Intraoperative nerve monitoring during minimally invasive esophagectomy and 3-field lymphadenectomy: Safety, efficacy and feasibility

Srinivas Kodaganur Gopinath
Tata Memorial Hospital, Homi Bhabha National Institute

Sabita Jiwnani (✉ sabitajiwnani@gmail.com)
Tata Memorial Hospital, Homi Bhabha National Institute

Parthiban Valiyuthan
Tata Memorial Hospital

Swapnil Parab
Tata Memorial Hospital

Devayani Niyogi
Tata Memorial Hospital, Homi Bhabha National Institute

Virendrakumar Tiwari
Tata Memorial Hospital, Homi Bhabha National Institute

CS Pramesh
Tata Memorial Hospital, Homi Bhabha National Institute

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Abstract

Purpose

To demonstrate the safety, efficacy and feasibility of intraoperative monitoring of the recurrent laryngeal nerves during thoracoscopic and robotic 3-field esophagectomies.

Methods

This is a retrospective analysis of our initial experience with intraoperative nerve monitoring during minimally invasive 3-field esophagectomies. Data were obtained from a prospectively maintained database and electronic medical records. To compare outcomes between IONM and non IONM group Fischer's exact test was used. All patients underwent a minimally invasive (VATS/Robotic) transthoracic esophagectomy with a neck anastomosis (McKeown procedure). Intraoperative nerve monitoring was carried out under general anesthesia with assisted ventilation and avoiding use of neuromuscular blockers during the period of nerve monitoring.

Results

24 patients underwent nerve monitoring during minimally invasive 3-field esophagectomy. 15 patients were operated thoraco-laparoscopically and 9 patients underwent a robotic-assisted procedure. 8/24 (33.3%) patients had vocal cord paresis in the immediate post op period. When we compared this to a historical cohort operated in the preceding 5 years in the same institution, we demonstrated a 26% reduction in nerve palsy rate (p-0.08). On follow-up, 6/8 patients reported returning to a normal voice.

Conclusions

Intra-operative neuro monitoring (IONM) is feasible during minimally invasive 3-field esophagectomy. Using this can potentially lead to a reduced rate of recurrent nerve palsies and a higher nodal yield.

Introduction/background

Esophagectomy remains an important component of curative intent therapy in esophageal cancer. The rate of lymph node metastases is close to 50% in national registries(1). While radical lymphadenectomy is an essential component of esophagectomy for cancer, the extent of lymphadenectomy remains controversial. A three-field lymphadenectomy involves lymph nodal dissection in the lower neck, mediastinum and upper abdomen. It also includes dissection of the lymph nodes along bilateral recurrent laryngeal nerves (RLN) in the mediastinum and neck. This procedure has been shown to improve survival in Japanese studies (2–4) but it has limited acceptance in the western world, although studies by Altorki et al and Lerut et al have demonstrated feasibility, acceptable morbidity and potentially improved survival(5,6). As total mediastinal and/or three-field esophagectomy involves dissecting the nerves around the recurrent laryngeal nerves, it is associated with significant rate of vocal cord paralysis ranging from 20 to 50%(3,4). Vocal cord paresis can result in hoarseness of voice, swallowing
dysfunction and aspiration pneumonia and may necessitate frequent bronchoscopy, tracheobronchial toileting and occasionally, tracheostomy(7).

Intra-operative nerve monitoring has been used by thyroid surgeons to identify and safeguard the recurrent nerves with mixed results(8) Recent studies have shown that the rate of vocal cord paresis can be reduced with the use of intra-operative nerve monitoring during esophageal surgeries even while utilizing the minimally invasive approach(9). This in turn can reduce the morbidity associated with extended lymphadenectomy during esophagectomy. However, esophageal surgeons have been reluctant to adopt intra-operative nerve monitoring due to the need for avoidance of muscle relaxants during surgery to aid nerve monitoring, limited evidence to demonstrate superiority of nerve monitoring in decreasing complications, lack of widespread availability of endotracheal tubes compatible with nerve monitoring, difficulties with using this technique during minimally invasive surgery, and likely prolongation of surgical duration(10)

Minimally invasive esophagectomy (MIE) is considered the current standard of care, as it reduces postoperative complications, mainly pulmonary(11,12). Both the robotic and thoracoscopic approaches have shown to reduce post esophagectomy pulmonary and overall morbidity(11–13). We conducted a study to demonstrate the safety, efficacy and feasibility of intra-operative nerve monitoring (IONM) during MIE.

