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Predictors of survival after total laryngectomy for recurrent/persistent laryngeal squamous cell carcinoma

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Abstract

Background: Total laryngectomy remains the treatment of choice for recurrent/persistent laryngeal squamous cell carcinoma (SCC) after radiotherapy (RT) or chemoradiotherapy (CRT). However, despite attempts at aggressive surgical salvage, survival in this cohort remains suboptimal.

Methods: A prospectively maintained single-institution database was queried for patients undergoing total laryngectomy for recurrent/persistent laryngeal SCC after initial RT/CRT between 1998 and 2015(n = 244). Demographic, clinical, and survival data were abstracted. The Kaplan-Meier survival curves and hazard ratios (HRs) were calculated.

Results: Five-year overall survival (OS) was 49%. Five-year disease-free survival (DFS) was 58%. Independent predictors of OS included severe comorbidity (Adult Comorbidity Evaluation-27 [ACE-27] scale; HR 3.76; 95% confidence interval [CI] 1.56-9.06), and positive recurrent clinical nodes (HR 2.91; 95% CI 1.74-4.88).

Conclusion: Severe comorbidity status is the strongest predictor of OS, suggesting that increased attention to mitigating competing risks to health is critical. These data may inform a risk prediction model to allow for focused shared decision making, preoperative health optimization, and patient selection for adjuvant therapies.

KEYWORDS
Adult Comorbidity Evaluation-27 (ACE-27), disease-specific survival, overall survival, recurrent laryngeal cancer, salvage laryngectomy

1 | INTRODUCTION

Advanced laryngeal squamous cell carcinoma (SCC) remains a highly morbid and fatal disease despite aggressive interventions. Mortality is high in this cohort: laryngeal cancer affects over 13 000 patients in the United States, with over 3500 deaths annually.[1] The results of the Veterans Affairs Cooperative Studies Program Laryngeal Cancer Trial and subsequent studies demonstrated similar overall survival (OS) rates for organ preservation protocols involving radiotherapy (RT) or chemoradiotherapy (CRT) when compared to surgery, with the benefit of preserving the larynx in a large majority of patients.[2–5] As such, the use of RT or CRT has become the predominant initial intervention for patients with laryngeal SCC.[6] However, the prognosis of recurrent and persistent laryngeal SCC is particularly dire.

Notably, a significant subset of patients undergoing RT or CRT for laryngeal SCC will develop recurrent disease. Five-year disease-free survival (DFS) rates for advanced laryngeal SCC treated with organ preservation protocols

ranges from 30%-60%[3,5,7]; for most with recurrent/persistent disease, salvage laryngectomy is often the only remaining curative therapeutic modality. Despite this, 5-year OS remains poor and is further compounded by a short DFS.[8] The morbidity of salvage surgery in such patients is considerable; moreover, survival for patients with recurrent or persistent laryngeal SCC is poor, but incompletely characterized.[9–11]

To date, there have not been studies focused on assessing prognostic variables for patients considering salvage laryngectomy. Although OS and recurrence rates are well described for primary laryngeal SCC, there is a paucity of data assessing outcomes for patients undergoing salvage laryngectomy. As organ-preservation protocols are increasingly being implemented as first-line therapy and failure drives poor survival, this patient population will be increasingly important to consider. Likewise, given recent increases in personalized medicine and immunotherapy approaches for advanced head and neck SCCs,[12,13] it is critical to identify predictors for patients with laryngeal SCC who may benefit from the addition of neo/adjuvant therapy in conjunction with salvage surgery.

In this study, we sought to identify preoperative predictors of survival for patients with recurrent or persistent laryngeal SCC in order to set patient expectations and address modifiable risk factors. Identification of predictors of survival may also identify patients who could benefit from novel therapeutic agents in a neo/adjuvant fashion. Herein, we examine a cohort of patients with recurrent or persistent laryngeal SCC after definitive RT/CRT who has undergone total laryngectomy in order to identify potential preoperative predictors of clinical outcomes.

