Schuman Ari (Orcid ID: 0000-0003-1373-7338)
Spector Matthew (Orcid ID: 0000-0001-7646-6075)
Rosko Andrew (Orcid ID: 0000-0001-6432-5451)

Predictors of Stricture and Swallowing Function Following Salvage Laryngectomy

Ari D. Schuman, MD, MS[1,2], Andrew C. Birkeland, MD[3], Janice L. Farlow, MD, PhD[4], Teresa Lyden, MA, CCC-SLP[4], Anna Blakely, MA, CCC-SLP[4], Matthew E. Spector, MD[4], Andrew J. Rosko, MD[4]

[1]Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, [2]University of Michigan Medical School, [3]Department of Otolaryngology-Head and Neck Surgery, University of California-Davis, [4]Department of Otolaryngology-Head and Neck Surgery, University of Michigan

Running Head: Salvage Laryngectomy Functional Outcomes

Corresponding Author:

Andrew J. Rosko, MD

1904 Taubman Center

1500 E Medical Center Dr

Ann Arbor, MI 48109

Phone: 734-232-0120

Fax: 734-232-0784

E-mail: arosko@med.umich.edu

Meeting Information: Presented at the American Academy of Otolaryngology in New Orleans, Louisiana on September 15, 2019.

ABSTRACT

BACKGROUND: Long-term functional outcomes are poorly characterized for salvage laryngectomy. We identified predictors of esophageal stricture and swallowing function after salvage laryngectomy in a large cohort.

METHODS: A retrospective study of 233 patients who underwent salvage total laryngectomy for recurrent/persistent squamous cell carcinoma of the larynx or hypopharynx after radiation (XRT) or chemoradiation (CRT) was performed. Primary outcomes were esophageal dilation within one year, time to dilation, and gastrostomy tube dependence. Multivariate logistic and Cox regressions were used for statistical analysis.

RESULTS: Dilation was performed in 29.9% of patients. Dilation was twice as likely in patients with post-operative fistula compared to those without (Hazard Ratio (HR) 2.10, 95% Confidence Interval (CI) 1.06-4.13, p=0.03). Every year between XRT/CRT and salvage was associated with 10% increase in dilation (HR 1.09, 95% CI 1.03-1.17, p=0.01). No factors were associated with dilation by one year. 10% of patients were at least partially gastrostomy tube dependent one year post-operatively. At last follow-up (median 29 months), this rate was 13%. Patients with supraglottic recurrence had an increased risk of gastrostomy tube dependence at one year compared to glottic (OR 16.7, 95% CI 1.73-160, p=0.02). For every 10 pack years pre-salvage, the OR of requiring tube feeds at last follow-up was 1.24 (95% CI 1.04-1.48, p=0.02).

CONCLUSIONS: Fistula and pre-salvage smoking were associated with stricture post-salvage laryngectomy. No factors were associated with dilation by one year. Supraglottic recurrence and smoking were associated with gastrostomy tube dependence. These findings are important for pre-operative counseling prior to salvage laryngectomy.

KEYWORDS: head and neck cancer, larynx cancer, quality of life

LEVEL OF EVIDENCE: Level 4

INTRODUCTION

Since the VA Larynx and Intergroup Radiation Oncology Group trials, laryngeal cancer has been treated with either radiation (XRT), radiation with chemotherapy (CRT), or surgical treatment, often with a goal of larynx preservation for early stage and other amenable tumors.[1–3] However, many patients develop recurrent disease, requiring salvage total laryngectomy. This salvage surgery is associated with significant complications in up to two thirds of patients, including pharyngocutaneous fistula, stricture, and difficulty with swallowing.[4]

