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Radical Resection or Chemoradiotherapy for Cervical Esophageal Cancer?

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Abstract
Background The prognosis and quality of life (QOL) for those with cervical esophageal cancer is extremely poor, and chemoradiotherapy remains the mainstay treatment. During the past few years, our surgical teams has implemented a more aggressive and radical resection: total laryngopharyngectomy with neck dissection, total esophagectomy, and reconstruction with stomach. This study compares the results of chemoradiotherapy and that of the aforementioned surgical approach.
Methods This is a retrospective study of 15 patients who underwent radical resection and 14 patients who received chemoradiation. Their age, sex, tumor stage and grade, pre- and posttreatment dysphagia scores, operating time, blood loss, length of intensive care and postoperative stay, days to resume oral intake, complications, Eastern Cooperative Oncology Group (ECOG) status, QOL score, and disease-specific survival were recorded and compared.
Results There were no significant differences in age, sex, pretreatment dysphagia score, cancer stage and grade, ECOG status (posttreatment), associate diseases, preoperative QOL, or follow-up period between the two groups. However, the posttreatment dysphagia score was significantly better for the operative group ($P < 0.001$). QOL improved in both groups, and the operative group seemed better although the difference was not significant. In addition, the survival between the two groups was statistically insignificant ($P = 0.97$, log-rank test).
Conclusions Our experience showed that radical surgery that includes total laryngopharyngectomy with neck dissection, total esophagectomy, and reconstruction with stomach for cervical esophageal cancer is beneficial to patients in terms of better eating.

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Introduction

Cervical esophageal cancer has a poor prognosis, with the best 5-year survival rates ranging from 18 to 35% [1–4]. According to the National Comprehensive Cancer Network (NCCN) treatment guidelines [5], radiotherapy and chemotherapy remain the mainstay management interventions.

However, the outcome is usually disappointing after treatment. Patients still have difficult swallowing and tend to choke easily. The use of an esophageal metallic stent [6] in recent years seems to be an acceptable choice in terms of quality of life (QOL) improvement. However, the location of the stent in such cases is high, and the larynx would be compressed, leading to much discomfort.

For the above reasons, it is questionable if a more aggressive and radical therapeutic modality is beneficial.

Laryngopharyngectomy with neck dissection, total esophagectomy, and resumption of gastrointestinal continuity in one stage is an ideal but challenging surgical procedure. The operating time is long [7–9], and the perioperative morbidity rate is high [10–12].

Since November 2002, for resectable cervical esophageal cancer (stages IIA–IVA), we have been suggesting radical procedures that were performed synchronously by two teams: head and neck surgeons for the cervical portion and thoracic surgeons for the abdominal and thoracic procedures. Because the stomach is the best substitute for the esophagus [1, 2, 13–15], we used the gastric tube for esophageal reconstruction. If the patient refused the surgery, chemoradiotherapy was administered.

This study retrospectively reviewed and compared the chemoradiation (CRT) group and the operative (OP) group to determine which of the treatment strategies is better for the patients.

Materials and methods

Patients

Between November 2002 and March 2007, a total of 29 patients with resectable cervical esophageal squamous cell carcinoma (stages IIA–IVA) were enrolled in the study. In all, 15 patients agreed to undergo the radical resection and reconstruction, and the rest received chemoradiation. All signed informed consent. Resectability of the tumor was confirmed by computed tomography (CT), bronchofiberscopy, and positron emission tomography (PET). Tumors with invasion of the trachea and vascular (carotid) sheath, encasement of neck vessels, and metastasis to distant organs (e.g., lungs, liver) were defined as unresectable and were excluded from the study.

The symptoms included dysphagia and odynophagia. The preoperative workup followed the NCCN guidelines [5]. Chest CT scans for ruling out adjacent organ invasion and distant metastasis, bronchofiberscopy for examining tracheobronchial invasion or infiltrations, and PET scans to survey the cervical, thoracic, and celiac lymph nodes and distant metastasis were performed routinely. Furthermore, lung function tests and cardiac sonography were carried out. The diagnoses were confirmed by endoscopic biopsy in all patients.

