

Impact of previous head and neck cancer on postoperative complications after surgical resection for lung cancer: a case-control study

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Background: Head and neck cancer (HNC) and lung cancer are often linked because of common risk factors. We aimed to assess the risk of postoperative complications in patients with previous HNC undergoing thoracic surgery for lung cancer.

Methods: Patients with previous HNC undergoing surgery for lung cancer were included in this retrospective, monocentric, case-control study. All patients were matched for age, sex, FEV₁, smoking history, and year of surgery with lung cancer patients without previous HNC. Major postoperative complication was defined as at least one of the following during the first 30 days post lung resection (LR): death, shock, need for mechanical ventilation, and pneumonia.

Results: From January 2006 to May 2012, 65 patients with previous HNC underwent LR. Fifty-nine of these patients were included and matched with 120 control patients without HNC. Major complications occurred in 25 [42.4% (95% CI, 29.4–55.4%)] vs. 19 [15.8% (95% CI, 9.2–22.5%)] patients in the HNC and non-HNC groups, respectively (P<0.001). Among the complications, pneumonia occurred in 19 (32.2%) vs. 12 (10%) (P=0.01), and death occurred in 5 (8.5%) vs. 2 (1.7%) patients in the HNC and non-HNC groups, respectively (P=0.04). The following factors were identified by multivariate analysis to be independently associated with postoperative complications: previous HNC [odds ratio (OR) =4.24; (95% CI, 1.84–9.74)], male gender [OR =8.99; (95% CI, 1.05–76.78)], cumulative smoking [OR =1.02 per unit; (95% CI, 1.01–1.04)] and elevated Charlson score [OR =1.45; (95% CI, 1.07–1.96)].

Conclusions: Previous HNC is a major independent risk factor for serious postoperative complications after LR for lung cancer. Postoperative pneumonia (POP) is the most frequent complication.

Keywords: Lung cancer; postoperative complications; lung resection (LR); head and neck cancer (HNC); swallowing disorders

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in Western countries. Lung resection (LR) is the main treatment for early NSCLC. Postoperative mortality after LR has decreased over the past decade due to improvements in surgical and anesthesia techniques (1,2), as well as better postoperative management (3-5). Known risk factors for postoperative complications after LR include anesthesia duration, preoperative lung function, older age, cardiovascular comorbidity, smoking status, preoperative chemotherapy, intraoperative bleeding, and type of surgery (6-13).

Head and neck cancer (HNC) is the most frequent primitive cancer associated with lung cancer (14,15). It may be synchronous or metachronous. The most frequent second malignant tumor among patients previously treated for HNC is lung cancer (14). Swallowing disorders are common after HNC treatment and are reported in up to 88% of patients depending on the tumor location, tumor size, and treatment (16,17). These problems mainly appear after radiation or partial laryngeal resection. Swallowing disorders may favor aspiration pneumonia (18,19). Few studies have evaluated the risk of postoperative complications after LR among patients who have previously been treated for HNC.

The objective of this retrospective, case-control study was to investigate the risk factors for postoperative complications in patients with previous HNC undergoing LR for lung cancer.

Methods

This retrospective, case-control study was carried out between January 2006 and May 2012 in a single academic thoracic surgery center at the Hôpital Européen Georges Pompidou, Paris, France.

Study population

Patients were selected from the hospital clinical database using three search criteria: (I) primary malignant lung tumor [ICD10 code (C34)]; (II) one of the following surgical procedures (pulmonary lobectomy, or pulmonary bilobectomy, or pneumonectomy, or wedge resection); and (III) HNC (ICD10 codes C00–C14, C31, C32). A specialist of HNC cancer (OL) checked that HNC had been diagnosed and treated before LR and reviewed

each patient's file. The head and neck surgeon clinically assessed swallowing function blinded for postoperative complications. Cases of synchronous cancer and HNC diagnosed after lung cancer surgery were excluded. A control group was selected of patients who fulfilled criteria 1 and 2 above, but did not have previous HNC.

The study population was divided into two groups. Group 1 (Gp1) consisted of control patients undergoing LR without previous HNC, and Group 2 (Gp2) consisted of patients undergoing LR after previous HNC. In Gp1, two patients were randomly selected for every patient in Gp2. Patients were matched 2/1 for the following variables: age at the time of thoracic surgery, gender, preoperative FEV₁, smoking status, and year of surgery.

