

In contrast, Gros et al. [18, 19] established an orthotopic esophageal cancer mouse model using a highly aggressive esophageal cancer cell line in the same way as ours, in which they detected metastatic spread to the liver and lungs as well as to the lymph nodes using high resolution imaging with GFP and by MRI while we were not able to detect metastases to the liver or other organs by luciferase imaging in our study. These reports from Quatromoni et al. and Gros et al., including our study, suggest that the orthotopic esophageal cancer model established at the gastroesophageal junction and its establishment method is universal and reproductive, and that this model can cause tumor progression, which is close to actual clinical practice, such as metastases to the lymph nodes, the peritoneum and the liver or other organs in addition to local tumor growth.

Unlike subcutaneous models, it is difficult to accurately analyze tumor progression in orthotopic tumor models. Although survival rate and body weight are commonly used as evaluation methods in orthotopic studies, these parameters do not directly reflect therapeutic efficacy because many other factors also influence the results. The use of tumor cells marked with luciferase reporter gene and bioluminescent imaging, which is currently a well-used method in research field, allows us to monitor tumor growth non-invasively in vivo, especially in deep tissues [13]. Therefore, we originally established TE8-Luc cells that were stably-transfected with the firefly luciferase gene and used for non-invasive monitoring.

In our study, using the IVIS imaging system, the luminescent intensity of photons emitted from TE8-Luc subcutaneous tumors strongly correlated with tumor growth. Based on this fact, it is therefore likely that an increase in luminescent intensity in an orthotopic model over time accurately reflects tumor progression. Indeed, in a previous study in which we quantitatively monitored therapeutic efficacy in this orthotopic model using the IVIS imaging system, the change in luminescent intensity did appear to accurately reflect therapeutic efficacy [20]. Therefore, the method that we describe in the present study for establishment of an orthotopic esophageal cancer model in mice and for non-invasive monitoring with the IVIS imaging system is a very useful and practicable method, and is expected to contribute to the development of novel therapeutic technologies for esophageal cancer.

## Supporting Information

**Movie S1. How to make an orthotopic esophageal cancer mouse model.**  
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## Author Contributions

Conceived and designed the experiments: S. Kuroda HT MN S. Kagawa TF. Performed the experiments: S. Kuroda. Analyzed the data: S. Kuroda TK KA S. Kikuchi. Wrote the paper: S. Kuroda.

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## Assistant-Based Standardization of Prone Position Thoracoscopic Esophagectomy

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Thoracoscopic esophagectomy in the prone position (TEPP) might enable solo-surgery in cases requiring resection of the esophagus and the surrounding lymph nodes due to the associated advantages of good exposure of the surgical field and ergonomic considerations for the surgeon. However, no one approach can be for all patients requiring extensive lymphadenectomy. We recently developed an assistant-based procedure to standardize exposure of the surgical field. Patients were divided into 1 of 2 groups: a pre-standardization group (n = 37) and a post-standardization group (n = 28). The thoracoscopic operative time was significantly shorter ( $p = 0.0037$ ) in the post-standardization group (n = 28;  $267 \pm 31$  min) than in the pre-standardization group (n = 37;  $301 \pm 53$  min). Further, learning curve analysis using the moving average method showed stabilization of the thoracoscopic operative time after the standardization. No significant differences were found in the number of mediastinal lymph nodes dissected or intraoperative blood loss between the 2 groups. There were also no significant differences in the complication rate. Assistant-based surgery and standardization of the procedure resulted in a well-exposed and safe surgical field. TEPP decreased the operative time, even in patients requiring extensive lymphadenectomy.

**Key words:** thoracoscopic esophagectomy, prone position, standardization

Thoracoscopic esophagectomy in the prone position (TEPP) was first reported by Cuschieri *et al.* [1] in 1994 and has gradually grown in popularity. Several reports have described the tolerability and efficacy of this procedure [2-4]. Planivelu *et al.* [5] conducted a study of 130 patients and reported that TEPP resulted in a decreased operative time and a decreased frequency of respiratory complications when compared with other techniques of minimally invasive esophagectomy and open esophagectomy, mainly due

to the associated advantages of good exposure of the surgical field and improved ergonomics for the surgeon. Other reports have described that TEPP permits solo-surgery for resection of the esophagus after isolation from the surrounding organs, regardless of the skill of the assistant [4-8].

