Original Article (Management of Foregut Malignancies and Hepatobiliary Tract and Pancreas Malignancies)

Anastomotic leak and neoadjuvant chemoradiotherapy in esophageal cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Anastomotic leaks (AL) cause significant morbidity after esophagectomy. Most patients receive neoadjuvant chemoradiation (NCR) prior to esophagectomy which has been associated with increase perioperative complications and mortality. We report on a comparison of AL rates in upfront surgical (UFS) and NCR patients.

Methods: An esophagectomy database was queried for UFS and NCR patients treated between 1996 and 2015. Predictors of AL rate were identified using univariate and multivariate (MVA) analysis and propensity score matching (PSM).

Results: We identified 820 patients (UFS, 288; NCR, 532). Overall AL rate was 5.4%. Decreased AL rate was observed in NCR patients on MVA (8.0% *vs.* 4.1%; P=0.02) but no difference was seen after PSM (7.7% *vs.* 4.2%; P=0.14). MVA of factors associated with decreased AL in UFS patients included distal esophageal tumors and body mass index (BMI) >25. Age, gender, year of surgery, histology, anastomotic location, and diabetes were not prognostic. Before PSM, MVA of NCR patients of factors associated with decreased AL revealed that only thoracic anastomosis was prognostic. However, this was not observed after PSM. MVA of factors associated with decreased AL in all patients revealed thoracic anastomosis, NCR, and BMI 25–30. After PSM, only distal esophageal tumors and thoracic anastomosis were prognostic for decreased AL.

Conclusions: There is no difference in the AL rate between UFS and NCR patients. Decreased AL rate was observed in patients with distal esophageal tumors and thoracic anastomosis.

Keywords: Esophageal cancer; neoadjuvant chemoradiotherapy (NCR); anastomotic leak (AL)

Submitted Apr 03, 2018. Accepted for publication Apr 23, 2018.
doi: 10.21037/jgo.2018.04.09
View this article at: http://dx.doi.org/10.21037/jgo.2018.04.09

Introduction

It is estimated that there will be 16,910 new cases of esophageal cancer diagnosed, with 15,690 dying from the disease in the United States in 2016 (1). The majority of esophageal cancers are either adenocarcinoma or squamous cell carcinoma. Trimodality therapy of neoadjuvant chemoradiation (NCR) followed by surgical resection has been established as the standard of care for advanced disease (2,3). However, neoadjuvant therapy has been associated with significant perioperative morbidity and mortality (4).

Surgical resection continues to remain the preferred modality for locoregional esophageal cancer and improved perioperative care and advanced surgical techniques have contributed to reduced postoperative mortality. However, despite these advances, esophagectomy continues to be associated with significant morbidity and mortality (5,6). One of the most dreaded complications is anastomotic leak

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(AL). The incidence of AL after esophagectomy has been reported to range from 5–40% and leak associated mortality from 2–12% (7-19). The presence of AL can result in the need for reoperation, endoscopic stenting, nasogastric tube placement, percutaneous drainage, need for broad spectrum antibiotics, and significant stricture requiring multiple endoscopic dilations (15,20-22).

Several factors have been identified that are associated with increased AL including anastomotic technique, location of anastomosis, type of conduit, comorbid conditions, and neoadjuvant therapy (9,12,23,24). However, the association between NCR and AL has been questioned (3,25-30). The purpose of this study was to compare AL rates of upfront surgery *vs.* NCR.

Methods

Patients

A prospectively maintained and institutional review board approved esophagectomy database of more than 800 patients who underwent upfront surgery of surgery after NCR was queried to determine factors related to AL. Patients underwent surgery between 1996 and 2015. AL was compared between upfront surgery and NCR patients.

NCR

Patients were discussed in a weekly multi-disciplinary tumor board conference and pathology was reviewed at our institution. Pre-operative staging including endoscopic ultrasound, CT chest, abdomen and pelvis and PET scans. Patients who had locally advanced disease (≥T2 and/or ≥N1) were treated with NCR. The choice of chemotherapy was left to the discretion of the treatment medical oncologist. Patients received infusional 5-fluorouracil (5-FU) and cisplatin or weekly carboplatin and Taxol concurrent external beam radiation for a total dose of 45–59.4 Gy over the course of 5–7 weeks.