Across all cases of total laryngectomy, stricture and difficulty swallowing are known complications,[5,6] but this rate is even higher in patients undergoing salvage total laryngectomy, as these patient have an increased rate of gastrostomy tube dependency related to swallowing difficulty—between 20 and 40% in various studies.[5–10] Swallowing difficulty is also among the most significant factors to patients when rating their own quality of life.[11,12] Further, gastrostomy tube dependency has been shown to be associated with longer length of stay, increased complications, higher readmission rates, and poorer quality of life across all types of head and neck cancer.[11,13,14] Studies examining predictors of these complications in salvage laryngectomy have been limited to small cohorts. Given the lack of powered studies of salvage patients, the long-term functional outcomes of salvage laryngectomy are not well understood. The goal of this study, therefore, was to determine the predictors for stricture and swallowing dysfunction in patients undergoing salvage total laryngectomy.

MATETRIALS AND METHODS

Patient Population

This study was approved by the University of Michigan Internal Review Board and conducted in accordance with the Helsinki Declaration. We performed a retrospective cohort study of patients who underwent salvage laryngectomy with concurrent neck dissection between 1997 and 2016 for recurrent or persistent laryngeal squamous cell carcinoma after radiation therapy or chemoradiation therapy at the University of Michigan.[15,16] Patients were excluded from the study if they died within ninety days of salvage surgery, developed an inability to eat related to a medical problem unrelated to laryngectomy, or if they had a history of glossectomy due to the expected effects on swallow function.

Two subsets of patients were created for subsequent analysis. For dilation and swallowing outcomes at the one-year time point, patients were included as long as recurrence occurred after one year. For the second analysis, looking at outcomes at the last follow-up, patients who had any recurrence were excluded, as were those who had complications not directly associated with salvage surgery. Data collected from the electronic medical record included demographic data, data associated with the initial and recurrent tumors (e.g. site and stage, in accordance with 7th edition American Joint Committee on Cancer staging system), primary and salvage treatment information, number and timing of dilations, oral intake, and post-operative complications (e.g. pharyngocutaneous fistula).

Dilation was defined as any attempted esophageal dilation in the office or operating room. Each instance of dilation was recorded. For oral intake, patients were classified as having no intake per mouth (complete gastrostomy tube dependence), a combination of tube feeds and oral intake, and oral intake alone.

Statistical Analysis

Recurrent stage and site were combined into binary variables for analysis, with patients with Stage I and II disease combined and compared to Stages III and IV. For subsite, subglottic and glottic disease were considered together and compared to supraglottic disease. Univariate and bivariate statistics were performed using nonparametric tests (e.g. Wilcoxon rank-sum test and Fisher's exact test). Variables that had a p-value less than 0.1 and those variables felt clinically to be strong predictors of the outcomes of interest were included in the subsequent multivariable models. Dilation at one year, dilation by the end of follow-up, oral intake at one year, and oral intake at the end of follow-up were assessed using logistic regression. Overall hazard of dilation was assessed using a Cox proportional hazards model. Data analysis was performed in Stata 15 (StataCorp, College Station, TX) and SPSS Statistical Software version 25 (IBM SPSS Inc., Armonk, NY).

RESULTS

Demographics and Exposures

In total, 233 patients were included in this study, 48 of whom (20.6%) were female. The mean age of patients at their initial tumor was 59.8 (standard deviation (SD) 10.4), with a mean age of recurrence of 63.0 (SD 10.0). The characteristics of the original tumor prior to XRT/CRT are shown in Table 1. All patients received radiation, and 43.8% (n=102) received concurrent chemotherapy. At the time of recurrence, 51.5% (n=120) of tumors involved the glottis, 47.2% (n=110) arose from the supraglottis, and 1.3% (n=3) were centered in the subglottis. Initial and recurrent stages were similar. There were 136 former smokers (61.3%) and 89 current smokers (38.7%) at the time of salvage surgery, with five never smokers (2.2%). Further data on patient characteristics, such as alcohol use, can be found in Table 1.

Patients received a regional or free flap in 125 of salvage cases (53.7%), with the rest closed primarily. Among flaps, 20 were regional and 105 were free. Post-operative pharyngocutaneous fistula occurred in 73 (31.3%) patients.

