

Original Research Article

Radiation dose mapping and anastomotic complications after trimodality therapy for esophageal cancers



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ABSTRACT

Background and purpose: There is conflicting evidence with respect to the correlation between neoadjuvant chemoradiation and anastomotic complications following trimodality therapy in patients with esophageal cancer. We aimed to analyze the relationship between their dosimetry and any resulting anastomotic complications.

Materials and methods: The medical records of 51 consecutive patients who underwent trimodality therapy between 2007 and 2014 were retrospectively reviewed. We analyzed the differences in the mean dose received by regions of the esophagus relative to the landmark of the azygous vein and the stomach to correlate the development of an anastomotic complication using nonparametric rank-sum tests.

Results: Anastomotic leakage and stricture rates were 12% and 22%, respectively. Patients with anastomotic complications received a statistically significant higher mean dose to the esophagus at the level of the azygous vein (0.0 cm) and lower (up to –2.7 cm) (28.4–42.2 Gy vs. 10.3–27.6 Gy, $p < 0.04$). There were no differences noted in mean gastric doses. Median follow up time was 30.9 months. Median overall survival and disease free survival of our patient cohort was 34.4 months and 22.5 months, respectively. The development of an anastomotic complication did not affect survival outcomes.

Conclusion: Patients who experienced anastomotic complication after trimodality therapy for esophageal cancer were more likely to have received a higher mean esophageal dose around the proximity of the azygous vein, where intrathoracic anastomoses most commonly occur. Communication between surgical and radiation oncologists regarding the anastomotic location may be an important consideration in planning for trimodality therapy in reducing potential anastomotic complications.

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1. Introduction

Esophageal carcinomas represent a common and lethal malignancy worldwide. Surgical resection has long been considered an integral component of curative treatment. Patients undergoing esophagectomy still have poor outcomes, however, with 5-year overall survival rates approaching 33% [1]. A previous meta-analysis has supported the delivery of neoadjuvant chemoradiotherapy with a hazard ratio of 0.78, and an absolute benefit in overall survival of 8.7% at 2 years [2]. Furthermore, a recently published phase III randomized-controlled trial has demonstrated a two-fold increase in median survival with the addition of

neoadjuvant chemoradiation, using more modern 3D-planning radiotherapy techniques [3].

Despite its proven benefits, neoadjuvant chemoradiation has been associated with significant toxicities, including anastomotic complications, which have a deleterious impact on morbidity and quality of life after an esophagectomy [4]. The impact of ionizing radiation on toxicity is dose-related, and as such, radiation prescription doses, planning algorithms and delivery methods all have a direct impact on radiation exposure to adjacent healthy tissues. The frequency of these anastomotic complications varies significantly in the literature, with reported rates of anastomotic leaks of 0–26% [5] and strictures of 10–56% [6]. Moreover, with regards to the impact of neoadjuvant chemoradiotherapy, there is disparate evidence as several studies seem to demonstrate higher rates of anastomotic complications [7,8], while others, including the phase III trial published by van Hagen et al., do not [3,9,10].

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One challenge that may contribute to the wide variation of complications rates is the lack of consensus in definitions. Given this discrepancy, the nuances of neoadjuvant therapy, such as radiation dosimetry, may help tease out factors that contribute to the development of these complications. Indeed, two studies have investigated the dosimetry of the stomach specifically (in patients who would go on to have a gastric conduit), but they produced differing conclusions regarding the impact of radiation dose to the proximal stomach on subsequent rates of anastomotic complications [11–13].

Therefore, the objective of this study is to explore any potential association between radiation dose delivered to both the proximal esophagus and gastric fundus, on the subsequent development of anastomotic complications when standard neoadjuvant chemoradiation regimens are utilized in the management of resectable esophageal cancers. We hypothesize that there is a direct relationship between tissue radiation dose and anastomotic complications.