Surgery

Six weeks after the conclusion of therapy, patients underwent restaging with PET-CT scans. Patients without evidence of metastatic disease and good performance status were then offered open, laparoscopic or robotic esophagectomy at the discretion of the surgeon. Esophagectomy was performed during the 6–10-week window after conclusion of NCR. Patients are referred to cardiac and pulmonary specialists for pre-operative risk assessment and optimization prior to surgery.

Statistics

The primary endpoint was incidence of AL. Baseline univariate comparisons of patient characteristics between the upfront surgery patients and the NCR patients was made for continuous variables using both the Mann-Whitney U and Kruskal Wallis tests as appropriate. Pearson's Chi-square test was used to compare categorical variables. Propensity score matching (PSM) was performed against a number of variables associated with AL. Multivariable Cox proportional hazard models were developed to identify predictors of AL included in the models were age, sex, tumor location, surgical technique, NCR, BMI, diabetes, and year of surgery. All statistical tests were two-sided and α (type I) error <0.05 was considered statistically significant. Statistical analysis was performed using SPSS® version 23.0 (IBM®, Chicago, IL, USA). This study was approved as exempt by the Institutional Review Board.

Results

There were 820 patients (288 UFS, 532 NCR) in the database that were identified. NCR patients were significantly younger, had increased use after 2010, were more likely to undergo robotic surgery, and were less likely to be obese. After PSM, there were 518 patients (259 UFS, 259 NCR) and the only difference between NCR and US patients was younger age (65 *vs.* 68; P=0.002) (*Table 1*).

Overall AL rate was 5.5% before PSM and 6% after PSM. Univariate analysis of factors related to differences in leak rates between upfront and neoadjuvant patients are presented in *Table 2*. Overall AL rates for UFS patients before and after PSM was 8.0% and 7.7% compared to 4.2% and 4.1% for NCR patients. Before PSM, there was a significantly decreased AL rate in NCR patients, however, this was not significant after PSM. There was a significantly decreased AL in NCR patients who had adenocarcinoma, underwent robotic Ivor-Lewis, were non-diabetic, and had normal BMI compared to UFS patients before PSM. After PSM, decreased AL in NCR patients was seen in non-diabetics and patients with normal BMI.

Table 3 displays multivariate analysis (MVA) of factors before and after PSM associated with AL in upfront

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Table 1 Patient characteristics

Variable	Non-PSM			PSM		
	Neoadjuvant (N=532)	Upfront (N=288)	P	Neoadjuvant (N=259)	Upfront (N=259)	P
Median age [range], years	64 [28–86]	68 [32–85]	<0.001	65 [28–85]	68 [36–85]	0.002
Gender			0.8			0.9
Male	444 (83.5)	242 (84.0)		221 (85.3)	222 (85.7)	
Female	88 (16.5)	46 (16.0)		38 (14.7)	37 (14.3)	
Year			<0.001			<0.001
1996–2000	49 (9.2)	80 (29.4)		40 (15.4)	73 (29.4)	
2001–2005	143 (26.9)	75 (27.6)		120 (46.3)	74 (29.8)	
2006–2010	197 (37.0)	86 (31.6)		87 (33.6)	80 (32.3)	
After 2010	143 (26.9)	31 (11.4)		12 (4.6)	21 (8.5)	
Histology			0.3			1
Adenocarcinoma	465 (87.4)	258 (89.6)		232 (89.6)	232 (89.6)	
Squamous cell	67 (12.6)	30 (10.4)		27 (10.4)	27 (10.4)	
Location			0.5			0.2
Middle	28 (6.0)	13 (4.9)		14 (5.4)	13 (5.1)	
Lower	278 (59.5)	153 (57.1)		168 (65.4)	147 (57.9)	
GEJ	161 (34.5)	102 (38.1)		75 (29.2)	94 (37.0)	
Technique			<0.001			0.7
Open TH	34 (6.4)	30 (10.4)		27 (10.4)	29 (11.2)	
Open IVL	270 (50.8)	186 (64.6)		178 (68.7)	173 (66.8)	
Open 3F	6 (1.1)	4 (1.4)		3 (1.2)	3 (1.2)	
Lap TH	42 (7.9)	20 (6.9)		24 (9.3)	20 (7.7)	
Lap TT	72 (13.5)	20 (6.9)		20 (7.7)	20 (7.7)	
RAIL	108 (20.3)	28 (9.7)		7 (2.7)	14 (5.4)	
Anastomosis			0.2			0.8
Thoracic	450 (84.6)	234 (81.3)		205 (79.2)	207 (79.9)	
Cervical	82 (15.4)	54 (18.8)		54 (20.8)	52 (20.1)	
RT Dose (Gy)			–			–
≤50.4	238 (77.8)			139 (79.4)		
>50.4	68 (22.2)			36 (20.6)		
Response			–			–
Complete	181 (36.6)			92 (38.3)		
Partial	222 (44.8)			102 (42.5)		
No response	92 (18.6)			46 (19.2)		
Diabetes			0.2			1
No	445 (83.6)	251 (87.2)		224 (86.5)	224 (86.5)	
Yes	87 (16.4)	37 (12.8)		35 (13.5)	35 (13.5)	
BMI			0.001			1
18.5–25	158 (35.3)	61 (23.6)		61 (23.6)	61 (23.6)	
25.1–30	165 (36.8)	94 (36.3)		94 (36.3)	94 (36.3)	
>30	125 (27.9)	104 (40.2)		104 (40.2)	104 (40.2)	