In Japan, thoracoscopic esophagectomy is conventionally performed in the left lateral decubitus position. Some studies have reported that the traditional Japanese technique of precise mediastinal lymph node dissection is equally or more effective than open surgery via thoracotomy, with an added advantage of a low respiratory complication rate [9, 10]. Several recent studies have also described the advantages of

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mediastinal lymph node dissection using TEPP [3, 4, 6, 11–13]. However, performing extensive and precise dissection consistently (as conducted in Japan), irrespective of the body type of the patient, can be difficult for a single surgeon. This is because the boundaries of the surgical field are limited when a single surgeon is involved. Therefore, we hypothesized that exposure of the surgical field by an assistant is necessary to achieve optimal outcomes for patients undergoing this procedure.

Teaching and university hospitals are increasingly moving towards: (1) decreased dependency on single expert surgeons, (2) increased recruitment of young surgeons who can function as assistants, and (3) development of defined safety measures that can apply to all members of the team, even staff working under short-term contracts who are not otherwise familiar with the facility. In this regard, standardization of procedures involving surgical assistants is important and necessary.

The purpose of this study was to establish and evaluate our new standardized procedure for performing thoracoscopic esophagectomy with patients in the prone position, with particular reference to the work of the surgical assistants.

## Materials and Methods

**Patients.** Thoracoscopic esophagectomy was performed for 65 patients (62 males, 3 females) in the prone position at our facility from June 2011 to September 2012. This group comprised 75.6% of the 86 patients with thoracic esophageal carcinoma who underwent resection at our facility during this time period. The preoperative diagnosis was squamous cell carcinoma in 61 patients, adenocarcinoma in 2 patients, and mixed squamous cell carcinoma combined with neuroendocrine tumor in 2 patients. No patient had a prior history of thoracic surgery. Preoperative adjuvant chemotherapy was administered to 45 patients, and 3 patients underwent salvage surgery following radical chemoradiotherapy. The inclusion criteria for the study were as follows: no pleural adhesions, no T4 or M1 cancer, and no serious impairment in circulatory, respiratory, or liver function. Patients were divided into 1 of 2 groups: a pre-standardization group ( $n=37$ ) that underwent surgery before April 2012 and a post-standardization group ( $n=28$ ) that underwent surgery after April 2012. Clinical out-

comes were compared between these 2 groups.

**Operative procedure.** The patient was immobilized in the prone position after endotracheal intubation using a single-lumen endotracheal tube and a bronchial blocker. The surgeon stood on the right of the patient. A 12-mm port was placed at the 9th intercostal space (ICS) at the inferior scapular line, and a thoracoscope was inserted at a 30-degree angle. In addition, a 12-mm port for the assistant was placed at the 3rd ICS at the mid-axillary line, while another 12-mm port for the right hand of the surgeon was placed at the 5th ICS at the posterior axillary line. A 5-mm port for the left hand of the surgeon was also placed at the 7th ICS at the posterior axillary line. Before procedure standardization (*i.e.*, through March 2012), the procedure was conducted with 4 ports. After procedure standardization (from April 2012), an additional 12-mm port for the assistant was placed at the 8th ICS between the mid-axillary line and the posterior axillary line (Fig. 1). A 6-mmHg artificial pneumothorax was induced using left one-lung ventilation and carbon dioxide (CO<sub>2</sub>).

