Minimally invasive oesophagectomy with a total two-field lymphadenectomy after neoadjuvant chemoradiotherapy for locally advanced squamous cell carcinoma of the oesophagus: A prospective study

Kuppusamy Sasikumar, Raja Kalayarasan, Senthil Gnanasekaran, Sandip Chandrasekar, Biju Pottakkat
Department of Surgical Gastroenterology, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India

Abstract
Introduction: In the era of neoadjuvant chemoradiotherapy (NACTRT), the safety and clinical significance of radical lymphadenectomy specifically lymphadenectomy along the recurrent laryngeal nerve (RLN) has been questioned. Furthermore, the compliance to NACTRT with the CROSS regimen has not been well studied in the Indian population. This prospective study aimed to determine the compliance with CROSS regimen, feasibility and short-term outcomes of minimally invasive oesophagectomy (MIE) with a total two-field lymphadenectomy after NACTRT.

Methods: A prospective study (January 2014 to December 2018) of patients with locally advanced oesophageal squamous cell carcinoma (SCC) eligible for NACTRT (cT1-4a, N0-1, M0) followed by MIE with total two-field lymphadenectomy. The compliance rate, post-operative complications and the pathological response rate were assessed.

Results: Of the 166 patients with locally advanced SCC, 76 (45.8%) were eligible for NACTRT and 34 completed NACTRT followed by MIE with a total two-field lymphadenectomy (study group). Twenty-nine (38.1%) patients did not complete NACTRT due to complications or poor compliance. Median (range) blood loss was 125 (50–450) ml and the median (range) operation time for the thoracoscopic phase was 205 (155–325) min. Total median (range) lymph node count and mediastinal lymph node counts were 20 (11–33) and 12, (8–21) respectively. Most common post-operative complications were pneumonia (n = 12, 35.3%) followed by RLN palsy (n = 10, 29.4%). Of the 22 patients who had a complete pathological response of the primary tumour, 7 (31.8%) patients had a node-positive disease.

Conclusion: NACTRT followed by MIE is feasible in patients with locally advanced SCC. The nodal disease is common even in patients with the complete pathological response of the primary tumour. The dropout rate with NACTRT using the CROSS regimen is high in the present study.

Keywords: Neoadjuvant chemoradiotherapy, oesophageal cancer, oesophagectomy robotic, thoracoscopy

Address for correspondence: Dr. Raja Kalayarasan, Department of Surgical Gastroenterology, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry - 605 006, India. E-mail: kalayarasanraja@yahoo.com
Submitted: 08-Oct-2019, Revised: 04-Nov-2019, Accepted: 25-Nov-2019, Published: 09-Jan-2020

How to cite this article: Sasikumar K, Kalayarasan R, Gnanasekaran S, Chandrasekar S, Pottakkat B. Minimally invasive oesophagectomy with a total two-field lymphadenectomy after neoadjuvant chemoradiotherapy for locally advanced squamous cell carcinoma of the oesophagus: A prospective study. J Min Access Surg 2021;17:49-55.
INTRODUCTION

Neoadjuvant therapy followed by surgery is the current recommended treatment for oesophageal cancer. Since the publication of the landmark trial on neoadjuvant chemoradiotherapy (NACTRT), CROSS regimen has been commonly used for locally advanced oesophageal cancer. Minimally invasive oesophagectomy (MIE) is the preferred approach as it is associated with fewer pulmonary complications compared to open transthoracic oesophagectomy with comparable oncological outcomes. As oesophageal cancer is an aggressive tumour with a high incidence of lymph-node metastasis, radical lymphadenectomy has been recommended for curative treatment. However, radical lymphadenectomy specifically lymph node dissection along the recurrent laryngeal nerve (RLN) is associated with a high incidence of post-operative complications. Hence, dissection along RLN is not a standard practice in many institutes. In the era of NACTRT, the role of radical lymphadenectomy has been questioned as clearance of occult lymph-node metastases by NACTRT may reduce the clinical usefulness of an extensive nodal dissection. Furthermore, mediastinal fibrosis induced by NACTRT may increase the technical difficulty and complications associated with lymph node dissection along RLNs. In the Indian population, squamous cell carcinoma (SCC) remains the predominant histological type, and most of the patients have locally advanced oesophageal cancer at presentation with associated malnutrition. In this population, the safety of NACTRT with the CROSS regimen has not been well studied. Furthermore, the feasibility and outcomes of MIE with a total two-field lymphadenectomy after CROSS regimen have not been prospectively studied. Majority of the published studies are retrospective in nature with limitations such as the inclusion of both SCC and adenocarcinoma, use of different surgical approaches and variable extent of lymphadenectomy. The aim of this prospective study was to determine the compliance with the CROSS regimen, feasibility and short-term outcomes of MIE with a total two-field lymphadenectomy after NACTRT.

