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ORIGINAL RESEARCH

The Radiation Dose to the Left Supraclavicular Fossa is Critical for Anastomotic Leak Following Esophagectomy – A Dosimetric Outcome Analysis

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Purpose: For locally advanced esophageal cancer, definitive concurrent chemoradiotherapy (CCRT) with a radiation dose of 50–50.4 Gy/25-28 Fx is prescribed, followed by adjuvant esophagectomy for better local control or salvage treatment if locoregional recurrence occurs. However, radiation injury before surgery may delay wound healing. We performed cervical anastomosis directly inside the left supraclavicular fossa (SCF), the irradiation target for esophageal cancer. The significance of radiation injury in patients with cervical anastomotic leak (AL) remains unclear. Thus, we assessed the influence of radiation on cervical AL in patients undergoing preoperative CCRT followed by esophagectomy.

Patients and Methods: We defined the SYC zone, a portion of the region overlapping the left SCF. The radiation dose to the SYC zone was analyzed and correlated with AL in patients with locally advanced esophageal squamous cell carcinoma (ESCC) who were administered preoperative CCRT (radiation dose with 50–50.4 Gy/25-28 Fx to the primary esophageal tumor) followed by esophagectomy between October 2009 and January 2018. Receiver operating characteristic curve analysis and logistic regression were used to identify the optimal radiation factor to predict AL and the cutoff value.

Results: The optimal radiation factor to predict AL was the mean dose to the SYC zone (area under the curve (AUC)=0.642), and the cutoff point of the mean dose was 48.55 Gray (Gy). For a mean SYC zone dose ≥48.55 Gy, the AL risk was sevenfold greater than that for <48.55 Gy (OR = 7.805; 95% CI: 1.184 to 51.446; P value = 0.033).

Conclusion: Recognizing the SYC zone as an organ at risk and performing radiation evaluation are meaningful. A reduced mean dose of the SYC zone below 48.55 Gy results in a lower cervical AL rate following esophagectomy.

Keywords: esophageal squamous cell carcinoma, preoperative concurrent chemoradiotherapy, radiation therapy

Introduction

Preoperative concurrent chemoradiotherapy (CCRT) followed by additional esophagectomy has demonstrated superior outcomes for locally advanced esophageal cancer compared with surgery alone.[1–3] However, this protocol is associated with some risks. Previous studies have reported that more than 60% of patients have postoperative morbidities, which

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result in excessive expenditures and a prolonged hospital stay.[4–6] One common postoperative complication is anastomotic leak (AL), which occurs in 0–34% of patients.[7–9] AL increases not only the chance for reoperation[4] but also the risk of anastomotic stricture because local inflammation due to leak induces scarring.[10,11]

Concerns have been raised regarding the increased surgical mortality resulting from preoperative CCRT. Specifically, radiation injury may occur even before a wound is formed and can subsequently delay the healing process. Factors that are related to radiation injury causing delayed wound healing include the dose, site, and volume. Ran et al[12] reported that the average healing time was significantly increased when the dose of total skin irradiation exceeded 4 Gray (Gy) in rats compared to that for a simple wound without irradiation. They also showed that unclosed damage with increased irradiation doses was significantly proportional to the recovery time kinetics. Additionally, Fujiwara et al[13] observed poor healing with mucosal color change, and subsequent mucosal necrosis of the proximal gastric graft increased the tendency of AL.

The influence of the radiation dose to the gastric fundus on esophageal AL has been discussed. Goense et al revealed that radiation dose to the gastric fundus has a significant impact on the risk of AL after transthoracic esophagectomy with cervical anastomosis.[14] Vande Walle et al found that the dose of preoperative CCRT to the gastric fundus determines anastomotic complications after esophagectomy with intrathoracic anastomosis.[15] However, hardly any data are available on the effect of radiation dose to the neck on the rate of cervical AL after esophagectomy. Cervical anastomosis performed deep into the neck is a commonly used method for esophagectomy but has demonstrated a higher risk of AL than intrathoracic anastomosis.[16] The conduit and cervical esophagus are sutured.[17] Because the cervical anastomosis area is just inside the supraclavicular fossa (SCF), which is the irradiated target for esophageal cancer at our hospital, the significance of radiation injury in cervical AL remains unknown. The present study aimed to evaluate the radiation dose to the modified left SCF (SYC zone) and its influence on cervical AL in patients undergoing esophagectomy.