PSM, propensity score match; GEJ, gastroesophageal junction; TH, transhiatal; IVL, Ivor-Lewis; TT, transthoracic; RAIL, robotic assisted Ivor-Lewis; BMI, body mass index.

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Table 2 Univariate analysis comparing leak rates of upfront surgery vs. neoadjuvant therapy

Variable	Non-PSM				PSM			
	Surgery/neoadjuvant leak (%)	OR*	95% CI	P	Surgery/neoadjuvant leak (%)	OR*	95% CI	P
Overall	8.0/4.1	0.50	0.27–0.91	0.02	7.7/4.2	0.53	0.25–1.13	0.14
Year								
1996–2000	10.0/2.0	0.19	0.02–1.55	0.12	8.2/2.5	0.29	0.03–2.47	0.25
2001–2005	9.3/4.2	0.42	0.14–1.31	0.14	9.5/2.5	0.24	0.06–0.98	0.05
2006–2010	5.8/5.6	0.96	0.32–2.85	0.94	6.3/6.9	1.11	0.33–3.79	0.87
After 2010	9.7/2.8	0.27	0.06–1.27	0.1	9.5/8.3	0.86	0.07–10.66	0.91
Histology								
Adenocarcinoma	8.5/4.1	0.46	0.24–0.86	0.01	8.2/4.7	0.56	0.26–1.20	0.14
Squamous cell	3.3/4.5	1.36	0.14–13.63	0.79	3.7/0	–	–	–
Location								
Middle	0/3.6	–	–	–	0/7.1	–	–	–
Lower	5.9/5.0	0.85	0.36–2.01	0.71	4.8/3.0	0.61	0.19–1.98	0.41
GEJ	12.7/3.7	0.26	0.10–0.72	0.01	13.8/6.7	0.44	0.15–1.31	0.14
Technique								
Open TH	16.7/11.8	0.67	0.16–2.75	0.57	13.8/7.4	0.50	0.08–2.98	0.45
Open IVL	7.0/3.3	0.46	0.19–1.10	0.08	6.9/3.4	0.47	0.17–1.28	0.14
Open 3F	0/25.0	–	–	–	0/66.7	–	–	–
Lap TH	10.0/4.8	0.45	0.06–3.45	0.44	10.0/0	–	–	–
Lap TT	0/5.6	–	–	–	0/5.0	–	–	–
RAIL	10.7/0.9	0.08	0.01–0.78	0.03	14.3/0	–	–	–
Anastomosis								
Thoracic	6.8/3.1	0.44	0.21–0.91	0.03	6.8/3.4	0.49	0.19–1.23	0.13
Cervical	13.0/9.8	0.73	0.25–2.13	0.56	11.5/7.4	0.61	0.16–2.31	0.47
Diabetes								
No	8.0/3.4	0.40	0.20–0.80	0.01	8.0/3.6	0.42	0.18–1.00	0.05
Yes	8.1/8.0	0.99	0.24–4.06	0.99	5.7/8.6	1.55	0.24–9.88	0.64
BMI								
18.5–25	14.8/4.4	0.27	0.09–0.75	0.01	14.8/0	–	–	–
25.1–30	5.3/1.8	0.33	0.08–1.41	0.13	5.3/3.2	0.59	0.14–2.53	0.47
>30	5.8/7.2	1.27	0.44–3.68	0.66	5.8/7.7	1.36	0.45–4.07	0.58

*, surgery as reference. PSM, propensity score match; GEJ, gastroesophageal junction; TH, transhiatal; IVL, Ivor-Lewis; TT, transthoracic; RAIL, robotic assisted Ivor-Lewis; BMI, body mass index.

