

Vocal Fold Paralysis is a Common Complication in Esophageal Cancer Patients with Esophagorespiratory Fistula

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ABSTRACT

Background & Aims: The development of an esophagorespiratory fistula (ERF) in patients with esophageal cancer (EC) is associated with poor prognosis. We observed a high rate of vocal fold paralysis (VFP) in patients with ERF. Data on prevalence and complications of VFP in ERF are lacking. The present study investigated the incidence of VFP in patients with malignant ERF and examined possible risk factors and the impact on survival.

Methods: We performed a retrospective case-control study of 46 institutional cases of EC patients with ERF in a time period of eleven years. Patients were matched to 92 randomly selected controls (EC patients without ERF) in a 1:2 fashion for tumor localization and histology. Demographics, clinical characteristics, recurrence, treatment modalities as well as survival were analyzed.

Results: Esophageal cancer patients with ERF developed more often VFP than EC patients without ERF (59% vs. 21%; $p=0.02$; odds ratio (OR) 4.9). Esophageal cancer patients with ERF had a more pronounced weight loss (7.1 vs. 11.5 kg; $P=0.008$), as well as higher rates of esophageal ($p<0.001$; OR 22.9) and tracheal stenting ($p<0.001$; OR 76.8). Proximal tumor growth ($p=0.004$; OR 7.9), fistula formation to the trachea ($p<0.001$; OR 17.2) and recurrent disease ($p=0.04$, OR 4.7) was associated with VFP development in EC patients with ERF. Vocal fold paralysis in ERF did not adversely affect five-year survival.

Conclusions: Vocal fold paralysis is a common complication in more than half of the patients with ERF in EC. It is associated with proximal tumor growth, fistula formation to the trachea and disease recurrence, but does not influence survival.

Key words: vocal fold paralysis – esophagorespiratory fistula – esophageal cancer.

Abbreviations: EC: esophageal cancer; ERF: esophagorespiratory fistula; RLN: recurrent laryngeal nerve; VFP: vocal fold paralysis.

INTRODUCTION

The development of esophagorespiratory fistula (ERF) in esophageal cancer (EC) is usually a sign of late stage disease, being associated with poor prognosis [1]. The strongest risk factors for ERF formation are proximal tumor growth in the esophagus and histology of squamous cell carcinoma [2]. The artificial connection between the esophagus and the trachea or bronchi leads to chronic inflammation and infection of the airways and

lung, partly explaining the high morbidity associated with this complication. Although sealing the fistula by esophageal or tracheal stenting is possible with high success rates, survival after fistula formation is still measured in weeks or months [3]. Therefore, there are likely to be other, unknown factors that adversely influence survival in patients with ERF in EC. We observed a high proportion of patients with ERF and vocal fold paralysis (VFP) during routine patient care.

The vocal folds are innervated by branches of the vagus nerve. One branch, namely the recurrent laryngeal nerve (RLN), provides innervation responsible for abduction of the vocal folds. The left recurrent laryngeal nerve passes in front of the aortic arch and makes a loop around it, to ascend back to the larynx in a groove between the esophagus and trachea. The right RLN dips posteriorly around the subclavian artery and ascends in the groove between the esophagus and trachea [4]. Therefore, a tumor that leads to fistula formation between

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the esophagus and trachea may also compress or infiltrate the RLN. One sided RLN paralysis leads primarily to hoarseness and sporadically to aspiration and difficulties with breathing or swallowing [5]. On the contrary, patients with bilateral VFP have varying degrees of airway narrowing through reduction of the glottal area [6]. Also dysphonia and dysphagia with aspiration occurs [7].

The rate of VFP in EC patients with ERF is unknown. We hypothesized that VFP in malignant ERF contributes to morbidity and mortality by dysphagia and weight loss, as well as chronic aspiration. Therefore, the aim of this study was to determine the rate of VFP in patients with malignant ERF and identify the risk factors, complications and mortality related to it.

