

Short-term outcomes of robotic radical esophagectomy for esophageal cancer by a nontransthoracic approach compared with conventional transthoracic surgery

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SUMMARY. Transthoracic esophagectomy (TTE) is believed to have advantages for mediastinal lymphadenectomy in the treatment of resectable esophageal cancer despite its association with a greater incidence of pulmonary complications and postoperative mortality. Transhiatal esophagectomy is regarded as less invasive, though insufficient in terms of lymph node dissection. With the aim of achieving lymph dissection equivalent to that of TTE, we have developed a nontransthoracic esophagectomy (NTTE) procedure combining a video-assisted cervical approach for the upper mediastinum and a robot-assisted transhiatal approach for the middle and lower mediastinum. We prospectively studied 22 accumulated cases of NTTE and verified feasibility by analyzing perioperative and histopathological outcomes. We compared this group's short-term outcomes with outcomes of 139 equivalent esophageal cancer cases operated on at our institution by conventional TTE (TTE group). In the NTTE group, there were no procedure-related events and no midway conversions to the conventional surgery; the mean operation time was longer (median, 524 vs. 428 minutes); estimated blood loss did not differ significantly between the two groups (median, 385 mL vs. 490 mL); in the NTTE group, the postoperative hospital stay was shorter (median, 18 days vs. 24 days). No postoperative pneumonia occurred in the NTTE group. The frequencies of other major postoperative complications did not differ significantly, nor were there differences in the numbers of harvested mediastinal lymph nodes (median, 30 vs. 29) or in other histopathology findings. NTTE offers a new radical procedure for resection of esophageal cancer combining a cervical video-assisted approach and a transhiatal robotic approach. Although further accumulation of surgical cases is needed to corroborate these results, NTTE promises better prevention of pulmonary complications in the management of esophageal cancer.

KEY WORDS: esophageal cancer, lymphadenectomy, minimally invasive esophagectomy, robot-assisted surgery, transhiatal esophagectomy.

INTRODUCTION

Whether a transthoracic or a transhiatal approach is better in esophageal cancer surgery is debated. Transthoracic esophagectomy (TTE) offers sufficient mediastinal lymph node (LN) clearance but is associated with such thoracotomy-related adverse events as postoperative pneumonia and empyema.^{1–5} Transhiatal esophagectomy reduces these complications and operative mortality,⁶ but compromises mediastinal LN dissection due to poorer access to the mediastinal surgical field.^{7,8} Recently, Kutup *et al.* asked whether the benefits of transthoracic media-

stinal lymphadenectomy outweighed the increased operative morbidity; their study concluded that TTE was beneficial for cT3, pT3, and node-positive patients.⁹ Another large international study has also shown that the number of dissected LNs was an independent predictor of survival after esophagectomy for cancer.¹⁰ Whether or not the benefits of TTE are disputable, the transthoracic approach to extended mediastinal dissection is indisputably more likely to achieve extended LN dissection.

Access to the mediastinal field via a transhiatal approach has been improved, however, by both robot-assisted and video-assisted surgery. Robot-assisted surgery is now widely used; its utility is most apparent in such narrow operative fields as the pelvic cavity or the mediastinum, where conventional laparoscopic or thoracoscopic manipulations are subject

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to severe restrictions. Robot-assisted transhiatal esophagectomy is reportedly feasible for transhiatal mediastinal LN dissection.^{11,12} Video-assisted transcervical dissection of the upper mediastinal LNs, which are distant from the hiatus, is another example of a nontransthoracic approach.^{13,14}

The combination of transhiatal robotic manipulation and a video-assisted transcervical procedure makes nontransthoracic esophagectomy (NTTE) potentially as radical as and equivalent to TTE. We have developed this combined surgery technique with the aim of achieving mediastinal lymphadenectomy outcomes equivalent to those of TTE, and to establish its feasibility, we conducted a study of this NTTE for the first time in a prospective cohort of patients. Here, we demonstrate the short-term outcomes of this NTTE.

