Radiation to the Gastric Fundus Increases the Risk of Anastomotic Leakage After Esophagectomy

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Background. **Concerns have been raised regarding the toxicity of neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer that could contribute to an increased risk of postoperative complications. The aim of this study was to determine the influence of the radiation dose to the gastric fundus on the risk of postoperative anastomotic leakage in patients undergoing nCRT followed by transthoracic esophagectomy.**

Methods. **Between January 2012 and July 2015, 97 consecutive patients who underwent nCRT followed by transthoracic esophagectomy were included in this single-center cohort study. The gastric fundus was contoured on the pretreatment planning computed tomography. Within this contour, dose-volume histogram variables were calculated, and logistic regression analysis was used to determine their influence on the risk of anastomotic leakage.**

Results. **In 25 of 97 patients (26%) anastomotic leakage occurred. The mean radiation dose to the gastric fundus was significantly higher in patients with than without leakage (median 35.6 Gy versus 24.9 Gy, respectively, $p = 0.047$). A mean dose more than versus less than 31.4 Gy was associated with leakage rates of 43% versus 15%, respectively. Adjusted for tumor location, clinical T stage, and radiation method, the mean radiation dose to the gastric fundus remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted odds ratio 1.05 per 1-Gy increase, 95% confidence interval: 1.002 to 1.10, $p = 0.043$).**

Conclusions. **Efforts should be made to minimize the radiation dose to the gastric fundus when planning nCRT for esophageal cancer, because higher dose levels to the gastric fundus are associated with an increased risk of anastomotic leakage after subsequent transthoracic esophagectomy and cervical anastomosis.**

(Ann Thorac Surg 2016;102:1798–804)

Esophagectomy is the cornerstone of curative treatment for esophageal cancer, and the long-term survival benefit of neoadjuvant chemoradiotherapy (nCRT) is well established [1–3]. Over the past decades, a steady decrease in postoperative mortality has been achieved by improvements of surgical techniques and perioperative management [4]. However, anastomotic leakage of the esophagogastrostomy remains one of the major complications negatively affecting surgical and oncologic outcomes [4, 5]. Reported incidence rates of anastomotic leakage after esophagectomy range between 6% and 41% [2, 6–10].

Concerns have been raised regarding the toxicity of nCRT that could contribute to an increased risk of postoperative complications. Several nonrandomized studies reported an increase in surgical morbidity in patients that underwent nCRT [11–14]. Postoperative pulmonary complications have convincingly been related to neoadjuvant radiation dose to the lungs [15–17]. However, the influence of neoadjuvant radiation on postoperative anastomotic leakage has been less extensively studied. In this respect, radiation dose to the gastric fundus is of interest because this part of the stomach is used for the esophagogastric anastomosis.

The available evidence on the potential association between neoadjuvant radiation dose to the gastric fundus and the risk of anastomotic leakage after esophagectomy is equivocal [18, 19]. Therefore, currently it remains unclear whether efforts should be made to limit the dose to the gastric fundus when planning neoadjuvant radiation

Accepted for publication Aug 8, 2016.

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Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.08.027

treatment for esophageal cancer. The aim of the present study was to determine the influence of neoadjuvant radiation dose to the gastric fundus on the risk of anastomotic leakage in a large homogeneous cohort of patients with esophageal cancer undergoing nCRT followed by transthoracic esophagectomy and cervical anastomosis.

Material and Methods

Study Population

This study was approved by our institutional review board, and the informed consent requirement was waived. From a prospectively acquired database, consecutive patients with esophageal or gastro-esophageal junction (GEJ) cancer were identified who underwent nCRT followed by transthoracic esophagectomy between January 2012 and July 2015 at our tertiary referral center. 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.

Treatment Protocol

The nCRT regimen consisted of a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy in 5 weeks combined with weekly intravenous administration of carboplatin/paclitaxel [2]. Some patients (with a clinical T4b tumor) received a total radiation dose of 50.4 Gy in 28 fractions of 1.8 Gy in 6 weeks. The gross tumor volume (GTV) was defined by the primary tumor and any suspicious regional lymph nodes as determined by all available information (endoscopy, endoscopic ultrasound, computed tomography [CT], and ^{18}F-fluorodeoxyglucose positron emission tomography if available). The clinical target volume (CTV) included the GTV plus a cranial and caudal margin of 3 cm; in case of tumor extension into the stomach a caudal margin of 2 cm was chosen. In addition, the CTV included a radial margin around the GTV of 0.5 cm, adjusted for anatomical structures. The planning target volume was defined as the CTV plus a margin of 1 cm in all directions. Patients were treated by either three-dimensional conformal radiotherapy or intensity-modulated radiotherapy.