METHODS

A prospective study of patients with locally advanced SCC of the oesophagus eligible for NACTRT (cT1-4a, N0-1, M0) followed by MIE during the study period from January 2014 to December 2018 [Table 1]. The study was approved by the institute scientific advisory and ethics committee. After a diagnostic upper gastrointestinal endoscopy and biopsy, pre-operative staging was done with contrast-enhanced computed tomography neck, thorax and abdomen. Endoscopic ultrasound was not used for staging and positron emission tomography was selectively performed in patients with T3/T4a tumour and extensive regional lymphadenopathy. Patients with high-grade dysphagia underwent an open or laparoscopic feeding jejunostomy before initiation of NACTRT. NACTRT was given to patients with T2 and above primary tumour or node-positive tumour as per CROSS protocol that includes five cycles of weekly administration of carboplatin and paclitaxel and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days/week). Response assessment imaging was done after 4–6 weeks, and surgery was done 6–10 weeks after completion of NACTRT.

The thoracic portion of MIE was performed predominantly using the thoracoscopic approach in a prone position with single-lumen endotracheal tube intubation and double-lung ventilation. A robotic approach was used in the later part of the study. A total mediastinal lymphadenectomy including clearance of (lymph node stations as per Edition of Japanese Classification of Esophageal Cancer) subcarinal nodes (107), main bronchus nodes (109), upper (105), middle (108) and lower thoracic (110) paraoesophageal nodes, right and left RLN nodes (106 rec), anterior thoracic para-aortic nodes (112aAO) and pulmonary ligament nodes (112pul) were performed in all patients [Figures 1 and 2]. Thoracic duct excision was selectively performed in patients with clinically evident thoracic duct leakage.
performed in patients with bulky lymph nodes in stations 112aoA, 106 and 108, as previously reported by us to ensure total mediastinal lymphadenectomy.[12] Abdominal lymphadenectomy and gastric mobilisation were done using laparoscopic approach in supine position. In the abdomen lymph node stations 1 (right paracardial nodes), 2 (left paracardial nodes), 3a (Lesser curvature lymph nodes along the branches of the left gastric artery), 7 (left gastric artery nodes), 9 (celiac artery nodes) and 20 (oesophageal hiatus nodes) were cleared. Gastric conduit formation with a conduit diameter of 4–5 cm was done through a minilaparotomy. The stomach was used as a conduit in all patients and was pulled up through posterior mediastinum for cervical anastomosis. Single stapled cervical oesophagogastric anastomosis by modified Collard’s technique was done in all patients.[13]

The parameters analysed were clinicopathological features, dropout rate with NACTRT, post-operative complications and pathological response rate. Oesophagectomy specific morbidity was classified as per the recommendations of oesophagectomy complications consensus group.[14] Post-operative pneumonia was defined as development of new lung infiltrates associated with the clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leucocytosis and decline in oxygenation.[15] Evaluation of the vocal cords by indirect laryngoscopy is done in all patients on the seventh post-operative day. RLN palsy is defined as any dysmotility affecting the vocal cords. The pathological response rate was assessed by the 2010 American Joint Committee on Cancer (AJCC) Tumor Regression Grading (TRG) system.[16] For the purpose of analysis, TRG0 is defined as a complete response. TRG1 and 2 are defined as partial response and TRG3 is defined as a poor response. The extent of tumour spread was recorded according to the Seventh Edition of TNM classification (AJCC staging).[16]

Categorical variables were expressed as frequencies and percentages and continuous variables as mean with standard deviation or median with range. Categorical variables were analysed using Fisher’s exact test. The statistical analysis was done using Statistical Package for the Social Sciences version 19.0 (SPSS, Chicago, IL, USA). P ≤ 0.05 is taken as statistically significant.

