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ORIGINAL SCIENTIFIC REPORT

Propensity-Matched Analysis Comparing Survival After Hybrid Thoracoscopic–Laparotomy Esophagectomy and Complete Thoracoscopic–Laparoscopic Esophagectomy

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Abstract

Background Hybrid thoracoscopic–laparotomy esophagectomy (hTE) and complete thoracoscopic–laparoscopic esophagectomy (cTLE) are the two most frequently used minimally invasive esophagectomy (MIE) procedures and are broadly utilized for esophageal cancer. We evaluated differences in short- and long-term outcomes between hTE and cTLE in patients with esophageal squamous cell carcinoma (ESCC).

Methods Patients who underwent MIE for ESCC between September 2009 and February 2016 were included in this retrospective study. Propensity score matching (PSM) was utilized to contrast the postoperative results of hTE and cTLE according to the obtained and analyzed pertinent patient features and postoperative variables. Univariate and multivariate Cox proportional hazard regression analysis was used on possible predictors of survival.

Results Eighty-six well-balanced pairs of patients were available for outcome comparison after PSM. Compared to Group 1 (hTE), the patients in Group 2 (cTLE) had significantly shorter operative times and less intraoperative blood loss, but a higher number of retrieved nodes ($p = 0.000$, $p = 0.003$, and $p = 0.000$, respectively). The incidence of postoperative complications was 40.7% (70/172) and did not significantly differ between the two groups. The patients in Group 2 exhibited higher disease-free survival and disease-specific survival (DSS) than those in Group 1 ($p = 0.048$ and $p = 0.041$, respectively). Univariate and multivariate Cox proportional hazard regression analyses showed that pT stage, pN stage, differentiation grade, and the surgical procedure had significant HRs, which suggested that cTLE is associated with better DSS.

Conclusions cTLE possibly shows better postoperative and oncologic outcomes than hTE.

Introduction

Esophageal cancer (EC) is one of the most lethal and fastest spreading cancers in patients across the globe. It is the sixth most frequently noted cause of cancer deaths in men and the ninth in women worldwide [1]. The main histological type of EC in China is esophageal squamous cell carcinoma (ESCC). The 5-year overall survival rate of ESCC remains poor (20.9%) [2] because of the high incidence of local recurrence and metastasis. Recurrence and metastasis can occur even in the early stages. Surgical resection is the cornerstone of the treatment and is geared toward extending survival and reaching a conclusive cure. Minimally invasive esophagectomy (MIE) has been increasingly performed worldwide since Cuschieri et al. [3] first reported thoracoscopic mobilization of the esophagus. There is inconsistency in the current terminology for MIE, including complete minimally invasive esophagectomies (cMIEs) and hybrid and minimally invasive esophagectomies (hMIEs). cMIE involves both esophagectomy using

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a thoracoabdominal approach and a combination of laparoscopy and thoracoscopy and transhiatal laparoscopy. hMIE includes performing the abdominal or thoracic portion of the procedure in a conventional open manner [4].

The two most common MIE procedures, namely hybrid thoracoscopic–laparotomy esophagectomy (hTE) and complete thoracoscopic–laparoscopic esophagectomy (cTLE), are performed on 59.9% of patients with superficial cancer and 38.3% of those with advanced cancer. According to the latest report of the Japanese Association for Thoracic Surgery, the number of hTE and cTLE surgeries performed for superficial or advanced cancer has recently increased [5]. Implementation of these new and demanding surgical techniques must be thoroughly planned and implemented. During the transition from performing open esophagectomies (OE) to performing cTLE, hMIE (including hTE and thoracotomy–laparoscopic esophagectomy) is a critical intermediate period.

It has been established over the past two decades that the feasibility, safety, and oncologic efficacy of MIE and OE are comparable [6–12]. However, possible differences in short- and long-term outcomes between hMIE and cTLE for ESCC remain unclear. Thoracotomy–laparoscopic esophagectomy is not commonly performed by our surgical team. Therefore, the aim of this study was to analyze a single-center's experience with hTE and cTLE procedures for ESCC performed by one surgical team and to evaluate the short- and long-term outcomes by propensity score matching (PSM).