Surgical treatment consisted of a transthoracic esophagectomy with en bloc two-field lymphadenectomy and gastric conduit reconstruction. A linear stapler (GIA 80; 3.8 mm; Covidien, Mansfield, MA) was used to create a gastric conduit 4 cm wide, and the gastric conduit staple line was oversewn by hand. A cervical esophagogastric anastomosis was performed end-to-side with hand-sewn continuous sutures (3-0 PDS) in monolayer. The surplus of the gastric conduit was removed with a stapling device (GIA 80; 3.8 mm; Covidien) in all patients.

Data Collection

Clinical patient characteristics, treatment details, and surgical outcome data were collected from the prospectively acquired database. Anastomotic leakage was defined as postoperative demonstration of saliva through the cervical wound, extravasation of water-soluble contrast during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy or surgical reintervention [8].

Image Analysis

The gastric fundus was retrospectively contoured on the pretreatment planning CT (section thickness: 3.0 mm) using Volumetool software [20]. After consultation with the researchers of a previous study [18], the boundaries of the delineated gastric fundus were standardized in accordance with the applied method in that study: the most proximal part of the stomach located within the diaphragmatic dome was determined in the transverse plane. From that point, four consecutive transverse sections in caudal direction were delineated following the boundaries of the stomach at these levels. The resulting region of interest in three dimensions was defined as the gastric fundus. The following dose-volume histogram variables were calculated from the region of interest: volume, mean dose, minimum dose, dose that covered at least 50% of the volume, maximum dose, V20, V25, V30, and V35 (ie, percentage of the volume that received at least 20, 25, 30, and 35 Gy, respectively).

Statistical Analysis

The association of baseline characteristics with anastomotic leakage was studied univariably. The χ^2 test (or Fisher's exact test in case of small cell counts) was used to compare categorical variables, whereas the Student's *t* test and Mann-Whitney *U* test were used to compare parametric and nonparametric continuous parameters, respectively. Univariable logistic regression models were used to analyze whether the different radiation dose and volume characteristics of the gastric fundus influenced the risk of anastomotic leakage. For the radiation dose parameters that were significantly related to anastomotic leakage, receiver operating characteristics (ROC) analysis was performed to identify ideal cutoff values in which equal weight was given to sensitivity and specificity.

Three baseline characteristics, including tumor location, clinical T stage, and radiation method, were thought to potentially confound the association between radiation dose to the gastric fundus and anastomotic leakage, by potentially influencing both predictor (radiation dose) and outcome (anastomotic leakage). Therefore, the (mean) radiation dose to the gastric fundus was entered in a multivariable logistic regression model together with the three potential confounders to study the independent influences on the risk of anastomotic leakage. High correlations between some parameters were expected (eg, V20 to V35 values and mean dose), resulting in the statistical problem of (multi)collinearity. Therefore, from these highly correlated pairs of parameters only the mean dose was preselected for the multivariable model. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY). A *p* value of less than 0.05 was considered statistically significant.

Results

In the study period a total of 115 patients with esophageal cancer were treated with nCRT followed by transthoracic

esophagectomy. Of these patients, 18 were excluded because they received radiotherapy at another institution (n = 15), the treatment planning CT did not include the level of the gastric fundus (n = 1), the quality of the treatment planning CT was insufficient (n = 1), or no surgical resection was performed due to unsuspected metastatic disease (n = 1).

Among the 97 included patients, 25 (26%) experienced postoperative anastomotic leakage. Of the patients with anastomotic leakage, treatment consisted of opening of the cervical wound and nil-by-mouth in 4 patients (16%), endoscopic reintervention (stent placement) in 7 patients (28%), and surgical reintervention in 14 patients (56%). Postoperative in-hospital mortality occurred in 3 of 97 patients (3.1%), of which two experienced anastomotic leakage. In 30 of 97 patients (31%) postoperative pneumonia was diagnosed. No significant difference in incidence of pneumonia among patients with or without anastomotic leakage was found (24% versus 33%, respectively, $p = 0.384$). Baseline characteristics and their univariable association with anastomotic leakage are presented in Table 1. None of the studied baseline characteristics were significantly associated with the occurrence of postoperative anastomotic leakage.