RESULTS

During the study period, 166 patients with oesophageal cancer were evaluated. Of the 166 patients, 76 patients who fulfilled the inclusion criteria were included in the study [Figure 3]. Feeding jejunostomy was performed in 66 patients before initiation of NACTRT. Of the 76 patients, 29 (38.1%) patients did not complete the full course of NACTRT due to complications or poor compliance. Chemotherapy related complications precluded completion of NACTRT in 12 patients and two patients died of chemotherapy-related toxicity. Non-compliance due to lack of family support to accompany the patient for NACTRT was noted in 11 patients. Four patients had disease progression due to delays in the initiation of NACTRT. Of the 47 patients who completed NACTRT, six patients refused to undergo oesophagectomy due to significant improvement in clinical symptoms. Seven patients who underwent oesophagectomy without a total two-field lymphadenectomy due to extensive periesophageal fibrosis were excluded. The clinical and demographic profile of 34 patients who completed the study protocol (NACTRT followed by oesophagectomy with a total two field lymphadenectomy) is summarised in Table 2. Most of the patients had a tumour in the middle thoracic oesophagus (n = 21). The thoracic portion of MIE was performed using a thoracoscopic approach in most of the patients (n = 28, 82.3%), and the robotic approach was used in six patients. Median (range) total operation time and operation time for the thoracoscopic phase were 405 (345–510) and 205 (155–325) min, respectively. Median (range) blood loss was 125 (50–450) ml, and there was no conversion to thoracotomy or laparotomy in any of the patients.

Most of the patients (n = 30, 88.2%) were electively kept on ventilator support in the immediate post-operative period and extubated on the first post-operative day. The pathological findings are summarised in Table 3. Total
median (range) lymph node count and mediastinal lymph node counts were 20 (11–33) and 12 (8–21), respectively. Twenty-two (64.7%) patients had a complete pathological response of the primary tumour (ypT0). Of these, seven (31.8%) patients had node-positive disease. The location of positive nodes in these seven patients are station 106 rec (n = 4), station 107 (n = 1) and station 7 (n = 2). Overall, 15 (44.1%) patients had a complete pathological response (ypT0N0) to NACTRT.

Most common post-operative complication was pneumonia (n = 12, 35.3%) followed by RLN palsy (n = 10, 29.4%). The cervical anastomotic leak occurred in seven (20.9%) patients and chylothorax requiring thoracoscopic ligation of the thoracic duct in one patient. There was no significant difference in the major post-operative complications between patients who had complete pathological response and patients who had partial/poor pathological response [Table 4]. Median (range) post-operative hospital stay was 10 (8–32) days. There was one post-operative mortality due to the development of gastric conduit bronchial fistula. The patient was readmitted on POD 24 with multiple episodes of severe cough and retching following oral intake. Tracheostomy, retrograde tube gastrostomy and duodenal exclusion were done in the initial stage for optimisation of pulmonary status followed by dismantling of bronchogastric fistula, repair of bronchial and gastric defect with serratus anterior interposition muscle flap by right post-erolateral thoracotomy. Post-operatively, the patient developed recurrent bronchogastric fistula and died of pulmonary sepsis.

DISCUSSION

The high failure rate associated with surgical treatment alone necessitated the use of NACTRT as a standard of...
Table 4: Comparison of post-operative complications in patients who had complete pathological response and partial/poor pathological response

| Parameter         | Complete pathological response (n=15), n (%) | Partial/poor pathological response (n=19), n (%) | P   |
|-------------------|--------------------------------------------|-------------------------------------------------|-----|
| Pneumonia         | 5 (33.3)                                   | 7 (36.8)                                        | 1.00|
| Anastomotic leak  |                                            |                                                 |     |
| Absent            | 13 (86.7)                                  | 14 (73.7)                                       | 0.43|
| Grade 1           | 0                                          | 2 (10.5)                                        |     |
| Grade 2           | 2 (13.3)                                   | 3 (15.8)                                        |     |
| Grade 3           | 0                                          | 0                                               |     |
| Chyle leak        |                                            |                                                 |     |
| Absent            | 15 (100)                                   | 18 (94.7)                                       | 1.00|
| Grade 1           | 0                                          | 0                                               |     |
| Grade 2           | 0                                          | 0                                               |     |
| Grade 3           | 0                                          | 1 (5.3)                                         |     |
| RLN palsy         |                                            |                                                 |     |
| Absent            | 11 (73.3)                                  | 13 (68.4)                                       | 1.00|
| Grade 1           | 3 (20.0)                                   | 5 (26.3)                                        |     |
| Grade 2           | 1 (6.7)                                    | 1 (5.3)                                         |     |
| Grade 3           | 0                                          | 0                                               |     |

RLN: Recurrent laryngeal nerve

of patients eligible for NACTRT. Despite nutritional optimisation, chemotherapy-related complications were the main factor that precluded the completion of five cycles of chemotherapy. Even patients who completed four cycles of chemotherapy were considered non-compliant, which could have contributed to the high non-compliance rate reported in the study. Another major reason is the lack of family support to patients from low socioeconomic status due to protracted treatment schedules, especially when there is a delay in the initiation of NACTRT due to the long waiting period. The long waiting period is a major problem in government institutes where entire treatment is given free of cost.