MATERIALS AND METHODS

Patients

From November 2012 to July 2014, 22 patients underwent NTTE at The University of Tokyo Hospital. Because we intended with this study to confirm the feasibility, safety, and effectiveness of NTTE, we excluded patients with disease possibly invading adjacent organs or fibrous changes caused by previous neoadjuvant therapies. The indications by were (i) written informed consent to undergo robot-assisted surgery without receiving financial support from the national health insurance system, (ii) histologically proven esophageal cancer, (iii) sufficiently good general condition to tolerate conventional open esophagectomy, and (iv) a tumor clinically staged T1-3 N0-1 M0 according to the 6th edition of the American Joint Committee on Cancer tumor-node-metastasis (TNM) classification. The exclusion criteria were (i) locally advanced cancer with suspicion of invasion to adjacent organs, (ii) prior chemotherapy or radiotherapy to the operative field, and (iii) patient age over 80 years.

We compared short-term outcomes in the NTTE series (NTTE group) with outcomes in transthoracic esophagectomies (the control TTE group), which consisted of a series of 139 patients operated on by the same surgical team at our institution from May 2008 to July 2014 using a standard TTE technique (McKeown's or Ivor-Lewis esophagectomy); these patients were selected according to inclusion and exclusion criteria identical to those of the NTTE group with the exception of the informed consent form. The institutional review board of The University of Tokyo Hospital had approved this study.

Surgical method

NTTE was performed in three stages, all with the patient in the supine position. In the first stage, LN dissections in the cervical and abdominal fields were performed simultaneously by two surgical teams. In the second, the robotic surgical device, da Vinci S (Intuitive Surgical, Sunnyvale, CA, USA), was brought in to perform the transhiatal robotic procedure; upon completion of the mediastinal dissection, the da Vinci S robotic system was moved away from the surgical field. The last stage included harvesting of surgical specimens, reconstruction with a gastric tube conduit, and cervical anastomosis.

The cervical procedure was performed via a collar incision under mediastinoscopic guidance. The abdominal procedure and the mediastinal robotic procedure were performed using a laparoscopic approach. Figure 1a,b show, respectively, the operative fields as viewed using the endoscope inserted via the cervical wound and using the da Vinci S system camera. The robotic mediastinal dissection provided excellent visualization of the middle mediastinal lymph stations including such features as the pulmonary ligament LN, the main bronchus LN, and the subcarinal LN. Figure 2 illustrates which mediastinal LN stations are to be dissected during the cervical, robotic mediastinal, and abdominal procedures. During the lymphadenectomy, LNs and surrounding

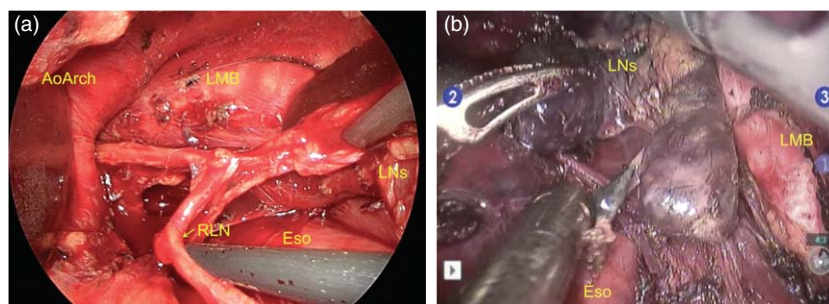


Fig. 1 (a) Lymph nodes (LNs) along the left recurrent laryngeal nerve (RLN) are being dissected en bloc with the esophagus (Eso), exposing the left main bronchus (LMB) and the aortic arch (AoArch). (b) An inverted V-shaped cluster of LNs is dissected en bloc with the Eso from the LMB. The cluster includes the bilateral main bronchus LNs and subcarinal LNs and forms a V shape molded by the bronchi.

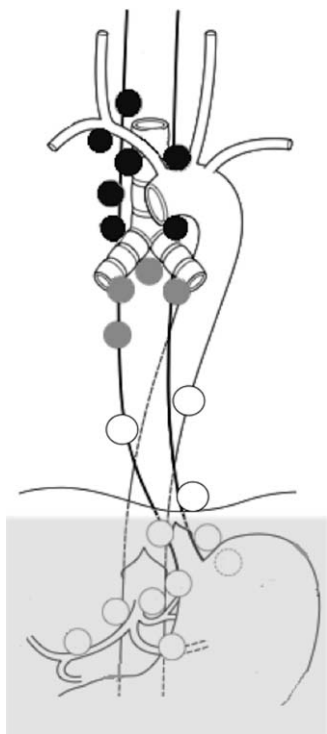


Fig. 2 Fields of lymphadenectomy by nontransthoracic esophagectomy. Black, gray, and white circles represent lymph nodes to be retrieved by the cervical, transhiatal robotic, and abdominal procedures, respectively. Nodes within the gray tone area were not considered to be mediastinal lymph nodes. This illustration is a modification of figures 1–4 in the Japanese Classification of Esophageal Cancer 10th Edition.