At one year after surgery, 186 (79.3%) of patients had follow-up data and had not died or developed recurrence. 193 patients (83.5%) of patients were without recurrence in the study period. Median follow-up time was 29 months (interquartile range 14-60).

Dilation

Over the entire study period, 68 patients required esophageal dilation (39.2%, Table 2). Among those dilated, 27 (39.7%) required only one dilation. On multivariable analysis adjusting for gender, time to recurrence, pre-operative pack years, chemotherapy status, recurrence site,

stage at recurrence, and type of reconstruction, patients who developed a post-operative pharyngocutaneous fistula had a rate of dilation twice that of those without fistula during the follow-up period (Hazard Ratio (HR) 2.10, 95% Confidence Interval (CI) 1.06-4.13, p=0.04, Table 3, Figures 1 and 2). For every 10 pack years before salvage surgery, the relative risk of requiring dilation increased by 19% (HR 1.19, 95% CI 1.10-1.30, p<0.0001). Every year between completion of initial radiation or chemoradiation and salvage was associated with a 9% relative increase in the risk of dilation (HR 1.09, 95% CI 1.03-1.17, p=0.01).

Among all patients dilated, 46 (67.6%) were dilated for the first time within a year of their salvage surgery; however, no factors emerged in our multivariable model, shown in Table 3, as significant predictors. The same covariates were included in the multivariable model as the logistic regression for dilation at any time. Female sex was associated with an odds ratio of 2.10, but it was not statistically significant (95% CI 0.82–5.39, p=0.12, Table 3).

Oral Intake

At one year of follow-up, 9 (4.9%) patients were completely gastrostomy tube dependent, 7 (3.8%) were using a combination of tube feeds and food by mouth, and 169 (91.4%) had a diet of oral intake alone. Supraglottic recurrence was associated with an increased risk of gastrostomy tube dependency at one year (OR 16.6, 95% CI 1.7–160, p=0.02, Table 4).

Among patients with no recurrence after salvage, 183 patients had data for oral intake at their last follow-up. Among these, 12 (6.6%) of patients were taking no food by mouth, 13

(7.1%) had a diet of both tube feeds and food by mouth, and 158 (86.4%) were able to meet their full needs by oral intake alone. On our multivariable logistic regression, adjusting for the same clinical characteristics as previous models, there was an odds ratio of 1.24 for gastrostomy tube dependence for every 10 pack years pre-salvage surgery (95% CI 1.04-1.48, p=0.02, Table 4, Figure 3).

DISCUSSION

In our study, we found that the factors most closely associated with the need for dilation over the course of follow-up were presence of a post-operative fistula, pre-operative pack years, and time from the completion of the initial course of radiation to salvage. However, none of our predictors in the multivariable model were associated with dilation within one year. Supraglottic recurrence was associated with gastrostomy tube requirement at one year. Similar to dilation, the pre-operative pack years were the primary factor associated with the requirement for a gastrostomy tube at the end of follow-up.

Overall, our study described similar rates of dilation and fistula to previously published literature on salvage laryngectomy.[4–8,12,17] Our rates of gastrostomy tube dependency were on the lower end of the literature, with a rate of 13.7% for any gastrostomy tube dependency at the end of follow-up, with only 6.6% taking no food by mouth.[6–8,10,18] It is possible that a relatively high percentage of reconstruction with flaps in our cohort might contribute to a lower rate of gastrostomy tube dependence based on previous studies.[19]

Our study—the largest institutional salvage laryngectomy database in a recent review—is the first to find that pre-operative pack years are a significant factor associated with both gastrostomy tube and dilation requirement over the full length of follow-up. Additionally, we are the first to find an association between post-operative pharyngocutaneous fistula formation and the need for dilation.[20] Similarly to other studies, CRT did not emerge as a significant factor compared to XRT during initial treatment in the need for gastrostomy tube or dilations.[5,10] Sweeny et al. did find a specific association between the type of flap used for reconstruction and the need for dilation; we did not find this when looking grossly at the utilization of flap compared to no flap at all. However, we did not have the specific information on type of flap used in the Sweeny study. Other specific data was also lacking for many patients—the type of radiation and the presence of induction chemotherapy. However, since many patients received their initial treatment at outside of the study institution, the sub-population with that information available would likely be significantly different from our overall study group.