Operation group

Preoperative preparations

After quitting smoking for at least 2 weeks, all patients were admitted to the ward at least 4 days before the operation for respiratory training and colon preparation. Total parenteral nutrition was given if body weight loss was $>10\%$ or the serum albumin level was <3.0 g/dl (three patients). A clear liquid diet was allowed until the night before the surgery. Laxative was given on the second and third days after admission to clear the bowel. Incentive spirometry was compulsory for respiratory training. Bronchofiberscopic pulmonary toilet was also performed if necessary. All patients were informed that they would lose their voice permanently after the operation.

Operations

Laryngopharyngectomy, neck dissection, transhiatal esophagectomy and gastric tube preparation

In cases in which the PET scan showed no mediastinal lymph node metastasis, the patients were placed in a supine position, under endotracheal tube general anesthesia.

Total laryngopharyngectomy and neck dissection (performed simultaneously with the abdominal procedure)

All patients underwent tracheostomy first. We performed neck dissections en bloc with the larynx and hypopharynx in all patients who had clinically detectable metastatic lymph nodes. Lateral neck dissection (levels II, III, IV) was done for the N0 neck. For the N1 neck, functional neck dissection that preserved the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle or a modified radical neck dissection (levels I–V) was performed. For laryngopharyngectomy, an apron incision was used in all patients. The skin flap was developed deep to the platysma muscle or superficial to the strap muscles, which were then transected before separating the thyroid isthmus. Using sharp and blunt dissection, the contralateral thyroid lobe was detached from the trachea with the intact blood supply, whereas the thyroid lobe on the lesion side was left attached to the trachea, which was to be removed later as a whole with the larynx. The trachea was then transected and separated from the adjacent esophagus distal to the stoma. The superior and inferior thyroid arteries and veins of the lesion side were then identified and ligated. All suprahyoid muscles were separated from their hyoid attachment. The hypopharynx was first entered superior to the hyoid bone at the level of the valleculae. Under direct visualization, we performed blunt dissection deep to the inferior constrictors of the pharynx posteriorly, separating the posterior hypopharyngeal wall completely from the deep neck muscle at the fascia layers of retropharyngeal space. Complete circumferential resection of the hypopharyngeal wall with adequate safe margins was finally performed. The larynx and hypopharynx were now

completely isolated, en bloc with the dissected cervical esophagus.

Abdominal procedures

The stomach was mobilized through a median laparotomy. The short and left gastric vessels were divided while the right gastroepiploic vessels were preserved as the pedicle. Celiac nodes were removed if enlarged or suspicious. The esophagogastric junction was freed from the hiatus. Transhiatal esophagectomy was then performed as described previously [16]. With the right hand through the diaphragmatic hiatus, blunt dissection was carried out along the esophagus until the whole organ was mobilized. If the esophagus had been mobilized through the thoracotomy (see below), the transhiatal procedure was omitted. The abdominal esophagus was transected, and both ends were sutured securely. The entire esophagus was removed through the thoracic inlet with the cervical specimen by the head and neck surgeons to prevent the tumor from seeding to the lower thorax and abdomen.

Esophagectomy through the right thoracotomy

In cases where the PET scan revealed thoracic lymph node metastasis, right thoracotomy for esophagectomy and mediastinal lymph nodes dissection were carried out before the cervical and abdominal procedures were started. The mediastinal pleura were incised, and the esophagus was separated from the adjacent mediastinal tissues and organs. The mediastinal nodes were dissected as completely as possible. After the dissection, the esophagus was left in its bed, and the chest was closed. The patient was then placed in the supine position for the cervical and abdominal procedure as described above. Again, the esophagus was removed with the hypopharynx and larynx through the thoracic inlet after the abdominal esophagus was transected and sutured.

Reconstruction

The stomach was tailored into a tube shape by resection of the esophagogastric junction and part of the lesser curvature using a curved Akiyama Petz auto-suture. Kocher's maneuver was done. The gastric tube was then pulled up to the neck through the esophageal route into the neck. End-to-end pharyngogastric anastomosis was performed with interrupted mattress sutures. Feeding jejunostomy and permanent tracheostomy were likewise performed. Drains were placed over the neck and splenic fossa.

Postoperative care

The patients were sent to the intensive care unit (ICU), and chest radiography was performed. Nothing was given per os, and nasogastric tube decompression was undertaken while intravenous fluids were given. Total parenteral nutrition (TPN) was prescribed the next day if there was no electrolyte or metabolic imbalance. Otherwise, we postponed the TPN until the imbalance was corrected. The patient was weaned from the ventilator as soon as possible.