adipose fat were dissected together with the esophagus from the bilateral mediastinal pleura. The robotic middle mediastinal dissection has been described in our previous report.¹⁵

Short-term surgical outcomes and their evaluation

The main purpose of this study was the comparison of LN retrieval rates using robot-assisted NTTE with conventional TTE. Additional outcomes analyzed in this study included estimated blood loss, operation time, occurrence of procedure-related complications,

frequency of postoperative morbidity, length of postoperative hospital stay, and histopathological features. JMP 11.0 (SAS Institute Inc. Cary, NC.) was used for statistical analysis. Wilcoxon's rank-sum test was used for the analysis of group differences and Fisher's exact test was used for the proportional differences.

Definition of postoperative complications

Postoperative complications were categorized using a modified Clavien-Dindo classification.¹⁶ The diagnosis of postoperative pneumonia was made in accordance with the Japanese Respiratory Society's Guidelines for Hospital Acquired Pneumonia in Adults.¹⁷ This diagnosis was contingent on the presence of pulmonary infiltrates in the standard chest radiography and at least two of the three criteria (i) pyrexia (>38.0 degrees), (ii) leukocytosis (>12 000/mm³) or leukocytopenia (<4000/mm³), and (iii) purulent airway exudates.

Category of LN station

Mediastinal LNs were defined as the regional LNs located caudal to the lower aspect of the thyroid gland and cranial to the hiatus. Supraclavicular nodes were not included in the harvested LN count. The upper, middle, and lower mediastinal stations were generally identical to the three groups shown in Figure 2. The borderlines of the upper-middle and the middle-lower stations were the bronchial bifurcation and the left pulmonary vein, respectively.

RESULTS

The clinicopathological characteristics of the two groups are shown in Table 1. No significant differences were observed between the two groups, although advanced disease accounted for a larger proportion of the TTE group. None of the 22 patients experienced procedure-related events or conversions

Table 1 Clinicopathological characteristics

	NTTE (n = 22)	TTE (n = 139)	P-value
Median age (range)	64 (46–79)	64 (39–80)	0.652
Gender (M/F)	20/2	106/33	0.166
Median BMI (range)	21.4 (12.8–31.4)	22.5 (18.4–26.7)	0.146
Histological type			
SCC/AC/Other	20/0/2	122/10/7	0.345
Location, TN factors			
Proximal/Middle/Distal/EGJ	2/10/9/1	16/60/47/16	0.863
cT (1/2/3)	12/5/5	52/25/62	0.128
cN (0/1)	12/10	69/70	0.819

AC, adenocarcinoma; BMI, body mass index; cN, clinical nodal status; cT, clinical tumor depth; EGJ, esophagogastric junction; NTTE, nontransthoracic esophagectomy; SCC, squamous cell carcinoma; TN factors, American Joint Committee on Cancer Tumor Node Metastasis Classification, 7th Edition; TTE, transthoracic esophagectomy.

Table 2 Short-term outcomes

	NTTE (n = 22)	TTE (n = 139)	P-value*
	Median (Range)		
Operation			
Duration of operation (minutes)	524 (445–724)	428 (250–786)	<0.0001
Blood loss (mL)	385 (30–890)	490 (20–2830)	0.117
Postoperative course			
Hospital stay (days)	18 (11–41)	24 (13–204)	0.0013
	Number of cases (%)		P value**
Morbidity			
Pneumonia	0 (0)	20 (14)	0.078
Anastomotic leakage	4 (18)	13 (9.4)	0.256
Empyema	0 (0)	7 (5.0)	0.595
Ventilator dependency	0 (0)	11 (7.9)	0.364
RLN palsy	1 (4.5)	12 (8.6)	1.000
Small bowel obstruction	1 (4.5)	1 (0.7)	0.132
Chylothorax	1 (4.5)	3 (2.2)	0.448
In-hospital mortality	0 (0)	2 (1.4)	0.571