Postoperative management

Antibiotic prophylaxis was administered based on national guidelines. Pain was managed with systemic opioids released by a patient-controlled administration system. Epidural analgesia or intercostal blocks were used at the discretion of the anesthesiology team. Physiotherapy was started at least twice-daily commencing the day after surgery. All patients were maintained in a semi-recumbent position and were confined to a chair on the first day after surgery. Postoperative pain levels were recorded using a visual analogue scale. The chest tube was removed if there was no bubbling and fluid loss was <150 mL/day. A chest X-ray was performed and examined daily.

Data collection

The following data on the previous HNC were collected from the patients' medical records: date of diagnosis, histology, TNM stage, localization, surgical procedure, associated treatments (radiotherapy or chemotherapy), and presence of tracheostomy. For the lung cancer the following data were recorded: histology, TNM stage, preoperative treatments, type of LR (pneumonectomy, lobectomy or wedge resection), duration of surgery, resection side, transfusion, Mallampati score. The maximum pain level during the first 24 h post-surgery was recorded.

Outcome

The primary endpoint was the occurrence of one of the following events during the first 30 days post LR: death, shock (use of a vasopressor agent), need for mechanical

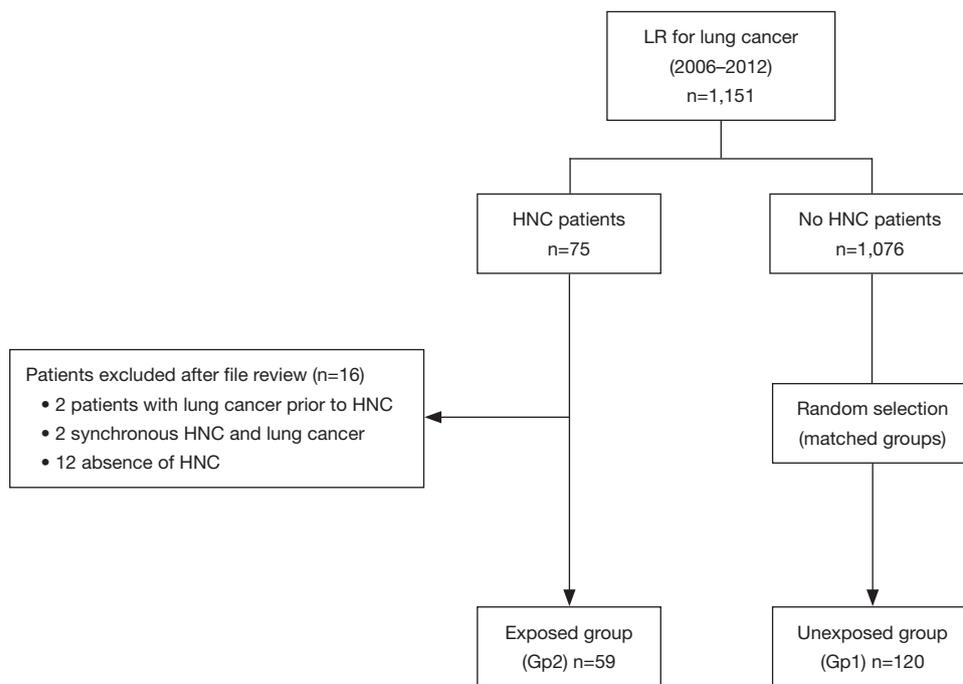


Figure 1 Flow chart for the study population. HNC, head and neck cancer; LR, lung resection.

ventilation (invasive or non-invasive), or postoperative pneumonia (POP).

POP was diagnosed using the following criteria: (I) fever $>38^{\circ}\text{C}$, or hypothermia $<36^{\circ}\text{C}$; (II) new or change in pulmonary infiltrate on chest X-ray; and (III) one of the following additional criteria: purulent sputum or leukocytosis $>10^9/\text{L}$ or $<2.5 \times 10^9/\text{L}$. Two investigators (BP and GM) blinded to the presence or absence of previous HNC assessed all diagnoses of POP to avoid any potential bias.

Statistical analysis

Statistical analysis was performed using STATA[®], v.11 for Windows (StataCorp., Texas, USA). Data are summarized as the mean \pm standard deviation for quantitative variables, or number and percentage for categorical variables. Postoperative outcome was studied by univariate analysis using the Chi² or Fisher's exact test to compare quantitative variables and Student's *t*-test or Kruskal Wallis test to compare continuous variables.

