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Does Radiation Dose to Gastric Fundus during Neoadjuvant Chemoradiotherapy for Esophageal Carcinoma Have an Impact on Postoperative Anastomotic Leak?

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Keywords
Gastric fundus · Esophageal carcinoma · Anastomotic leak · Neoadjuvant chemoradiotherapy · Radiation dose

Abstract
Background: Radiation dose received by the gastric fundus (GF) in neoadjuvant chemoradiotherapy (NACRT) may influence the development of postoperative anastomotic leak (AL) in the management of resectable esophageal carcinoma (EC) by trimodality therapy. The present study aims to evaluate dose-volume parameters of the GF and their association with occurrence of AL in EC. ***Materials and Methods:*** A retrospective analysis was performed of 27 patients with EC who underwent NACRT followed by esophagectomy with cervical esophagogastric anastomosis between January 2015 and July 2018. The GF was retrospectively contoured; dose-volume parameters of the GF were recorded. Postoperative AL was identified from surgical records. Logistic regression analysis was used to identify risk factors associated with AL. ***Results:*** The mean age of the patients was 51 ± 10.5 years; 56% (15/27) had involvement of lower 1/3 esophagus, 10/27 (37%) midthoracic esophagus, and 2/27 (7%) upper thoracic esophagus; 40% (11/27) patients developed postoperative AL and 7/11 had distal and 4/11 had mid thoracic esophageal lesions. Four of five (80%) patients treated by 3-dimensional conformal radiotherapy versus 7/22 (32%) patients treated by volumetric modulated arc therapy developed AL ($p = 0.12$). Univariate logistic regression revealed no significant correlation between D_{mean}, D_{max}, V20, V25, V30, V35, D50, and AL. 8/27 patients underwent ischemic preconditioning of gastric conduit, and 2/8 had AL; 19/27 did not undergo preconditioning, and 9/19 patients experienced AL ($p = 0.4$). ***Conclusion:*** There was no significant negative impact of the dose received by the GF in NACRT upon AL rates. Further studies with a larger sample size are required to clarify this issue.

Introduction

Neoadjuvant chemoradiotherapy (NACRT) followed by esophagectomy is the standard of care for resectable esophageal carcinoma [1]. The overall survival benefit of NACRT is well established [1–4]. Though refinements in surgical techniques and improved perioperative management have led to a decrease in postoperative complica-

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tions, NACRT is associated with an increase in postoperative morbidity and mortality [3, 4]. Anastomotic leak (AL) of the esophagogastric anastomosis is one of the major complications, which negatively impacts the quality of life and surgical outcome. In various studies, the incidence of AL ranged from 5 to 40% [5]. The mortality associated with leak ranged between 11 and 14% [6]. Risk factors that influenced the development of AL include the anastomotic technique (hand sewn vs. stapled vs. hybrid) [7], location of the anastomosis (neck vs. chest) [8–10], type of conduit (stomach vs. colon vs. small bowel) [11], neoadjuvant therapy [1, 2, 12–14], and comorbid conditions [11, 15]. In a single-center retrospective review of 393 esophagectomy patients, neoadjuvant therapy was associated with an odds ratio of 2.2 (OR 2.2, 95% CI 1.1–4.5) for developing AL [11].

The stomach is the best choice for conduit, and the gastric fundus (GF) is the ideal site for anastomosis due to least tension at this site. Dose received by the GF in neoadjuvant radiation is, therefore, important and may have a role in the development of an AL. Whether it negatively impacts the development of leak is unclear with conflicting evidences [16, 17]. Our retrospective study was performed to shed light on the possibility of considering the GF as an organ at risk and to evaluate the relationship between the doses received by the GF and the occurrence of AL.

Materials and Methods

Study Population

A retrospective analysis of patients with esophageal or gastroesophageal junction cancer (Sievert I and II) who underwent NACRT followed by transthoracic esophagectomy between January 2015 and July 2018 at our tertiary referral center was performed. All patients had biopsy-proven resectable carcinoma with no evidence of distant metastases. Patients who underwent transhiatal esophagectomy, salvage esophagectomy, or nonelective operation and patients in whom no gastric conduit reconstruction was performed were excluded. Ethical clearance was obtained from the institutional Ethics Committee.

Chemoradiotherapy

Tumor volumes were delineated on a contrast-enhanced simulation computerized tomography scan, using the information from endoscopy and diagnostic contrast-enhanced computerized tomography based on the contouring guidelines provided by Wu et al. [18]; 41.4–45 Gray (Gy) in 23–25 fractions was delivered at 1.8 Gy per fraction over 5 weeks by volumetric modulated arc therapy or 3-dimensional conformal radiotherapy on Varian Clinac IX, planned on Eclipse 10.1.

