

# Effects of anesthetic technique on postoperative pulmonary metastasis in patients undergoing laryngectomy

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## Research Article

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# Abstract

**Background:** Whether laryngeal cancer is directly implanted into the lungs through the respiratory tract during orotracheal intubation remains unclear. The present study aimed to determine whether orotracheal intubation was an independent risk factor for postoperative pulmonary metastasis, recurrences and survival in patients undergoing laryngectomy.

**Methods:** Medical records between January 1, 2006 and December 31, 2016 were reviewed. Patients who underwent orotracheal intubation (intubation group) were matched 1:1 with those who received tracheotomy (tracheotomy group) during the induction of general anesthesia. The primary outcome was postoperative pulmonary metastasis. Secondary outcomes included local recurrences, lymphatic metastasis and overall survival. Data were analysed by Kaplan-Meier curves, log-rank test, hazards regression and Cox regression.

**Results:** Comparing the tracheotomy group and orotracheal intubation group, no statistically significant differences were found in postoperative pulmonary metastasis ( $P = 0.688$ ), local recurrence ( $P = 0.215$ ), lymphatic metastasis ( $P = 0.480$ ) and all-cause death ( $P = 0.299$ ). Primary cancer site was an independent risk factor for pulmonary metastasis [hazard ratio (HR) 0.29, 95% confidence interval (CI) 0.13-0.68;  $P = 0.013$ ] and local recurrence (HR 2.69, 95% CI 1.39-5.21;  $P = 0.003$ ). Unexpectedly, postoperative chemotherapy was an independent risk factor for lung metastasis (HR 7.58, 95% CI 3.11-18.47;  $P < 0.001$ ) and lymphatic metastasis (HR 5.18, 95% CI 2.57-11.91;  $P < 0.001$ ). Five-year overall survival was not associated with anesthetic technique ( $P = 0.473$ ).

**Conclusions:** This retrospective study suggested that orotracheal intubation during laryngectomy was not a risk factor for postoperative pulmonary metastasis, local recurrence and overall survival.

**Keywords:** Anesthetic technique, Postoperative pulmonary metastasis, Laryngectomy

## Background

Laryngeal cancer is one of the most common head and neck cancers [1, 2]. The main treatment modality for laryngeal squamous cell carcinoma (LSCC) is surgery, which is sometimes followed by radiotherapy and/or chemotherapy, if the size of tumor is large or high risk factors exist [3]. A review by the American Cancer Society suggested that the overall incidence of LSCC is declining, whereas the 5-year survival rate has decreased slightly from 66% to 63% [4]. The main target organ of laryngeal cancer distant metastasis is the lung, followed by liver and bone metastasis [5]. Metastatic disease is the most important cause of cancer-related death in patients after cancer surgery. Whether the tumor cells in laryngeal cancer are directly implanted into the lungs through the respiratory tract or metastasized by lymph nodes or haematogenous spread remains unclear. Minimizing the likelihood of postoperative pulmonary metastasis during laryngeal cancer surgery is of great clinical importance.

Inevitably, orotracheal intubation or tracheotomy is necessary during general anesthesia for laryngeal surgery. Intact lung mucosa provides protection against implantation of tumor cells. However, mechanical ventilation during surgery can cause lung injury, which may be conducive to the growth of exfoliated tumor cells, resulting in implantation lung metastasis [6]. During general anesthesia, immunosuppression is usually inevitable [7], especially as a basic disease such as cancer requires surgical intervention [8]. Perioperative factors, including

immunosuppression and anesthetic technique, have been suggested to affect cancer cell survival and metastasis [9, 10]. Thus, due to the anatomic location of laryngeal cancer, tumor tissue may fall into the lungs especially during orotracheal intubation step. Unfortunately, whether orotracheal intubation will increase the risk of postoperative pulmonary metastasis has not been studied.