Variables yielding *P* values <0.1 in univariate analysis were included in a forward multivariate logistic regression analysis taking collinearity into account, to identify the factors that were predictive for postoperative outcome/

event. Likelihood ratio statistics were used as a criterion for selection in a backward stepwise procedure. All tests were two-tailed and $P < 0.05$ was considered statistically significant.

Results

Study population

From January 2006 to May 2012, 1,151 patients underwent LR for lung cancer. Among these patients, 75 were identified as having previous HNC. Sixteen patients were excluded after a review of their files because two patients had lung cancer prior to HNC, two had synchronous HNC and lung cancer, and 12 had no HNC. The remaining 59 patients defined the exposed group and were included in Gp2 (Figure 1).

A total of 1,076 patients without previous HNC underwent LR for lung cancer and 120 of these were matched and comprised the unexposed group (Gp1) (Figure 1).

This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review board (N^o3001 on the 10th May, 2011) and Commission Nationale Informatique et Liberté (CNIL) (N^o1922081;

Table 1 Clinical characteristics, surgical and perioperative data for the two study groups

Variables	Missing data	All patients (N=179)	Patients without previous HNC (Gp1) (N=120)	Patients with previous HNC (Gp2) (N=59)	P
Age (years)		62±8.5	62.1±8.5	62.6±8.7	0.69
Male	0	153 (85)	101 (84.1)	52 (88.1)	0.65
Body mass index (kg/m ²)	9	24.7±4	25.1±3.7	23.8±4.6	0.06
Congestive heart failure	0	5 (2.8)	5 (4.2)	0 (0)	0.17
Diabetes mellitus	0	15 (8.4)	9 (7.5)	6 (10.2)	0.57
COPD	11	82 (48.8)	51 (44.7)	31 (57.4)	0.14
Smoking status	0	177 (98.8)	118 (98.3)	59 (100)	1.0
Cumulative smoking (packs/year ± SD)	10	46±24	46±24	46±22	0.92
Current smokers	6	36 (20.8)	25 (21)	11 (20.3)	1.0
Alcoholism	1	38 (21.3)	22 (18.3)	16 (27.6)	0.17
Charlson comorbidity index	1	3.05±1.3	2.8±1	3.4±1.7	0.003
Preoperative lung function					
FEV ₁ ± SD (% predicted)	1	83±18	82.8±17	83.2±20	0.9
Type of surgery					0.25
Pneumonectomy		22 (12.3)	15 (12.5)	7 (11.8)	
Lobectomy		141 (78)	92 (76)	49 (83)	
Wedge		16 (8.9)	13 (10.8)	3 (5)	
Left side resection	2	69 (39)	46 (39)	23 (39)	0.5
Surgery duration (h)	18	3.45±1	3.35±1.02	3.67±0.8	0.06
Transfusion	12	6 (3.6)	5 (4.3)	1 (1.9)	0.66
Paravertebral block	9	22 (12.9)	16 (13.8)	6 (11.1)	0.8
Pain level*	16	5±2.1	4.9±2.1	5.3±2.2	0.22
ICU admission	0	97 (54.0)	63 (52.5)	34 (57.6)	0.52
Length of hospital stay (median) (range)	3	10 [7–24]	10 [7–23]	11 [6–24]	0.7

All values shown are mean ± standard deviation (SD), or n (%), unless stated otherwise. *, maximum pain level during the first postoperative 48 hours. COPD, chronic obstructive pulmonary disease; HNC, head and neck cancer; FEV₁, forced expiratory volume in one second; ICU, intensive care unit.

02/02/2016) approved the protocol.

Clinical characteristics and management of lung cancer

The demographic and clinical characteristics of the study population are shown in *Tables 1,2*. Most patients (85%) were male, and mean age at the time of surgery was 62±8 years. The Charlson score was significantly higher in Gp2 (3.4±1.7

vs. 2.8±1; P=0.003) and there were more squamous cell carcinomas in Gp2 than in the control group (Gp1) (57.6% vs. 31.6%, P=0.003%) (*Table 2*).