**Methodology**

This study highlights our initial experience with intra-operative nerve monitoring during minimally invasive esophagectomy. Demographic characteristics, type of neoadjuvant therapy received, tumor characteristics, surgical and anesthesia details were recorded along with the feasibility of using intra-operative nerve monitoring during these procedures.

Indication for doing a three field esophagectomy were presence of clinic-radiologically enlarged, suspicious nodes on pre-operative imaging (CECT, PET scan) in the upper mediastinum or neck. Patients with a fixed vocal cord pre-operatively were not offered surgery as per our institutional protocol.

Technique of nerve monitoring during a MIE three-field Esophagectomy.

Anesthesia: General anesthesia with assisted ventilation with an endotracheal tube was used for all patients. A special endotracheal tube (NIM Contact Reinforced EMG endotracheal tube) designed by Medtronic (Medtronic Xomedä, Jacksonville, FL, USA) that carried the surface electrodes to record electromyographic (EMG) responses from the vocal cords, was used in all patients(Fig 1). Induction of anesthesia was performed using an intravenous injection of propofol (2 mg/kg) and fentanyl (2 microgram per kg). A single dose of an intermediate-acting neuromuscular blocker (injection Atracurium 0.5 mg/kg IBW) was administered to facilitate endotracheal intubation. The largest possible size of endotracheal tube was chosen to improve the contact of surface electrodes with the vocal cords. Also, whenever possible, a video-laryngoscope was used to confirm the position of the endotracheal tube by...
the anesthesiologist and the neurophysiologists. The endotracheal tube was so positioned that the area of surface electrodes was aligned at the level of the vocal cords. The endotracheal tube was fixed at the angle of the mouth to prevent any further change in the position of the tube.

Thereafter, the depth of anesthesia was maintained by using a combination of propofol infusion at 50 micrograms per kg per minute (to depress the laryngeal reflexes), and inhalational agents (oxygen-air-sevoflurane- at Minimum Alveolar Concentration less than 1.0). Intermittently, topical anesthesia was applied to the tracheal mucosa by the instillation of 4% lignocaine solution (2 ml aliquots) through the endotracheal tube. Muscle relaxation during the surgery was either avoided or used minimally so that at least 2 out of 4 train of Four (TOF) stimuli are present on the neuromuscular monitor, especially during the dissection around the recurrent laryngeal nerves. Lung isolation was achieved by using a Coopdechä Endobronchial Blocker (Daikin Medical Co. Ltd, Osaka, Japan) placed under the guidance of a pediatric bronchoscope.

For nerve monitoring, monopolar stimulation with either short (100mm) or longer (175mm length) ball-tip probe (Medtronic Xomedä, Jacksonville, FL, USA) was used. A current of 1.0 – 3.0 mA (supramaximal stimulation) at the rate of 4Hz/second with 100µs pulse width was delivered to monitor the integrity of both the vagus and recurrent laryngeal nerve. The EMG (electromyographical) activity was recorded on a NIMä-response 3.0 monitor (Medtronic Xomed). The monitoring system-generated stimuli with a time window of 25ms and an amplitude scale was set to 500µV/division. The event threshold on the NIM was set to 100µV, and impedance differences were recorded to be less than 1.0 mΩ on each channel (left and right vocalis muscles). The neuromonitoring device was used in various phases during surgery. Specifically, before draping the patient, mechanical stimulation was applied by gently tapping the trachea at a level corresponding to vocalis muscles to ensure that the monitoring system was working; later, stimulation was then applied to the structure believed to be the vagus and RLN. The baseline EMG (vocalis) amplitude reduction by >50 % and the latency increase by >10 % was considered as major warning criteria.

Surgical Technique (video available at- https://mmcts.org/tutorial/1746)(14)

Patient positioning: the patient was placed in left lateral decubitus for video-assisted thoracoscopic surgery (VATS) and semi-prone position for the robotic approach. For VATS, the patient was placed in the edge of the table and a bolster was used to elevate the lower intercostal spaces. For Robotic, a bolster in front of the patient was used to maintain the semi-prone position.