This study conducted propensity matching to balance the differences in the patients' baseline characteristics and reviewed a LSCC database mainly to identify the causal relationship between anesthetic technique and postoperative pulmonary metastasis of LSCC, as well as the risk factors for recurrences, lymphatic metastasis and survival rates following orotracheal intubation or not.

## Methods

This was a retrospective cohort study. After obtaining approval of the ethics committee of our centre and the patients' written consent, the oncology and anesthesia databases were analyzed.

With retrospective screening of the laryngeal database, anesthesia database, electronic medical records, and follow-up status, we identified patients who had partial laryngectomy or total laryngectomy for LSCC between January 1, 2006, and December 31, 2016. Among them, 881 cases that underwent partial laryngectomy or total laryngectomy were enrolled into this study. The therapy for each patient was based on the guideline of National Comprehensive Cancer Network (NCCN), and the tumor location and the status of the tumor nodal and distant metastasis were defined on the basis of the 3<sup>rd</sup> to 6<sup>th</sup> editions of the Union for International Cancer Control (UICC) classification system and the 2<sup>nd</sup> to 7<sup>th</sup> editions of the American Association of Cancer (AJCC) staging system. Patients were excluded based on the following criteria: (1) pulmonary metastasis before surgery, (2) non-squamous cell carcinoma confirmed by postoperative pathology and (3) lost to follow-up.

During the study period, anesthesia induction was performed with propofol (1.5-2 mg/kg) or etomidate (0.3 mg/kg), fentanyl (0.003 mg/kg) or sufentanil (0.5 ug/kg), and cisatracurium (0.15-0.2 mg/kg). Anesthesia was maintained with sevoflurane (minimal alveolar concentration = 0.7-1.5), remifentanil (0.05-0.15 ug/kg/min) and cisatracurium (1-2 ug/kg/min). Opioids (fentanyl) and non-steroidal anti-inflammatory (flurbiprofen or parecoxib) were used for postoperative analgesia. The use of orotracheal intubation mainly depended on the condition of the tumor, especially the tumor size. In addition, the use of this procedure depended on the preference of the surgeons and anaesthesiologists for patients with advanced stage LSCC. In the tracheotomy group, tracheotomy was performed before induction of general anesthesia and required local infiltration anesthesia with 2% lidocaine. For patients in the intubation group, laryngoscopic orotracheal intubation was performed following the anesthesia induction. In both groups, male patients were intubated with a tracheal tube number 7.0, and female patients with a number 6.5. Opioid dosage was converted to equianalgesic (morphine) dosage to allow comparison of the two patient groups.

Patients at Sun Yat-Sen University Cancer Center had their first clinical and radiological evaluation 1 month after the final treatment, then had subsequent evaluations every 3 months during the first year, 2-3 times during the second and third years, and annually thereafter. Pulmonary metastasis was defined by histological verification or imaging (computerized tomography or enhancement computerized tomography), which manifested as single or multiple nodules of different sizes scattered in the lungs that gradually grew over time, some with pleural effusion. Clinical and histological confirmation of LSCC more three months after the initial

treatment was defined as local recurrences, whereas LSCC diagnosed within three months of the primary therapy was defined as residual tumor [5]. Meanwhile, lymph node metastasis detected by colour Doppler ultrasonography or computerized tomography was defined as growing lymph nodes [11], and some tissue samples were submitted to pathology for confirmation. Death was considered to be related to LSCC when patients died during treatment, or within the first 30 postoperative days, or if the medical records or death certificate documented laryngeal cancer as the underlying cause of death. Generally, the patients' status and death causes were confirmed from death certificates or follow-up data. Postoperative complications included surgical incision bleeding, laryngeal fistula and subcutaneous emphysema.

Sex, age, height, weight, body mass index (BMI), smoking history, alcohol consumption and historical diseases were documented for each patient in the hospital information system. Historical diseases were defined as previously described health conditions [12], including cardiac diseases, chronic kidney diseases, hypertension, diabetes mellitus, and history of other cancers. In addition, patients in the intubation group were 1:1 matched with those in the tracheotomy group, based on operative time, pathological stage (T1/2, T3/4), clinical stage (1-4), type of surgery (partial laryngectomy, total laryngectomy), preoperative radiotherapy (yes, no) and postoperative chemotherapy (yes, no).