A comparison of gastric fundus radiation dose characteristics for patients with and without anastomotic leakage is shown in Table 2. In univariable logistic regression analysis, the mean radiation dose to the gastric fundus was significantly higher in patients with anastomotic leakage than in patients without anastomotic leakage (median 35.6 Gy, interquartile range [IQR]: 20.2 to 39.9 Gy versus 24.9 Gy, IQR: 11.9 to 35.1 Gy, respectively, $p = 0.047$). In addition, in patients with anastomotic leakage the minimum radiation dose to the gastric fundus was significantly higher than for patients without leakage (15.1 Gy, IQR: 11.9 to 26.1 Gy versus 8.9 Gy, IQR: 2.8 to 16.9 Gy, $p = 0.006$) (Fig 1A). In addition, univariable analysis showed that percentages of the gastric fundus volume receiving a minimal dose of 25, 30, and 35 Gy (ie, V25, V30, and V35, respectively) were significantly higher in patients with anastomotic leakage (Fig 1B). In 32 of 97 included patients (33%) the maximum dose given to the fundus was as high as the dose given to the tumor. The volume of the gastric fundus and other radiation dose characteristics were not significantly associated with anastomotic leakage. Two typical examples of dose distributions in relation to the gastric fundus in patients with and without anastomotic leakage are depicted in Figure 2.

Ideal cutoff values as determined by ROC analysis for the variables that were significantly related to anastomotic leakage are presented in Table 3. For example, the mean dose to the gastric fundus above which the risk of anastomotic leakage increased significantly was determined at 31.4 Gy. Patients with a mean dose more than versus less than this threshold experienced anastomotic leakage in 43% versus 15% of cases, respectively.

The mean gastric fundus radiation dose given to proximal, middle, distal, or GEJ tumors were 0.95 ± 1.5 Gy, 15.6 ± 13.9 Gy, 28.9 ± 10.7 Gy, and 34.4 ± 6.7 Gy, respectively. In multivariable analysis, the association between the (mean) neoadjuvant radiation dose to the gastric fundus and postoperative anastomotic leakage appeared not to be confounded by tumor location, clinical T stage, or radiation method (Table 4). Adjusted for these factors, the mean radiation dose to the gastric fundus remained significantly and independently associated with an increased risk of anastomotic leakage (adjusted odds ratio 1.05 per 1-Gy increase, 95% confidence interval: 1.002 to 1.10 per 1-Gy increase, $p = 0.043$).

Comment

This study demonstrates that the neoadjuvant radiation dose to the gastric fundus in patients with esophageal cancer has a significant impact on the risk of anastomotic leakage after transthoracic esophagectomy with cervical anastomosis. Several radiation dose characteristics appeared to be significant predictors of anastomotic leakage, including the mean and minimum dose, V25, V30, and V35. These findings suggest that efforts should be made to limit the dose to the gastric fundus when planning neoadjuvant radiation for esophageal cancer with planned transthoracic esophagectomy. Overall, 26% of patients experienced anastomotic leakage in this series. According to the results of this study, limiting the mean dose to 31 Gy could decrease the risk of anastomotic leakage to 15% in this setting.

Two previous studies have reported on the relation between neoadjuvant radiation dose to the gastric fundus and the risk of postoperative anastomotic leakage [18, 19]. Similar to the present series, one study that included 54 patients treated with nCRT followed by Ivor-Lewis esophagectomy with intrathoracic anastomosis reported that the radiation dose to the gastric fundus was significantly related to the risk of anastomotic leakage [18]. However, in that study a different neoadjuvant treatment regimen (36 Gy in 20 fractions combined with fluorouracil and cisplatin) and surgical procedure (Ivor-Lewis esophagectomy with intrathoracic anastomosis) were applied [18]. Of note, neoadjuvant treatment according to the CROSS (neoadjuvant chemoradiotherapy plus surgery versus surgery alone for esophageal or junctional cancer) regimen as applied in the present study is currently regarded as the standard of care in many countries worldwide for patients with resectable locally advanced esophageal cancer [3].