Port positions : Five ports were used for VATS and four ports for robotic surgery as shown in figures 2a and 2b respectively.

Procedure of recurrent laryngeal nerve identification, dissection and neurogenic monitoring.

Thoracic part:
After complete mobilization of the esophagus, the right vagus is identified in the upper paraesophageal area and the impulse confirmed by IONM. The right vagus is traced all the way superiorly up to the right subclavian artery with all fibres going posteriorly and upwards at this junction being presumed to be the right recurrent nerve, unless proved otherwise (Fig 3). The IONM probe is then carefully placed at various points and the RLN identified by a combination of visual inspection and the presence of a positive signal on the nerve monitor. Once identified, all the fibrofatty tissue along with the nodes along the nerve is dissected carefully and the probe is brought in again and the viability of the right nerve confirmed before proceeding to the left.

The left recurrent laryngeal nerve is identified in the left paratracheal area, when the trachea and left main bronchus are retracted, the nerve is usually seen lateral to the left main bronchus or the junction of the left main bronchus and trachea, where it hooks around the ligamentum arteriosum and traverses upwards in the left tracheo-oesophageal groove (Fig 4). Once confirmed by a positive signal on the nerve monitor, the nodes are carefully dissected all along the nerve and again, the viability along the entire length of the nerve is confirmed at the end of the procedure.

Care is taken to minimize the use of energy devices during the lymphadenectomy around the RLN and to avoid excessive traction while separating the nodal and fibro-fatty tissue along the length of the nerve.

Cervical part: The cervical esophagus is approached through a transverse neck incision and the region of the cervical component of the RLN group of lymph nodes exposed. After confirming the signals from the vagus nerve in the carotid sheath, we proceed to identify the recurrent nerve in the tracheo-oesophageal groove at the cervicothoracic junction and trace it upwards into the thyroid area. Using a shorter length nerve monitoring probe in the cervical part of the procedure and confirming the nerve impulse, nodal dissection is carried out along the nerves bilaterally. The esophagus is then looped in the left neck and prepared for anastomosis. During the cervical part of the operation, muscle relaxants are completely avoided.

The signal is also checked after looping the esophagus to check if there has been any traction injury during this part of the procedure. During the entire operation, the “no-touch” technique is preferred to dissect the nerve.

Results

Intra-operative nerve monitoring was used for 24 patients undergoing minimally invasive esophagectomy (18 patients underwent three field lymphadenectomy, five patients underwent total mediastinal lymphadenectomy and 1 patient underwent an extended two-field lymphadenectomy) between August 2020 and June 2022. Video-assisted thoracoscopic approach was used in 15 and robotic surgery was performed in 9 patients. During the same period, 111 three hole (McKeown) transthoracic esophagectomies were performed at our institution of which 70 (63%) were minimally invasive (42 VATS, 28 robotic) with three field lymphadenectomy being performed in 36 out of the 111 cases. Patient characteristics are described in Table 1.
In the MIE cohort undergoing intra-operative nerve monitoring, the total operative time was $372 \pm 48$ mins, average blood loss was $312.5 \pm 105.5$ ml, average hospital stay was $13.3 \pm 10.2$ days. Average nodal yield was $44.4\pm15.4$ nodes in the IONM group (IQR-24, max- 79, min-11, range- 68), in patients underwent a MIS 3F TTE without IONM had an average nodal yield of $38.8 \pm 14.2$ nodes. Post operatively all patients underwent vocal cord examination by direct visualization with a rigid Hopkins lens. $8/24$ (33.3%) patients were found to have vocal cord palsy, 5 on the left, 3 on the right. Out of the 8, 7 were managed conservatively and 1 patient needed tracheostomy. No patients had bilateral vocal cord palsy.

Between 2015 to 2020, 182 three field esophagectomies were performed, out of which 44 were done by MIE. $26/44$(59%) had vocal cord palsy post esophagectomy. When we compared this to the patients in our study, there was a 26% decrease in the nerve palsy rate. But this was not found to be statistically significant ($p$- 0.08)

In all patients, we were able to identify the nerve intra-operatively with the assistance of the nerve monitor. In 1 patient there was loss of signal at the end of surgery. In the other 15 patients bilateral signals were intact. 4 patients developed palsy despite signals being present at the end of surgery. Functional evaluation (FEES) was done in $6/8$ patients before initiating oral feeds.