2 | MATERIALS AND METHODS

2.1 | Patient identification and data collection

A prospectively maintained single-institution epidemiology database of patients with head and neck cancer was queried for eligible patients. University of Michigan Institutional Review Board approval was obtained for this study (HUM00081554). Inclusion criteria specified adult patients with a diagnosis of laryngeal SCC initially treated with RT/CRT between 1998 and 2015 who had a salvage laryngectomy for recurrent/persistent disease at the primary site (n = 244). Demographic, clinical, and survival data were abstracted (Table 1). Death was verified via medical records and the social security death index. Primary outcome measures were OS (time from salvage laryngectomy to death from any cause), disease-specific survival (DSS; time from salvage laryngectomy to death from recurrent/persistent laryngeal SCC), and DFS (time from salvage laryngectomy to laryngeal

SCC recurrence). Survival was described with the Kaplan-Meier methodology. We focused our analysis on survival patterns during the first 5 years after salvage surgery. For comorbidities, the Adult Comorbidity Evaluation-27 (ACE-27) index was used, as previously described,[14] with comorbidity status classified as none, mild, moderate, and severe.

Preoperative data (Table 1) included patient demographics, smoking history (defined as current, former: quit over 1 year ago, or never), comorbidity status (ACE-27 scale), initial cancer characteristics, initial cancer treatment, and recurrent cancer clinical characteristics.

2.2 | Statistical analysis

We aimed to identify factors at the time of the preoperative evaluation, as this would be a key timepoint in which to discuss patient care options and prognosis. Thus, we included variables available to clinicians at the preoperative appointment for recurrent/persistent laryngeal SCC. We first calculated summary statistics to describe the analytical sample of 244 patients with recurrent laryngeal cancer. The Kaplan-Meier method was used to estimate survival curves for OS, DFS, and DSS. We then estimated the predicted state probabilities (alive, died of cancer, died of other causes) over time broken down by comorbidity level. The probability of death from any cause was estimated using the Kaplan-Meier method, and the probability of death specifically from other causes was estimated using cumulative incidence, which accounts for the competing risks between death of other causes and death of cancer. To identify additional preoperative factors associated with OS, DSS, and DFS, we fit a multivariable Cox proportional hazards regression model for each outcome. Due to the large number of predictors, we used forward selection to identify the most important covariates for each model. All analyses were performed using R version 3.3.0 (Vienna, Austria).

3 | RESULTS

3.1 | Thirty-day mortality after laryngectomy for recurrent/persistent laryngeal squamous cell carcinoma

The 30-day mortality for the entire cohort was 5% (13/244). Cause of death in this cohort included cardiopulmonary arrest (3 patients), carotid blowout (2 patients), metastatic disease (2 patients), stroke (1 patient), bowel ischemia (1 patient), pulmonary embolus (1 patient), respiratory failure (1 patient), infection (1 patient), and unknown but not laryngeal cancer (1 patient). To understand the association between common perioperative morbidity and 30-day mortality, we compared fistula rate, return to the operating room

TABLE 1 Cohort Characteristics (n = 244)

Patient characteristics	No. of patients (%) or mean (SD)	Missing no. of patients (%)
Sex		
Male	208 (85.2)	0 (0)
Female	36 (14.7)	
Ethnicity		
White	223 (91.3)	0 (0)
Black/other/unknown	21 (8.6)	
Comorbidities		
None	49 (20.0)	0 (0)
Mild	129 (52.8)	
Moderate	51 (20.9)	
Severe	15 (6.1)	
Tobacco use		
Current	92 (37.7)	0 (0)
Former	146 (59.8)	
Never	6 (2.4)	
Initial cancer		
Age at initial tumor, years	59.2 (10.1)	1 (0.4)
Initial site		
Glottis	143 (58.6)	3 (1.2)
Supraglottis	98 (40.1)	
Subglottis	0 (0)	
Initial clinical T classification		
cT1	63 (25.8)	17 (6.9)
cT2	71 (29.0)	
cT3	65 (26.6)	
cT4	28 (11.4)	
Initial clinical N classification		
N0	188 (77.0)	16 (6.5)
N+	40 (16.3)	
Initial stage		
I	63 (25.8)	17 (6.9)
II	62 (25.4)	
III	63 (25.8)	
IV	39 (15.9)	
Initial treatment		
RT	139 (56.9)	0 (0)
CRT	105 (43.0)	
Initial treatment site		
Outside hospital	192 (78.6)	0 (0)
University of Michigan	52 (21.3)	
Recurrent cancer		