Materials and Methods

Patients

We retrospectively reviewed the medical records of esophageal cancer patients who underwent esophagectomy between October 2009 and January 2018. Two hundred thirty-one patients were pathologically confirmed to have squamous cell carcinoma. We screened patients who had received preoperative CCRT before esophagectomy for eligibility. Patients with cervical esophageal cancer, those who received radiation doses less than 50 Gy and those with noncervical anastomosis were excluded. Ultimately, a total of 75 patients who had undergone preoperative CCRT with a dose ≥50 Gy followed by adjuvant or salvage esophagectomy for thoracic esophageal squamous cell carcinoma (ESCC) were included. Among the 75 patients, 15 had original computed tomography (CT) simulation scans that were not assessed for damage, so radiation dose-volume (D-V) evaluation could not be performed. Eventually, 60 patients were included in the radiation D-V analysis, and all the conduits were gastric tubes. All the database records are deidentified. The study was approved and exempted from written informed consent by the Institutional Review Boards of the Chang Gung Medical Foundation at Taipei, Taiwan (permit number: 202100956B0) and was conducted in compliance with the Declaration of Helsinki and other ethical guidelines.

Treatment

The prescribed radiation therapy (RT) dose to the primary esophageal tumor and thoracic gross lymph nodes (LNs) was at least 50–50.4 Gy in 25–28 fractions (fx). The gross LNs located in the SCF or mediastinum above the sternal notch level received a local boost (total dose: 60–66.6 Gy in 30–37 fx). No other boost dose was delivered to the primary esophageal tumor or non-SCF LNs, except the mediastinal LNs located above the sternal notch level where surgical approach is difficult, to avoid additional toxicity to lung, heart and spinal cord.

A prophylactic field covering the bilateral SCF, esophagus, mediastinum, and celiac trunk area was determined based on the doctor's experience and clinical considerations. The prophylactic dose prescribed ranged from 40 to 41.4 Gy in 20–23 fx to 50–50.4 Gy in 25–28 fx. The planning target volume was expanded with 0.5–1.0 cm margins from the targets in all directions for setup error. Two-dimensional RT, three-dimensional conformal RT, inverse plan intensity-modulated radiotherapy or volumetric modulated arc therapy were performed, with 6- or 10-MV photons delivered.

Chemotherapy was performed concurrently with RT and consisted of cisplatin (75 mg/m^2; 4-hour drip) on day one and 5-fluorouracil (1000 mg/m^2; continuous infusion) on days 1–4 every 3–4 weeks. Carboplatin was prescribed instead of cisplatin for patients with creatinine clearance <60 mL/min.

The patients who received surgery underwent esophagectomy with cervical esophagogastrostomy, two-field lymphadenectomy, and reconstruction of the gastrointestinal tract with a gastric tube. Esophagectomy was performed via video-assisted thoracic surgery (VATS), robotic-assisted surgery, or open thoracostomy. The esophagus was transected above the level of the sternal notch, and a cervical incision was made parallel to the medial part of the left sternocleidomastoid muscle (SCM). The cervical esophagus was then brought to the site of cervical anastomosis. The proximal gastric conduit was delivered via the posterior mediastinal or retrosternal route into the left cervical lesion, and hand-sewn or hybrid-stapled anastomosis was performed. There was no routine procedure to perform neck dissection, even for those with gross LNs who received an RT boost, unless the preoperative survey results revealed a positive neck lymph node. In our study, no further neck dissection was performed.

Defining the SYC Zone

The SYC zone is a frame from a particular region that overlaps with the left SCF and is defined as follows: the upper edge starts at the end of the inferior margin of the cricoid cartilage, the lower edge ends above the sternal notch, the medial border is the vertical midline of the anterior surface of the spinal cord, the trachea is subtracted, the esophagus is added, the posterior edge is the horizontal line of the front surface of the vertebral body minus the lung, the lateral boundary is the vertical line of the lateral margin of the left SCM or the medial edge of the clavicle, and the anterior border is the cover of the neck skin. This area can be outlined in the order shown in Figure 1. An example of the delineation is provided in Figure 2.