On histopathology, $12/24$(50%) patients had nodal positivity, maximum positivity was seen in station 1 (right paracardiac/lesser curvature), followed by station 101r (right cervical paraesophageal). $5/12$(41.6%) patients had positive nodes along either the right or left recurrent nerves. Out of the 8 patients who had vocal cord palsy, 3 had positive nodes along the recurrent nerves.

Median hospital and ICU stay for the entire group was 11 and 1 day(s) respectively. For those who had a vocal cord palsy, it was 12 and 1 day(s) respectively.

On a median follow up of 12.5 months(max-24, min- 6), $8$ patients who had vocal cord palsy, 6 have reported a recovery to a normal voice. Of the 24 patients, 22 are alive and disease free, 2 patients have had systemic relapse and expired. The patient who required a tracheostomy was successfully decannulated and currently reports a normal voice and is able to take normal diet.

Discussion

Our study demonstrated the safety and feasibility of IONM in patients undergoing MIE. However, the incidence of RLN paresis remained relatively high in spite of IONM, and might be related to the learning curve associated with the technique.

Minimally invasive surgery is currently the standard of care for esophageal cancer, based on the results of the randomized trials showing significant reduction in complications.(11–13). In both the TIME and MIRO trials, only a standard infracarinal two-field lymphadenectomy was performed. Retrospective studies published have shown that an extended lymphadenectomy is possible thoracoscopically and robotically(15, 16) with good short term outcomes. But, the rate of RLN paresis/paralysis remains high
A recent nationwide database review in Japan showed high rates of RLN palsy and pulmonary complications after thoracoscopic esophagectomies (19). Hence, there is a need to reduce the RLN palsy rate to improve outcomes after MIE.

The value of an extended radical lymphadenectomy including a cervical field, in esophageal cancer surgery is still being debated. Nishihara et al (2) demonstrated an 18% survival improvement in patients who had undergone a three-field esophagectomy, without significant increase in morbidity compared to a standard two-field approach. Recent randomized data from China (20) has demonstrated no significant difference in OS or DFS in a cohort of 400 patients between two and three field lymphadenectomies. However, in this trial, patients in the two-field arm underwent a total mediastinal lymphadenectomy and hence these results may not be generalizable. A recently published meta-analysis by Bona et al (21) showed an improved trend for 5-year overall survival with a three-field lymphadenectomy. When there is obvious nodal disease on imaging in the upper mediastinum and the neck, a three-field lymphadenectomy still remains the standard of care. We have just finished accrual of 700 patients in a randomized controlled trial comparing two field versus three field lymphadenectomy in patients without superior mediastinal nodes (NCT-00193817) and the long term and survival results of this study are awaited (22).

One of the common complications after a radical three-field lymphadenectomy is injury or traction on the recurrent laryngeal nerves resulting in temporary or permanent vocal cord palsy. Vocal cord paralysis/paresis results in significant morbidity and deterioration in quality of life (7). Immediate concerns are an increased risk of aspiration pneumonia and need for a tracheostomy (23). Apart from this, there is a significant increase in pulmonary complications and need for prolonged mechanical ventilation (7, 24). In the long term, untreated vocal cord paralysis leads to hoarseness of voice and difficulty in swallowing. Hence, all necessary precautions need to be employed to prevent injury to the RLN.

Intra-operative nerve monitoring was first introduced in the 1930s by neurosurgeons, but it was not until the 1980s that IONM became mainstream with introduction of commercially available nerve monitors (25). Due to technical difficulties and need for longer probes, IONM was not routinely employed in the thorax until the turn of the millenium. Hemmerling et al (26) first described the use of IONM for esophagectomies in 2001, when they used a double lumen endotracheal tube with a surface electrode, and were able to achieve successful lung isolation while being able to satisfactorily monitor the nerve. This was followed by various case series demonstrating the feasibility and efficacy of IONM during open esophagectomies (27–30). Takeda et al (9) have demonstrated the efficacy of IONM during thoracoscopic esophagectomy. They reported a 5.1% reduction in the nerve palsy rate with the crude data and 14.9% reduction after propensity matching. A systematic review by Wang et al (31) demonstrated that these studies showed a significant decrease in the rate of hoarseness of voice between the IONM and non-IONM groups (OR 0.14, 95% CI 0.03–0.63, p < 0.05) and a significant increase in the number of nodes dissected (mean-diff 4.30, 95% CI 2.75–5.85, p < 0.001). Our study demonstrated a nerve palsy rate of 31.3%, which is higher than reported by other studies (5–45%). This can be attributed to the learning
curve associated with the procedure. The average number of nodes dissected in our study was around 43 nodes, which is comparable to other similar studies. In our unit, all patients undergo vocal cord examination after a three-field esophagectomy irrespective of the quality of their voice, this could have also resulted in a higher nerve palsy rate. We compared these results to our historical cohort of patients who underwent MIE with three-field lymphadenectomy, there was a reduction in the nerve palsy rate, but this was not statistically significant.