In Gp2, the median time between HNC treatment and lung cancer surgery was 80 months. Laryngeal cancer was the most frequent localization of HNC (n=24, 40.6%). Most patients underwent surgical treatment (n=31, 62%) and 27 (50.0%) received chemotherapy and/or radiotherapy.

Table 2 Characteristics of the lung cancer in the two groups of patients

Variables	Missing data	All patients (N=179)	Patients without previous HNC (Gp1) (N=120)	Patients with previous HNC (Gp2) (N=59)	P
Preoperative chemotherapy	0	36 (20.1)	23 (19.2)	13 (22)	0.69
Preoperative radiotherapy	0	5 (2.8)	1 (0.8)	4 (6.8)	0.04
Histology	3				0.003
Squamous cell carcinoma		71 (40.3)	37 (31.6)	34 (57.6)	
Adenocarcinoma		73 (41.5)	54 (46.2)	19 (32.2)	
Other		32 (18.2)	26 (22.2)	6 (10.2)	
Stage	0				0.16
I		60 (37.7)	36 (33)	24 (48)	
II		53 (33.3)	41 (37.6)	12 (24)	
III		42 (26.4)	30 (27.5)	12 (24)	
IV		24 (2.5)	13 (10)	11 (18)	

All values shown are n (%). HNC, head and neck cancer.

Among these 59 patients, 41 were evaluated for swallowing disorders before LR and 6 (14%) had a major swallowing disorder (*Table S1*).

All pulmonary resections were included. Concerning extended resections, one patient in Gp1 and two patients in Gp2 underwent intrapericardial pneumonectomies, five LRs in Gp1 and one patient in Gp2 were associated with chest wall resection, one patient in Gp2 had diaphragm resection and one patient in Gp1 was treated with left atrium resection.

Thoracic surgery management did not differ between the two groups (*Table 1*). Thirty-four patients in Gp2 (57%) were cared for in the intensive care unit (ICU) *vs.* 63 patients (52%) in Gp1. Median length of stay in the ICU after surgery was significantly higher in Gp2 than in Gp1 patients [6 days (3–16) *vs.* 4 days (1–11), $P=0.004$]. There was no difference in the total length of hospital stay between the two groups [10 days (7–23) for Gp1 *vs.* 11 days (6–24) for Gp2, $P=0.7$].

Primary endpoint

In the overall population, 44 patients (24.6%) experienced at least one postoperative event during the first 30 days post-surgery (*Table 3*). Among them, 31 patients (17.3%) had POP, which was confirmed bacteriologically in 22 cases (71%). Postoperative complications [42.4% (95% CI, 29.4–55.4%) *vs.* 15.8% (95% CI, 9.2–22.5%), $P<0.001$], POP

(32.2% *vs.* 10%, $P=0.001$), and all-cause mortality (8.5% *vs.* 1.7%, $P=0.04$) were significantly more common in HNC patients (Gp2) when compared to Gp1. The documented bacterial species in the HNC patients with pneumonia were all enterobacterias.

Type and treatment received for HNC according to the occurrence of postoperative complication

In the group of patients with HNC, 7 were treated by total laryngectomy, 1 of whom experienced a postoperative complication. Eleven patients were treated by supraglottic partial laryngectomy. Among them, a postoperative complication occurred in 7 patients; a tracheostomy was performed during thoracic surgery (i.e., “prophylactic”) in only one patient (*Table 4*). Six patients were classified as high risk for swallowing disorders: four of these experienced a serious postoperative event (*Table S1*).

Risk factors for postoperative complications

Multivariate analysis revealed the following risk factors to be independently associated with a high risk of complications in the first 30 days post-surgery: history of HNC [OR =4.24 (95% CI, 1.84–9.74)], male gender [OR =8.99 (95% CI, 1.05–76.78)], cumulative smoking [OR =1.02 for an increase of 1 pack-year (95% CI, 1.01–1.04)], Charlson comorbidity index [OR =1.45 (95% CI, 1.07–1.96)] (*Table 5*).