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Table 3 Upfront and neoadjuvant leak rate multivariate analysis

Variable	Upfront surgery								Neoadjuvant chemoradiation							
	Non-PSM				PSM				Non-PSM				PSM			
	Leak (%)	OR	95% CI	P	Leak (%)	OR	95% CI	P	Leak (%)	OR	95% CI	P	Leak (%)	OR	95% CI	P
Age	–	1.00	0.95–1.06	0.95	–	1.00	0.95–1.06	0.95	–	0.97	0.93–1.02	0.26	–	0.95	0.89–1.02	0.16
Gender																
Male	9.5	Ref	Ref	Ref	9.0	Ref	Ref	Ref	3.8	Ref	Ref	Ref	4.1	Ref	Ref	Ref
Female	0	–	–	–	0	–	–	–	5.7	1.48	0.44–5.01	0.52	5.3	2.26	0.36–14.29	0.39
Year																
1996–2000	10.0	Ref	Ref	Ref	8.2	Ref	Ref	Ref	2.0	Ref	Ref	Ref	2.5	Ref	Ref	Ref
2001–2005	9.3	1.27	0.36–4.48	0.71	9.5	1.27	0.36–4.48	0.71	4.2	1.13	0.12–10.62	0.91	2.5	0.56	0.04–7.03	0.66
2006–2010	5.8	0.68	0.18–2.56	0.56	6.3	0.68	0.18–2.56	0.56	5.6	1.43	0.16–12.76	0.75	6.9	0.84	0.07–9.82	0.89
After 2010	9.7	2.05	0.31–13.67	0.46	9.5	2.05	0.31–13.67	0.46	2.8	1.14	0.08–15.12	0.92	8.3	1.1	0.04–31.58	0.95
Histology																
Adenocarcinoma	8.5	Ref	Ref	Ref	8.2	Ref	Ref	Ref	4.1	Ref	Ref	Ref	4.7	Ref	Ref	Ref
Squamous cell	3.3	1.42	0.14–14.78	0.77	3.7	1.42	0.14–14.78	0.77	4.5	0.4	0.05–3.37	0.4	0	–	–	–
Location																
Middle	0	–	–	–	0	–	–	–	3.6	–	–	–	7.1	–	–	–
Lower	5.9	0.25	0.09–0.72	0.01	4.8	0.25	0.09–0.72	0.01	5.0	1.11	0.35–3.50	0.86	3	0.29	0.06–1.34	0.11
GEJ	12.7	Ref	Ref	Ref	13.8	Ref	Ref	Ref	3.7	Ref	Ref	Ref	6.7	Ref	Ref	Ref
Anastomosis																
Cervical	13.0	Ref	Ref	Ref	11.5	Ref	Ref	Ref	9.8	Ref	Ref	Ref	7.4	Ref	Ref	Ref
Thoracic	6.8	0.46	0.14–1.48	0.19	6.8	0.46	0.14–1.48	0.19	3.1	0.29	0.10–0.87	0.03	3.4	0.47	0.08–2.60	0.38
Diabetes																
No	8.0	Ref	Ref	Ref	8.0	Ref	Ref	Ref	3.9	Ref	Ref	Ref	4.3	Ref	Ref	Ref
Yes	8.1	0.61	0.12–3.09	0.55	5.7	0.61	0.12–3.09	0.55	4.5	1.22	0.41–3.61	0.71	3.9	0.48	0.10–2.30	0.36
BMI																
18.5–25	14.8	Ref	Ref	Ref	14.8	Ref	Ref	Ref	3.3	0.58	0.11–3.15	0.53	4.3	0.52	0.07–3.88	0.52
25.1–30	5.3	0.24	0.07–0.85	0.03	5.3	0.24	0.07–0.85	0.03	4.2	Ref	Ref	Ref	5.8	Ref	Ref	Ref
>30	5.8	0.29	0.08–0.97	0.04	5.8	0.29	0.08–0.97	0.04	0	–	–	–	0	–	–	–

PSM, propensity score matched; OR, odds ratio; CI, confidence interval; GEJ, gastroesophageal junction; BMI, body mass index.