(Continues)

TABLE 1 (Continued)

Patient characteristics	No. of patients (%) or mean (SD)	Missing no. of patients (%)
Age at recurrence, years	61.2 (10.0)	0 (0)
Time to recurrence, months	21.4 (30.2)	0 (0)
Time to recurrence <2 y		
Yes	126 (51.6)	0 (0)
No	118 (48.4)	
Recurrent site		
Glottis	136 (55.7)	0 (0)
Supraglottis	108 (44.2)	
Recurrent clinical T classification		
cT1	14 (5.7)	0 (0)
cT2	97 (39.7)	
cT3	65 (26.6)	
cT4	68 (27.8)	
Recurrent clinical N classification		
cN0	215 (88.1)	0 (0)
cN+	29 (11.8)	
Recurrent clinical stage		
I	13 (5.3)	0 (0)
II	93 (38.1)	
III	62 (25.4)	
IV	76 (31.1)	

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.
Percentages calculated including the missing values where applicable. Smoking status is defined as current (smoking within 1 year before surgery), or former (quit >1 year before surgery).

for management of fistula/wound issues, and ACE-27 comorbidity status. Our fistula rate was 34% (84/244; Table 2). Our operative takeback rate was 12% (30/244). There was no association with the development of a fistula or return to the operating room and 30-day mortality. There was an increasing and significantly worsened 30-day mortality for patients with mild/moderate and severe comorbidity status.

TABLE 2 Perioperative complications in patients undergoing surgery for recurrent/persistent laryngeal squamous cell carcinoma

Comorbidity	Fistula	OR takeback	30-d mortality
None	39%	12%	0%
Mild/moderate	33%	12%	4%
Severe	40%	20%	7%[a]

Abbreviation: OR, operating room.
[a] $P = .001$ comparing severe versus none comorbidity status.
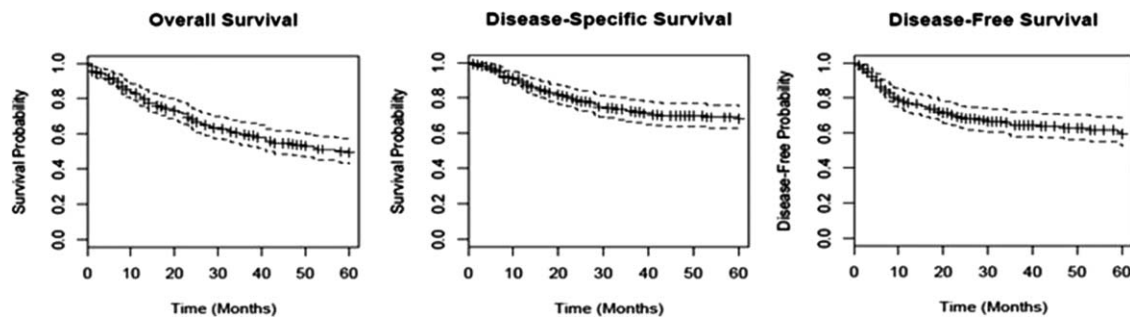
FIGURE 1 Five-year Kaplan-Meier survival curves. A, Five-year survival patterns demonstrate an overall survival of 49% (95% confidence interval [CI] 42%-56%); B, a disease-specific survival of 68% (95% CI 61%-75%), and C, disease-free survival of 59% (95% CI 52%-67%)