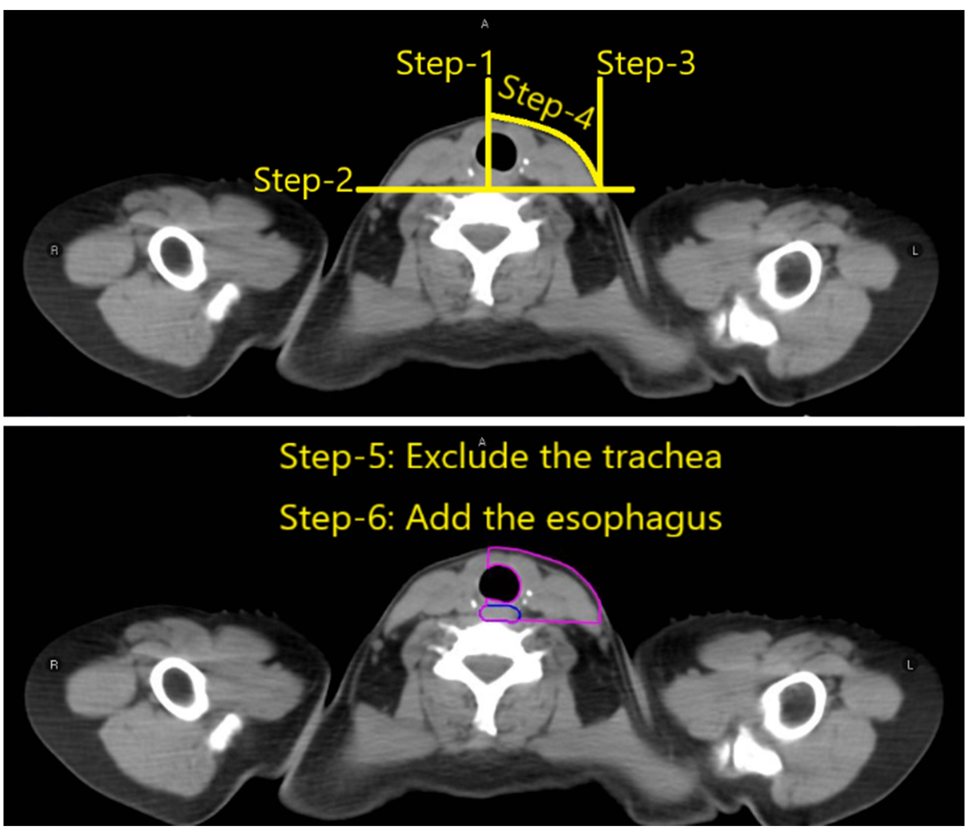

Figure 1 The SYC zone should be outlined in this order.

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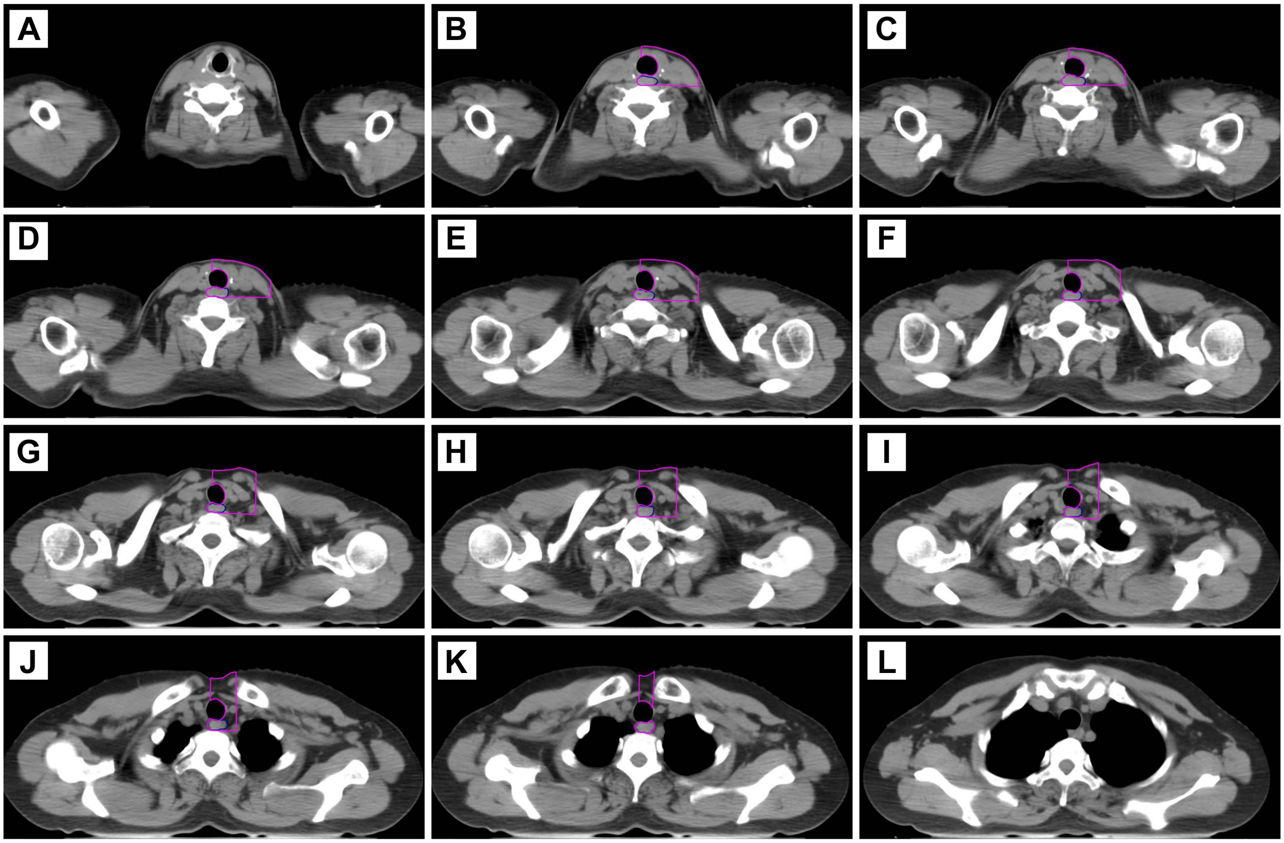

Figure 2 An example of the delineation of the SYC zone is shown in the sub-figures (**A**–**L**) sequentially. The upper edge starts at the inferior margin of the cricoid cartilage (**A** and **B**), and the lower edge ends above the sternal notch (**K** and **L**).