Descriptive statistics were presented as percentage, and continuous variables were presented as the mean  $\pm$  standard. Data were compared by  $\chi^2$ -test and two-sample *t* test. All imbalanced variables with a significance level of  $P < 0.05$  on  $\chi^2$ -test or *t* test were used to calculate the propensity score by logistic regression. According to Dr. Austin's [13] recommendations, nearest-neighbour matching method with a calliper of 0.02 (0.2 x standard deviation) was used to perform a one-to-one match without replacement. Kaplan-Meier curves, log-rank test and hazards regression were used to analyse pulmonary metastasis, local recurrences, lymphatic metastasis and overall survival. In addition, considering the clinical significance but also the sample capacity, Cox regression was also used to analyse the risk factors with  $P$ -value  $< 0.1$  in Kaplan-Meier curves of metastasis and recurrences. The results were expressed as 95% CI. The statistical significance was set at  $P < 0.05$  and all tests were two-sided. All statistical analyses were performed using SPSS statistics 24.0 software for Windows (SPSS Inc, Chicago, IL, USA).

## Results

**Baseline patient characteristics** The selection and matching process of this study is shown in Figure 1. Among 841 participants, 515 patients underwent orotracheal intubation, and the other 326 received tracheotomy. These two groups were 1:1 matched based on similar propensity scores, which were estimated by anesthesia time ( $P = 0.03$ ), pathological stage ( $P < 0.001$ ), clinical stage ( $P < 0.001$ ), type of surgery ( $P < 0.001$ ), preoperative radiotherapy ( $P = 0.031$ ) and postoperative chemotherapy ( $P = 0.004$ ), yielding 298 patients in each group. The baseline and clinicopathological characteristics of the two groups, before and after matching, are summarized in Table 1.

**Anesthetic technique and outcomes** The total incidence of pulmonary metastasis in the selected patients was 5.0% before matching, and 4.4% after matching. The incidence of pulmonary metastasis in the intubation group was 4.7%, which was higher than that in the tracheotomy group (4.0%), but did not reach statistical significance ( $P = 0.688$ ). In addition, the incidence of local recurrence (22.1%), lymphatic metastasis (5.0%), postoperative complications (6.0%) and all-cause death (23.2%) in the intubation group were lower than that in the tracheotomy group (26.5%, 6.4%, 7.0%, 27.2%, respectively), but was not significantly different either.

The factors contributing to pulmonary metastasis Figure 2 and Table 2 clearly demonstrate that orotracheal intubation may not be an independent risk factor for lung metastasis ( $P = 0.333$ ). However, the primary cancer site (HR = 0.29, 95% CI 0.13-0.68,  $P = 0.013$ ) and postoperative chemotherapy (HR = 7.58, 95% CI 3.11-18.47,  $P < 0.001$ ) were independent risk factors for postoperative pulmonary metastasis. The factors contributing to local recurrences and lymphatic metastasis Types of surgery (total laryngectomy HR = 3.13, 95% CI 2.03-4.84,  $P < 0.001$ ), N-status [N-status (2) HR = 0.27, 95% CI 0.10- 0.75,  $P = 0.012$ ] and primary cancer site (glottic laryngeal HR = 2.69, 95% CI 1.39-5.21,  $P = 0.003$ ) were independent risk factors of local recurrences. In Table 3, BMI showed statistically significant differences by univariate ( $P = 0.007$ ) and by multivariate analysis ( $P = 0.007$ ). Hence, according to World Health Organization [14], BMI was classified as normal weight ( $18.5 \leq \text{BMI} < 25.0 \text{ kg/m}^2$ ), underweight ( $\text{BMI} \leq 18.5 \text{ kg/m}^2$ ), overweight ( $25.0 \leq \text{BMI} < 30.0 \text{ kg/m}^2$ ), and obese ( $\text{BMI} \geq 30.0 \text{ kg/m}^2$ ). Considering that there were only 4 participants whose  $\text{BMI} \geq 30.0 \text{ kg/m}^2$ , we included them in the overweight group. After classifying the BMI of patients, no statistically significant difference was found ( $P = 0.774$ ). The only independent risk factor for lymphatic metastasis was postoperative chemotherapy (HR = 5.18, 95% CI 2.57-11.91,  $P < 0.001$ ) in Supplemental Table 1. The factors contributing to patients' survival The 5-year overall survival rate of the orotracheal intubation group and tracheotomy group was 61.4% (95% CI 0.53-0.69) and 65.3% (95% CI 0.58-0.73, log-rank  $P = 0.473$ ; Fig. 3A), respectively. Additionally, age ( $P = 0.028$ ; Fig. 3B), clinical stage ( $P < 0.001$ ; Fig. 3C) and postoperative chemotherapy ( $P = 0.003$ ; Fig. 3D) showed statistically significant differences for survival.