The surgical procedure was also standardized with the goal of obtaining a well-exposed surgical field. The standardized procedure is as follows. The surgeon mainly uses the 5th and 7th ICS ports, while the assistant uses the 3rd or 8th port. Exposure of the surgical field by the assistant is important to facilitate the procedure. For middle and lower mediastinal surgeries, the surgical field is exposed, with exclusion of the diaphragm or pericardium, by manipulation using thoraco-cotton (Wyeth Lederle, Tokyo, Japan) from the 8th ICS by the assistant prior to esophageal transection in the initial phase of the surgery (Fig. 2A). Following esophageal transection using autosutures, the pericardium is excluded using thoraco-cotton from the 3rd ICS port while the assistant pulls the esophagus caudally with forceps from the 8th ICS port (2 assistants may be needed at times; Fig. 2B). At this point, it is essential that the contralateral pleura develops into a trapezoid shape in order to prevent the procedure from converting into a left thoracotomy. As the esophageal hiatus is caudally approached by dissection and isolation of the esophagus, the diaphragm is excluded with thoraco-cotton from the 8th ICS port while the assistant pulls the esophagus cranially with forceps from the 3rd ICS port (Fig. 2C). This readily allows for accurate dis-

section of the lymph nodes above the diaphragm. In our cases, exposure with thoraco-cotton or forceps from the 3rd ICS port is also useful while operating on the superior mediastinum, even in patients requir-

ing dissection along both sides of the recurrent laryngeal nerve, and in the subcarinal area (Fig. 2D, E and Fig. 3).

*Description and statistical analysis.* Clini-

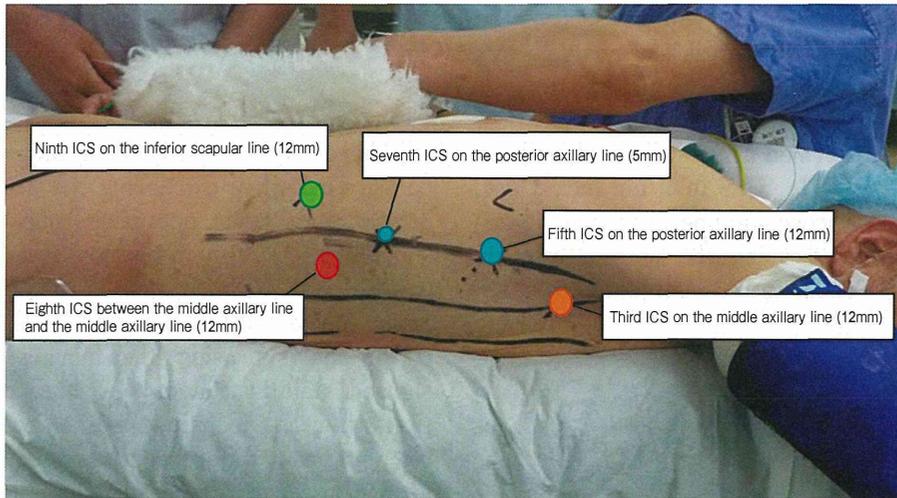


Fig. 1 Port insertion point. Green indicates the camera point, blue the surgeon, orange and red the assistant. The port at the 8th intercostal space was added from April 2012. ICS, intercostal space.