Table 3 Postoperative complications in the two groups of patients within the first 30 days post-surgery

Variables	Missing data	All patients (N=179)	Patients without previous HNC (Gp1) (N=120)	Patients with previous HNC (Gp2) (N=59)	P
At least one event*	0	44 (24.6)	19 (15.8)	25 (42.4)	<0.001
All-cause death	0	7 (3.9)	2 (1.7)	5 (8.5)	0.04
Ventilatory support	0	20 (11.2)	8 (6.7)	12 (20.3)	0.01
Non-invasive ventilation	0	13 (7.2)	6 (5)	7 (11.8)	0.12
Invasive ventilation	0	14 (7.8)	5 (4.2)	9 (15.2)	0.01
Shock	0	12 (6.7)	5 (4.2)	7 (11.8)	0.06
Cardiorespiratory arrest	0	7 (3.8)	4 (3.3)	3 (5)	0.68
Postoperative pneumonia	0	31 (17.3)	12 (10)	19 (32.2)	0.001
Bacteriological evidence	0	22 (12.3)	8 (6.7)	14 (23.7)	0.003

All values shown are n (%). *, occurrence of at least one postoperative complication in the first 30 days post-surgery: need for respiratory assistance, shock, cardiorespiratory arrest, postoperative pneumonia and death. HNC, head and neck cancer.

Table 4 Type and treatment received for head and neck cancer according to the occurrence of postoperative complication

Variables	Missing data	All HNC patients	No postoperative event (N=34)	Postoperative event (N=25)
Type of cancer	5		2	3
Buccal cavity		5	4	1
Oropharynx		8	6	2
Hypopharynx		13	7	6
Larynx		23	11	12
Others		5	4	1
Type of surgery	8			
Total laryngectomy		7	6	1
Supraglottic laryngectomy without preoperative «prophylactic» tracheostomy		7	1	6
Supraglottic laryngectomy with preoperative «prophylactic» tracheostomy		4	3	1
Others		11	4	7
Chemotherapy and radiotherapy	2	27	15	12
Radiotherapy alone	9	17	9	8

HNC, head and neck cancer.

Discussion

The present study assessed the incidence of serious postoperative complications in 179 patients undergoing lung cancer surgery with or without previous HNC. The

data suggest that patients with previous HNC have an increased risk of postoperative complications including POP and death. Previous HNC was identified as an independent risk factor for severe postoperative complications after LR. Other independent risk factors for postoperative

Table 5 Univariate and multivariate analysis of risk factors for postoperative complications

Variables	Missing data	Univariate analysis			Multivariate analysis	
		No postoperative event (N=135)	Postoperative event (N=44)	P	OR* [95% CI]	P
Previous head and neck cancer	0	34 (25.2)	25 (56.8)	<0.001	4.24 [1.84–9.74]	0.001
Male gender	0	110 (81.5)	43 (97)	0.06	8.99 [1.05–76.78]	0.045
Cumulative smoking (pack/years ± SD)	0	42.8±22	55.9±25	0.002	1.02 [1.01–1.04]	0.005
Charlson score	1	2.8±1.2	3.6±1.4	<0.001	1.45 [1.07–1.96]	0.017
Age at time of surgery	0	61.3±8.9	65.2±6.7	0.018		
Alcoholism	0	22 (16.4)	16 (36.3)	0.01		
COPD	11	57 (44.2)	25 (64.1)	0.04		
Heart failure	0	3 (2.2)	2 (4.5)	0.59		
Diabetes mellitus	0	10 (7.4)	5 (11.3)	0.53		
BMI	0	24.9±4	24.0±4	0.55		
Current smoker	6	26 (19.8)	10 (23.8)	0.67		
FEV ₁ (%)	1	83±18.7	82±15.5	0.82		
Preoperative chemotherapy	0	29 (21.5)	7 (15.9)	0.52		
Preoperative radiotherapy	0	3 (2.2)	2 (4.5)	0.59		
Type of surgery	0			0.91		
Pneumonectomy		17 (12.6)	5 (11.4)			
Lobectomy		107 (74.3)	34 (77.2)			
Wedges		11 (8.2)	5 (11.4)			
Duration of surgery (h)	18	3.4±1	3.7±0.8	0.07		

Values shown are mean ± SD, or n (%). *, for continuous data, odds ratio (OR) means the increase per unit of data. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; BMI, body mass index; CI, confidence interval; SD, standard deviation.

complications included cumulative smoking status, male gender, and high Charlson comorbidity score.