2. Methods and materials

2.1. Study design and endpoints

This is a single institution retrospective review investigating the impact of radiation dose to the esophagus and stomach on anastomotic complication rates in patients treated with trimodality therapy. Our institution serves a region of 1.3 million people as the sole provider for oncologic care [14]. End points included anastomotic complications, including both anastomotic leaks and stricture rates, as well as pulmonary and cardiac complication rates. We also reviewed overall and disease free survival outcomes.

Following institutional research ethics board approval, we retrospectively identified consecutive patients who underwent neoadjuvant chemoradiation followed by esophagectomy from January 1, 2007 to December 31, 2014 inclusive. Patients were identified through multiple sources including the regional cancer center database, hospital medical records, and Division of Thoracic Surgery Quality Monitoring System [15]. Patients for analysis included those with a pathologically-diagnosed esophageal carcinoma with no evidence of metastatic disease on initial staging. The majority of patients underwent FDG-18 PET-CT and endoscopic ultrasound for initial staging. These patients were required to have neoadjuvant concurrent chemoradiation followed by esophagectomy within 4 months. Patients who did not have a retrievable radiotherapy plan for dosimetric analysis were excluded.

2.2. Treatment details

Esophagectomy and lymphadenectomy were performed by one of six thoracic surgeons, most commonly with a right transthoracic approach. Both open and minimally invasive approaches were utilized. In patients with a transthoracic anastomosis, transection of the esophagus occurred approximately at the level of the azygous vein and the anastomosis was constructed with a gastric conduit either using a handsewn or stapling technique. The location of the anastomosis was verified by carefully reviewing data from operative reports, contrast esophagograms, and postoperative endoscopy reports.

Six radiation oncologists participated in the delivery of radiotherapy, with the total dose ranging from 41.4 to 50.4 Gy in 23–28 fractions using either a one or two-phase technique. Patients were treated using three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) technique. The gross tumor volume (GTV) included all the visible primary tumor and involved regional lymph nodes, as described by CT, PET and/or endoscopic findings. The clinical target volume

included the GTV with a 3–4 cm expansion in the cranial-caudal direction and 1.5 cm radially. The creation of an internal target volume (ITV) using a 4D-CT image set at the time of CT simulation was optional. A further 0.5–1 cm circumferential expansion from the CTV/ITV was used to generate the planning target volume (PTV).

Systemic chemotherapy was given concurrently with radiotherapy, with a combination of platinum based chemotherapy and 5-fluorouracil (5-FU) or carboplatin and paclitaxel as per the CROSS protocol. The patients did not receive adjuvant chemotherapy.

2.3. Data collection and analysis

Pertinent demographic and clinical data were extracted from electronic medical records and local databases. Pathologic staging was completed as per the AJCC 7th edition TNM staging system. Tumor regression grade was assessed when possible using the Mandard classification system. An anastomotic leak was defined as any extravasation of oral contrast during a barium swallow. Anastomotic stricture was documented when esophagoscopy findings were consistent with narrowing of the anastomotic lumen requiring at least one endoscopic dilatation.

All gastroesophageal anastomoses consist of both an esophageal and a gastric anastomotic region. The esophageal region represents the cranial component of the anastomotic site, and is typically found above the azygous arch when a right intra-thoracic anastomosis is created. The gastric region, typically along the greater curvature of the stomach at the level of the fundus or proximal body, then forms the conduit. With this knowledge, we created new contour sets on previously planned treatments and recalculated the dose to those sites to create a dose map (Fig. 1).

The most superior aspect of the azygous arch was identified on the treatment-planning CT. At this level, a contour was generated outlining the esophagus and designated the origin (0.0 cm). To characterize the dose gradient within the esophagus, contours were generated in 0.9 cm increments inferiorly and superiorly from the point of origin from a range of –2.7 cm to 6.3 cm. The entire stomach was contoured from the gastroesophageal junction to the gastric pylorus. The structure was subdivided equally into superior, middle and inferior regions. The superior gastric contour was further subdivided into medial and lateral components. The medial subdivision was representative of the gastroesophageal junction and medial portion of the fundus, which are typically resected at the time of esophagectomy. Conversely, the lateral subdivision is representative of the greater curvature portion of the superior stomach, which is typically tubularized and used to create the gastric anastomotic region. The airways were also contoured and defined as the carina, right mainstem bronchus and left mainstem bronchus.