Concurrent chemotherapy was administered as per CROSS protocol [1] on days 1, 8, 15, 22, and 29 using paclitaxel (50 mg/m^2) and carboplatin with AUC = 2 mg/mL/min. Weekly hemogram, serum electrolytes, renal functions, and liver functions were monitored. Chemotherapy was delayed by 1 week if ANC <1,000, Hb <9 g%, and platelets <50,000. Chemotherapy was withheld if febrile neutropenia set in or the patient developed bleeding requiring >2 platelet transfusions.

Surgery

Feeding jejunostomy was performed for patients with grade 3/4 dysphagia. Eight patients underwent ischemic preconditioning of the stomach at the time of feeding jejunostomy.

All patients underwent transthoracic esophagectomy with extended 2-field lymph node dissection and cervical esophagogastric anastomosis using the modified Orringer technique, 6–8 weeks after completion of NACRT. The stomach was tubularized, and the gastric conduit was brought through the posterior mediastinum into the neck. Esophagogastric anastomosis was performed by staplers or a hand-sewn technique. A 75-mm linear cutter was used to create a gastric conduit 4–5 cm wide, and the gastric conduit staple line was oversewn by hand. A cervical esophagogastric anastomosis was performed with either an end-to-side with hand-sewn continuous sutures (3–0 PDS) in monolayer or a posterior layer stapled and anterior layer with hand-sewn interrupted sutures.

AL was defined as "full-thickness defects involving the esophagus, anastomosis, staple line, or conduit, irrespective of the presentation or method of identification" as per the Esophagectomy Complications Consensus Group (ECCG) [19]. All patients underwent a contrast gastrografin swallow study for the diagnosis of AL between postoperative days 7–10. The results were documented, and surgical interventions were carried out, when clinically indicated.

Retrospective Contouring

The contours and plans of 27 patients were retrieved. The GF was delineated according to the recommendations by Goense et al. [12]. The superiormost sections of the stomach, visible within the dome of the diaphragm, were determined on the axial CT slices of 3 mm thickness. From that level, the gastric contour was delineated in 4 consecutive axial sections in the caudal direction. The resulting structure in 3 dimensions was defined as the GF (Fig. 1).

Plan Evaluation

From the executed plans for each of the patients, the mean dose (D_{mean}) received by the GF, maximum dose (D_{max}) received by the GF, volume receiving 20 Gy (V20), V25, V30, and V35, and dose received by 50% of the volume of the GF (D50) were computed using the dose-volume histogram. Whether the anastomosis was in the field of radiation or not was also documented.

Statistical Methods

Dosimetric parameters were expressed with mean and standard deviation. Fisher's test, Student's *t* test, and Mann-Whitney U test were used to compare categorical, parametric, and nonparametric parameters. Univariable logistic regression models were used to analyze whether the different radiation dose and volume characteristics of the GF influenced the risk of AL. If the radiation dose parameters were to be found significantly related to AL, multivariable logistic regression would be used to assess the risk factors associated with AL. Statistical tests were performed using Stata version 14.0, and p value <0.05 was considered as significant.

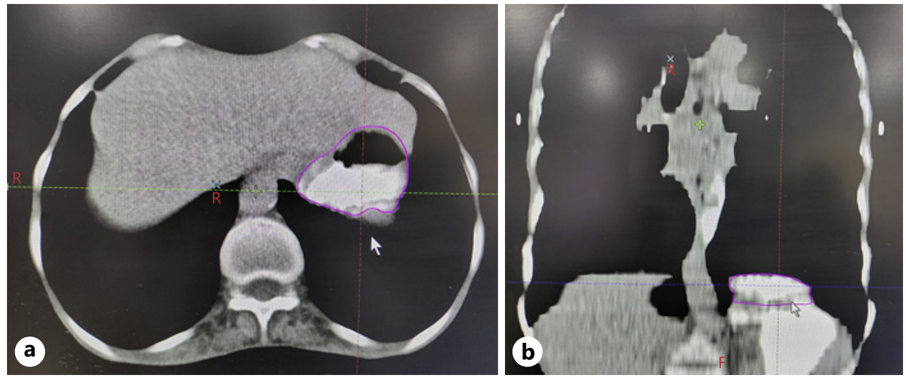

Fig. 1. a Axial section of the planning CT scan showing the contoured GF (white arrow). **b** Coronal section of the planning CT scan showing the contoured GF (white arrow). GF, gastric fundus; CT, computed tomography.