## Discussion

The cause of death of most laryngeal cancer patients is owing to the distant metastasis, and lung metastasis occur most commonly in distant metastasis in laryngeal cancer [15]. Whether the tumor cells are directly implanted into the lungs through the respiratory tract or metastasise by lymph nodes or haematogenous spread remains unclear in laryngeal cancer. The mechanism may be related to genes, molecular protein, haematogenous metastasis and implantation metastasis. Implantation metastasis has been shown to occur in the enterocoeliac spread of ovarian cancer [16] and the spread of colon cancer in colonoscopic biopsy sites or laparoscopic port sites [17]. Some previous articles have reported that implantation could happen occasionally after a needle biopsy for malignant lung tumor [18] or after a bronchoscopic procedure [19]. Orotracheal intubation must go through the tumor site, so the possibility of tumor cells being brought into the lower respiratory tract exists. However, this hypothesis has not been confirmed yet. In our study, we found that the anesthetic technique had no effect on postoperative pulmonary metastasis. Orotracheal intubation did not increase the risk of pulmonary metastasis after laryngectomy. However, in some recent studies, a fairly high tendency of pulmonary metastasis after laryngeal cancer surgery has been reported [20]. The underlying mechanism of this observation may be related to the unique immune microenvironment of lung. In this study, we also found that the anesthetic technique had no effects on local recurrence, lymphatic metastasis, postoperative complications, all-cause death and survival. This finding is in contrast to other studies [21, 22].

Our results showed that anesthesia time, cancer history, primary cancer site, tumor differentiation, N-status, preoperative chemotherapy and postoperative chemotherapy had a significant influence on lung metastasis after laryngeal cancer surgery by univariate analysis. After multivariable analysis, primary cancer site and postoperative chemotherapy were the independent risk factors of postoperative pulmonary metastasis from LSCC. It had been reported that the N-status, tumor differentiation and clinical stage of laryngeal cancer were

the factors influencing lung metastasis [23] which were consistent with our results. Additionally, the primary cancer site (supraglottic laryngeal vs. glottic) was an independent risk factor for developing a second primary tumor in the lung, with the risk being higher for supraglottic laryngeal than for glottic, which is consistent with a previous report [24].

Many studies have found that postoperative chemotherapy had no survival or recurrent benefit. Relatedly, we found postoperative chemotherapy may be a risk factor for distant metastasis, lymph nodes metastasis and overall survival. It should be considered that the toxicity of chemotherapeutic drugs might have caused patients to be intolerant to chemotherapy. Previous studies also reported that multidrug resistance (MDR) of malignant cells to different chemotherapeutic agents may cause the recurrences, metastasis and treatment failure. The detection of MDR genes or proteins is needed to confirm this hypothesis [25].