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Table 4 Multivariate analysis

Variable	Non-PSM				PSM			
	Leak (%)	OR	95% CI	P	Leak (%)	OR	95% CI	P
Age	–	0.99	0.96–1.02	0.53	–	0.99	0.95–1.03	0.68
Gender								
Male	5.8	Ref	Ref	Ref	6.5	Ref	Ref	Ref
Female	3.7	0.70	0.23–2.11	0.53	2.7	0.42	0.09–1.93	0.27
Year								
1996–2000	7.0	Ref	Ref	Ref	6.2	Ref	Ref	Ref
2001–2005	6.0	1.06	0.39–2.88	0.91	5.2	0.94	0.33–2.69	0.91
2006–2010	5.7	0.92	0.34–2.47	0.87	6.6	1.03	0.37–2.92	0.95
After 2010	4.0	1.02	0.27–3.90	0.98	9.1	2.04	0.46–9.01	0.35
Histology								
Adenocarcinoma	5.7	Ref	Ref	Ref	6.5	Ref	Ref	Ref
Squamous cell	4.1	0.53	0.11–2.45	0.42	1.9	0.42	0.05–3.68	0.44
Location								
Middle	2.4	0.35	0.04–3.05	0.34	3.7	0.46	0.05–4.23	0.49
Lower	5.3	0.59	0.29–1.16	0.13	3.8	0.33	0.15–0.73	0.01
GEJ	7.2	Ref	Ref	Ref	10.7	Ref	Ref	Ref
Anastomosis								
Cervical	11.0	Ref	Ref	Ref	9.4	Ref	Ref	Ref
Thoracic	4.4	0.32	0.15–0.68	0.003	5.1	0.38	0.16–0.90	0.03
Neoadjuvant								
No	8.0	Ref	Ref	Ref	7.7	Ref	Ref	Ref
Yes	4.1	0.48	0.23–0.98	0.04	4.2	0.55	0.25–1.22	0.14
Diabetes								
No	5.0	Ref	Ref	Ref	5.8	Ref	Ref	Ref
Yes	8.1	1.73	0.76–3.96	0.19	7.1	1.25	0.44–3.56	0.67
BMI								
18.5–25	7.3	Ref	Ref	Ref	7.4	Ref	Ref	Ref
25.1–30	3.1	0.36	0.15–0.87	0.02	4.3	0.49	0.18–1.36	0.17
>30	6.6	0.65	0.29–1.44	0.29	6.7	0.74	0.29–1.93	0.54

PSM, propensity score matched; OR, odds ratio; CI, confidence interval; GEJ, gastroesophageal junction; BMI, body mass index.

surgery and NCR patients. MVA of factors associated with decreased AL in US patients were tumors of the lower esophagus and BMI >25, and confirmed on PSM. Age, gender, year of surgery, histology, anastomotic location, and diabetes were not predictive of AL in upfront surgery patients. In NCR patients, significantly decreased AL was observed in patient undergoing thoracic anastomosis. However, after PSM, no factors were prognostic for AL in NCR patients.

Table 4 displays MVA before and after PSM of factors

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Table 5 Studies correlating neoadjuvant chemoradiation and anastomotic leak

Study	PSM/RCT	N	NCR regimen	NCR leak (%)	Upfront leak (%)	p
Reynolds [2006]	Non-PSM	200	Cisplatin/5-FU 40–50 Gy	6.0	2.0	0.26
CALGB 9781 [2008]	RCT	48	Cisplatin/5-FU 50.4 Gy	8.0	0	NS
Merritt [2011]	Non-PSM	138	Platinum doublet 40–60 Gy	14.8	10.7	0.45
CROSS [2012]	RCT	366	Carboplatin/taxol 41.4 Gy	22.0	30.0	NS
Markar [2013]	Non-PSM	340	Cisplatin/5-FU 50.4 Gy	2.9	4.6	0.51
Bosch [2014]	PSM	326	Carboplatin/taxol 41.4 Gy	11.5	13.5	0.63
Gronnier [2014]	Non-PSM	2,080	Cisplatin/5-FU 45 Gy	8.8	10.6	0.22
	PSM	1,086		8.8	11.0	0.23
Current study	Non-PSM	820	Cisplatin/5-FU or carboplatin/taxol 45–59.4 Gy	4.1	8.0	0.04
	PSM	518		4.2	7.7	0.12

PSM, propensity score matched; RCT, randomized controlled trial; NCR, neoadjuvant chemoradiation; 5-FU, 5-fluorouracil; Gy, Gray.

associated with AL in all patients. Decreased AL was observed in NCR patients, patients with distal esophageal patients, thoracic anastomosis, and in patients with BMI from 25–30. However, after PSM, only distal esophageal tumors and thoracic anastomosis were prognostic of decreased AL.