In contrast, another recent study with 53 patients that underwent nCRT followed by transhiatal esophagectomy with cervical anastomosis found no influence of radiation dose to the gastric fundus on the occurrence of anastomotic leakage [19]. That study applied a similar neoadjuvant treatment regimen to the present series, but the surgical procedure (transhiatal esophagectomy with cervical anastomosis) was different [19]. However, transthoracic esophagectomy with en bloc radical lymphadenectomy as was performed in the present study is currently considered the preferred approach of oncologic esophagectomy [21, 22]. Therefore, in contrast to other studies, the association between radiation dose to the gastric fundus and anastomotic leakage was

Table 1. Baseline Characteristics

Characteristic	Anastomotic Leakage (n = 25)	No Anastomotic Leakage (n = 72)	*p* Value
Male sex	19 (76.0)	53 (73.6)	0.814
Age, y	64.9 ± 7.6	66.3 ± 7.3	0.414
BMI, kg/m^2	25.6 ± 4.6	25.5 ± 4.7	0.947
ASA score			0.262
I	5 (20.0)	14 (19.4)	
II	12 (48.0)	48 (66.7)	
III	8 (32.0)	10 (13.9)	
COPD	6 (24.0)	9 (12.5)	0.203
Cardiac comorbidity	7 (28.0)	25 (34.7)	0.538
Vascular comorbidity	12 (48.0)	33 (45.8)	0.852
Diabetes mellitus	4 (16.0)	10 (13.9)	0.751
History of smoking	17 (68.0)	52 (72.2)	0.688
Clinical T stage			0.104
cT1	0 (0.0)	1 (1.4)	
cT2	3 (12.0)	19 (26.4)	
cT3	19 (76.0)	47 (65.3)	
cT4	3 (12.0)	5 (6.9)	
Clinical N stage			0.529
cN0	5 (20.0)	19 (26.4)	
cN1	12 (48.0)	34 (47.2)	
cN2	7 (28.0)	15 (20.8)	
cN3	1 (4.0)	4 (5.6)	
Tumor histology			0.799
Adenocarcinoma	17 (68.0)	43 (59.7)	
Squamous cell carcinoma	8 (32.0)	27 (37.5)	
Other	0 (0.0)	2 (2.8)	
Tumor location			0.629
Proximal third of esophagus	2 (8.0)	6 (8.3)	
Middle third of esophagus	5 (20.0)	18 (25.0)	
Distal third of esophagus	15 (60.0)	41 (56.9)	
Gastroesophageal junction	3 (12.0)	7 (9.7)	
Radiation method			0.339
3D-CRT	11 (44.0)	24 (33.3)	
IMRT	14 (56.0)	48 (66.7)	
Radiation planning method			0.576
CT	7 (28.0)	19 (26.4)	
^{18}F-FDG-PET/CT	18 (72.0)	53 (73.6)	
Total radiation dose			1.000
41.4 Gy (23 × 1.8 Gy)	23 (92.0)	67 (93.1)	
50.4 Gy (28 × 1.8 Gy)	2 (8.0)	5 (6.9)	
Intraoperative blood loss mL	500 ± 295	502 ± 336	0.985

Values are n (%) or mean ± SD unless otherwise indicated.

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CT = computed tomography; IMRT = intensity-modulated radiotherapy; ^{18}F-FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; 3D-CRT = three-dimensional conformal radiotherapy.

analyzed under the circumstances of present-day standardized radical operation and standardized neoadjuvant chemoradiotherapy in the present study. In addition, sample sizes across the two previous reports [18, 19] were small with only a few events of anastomotic leakage (n = 7 and n = 13, respectively), which resulted in a substantial uncertainty of estimates and conclusions. This may be the reason for the more nuanced discriminatory ability of the mean dose to the gastric fundus to differentiate between patients with versus without leakage found in the present series (ie, area under the ROC curve 0.66; Table 3) compared with those found in the other two studies (area under the ROC curve 0.77 [18], and approximately 0.50 [19]).