Results

Records of 47 patients diagnosed with esophageal carcinoma, who have received NACRT and underwent surgery between 2015 and 2018, were available for retrospective analysis. Of these, 13 patients underwent chemoradiation in other hospitals owing to waiting periods and were, hence, excluded from dosimetric analysis. Three patients did not complete NACRT; 2 refused surgery, 1 died after NACRT, and 1 patient developed omental deposits after NACRT. Thus, the remaining 27 records were used for analysis. The baseline characteristics have been described in Table 1.

The age of the patients ranged from 30 to 70 years (mean = 51 years; SD = 10.5). The majority of the patients (23/27 [85%]) had squamous cell carcinoma, while 15% (4/27) had adenocarcinoma. 30% of the patients had T3 tumors, while 70% had T4 tumors. 52% had N0 disease, 40.7% had N1, and 7.4% had N2 disease. 15/27 (56%) patients had involvement of lower 1/3 of the esophagus, 10/27 (37%) had involvement of the midthoracic esophagus, and 2/27 (7%) had lesion involving the upper thoracic esophagus. 22/27 (81.5%) of the patients received volumetric modulated arc radiation, while 5/27 (18.5%) received 3D conformal radiation.

All 27 patients underwent thoracolaparoscopic esophagectomy with 2-field esophagectomy and cervical esophagogastric anastomosis. 8/27 patients had undergone gastric ischemic preconditioning at the time of FJ. The mean duration between completion of NACRT and surgery was 54 ± 11 days.

The mean volume of the contoured fundus was 21.78 ± 13.62 cc. 11/27 (40%) patients developed postoperative AL, among which 7 patients had distal third and 4 patients had middle esophageal lesions. Four of five patients treated by 3-dimensional conformal radiothera-

Table 1. Baseline characteristics

Characteristics	With AL (n = 11)	Without AL (n = 16)
Gender		
Female	6	10
Male	5	6
Age, years	47±8	53±10
ECOG PS		
1	5	14
2	6	2
BMI	18.68±2.47	19.65±1.85
Level of lesion		
Upper thoracic	0	2
Mid thoracic	4	6
Lower thoracic	7	8
Clinical T stage		
cT1	0	0
cT2	0	0
cT3	8	13
cT4	3	3
Clinical N stage		
cN0	1	11
cN1	9	4
cN2	1	1
cN3	0	0
Tumor histology		
Squamous cell carcinoma	10	13
Adenocarcinoma	1	3
Radiation technique		
VMAT	7	15
3DCRT	4	1
Ischemic preconditioning		
Performed	2	6
Not performed	9	10
Gap between NACRT and surgery, days	51±8	56±12

AL, anastomotic leak; VMAT, volumetric modulated arc therapy; 3DCRT, 3-dimensional conformal radiotherapy; NACRT, neoadjuvant chemoradiotherapy.

Table 2. Dose-volume parameters for the GF as an organ at risk

	Without leak (n = 16)			With leak (n = 11)			p value
	mean	SD	median (IQR)	mean	SD	median (IQR)	
D_{mean}, Gy	29.59	14.53	35.75 (18.61–41.35)	30.88	15.75	37.76 (24.89–42.59)	0.82
D_{max}, Gy	38.90	12.59	43.21 (39.56–44.34)	39.19	14.11	44.88 (43.16–46.01)	0.95
V20, %	71.59	42.36	97.79 (31.21–100)	75.45	38.81	100 (71.74–100)	0.81
V25, %	64.57	43.12	92.57 (15.08–100)	68.98	40.20	98.13 (42–100)	0.79
V30, %	57.57	43.88	72.33 (8.83–100)	63.48	42.18	86.42 (23.25–100)	0.72
V35, %	52.20	44.69	60.38 (4.35–98.9)	58.87	43.90	68.86 (12.91–100)	0.70
D50, %	30.94	15.06	37.18 (18.76–42.14)	34.56	13.62	40.44 (32.4–42.26)	0.56
Volume of the GF, cm^3	21.69	16.98	16.68 (12.78–22.65)	21.92	7.04	23.1 (17.77–24.37)	0.96

GF, gastric fundus; IQR, interquartile range

Table 3. Logistic regression analysis anastomotic leak versus dosimetric parameters

Dosimetric parameters	OR	CI	p value
D_{mean}	1.006	0.95–1.06	0.81
D_{max}	1.001	0.94–1.06	0.95
V20	1.002	0.98–1.02	0.8
V25	1.002	0.98–1.02	0.78
V30	1.003	0.98–1.02	0.72
V35	1.003	0.98–1.02	0.69
D50	1.019	0.95–1.08	0.54
Volume	1.001	0.94–1.06	0.96

OR, odds ratio; CI, confidence interval.

py developed leaks, whereas only 7/22 patients treated by volumetric modulated arc therapy developed AL (p = 0.12).