MIE has been accepted as the standard surgical modality for oesophagectomy as it improves short term outcomes compared to open oesophagectomy with equivalent oncological outcomes.[2,3] However, the safety of minimally invasive radical lymphadenectomy, especially lymph node dissection along RLN after NACTRT, has not been well studied. In the majority of the published studies, including the landmark CROSS and TIME trial, a significant proportion of patients underwent only a standard two-field lymphadenectomy.[2,3] Lymph node metastasis is an important prognostic factor in oesophageal cancer and radical lymphadenectomy has been shown to improve lymph node yield, locoregional disease control and survival.[4] As lymph nodes along RLN are an important site of metastasis, a total two-filed lymphadenectomy is recommended in patients with middle and lower thoracic oesophageal cancer, especially SCC. However, authors of the CROSS study group recently reported a lack of correlation between the number of resected lymph nodes and survival in patients who received NACTRT due to sterilisation of regional lymph nodes.[19] While the number of resected and positive lymph nodes is used for lymph node staging in AJCC classification, its prognostic value becomes unreliable if the high-risk lymph node stations are not cleared. The number of resected lymph nodes will act as a surrogate marker for adequate lymphadenectomy only when the high-risk lymph node stations are systematically dissected and removed. Hence, only patients who underwent a total two field lymphadenectomy were included in the present study. Recent studies from Asia have reported that the therapeutic value of radical lymph node dissection was not altered by neoadjuvant therapy.[20,21]

Pathological response to NACTRT has been recognised as an important predictor of the outcome as patients who achieved complete pathological response were less likely to develop recurrence.[22,23] While multiple molecular markers have been evaluated; none of the pre-operative

...care for locally advanced oesophageal cancer. Improved survival with acceptable adverse events established CROSS protocol as a commonly used NACTRT regimen.[1] In the CROSS-group study, the median OS was 49.4 months in the NACTRT arm, compared to 24 months in the surgery alone group. The benefit of the CROSS protocol was more pronounced in patients with the SCC compared to adenocarcinoma, although the number of patients with SCC was less in the study.[1] Tang et al. studied the CROSS regimen in Asian patients with SCC and reported a higher pathological response rate compared to neoadjuvant chemotherapy (27.6% vs. 4.8%).[17] Nabavizadeh et al. evaluated the efficacy of a modified CROSS regimen with a higher radiotherapy dose of 50.4 Gy.[18] They reported that radiation doses higher than 41.4 Gy resulted in increased pulmonary complications rate without an increase in the pathological complete response rate. Hence, in the current study, standard CROSS regimen was used in all patients.

Oesophageal cancer is the eighth most common cancer in India and approximately 47,000 cases are reported annually.[7] In contrast to the western population where oesophageal and gastrooesophageal junction adenocarcinoma is common, SCC remains the predominant histological subtype in the Indian population.[1] The results of the present study suggest that compliance with the CROSS regimen is poor in Indian patients, with 38% of locally advanced SCC patients could not complete the regimen due to complications or poor compliance. Due to delayed presentation with high-grade dysphagia, malnutrition was common in the present study population with a mean BMI of 17.8. Hence feeding jejunostomy was performed in 87% (66/76)
investigations can reliably predict complete pathological response in various studies. Hence surgery is recommended even in patients with complete clinical response to NACTRT. In the CROSS trial, overall pathological complete response rate was 29%, but it was higher in patients with SCC compared to adenocarcinoma (49% vs. 23%).[1] The 44% complete pathological response reported in the present series is comparable to the reported response rate in other series with predominant SCC patients.[8,10] An important finding of the present study is 31% (7/22) of patients with the complete pathological response of the primary tumour had a node-positive disease, which underscores the need for lymphadenectomy even in patients with a presumed complete response of the primary tumour. Furthermore, four of the seven patients had isolated lymph node metastasis of the recurrent laryngeal group of lymph nodes, highlighting the importance of a total two-field lymphadenectomy post-NACTRT. Radical lymphadenectomy post-NACTRT can identify the patients with a true complete pathological response (ypT0N0) with the potential for long term survival. Failure to clear high-risk nodal stations would have ensued erroneous classification of some ypT0N + patients as ypT0N0, resulting in an inaccurate prognostic stratification.

