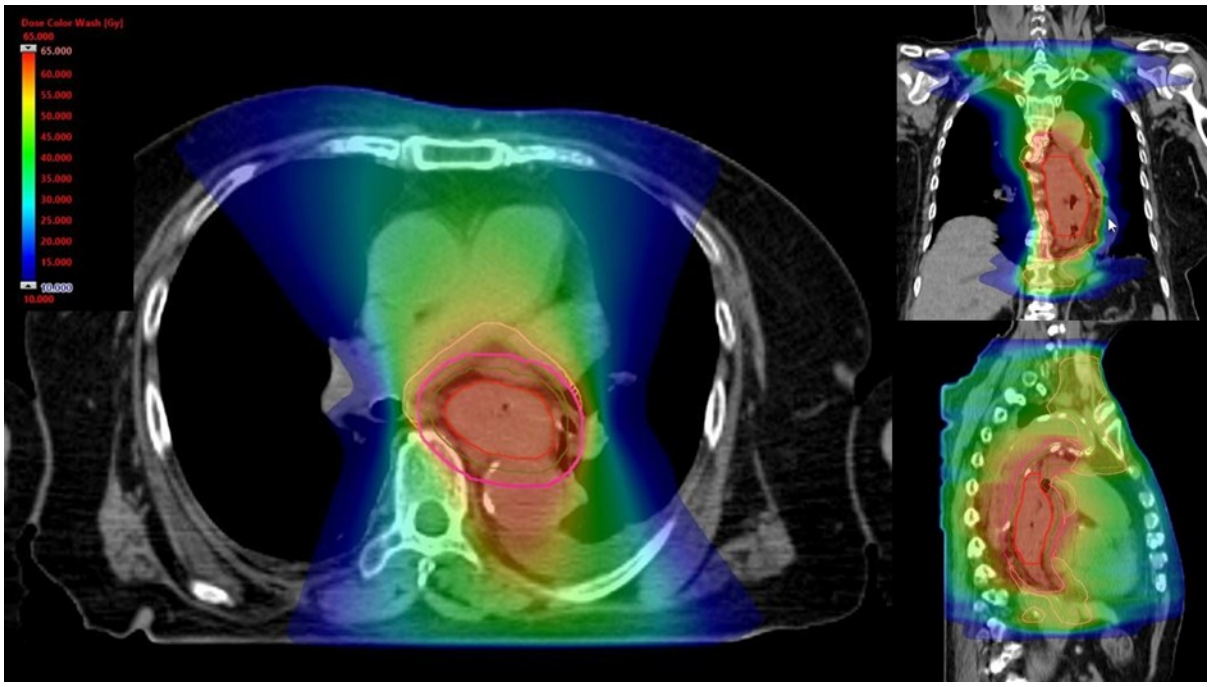


Table S1. Planning target volume dose parameter

PTV	**Tumor location**	**D2 [Gy] median (range)**	**D98 [Gy] median (range)**	**D95 [Gy] median (range)**	**D50 [Gy] median (range)**
PTV primary	Ce-Ut	66.5 (63.9-69.8)	58.5 (53.9-59.5)	59.7 (56.3-60)	63.7 (61.1-65.7)
	Mt-Lt	64.3 (53.3-68.1)	41.3 (4.15-51.1)	59.0 (53.3-60)	62.0 (50.4-69.6)
PTV subclinical	Ce-Ut	60.9 (54.7-69.2)	46.5 (42.8-48.4)	48.1 (45.1-49.9)	52.0 (46.9-58.4)
	Mt-Lt	60.1 (53.2-68.1)	42.4 (6.0-51.1)	45.3 (26.3-52.9)	52.5 (47.9-68.1)

PTV — planning target volume; Ce — cervical esophagus; Ut — upper thoracic esophagus; Mt — middle thoracic esophagus; Lt — lower thoracic esophagus; D2,98,95,50 — dose received by 2. 98, 95, 50% volume of the considered organ

Table S2. Dosimetric results

Volume	**Parameter (median and range)**	**Ce-Ut**	**Mt-Lt**
Lung	V5(%)	52.0(36.4-73.0)	78.2(50.1-98.9)
	V10(%)	38.6(27.0-49.9)	46.6(24.0-75.1)
	V20(%)	18.2(10.9-28.0)	21.2(5.7-32.7)
	MLD (Gy)	10.5(7.5-14.7)	13.5(7.7-18.1)
Heart	V30(%)	7.1(0-66.2)	53.0(0.1-84.6)
	V45(%)	4.2(0-46.3)	25.1(2.8-70.6)
	MHD (Gy)	6.1(0-39.0)	31.5(4.1-44.8)