METHODS

Study patients

From 2008 to 2018 patients developing ERF in EC were retrospectively reviewed. In the local patient record database at the Klinikum Stuttgart, 50 adult patients with ERF in EC were identified. Four patients had to be excluded from the analysis, because they had prior laryngectomy. Multiple databases were used (the institutional endoscopy database and databases containing discharge diagnosis). Esophagorespiratory fistula was diagnosed by either direct visualization during upper gastrointestinal endoscopy and bronchoscopy or contrast radiography of the upper gastrointestinal tract. Vocal fold paralysis was diagnosed by direct or indirect laryngoscopy by an ear-nose-throat specialist or by bronchoscopy. We matched the 46 patients with ERF in EC in a 1:2 fashion to 92 randomly selected controls with esophageal cancer, but without ERF. Random selection was performed by software based random allocation. Matching was performed by MedCalc Version 19.0.5 (MedCalc Software bv, Ostend, Belgium). Controls were selected from a total cohort of 573 patients with EC.

Data acquisition

Information recorded was: age at initial diagnosis, sex, location of tumor (proximal, middle, distal part of esophagus and distance in centimeters from dental arch), histology (squamous vs. non-squamous), grading (1-3), initial tumor (T) stage (1-4), node (N) stage (0 or +), or metastasis (M) stage (0 or 1), former or current smoking status, VFP development (yes/no and unilateral/bilateral), need for esophageal or airway stent placement, need for bougienage, therapy (chemotherapy, radiotherapy, surgery) and survival in days. TNM information was obtained by imaging techniques and by endoscopic ultrasound. Proximal esophagus was defined as majority of tumor growth up to 25 cm from incisors, middle as 25-32 cm from incisors and distal from 32 cm and beyond. To calculate mean weight loss, two weight measurements were considered: first weight documented at initial diagnosis and last weight documented within the last 21 days before death. In patients with long term survival, last weight measurement available was used for calculation. Not all variables were readily available for every patient in the database, resulting in partly missing cases. In case of satellite tumors, only the main tumor, respectively the tumor that led to fistula formation was considered.

Statistic analysis

The primary goal of this study was to evaluate the prevalence of VFP in patients with ERF in EC, compared to patients without ERF. The secondary goal was to evaluate the risk factors and survival of patients with VFP and ERF. Characteristics of patients with or without ERF were compared using Fisher's exact test for categorical variables and student t-test for metric variables. A matched dataset was used for the analysis. Therefore, conditional logistic regression analysis was conducted to estimate the odds ratio (OR) and 95% confidence interval (CI) and to investigate the association between clinical characteristics and risk factors for ERF formation. Covariates were selected through a backward stepwise selection. Log-rank (Mantel-Cox) test was used to determine five-year survival. Continuous data are either represented as median \pm (interquartile) range or mean and standard deviation. Reported p-values are 2-tailed, with $p < 0.05$ being considered statistically significant. SPSS (SPSS 24, SPSS Inc., Armonk NY, USA) and GraphPad Prism 7 (GraphPad Software, La Jolla, California USA) were used for statistical analysis.

Ethics approval

The study was approved and authorized by the hospital ethics committee of University Tübingen, Project number: 879/2017BO2. Since diagnosis and treatment correspond to the quality standard of current guidelines, no written informed consent of the patients was considered necessary.