3.2 | Survival analysis after laryngectomy for recurrent/persistent laryngeal squamous cell carcinoma

In the Kaplan-Meier analysis, the estimated 5-year OS was 49% within the entire cohort (95% confidence interval [CI] 42%-56%; Figure 1A). Five-year DSS for the entire cohort was 68% (95% CI 61%-75%; Figure 1B). Five-year DFS for the cohort was 59% (95% CI 52%-67%; Figure 1C). We next stratified the cohort by type of recurrence (locoregional vs distant). In the Kaplan-Meier analysis, the estimated 5-year locoregional DFS was 71% (95% CI 65%-78%). Five-year distant DFS was 78% (95% CI 71%-85%).

3.3 | Multivariable modeling of preoperative predictors of survival

We performed multivariable analysis in order to predict variables contributing to OS, DSS, and DFS. Using a forward step model, we included demographic (sex, ethnicity, ACE-27 comorbidity status, and tobacco use), initial tumor characteristic (age at initial tumor, initial site, initial clinical T classification, initial clinical N classification, initial overall stage, initial treatment, and initial treatment location), and recurrent tumor characteristic (age at recurrence, time to recurrence, recurrent site, recurrent clinical T classification, recurrent clinical N classification, and recurrent overall stage; Table 1) variables. In multivariable analysis, significant preoperative predictors of OS (Table 3) included severe comorbidity (ACE-27 scale; hazard ratio [HR] 3.76; 95% CI 1.56-9.06), recurrent clinical node positive status (HR 2.91; 95% CI 1.74-4.88), and initial overall stage >I. For DSS, predictors included recurrent clinical node positive status (HR 3.95; 95% CI 2.16-7.22), and initial overall stage >I. Multivariable independent predictors of DFS (Table 3) included recurrent clinical node positive status (HR 3.26; 95% CI 1.83-5.78), and initial overall stage >I.

To better assess the preoperative effect size of medical comorbidities on OS, we further stratified causes of death between cancer and noncancer (namely, comorbidity) causes over time (Figure 2A-C). Noncancer causes of death contributed to significant decreased OS over a 5-year period in our

TABLE 3 Multivariable preoperative predictors of survival for recurrent/persistent laryngeal squamous cell carcinoma

Characteristic	OS HR (95% CI)	DSS HR (95% CI)	DFS HR (95% CI)
Recurrent clinical N+			
No (ref)	...	...	...
Yes	2.91 (1.74-4.88)	3.95 (2.16-7.22)	3.26 (1.83-5.78)
Initial stage			
I (ref)	...	...	...
II	2.96 (1.59-5.51)	2.62 (1.15-5.98)	2.36 (1.12-4.97)
III	3.40 (1.82-6.34)	2.13 (0.82-5.53)	3.14 (1.54-6.39)
IV	1.73 (0.81-3.66)	0.99 (0.31-3.15)	1.71 (0.73-4.00)
Comorbidities			
None (ref)	...	...	...
Mild/moderate	1.43 (0.86-2.38)	...	...
Severe	3.76 (1.56-9.06)	...	...