*Wilcoxon rank sum test, **Fisher's exact test. NTTE, nontransthoracic esophagectomy; RLN, recurrent laryngeal nerve; TTE, transthoracic esophagectomy.

to the conventional operation. Twenty patients were extubated in the operating room; two patients were not immediately extubated because of delayed recovery from general anesthesia or vocal cord paralysis. Table 2 shows the perioperative outcomes of NTTE and TTE with frequencies of the postoperative complications categorized as grade II or more by the Clavien-Dindo classification.

The operation time was significantly extended and anastomotic leakage was more frequent (though not significantly) in the NTTE group (18%) than in the TTE group (9.4%). In the TTE group, 23 patients underwent cervical anastomosis and 116 patients intrathoracic anastomosis. Fifteen among the 23 underwent the same retromediastinal gastric conduit reconstruction as the NTTE group; the remaining eight underwent either subcutaneous or retrosternal reconstruction. Four (27%) of the 15 patients who underwent retromediastinal gastric conduit reconstruction developed an anastomotic leakage, compared with only five (4.3%) of the 116 patients who

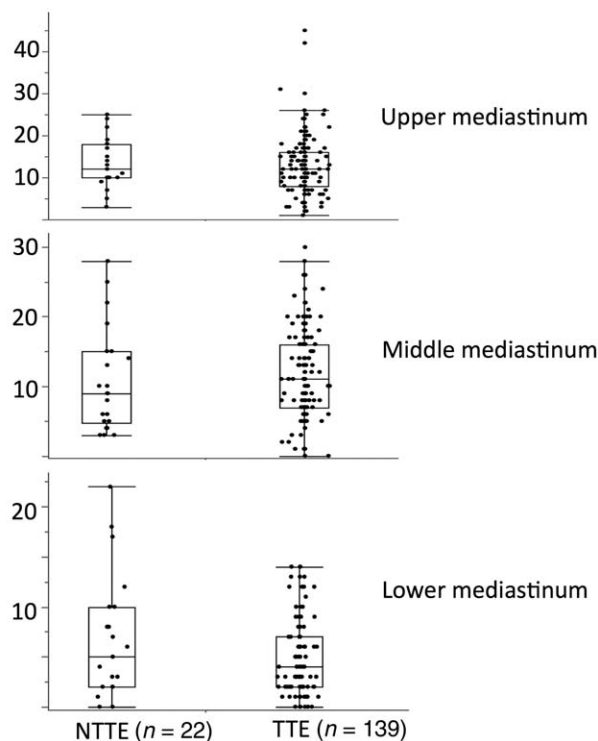


Fig. 3 Box-and-whisker plot of the lymph node yield (numbers) by the two approaches. The distributions of the lymph node yield by the two approaches were quite similar to each other in the three loci of the mediastinum.

underwent intrathoracic anastomosis. Postoperative pneumonia, ventilator dependency, empyema, and other postoperative life-threatening events were not observed in the NTTE group. Postoperative hospital stays were shorter in the NTTE group than in the TTE group.

The histopathological features of the surgery are summarized in Table 3. The comparison between the NTTE and the TTE groups showed no significant differences in the TNM category, the R category, or the frequency of nodal metastasis in each station.

The numbers of LNs retrieved from each locus of the mediastinal lymph stations are plotted in Figure 3. The median numbers of the retrieved LNs from the mediastinal stations were 30 (NTTE) versus 29 (TTE) (12 vs. 12, 9 vs. 11, and 5 vs. 4 in the upper,

Table 3 Pathology findings

	NTTE (n = 22)	TTE (n = 139)	P-value*
TNM			
T category	1/2/3/4	16/2/4/0	0.22
N category	0/1	12/10	0.650
Nodal metastasis			
Upper mediastinum	Yes/No	4/18	0.441
Middle mediastinum	Yes/No	1/21	0.314
Lower mediastinum	Yes/No	1/21	1.000
R category	0/1	21/1	0.592

*Fisher's exact test. N, node; NTTE, nontransthoracic esophagectomy; R, resection; T, tumor; TTE, transthoracic esophagectomy.

middle, and lower mediastinum, respectively). There was no significant difference between the NTTE and TTE groups in such histopathological features as the number of retrieved mediastinal LNs.