Patients were transferred to the ward once their conditions were stable and they were extubated. Early ambulation was encouraged, and jejunostomy feeding was given if the patient had a bowel movement. If there were no signs of anastomotic leakage, oral intake was resumed 12 days following the operation.

Pneumatic artificial larynx and phonation training programs were introduced to the patients. Adjuvant chemoradiation would be given in the case of pathological stage T3, N1, or M1a. All patients were followed up monthly in the clinic.

Chemoradiotherapy group

All patients with cancer in comparable stages who underwent evaluation similar to the OP group but refused operative treatment received concurrent chemoradiation as the main treatment modality. The regimen consisted of cisplatin (60 mg/m^2, day 1), 5-fluorouracil (5FU) (600 mg/m^2, days 1–5), and leucovorin (20 mg/m^2, days 1–5). Chemotherapy was started on the first day of radiation therapy. Two to three cycles were given, depending on the tolerance and compliance of the patients, during the full course of radiation therapy. Radiation therapy was performed with a 6- or 10-MN linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The median radiation dose to the mediastinum was 65 Gy (60–70 Gy). The daily fraction was 1.8–2.0 Gy, 5 days a week.

Calculation of QOL score

A World Health Organization (WHO) Questionnaire on quality of life—BREF-Taiwan version 100, April 1998—was given to each patient before treatment and during the posttreatment follow-up. The QOL score in the questionnaire was calculated as follows: not satisfied at all, 1; somewhat satisfied, 2; moderately satisfied, 3; very satisfied, 4; extremely satisfied, 5.

Statistical analysis

Mann–Whitney tests were performed to compare age and dysphagia scores [17]; the Pearson chi-squared test compared the pathologic stage of the OP and CRT groups; the chi-squared test compared tumor grading, ECOG status, and associate diseases; Fisher's exact test compared the

number of deaths; and the log-rank test compared survival time (in months); the paired-sample *t*-test compared pre- and posttreatment QOL; and the *t*-test compared the improvement of QOL between the two groups.

The study was approved by our institutional review board.

Results

The demographic data of the two groups of patients are shown in Tables 1 and 2, respectively. The comparison of the two groups is shown in Table 3.

The average ages of the OP and CRT groups were 56.6 ± 10.9 and 58.8 ± 9.8 years, respectively, with no significant difference ($P = 0.555$). All patients were male. Two patients started with the right thoracotomy esophagectomy, and the rest started with the cervical and abdominal procedures. Tumor grading, ECOG status, associated diseases, and tumor staging were all statistically nonsignificant ($P = 0.842, 0.564, 0.858$, and 0.631 respectively); that is, there was no difference between the two groups in terms of medical co-morbidities.

The average operating time was 412.2 ± 51.7 min, blood loss was 606.5 ± 333.6 ml, and interval to oral intake was 12.5 ± 0.6 days. The ICU stay was 2.45 ± 0.8 days, and the postoperative stay was 12.8 ± 1.3 days. Seven patients had mild to moderate left-side pleural effusion, but it subsided after tube thoracostomy or was reabsorbed. There was greater improvement in dysphagia scores after operation than that after chemoradiation ($P < 0.001$).

Three patients in the OP group could not complete all the cycles of chemotherapy due to bone marrow suppression (two cases) and hyperammonemia (one case). In the CRT group, two patients could not complete the regimen due to bone marrow suppression. The numbers of deaths were not significantly different ($P = 0.462$). The mean survival time between the groups was not statistically significant ($P = 0.97$, log-rank test). The follow-up period for the OP and CRT group has been 36.17 ± 7.14 months (95% confidence interval (CI) 22.57–50.17) and 34.93 ± 5.23 months (95% CI 24.69–45.17), respectively. These data are all illustrated in Table 3 and Fig. 1.

The preoperative and postoperative QOL scores for the OP group were 72.73 ± 1.22 and 74.27 ± 1.83, respectively ($P = 0.003$). For the CRT group they were 72.64 ± 1.08 and 73.36 ± 0.63, respectively ($P = 0.019$).