Patients and methods

Patients

Two hundred and ninety-three consecutive patients with ESCC of the thoracic esophagus underwent thoracoscopic McKeown esophagectomies (three incisions) from September 2009 to February 2016 at the Department of Thoracic Surgery, Daping Hospital and Research Institute of Surgery, Army Military Medical University (Chongqing, China). Patient data were obtained via retrospective chart assessment. Evaluation of the intraoperative and postoperative variables and the pertinent features of the patients was conducted. The exclusion criteria were as follows: noncurative (R1 or R2) resection (tumor-free margin < 1 mm), neoadjuvant therapy, loss to follow-up, and death due to causes not connected to esophageal cancer. The patients were divided into two groups: Group 1, patients who had undergone hTE, and Group 2, patients who had undergone cTLE. Each of the surgeries was completed by a single surgical team led by W.G. Preoperative staging was conducted according to endoscopic ultrasound and thoracoabdominal computed tomography scanning. The staging protocol of the American Joint Committee on Cancer (7th edition) was utilized for postoperative TNM staging [13]. Death within 30 days following surgery was established as postoperative death. Each of the patients in this evaluation provided written consent for the surgery. The evaluation was authorized by the Ethics Committee of Daping Hospital and Research Institute of Surgery, Army Military Medical University.

Operative procedures

All 293 of the patients in this study had undergone thoracoscopic McKeown esophagectomy as previously described [14–16]. Briefly, cauterization of the mediastinal pleura overlying the anterior portion of the esophagus was first performed, and the esophagus was shifted from the hilum and pericardium to the area of the azygos vein; then, the vein was skeletonized and ligated with 10-mm liga-clips. After dissecting the esophagus and mediastinal lymph nodes, the thoracic duct was routinely mass ligated immediately above the diaphragmatic hiatus [15]. For the next stage, laparotomy or laparoscopy was performed with the patient in a supine position, and the stomach was formatted to the gastric tube with a stapler, after dissection of the celiac nodes. In the last stage, the cervical esophagus was dissected using a left oblique incision, and the gastric tube was pulled up through the posterior mediastinum. The procedure ended with a cervical esophagogastric anastomosis [17].

Follow-up

All of the patients were followed up in the outpatient clinic after surgery every 3 months during the first year, every 6 months until the fifth year, and subsequent follow-ups were performed annually [17]. Follow-up information was obtained for all of the subjects included in the study until February 2016 or death. The follow-up duration ranged between 5.0 and 91 months (mean 34.3 ± 20.0 months). Particular evaluations, including magnetic resonance imaging, barium swallow, and biopsy, were conducted as noted at follow-up appointments. A diagnosis of recurrence was established according to pathologic or radiologic discoveries. Recurrences were identified as locoregional recurrences, distant metastasis, or death from ESCC. Disease-free survival (DFS) was established as survival from surgery to the date of recurrence. Disease-specific survival (DSS) was established as survival from surgery to the date of death due to ESCC.

Statistics

Numerical data are presented as the mean ± standard deviation, and continuous and categorical variables were compared with the *t* test and Fisher's exact test or *Chi-square* test, respectively. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify potential prognostic factors. Survival curves were constructed using the Kaplan–Meier method, and the log-rank test was used to compare survival differences between the groups for each variable. To minimize confounding effects caused by nonrandomized assignment, the postoperative outcomes of hTE and cTLE were compared using PSM. Briefly, a propensity score for each patient was determined using a logistic regression with the variables pT stage, pN stage, differentiation grade, tumor location, and postoperative TNM stage. Nearest neighbor score matching without replacement within specified caliper widths of 0.2 of the standard deviations of the logit of propensity score was conducted to accomplish 1:1 matching between the two groups [18]. The statistical power of the Cox model was determined with XLSTAT (Addinsoft, New York, NY, USA). All of the statistical calculations were performed with SPSS statistical software, version 22.0 (IBM SPSS, Chicago, IL, USA). A p value of <0.05 denoted statistical significance.

Results

Relevant patient characteristics before and after PSM

Two hundred ninety-three thoracoscopic McKeown esophagectomies for squamous cell carcinoma of the thoracic esophagus took place throughout the evaluation period by a single surgical team led by W.G. Fourteen of these patients received neoadjuvant therapy (14/293, 4.8%), nine were lost to follow-up (9/293, 3.1%), five underwent R1 or R2 resection, two committed suicide postoperatively, one patient died from oropharyngeal cancer, and another died due to asphyxia with an undetermined cause on the 51st postoperative day. Two hundred sixty-one patients stayed in this evaluation following the elimination of the above-listed patients, and the overall 30-day postoperative mortality was 2.0% (6/293).