Though most studies have demonstrated a reduction in the incidence of nerve palsies, this has not been found to be statistically significant when compared to visual inspection alone. On reviewing the data available on IONM, the use of IONM has not definitely proven to reduce complications whether in thyroid or esophageal surgeries (8, 31). However most studies have been single institution cohorts with limited number of patients. Some authors hypothesize that low volume surgeons tend to benefit more from IONM (32) than high-volume surgeons, but more data is needed to substantiate this claim.

One of the problems with IONM is that, despite signals being present at the end of the procedure on the nerve monitor, a significant number of patients (8/54- Hikage et al(28). and 9/60- Takeda et al(9).) went onto develop vocal cord paresis/paralysis. Hence, the pooled sensitivity of IONM remained low at a maximum of 66.7%. This is also reflected in our data, where four of five patients who developed a vocal cord palsy postoperatively had intact signals on IONM at the end of surgery. This may be due to the nerve remaining anatomically intact, but having some reduction in physiologic function (neuropraxia). Long term follow up data is needed to evaluate if these patients recover vocal cord function.

Intra-operative nerve monitoring poses difficulties during minimally invasive surgery. Longer probes are required to simulate the nerves; sometimes, even with longer probes, the angles are difficult to negotiate to be able to make contact with the nerve. During robotic surgeries, the same problems exist, which are compounded by the fact that the bed-side assistant has to handle the IONM probe. These problems can however be minimized with experience. The magnification and better resolution provided by current technology can help in better visualization of the nerves and permit the dissection of more lymph nodes in the mediastinum.

Conduct of intraoperative nerve monitoring during esophagectomy requires few modifications in the anesthesia technique. First, since neuromuscular blockade is not used during the surgery, there may be few episodes of spontaneous breathing, coughing or patient movement during the surgery. In addition, the minimum alveolar concentration of inhalational anesthetic agents needs to be less than 1.0 to prevent the suppression of evoked potentials. In such cases, an additional infusion of intravenous anesthetic like propofol and remifentanil is used to maintain depth of anesthesia and to depress the laryngeal reflexes. Bi-spectral index guided titration of propofol infusion reduces the incidence of delayed recovery and haemodynamic instability associated with propofol infusion (33). Second, the device for airway management should be chosen wisely especially for minimally invasive surgeries. A double-lumen tube with surface embedded electrodes or a bronchial blocker through an electrode-embedded
endotracheal tube should be ideally used for lung isolation. The position of the lung isolation device and surface electrodes must be confirmed after changing the position of the patient.

All our patients underwent intermittent nerve monitoring. Continuous nerve monitoring was attempted initially, but we faced a number of issues. It required a cervical-first approach, which led to a significant increase in operative time. Once the patient position was changed, the electrodes placed on the vagus sometimes tended to get displaced. Hence, for practical reasons we adopted the intermittent method.

The use of intra-operative nerve monitoring logically seems useful as the surgeon can be more confident of the anatomy, especially in cases with high nodal burden, anatomical variations and salvage esophagectomies. The lymph node yield has shown to be higher, this has been demonstrated previously and re-confirmed in our study. Another area, where nerve monitoring can be extremely useful is when there is variant anatomy such as a non-recurrent laryngeal nerve or an aberrant subclavian artery, in these cases the usual landmarks for visual identification are absent and hence nerve monitoring has been demonstrated to be helpful to identify and preserve the recurrent nerve\(^{(34, 35)}\).