Discussion

Patients with cervical esophageal cancer suffer due to (1) being unable to swallow (2) choking easily, and (3) impeded compromise of the airway. Chemoradiation provides palliation, although the results are not promising and patients still experience poor eating. In our study, four patients in the CRT group were unable to swallow, and

Table 1 Demographic data for the resection group

No.	Age (years)	Sex	Preoperative tumor stage	Tumor grade	Associated disease	Pathologic stage	Postop. ECOG performance status
1	69	M	T3N1M0 (III)	G2	Hypertension	T3N1M0 (III)	1
2	67	M	T3N1M1a (IVA)	G3	Diabetes	T3N1M1a (IVA)	1
3	54	M	T3N0M0 (IIA)	G1	Nil	T3N0M0 (IIA)	0
4	37	M	T3N1M0 (III)	G2	Nil	T3N0M0 (IIA)	0
5	48	M	T3N0M0 (IIA)	G2	Diabetes	T3N0M0 (IIA)	0
6	45	M	T2N0M0 (IIA)	G2	Nil	T2N0M0 (IIA)	0
7	64	M	T3N0M0 (IIA)	G3	Mild liver function impairment	T3N0M0 (IIA)	0
8	70	M	T2N1M0 (IIB)	G1	Nil	T2N1M0 (IIB)	1
9	66	M	T3N0M0 (IIA)	G2	Hypertension	T3N0M0 (IIA)	0
10	49	M	T3N1M1a (IVA)	G2	Nil	T3N1M1a (IVA)	0
11	39	M	T2N0M0 (IIA)	G3	Nil	T2N1M0 (IIB)	0
12	58	M	T2N1M0 (IIB)	G2	Hypertension	T2N1M0 (IIB)	0
13	66	M	T3N0M0 (IIA)	G1	Diabetes	T3N0M0 (IIA)	1
14	55	M	T3N0M0 (IIA)	G2	Nil	T3N0M0 (IIA)	0
15	62	M	T2N1M0 (IIB)	G1	Nil	T2N1M0 (IIB)	0

ECOG Eastern Cooperative Oncology Group, *M1a* upper thoracic lymph node metastasis seen by preoperative positron emission tomography (PET) or by its pathology, *N1* cervical nodes metastasis

Table 2 Demographic data for the chemoradiotherapy group

No.	Age (years)	Sex	Pretreatment stage	Tumor grade	Associated disease	Posttreatment ECOG performance status
1	50	M	T2N1M0 (IIB)	G2	Nil	0
2	74	M	T2N0M0 (IIA)	G1	Hypertension	1
3	55	M	T3N1M1a (IVA)	G3	Nil	0
4	48	M	T3N1M0 (III)	G2	Diabetes	0
5	72	M	T2N0M0 (IIA)	G2	Diabetes	1
6	67	M	T2N1M0 (IIB)	G3	Nil	1
7	59	M	T3N1M1a (IVA)	G2	Nil	0
8	69	M	T3N0M0 (IIA)	G1	Hypertension	0
9	42	M	T3N1M0 (III)	G2	Nil	0
10	68	M	T3N0M1a (IVA)	G2	Liver function impairment	0
11	53	M	T3N1M0 (III)	G1	Nil	1
12	57	M	T3N0M0 (IIA)	G1	Cardiomegaly	0
13	51	M	T3N0M0 (IIA)	G1	Diabetes	1
14	58	M	T3N1M0 (III)	G2	Nil	0

Table 3 Comparison of characteristics between the operation and chemoradiotherapy groups

Factor	OP group ($n = 15$)	CRT group ($n = 14$)	P*
Age	56.6 ± 10.9	58.8 ± 9.8	0.555
Tumor grading			0.842
ECOG status			0.564
Associate diseases			0.858
Cancer stage			0.631
Dysphagia score			
Pretreatment	3.4 ± 0.5	3.5 ± 0.5	0.595
Posttreatment	0.6 ± 0.5	2.3 ± 0.7	<0.001
No. of deaths	7 (46.7%)	9 (64.3%)	0.462
Disease-specific survival time (months), mean	36.2	34.4	0.97
QOL			
Pretreatment	72.73 ± 1.22	72.64 ± 1.08	0.835
Posttreatment	74.27 ± 1.83	73.36 ± 0.63	0.09
Follow-up period (months) and 95% CI	36.17 ± 7.14 (22.57–50.17)	34.93 ± 5.23 (24.69–45.17)	0.93

OP operation, *CRT* chemoradiotherapy, *QOL* quality of life

* Mann–Whitney test for the comparisons of age and dysphagia scores; chi-squared test for tumor grading, ECOG status, and associated diseases; Pearson's chi-squared test for cancer stage; Fisher's exact test for comparisons of the numbers of deaths; log-rank test for comparisons of survival time and the follow-up period; *t*-test for comparison of pretreatment and posttreatment QOL

most of the other patients were only able to ingest a liquid diet. Aspiration pneumonia was usually was a complication as well.