Of the 261 patients included in this study, 141 underwent hTE (Group 1, before PSM) and 120 cTLE (Group 2, before PSM). Table 1 shows the clinical and other relevant patient characteristics. Patients in Group 1 were older and had more advanced tumors compared to those in Group 2. There were more Tis/T1 stage tumors (28/120, 23.3% vs. 16/141, 11.3%; $p = 0.003$) and in the lower thoracic esophagus (20/120, 16.7% vs. 14/141, 9.9%; $p = 0.004$) in Group 2 than in Group 1.

After PSM, 86 well-balanced pairs of patients (172 patients) remained in the study for outcome comparison (Table 2). Of these, 134 were males, and the sex ratio (male/female) was 3.53/1. The average age was 61.0 ± 7.9 years (range 37–79 years). One hundred and twenty patients (69.8%) had a history of smoking, and 52 (30.2%) had never been smokers. Sex, age, BMI, pT stage, pN stage, differentiation grade, tumor location, and postoperative TNM stage did not significantly differ between the two groups.

Surgical outcomes and perioperative complications after PSM

Overall, the average duration of surgery, intraoperative blood loss, number of retrieved nodes, and postoperative hospital stay were 279.6 ± 66.8 min, 279.4 ± 227.6 ml, 18.5 ± 8.1, and 21.4 ± 11.5 days, respectively. Compared to Group 1, the patients in Group 2 had significantly shorter operative times and less intraoperative blood loss, but a higher number of retrieved nodes ($p = 0.000$, $p = 0.003$, and $p = 0.000$, respectively). However, the postoperative hospital stays of the two groups did not significantly differ ($p = 0.832$).

The incidence of postoperative complication was 40.7% (70/172) (summarized in Table 3). Of note, the incidence of the five most common postoperative complications, i.e., anastomotic leakage (13/86, 15.1% vs. 17/86, 19.8%; $p = 0.422$), pleural effusion (15/86, 17.4% vs. 13/86, 15.1%, $p = 0.680$), pulmonary infection (14/86, 16.3% vs. 8/86, 9.3%; $p = 0.171$), pneumothorax (7/86, 8.1% vs. 6/86, 7.0%; $p = 0.773$), ARDS (4/86, 4.7% vs. 4/86, 4.7%; $p = 1.000$), and chylothorax (5/86, 5.8% vs. 3/86, 3.5%; $p = 0.469$) did not significantly differ between the two study groups.

Recurrence and survival after PSM

Figure 1 shows that the respective DFS of patients in Groups 1 and 2 was 81.3% and 90.6% at 1 year; 49.7% and 64.4% at 3 years; and 42.6% and 59.4% at 5 years after surgery. The DSS was 89.5% and 96.5% at 1 year, 52.9% and 70.5% at 3 years, 42.1% and 60.0% at 5 years after surgery in Groups 1 and 2, respectively. The patients in Group 2 had better DFS and DSS than those in Group 1 ($p = 0.048$, $p = 0.041$, respectively).

The prognostic factors for DSS are presented in Table 4. Univariate analysis showed that sex, age, smoking history, and tumor location did not significantly influence DSS. However, pN stage ($p = 0.000$), pT stage ($p = 0.001$), differentiation grade ($p = 0.005$), and surgical procedure

Table 1 Clinical and other relevant patient characteristics of 261 patients before matching