Abbreviations: CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival.
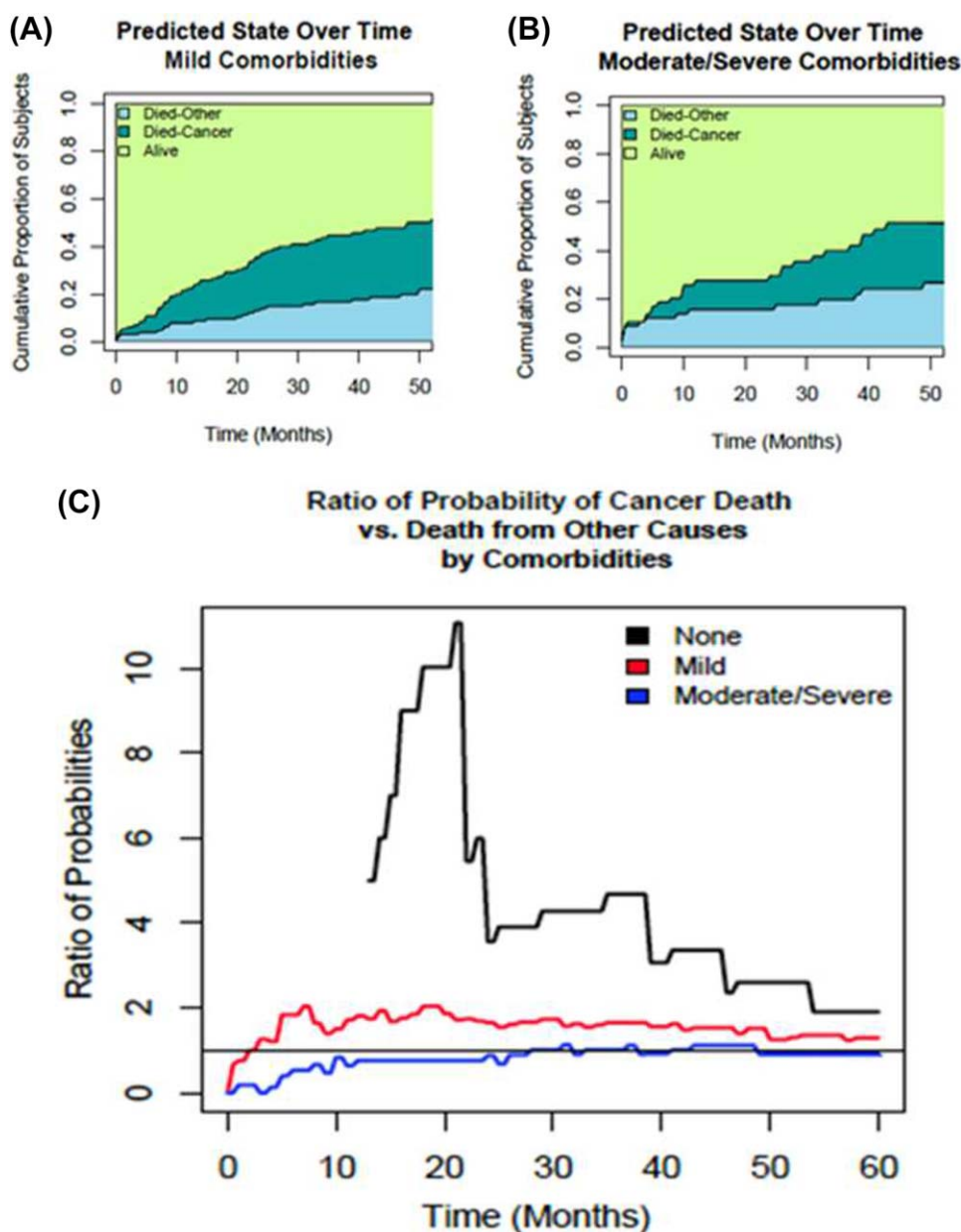
FIGURE 2 Contribution of comorbidity status to overall survival. A, Cumulative proportion of subjects who died of cancer and noncancer causes over 5 years. B, C, Patients with moderate or severe comorbidities are more likely to die of their comorbidities and other causes than cancer through 30 months. The y-axis is the ratio of probability of dying of laryngeal squamous cell carcinoma (SCC) versus noncancer causes. Ratio of probability at 1 (horizontal line) denotes an equal probability of dying of noncancer causes as dying of cancer. C, Lines below 1 suggest a greater risk of dying of noncancer causes and lines above 1 denote greater risk of dying of laryngeal SCC [Color figure can be viewed at wileyonlinelibrary.com]