We also found that the patients who received total laryngectomy had a higher risk of recurrence than partial laryngectomy, and glottic laryngeal cancer had a greater tendency on local recurrence than did supraglottic laryngeal cancer. Therefore, we suspect that the patients who received total laryngectomy had higher clinical stages or that some of them had local recurrence before they were admitted to our hospital. This causal relationship needs to be further analysed. A study from Norway reported that supraglottic laryngeal cancer presented a more frequent recurrence than did glottic laryngeal cancer [26] in contrast to our results. However, the study results that a N-status of 2 has less risk of local recurrence was contrary to the experience; this finding might be accounted for the fact that patients with advanced N-status before surgery might undergo a more complete lymph node dissection.

Last but not least, age, clinical stage and postoperative chemotherapy were risk factors of the overall survival, whereas orotracheal intubation had no effect on survival rates. The effect of postoperative chemotherapy has been discussed in a previous section. According to a previous report [27], age may affect medical care, resulting in an appropriate treatment not being provided to older patients. The decline of treatment compliance, affected by progressive loss of stress tolerance, decline in multiple organ systems, high prevalence of comorbid conditions, reduced cognition, and higher prevalence of depression, were reasons why the elderly patients had poor survival rates [28, 29]. In addition, comparison of clinical stage 1/2 and clinical stage 3/4 outcomes showed significant statistical differences, but no significant differences were found between each of them, which meant that the early stage patients had higher survival rates than those at an advanced stage.

We should objectively evaluate the limitations of our data. First, as a non-randomized, retrospective cohort study, selection bias and incomplete information may be present. Although propensity-score matching was used to balance the differences in baseline characteristics, intrinsic biases may not be avoided. Second, the regimen and dose of preoperative or postoperative chemotherapy or radiotherapy were sometimes unclear, which may affect the accuracy of results between the two groups. Additionally, the overall survival was analysed while disease-free survival was not analysed, which is also important for patients with laryngeal cancer. Finally, because of the relatively short follow-up time of some patients and the relatively small number of cases in the study, the findings must be interpreted cautiously.

## Conclusions

This retrospective study reveals that orotracheal intubation in laryngectomy does not increase the risk of lung metastasis, local recurrence and overall survival, which means that routine anesthesia is relatively safe for the prognosis of laryngeal cancer. Doctors can choose orotracheal intubation or tracheotomy based on the tumor size and patients' comfort. However, due to the limitation of this study, prospective, randomized, clinical trials with a larger number of patients are certainly warranted.

## **Abbreviations**

HR: hazard ratio; CI: Confidence interval; LSCC: Laryngeal squamous cell carcinoma; NCCN: National Comprehensive Cancer Network; AJCC: American Association of Cancer; UICC: Union for International Cancer Control; BMI: Body mass index; MDR: Multidrug resistance.

## **Declarations**

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### **Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Authors' contributions**

HX and WX analyzed and interpreted the patients data regarding laryngectomy and were major contributors in writing the manuscript. LJ and DK helped to collect data and review the analysis of the data. LY and LR designed this study, reviewed the analysis of the data and revised the manuscript. All authors read and approved the final manuscript.

### **Ethics approval and consent to participate**

This study was approved by the ethical committee of Cancer Center, Sun Yat-sen University.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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## Tables

Table 1 Distribution of the patients' characteristics of the intubation and tracheotomy groups, before and after propensity score matching