Factor	Total	Group 1 (hTE) (n = 141)	Group 2 (cTLE) (n = 120)	p Value[a]
Gender				0.056
Males	206	105	101	
Females	55	36	19	
Age (years)	61.0 ± 8.0	59.9 ± 8.0	62.5 ± 7.7	0.008[b]
Smoking history				
No	81	50	31	0.094
Yes	180	91	89	
BMI (kg/m^2)	21.7 ± 3.0	22.0 ± 3.0	21.4 ± 2.9	0.089[b]
pT				0.003
Tis	12	1	11	
T1	32	15	17	
T2	50	34	16	
T3	137	70	67	
T4	30	21	9	
pN				0.647
N0	142	74	68	
N1	73	44	29	
N2	38	19	19	
N3	8	4	4	
Distant metastasis (*M*)				>0.999
M0	261	141	120	
M1	0	0	0	
pStage				0.005
0	12	1	11	
I	30	14	16	
II	104	64	40	
III	115	62	53	
Tumor location				0.004
Upper thoracic	54	21	33	
Middle thoracic	173	106	67	
Lower thoracic	34	14	20	
Grade				0.218
Well differentiated (G1)	56	30	26	
Moderately differentiated (G2)	135	79	56	
Poorly differentiated (G3)	70	32	38	
Operation duration (min)	270.7 ± 65.9	301.0 ± 62.8	235.2 ± 50.0	0.000[b]
Intraoperative blood loss (ml)	262.6 ± 199.1	311.1 ± 217.0	207.0 ± 157.0	0.000[b]
Number of retrieved nodes	18.7 ± 8.2	16.5 ± 8.2	21.3 ± 7.3	0.000[b]
Postoperative hospital stay (days)	21.1 ± 12.0	21.5 ± 10.8	20.3 ± 13.4	0.393[b]

T tumor stage (depth of invasion); *N* lymphatic dissemination stage (based on the American Joint Committee on Cancer (AJCC); 7th edition [13]: N0: no positive lymph nodes; N1: 1–2 positive lymph nodes; N2: 3–6 positive lymph nodes; N3: >6 positive lymph nodes)

[a] *Chi-square* test

[b] Two independent sample *t* test

(p = 0.043) were associated with DSS. In addition, the findings were similar after multivariate Cox proportional hazards regression analysis. This analysis showed that pT stage (p = 0.004), pN stage (p = 0.001), differentiation grade (p = 0.010), and surgical procedure (p = 0.046) had significant HRs and were significantly correlated with DSS, which suggested that cTLE is associated with better DSS.

Table 2 Clinical and other relevant patient characteristics of 172 patients after matching

Factor	Total	Group 1 (hTE) (n = 86)	Group 2 (cTLE) (n = 86)	p Value[a]
Gender				0.540
Males	134	69	65	
Females	38	17	21	
Age (years)	61.0 ± 7.9	61.6 ± 8.1	60.4 ± 7.7	0.306[b]
Smoking history				
No	52	19	33	0.020
Yes	120	67	53	
BMI (kg/m^2)	21.8 ± 3.0	21.5 ± 2.9	22.1 ± 3.0	0.152[b]
Tumor location				0.726
Upper thoracic	19	11	8	
Middle thoracic	129	63	66	
Lower thoracic	24	12	12	
pT stage				0.987
T1	22	10	12	
T2	34	18	16	
T3	94	48	46	
T4	22	10	12	
pN stage				0.395
N0	97	47	50	
N1	47	27	20	
N2	23	11	12	
N3	5	1	4	
Distant metastasis (M)				>0.999
M0	172	86	86	
M1	0	0	0	
pStage				0.996
I	20	10	10	
II	79	40	39	
III	73	36	37	
Grade				0.747
Well differentiated (G1)	34	18	16	
Moderately differentiated (G2)	89	42	47	
Poorly differentiated (G3)	49	26	23	
Operation duration (min)	279.6 ± 66.8	308.6 ± 58.9	250.5 ± 61.7	0.000[b]
Chest operation duration	102.3 ± 26.4	104.8 ± 25.7	99.9 ± 27.1	0.230[b]
Abdominal operation duration	87.2 ± 53.0	123.9 ± 44.1	70.6 ± 47.7	0.000[b]
Intraoperative blood loss (ml)	279.4 ± 227.6	329.8 ± 233.8	229.1 ± 210.8	0.003[b]
Number of retrieved nodes	18.5 ± 8.1	15.4 ± 7.5	21.5 ± 7.6	0.000[b]
Postoperative hospital stay (days)	21.4 ± 11.5	21.6 ± 9.9	21.2 ± 12.9	0.832[b]
Postoperative adjuvant therapy				0.080
Yes	111	50	61	
No	61	36	25	

T tumor stage (depth of invasion); *N* lymphatic dissemination stage (based on the American Joint Committee on Cancer (AJCC), 7th edition [13]: N0: no positive lymph nodes; N1: 1–2 positive lymph nodes; N2: 3–6 positive lymph nodes; N3: >6 positive lymph nodes)