Gastric Fundus Delineation

The gastric fundus was retrospectively contoured on the pretreatment planning CT. From the most proximal part of the stomach located within the diaphragmatic dome, 1-cm transverse sections in the caudal direction were contoured.[14,15]

Data Collection and Analysis

The diagnosis of AL depended on an esophagogram on the 7th to 10th postoperative day or the clinical presentation. To evaluate RT dosimetry, all the original RT data from each patient were retrieved and transferred to the RayStation v8.1 (RaySearch Laboratories AB, Sweden) radiation treatment planning system (TPS) software for analysis. One radiation oncologist contoured each eligible patient's SYC zone and gastric fundus on the CT simulation scan using RayStation v8.1 TPS software. Within the SYC zone and gastric fundus, the dose distribution was analyzed using D-V histograms.

The mean dose, maximum dose and percentage of the SYC zone and gastric fundus volume that received 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25), 30 Gy (V30), 35 Gy (V35), 40 Gy (V40), 45 Gy (V45), and 50 Gy (V50) were analyzed. Proportions and means with standard deviations (SDs) were used to describe the distributions of the categorical and continuous variables of demographic characteristics, clinical data, and radiation dose factors. Receiver operating characteristic (ROC) curve analysis was performed to identify the RT cutoff value, followed by converting the continuous radiation dose factor into a binary variable. A logistic regression model was used to verify the relationship between the binary radiation dose factor and cervical AL. All significance testing was unpaired and 2-sided, with $p < 0.05$ required to claim statistical significance. The statistical software SPSS was used (version 22.0; IBM Corp., Armonk, NY).

Results

A total of 60 patients were reviewed in this study, comprising 56 (93.3%) men and 4 (6.7%) women with a median age of 52.7 years (from 36.0 to 68.0 years). Most of the patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 1 (76.7%) and a preoperative albumin level of ≥4 (70.0%). The mean (SD) preoperative albumin level and estimated glomerular filtration rate (eGFR) were 4.2 g/dL (0.6) and 89.7 mL/min (24.4), respectively. The duration between RT completion and operation was 10.8 weeks (from 5.0 to 27.0 weeks). The major route for reconstruction was the posterior mediastinal route (85.0%), the most anastomotic technique was hand-sewn (93.3%), and the most common surgery type was robot-assisted surgery and VATS (88.3%). The pathological complete response (pCR) rate was 48.3%, and 28.3% of patients had AL. Eighteen of the 60 patients received a lymph node boost dose. The boost dose prescribed to the LNs located in the SCF or above the sternal notch level was 65.7 Gy (1.2). The mean and maximum doses to the SYC zone were 41.9 Gy (17.2) and 57.2 Gy (19.2), respectively. The percentage of the SYC zone volume between V5 and V50 was 87.9% (27.8) and 45.2% (34.6), respectively (Table 1). Table 2 shows the results of ROC curve analysis for the ability of the radiation dose factors of the SYC zone to predict AL in ESCC patients. The mean dose had the largest area under the curve (AUC), which revealed an optimal diagnostic cutoff point of 48.55 Gy for AL (AUC = 0.642; sensitivity = 0.647; specificity = 0.651). Table 3 shows the results of ROC curve analysis to determine the ability of the radiation dose delivered to the gastric fundus to predict AL in ESCC patients. V10 had the largest area under the curve (AUC), which revealed an optimal diagnostic cutoff point of 98.50% for AL (AUC = 0.595; sensitivity = 0.588; specificity = 0.326). Table 4 shows the result of univariate and multivariate logistic regression analyses to verify the cutoff point of the radiation dose factor from the ROC curve analysis. The binary variable of the mean dose of the SYC zone was associated with AL in esophageal cancer patients in the univariate logistic model (OR = 3.422; 95% CI: 1.056 to 11.092; P value = 0.040). After controlling for gender, age, ECOG performance status, preoperative albumin level, duration between RT completion and operation, placement route, anastomotic technique, surgery type and V10 of the gastric fundus, the binary variables of the mean dose of the SYC zone were still associated with AL in esophageal cancer patients (OR = 7.805; 95% CI: 1.184 to 51.446; P value = 0.033). For a mean dose of the SYC zone ≥48.55 Gy, the risk of AL was sevenfold greater than that for <48.55 Gy. Twenty-six (43.3%) cases had a SYC zone mean dose ≥48.55 Gy, and the AL rate was 42.3%. The SYC zone mean dose of the remaining 34 (56.7%) cases was <48.55 Gy, and the probability of AL was 17.6%.