Characteristics	Before Matching			After Matching		
	Intubation group	Tracheotomy group	<i>P</i> value	Intubation group	Tracheotomy group	<i>P</i> value
Total	515	326		298	298	
Age	60.17 ± 8.9	60.93 ± 9.4	0.248	60.38 ± 9.5	60.79 ± 8.8	0.623
Age < 60 yr	252 (49)	151 (46)	0.479	137 (46)	138 (46)	1.000
Male	500 (97)	316 (97)	0.897	288 (96)	289 (97)	0.816
BMI (kg/m <sup>2</sup> )	21.8 ± 3.1	22.0 ± 3.2	0.255	21.5 ± 3.1	21.9 ± 3.1	0.752
Smoking index	531	604	0.058	591	552	0.896
Alcohol intake	135 (26)	92 (28)	0.523	77 (25)	84 (28)	0.518
Hypertension	88 (17)	48 (14)	0.364	50 (16)	44 (15)	0.500
Diabetes	29 (6)	16 (5)	0.650	14 (5)	15 (5)	0.849
Cardiac disease	16 (3)	10 (3)	0.974	13 (4)	10 (3)	0.523
ASA						
2	237 (46)	137 (42)	0.178	132 (44)	123 (41)	0.524
3	257 (50)	181 (56)		156 (52)	168 (56)	
4	21 (4)	8 (2)		10 (4)	7 (3)	
History cancer	24 (5)	8 (3)	0.103	14 (5)	6 (2)	0.069
Opioids (morphine, mg)	62.3 ± 1.1	74.1 ± 1.6	0.007	70.4 ± 1.5	70.9 ± 1.6	0.436
Types of surgery						
Partial laryngectomy	247 (48)	89 (27)	< 0.001	99 (33)	88 (30)	0.332
Total laryngectomy	268 (52)	237 (73)		199 (67)	210 (70)	
Neck dissection	271 (53)	190 (58)	0.108	184 (62)	170 (57)	0.243
Anesthesia time (h)	2.8 ± 1.3	3.4 ± 1.4	0.030	3.2 ± 1.3	3.2 ± 1.3	0.914
Blood transfusion	1 (0.2)	0	0.426	1 (0.3)	0	0.317
Primary cancer site						
Supraglottic	104 (20)	78 (24)	0.438	59 (20)	70 (24)	0.505
Glottic	400 (78)	241 (74)		230 (77)	221 (74)	
Subglottic	11 (2)	7 (2)		9 (3)	7 (2)	
tumor						
Differentiation						
Poorly differentiated	80 (16)	46 (14)	0.755	47 (16)	39 (13)	0.626
Moderately differentiated	289 (56)	181 (56)		162 (54)	170 (57)	

Highly differentiated	146 (28)	99 (30)		89 (30)	89 (30)	
T-status						
1	75 (15)	19 (6)	< 0.001	21 (7)	19 (6)	0.967
2	159 (30)	79 (24)		74 (25)	78 (26)	
3	180 (35)	130 (40)		113 (38)	114 (38)	
4	101 (20)	98 (30)		90 (30)	87 (30)	
N-status						
0	394 (77)	244 (75)	0.208	220 (74)	228 (77)	0.213
1	51 (9)	44 (14)		30 (10)	36 (12)	
2	67 (13)	38 (12)		46 (15)	34 (11)	
3	3 (1)	0		2 (1)	0	
Clinical stage						
I/II	204 (40)	85 (26)	< 0.001	85 (28)	84 (28)	0.920
III/IV	311 (60)	241 (74)		213 (72)	214 (72)	
Postoperative complications	23 (4)	22 (7)	0.152	18 (6)	21 (7)	0.619
Preoperative radiotherapy	18 (4)	22 (7)	0.031	13 (4)	16 (5)	0.568
Preoperative chemotherapy	15 (3)	10 (3)	0.897	10 (3)	8 (3)	0.632
Postoperative radiotherapy	88 (17)	52 (16)	0.666	62 (21)	45 (15)	0.070
Postoperative chemotherapy	19 (4)	27 (8)	0.004	15 (5)	15 (5)	1.000

BMI, body mass index; ASA, American Society of Anesthesiology.