Table 2. Univariable Logistic Regression Analysis of Gastric Fundus Dose Characteristics Among Patients With Versus Without Anastomotic Leakage

Characteristic	Anastomotic Leakage (n = 25)	No Anastomotic Leakage (n = 72)	OR (95% CI)	p Value
Volume, mL	11.1 [8.1–12.8]	11.8 [8.3–15.9]	0.92 (0.83–1.02)	0.121
Mean dose, Gy	35.6 [20.2–39.9]	24.9 [11.9–35.1]	1.04 (1.00–1.08)	0.047[a]
Minimum dose, Gy	15.1 [11.9–26.1]	8.9 [2.8–16.9]	1.06 (1.02–1.11)	0.006[a]
D50, Gy	39.0 [16.7–41.2]	21.8 [11.7–38.9]	1.03 (1.00–1.07)	0.054
Maximum dose, Gy	42.5 [40.9–43.0]	41.9 [23.2–42.7]	1.02 (0.98–1.05)	0.328
V20, %	94.5 [27.5–100]	60.0 [2.6–93.9]	1.12 (0.99–1.27)[b]	0.066
V25, %	90.1 [22.3–99.8]	38.3 [0.0–81.3]	1.15 (1.02–1.30)[b]	0.025[a]
V30, %	73.1 [17.9–96.1]	26.2 [0.0–76.5]	1.16 (1.02–1.31)[b]	0.021[a]
V35, %	63.4 [13.2–93.3]	17.4 [0.0–65.2]	1.16 (1.03–1.32)[b]	0.018[a]

[a] Significant difference between patients with versus without anastomotic leakage ($p < 0.05$). [b] OR per 10% increase in volume percentage.

Values are median [interquartile range] unless otherwise indicated.

CI = confidence interval; D50 = dose that covered at least 50% of the volume; OR = odds ratio; V20, V25, V30, V35 = percentage of the volume that received at least 20, 25, 30, and 35 Gy, respectively.

The current evidence concerning the influence of nCRT on postoperative anastomotic leakage rates remains equivocal. A recent meta-analysis including 11 randomized controlled trials comparing outcomes of patients undergoing nCRT followed by operation with patients who undergo operation alone found that nCRT did not seem to increase the risk of postoperative anastomotic leakage (pooled risk ratio 1.00, 95% confidence interval: 0.74 to 1.35, $p = 0.878$) [10]. However, another meta-analysis including 12 randomized controlled trials reported that nCRT potentially increases the risk of surgical morbidity, but that surgical morbidity was inconsistently reported across trials which impeded direct comparisons [1]. A retrospective analysis of 686 patients reported that anastomotic leakage developed more frequently in 376 patients who received nCRT than in the remaining patients who underwent operation alone (28% versus 17%, respectively, $p < 0.01$) [14]. The present study was not designed, and hence does not allow, to answer the question whether nCRT per se increases the risk of postoperative anastomotic leakage, but rather to determine whether the variability of radiation doses to the gastric fundus relates to the risk of leakage. In the present study the maximum radiation dose given to the fundus was not associated with anastomotic leakage, whereas the mean dose and V25, V30, and V35 were associated with leakage. These results indicate that a higher dose spread over a larger volume rather than a high absolute maximum dose is indicative for the risk of anastomotic leakage after esophagectomy.