DISCUSSION

In the history of esophageal cancer treatment, achieving an optimal balance between radicality on the one hand and reduction of postoperative pulmonary complications with quality of life improvement on the other has presented a dilemma that we sought to overcome by developing NTTE. In this study, an equivalent number of LNs were retrieved from each level of the mediastinal lymph stations in comparison with the historical control group, although survival analyses of the long-term outcomes will be needed to confirm oncological equivalence. The number of retrieved mediastinal nodes by NTTE was comparable to the numbers reported (from 23 to 33) in literature on TTE.^{18–21}

In our series of patients, no reduction was observed in the operation time or in the blood loss. Prolongation of operation time has been reported in robotic surgeries and, together with high running costs, is considered a disadvantage of the robotic approach.^{22,23} However, no postoperative respiratory complications have been observed in the current series of patients, and there were no severe postoperative events requiring intensive care. In addition, the median hospital stay of 18 days was shorter than the median length reported in Japan (22 to 35 days).^{24–26} Although these advantages may reflect the small proportion of advanced disease in the NTTE group, the extent of lymph dissection was clearly not compromised in the NTTE group, given that LN retrievals were virtually identical (30 [NTTE] vs. 29 [TTE]) in both groups. If these findings are replicated with a larger population of patients, the low incidence of pulmonary complications and shorter hospital stays observed in the NTTE group in this study will outweigh the disadvantages (prolongation of operation time, cost, etc.) of using the robotic device. The length of hospital stay is longer in Japanese studies reflecting differences between Japanese and Western cultures and medical systems. Therefore, the advantages of the shorter hospital stays found in this Japanese study might not be universally generalizable and will require verification in Western settings. Another potential discrepancy stems from differences in body mass index (BMI): the participants in this study were all Japanese, whose median BMI is approximately 22.5. The perioperative data, such as estimated blood loss or operation time, and the complication rate should be re-validated with Western patients to better establish NTTE's feasibility.

In the NTTE group, estimated blood loss was not decreased and anastomotic leakage was more frequent. However, with better understanding of the mediastinal structures viewed transhiatally, the blood loss was decreased (to median 260 mL) in the 10 most recent cases (data not shown). The increased anastomotic leakage might be attributable to the cervical anastomosis, as the anastomotic site is, on average, more distant from the feeding vessels of the gastric conduit, as reported in previous studies comparing transhiatal esophagectomy and TTE.^{27,28} In our current study, the anastomotic leakage was highest among the subgroup of TTE patients who underwent cervical anastomosis. Leakage of intrathoracic anastomosis often results in empyema with occasionally life-threatening consequences, but did not in our series of patients, in whom none of these anastomotic failures led to lethal complications or required surgical interventions.

In this study, both the NTTE and the TTE groups' histopathological findings showed that the upper station was the most frequent site of mediastinal LN metastases. A majority of surgeries in the previous radical esophagectomy for esophageal squamous cell carcinoma series included upper mediastinal dissection.^{18,19,21,29–31} Therefore, without transcervical upper mediastinal dissection, NTTE that is oncologically equivalent to TTE is not feasible.

Conventional minimally invasive esophagectomy (MIE) has been reported to reduce mortality and morbidity^{18,19}; however, a recent report on the Japanese national database revealed that MIE prolongs operation times and increases the rate of surgical complications.³² Notably, this study also reported that postoperative pneumonia was not decreased in MIE (15.0% in MIE vs. 15.4% in open esophagectomy). Meanwhile, in our current study, the occurrence of postoperative pneumonia was decreased in the NTTE group with a statistically marginal difference (0% in NTTE vs. 14% in TTE). Although our current findings did not attain statistical significance due to the small number of cases, they nonetheless showed that the nontransthoracic approach is feasible and may help to prevent postoperative pulmonary complications. Further accumulation of NTTE cases should be continued to conclusively establish the method's perioperative safety and confirm the reduction in pulmonary complications; we are confident that the nontransthoracic approach is at least equivalent to the conventional transthoracic approach in obtaining sufficient surgical control over the mediastinal lymph stations.

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