Table 2 Univariate and multivariable Cox proportional hazard models of pulmonary metastasis after surgery for LSCC

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age > 60 yr	1.22 (0.56, 2.66)	0.617		
Sex (Female)	0.05 (0.00, 483.46)	0.517		
BMI (kg/m <sup>2</sup> )	0.88 (0.77, 1.00)	0.058		0.221
Smoking	1.80 (0.62, 5.24)	0.279		
Alcohol intake	0.96 (0.40, 2.29)	0.929		
ASA	1.16 (0.53, 2.56)	0.715		
History cancer	2.57 (0.61, 10.90)	0.200		
Opioids (morphine, mg)	1.01 (0.99, 1.02)	0.061		0.283
Types of surgery	1.20 (0.52, 2.77)	0.664		
Neck dissection	2.16 (0.90, 5.14)	0.083		0.490
Intubation	1.46 (0.67, 3.17)	0.336		0.264
Anesthesia time	1.33 (1.03, 1.71)	0.029		0.334
Primary cancer site		0.015		0.013
Supraglottic	Reference		Reference	
Glottic	0.32 (0.15, 0.70)	0.005	0.29 (0.13, 0.68)	0.004
Subglottic	0.99 (0.13, 7.67)	0.989	1.30 (0.16, 10.38)	0.804
tumor differentiation		0.009		0.095
T-status	1.37 (0.88, 2.12)	0.162		0.510
N-status	1.83 (1.16, 2.88)	0.019		0.224
Clinical stage	1.52 (0.97, 2.39)	0.068		0.591
Preoperative radiotherapy	1.82 (0.43, 7.71)	0.416		
Preoperative chemotherapy	5.07 (1.52, 16.92)	0.008		0.052
Postoperative radiotherapy	2.01 (0.87, 4.62)	0.102		
Postoperative chemotherapy	9.40 (4.06, 21.75)	< 0.001	7.58 (3.11, 18.47)	< 0.001

BMI, body mass index; ASA, American Society of Anesthesiology; HR, hazard ratio; CI, confidence interval.

Table 3 Univariate and multivariable Cox proportional hazard models of local recurrence after surgery for LSCC.

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age > 60 yr	0.82 (0.59, 1.14)	0.245		
Sex (Female)	0.90 (0.33, 2.44)	0.839		
BMI (kg/m <sup>2</sup> )	1.02 (0.96, 1.07)	0.590		
Smoking	1.12 (0.76, 1.65)	0.579		
Alcohol intake	0.55 (0.36, 0.83)	0.005		0.058
ASA	1.00 (0.72, 1.39)	0.985		
History cancer	0.58 (0.18, 1.82)	0.348		
Opioids (morphine, mg)	0.99 (0.99, 1.01)	0.848		
Types of surgery	2.86 (1.86, 4.42)	< 0.001	3.13 (2.03, 4.84)	< 0.001
Neck dissection	0.92 (0.66, 1.27)	0.590		
Intubation	1.08 (0.78, 1.51)	0.630		0.595
Anesthesia time	0.94 (0.83, 1.07)	0.361		
Primary cancer site		0.001		0.003
Supraglottic	Reference		Reference	
Glottic	3.59 (1.89, 6.84)	< 0.001	2.69 (1.39, 5.21)	0.003
Subglottic	3.41 (0.94, 12.40)	0.063	2.02 (0.55, 7.39)	0.29
tumor differentiation		0.140		0.697
T-status	1.15 (0.96, 1.37)	0.129		0.608
N-status		0.004		0.004
0	Reference		Reference	
1	0.56 (0.30, 1.03)	0.063	0.61 (0.33, 1.15)	0.127
2	0.24 (0.09, 0.64)	0.005	0.27 (0.10, 0.75)	0.012
Clinical stage	1.06 (0.89, 1.27)	0.498		
Preoperative radiotherapy	0.98 (0.43, 2.21)	0.951		
Preoperative chemotherapy	0.51 (0.13, 2.06)	0.343		
Postoperative radiotherapy	0.93 (0.61, 1.43)	0.750		
Postoperative chemotherapy	1.21 (0.62, 2.39)	0.574		

BMI, body mass index; ASA, American Society of Anesthesiology; HR, hazard ratio; CI, confidence interval.