Based on the philosophy that surgery provides the best chance of curing esophageal cancer [18], the authors of the present series selected a much more aggressive strategy to see if it would be more beneficial to the patients. Owing to the high location of the lesion, the free margin of the section line is of great concern be it proximal or distal. For the esophagus, the histopathologic safe resection margin is at least 4–7 cm [19, 20]. Therefore, total esophagectomy should be safe for the distal section margin. The main problem remains with the proximal margin. For a cervical lesion, laryngopharyngectomy seems inevitable.

Swallowing malfunction after hypopharyngectomy and pharyngogastrostomy always leads to choking should the larynx be preserved. Therefore, the patients do not dare to eat or drink. The continuity of the gastrointestinal tract thus

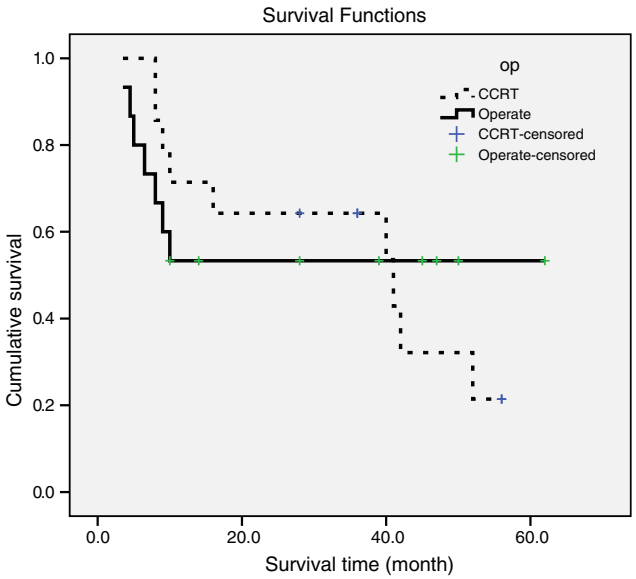

Fig. 1 Survival curve by Kaplan–Meier method: cumulative survival. *CCRT* concurrent chemoradiotherapy, *op* operation

becomes meaningless. Furthermore, the larynx is seldom spared during such an esophagectomy [20].

The esophageal stent, as mentioned earlier, is not suitable for such a high lesion owing to compression of the larynx in front, causing much discomfort. We used the gastric tube as the esophageal substitute. There is no question that the length can reach even the pharynx without significant tension, and only one anastomosis is required, with a small possibility of contamination. Another option, colon interposition, requires three anastomoses, carries a significant risk of contamination to the operative field, and is not a physiological continuity of the gastrointestinal (GI) tract. It is used only in some special cases, such as in the event of previous gastric surgery. The free jejunal flap is seldom considered because microscopic technique by plastic surgeons is always required.

For such a major operation, the long operating time is another point to be considered. The average operating time for the entire procedure at other medical facilities is 468–520 min [7–9], whereas our average incision-to-closure time was only 412.2 ± 51.7 min. This time-saving is due to the synchronous performance of the cervical and abdominal procedures by two groups of experts. Even in the cases of thoracotomy, the time spent would not be much longer as the esophagus is easily dissected in these cases. In contrast, more time is spent on mediastinal lymph node dissection. However, with two groups of surgeons working synchronously, we have to get used to the "crowded" space.