There was no statistically significant difference between the dose-volume parameters of the GF in patients with AL versus those without AL (Table 2). Univariate logistic regression studies revealed no significant correlation between the dose-volume parameters and the leak rates (Table 3). Subgroup analysis to study the impact of the radiotherapy technique on the dose-volume parameters could not demonstrate a significant difference in the dose-volume parameters of the GF with respect to technique (Table 4). 8/27 patients underwent ischemic preconditioning of the gastric conduit, out of which only 2 patients had a postop AL. 19/27 patients did not undergo any preconditioning of the gastric conduit, out of which 9 experienced AL. However, a statistically significant benefit could not be established (Fisher exact test p = 0.4) (Table 5). Multivariate analysis was not performed since none of the factors were significant on univariate analysis.

Discussion

In our study, we evaluated the relationship between the dose received by the GF and the occurrence of AL in patients with esophageal cancer treated with NACRT followed by transthoracic esophagectomy with gastric tube reconstruction and cervical anastomosis. Overall, 40% (11/27) of our patients developed AL. In our study, several dose parameters which were postulated to have an impact on AL did not influence AL rates.

AL is defined as a disruption of the esophagogastric anastomosis which is diagnosed by radiographic examination using contrast, endoscopy, or clinical signs and symptoms. AL is a common complication following esophagectomy with the incidence ranging between 10 and 25% for cervical and 3–25% for intrathoracic anastomoses [1, 5, 10–14]. ALs are associated with severe morbidity and mortality. The reported mortality rates among patients who develop AL range between 11 and 14% [6].

Factors which influence the development of AL include the anastomotic technique (hand sewn vs. stapled vs. hybrid) [7], site of the anastomosis (cervical vs. thoracic) [8–10], the type of conduit used for anastomosis (stomach vs. colon vs. small bowel) [11], and NACRT [1, 2, 12–14]. All our patients underwent NACRT and underwent cervical anastomosis using the stomach as the conduit. A retrospective analysis by Morita et al. [13] showed that AL developed more frequently in patients who received NACRT than in the patients who under-

Table 4. Subgroup analysis of dose-volume parameters for the GF of patients treated by 3DCRT/VMAT versus anastomotic leak

	With leak (n = 11)		Mann-Whitney U p value	Without leak (n = 16)		Mann-Whitney U p value
	VMAT (n = 7), median (IQR)	3DCRT (n = 4), median (IQR)		VMAT (n = 15), median (IQR)	3DCRT (n = 1), median	
D_{mean}, Gy	37.76 (26.98–42.59)	22.25 (2.00–44.14)	0.78	36.23 (20.79–40.1)	1.23	0.12
D_{max}, Gy	44.94 (43.83–46.08)	33.62 (7.05–45.13)	0.10	43.27 (41.08–44.62)	1.85	0.12
V20, %	100 (75.5–100)	50 (0–100)	0.47	98 (42.43–100)	0	0.17
V25, %	98.13 (53.45–100)	50 (0–100)	0.61	93.11 (20.97–100)	0	0.17
V30, %	86.42 (34.5–100)	50 (0–100)	0.61	72.4 (12.47–100)	0	0.18
V35, %	68.86 (20.04–100)	50 (0–100)	0.62	65.16 (5.75–99)	0	0.19
Volume of the GF, cm^3	23.1 (14.22–24.24)	22.96 (18.36–35.07)	0.31	16.1 (12.33–24.34)	19.53	0.75

GF, gastric fundus; 3DCRT, 3-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; IQR, interquartile range.

Table 5. Subgroup analysis for patients with and without ischemic preconditioning versus anastomotic leak

Ischemic preconditioning	Patients with AL	Patients without AL	Fisher test p value
Performed	2	6	0.40
Not performed	9	10	
Total	11	16	

AL, anastomotic leak.

went surgery alone (28 vs. 17%, respectively, $p < 0.01$). The CROSS study demonstrated a similar difference of 22 versus 16% between NACRT and surgery-alone cohorts [1]. Goense et al. [12] had a leak rate of 26% in their study of 97 patients who received NACRT. AL was identified in 40% of patients in our study. The leak rates in our study were higher than those reported in the literature.