Another possible limitation of our statistical analysis is the utilization of Cox proportional hazards modelling to model the hazard of dilation at any point during follow-up. This model was chosen to take advantage of the presence of person-time data. However, more recently, epidemiologists have become concerned that Cox models present a form of selection bias.[21] For sensitivity analysis, we performed logistic regression modelling the need for dilation at any point during follow-up and found similar results to the Cox model. Another limitation to our study is we do not have a granular patient-reported assessment of swallowing that other studies have

used, such as the M.D. Anderson Dysphagia Inventory (MDADI), as this was not routinely used at our institution over the study period.[12,22] This limits our ability to make specific conclusions about details of patient experience that are otherwise included in the MDADI.

Our data still show important factors associated with long-term functional outcomes for patients undergoing salvage laryngectomy—vital for pre-operative discussions with these patients. Recent research has shown that there is wide variation in how patients are counseled about post-operative complications before their salvage laryngectomy.[23] Our study highlights the particular importance of pre-salvage risk factors for dysphagia: pack years, site of recurrence, and time to recurrence. Unfortunately, these are not factors that can be changed by patient or provider at the time of salvage; however, in understanding these associations, we can better counsel patients undergoing salvage laryngectomy on their relative risk of requiring dilation or a gastrostomy tube during their follow-up.

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Table 1: Demographic, Oncologic, and Treatment Factors across Population

Variable	N	%
Gender		
Male	185	79.4%
Female	48	20.6%
Chemotherapy with initial RT		
XRT	131	56.2%
CRT	102	43.8%
Time to recurrence		
<2 years	166	71.2%
≥2 years	66	28.4%
Missing	1	0.4%
Initial Site		
Glottis	120	51.5%
Supraglottis	100	42.9%
Subglottis	0	0.0%
Hypopharynx	2	0.9%
Unknown	11	4.7%
Initial Stage		
Stage I	57	24.5%
Stage II	54	23.2%
Stage III	51	21.9%
Stage IV	45	19.3%
Missing	26	11.2%
Site of Recurrence		
Glottis	120	51.5%
Supraglottis	110	47.2%
Subglottis	3	1.3%
Clinical Stage at Recurrence		

Stage I	12	5.2%
Stage II	76	32.6%
Stage III	63	27.0%
Stage IV	80	34.3%
Missing	2	0.9%

Table 1, con't: Demographic, Oncologic, and Treatment Factors across Population

Variable	N	%
Pre-salvage pack years		
0-25	31	13.3%
25-50	82	35.2%
50-100	80	34.3%
100+	18	7.7%
Missing	22	9.4%
Flap at Salvage		
No flap	108	46.4%
Regional flap	20	8.6%
Free Flap	105	45.1%
Post-operative fistula		
None	160	68.7%
Present	73	31.3%

XRT = Radiation therapy, CRT = chemotherapy + RT. Staging is per American Joint Committee on Cancer 7th Edition criteria.

Table 2: G-tube and dilation requirements

Variable	N	%
G-tube dependence at one year		
Dependent	11	4.7%
No dependence	175	75.1%
Missing	47	20.2%
G-tube dependence at last follow-up		
Dependent	$24	10.3%
No dependence	204	87.6%
Missing	5	2.1%
Dilated within first year		
No	187	80.3%
Yes	46	19.7%
Esophageal dilation by last follow-up		
None	165	70.8%
One or more times	68	29.2%

Table 3: Cox Proportional Hazards Model for Dilation Requirement and Logistic Regression
Model for Dilation Requirement at One Year