overall cohort. This was particularly evident in patients with moderate or severe comorbidities (Figure 2B), more than those with mild comorbidities (Figure 2A). In analysis of the rate of cancer versus noncancer causes of death, for patients with moderate or severe comorbidities, noncancer causes of death (ie, comorbid conditions) was a greater cause of death than cancer-related causes through 30 months after salvage laryngectomy (Figure 2C). From 30 months to 5 years, patients with moderate or severe comorbidity status had an equal probability of dying of their comorbidities as their

laryngeal SCC. Cause of death for patients with no or mild comorbidity status is more likely to be due to a recurrence of disease.

4 | DISCUSSION

The prognosis after laryngectomy for recurrent/persistent laryngeal SCC remains guarded; we observed a 5-year OS probability of 49%. Severe comorbidity status is the strongest

independent predictor thereof, suggesting that careful preoperative discussions and increased attention to mitigating competing risks to health is critical in this population. Overall, in our cohort, we found that the strongest independent predictors included severe comorbidity and recurrent clinical node positive status for OS, and clinical node positive status for DFS. These data may allow for focused shared decision making between patient and physician, and patient selection for potential adjuvant therapies.

To date, there have been no multivariable analyses for prognostic factors for patients undergoing salvage laryngectomy. For patients and physicians alike, identification of patients who may have poor predicted survival after salvage laryngectomy will be important to guide physician-patient discussions on goals of care, expectations, and follow-up, and to consider for potential adjuvant or investigational treatment.

Increasingly, management of comorbidities and chronic care are becoming key issues in the survivorship phase of head and neck cancer management.[15] Our data support that increased comorbidities have a significant effect on OS in patients undergoing salvage laryngectomy. Thus, strong consideration of patients' competing risks of mortality in the preoperative setting may frame a realistic discussion on OS. Additionally, there may be a role for active interventions to modify the life-limiting impact of specific comorbidities (eg, medications for depression or hypertension, treatment of cardiovascular and pulmonary disease, counseling on alcohol, or preoperative smoking cessation). Common modifiable risk factors included in the ACE-27 score include poorly controlled diabetes, hypertension, depression, obesity, and alcohol abuse.

Interestingly, smoking status did not demonstrate significance on multivariable analysis. We postulate that the extensive smoking history of our patients with cumulative effects of smoking and almost universal smoking cessation after laryngectomy may explain any lack of effect on current smoking status on survival. Additionally, the effects of smoking may be best reflected on the severity of comorbidities collected by ACE-27 (cardiovascular, respiratory, neurologic disease, and malignancy), thus making ACE-27 comorbidity status a more comprehensive factor in accounting for the effects of smoking on a patient's survival. Similarly, we did not see significance of clinical T classification on multivariable analysis. Although advanced clinical T classification was associated with a worse outcome on univariable analysis, it was also correlated with clinical nodal positivity. We postulate that this correlation and other variables (initial tumor factors and time to recurrence factors) may account for the lack of effect in multivariable analysis.

Our analysis did not show any survival difference with initial treatment between RT or CRT at our institution versus outside hospitals. In regard to outside hospital treatment, the University of Michigan collaborates closely with local hospitals in regard to radiation planning, in many cases assisting in the radiation fields to be implemented. In addition, patients treated at the University of Michigan were more like to have supraglottic cancers (62% University of Michigan vs 36% outside hospital) and advanced stage cancers (57% University of Michigan vs 29% outside hospital), which may explain the lack of significance.

Counseling and surgical decision making when facing salvage surgery should emphasize the significant effect of comorbidities on survival, as well as the suboptimal observed survival within this cohort. Furthermore, counseling in regard to optimizing modifiable comorbidities (eg, improved control of hypertension or chronic obstructive pulmonary disease) may have valuable effects in a patient's estimated 5-year survival. Honest discussions about patient expectations and outcomes may guide further treatment plans. Our data demonstrates increasingly worsening 30-day perioperative mortality with increasing comorbidity status, suggesting a need for careful preoperative patient stratification, risk reduction of modifiable comorbidity factors, and counseling on perioperative complications and survival.