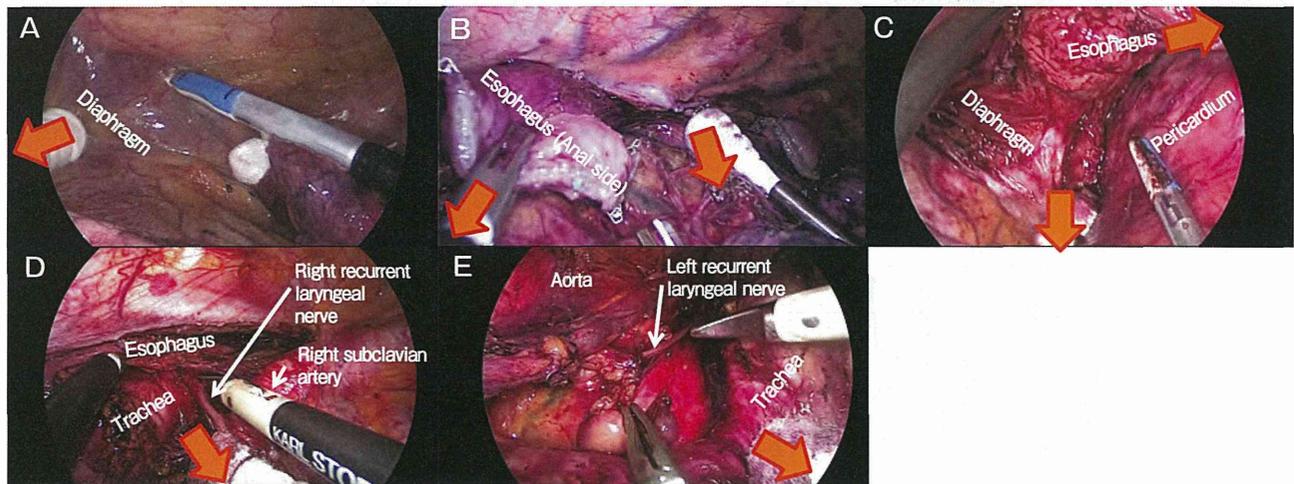


Fig. 2 Exposure of the surgical field by the assistant in thoracoscopic esophagectomy in the prone position. **A**) In the initial stage of the middle and lower mediastinal procedures, the assistant expands the visual field by excluding the diaphragm by pulling it caudally using thoraco-cotton inserted from the port at the 8th intercostal space (ICS). **B**) After esophageal transection, the assistant expands the visual field by excluding the pericardium and right main bronchus by pulling them with thoraco-cotton inserted from the port at the 3rd ICS and by pulling the esophagus caudally on the anal side using forceps inserted from the port at the 8th ICS. **C**) During surgery around the esophageal hiatus, the assistant expands the visual field by pulling the diaphragm ventrally with thoraco-cotton inserted from the port at the 8th ICS and by pulling the esophagus cranially with forceps inserted from the port at the 3rd ICS. **D**) During lymph node dissection around the right recurrent laryngeal nerve, the assistant expands the visual field by rolling the right subclavian artery cranially with thoraco-cotton inserted from the port at the 3rd ICS. **E**) During lymph node dissection around the left recurrent laryngeal nerve, the assistant expands the visual field by rolling the trachea to the right-hand side with thoraco-cotton inserted from the port at the 3rd ICS.

copathological factors were noted as per the 10th edition of the General Rules for Esophageal Cancer [14] and the Union for International Cancer Control (UICC) Tumor Nodes Metastasis (TNM) Classification of Malignant Tumors, 7th edition [15]. Postoperative complications were categorized as per the Clavien-Dindo classification [16]. Data are expressed as the mean  $\pm$  standard deviation. Statistical analysis was conducted using Student's *t*-test, the Chi-square test, or Fisher's exact test to suit the category in question. All analyses were performed using statistical analysis software (JMP version 11; SAS Institute Inc., Cary, NC, USA). The thoracoscopic operative time learning curve was analyzed using the moving average method [17, 18]. Trends in thoracoscopic operative



Fig. 3 Thoracoscopic view after completing lymphadenectomy along both sides of the recurrent laryngeal nerve.

times may be unclear based on changes in individual cases. With the moving average method, using the mean thoracoscopic operative times, the individual changes are removed, and the trends are clarified. In addition, as new data are added, by shifting the mean values, the changes in thoracoscopic operative times are smoothed. A 5-cases moving average was used.

## Results

There were no significant differences in patient background when comparing the 2 groups (Table 1). The thoracoscopic operative time was significantly shorter ( $p = 0.0037$ ) in the post-standardization group ( $n = 28$ ;  $267 \pm 31$  min) than in the pre-standardization group ( $n = 37$ ;  $301 \pm 53$  min) (Table 2). The learning curve analysis using the moving average method showed stabilization of the thoracoscopic operative time after the technique was standardized (Fig. 4). No significant differences were found between the 2 groups in terms of the number of mediastinal lymph nodes dissected or the amount of intraoperative blood loss. None of the patients in either group required conversion to thoracotomy (Table 2). There were no significant differences in the overall complication rate or incidence of respiratory complications or recurrent nerve palsy when comparing the 2 groups (Table 3). However, 1 patient developed chylothorax in the pre-standardization group. There were no mortalities in either group.