The characteristics of our study population are consistent with previous LR cohorts (5). Patients with a high Charlson comorbidity index and cumulative smoking of over 40 packs/year usually present with cardiovascular comorbidities (5). The type of surgery was also similar to that reported in the literature although the incidence of pneumonectomy was higher than reported (20). The incidence of serious postoperative events was higher than that reported elsewhere. Nevertheless, postoperative mortality in our study remained within the usual range, from 1.3–5.2% (5,20). The higher complication rate including higher POP (21) could be explained by the selection of high-risk

patients, mostly HNC patients, and the large proportion of patients undergoing pneumonectomy. The postoperative events in the HNC group were similar in type to those in Gp1.

Our study confirms several risk factors for severe postoperative complications, namely male gender (21), and Charlson comorbidity index (22,23). Smoking history is a known risk factor for severe postoperative complications after LR (24). However, we found no protective effect of smoking cessation before surgery, as reported recently by Rodriguez *et al.* (25).

Only a few studies have reported the outcome of patients with previous HNC who undergo LR. Massard *et al.* carried out an observational study of 114 patients with previous

HNC undergoing LR (26). They reported a mortality rate of 3.5% and a POP rate of 17.6%. More recently, Herrera *et al.* reported a larger exposed/unexposed study and found an increase in POP, mainly after partial laryngeal surgery (27).

Swallowing disorders seem to be the main problem in HNC patients. Four out of six of our patients who were evaluated as high-risk for swallowing before LR developed POP (Table S1). All had previously been treated by partial laryngeal resection. Furthermore, although POP was not documented systematically by microbiological sampling, the documented bacteria in HNC patients with POP were all enterobacteria species, supporting the hypothesis that an aspiration mechanism is involved. It has recently been suggested that up to 25% of patients will develop aspiration pneumonia within 5 years after receiving chemo-radiotherapy for HNC (28). These data suggest that a systematic evaluation of preoperative swallowing disorders could help in identifying high-risk patients for postoperative complications in whom preventive strategies could be proposed.

Even if our results and those of Herrera *et al.* (27) support the hypothesis that swallowing disorders may increase the risk of POP in the early postoperative phase, the benefit of preventive tracheostomy in HNC patients has not been validated. However, temporary “prophylactic” tracheostomy during LR surgery could facilitate the clearance and aspiration of bronchial secretions and help to introduce respiratory assistance if necessary. Although many centers have adopted this strategy for some patients, there is no consensus regarding the treatment of these high-risk patients. As we noted, among the 11 HNC patients treated by supraglottic partial laryngectomy, seven experienced at least one serious postoperative complication. However, a prophylactic tracheostomy was performed during LR in four of these patients and only one had a serious postoperative complication. Moreover, patients treated by total laryngectomy cannot have swallowing disorders. Only 1 out of 7 patients treated by total laryngectomy had a postoperative complication. After exclusion of these 7 patients, the results of the multivariate analysis remained unchanged.

The main strength of our work is its exposed/non-exposed study design with groups matched for most of the usual risk factors for postoperative complications. However, our study has several limitations. It was a monocenter analysis with only a small number of patients with previous HNC. Because of its retrospective design, some data were also missing, especially data regarding the preoperative swallowing evaluation. Finally, not all POPs were documented by a positive bacterial culture from a

respiratory sample. However, we used a well-accepted definition of nosocomial pneumonia and all events were independently assessed by two investigators blinded to the presence or absence of previous HNC.

Conclusions

The present study confirms that previous HNC is a major risk factor for serious postoperative complications in patients undergoing LR for lung cancer. Male gender, high Charlson comorbidity index, and smoking status were independently associated with the occurrence of postoperative complications. This increased risk of complications may be related to swallowing disorders, a frequent complication after HNC surgery. Our data support the systematic preoperative clinical assessment of swallowing disorders to identify patients at risk. The risk:benefit ratio of a temporary “prophylactic” tracheostomy should be evaluated.

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None.

Footnote

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

Ethical Statement: This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review board (N°3001 on the 10th May, 2011) and Commission Nationale Informatique et Liberté (CNIL) (N°1922081; 02/02/2016) approved the protocol.

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Supplementary

Table S1 Evaluation of swallowing disorders by the head and neck surgeon

Swallowing disorders	Missing data	No risk	Low risk	High risk
HNC patients	18	27	8	6
Major complications	–	7 (26%)	3 (37%)	4 (66%)

This analysis was not established with a swallowing function score but was a clinical evaluation performed by the head and neck surgeon (OL) blinded for postoperative complications results. In 18 out of 59 patients (30%), information was not available. HNC, head and neck cancer patients.