## Figures

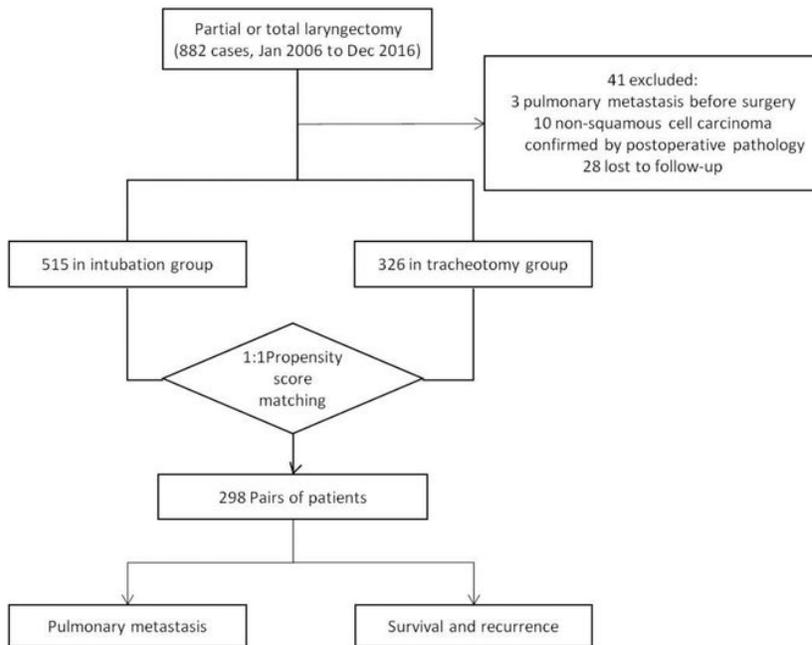


Fig. 1. The selection and matching process of study patients.

### Figure 1

The selection and matching process of study patients.

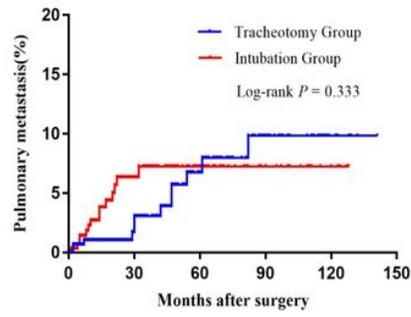
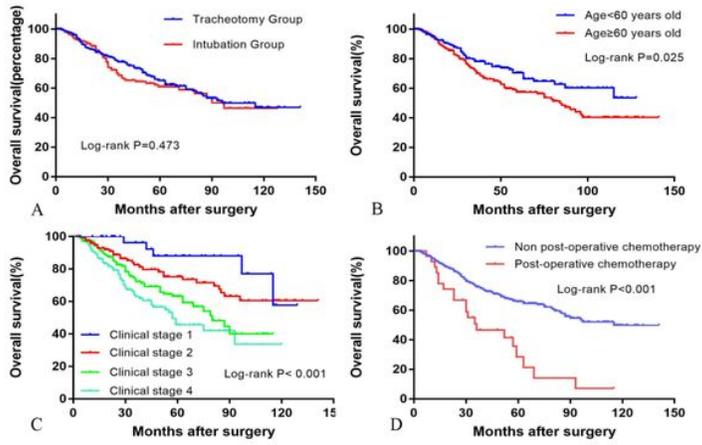


Fig. 2. Cumulative incidence of pulmonary metastasis in the intubation group and the tracheotomy group.

## Figure 2

Cumulative incidence of pulmonary metastasis in the intubation group and the tracheotomy group.



**Fig 3.** Overall survival of LSCC patients according to intubation (A), age (B), clinical stage (C) and postoperative chemotherapy (D).

### Figure 3

Overall survival of LSCC patients according to intubation (A), age (B), clinical stage (C) and postoperative chemotherapy (D).

## Supplementary Files

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- [supplement1.doc](#)