All treatment plans were then exported into Monaco (Elekta; Stockholm, Sweden) for dose recalculation using the exact beam geometry and weighting as their original treatments. Mean doses were extracted for all new esophageal and gastric contours. While a post-operative scan would be an attractive option for dose recalculation as the exact location of the anastomosis could be pinpointed, the decision to use a pre-operative scan was two-fold: 1) Dosimetric calculation fidelity – the post-operative scan would have significant anatomic changes which would impact the dose calculations, 2) Treatment utility – we are aiming to determine radiotherapy factors to predict post-operative complications, which in application would need to be determined pre-operatively.

Patients were divided in two groups in accordance to anastomotic complications. Patient demographics, tumor characteristics, surgical outcomes and radiotherapy planning details were compared between patients with and without anastomotic complications. For dosimetric comparisons, only patients who underwent transthoracic anastomoses were included for analysis. Discrete



Fig. 1. Three dimensional representation of the reconstructed structures used for dose calculation. The midline contours represent a slice of the esophagus ranging from -2.7 cm to 6.3 cm relative to the top of the azygous vein (0.0 cm). The origin slice is represented by the white asterisk. The stomach is subdivided into 4 groups: superior medial, superior lateral, middle and inferior.

variables were analyzed using a Fisher's exact test and nonparametric rank-sum tests were employed to analyze comparisons between continuous variables. A p -value less than 0.05 was considered significant. Overall survival and disease free survival were estimated using the Kaplan-Meier method. Statistical calculations were performed using JMP 12 (SAS Institute; Cary, NC).

3. Results

3.1. Patient and tumor characteristics

We identified 51 patients who met the inclusion and exclusion criteria for analysis. The mean age was 61.3 years (range 34–79), and the majority were male (94.1%). There was a larger proportion of adenocarcinoma (86.3%) compared to squamous cell carcinoma (13.7%). The final pathologic stage distribution (ypStage) for stages 0, I, II, III and IVA was 11.8%, 25.5%, 23.5%, 33.3% and 5.9%, respectively. Tumor regression grade by the Mandard classification system [1–5] was 13.7%, 56.9%, 11.8%, 3.9% and 15.7%, respectively. There was no statistically significant difference between patients who developed an anastomotic complication and those who did not for age, gender, histology, final pathologic stage or tumor regression grade (Table 1).

3.2. Treatment characteristics

Of the 51 patients, the vast majority underwent transthoracic resection (90.2%), of which 39.2% had an open procedure while 51.0% underwent a minimally invasive surgery. Similarly, 84.3% of

patients had a thoracic esophageal anastomosis. Finally, there was a relatively balanced use of a handsewn anastomosis technique (41.1%) and use of a stapled functional end-to-end anastomosis (58.9%). The variation in surgical techniques did not appear to impact the frequency of anastomotic complications. The median time between neoadjuvant chemoradiation and surgery was 43 days (range 19–82 days). There was a disparate use of chemotherapies noted in patients who had anastomotic complications versus those who did not. Patients who had anastomotic complications were more likely to have had the combination of cisplatin/5-FU (84.6% vs. 47.4%, $p = 0.02$). No differences were noted between radiation doses delivered for neoadjuvant therapy ($p = 0.25$).

3.3. Survival outcomes

Patients were followed for a median of 30.9 months. The median overall survival was found to be 34.4 months with a 3-year and 5-year overall survival of 53.5% and 30.4% (Fig. 2a). The median disease free survival was 22.5 months and the 3-year and 5-year disease free survival was 31.3% and 14.4%, respectively (Fig. 2b). When comparing patients who had an anastomotic complication and those who did not, there was no difference in overall survival ($p = 0.94$) and disease free survival ($p = 0.62$).