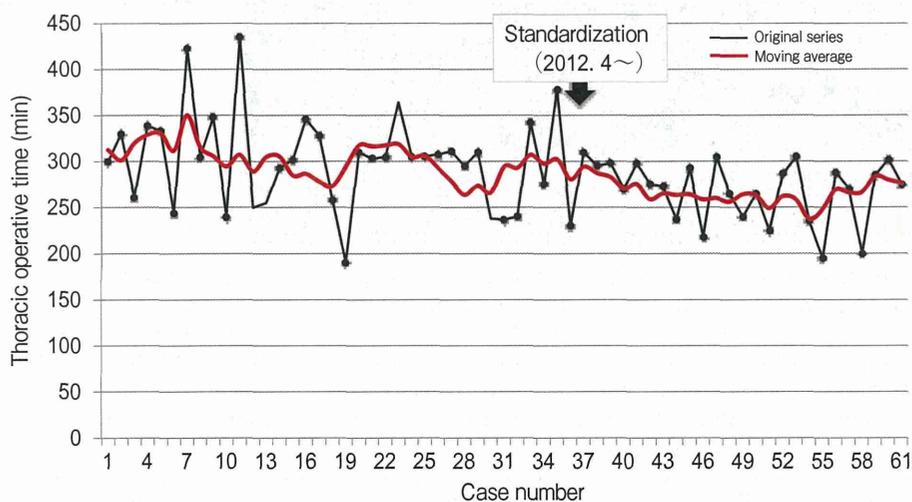


Fig. 4 The moving average method was used to determine changes in thoracoscopic operative time.

Table 1 Clinical characteristics (n=65)

		Pre-standardization group (n = 37)	Post-standardization group (n = 28)	P-value
Age (years)		67.3 ± 1.3	64.5 ± 1.6	0.188
Gender	Male	35	27	0.75
	Female	2	1	
Location	Upper	7	4	0.667
	Middle	17	16	
	Lower	13	8	
Histology	SCC	34	27	0.451
	Adeno	1	1	
	NET	2	0	
pTNM Stage	Stage 0	6	3	0.883
	Stage I	8	7	
	Stage II	13	10	
	Stage III	9	6	
	Stage IV	1	2	
Administration of neoadjuvant chemotherapy		24	21	0.381

NET, neuroendocrine tumor.

Table 2 Clinical outcomes of thoracoscopic esophagectomy in the prone position

	Pre-standardization group (n = 37)	Post-standardization group (n = 28)	P-value
Conversion to thoracotomy	0	0	1.000
Thoracic operative time (min)	301 ± 53	267 ± 31	0.004
Estimated blood loss (g)	184 ± 190	171 ± 129	0.757
Number of dissected mediastinal lymph nodes	33.9 ± 12.1	33.6 ± 12.6	0.911

Table 3 Complications after thoracoscopic esophagectomy in the prone position

	Pre-standardization group (n = 37)	Post-standardization group (n = 28)	P-value
Morbidity	5	3	0.734
Pneumonia (Grade IIIa-IVa)	0	0	1.000
Recurrent laryngeal nerve palsy (Grade I-II)	4	3	0.878
Chylothorax (Grade IIIa-IIIb)	1	0	0.407
Operative mortality	0	0	1.000
Hospital mortality	0	0	1.000

Complications are described on the Clavien-Dindo classification [16].

## Discussion

Conventional open esophagectomy is a highly invasive procedure [19–21]. A key disadvantage of this procedure is the size of the incision involved in the thoracotomy, laparotomy and cervical incision. In fact,

some studies have reported that these factors are associated with systemic inflammatory response syndrome [22, 23]. The overall operative mortality after open esophagectomy is approximately 10%, and the rate of serious complications is also high [24]. Respiratory complications (*e.g.*, respiratory failure,

pneumonia) are the most common, and patients with these complications have a 20% rate of operative mortality [25].

Thoracoscopic esophagectomy was introduced as a minimally invasive option to minimize postoperative complications and operative mortality. Initially, thoracoscopic esophagectomy was performed in the left lateral decubitus position [9, 10, 26], and the survival benefits were the same as those seen in response to open procedures [3, 9, 10]. In addition, when the left lateral decubitus position was used during thoracoscopic surgery, the operative time was almost the same as when it was used during open surgery via thoracotomy [10]. However, a special team composed of 3 experts (*i.e.*, a surgeon, an assistant, and an endoscopist) is required to perform this procedure smoothly. Therefore, thoracoscopic esophagectomy has not been widely utilized.