RESULTS

Demographics and clinical characteristics

In a time period of eleven years, 50 out of 573 EC patients developed ERF, resulting in a cumulative incidence of 8.7%. Four of these patients had to be excluded from the analysis, because they had partial or total laryngectomy prior to EC development. The remaining 46 cases were matched in a 1:2 fashion to 92 randomly selected controls for the variables tumor localization and histology. Squamous cell carcinoma was present in 93% of all patients, whereas 7% had non-squamous cell carcinoma (all of them adenocarcinoma). In the ERF group there were 30 patients with proximal, 14 with middle and two with distal squamous cell carcinoma and ERF. The control group was comprised of 60 patients with proximal EC, 28 with middle and 4 with distal EC without ERF. Esophageal cancer patients with ERF were younger (61.5 years; range 48-82 years) than EC patients without ERF (66 years; range 45-94 years) ($p = 0.03$). Gender distribution was 75% male in the control group and 78% male in the ERF group. More patients with ERF underwent esophageal stenting (15% vs. 80%; $p \leq 0.001$) or airway stenting (2% vs. 63%; $p \leq 0.001$). Significantly more patients in the ERF group had vocal fold paralysis (59% vs 21%; $p = 0.02$). Patients with ERF had a more pronounced mean weight loss (11.5 ± 6.2 kg) than patients in the control group (7.1 ± 8.8 kg) ($p = 0.008$). Results are summarized in Table I.

Risk factors for VFP in EC with ERF

In a second step, risk factors for VFP development in EC patients with ERF were evaluated. Proximal tumors were

Table I. Demographics and clinical characteristics of patients with and without esophagorespiratory fistula formation in esophageal cancer

	EC without ERF (N=92)	EC with ERF (N=46)	Odds ratio (95%CI)	p
Median age (years, range)	66 (45-94)	61.5 (48-82)	-	0.03
Gender (%)				
Male	69 (75)	36 (78)		
Female	23 (25)	10 (22)	0.96 (0.79-1.16)	0.83
Vocal fold paralysis (%)				
No-VFP	73 (79)	19 (41)		
VFP	19 (21)	27 (59)	5.46 (2.52-11.84)	<0.001
T-stage (%)				
Non-T4	62 (68)	36 (78)		
T4	29 (32)	10 (22)	0.59 (0.26-1.36)	0.24
N-stage (%)				
N0	14 (16)	13 (28)		
N+	74 (84)	33 (72)	0.48 (0.2-1.13)	0.11
M-stage (%)				
M0	66 (73)	35 (76)		
M1	24 (27)	11 (24)	0.86 (0.38-1.97)	0.84
Grading (%)				
G1+ G2	50 (58)	24 (52)		
G3	37 (42)	22 (48)	1.24 (0.6-2.54)	0.59
Relapse (%)				
No relapse	56 (62)	28 (61)		
Relapse	35 (38)	18 (39)	1.03 (0.5-2.13)	1
Bougienage (%)				
No bougienage	35 (39)	17 (37)		
Bougienage	56 (61)	29 (63)	1.07 (0.51-2.22)	1
Chemotherapy (%)				
No chemotherapy	10 (11)	9 (20)		
Chemotherapy	82 (89)	37 (80)	0.5 (0.19-1.34)	0.19
Radiotherapy (%)				
No radiotherapy	23 (25)	17 (37)		
Radiotherapy	68 (75)	29 (63)	0.58 (0.27-1.24)	0.17
Surgery (%)				
No surgery	75 (82)	36 (78)		
Surgery	16 (18)	10 (22)	1.3 (0.54-3.15)	0.65
Esophageal stenting (%)				
No esophageal stenting	78 (85)	9 (20)		
Esophageal stenting	14 (15)	37 (80)	22.9 (9.1-57.72)	<0.001
Airway stenting (%)				
No airway stenting	90 (98)	17 (37)		
Airway stenting	2 (2)	29 (63)	76.77 (16.73-352.31)	<0.001
Weight loss, kg (standard deviation)	7.1 (8.8)	11.5 (6.2)	-	0.008

EC: esophageal cancer; ERF: esophagorespiratory fistula

significantly more often associated with VFP (42% vs. 85%; $p=0.004$). The strongest risk factor for VFP formation was fistula location in the trachea rather than more distal airways (42% vs. 93%; $p\leq 0.001$). Relapse rate also increased the occurrence of VFP besides tumor localization and tracheal fistulation. More

patients with VFP had a local or distant recurrence of their EC ($p=0.04$). Vocal fold paralysis had no influence on mean weight loss between groups ($p=0.78$). Mean weight loss was 10.6 ± 6.2 kg in patients without VFP and 12.2 ± 6.4 kg in patients with VFP. Results are summarized in Table II.