Discussion

Preoperative CCRT followed by esophagectomy is the standard therapy for locally advanced esophageal cancer. Some studies have concluded that preoperative CCRT increased the risk of AL after esophagectomy, but others have reported conflicting results. Morita et al retrospectively reviewed 686 patients, 376 of whom had received preoperative CCRT (30–42 Gy).[18] Preoperative CCRT was found to be an independent predictor of postoperative complications, and the incidence of AL was 28% in the preoperative CCRT group vs 16.5% in the primary surgery group ($p < 0.01$). However, another randomized controlled trial revealed that the rates of postoperative AL were similar between the preoperative CCRT (40 Gy/20 fx) plus surgery group and surgery alone group (8.6% vs 12.3%; $p = 0.228$).[19] It is speculated that this contradictory conclusion may be because only the presence or absence of CCRT has an effect on the rate of surgical complications, and there is a lack of radiation dose-related factors for specific regions. We believe that, for investigations exploring whether CCRT affects postoperative complications, the focus should be on the irradiated field and the radiation dose. Vande Walle et al[15] reported that in patients undergoing preoperative CCRT (36 Gy) followed by Ivor Lewis esophagectomy, the rate of AL was related to the median total dose to 50% of the volume (D50) of the gastric fundus. In their study, gastric fundus was outlined, and the radiation dose in this area was analyzed. In contrast, Koëter et al[20] showed that the radiation dose (CCRT: 41.4 Gy) to the proximal part of the stomach had no influence on AL after transhiatal esophagectomy. Our results revealed that there was no significant difference in the incidence of postoperative AL between the patients with different fundus radiation doses. Possible reasons are that the radiation dose delivered to the primary lesions in this study was a definitive dose of 50–50.4 Gy, which was higher than the dose of nCCRT in the abovementioned studies and exceeded the dose cutoff point by approximately 30 Gy, resulting in no difference in the

Table 1 Characteristics of ESCC Patients Treated with Preoperative CCRT Followed by Additional Esophagectomy (N = 60)

Characteristic	Value
Gender	
Male	56 (93.3%)
Female	4 (6.7%)
Age	52.7 ± 6.3 (36.0–68.0)
ECOG	
1	46 (76.7%)
2	14 (23.3%)
Preop albumin	
<4 g/dL	14 (23.3%)
≥4 g/dL	42 (70.0%)
Unknown	4 (6.7%)
Preop albumin (g/dL)	4.2 ± 0.6 (2.6–6.8)
Preop eGFR (mL/min)	89.7 ± 24.4 (45.0–162.0)
Duration between RT completion and operation (week)	10.8 ± 4.2 (5.0–27.0)
Placement route	
Posterior mediastinal route	51 (85.0%)
Retrosternal route	9 (15.0%)
Anastomotic technique	
Hand-sewn	56 (93.3%)
Hybrid & stapled	4 (6.7%)
Surgery type	
Open	7 (11.7%)
Robot-assisted surgery and VATS	53 (88.3%)
T stage	
T1b	2 (3.3%)
T2	2 (3.3%)
T3	27 (45.0%)
T4a	9 (15)
T4b	20 (33.3%)
N stage	
N1	24 (40%)
N2	27 (45%)
N3	9 (15%)
pCR	
Yes	29 (48.3%)
No	31 (51.7%)
Anastomotic leak	
Yes	17 (28.3%)
No	43 (71.7%)
Lymph nodes boost dose (Gy)	65.7 ± 1.2 (50.0–66.6)
Radiation dose factors of the SYC zone	
Mean dose (Gy)	41.9 ± 17.2 (21.0–64.4)
Max. dose (Gy)	57.2 ± 19.2 (12.7–43.0)
V5	87.9 ± 27.8 (0–100)
V10	85.2 ± 30.1 (0–100)
V15	83.5 ± 31.0 (0–100)
V20	82.0 ± 31.6 (0–99.9)
V25	80.0 ± 32.0 (0–99.7)
V30	77.4 ± 32.4 (0–99.4)
V35	73.8 ± 32.3 (0–99.0)

(*Continued*)

Table 1 (Continued).