Variable	HR (95% CI)	p	OR (95% CI)	p
Gender				
Male	-		-	
Female	1.39 (0.67, 2.90)	0.38	2.10 (0.82, 5.39)	0.12
Time to recurrence, years	1.09 (1.03, 1.17)	0.01	1.03 (0.92, 1.15)	0.61
Pre-operative pack years[†]	1.19 (1.10, 1.30)	<0.001	1.09 (0.95, 1.26)	0.22
XRT vs. CRT				
XRT	-		-	
CRT	0.64 (0.32, 1.28)	0.21	0.86 (0.34, 2.17)	0.75
Recurrence Site				
Glottic or subglottic recurrence	-		-	
Supraglottic recurrence	1.38 (0.67, 2.84)	0.38	1.82 (0.70, 4.66)	0.22
Stage at Recurrence				
Stage I and II	-		-	
Stage III and IV	1.31 (0.67, 2.56)	0.43	2.07 (0.80, 5.4)	0.13
Reconstruction at Salvage				
No flap	-		-	
Flap	1.28 (0.66, 2.48)	0.46	1.34 (0.55, 3.24)	0.52
Post-operative fistula				
No	-		-	
Yes	2.10 (1.06, 4.13)	0.03	1.71 (0.70, 4.17)	0.24

[†]Per 10 pre-operative pack years

XRT = radiotherapy alone, CRT = radiotherapy with chemotherapy, - = reference.

Table 4: Logistic Regression Models for G-tube Requirement

	G-tube requirement at one year		G-tube requirement at end of follow-up	
	OR (95% CI)	p	OR (95% CI)	p
Gender				
Male	-		-	
Female	0.24 (0.02, 2.26)	0.21	0.85 (0.16, 4.54)	0.85
Time to recurrence, years	1.07 (0.90, 1.28)	0.45	1.02 (0.90, 1.16)	0.73
Pre-operative pack years[†]	0.92 (0.68, 1.26)	0.61	1.24 (1.04, 1.48)	0.02
XRT vs. CRT				
XRT	-		-	
CRT	0.36 (0.07, 1.77)	0.21	0.57 (0.14, 2.31)	0.43
Recurrence Site				
Glottic or subglottic recurrence	-		-	
Supraglottic recurrence	16.61 (1.73, 160.23)	0.02	1.08 (0.26, 4.48)	0.91
Stage at Recurrence				
Stage I and II	-		-	
Stage III and IV	0.54 (0.11, 2.71)	0.46	1.44 (0.38, 5.47)	0.59
Reconstruction at Salvage				
No flap	-		-	
Flap	3.10 (0.51, 18.89)	0.22	2.01 (0.50, 8.04)	0.32
Post-operative fistula				
No	-		-	
Yes	1.61 (0.37, 7.08)	0.53	2.03 (0.53, 7.74)	0.30

[†]Per 10 pre-operative pack years. XRT = radiotherapy alone, CRT = radiotherapy with chemotherapy, - = reference.

Figure 1: Dilation over Time by Fistula

Kaplan-Meier estimate of dilation-free survival stratified by presence of post-operative fistula.