3.4. Complication details

All post-operative complications were recorded and divided into anastomotic, pulmonary and cardiac adverse events (Table 2).

Table 1
Patient and treatment characteristics.

	Anastomotic Complications (n = 13)	No Anastomotic Complications (n = 38)	p-value
Age (years)			
Mean	60.7	62.8	0.75
Range	34–79	44–72	
Male gender	11 (84.6%)	37 (97.3%)	0.16
Pathologic stage			
0	3 (23.1%)	3 (7.9%)	0.46
I	2 (15.4%)	11 (28.9%)	
II	4 (30.8%)	8 (21.1%)	
III	4 (30.8%)	13 (34.2%)	
IVA	0 (0.0%)	3 (7.9%)	
Histology			
Adenocarcinoma	9 (69.2%)	35 (92.1%)	0.06
Squamous cell	4 (30.8%)	3 (7.9%)	
Tumor regression grade			
1	3 (23.1%)	4 (10.5%)	0.80
2	7 (53.8%)	22 (57.9%)	
3	1 (7.7%)	5 (13.2%)	
4	0 (0.0%)	1 (2.6%)	
5	2 (15.4%)	6 (15.8%)	
Non-CR	10 (76.9%)	34 (89.5%)	
Surgery			
Esophagectomy Technique			
Transthoracic	11 (84.6%)	35 (92.1%)	0.59
Open	8 (61.5%)	12 (31.6%)	
MIS	3 (23.1%)	23 (60.5%)	
Transhiatal	2 (15.4%)	3 (7.9%)	
Anastomosis Location			
Neck	3 (23.1%)	5 (13.2%)	0.40
Chest	10 (76.9%)	33 (86.8%)	
Anastomosis Technique			
Handsewn	8 (61.5%)	13 (34.2%)	0.11
Stapled	5 (38.5%)	25 (65.8%)	
Pyloric Drainage			
Pyloromyotomy	6 (46.2%)	13 (34.2%)	0.51
Pyloroplasty	7 (53.8%)	25 (65.8%)	
Chemotherapy			
Cisplatin & 5-FU	11 (84.6%)	18 (47.4%)	0.02
Carboplatin & Paclitaxel	2 (15.4%)	20 (52.6%)	
Radiotherapy			
41.4 Gy	1 (5.9%)	12 (27.9%)	0.25
45.0 Gy	9 (58.8%)	20 (48.8%)	
50.0–50.4 Gy	3 (35.3%)	6 (23.3%)	

Abbreviations: CR – Complete response; MIS – Minimally invasive surgery; 5-FU – 5-fluorouracil; Gy – Gray.

Forty out of 51 (78.4%) patients had at least one post-operative complication. Anastomotic complications occurred in 13 (25.5%) of our patients, with 6 (11.8%) patients experiencing an anastomotic leak, 11 (21.6%) patients with an anastomotic stricture and 4 (7.8%) experiencing both. A total of 15.7% and 17.6% of patients had post-operative pneumonia and pleural effusions respectively. Finally, 5.9% of patients developed an acute coronary syndrome.

3.5. Dosimetric details

When comparing patients by their development of an anastomotic complication (AC), there were several differences noted in their dosimetry. Overall, there was no difference in ACs between the mean prescribed doses (45.4 vs. 44.8 Gy, $p = 0.47$). When examining the mean dose delivered to each level of the esophagus, there was a trend of higher doses overall in the AC group (Fig. 3). The difference was more notable at the levels below the most superior aspect of the azygous vein, with the mean dose differences between the AC group and no AC group as follows:

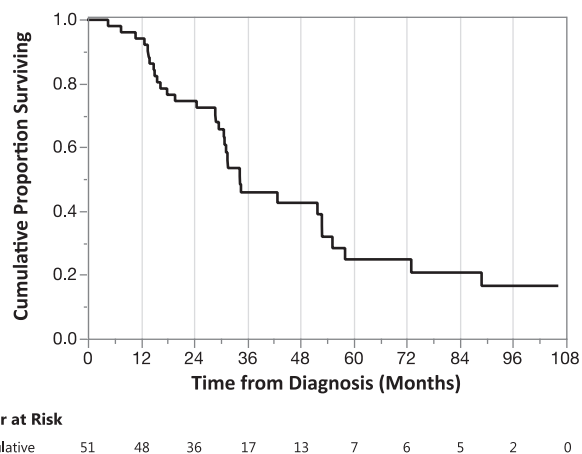


Fig. 2a. Overall Survival (OS). Kaplan meier survival curve of patients receiving trimodality therapy. The median OS was 34 months (95% CI: 31–53 months) with a 3y-OS and 5y-OS of 53% and 30% respectively.

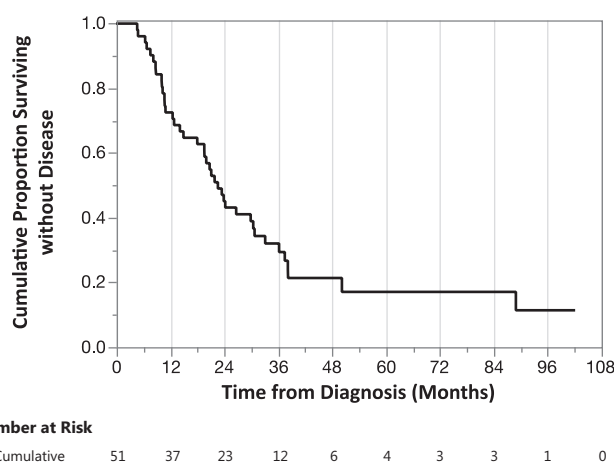


Fig. 2b. Disease Free Survival (DFS). Kaplan meier survival curve of patients receiving trimodality therapy. The median DFS was 23 months (95% CI: 15–30 months) with a 3y-DFS and 5y-DFS of 31% and 14% respectively.

Table 2
Post-operative complications.

Complications	N (%)
Total	40 (78.4)
Anastomotic	
Leak	6 (11.8)
Stricture	11 (21.6)
Pulmonary	
Pneumonia	8 (15.7)
Pleural effusion	9 (17.6)
Cardiac	
Atrial fibrillation	6 (11.8)
Heart block	1 (2.0)
Acute coronary syndrome	3 (5.9)

–2.7 cm (42.2 Gy vs. 27.6 Gy, $p = 0.007$), –1.8 cm (38.9 Gy vs. 23.5 Gy, $p = 0.009$), –0.9 cm (33.1 Gy vs. 18.8 Gy, $p = 0.02$) and 0.0 cm (28.4 Gy vs. 10.3 Gy, $p = 0.04$) (Table 3). As mentioned previously, dose differences above the level of the azygous vein continue to trend higher in the AC group despite not being statistically significant (Table 3). Examining the gastric doses, there was no statistically significant differences in mean dose to