Ce — cervical esophagus; Ut — upper thoracic esophagus; Mt — middle thoracic esophagus; Lt — lower thoracic esophagus; V5,10,20,30,45 — relative volume of the consider organ receiving 5, 10, 20, 30, 45 Gy; MLD — mean lung dose; MHD — mean heart dose

Table S3. First site of recurrence and radiation field in resectable/unresectable

Recurrences site	**All N (%) n = 47**	**Resectable N (%) n = 23**	**Unresectable N (%) n = 24**
Local	14 (57%)	7 (30.9%)	7 (29.2%)
In-field	13 (28.1%)	7 (30.9%)	6 (25%)
Out-field	1 (2%)	0 (0%)	1 (4.2%)
Regional	8 (17.0%)	3 (13.0%)	5 (20.8%)
In-field	3 (13%)	1 (4.3%)	2 (8.3%)
ENI field	5 (10.6%)	2 (8.7%)	3 (12.5%)
Out-field	1 (2.1%)	0 (0%)	1 (2.1%)
Distant	7 (15%)	4 (17.4%)	10 (41.7%)

resetabe stageⅠ–Ⅲ, unresectable stage Ⅳ, ENI — elective nodal irradiation

Table S4. Univariate and Multivariate analyses of overall survival rate

			UMA	**MVA**		
Factor	**No.**	**1-year OS**	**p-value**	**p-value**	**HR**	**95% CI**

		rate (%)				
Age (y)						
> 70 years	27	55%	0.486	ns	□	□
< 70 years	20	60%				
Sex						
Male	37	51%	0.009	ns	□	□
Female	10	82%				
PS						
0–2	39	63%	0.233	ns	□	□
3–4	8	38%				
ICT						
Yes	6	59%	0.673	ns	□	□
No	41	56%				
CRT						
Yes	40	56%	0.735	ns	□	□
No	7	72%				
Tumor stage						
Non-T4	29	70%	0.031	ns	□	□
T4	18	41%				
Stage						
< Ⅳ	23	71%	0.055	ns	□	□
Ⅳ	24	46%				
Dysphagia						
No	34	65%	0.001	ns	□	□
Yes	13	38%				
BMI						
> 18.5	33	70%	0.048	ns	□	□
< 18.5	14	36%				
GTV boost volume [cc]						
< 60	37	55%	0.136	ns	□	□
> 60	10	71%				
NLR						
< 3	19	78%	0.0003	0.026	5.21	1.221 - 22.236
> 3	27	42%				
LMR						

> 3.2	23	56%	0.078	ns	□	□
< 3.2	23	60%				
PLR						
< 207	23	69%	0.001	ns	□	□
> 207	23	44%				
mGPS						
0	18	82%	0.002	ns	□	□
1–2	28	41%				
PNI						
> 40	21	71%	0.02	ns	□	□
< 40	26	41%				

Table S5. Lung dose constraints, lung irradiation dose, and rate of pneumonia in previous studies

First author	**Year**	**Study design**	**Patient, n**	**Esophagus site**	**Prescribed lung constraints**	**Irradiation lung doses**	**Incidents pneumonitis**
Fan	2019	Prospective	88	Cervical, upper, mid, lower thoracic	V20 ≤ 30%	NA	Grade Ⅰ–Ⅱ: 19.3% Grade Ⅲ: 2.3%
Li	2019	Prospective	53	Upper, mid, lower thoracic	V20 < 28%, mean < 15 Gy	NA	Grade Ⅲ: 6%
Chen	2015	Prospective	50	Cervical, upper, mid thoracic	V20 < 30% V10 < 50% V5 < 60%	NA	Grade Ⅲ: 3.3%
Gerbe	201	Retrospecti	41	GEJ,	V20 <	NA	Grade Ⅱ:

r	4	ve		thoracic	20% V30 < 15% V40 □ 10□		2.4%, Grade Ⅲ: 2.3%
Hsiech	2016	Retospective	39	Cervical, upper, mid, lower thoracic	MLD < 15 Gy V20 < 30%	V5 = 67.8%, V20 = 23.4%	Grade Ⅲ/Ⅳ: 0%
our study		Retrospective	47	Cervical, upper, mid, lower thoracic	V20 □ 25% V10 □50% V5 < 60% MLD □20 Gy	Ce-Ut/Mt-Lt V5 = 52.0%/78.2 %, V10 = 38.6%/46.6 %, V20 = 18.2%/21.2, MLD = 10.5 Gy/13.5 Gy	Grade Ⅱ: 2.1%, Grade Ⅲ: 8.5%

NA — information not available; MLD — mean lung dose; Ce — cervical; Ut — upper thoracic; Mt — middle thoracic; Lt —lower thoracic