Figure 2: Forest plot of Cox proportional hazards model for dilation.
*Odds ratio is per 10 pack years. Reference groups are: male vs. female, XRT alone vs. CRT, glottic or subglottic recurrence vs. supraglottic, Stage I and II vs. III and IV, no flap vs. flap at salvage, and no fistula vs. post-operative fistula.
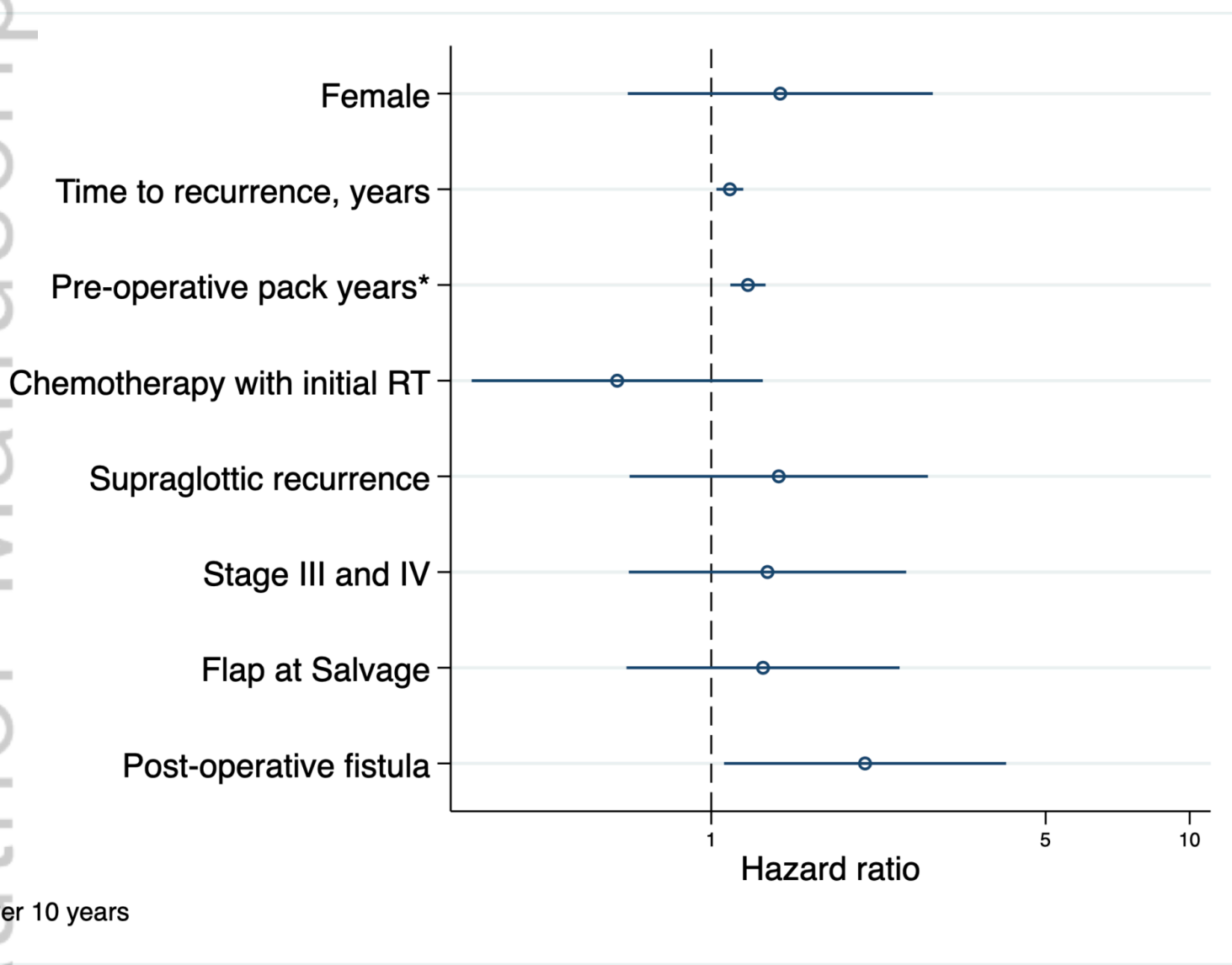
Figure 3: Forest plot of logistic regression models for tube feeds and dilation.