The average blood loss was 606.5 ± 333.6 ml compared to 520–1329 ml reported in the literature [7, 8]. Five patients received four units of blood. The reported leakage rate of pharyngogastrostomy is 5–10% [2, 4, 8, 12, 21]. No leakage was found in our series. The possible reasons are that (1) a definitive, meticulous Kocher's maneuver resulted in no tension in the gastric tube; (2) we used careful interrupted mattress suture for the anastomosis; and (3) perioperative vital signs, electrolytes, and metabolic and nutrition conditions were carefully monitored. Two patients had postoperative stricture (2/15); the strictures were dilated, and the resultant swallowing was satisfactory.

Pulmonary complications are common after esophagectomy and gastric interposition [2, 7, 9, 12, 22], with a reported incidence of 21.6–40.0% [1, 12]. There were no pneumonia cases in our series, possibly due to: (1) strict preoperative cessation of smoking for at least 2 weeks; (2) intensive pre- and postoperative bronchofiberscopic pulmonary toilet; and (3) the short operating time. Our operating time was about 1.0–1.5 h less than has been reported. We must emphasize that the operating time is one of the many factors that contributes to morbidity and mortality. Hence, a shorter operating time would reduce the rate of complications [23, 24]. These factors include operating time, operative blood loss, leakage, and pulmonary complications, among others. The effect of these factors is additive, so it is difficult to say how great the effect of one factor is because if only one factor is considered it may not account too much. Should these factors come into play at the same time, however, the effect could be devastating.

Another point is the permanent tracheostomy that is convenient for tracheal toilet. There were seven patients with mild to moderate left pleural effusion, probably due to pleural reaction. Four were absorbed without intervention, and three needed short periods of chest tube drainage.

There was one case of active neck bleeding on the second postoperative day. He was taken back to the operating room and a small bleeding vessel adjacent to the anastomosis was found to be the source. On follow-up, this patient has had the longest survival (70 months at the time of writing).

Other reported complications include wound infection, mediastinitis, pneumothorax, hydrothorax, and cardiac arrhythmia [3, 4, 9]. None of them occurred in our series.

There was no hospital mortality in the entire series. The reported mortality is 8.3–33.0% [2, 4, 8, 11], and the usual causes are sepsis and myocardial infarction. The postoperative stay (12.8 ± 1.3 days) in this study is much shorter than that of previously reported series [7–10, 12]. Our average time for oral intake resumption was only 12.5 ± 0.6 days, compared with the reported 15–22 days [1, 10].

For the OP group, the operative courses were smooth. Compared with previous reports, our morbidity and complication rates were lower. The time for oral intake resumption was shorter. The post-operative dysphagia score was significantly improved (from 3.4 ± 0.5 to 0.6 ± 0.5), which was much better than the improvement in the CRT group ($P < 0.001$). In the CRT group, four

patients could not even swallow liquids; although they had improved after treatment, their condition was still not as good as that in the OP group. The disease-specific survival rate is 53.3%, compared with the reported 13–36% [1, 3, 4, 7, 9]. There was no preoperative difference in QOL between the two groups (OP group 72.73 ± 1.22, CRT group 72.64 ± 1.08; $P = 0.835$). However, both groups improved significantly after treatment (OP group $P = 0.003$; CRT group $P = 0.019$). Also, the improvement in the OP group was greater, although of no statistical significance ($P = 0.126$). The only problem was the loss of voice. However, patients could be assisted with an artificial larynx. Also, psychological problems were trivial because of detailed preoperative counseling.

Another important point is the survival time. The mean survival times for the OP and CRT groups were 36.2 and 34.4 months, respectively. It seemed there was 1.8 months longer survival for the OP group despite it being non-significant ($P = 0.97$, log-rank test; Fig. 1).

The major drawback of the present series is that it is a retrospective study. Also, even though the basic variables and characteristics of the two groups were not significantly different, the two populations would not be absolutely clinically identical. The authors are merely interested in presenting our surgical procedural experience, hoping to benefit the sufferers of such cancer. A second drawback is that this was a small series and thus was underpowered to see a difference in QOL between the groups. A larger series of prospective randomized studies should be carried out in the future if possible.

Conclusions

Our experience showed that resectable cervical esophageal cancer treated with total laryngopharyngectomy, total esophagectomy, neck dissection, and reconstruction using stomach achieved better eating. Teamwork is important. The cooperation of head and neck surgeons and thoracic surgeons not only allows the best technical expertise, but also results in shorter operating and anesthesia times, fewer complications, a shorter postoperative stay, faster resumption of oral intake, and faster recovery.

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