Table II. Risk factors for the development of vocal fold paralysis in patients with malignant esophagorespiratory fistula in esophageal cancer

	No VFP (N=19)	VFP (N=27)	Odds ratio (95%CI)	p-value
Gender (%)				
Female	6 (32)	4 (15)		
Male	13 (68)	23 (85)	2.65 (0.63-11.16)	0.28
Median age (range)	64 (45-82)	61 (49-79)	-	0.78
T stage (%)				
Non T4	13 (68)	23 (85)		
T4	6 (32)	4 (15)	0.37 (0.09-1.59)	0.28
N stage (%)				
N0	5 (26)	8 (30)		
N+	14 (74)	19 (70)	0.85 (0.23-3.15)	1
M stage (%)				
M0	15 (79)	20 (74)		
M1	4 (21)	7 (26)	1.31 (0.32-5.32)	1
Grading (%)				
G1 + G2	11 (58)	13 (48)		
G3	8 (42)	14 (52)	1.48 (0.45-4.83)	0.56
Primary tumor localization (%)				
Non-proximal	11 (58)	4 (15)		
Proximal	8 (42)	23 (85)	7.91 (1.95-32.03)	0.004
Fistula localization				
Other than trachea	11 (58)	2 (7)		
Trachea	8 (42)	25 (93)	17.19 (3.13-94.47)	<0.001
Relapse (%)				
No relapse	15 (79)	12 (44)		
Relapse	4 (21)	15 (56)	4.69 (1.23-17.88)	0.03
Bougienage (%)				
No bougienage	9 (47)	8 (30)		
Bougienage	10 (53)	19 (70)	2.14 (0.63-7.26)	0.35
Chemotherapy (%)				
No chemotherapy	6 (32)	3 (11)		
Chemotherapy	13 (68)	24 (89)	3.69 (0.79-17.25)	0.13
Radiotherapy (%)				
No radiotherapy	7 (37)	10 (37)		
Radiotherapy	12 (63)	17 (63)	0.99 (0.29-3.35)	1
Surgery (%)				
No surgery	15 (79)	21 (78)		
Surgery	4 (21)	6 (22)	1.07 (0.26-4.47)	1
Esophageal stenting (%)				
No esophageal stenting	3 (16)	6 (22)		
Esophageal stenting	16 (84)	21 (78)	0.66 (0.14-3.03)	0.72
Airway stenting (%)				
No airway stenting	9 (47)	8 (30)		
Airway stenting	10 (53)	19 (70)	2.14 (0.63-7.26)	0.35
Weight loss, kg (standard deviation)	10.6 (6.2)	12.2 (6.4)	-	0.78

VFP: vocal fold paralysis

Out of 27 patients with ERF and VFP, ten had right-sided VFP (37%), nine left-sided VFP (33%) and eight bilateral VFP (30%). In one patient with left-sided VFP, tracheostomy had

to be performed, due to rapidly worsening dyspnea. In two patients with bilateral VFP, tracheostomy was performed, and two patients had laser surgery with resection of the posterior

vocal cord. In four patients with bilateral VFP no intervention was performed. Two patients had only moderate symptoms and in two patients no intervention was performed due to advanced disease and very limited life expectancy. The need for esophageal stent placement was not different between groups ($p=0.72$). Two patients without VFP and four patients with VFP experienced esophageal stent migration and need for replacement. Six patients without VFP and five patients with VFP suffered from overgrowth of stent by granulation tissue or tumor. In one patient in the VFP group the esophageal stent had to be removed because of severe chest pain. In the same patient rapid tumor growth led to tumor overgrowth of the airway stent and airway narrowing, resulting in the need for revision and extension of the airway stent. Airway stent migration occurred in two patients in each group. Removal of granulation tissue or tumor overgrowth was necessary in three patients without VFP and four patients with VFP.