[*]Odds ratio is per 10 pack years. Model is additionally adjusted for gender, XRT vs. CRT, recurrent subsite, recurrent stage, flap utilization, and post-operative fistula.
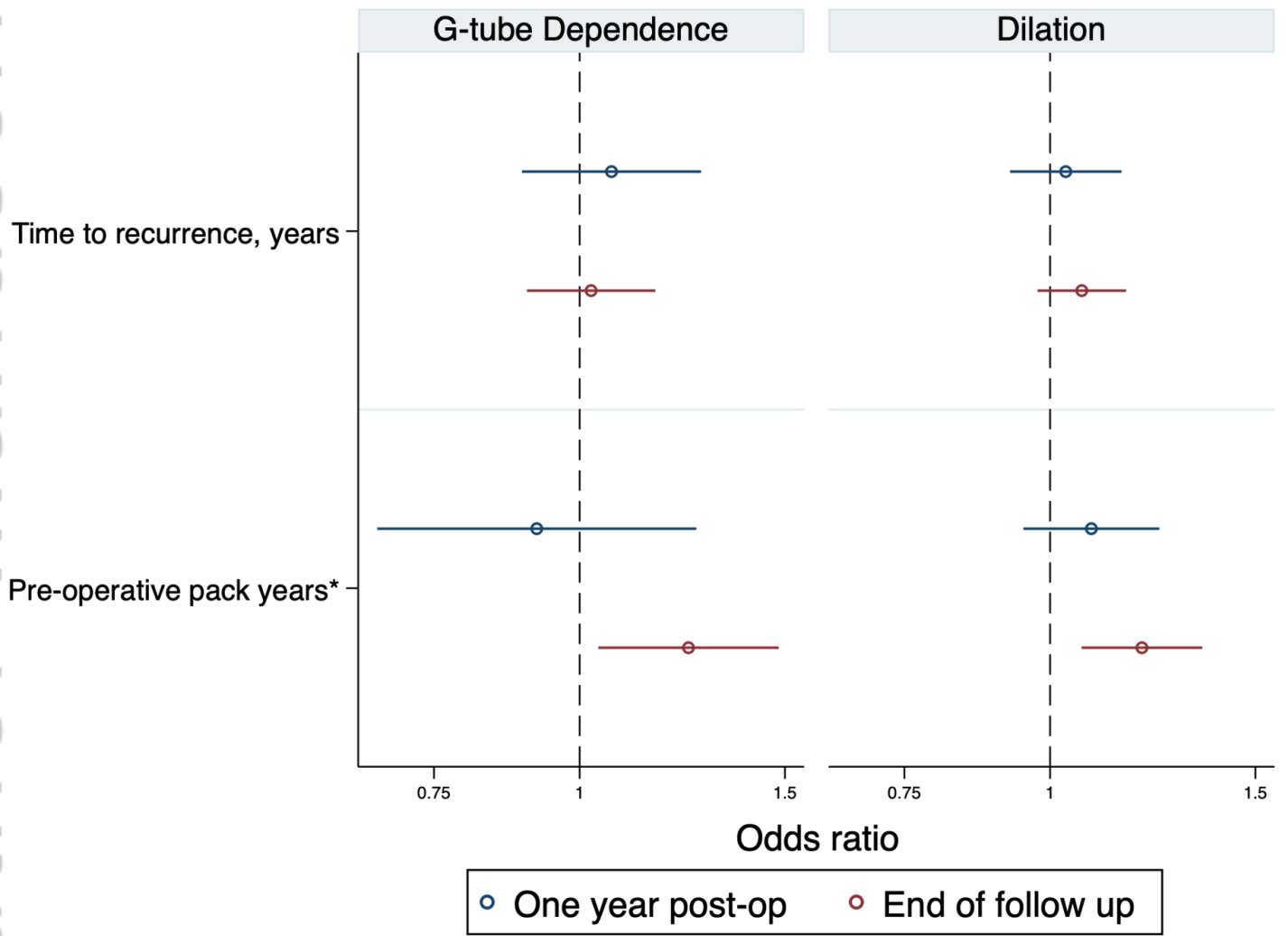