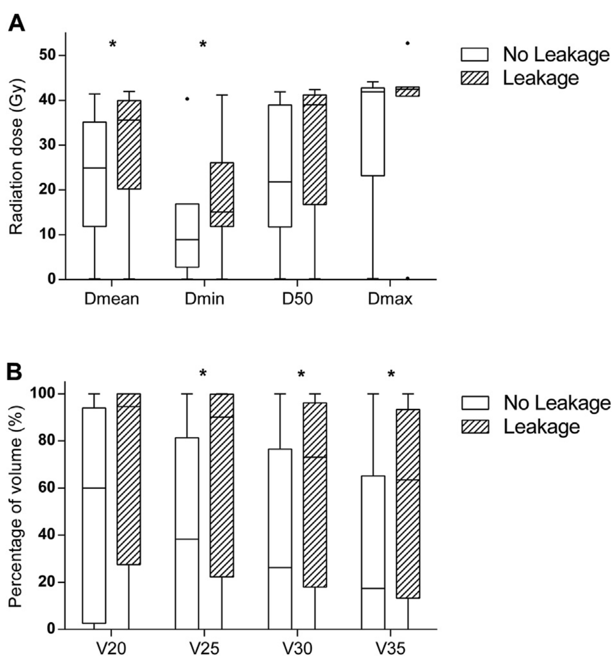

*Fig 1. Box plots showing (A) the distribution of gastric fundus dose variables (mean dose [Dmean], minimum dose [Dmin], dose that covered at least 50% of the volume [D50], maximum dose [Dmax]), and (B) the distribution of gastric fundus volume percentages receiving a minimum amount of Gy (percentage of the volume that received at least 25, 30, and 35 Gy [V20, V25, V30, V35, respectively]) between patients with and without anastomotic leakage. *Variables significantly associated with anastomotic leakage.*

The conflicting evidence in the literature on the influence of nCRT on the risk of postoperative anastomotic leakage may in part be explained by the various definitions that are used for leakage. In some studies, anastomotic leakage is defined as clinical or radiologic evidence of anastomotic dehiscence, whereas other definitions include only clinical leakage or anastomotic leakage that requires reintervention only. In the present study, anastomotic leakage was defined as any postoperative evidence of leakage (either clinically or radiologically confirmed, and either or not requiring reintervention), explaining the relatively high incidence rate of 26% in this study compared with other series [6, 7, 9, 10]. However, the leakage rate in this study appears to be comparable with the leakage rates of 22% to 30% that were reported in

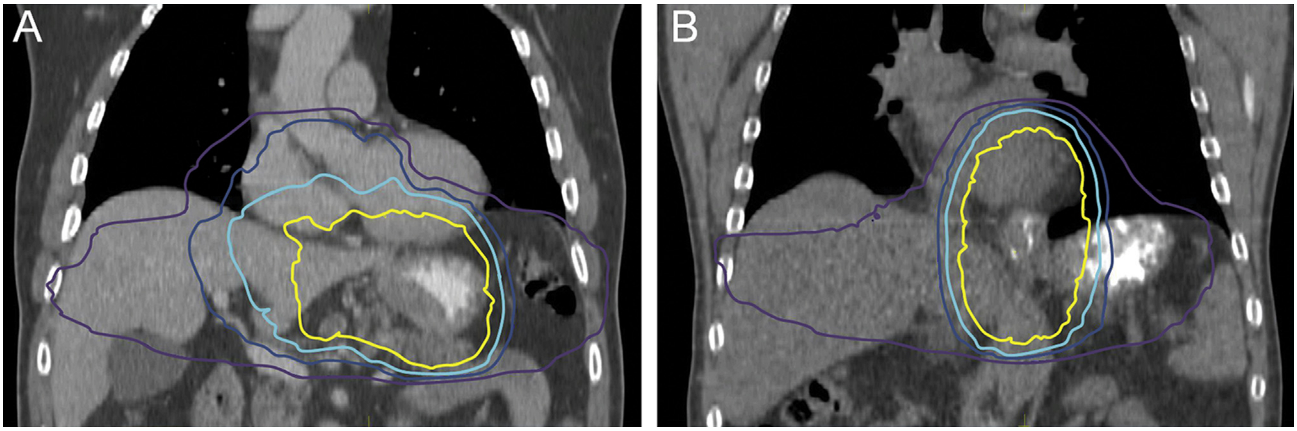

Fig 2. Examples of treatment planning computed tomographic (CT) scans with dose distributions in (A) a patient who experienced postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 41.2 Gy and (B) a patient who did not experience postoperative anastomotic leakage after receiving a mean dose to the gastric fundus of 11.8 Gy. The areas within the yellow, light blue, dark blue, and purple lines received at least 40, 30, 20, and 10 Gy, respectively.

the CROSS trial [2] which used the same nCRT regimen as the present study. In addition, in accordance with the CROSS trial [2], the definition for anastomotic leakage used in this study included subclinical leakage diagnosed on radiologic examination or endoscopy without clinical signs.