Survival of ERF patients with VFP

Median survival after initial diagnosis of EC in patients with ERF but without VFP was 256 days (interquartile range 485 days). Median survival in patients with ERF and VFP was 465 days (interquartile range 451 days). Survival did not differ significantly ($p=0.49$; hazard ratio 1.25, 95%CI: 0.7-2.3). Five-year survival is shown in Fig. 1.

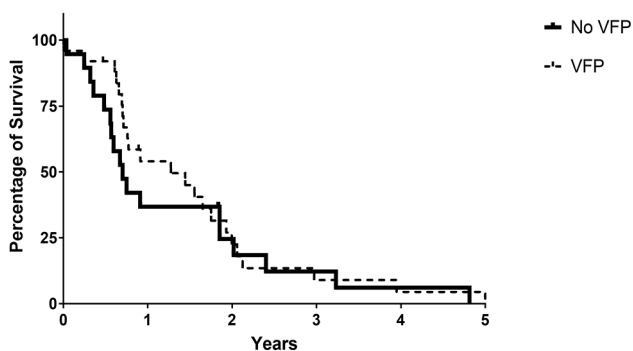


Fig. 1. Five-year survival of patients with esophagorespiratory fistula in esophageal cancer with and without vocal fold paralysis (VFP).

DISCUSSION

To our knowledge this is the first study assessing VFP in patients with malignant ERF. The key finding of this study was that VFP is a common complication of ERF in EC. The strongest risk factors for VFP development were proximal tumor growth, fistula formation to the trachea and disease relapse. Despite obvious concerns regarding a higher mortality, we could not establish any adverse effect of VFP on survival in EC patients with ERF.

Vocal fold paralysis may complicate thoracic and thyroid cancers and is associated with increased morbidity [8, 9]. Literature shows that around five percent of intrathoracic esophageal carcinomas are associated with VFP [10]. During routine patient care we observed that a large proportion of EC patients with ERF had VFP. In the literature, we could not find any data on this set of patients. This study shows that VFP

is a very common finding in EC patients with ERF, as more than half of the patients had uni- or bilateral VFP. Previous publications have shown that patients with ERF in EC are significantly younger than without ERF [2, 11, 12]. We were able to reproduce this finding, explaining the age difference in our study. Patients with ERF showed a higher level of morbidity expressed by a more pronounced weight loss, as well as a higher need for esophageal or airway stenting. In contrast to the literature, we also observed a very high rate of VFP in our control group. As the patients were matching for histology and primary tumor localization, we had a high rate of proximal ECs in the control group. Matching was necessary, as past publications have shown that histology of squamous cell carcinoma and proximal tumor growth are the strongest risk factors for ERF formation [2]. As the recurrent laryngeal nerve (RLN) is part of the superior mediastinum, only proximal tumors of the esophagus can lead to direct infiltration of the RLN [10]. Patients with VFP due to RLN invasion or lymph node metastasis along the RLN have a poor prognosis, which has been shown for different tumor entities, including esophageal cancer [13–15]. In these cases, VFP is usually caused by direct extension of the tumor to the RLN, but also by involvement of metastatic lymph node metastasis. Therefore, one could expect that VFP in ERF is associated with a higher T and N stage. Surprisingly, we were able to show that this is not the case. Direct tumor invasion of the nerve also does not seem to play a key role in recurrent laryngeal nerve palsy, as the T stage was not linked to VFP either. In past publications, T stage was also not associated with ERF formation in EC [16]. Instead, one might hypothesize that tumors leading to ERF induce an inflammatory response in their surroundings. As the RLN is situated between the esophagus and the trachea, it would be frequently affected by this inflammatory process.