[a] *Chi-square* test

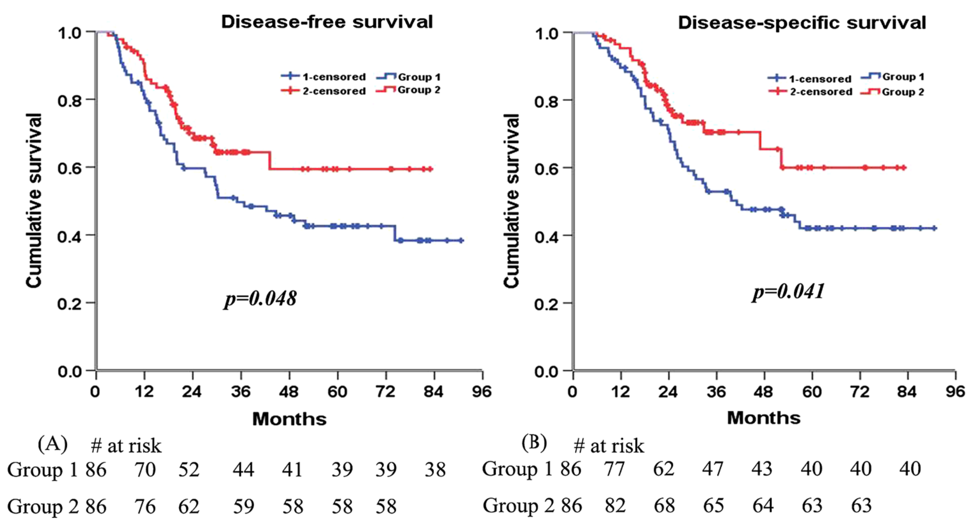
[b] Two independent sample t test

Table 3 Incidence of postoperative complications between the two groups

Postoperative complications	Total	Group 1 (hTE) (n = 86)	Group 2 (cTLE) (n = 86)	p Value
Anastomotic complications				
Anastomotic leakage	30	13	17	0.422
Anastomotic bleeding	1	1	0	0.316
Anastomotic pleural fistula	4	2	2	1.000
Respiratory complications				
Pulmonary infection	22	14	8	0.171
ARDS	8	4	4	1.000
Pleural complications				
Pneumothorax	13	7	6	0.773
Pleural effusion	28	15	13	0.680
Chylothorax	8	5	3	0.469
Cardiac complications				
Atrial fibrillation	2	2	0	0.155
Ventricular tachycardia	1	1	0	1.000
Atrial flutter	1	1	0	1.000
Wound infection	7	4	3	0.700
Vocal cord palsy	5	4	1	0.369
Gastric emptying disturbance	5	4	1	0.369
Acute renal insufficiency	1	1	0	1.000

ARDS acute respiratory distress syndrome

Fig. 1 Kaplan–Meier survival curves for DFS (**a**) and DSS (**b**) of 216 patients after propensity score matching, patients in Group 2 had better DFS and DSS than those in Group 1 (p = 0.048, p = 0.041, respectively)



Discussion

Over the past two decades, MIE and OE have been demonstrated to have comparable feasibility, safety, and oncologic efficacy [6–12], and the benefits of thoracoscopic esophagectomy have gradually been accepted with continuous improvements in relation to surgical instruments and skills required for the procedure. Palazzo et al. [12] found that MIE was better in survival compared to hybrid Ivor Lewis esophagectomy or OE; however, differences between the outcomes of hTE and cTLE, the two

Table 4 DSS differences after multivariate cox proportional hazard regression analysis for the matched patients

Variables	No. of patients	Univariate log-rank *p* value	Multivariate regression *p* value	Hazard ratio (95.0% CI for HR)
T stage		0.001	0.004	1.422 (1.118–1.810)[a]
T1	22			
T2	34			
T3	94			
T4	22			
N stage		0.000	0.001	1.569 (1.193–2.062)[b]
N0	97			
N1	47			
N2	23			
N3	5			
Grade		0.005	0.010	1.636 (1.128–2.374)[c]
Well differentiated (G1)	34			
Moderately differentiated (G2)	89			
Poorly differentiated (G3)	49			
Surgical approaches		0.043	0.046	1.680 (1.010–2.797)[d]
hTE	86			
cTLE	86			
Age (years)				
<61(median)	77	0.964		
≥61	95			
Gender				
Male	134	0.537		
Female	38			
Smoking history				
No smoking	52	0.597		
Smoking	120			
Tumor location				
Upper thoracic	19	0.542		
Middle thoracic	129			
Lower thoracic	24			

Statistical powers of the COX model were calculated by using XLSTAT (Addinsoft Inc., New York, NY, USA) and presented as follows: (a) 1.000, (b) 1.000, (c) 1.000, (d) 1.000

hTE hybrid thoracoscopic–laparotomy esophagectomy; *cTLE*: complete thoracoscopic–laparoscopic esophagectomy

most commonly performed MIE procedures, remain unclear.