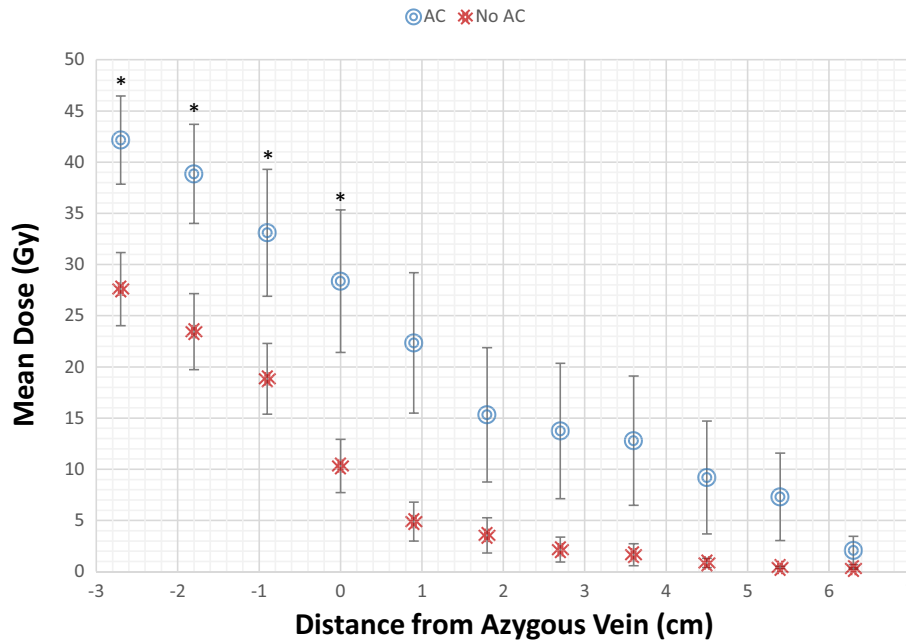


Fig. 3. Mean dose of the esophagus in patients with and without anastomotic complications. Mean dose received by the esophagus at distances above and below the level of the azygous vein. Distances less than 0 cm are below, while distances greater than 0 cm are above. The standard errors are represented. Abbreviations: AC – Anastomotic complications; Gy – Gray; cm – Centimeter *Statistically significant difference (p < 0.05).

the superior or middle regions. Patients in the AC group had a higher mean airway dose at the carina (34.3 Gy vs. 19.2 Gy, p = 0.03).

4. Discussion

Given the greater acceptance of neoadjuvant chemoradiation in the treatment of esophageal carcinomas, we sought to review our institution’s experience on anastomotic complication and the radiotherapy factors which may contribute to their occurrence. Therefore, we evaluated 51 consecutive patients treated at our institution with trimodality therapy. Our leakage and stricture

rates of 12% and 22% were consistent with historical rates [5,6]. We did not find a difference in anastomotic complication rates when comparing prescription doses broadly. However, when analyzing the dosimetric data, we found that rates of anastomotic complications were correlated with mean dose received by the esophagus at or near the level of the azygous vein, a common landmark used in the creation of a transthoracic gastroesophageal anastomosis. The analysis was limited to patients with thoracic anastomoses to reduce the potential bias of increased rates of leaks with cervical anastomoses [16]. We also found that increased toxicity rates were correlated with mean dose to the carina, but not the stomach.

Table 3

Dosimetric comparison of radiotherapy in patients with and without anastomotic complications following esophagectomy with an intrathoracic anastomosis.

	Anastomotic Complications (n = 10)	No Anastomotic Complications (n = 33)	p-value
Mean prescribed dose (Gray)	45.36	44.78	0.47
Mean airway dose (Gray)			
Carina	34.28	19.24	0.03
Right mainstem bronchus	35.04	24.21	0.04
Left mainstem bronchus	35.50	25.79	0.12
Mean esophageal dose (Gray)			
–2.7 cm	42.15	27.60	0.007
–1.8 cm	38.85	23.45	0.009
–0.9 cm	33.10	18.83	0.02
Azygous vein (0.0 cm)	28.37	10.33	0.04
+0.9 cm	22.34	4.89	0.08
+1.8 cm	15.31	3.54	0.10
+2.7 cm	13.74	2.15	0.18
+3.6 cm	12.79	1.66	0.26
+4.5 cm	9.19	0.86	0.48
+5.4 cm	7.30	0.42	0.76
+6.3 cm	2.06	0.31	0.81
Mean gastric dose (Gray)			
Superior	30.81	35.04	0.58
Medial	37.68	40.49	0.97
Lateral	26.67	31.16	0.58
Middle	21.49	30.10	0.08