The two strongest risk factors for VFP in ERF were localization of the fistula between the esophagus and the trachea and proximal tumor growth. In our study, 93% of patients with VFP in ERF had fistula formation to the trachea, in contrast to 42% of patients without VFP in ERF. This is explained anatomically, as the RLN ascends to the larynx in a groove between the proximal esophagus and the trachea. A tumor extending from the esophagus to the trachea that induces an inflammatory response leading to fistula formation, should also lead to infiltration of the RLN.

The third identified risk factor was disease relapse. The reason for this phenomenon is unclear. In papillary thyroid cancer, direct invasion of the RLN observed during operation, resulted only in 36% of cases in VFP [14]. This observation shows that other mechanisms are involved in malignant RLN paralysis. Several studies in thyroid cancer showed that RLN invasion is associated with a higher recurrence rate, even when the RLN was also resected operatively [14, 17]. Hence, one might hypothesize that tumors leading to VFP or RLN invasion are somewhat biologically different, being more prone to metastasize earlier. Recurrent laryngeal nerve injury may be caused by placement of self-expandable metal stents in the proximal esophagus [18]. We hypothesized that disease recurrence leads more often to the need for esophageal or airway stenting and thereby increases the risk for RLN. But airway or esophageal stenting was not associated with the

occurrence of VFP in malignant ERF patients. Tumors in the cervical portion of the esophagus are difficult to manage. Though, studies have shown that early and late complications after stent implantation are not different between proximal and distal esophageal cancers [19]. Also surgery for esophageal cancer, a known risk factor for VFP, was not associated with RLN injury in our study cohort [20]. We mostly attribute this to the small sample size in this study. As VFP after esophagectomy occurs only in around 24% of patients, we were not able to discern this statistically with only a few patients in each group [21]. In our study population, surgery was performed for the treatment of EC and not for the treatment of ERF. Esophagorespiratory fistula formation after surgery was a result of disease relapse. Especially in patients after thoracic surgery, VFP was associated with increased risk of pneumonia, respiratory failure, longer hospital stay and recurrent aspiration [22,23]. Breathing and swallowing symptoms affected 76% and 66% of patients with unilateral VFP [24]. We thereby hypothesized that VFP contributes to morbidity and mortality in patients with ERF in EC. However, no difference was seen in weight loss or five-year survival in patients with or without VFP in ERF. Although survival appears to be higher in patients with VFP in ERF after one year, resulting in a higher median survival (median 256 vs. 465 days), survival curves approach each other after two years, resulting in a comparable overall survival. The seemingly big difference in median survival is mostly attributable to the small sample size. A study by Loochtan et al [21], also reported that VFP after esophagectomy for EC was associated with a higher risk of tracheotomy and longer lengths of stay in the hospital, but did not influence survival rates. So, survival in patients with EC with or without ERF seems to be mainly influenced by tumor burden and infectious complications and not by VFP.

A limitation of our study is the retrospective approach. Charts were reviewed individually, but data quality relies on accurate documentation in the past. As ERF development is a rare complication, prospective studies can only be performed over a long period of time and in conjunction of several centers. As this study was conducted retrospectively in a single center, we only report a small size study population. The small patient numbers, especially in our analysis of risk factors for VFP, limits the exploration of more variables. Larger studies are needed to verify our findings and explore other potential risk factors that may influence survival in patients with ERF.

CONCLUSIONS

Our analysis revealed that VFP is a common complication in more than half of patients with ERF in EC. The strongest risk factors for VFP development were proximal tumor growth and fistula formation from the esophagus to the trachea. Disease relapse is another identified risk factor for VFP in patients with malignant ERF. Although increased morbidity with VFP has been published in the past, we were not able to identify any influence on survival in patients with ERF. Nevertheless, the high incidence of recurrent laryngeal nerve paralysis in this patient population should encourage clinicians to screen for this complication and to facilitate the early initiation of appropriate treatment.