Characteristic	Value
V40	67.9 ± 33.4 (0–98.4)
V45	57.4 ± 35.0 (0–96.4)
V50	45.2 ± 34.6 (0–94.3)
Radiation dose factors of the gastric fundus	
Mean dose (Gy)	24.3 ± 14.5 (0.6–53.5)
Max. dose (Gy)	42.6 ± 18.6 (1.0–56.7)
V5	80.3 ± 35.1 (0–100)
V10	70.4 ± 38.1 (0–100)
V15	61.8 ± 38.5 (0–100)
V20	52.4 ± 36.8 (0–100)
V25	44.2 ± 33.7 (0–100)
V30	37.8 ± 31.4 (0–100)
V35	32.1 ± 29.7 (0–100)
V40	27.0 ± 27.2 (0–100)
V45	20.4 ± 24.8 (0–100)
V50	11.5 ± 19.0 (0–98.9)

Notes: Values are number (%) or mean ± SD (range).
Abbreviations: ESCC, esophageal squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; Preop, preoperative; eGFR, estimated glomerular filtration rate; RT, radiation therapy; VATS, video-assisted thoracic surgery; pCR, pathological complete response; Gy, gray; Max, maximum.

Table 2 ROC Value Between AL and Dose to the SYC Zone

Radiation Dose Factor	AUC	95% CI	Cutoff Point	Sensitivity	Specificity
Mean dose (Gy)	0.642	0.478 to 0.805	48.55	0.647	0.651
Max. dose (Gy)	0.636	0.456 to 0.816	59.45	0.647	0.744
V5	0.447	0.301 to 0.594	98.355	0.882	0.326
V10	0.447	0.301 to 0.593	95.19	0.882	0.326
V15	0.466	0.318 to 0.615	96.795	0.824	0.372
V20	0.470	0.319 to 0.621	91.995	0.824	0.372
V25	0.523	0.368 to 0.677	72.135	0.882	0.279
V30	0.526	0.368 to 0.684	55.48	0.882	0.256
V35	0.530	0.368 to 0.692	92.03	0.588	0.535
V40	0.539	0.375 to 0.703	92.85	0.412	0.744
V45	0.530	0.359 to 0.701	87.595	0.412	0.767
V50	0.562	0.390 to 0.734	55.715	0.647	0.558

Abbreviations: ROC, receiver operating characteristic; AL, anastomotic leak; AUC, area under the curve; CI, confidence interval; Gy, gray; Max, maximum.

effect on AL. In addition, since the gastric fundus is hollow, the area outlined on the preoperative CT simulation scan cannot be equal to the true area of the gastric fundus that is irradiated, which may lead to inaccurate dose analyses. When performing esophagectomy, the surgeon will decide how much of the fundus to remove based on factors such as the patient's body size, the need for a safe margin, the length of the gastric tube, and intraoperative blood flow in the stomach. Therefore, there is more uncertainty in the dose assessment of the preoperative gastric fundus. We cannot ignore the fact that since the fundus or proximal stomach is hollow, the actual shape will change irregularly. In addition, this region may be partially removed during esophagectomy. There may also be errors in the analysis of radiation dose, causing inconsistent results. At our hospital, the gastric tube and cervical esophagus were sutured together to the SYC zone. Our results highlighted that the radiation mean dose to the SYC zone, an undistorted area, significantly correlated

Table 3 ROC Value Between AL and Dose to the Gastric Fundus

Radiation Dose Factor	AUC	95% CI	Cutoff Point	Sensitivity	Specificity
Mean dose (Gy)	0.531	0.364 to 0.697	32.50	0.412	0.279
Max. dose (Gy)	0.481	0.309 to 0.653	55.17	0.235	0.093
V5	0.575	0.414 to 0.737	99.64	0.706	0.535
V10	0.595	0.432 to 0.758	98.50	0.588	0.326
V15	0.583	0.419 to 0.746	92.56	0.529	0.302
V20	0.568	0.400 to 0.735	84.67	0.412	0.209
V25	0.536	0.370 to 0.701	70.94	0.412	0.233
V30	0.521	0.353 to 0.688	47.59	0.471	0.326
V35	0.511	0.346 to 0.676	16.72	0.706	0.581
V40	0.488	0.319 to 0.656	47.76	0.294	0.209
V45	0.462	0.292 to 0.633	40.63	0.235	0.093
V50	0.436	0.277 to 0.596	27.05	0.176	0.116

Abbreviations: ROC, receiver operating characteristic; AL, anastomotic leak; AUC, area under the curve; CI, confidence interval; Gy, gray; Max, maximum.