Our dosimetric outcomes are consistent with the findings of Koeter et al. and Juloori et al. – the former of whom found that increased esophageal dose near the carina/azygous vein was an independent predictor of severe complication rates, while dose to the gastric anastomotic region was not [17]. From this finding, they suggested that a more superior mediastinal PTV border in trimodality treatment may increase complications [17]. There were several differences in the study methodology, most notably concerning the site of anastomosis. Their study reviewed only patients who underwent a cervical anastomosis, while our dosimetry analysis included only those with a thoracic anastomosis. Juloori et al. investigated only anastomotic leaks, and they reported increased rates when the site of anastomosis was created within the irradiated field (OR 6.15, $p < 0.001$) [13]. This study was conducted by superimposing the pre-operative radiation plan on a post-operative scan [13]. In contrast, our study utilized the pre-operative scan, which has the disadvantage of approximating the location of the thoracic anastomosis, but ensures dosimetric reliability when recalculating. Taken together, these studies align with ours in demonstrating that radiation dose to the site of potential anastomosis may be associated with subsequent rates of anastomotic strictures and leakage.

Our findings suggest that restricting the margins of a radiotherapy plan near the site of future anastomosis could be beneficial. This however, is not always practical as historically, the superior/inferior CTV margin has been delineated generously (up to 5 cm) to account for the propensity of vertical spread along the esophagus and associated lymphatics. Certainly, preserving the survival and local control benefits of neoadjuvant radiotherapy should take priority over a marginal increased rate of toxicities. In our series, there were no differences in overall or disease free survival when considering anastomotic complications. Nevertheless, more recent pathologic evidence appears to suggest that a smaller margin of 3 cm may be acceptable in accounting for microscopic spread [18]. Indeed, the CROSS protocol, which is rapidly being adopted as standard of care for neoadjuvant chemoradiation, utilizes a GTV to PTV margin of only 4 cm, representing a move towards reducing pre-operative radiation volumes [3]. Aside from reducing target margins, there are several other strategies that could be considered. From a radiotherapy planning perspective, ensuring that there are no hot spots within the PTV in the proximity of the azygous vein/carina could be performed as a precaution. Communication between surgical and radiation oncologists is also critical, as planning operative strategies could benefit from the knowledge of the location of the radiation fields. Should the esophagus near the azygous vein receive a high dose, the thoracic surgeon could consider a more superior transection.

As part of the limitations of our retrospective study, we found differences in several tumor and treatment characteristics between those who did and did not have an anastomotic complication. There was a trend towards an increased prevalence of squamous cell carcinomas ($p = 0.06$) in the complication group which has been associated with increased overall post-operative complication rates in the literature [19]. Patients with a complication also had a disproportionately higher use of cisplatin and 5-FU compared to carboplatin and paclitaxel. In a previous study comparing these two regimens, the type of chemotherapy did not affect non-hematologic post-operative complications [20]. In fact, this study showed a trend of increased anastomotic complications in patients who received carboplatin/paclitaxel (33% vs. 15%, $p = 0.27$) [17]. The groups in our study were otherwise well balanced, including differences in prescription radiation doses which ranged from 41.4 to 50.4 Gy in 23–28 fractions. The variability in practices of both radiation oncologists and surgeons represents another limitation of our study. The delineation of our target volumes, in particular the CTV, was subject to inter-observer variability across the six

radiation oncologists involved in the treatment of our patients. We attempted to reduce the impact of this variability by analyzing the dosimetry as opposed to target volumes. The eventual location of the anastomosis is also subjected to variability, as the patient's anatomy or surgeon preference could have a case-by-case impact. Although we utilized the superior border of the azygous vein as a reference for the site of transection and anastomosis, levels above and below could also be used as a surrogate. Indeed, our data seems to support a gradient of increased rates of toxicities nearby the azygous as represented in Fig. 3, which is congruent with the notion that the site of anastomosis cannot be precisely predicted on the pre-operative scan.

Our results demonstrate interesting and hypothesis-generating findings that correlate increased dose to the esophagus near the site of potential anastomosis and the development of subsequent anastomotic complications. In light of these findings, careful radiotherapy planning and emphasizing interdisciplinary treatment planning may be able to improve the complication rates in patients undergoing trimodality therapy.

Conflict of interest notification

None.

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