Conflicts of interest: None to declare.

Authors' contributions: G.P. designed the study, collected and analyzed the data, drafted the manuscript. F.E., W.B. and W.Z. reviewed the manuscript and contributed to data collection. All authors critically revised the manuscript, approved the final version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. Silon B, Siddiqui AA, Taylor LJ, Arastu S, Soomro A, Adler DG. Endoscopic Management of Esophagorespiratory Fistulas: A Multicenter Retrospective Study of Techniques and Outcomes. *Dig Dis Sci* 2017;62:424–431. doi:10.1007/s10620-016-4390-0
2. Paul G, Bohle W, Zoller W. Risk Factors for the Development of Esophagorespiratory Fistula in Esophageal Cancer. *J Gastrointest Liver Dis* 2019;28:265–270. doi:10.15403/jgld-271
3. Kim PH, Kim KY, Song HY, et al. Self-Expandable Metal Stent Use to Palliate Malignant Esophagorespiratory Fistulas in 88 Patients. *J Vasc Interv Radiol* 2018;29:320–327. doi:10.1016/j.jvir.2017.07.025
4. Henry BM, Sanna B, Graves MJ, et al. The Reliability of the Tracheoesophageal Groove and the Ligament of Berry as Landmarks for Identifying the Recurrent Laryngeal Nerve: A Cadaveric Study and Meta-Analysis. *Biomed Res Int* 2017;2017:4357591. doi:10.1155/2017/4357591
5. Walton C, Carding P, Flanagan K. Perspectives on voice treatment for unilateral vocal fold paralysis. *Curr Opin Otolaryngol Head Neck Surg* 2018;26:157–161. doi:10.1097/MOO.0000000000000450
6. Li Y, Garrett G, Zelear D. Current Treatment Options for Bilateral Vocal Fold Paralysis: A State-of-the-Art Review. *Clin Exp Otorhinolaryngol* 2017;10:203–212. doi:10.21053/ceo.2017.00199
7. Brake MK, Anderson J. Bilateral vocal fold immobility: a 13 year review of etiologies, management and the utility of the empey index. *J Otolaryngol Head Neck Surg* 2015;44:27. doi:10.1186/s40463-015-0080-8
8. Kay-Rivest E, Mitmaker E, Payne RJ, et al. Preoperative vocal cord paralysis and its association with malignant thyroid disease and other pathological features. *J Otolaryngol Head Neck Surg* 2015;44:35. doi:10.1186/s40463-015-0087-1
9. Mor N, Wu G, Aylward A, Christos PJ, Sulica L. Predictors for Permanent Medialization Laryngoplasty in Unilateral Vocal Fold Paralysis. *Otolaryngol Head Neck Surg* 2016;155:443–453. doi:10.1177/0194599816644716
10. Tachimori Y, Kato H, Watanabe H, Ishikawa T, Yamaguchi H. Vocal cord paralysis in patients with thoracic esophageal carcinoma. *J Surg Oncol* 1995;59:230–232. doi:10.1002/jso.2930590406
11. Balazs A, Galambos Z, Kupcsulik PK. Characteristics of esophagorespiratory fistulas resulting from esophageal cancers: a single-center study on 243 cases in a 20-year period. *World J Surg* 2009;33:994–1001. doi:10.1007/s00268-009-9988-3
12. Choi MK, Park YH, Hong JY, et al. Clinical implications of esophagorespiratory fistulae in patients with esophageal squamous cell carcinoma (SCCA). *Med Oncol* 2010;27:1234–1238. doi:10.1007/s12032-009-9364-z
13. Gorphe P, Blanchard P, Breuskin I, Temam S, Tao Y, Janot F. Vocal fold mobility as the main prognostic factor of treatment outcomes and survival in stage II squamous cell carcinomas of the glottic larynx. *J Laryngol Otol* 2015;129:903–909. doi:10.1017/S002221511500184X