Table 4 Predictors of AL in Patients with ESCC Treated with Preoperative CCRT Followed by Esophagectomy (N = 60)

Variable	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Gender						
Female	Ref.			Ref.		
Male	1.200	0.116 to 12.411	0.878	1.821	0.099 to 33.546	0.687
Age	1.018	0.930 to 1.114	0.702	0.949	0.821 to 1.097	0.480
ECOG						
1	Ref.			Ref.		
2	1.574	0.439 to 5.639	0.486	5.972	0.846 to 42.155	0.073
Preop albumin						
<4 g/dL	Ref.			Ref.		
≥4 g/dL	0.235	0.064 to 0.864	0.029	0.225	0.027 to 1.866	0.167
Duration between RT completion and Operation (week)	1.039	0.911 to 1.184	0.569	1.056	0.862 to 1.292	0.599
Placement route						
Posterior mediastinal route	Ref.			Ref.		
Retrosternal route	0.273	0.031 to 2.374	0.240	0.564	0.036 to 8.870	0.684
Anastomotic technique						
Hand-sewn	Ref.			Ref.		
Hybrid & stapled	2.737	0.353 to 21.174	0.336	8.558	0.495 to 147.851	0.140
Surgery type						
Open	Ref.			Ref.		
Robot-assisted surgery and VATS	0.987	0.172 to 5.652	0.988	1.053	0.038 to 28.908	0.976
Mean dose of the SYC ZONE						
<48.55 Gy	Ref.			Ref.		
≥48.55 Gy	3.422	1.056 to 11.092	0.040	7.805	1.184 to 51.446	0.033
V10 of the gastric fundus						
<98.5	Ref.			Ref.		
≥98.5	2.959	9.416 to 0.930	0.066	2.801	0.517 to 15.164	0.232

Abbreviations: AL, anastomotic leak; ESCC, esophageal squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; OR, odds ratio; CI, confidence interval; Ref., reference group; ECOG, Eastern Cooperative Oncology Group; Preop, preoperative; RT, radiation therapy; VATS, video-assisted thoracic surgery; Gy, gray.

with postoperative AL in ESCC patients who had received preoperative CCRT. We emphasize that the reference point of the SYC zone is straightforward to reduce the intra observational variability in delineation. This reference point is helpful to evaluate the radiation D-V to the SYC zone more consistently. To the best of our knowledge, no published study has examined the impact of the radiation field on cervical anastomotic healing after esophagectomy. This study is the first to assess the SYC zone, which includes the cervical esophagus and adjacent area of cervical anastomosis. According to some experts, poor healing at the anastomosis site is a sign of AL.[13] In our opinion, radiation is an extrinsic factor that affects wound healing. Our study revealed that a mean dose to the SYC zone greater than 48.55 Gy increased the tendency of AL, a finding that might be related to the effect of radiation on wound healing.

In Taiwan, up to 70% of patients with esophageal cancer have advanced disease at the time of diagnosis, making surgery alone futile in most cases. Neoadjuvant concurrent chemoradiotherapy (nCCRT) with a lower RT dose followed by planned esophagectomy, also known as trimodal therapy, is the current standard of care for the treatment of certain esophageal cancers (eg, nonmetastatic and potentially operable). Yang et al[19] included patients with potentially resectable thoracic ESCC who were clinically staged as T1-4N1M0/T4N0M0 (stage IIB or III). The CROSS trial[1] revealed clinical stage T1N1M0 or T2–3N0–1M0 for inclusion. The nCCRT dose was prescribed at 40 Gy/20 fx or 41.4 Gy/23 fx, and planned surgery at 4–6 weeks. The incidences of postoperative complications might be similar between the trimodal therapy and surgery groups. According to the current National Comprehensive Cancer Network guidelines,[21] a preoperative RT dose of 41.4–50.4 Gy/23-28 fx, and a definitive RT dose of 50–50.4 Gy/25-28 fx were suggested. In 2015, nCCRT (41.4 Gy/23 fx) followed by esophagectomy was added to our treatment guidelines for select patients. However, more than 90% of patients with locally advanced esophageal cancer were unfit for nCCRT or refused surgery and had undergone CCRT with 50–50.4 Gy/25-28 fx for noncervical esophageal cancer. In this study, 20 (33.3%) patients were T4b, 36 (60.0%) patients were N2 or N3, and the CCRT dose was higher than that commonly used in nCCRT, followed by esophagectomy for esophageal cancer. For local control is still unsatisfactory, additional esophagectomy following definitive CCRT remains the superior modality to achieve local disease control. Fifty-seven patients underwent adjuvant esophagectomy, and 3 patients underwent salvage esophagectomy for recurrent esophageal cancer after definitive CCRT. To avoid the risks associated with radiation pneumonitis, which usually occurs 6 weeks after CCRT, adjuvant esophagectomy is usually scheduled 8–10 weeks after CCRT.