Discussion

AL is a dreaded complication of esophagectomy associated with significant morbidity and mortality. There is a wide range of incidence of AL as high as 40% with reported mortality associated with leak as high as 12% (7-19). The success of esophageal anastomosis depends not only on surgical technical factors but also patient related factors. Technical factors include location of anastomosis, type of conduit, and how the conduit is dissected and mobilized to ensure the formation of a tension-free anastomosis and maintaining a healthy blood supply to the conduit (9,12,23,24). Patient related factors include nutritional status, comorbid conditions, BMI, and NCR (9,12).

Overall AL was 5.4%. While we observed an overall decreased AL rate in NCR patients compared to US patients, after PSM the difference was not statistically significant. Factors correlating with decreased AL in UFS patients are distal tumors and BMI >25. While thoracic anastomosis correlated with decreased AL in NCR patients, the difference wasn't significant after PSM. The only 2 factors we identified that were prognostic for decreased AL in all patients were distal tumors and thoracic anastomosis.

Decreased AL in NCR patients was restricted to patients undergoing a thoracic anastomosis but not in patients with cervical anastomosis. Very few studies have addressed the role of NCR on incidence of AL. In the CROSS trial, where most patients underwent a transhiatal technique with cervical anastomosis, there was a nonsignificant decrease in AL in patients who received NCR (22% *vs.* 30%) (3). However, Briel *et al.* reported an analysis of 393 patients with cervical anastomosis and demonstrated an increased incidence of AL in patients who received neoadjuvant therapy (9). This was hypothesized to be due to an increase in conduit ischemia which increased AL. However, cervical anastomosis requires the formation of a longer conduit and traverses a greater distance in the mediastinum, placing it under tension and potentially compromising the vascularity. Additionally, anatomic variations in the anatomy of the gastroepiploic artery may play a significant role, particularly in patients undergoing transhiatal esophagectomy. An analysis of >7,500 esophagectomy patients from the Society of Thoracic Surgeons Thoracic Database revealed that NCR was not associated with AL (12). *Table 5* lists the most recent studies comparing AL between UFS and NCR patients. AL rates of UFS patient and NCR patients ranged between 0–30% and 2.9–14.8%, respectively, with no statistically significant differences (3,25-30).

Several studies have confirmed comorbid conditions like diabetes correlate with AL but not BMI (31-33). Briel *et al.* reported that comorbid conditions requiring treatment strongly correlated with increased AL (9). In addition, while they demonstrated that an increased BMI correlated

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with stricture, it did not correlate with AL. Kayani *et al.* reported that diabetes in obese patients correlated with AL, but not in obese patients without diabetes (34). In an analysis of >7,500 esophagectomy patients from the Society of Thoracic Surgeons Thoracic Database revealed that diabetes and BMI >35 correlated with increased AL (12). It wasn't reported but it is likely possible that the obese patients also were diabetic. The presence of comorbid conditions is thought to cause conduit ischemia resulting in AL. We found that non-diabetic patients undergoing NCR had lower AL compared to UFS on UVA but it was not significant on MVA and overall, we found that diabetes did not correlate with AL. On UVA, NCR patients with normal BMI had lower AL compared to UFS. In addition, we found that BMI >25–30 was associated with decreased AL in UFS patients but not in NCR patients. The additional fat/omentum in heavier patients may compress the conduit in the confined space of the posterior mediastinum and serve as a protective flap in overweight patients.

Conclusions

AL is a dreaded complication related to both technical and patient related factors. There is no association between NCR and AL in esophagectomy patients. Decreased AL is observed in US patients with distal tumors and BMI >25, while no factors correlated with AL in NCR patients. Distal tumors and thoracic anastomosis correlate with decreased AL.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by IRB Sarasota Memorial Hospital # GI-ONC.

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Cite this article as: Shridhar R, Takahashi C, Huston J, Doepker MP, Meredith KL. Anastomotic leak and neoadjuvant chemoradiotherapy in esophageal cancer. J Gastrointest Oncol 2018;9(5):894-902. doi: 10.21037/jgo.2018.04.09

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