In this study, we excluded patients who had undergone preoperative neoadjuvant therapy because the effect of preoperative neoadjuvant therapy on long-term survival remains controversial [19], and no staging system was available for patients who had received preoperative chemoradiotherapy before the year 2017. Furthermore, precise surgical pathologic staging usually cannot be determined after preoperative chemoradiotherapy, especially when complete tumor remission has been achieved.

The pT and pN stages, tumor location, differentiation grade, and postoperative TNM stage are factors that affect the long-term survival by the AJCC staging classification, and these are the confounding factors in the evaluation of surgical approaches and long-term survival. Thus, the present study used PSM to minimize the effects caused by nonrandomized assignment. The other confounding factors, such as age, gender, and BMI, were excluded by univariate analysis; and smoking history was significantly different between the two groups by univariate analysis. However, no reports have shown that smoking history could contribute to the long-term survival of esophageal cancer who accepted esophagectomy to date, and we did not address these factors using the PSM. After PSM, the variables of age, sex, pT and pN stage, tumor location, and differentiation grade did not significantly differ between the two groups. In terms of short-term outcomes, operation duration and blood loss are reportedly associated with postoperative complications, especially pulmonary infection [20]. In this study, we observed that the duration of the operation was significantly shorter, intraoperative blood loss was relatively lower, and the number of retrieved nodes was greater in Group 2 than in Group 1. However, major postoperative complications did not significantly differ between the two groups. We believe that good visualization of the surgical field and precise surgical technique during laparoscopic surgery better ensures hemostasis, contributes to a reduction in blood loss, and enables retrieval of more lymph nodes than laparotomy.

In terms of long-term survival, the 5-year DFS was 42.6% and 59.4% ($p = 0.048$) and 5-year DSS was 42.1% and 60.0% ($p = 0.041$) for Groups 1 and 2, respectively. Thus, patients who underwent cTLE had significantly greater DFS and DSS than those who underwent hTE. These findings agree with the results of other reports in that the number of retrieved nodes is an independent prognostic factor for survival [21, 22].

Univariate and multivariate Cox proportional hazard regression analysis determined the pN and pT stages and the differentiation grade are independent prognostic factors for long-term survival. These findings agree with the results of the previous studies [15, 23, 24]. The HR was significant when we compared surgical approaches, suggesting that cTLE is associated with a better DSS, probably because more lymph nodes were retrieved by cTLE than by hTE, and many studies have found that the extent of lymph node involvement, including more positive or negative lymph nodes, is one of the most important prognostic factors [25–28]. However, we must acknowledge that hTE, which was performed by experienced surgeons who are particularly adept in laparotomy, could retrieve the appropriate lymph nodes during the laparoscopy, which resulted in oncology outcomes similar to the cTLE results [29], and thus may have no need to transition to cTLE.

The present study has a number of limitations. First, it is a relatively small single institution study compared to global collaborative esophageal cancer databases. Second, MIE is an advanced technique with a long learning curve [30, 31]; thus, the experience of the surgeon can affect postoperative outcomes [32]. Third, our single surgical team began to perform cTLE in 2011, which was after we started to perform hTE. This may have affected the number of retrieved lymph nodes. However, our surgical team had reached a plateau in their learning curve for MIE rapidly, as previously described [30]. Fourth, our departmental database and the follow-up system are well constructed. The surgical techniques, pathologic evaluation, and patient follow-up were thus highly consistent during the whole evaluation. These factors may have moderated the bias between the two groups to some extent.

In conclusion, this propensity-matched analysis demonstrated that cTLE is possibly a more effective surgical procedure than hTE with regard to postoperative and oncologic outcomes. A prospective, randomized clinical trial and longer follow-up are warranted to validate our findings.

Compliance with ethical standards

Conflicts of interest The authors declared that they have no conflict of interest.

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