Since the stomach is used as a conduit for anastomosis and NACRT showed higher leak rates, the possibility of considering the dose received by the GF as a predictor for AL evolved. Goense et al. [12] studied 97 patients who received 41.4 Gy in 23 fractions and paclitaxel/carboplatin-based NACRT followed by transthoracic esophagectomy with 2-field lymphadenectomy and cervical anastomosis using a gastric conduit. AL was identified in 26% (25/97) of the patients. A mean dose more than 31.4 Gy was associated with leakage rates of 43 versus 15% for <31.4 Gy with adjusted odds ratio 1.05 per 1-Gy increase, 95% confidence interval: 1.002–1.10, and $p = 0.043$. In our study, the D_{mean} was 29.6 ± 14.5 Gy in patients without AL and 30.9 ± 15.8 Gy in patients with AL ($p = 0.83$).

Vande Walle et al. [16] studied the AL rates after 36 Gy and cisplatin/5-FU based NACRT followed by Ivor Lewis esophagectomy and intrathoracic anastomosis. AL was identified in 13% (7/54) of patients. The median D50 of the GF was 33 Gy in patients with AL and 18 Gy in patients without AL ($p = 0.024$). Using receiver operating characteristic analysis, the D50 limit on the GF for AL was defined as 29 Gy. In our study, the median D50 was 40.44 Gy in patients with AL and 37.18 Gy in patients without AL.

However, other studies have shown conflicting reports. Koeter et al. [17] and Ermenc et al. [14] observed that the radiation dose to the GF did not influence the risk of AL. Koeter et al. [17] studied 41.4 Gy in 23 fractions and paclitaxel/carboplatin-based NACRT followed by transhiatal esophagectomy with cervical anastomosis using a gastric tube. AL was identified in 25.5% (13/53) of the patients. In their multivariate analysis, they found no significant correlation between V20–40, mean dose to the GF, and AL rates. Ermenc et al. [14] retrospectively analyzed records of 37 patients with Siewert I and II gastroesophageal junction cancer. A lower leak rate of 13.5% was reported, and no statistically significant relation with D_{mean}/D_{max}/median dose received by the fundus was available for analysis. The median D50 was 45.6 Gy in patients with AL and 46.0 Gy in patients without AL. The current study also did not find a statistically significant relation between the D_{max}, D_{mean}, V20–35 to the GF, and the occurrence of AL.

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Bang et al. [20] observed a higher incidence of AL when the anastomosis was placed inside the radiation field. The current study had 2 subjects with upper thoracic esophageal lesions, thus requiring inclusion of a supraclavicular field. These 2 patients, however, did not develop any AL after surgery.

In our study, gastric ischemic preconditioning was performed in 8 patients prior to NACRT by ligation of the left and short gastric vessels. Pham et al. [21] demonstrated, by immunohistologic analysis, a 29% increase in the microvascular density following short gastric vessel ligation and 67% increase after ligation of both short and left gastric vessels ($p < 0.0001$). A meta-analysis by Heger et al. [22] showed that there was no significant reduction in the incidence of leakage in the conditioned group compared to control patients (OR 0.76; 95% CI: 0.51–1.13; $p = 0.18$). However, the leaks were less severe, and the reoperation rates were lower (24.4 vs. 69%; $p = 0.001$) in preconditioned patients. In our study, AL was 2/8 (25%) in preconditioned versus 9/19 (47%) in those who did not undergo preconditioning ($p = 0.4$), similar to the results reported by Zahedi et al. [23] and Nguyen et al. [24].

The major limitations of our study included the retrospective nature of the study and a relatively small sample size. We did not use respiratory gating in our patients. The position of the GF can vary considerably with respiratory motion [25, 26]. Hence, the dose-volume parameters of the GF may not accurately represent the doses received during daily fractions of radiation. It is at best an approximation.

Conclusion

There was no significant negative impact of dose received by the GF in NACRT on the risk of AL in our study. Various dose parameters which have been postulated to have an impact on AL such as mean dose, V25, V30, V35, and D50 failed to show significance. Further studies with a larger sample size are required to clarify this issue.

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Statement of Ethics

This retrospective study has been approved by the Institutional Ethics Committee (Human Studies) at the Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER) – JIP/IEC/2018/0117. In view of the retrospective nature of the study which does not reveal any patient's identity, waiver of consent has been granted by the institutional Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Nikhila Radhakrishna: study concepts, study design, data acquisition, analysis, and interpretation, and manuscript preparation. Dr. Shyama Prem Sudha: study concepts, study design, data analysis and interpretation, and manuscript preparation, editing, and review. Dr. Raja Kalayarasan: study concepts, data analysis and interpretation, and manuscript editing and review. Dr. Prasanth Penumadu: study concepts, data analysis and interpretation, and manuscript editing and review.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

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