While IONM technology continues to evolve, our study has demonstrated its safety and feasibility in MIE, both VATS as well as robot-assisted. IONM can be used without a significant increase in operative time or post-operative complications. However, our study has some limitations. First, the technique failed to show a marked reduction in the incidence of RLN paresis. One of the inherent problems with IONM seems to be that there is a possibility of RLN paresis with an anatomically intact nerve resulting in signals being maintained till the end of the procedure in spite of functional paresis. Second, the sample size in our study is relatively small; nevertheless, it remains one of the larger studies done so far in patients undergoing MIE. Larger, well conducted, preferably randomized trials are needed to answer the question regarding its role in markedly reducing vocal cord paresis or palsy.

**Conclusions**

We have demonstrated the safety and feasibility of intra-operative recurrent laryngeal nerve monitoring during robotic and thoracoscopic minimally invasive esophagectomy. Using IONM results in lesser incidence of recurrent nerve palsies and higher nodal yield. Larger multicentric prospective studies and randomized trials are needed to evaluate the role of intra-operative nerve monitoring in aiding more precise and safe lymphadenectomy along the recurrent laryngeal nerves and reducing pulmonary complications.

**Abbreviations**

RLN- recurrent laryngeal nerve

IONM- intra-operative nerve monitoring

EMG- electromyography
CECT- contrast enhanced computed tomography

PET- Positron Emission Tomography

MIE- minimally invasive esophagectomy

TOF- Train-of-four

VATS- video assisted thoracic surgery

ICU- Intensive care unit

FEES- Functional endoscopic evaluation of swallowing

Declarations

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Disclosures- Authors have no disclosures relevant to the topic of this paper

Institutional Ethics Committee approval obtained on 04-01-2022 (vide letter no-0IEC/3352/2022/00001)

Informed consent was obtained from all patients for participating in the study and for publication of data and photographs in a scientific journal

References


**Tables**

Table 1 Patient characteristics
<table>
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<th>Characteristic</th>
<th>Value(n=24)</th>
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<tr>
<td>1.</td>
<td>Age (years) mean + SD</td>
<td>53.6 ±13.8 y</td>
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<tr>
<td>2</td>
<td>Gender</td>
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</tr>
<tr>
<td></td>
<td>Male</td>
<td>14 (56.2%)</td>
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<tr>
<td></td>
<td>Female</td>
<td>10 (43.7%)</td>
</tr>
<tr>
<td>3</td>
<td>Location of the growth</td>
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</tr>
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<td></td>
<td>Middle 1/3(^{rd})</td>
<td>12(50%)</td>
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<tr>
<td></td>
<td>Lower 1/3(^{rd})</td>
<td>12(50%)</td>
</tr>
<tr>
<td>4</td>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous</td>
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<tr>
<td></td>
<td>Adeno</td>
<td>01(4.2%)</td>
</tr>
<tr>
<td>5</td>
<td>Type of Surgery</td>
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</tr>
<tr>
<td></td>
<td>VATS</td>
<td>15 (62.5%)</td>
</tr>
<tr>
<td></td>
<td>Robotic</td>
<td>09 (37.5%)</td>
</tr>
<tr>
<td>6</td>
<td>Clinical Stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>23 (95.8%)</td>
</tr>
<tr>
<td>7</td>
<td>Neo-Adjuvant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
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<td>Chemo-radiotherapy</td>
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<td>8</td>
<td>Nodal involvement(HPR)</td>
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<tr>
<td></td>
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<td>11(45.8%)</td>
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<td></td>
<td>N1</td>
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<td>03(12.5%)</td>
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<tr>
<td></td>
<td>N3</td>
<td>02(08.3%)</td>
</tr>
</tbody>
</table>

Table 2- Involvement of nodes around RLN
Stations along RLN (as per Japanese classification) | Number of patients with positive nodes | Number of patients with vocal cord paresis
--- | --- | ---
101 R | 1 | 1
101 L | 1 | 0
106rec R | 2 | 2
106rec L | 2 | 1

**Figures**

*Figure 1*

Equipment needed for neuro monitoring
Figure 2

a- Port positions for Robotic Esophagectomy

b- Port positions for VATS Esophagectomy
**Figure 3**

Intraoperative snapshot showing dissection and neuro-monitoring of right RLN.

**Figure 4**

Intraoperative snapshot showing dissection and neuromonitoring of left RLN.