Despite our study's strength as the largest cohort of patients with recurrent/persistent laryngeal SCC undergoing salvage laryngectomy, it does have limitations. Initial tumor staging and treatment data were limited in some instances due to limited outside hospital records. The majority of our patients have their outside records sent to our institution, and staging reviewed at our tumor board, but, in some cases, this could be suboptimal. However, this is a common clinical scenario for patients presenting with recurrent or persistent laryngeal SCC to tertiary cancer centers. The vast majority of our patients had neck dissections, as this is standard practice among most of the surgeons in our institution (n = 225/244); no survival difference was seen with the performance of neck dissection. The importance of neck dissection with salvage laryngectomy remains debated,[16] and some institutions do not perform neck dissections regularly. Further multiinstitutional investigation by accruing survival data from patients with and without neck dissection may provide definitive data on this topic.

Patients undergoing salvage laryngectomy have a guarded prognosis. By stratifying based upon preoperative risk factors, we are able to define which subset of patients may have better or worse predicted outcomes. This information may be crucial to guide preoperative discussions on goals of care and consideration of adjuvant treatment modalities. As cancer care increasingly implements genetic biomarkers and targeted therapies, we must continually consider additional methodologies for risk stratification. Further validation of these predictive variables across additional cohorts will be invaluable to further refine management algorithms.

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REFERENCES

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.

[2] Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med.* 1991;324(24):1685-1690.

[3] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349(22):2091-2098.

[4] Lefebvre JL, Andry G, Chevalier D, et al. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. *Ann Oncol.* 2012;23(10):2708-2714.

[5] Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol.* 2013;31(7):845-852.

[6] Megwalu UC, Sikora AG. Survival outcomes in advanced laryngeal cancer. *JAMA Otolaryngol Head Neck Surg.* 2014;140(9):855-860.

[7] Denaro N, Russi EG, Lefebvre JL, Merlano MC. A systematic review of current and emerging approaches in the field of larynx preservation. *Radiother Oncol.* 2014;110(1):16-24.

[8] Sandulache VC, Vandelaar LJ, Skinner HD, et al. Salvage total laryngectomy after external-beam radiotherapy: a 20-year experience. *Head Neck.* 2016;38 Suppl 1:E1962-E1968.

[9] Davidson J, Keane T, Brown D, et al. Surgical salvage after radiotherapy for advanced laryngopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg.* 1997;123(4):420-424.

[10] Brenner B, Marshak G, Sulkes A, Rakowsky E. Prognosis of patients with recurrent laryngeal carcinoma. *Head Neck.* 2001;23(7):531-535.

[11] Li P, Hu W, Zhu Y, Liu J. Treatment and predictive factors in patients with recurrent laryngeal carcinoma: a retrospective study. *Oncol Lett.* 2015;10(5):3145-3152.

[12] Ludwig ML, Birkeland AC, Hoesli R, Swiecicki P, Spector ME, Brenner JC. Changing the paradigm: the potential for targeted therapy in laryngeal squamous cell carcinoma. *Cancer Biol Med.* 2016;13(1):87-100.

[13] Birkeland AC, Yanik M, Tillman BN, et al. Identification of targetable ERBB2 aberrations in head and neck squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg.* 2016;142(6):559-567.

[14] Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA.* 2004;291(20):2441-2447.

[15] Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. *CA Cancer J Clin.* 2016;66(3):203-239.

[16] Birkeland AC, Rosko AJ, Issa MR, et al. Occult nodal disease prevalence and distribution in recurrent laryngeal cancer requiring salvage laryngectomy. *Otolaryngol Head Neck Surg.* 2016;154(3):473-479.