In 1994, Cuschieri *et al.* [1] first described the use of TEPP in a series of 6 patients and reported that there were no differences in the postoperative course between these patients and 20 patients who underwent open surgery via thoracotomy in the left lateral decubitus position during the same period. The same investigators also suggested that the prone position was practically and physiologically superior to the left lateral decubitus position. In 2006, Planivelu *et al.* [5] described their experience with 130 patients undergoing TEPP and reported that this procedure was associated with a shorter operative time, excellent exposure of the surgical field, improved ergonomics for the surgeon, and a lower rate of respiratory complications.

Open or thoracoscopic procedures in the left lateral decubitus position have been performed in Japan over the previous decade. Some recent reports suggest that the prone position is advantageous for esophagectomy, as it is associated with an excellent surgical view [4, 6]. However, there have been no reports in Japan showing that TEPP is superior in terms of operative time over open surgery via thoracotomy or thoracoscopic surgery in the left lateral decubitus position. The thoracic operative time in the prone position might be decreased for dissections involving en-bloc resection of the esophagus and surrounding lymph nodes; however, while this procedure is widely performed in Western countries, it is quite different from the approach used in Japan. When

thorough dissection of the mediastinal lymph nodes (including those in the upper mediastinum) is undertaken as recommended in Japan, an average of approximately 5 h is required for patients in the prone position [4, 6]. Also, in this position the difficulty of mediastinal lymph node dissection differs according to the patient's body type. It is very difficult to constantly maintain an optimal surgical field without the use of an assistant, particularly in the case of a narrow space between vertebral bodies and the trachea in the superior mediastinum or in the case of a raised dome of the diaphragm in the inferior mediastinum. It is important to conduct thorough lymph node dissection at these sites, because these are common sites of lymph node metastases. To summarize, it is difficult to maintain a short thoracic operative time when using conventional methods, since it is difficult to achieve an optimal visual field and to perform extensive and precise mediastinal lymph node dissection.

Better exposure of the surgical field through the use of a surgical assistant during surgery may help to improve outcomes. In the present study, we used a protocol to standardize the assistant-based exposure of the surgical field by organizing the procedure in each section and by adding an assistant port in the 8th ICS. The standardization of this assisted procedure resulted in a significant decrease in thoracic operative time without compromising the quality of dissection. Standardization also resulted in a smaller variation in thoracic operative time. Furthermore, this protocol is playing an important role in the development of the next generation of surgeons at our institution and will likely lead to increased satisfaction by the assistants, since it allows them to actively participate in procedures. Finally, none of the patients in this study complained of increased postoperative pain related to the use of an additional port.

Despite standardization, the operative time tended to be longer with TEPP than that of open surgery via thoracotomy or thoracoscopic esophagectomy in the left lateral decubitus position. Further, the incidence of recurrent nerve palsy was also slightly higher with our procedure than with open surgery via thoracotomy [10], and most of these cases were unilateral left-sided palsies. Although we have generally avoided using energy devices during lymph node dissection at that site in order to avoid heat damage, the handling and traction of en block lymph nodes may be issues in

cases of palsy. With the greater visibility of the superior mediastinum in response to this assistant-based exposure, there may be a tendency to dissect up to the nerve, which might contribute to the higher incidence of nerve palsy. Recurrent nerve palsy is a cause of both aspiration and dysphagia and is a major factor contributing to decreased postoperative quality of life. Therefore, further studies are needed to determine how to reduce the incidence of this complication.

In conclusion, TEPP performed by a single surgeon is still technically difficult, mainly because a suboptimal surgical field can otherwise impede thorough dissection of the mediastinal lymph nodes and performance of esophagectomy. The present study demonstrated that assistant-based surgery with the addition of an assistant port and standardization of the procedures involved resulted in greater safety and better outcomes in TEPP.

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