The prominent disease phenotype in the Asia-Pacific region is ESCC rather than adenocarcinoma arising from Barrett's esophagus in Western countries. LN metastasis is common in ESCC patients, particularly those with locally advanced disease. LN spread may extend from the neck and SCF to the celiac area. In Taiwan, ESCC accounts for up to 90% of all esophageal cancer cases. Some studies found that in ESCC patients, excluding those with celiac LN and distant metastasis, up to 18.9% had supraclavicular LN (SCLN) metastasis, and 8.6% had neck LN metastasis at the time of diagnosis.[22,23] Although the dose was increased to the SYC zone, most physicians routinely irradiated the bilateral SCF for prophylactic and curative intent. This enlarged radiation field decreases the rate of locoregional recurrence considerably with respect to the results reported in the literature using standard radiation fields (18% vs >50%), in which the clinical target volume was obtained by providing 4–5 cm globally accepted margins.[24] For patients with gross LNs located in the neck, SCF, or above the sternal notch level, where the surgical approach is complex, a boost dose of 60–66.6 Gy was also routinely delivered to these LNs. Chen et al[23] reported that SCLN metastasis was not a prognostic factor in locally advanced ESCC patients receiving curative CRT with a local RT boost to the gross SCLNs (total dose: 60–66.6 Gy) and suggested that SCLNs should be considered regional LNs rather than distant LNs. SCLNs and LNs located above the sternal notch level make the surgical approach more difficult. Local radiation boosts the elimination of these difficult-to-resect LNs, making radical esophagectomy a worthwhile option to achieve a chance of cure.

For decades, the best anastomotic location (cervical and intrathoracic) for esophagectomy has been challenged by surgeons. Krasnoff et al[25] published that the AL rate was higher in cervical anastomosis than in intrathoracic anastomosis. Biere et al[16] reported that cervical anastomosis could be associated with a higher AL rate than thoracic anastomosis (2–30% vs 0–10%). However, many surgeons believe that once an intrathoracic AL occurs, it may be more serious than a cervical AL. This consideration has been confirmed again in a recent randomized trial,[26] which showed that although the overall AL rate of intrathoracic anastomosis was significantly lower than that of cervical anastomosis (12.3% vs 31.7%), the severity of grade 3 or higher was much higher in the intrathoracic group (26.7% vs

9.5% by the Complications Consensus Group classification and 100% vs 69% by the Clavien–Dindo classification). Thus, severe AL causes patients with thoracic AL to stay in the hospital longer than those with cervical AL. In contrast, the sequelae of cervical AL may be less severe.[27] No difference was found in leak-associated mortality between the two approaches, and cervical anastomosis had little effect on postoperative symptoms and long-term survival.[28] In our analysis, the cervical AL rate was 28.3%, compatible with other studies. Between 2009 and 2018, 289 patients had undergone esophagectomy at our hospital. Metzger et al[29] revealed that high-volume hospitals with more than 20 esophagectomies per year can decrease postoperative mortality. Our hospital is an experienced center, and we believe that most cervical ALs are clinically manageable and could be minimized by a mean dose reduction to the SYC zone.

The risk factors for ESCC and head/neck squamous cell carcinoma (HNSCC), such as smoking, alcohol consumption, betel quid chewing, chronic mucosal irritation, and upper aerodigestive cancer history, overlap. In Taiwan, 15–20% of patients with HNSCC may develop secondary ESCC, and vice versa. Additionally, Chen et al[30] reported that the rate of synchronous ESCC and HNSCC was 8.6%. Once a patient is diagnosed with HNSCC, chemotherapy and RT may be prescribed, and the neck or SCF may be irradiated. Our results suggest that decreasing the mean dose to the SYC zone can reduce the tendency of cervical AL in metachronous and synchronous ESCC patients who have undergone subsequent esophagectomy. However, the results from our trial may not indicate the timing between RT and esophagectomy associated with AL tendency, a topic that must be confirmed in future studies.

There are several limitations to this study. First, the time span in this study was long, and different TPSs and versions were used during this period; thus, the planning/optimization algorithm varied. All dosimetric parameters were generated by our current TPS after we restored and converted the original datasets into it. Second, the reimbursement policy of our National Health Insurance changed during this study period, which could result in some variation in the surgical instrumentations and medical care protocols used. Third, missing data exist, as this was a retrospective study.

Conclusion

Recognition of the SYC zone as an organ at risk is meaningful because the mean dose of the SYC zone can predict the occurrence of cervical AL following esophagectomy. A reduction in the mean dose of the SYC zone of less than 48.55 Gy results in a lower rate of cervical AL. However, future clinical studies are needed to confirm this result.

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Informed Consent

This was a retrospective study, so the Institutional Review Board (IRB) waived the need for participant consent. All the database records are deidentified. The study was approved and exempted from written informed consent by the Institutional Review Boards of the Chang Gung Medical Foundation at Taipei, Taiwan (permit number: 202100956B0) and was conducted in compliance with the Declaration of Helsinki and other ethical guidelines.

Disclosure

The authors report no conflicts of interest in this work.

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