14. Chen W, Lei J, You J, et al. Predictive factors and prognosis for recurrent laryngeal nerve invasion in papillary thyroid carcinoma. *OncoTargets Ther* 2017;10:4485–4491. doi:[10.2147/OTT.S142799](https://doi.org/10.2147/OTT.S142799)
15. Malassagne B, Tiret E, Duprez D, Coste J, de Sigalony JP, Parc R. Prognostic value of thoracic recurrent nerve nodal involvement in esophageal squamous cell carcinoma. *J Am Coll Surg* 1997;185:244–249. doi:[10.1016/s1072-7515\(97\)00046-x](https://doi.org/10.1016/s1072-7515(97)00046-x)
16. Tsushima T, Mizusawa J, Sudo K, et al. Risk Factors for Esophageal Fistula Associated With Chemoradiotherapy for Locally Advanced Unresectable Esophageal Cancer: A Supplementary Analysis of JCOG0303. *Medicine (Baltimore)* 2016;95:e3699. doi:[10.1097/MD.0000000000003699](https://doi.org/10.1097/MD.0000000000003699)
17. Shah JP, Loree TR, Dharker D, Strong EW, Begg C, Vlamis V. Prognostic factors in differentiated carcinoma of the thyroid gland. *Am J Surg* 1992;164:658–661. doi:[10.1016/s0002-9610\(05\)80729-9](https://doi.org/10.1016/s0002-9610(05)80729-9)
18. Moreels TG, De Schepper HU, Macken EJ, Hubens GJ, Pelckmans PA. Vocal cord paralysis due to self-expandable metal stent in the proximal esophagus. *Endoscopy* 2014;46 Suppl 1 UCTN:E155-E156. doi:[10.1055/s-0034-1364954](https://doi.org/10.1055/s-0034-1364954)
19. Parker RK, White RE, Topazian M, Chepkwony R, Dawsey S, Enders F. Stents for proximal esophageal cancer: a case-control study. *Gastrointest Endosc* 2011;73:1098–1105. doi:[10.1016/j.gie.2010.11.036](https://doi.org/10.1016/j.gie.2010.11.036)
20. Shimizu H, Shiozaki A, Fujiwara H, et al. Short- and Long-term Progress of Recurrent Laryngeal Nerve Paralysis After Subtotal Esophagectomy. *Anticancer Res* 2017;37:2019–2023. doi:[10.21873/anticancer.11546](https://doi.org/10.21873/anticancer.11546)
21. Loochtan MJ, Balcarcel D, Carroll E, Foecking EM, Thorpe EJ, Charous SJ. Vocal Fold Paralysis after Esophagectomy for Carcinoma. *Otolaryngol Head Neck Surg* 2016;155:122–126. doi:[10.1177/0194599816644738](https://doi.org/10.1177/0194599816644738)
22. Lodewyckx CL, White CW, Bay G, et al. Vocal Cord Paralysis After Thoracic Aortic Surgery: Incidence and Impact on Clinical Outcomes. *Ann Thorac Surg* 2015;100:54–58. doi:[10.1016/j.athoracsur.2015.02.021](https://doi.org/10.1016/j.athoracsur.2015.02.021)
23. Lee SY, Cheon HJ, Kim SJ, Shim YM, Zo JI, Hwang JH. Clinical predictors of aspiration after esophagectomy in esophageal cancer patients. *Support Care Cancer* 2016;24:295–299. doi:[10.1007/s00520-015-2776-8](https://doi.org/10.1007/s00520-015-2776-8)
24. Francis DO, McKiever ME, Garrett CG, Jacobson B, Penson DF. Assessment of patient experience with unilateral vocal fold immobility: a preliminary study. *J Voice* 2014;28:636–643. doi:[10.1016/j.jvoice.2014.01.006](https://doi.org/10.1016/j.jvoice.2014.01.006)