Sparing of the gastric fundus in radiation treatment planning for esophageal cancer could be achieved in various ways. The most obvious method would be the use of intensity-modulated radiotherapy as highly conformal radiation therapy technique providing greater target volume conformity, greater dose homogeneity, and an increased ability to control dose to adjacent normal structures, including the gastric fundus if desired. In this regard, it could be helpful if the radiation oncologist together with the surgeon assesses the radiation treatment planning to define which part of the fundus will be used for the gastro-esophageal anastomosis. In addition, one could think of reducing the caudal CTV margin in distal esophageal and GEJ tumors in the neoadjuvant setting to spare the gastric fundus, because the microscopic spread beyond the gross tumor is likely dealt with by surgical resection. This suggestion is supported by the finding that an irradical resection after nCRT, which occurs in 8% of patients [2], mostly involves microscopically positive surgical margins at the lateral (circumferential) borders rather than the caudal border [23]. However, such a margin-reducing strategy may increase the amount of residual tumor after nCRT outside the radiation field, which has been shown to negatively affect survival [24]. Finally, assessment of radiation dose to the gastric fundus could aid in individualized risk estimation of anastomotic leakage after esophagectomy.

Certain limitations apply to this study. First, although the largest study in this field, the sample size was relatively small, hindering a more extensive multivariable analysis. Second, this study is limited by the retrospective nature of the analysis, which impedes adjustment for all potential factors that could explain our findings. Third, the gastric fundus is susceptible to breathing-induced organ motion,

Table 3. Receiver Operating Characteristics Analysis of Gastric Fundus Dose Characteristics Among Patients With Versus Without Anastomotic Leakage

Characteristic	AUC	Ideal cutoff	SE, %	SP, %	PPV, %	NPV, %
Mean dose	0.66	31.4 Gy	64.0	70.8	43.2	85.0
Minimum dose	0.65	10.9 Gy	84.0	54.2	38.9	90.7
V25	0.65	89.7%	52.0	80.6	48.1	82.9
V30	0.65	59.3%	60.0	70.8	41.7	83.6
V35	0.65	54.7%	60.0	72.2	42.9	83.9

AUC = area under the receiver operating characteristics curve; NPV = negative predictive value; PPV = positive predictive value; SE = sensitivity; SP = specificity; V25, V30, V35 = percentage of the volume that received at least 25, 30, and 35 Gy, respectively.

Table 4. Results of Multivariable Logistic Regression Analysis With Anastomotic Leakage as Outcome Variable

Characteristic	OR (95% CI)	*p* Value
Tumor location		0.432
Proximal or middle third of esophagus	1.00 (ref)	
Distal third of esophagus or GEJ	0.60 (0.16–2.17)	
Clinical T stage		0.132
cT1–2	1.00 (ref)	
cT3–4	2.81 (0.73–10.77)	
Radiation method		0.398
3D-CRT	1.00 (ref)	
IMRT	0.65 (0.25–1.74)	
Mean radiation dose to gastric fundus, Gy	1.05 (1.002–1.10)	0.043*

CI = confidence interval; GEJ = gastro-esophageal junction; IMRT = intensity-modulated radiotherapy; OR = odds ratio; ref = reference; 3D-CRT = three-dimensional conformal radiotherapy.

which could have altered radiation dose calculations. Because no daily imaging information was available we were not able to compensate for organ motion of the stomach or for day-to-day treatment variations. Finally, unlike in other studies [18, 19] we decided not to exclude patients with proximal and middle esophageal tumors. However, this decision was made deliberately to increase the observed variability of gastric fundus doses across patients, which increases the statistical power and precision of the effect estimates. The potential confounding effect of the resulting heterogeneity on the studied association between radiation dose and anastomotic leakage was corrected for in multivariable analysis.

In conclusion, this study demonstrates that the neoadjuvant radiation dose to the gastric fundus is associated with the risk of postoperative anastomotic leakage in patients with esophageal cancer treated with nCRT followed by transthoracic esophagectomy and cervical anastomosis. This finding is important for clinical practice because it suggests that efforts should be made to minimize the radiation dose to the gastric fundus when planning neoadjuvant chemoradiotherapy for esophageal cancer.

The authors wish to thank Dr G.H. Bol, computer scientist at the Department of Radiotherapy, University Medical Center Utrecht, The Netherlands, for his valuable contribution to the radiation dose calculations involved in this manuscript. In addition, the authors wish to thank the research group of Prof. P. Pattyn from the University Hospital Gent, Belgium, for their input in determining a proper contouring method.

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