Kaplan-Meier Estimate of Dilation
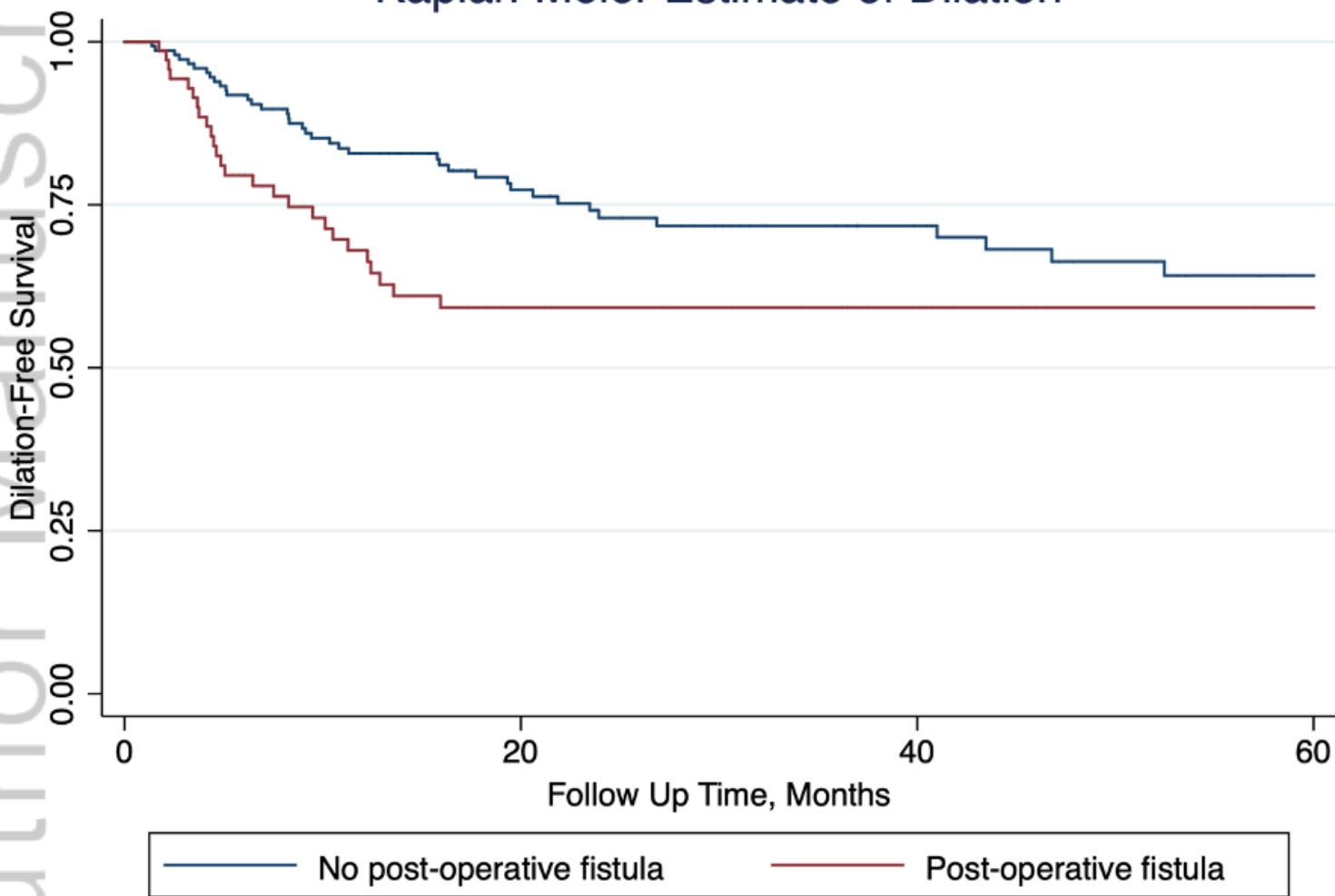
LARY_29215_Schumanetal_Salvage_Fig1.png

*Per 10 years

LARY_29215_Schumanetal_Salvage_Figure2.png

LARY_29215_Schumanetal_Salvage_Figure3.png