Morbidity associated with lymph node dissection along RLN is the primary concern against a total two-field lymphadenectomy. Furthermore, mediastinal fibrosis due to NACTRT might increase the technical difficulty as evident in the present series where supracarinal lymph node dissection could not be completed in seven patients. Of the patients who underwent a total two-field lymph node dissection, 29% had RLN palsy. While the rate of RLN palsy is relatively higher in the present series only two patients had permanent nerve palsy at the end of 6 months.[24] Routine vocal cord evaluation on seventh post-operative day irrespective of symptoms could have contributed to higher nerve palsy rate as increased rates were reported in series with similar post-operative vocal cord evaluation protocol.[5] Also, there was no significant difference in the RLN palsy rate between patients who had complete pathological response and patients who had partial/poor pathological response. Pre-operative prediction of RLN node involvement can avoid morbidity related to RLN palsy. However, no reliable predictors of RLN node involvement are currently available to facilitate selective RLN node dissection. In the present series, all patients who had RLN node metastasis had enlarged node prior to initiation of NACTRT. Whether RLN dissection can be omitted in patients without radiological evidence of RLN node before initiation of NACTRT needs to be evaluated in a large series of patients.

The limitations of the present study are small sample size and lack of long-term outcomes as the study was designed to evaluate short term outcomes. Furthermore, the study was done in a public sector hospital that predominantly treats patients from low socioeconomic status. Hence, a similar high non-compliance rate may not be universally observed. Furthermore, the number of patients with positive RLN lymph node involvement is less. Therefore, a reliable pre-operative predictor of RLN nodal metastasis could not be determined from the present study. The strengths of the study are prospective evaluation using a standardised treatment protocol, the inclusion of only SCC, uniform surgical approach, standardisation of lymphadenectomy and grading of complications. The results of the present study suggest that NACTRT followed by MIE is feasible in patients with locally advanced SCC with a high complete pathological response rate. The nodal disease is common even in patients with the complete pathological response of the primary tumour. The dropout rate with NACTRT using the CROSS regimen is high in the present study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
2. Biere SS, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicentre, open-label, randomised controlled trial. Lancet 2012;379:1887-92.
3. Straatman J, van der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally invasive versus open esophageal resection: Three-year follow-up of the previously reported randomized controlled trial: The Time trial. Ann Surg 2017;266:232-6.
4. Akiyama H, Tsurumaru M, Udagawa H, Kaijyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364-72.
5. Sato Y, Kosugi S, Aizawa N, Ishikawa T, Kano Y, Ichikawa H, et al. Risk factors and clinical outcomes of recurrent laryngeal nerve paralysis after esophagectomy for thoracic esophageal carcinoma. World J Surg 2016;40:129-36.
6. Fujita H, Sueyoshi S, Tanaka T, Fujii T, Toh U, Mine T, et al. Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: Comparing the short- and long-term outcome among the four types of lymphadenectomy. World J Surg 2003;27:571-9.
7. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: The Global Burden of Disease Study 1990-2016. Lancet Oncol 2018;19:1289-306.
8. Krishnamurthy A, Mohanraj N, Radhakrishnan V, John A,
Sasikumar, et al.: Minimally invasive oesophagectomy post-neoadjuvant chemoradiotherapy

Selvaluxmy G. Neoadjuvant chemoradiation for locally advanced resectable carcinoma of the esophagus: A single-center experience from India with a brief review of the literature. Indian J Cancer 2017;54:646-56.

9. Liu G, Han Y, Peng L, Wang K, Fan Y. Reliability and safety of minimally invasive esophagectomy after neoadjuvant chemoradiation: A retrospective study. J Cardiothorac Surg 2019;14:97.

10. Goel A, Shah SH, Selvakumar VP, Kakhasha S, Garg S, Pahuja AK, et al. Radical esophagectomy after neoadjuvant chemoradiation: Single institutional experience from tertiary cancer Centre in India. Indian J Surg Oncol 2015;6:207-12.

11. Japan esophageal society. Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus. 10th ed. Tokyo, Japan: Kanehara Co.; 2007.

12. Anand S, Kalayarasan R, Chandrasekar S, Gnanasekaran S, Pottakkat B. Minimally invasive esophagectomy with thoracic duct resection post neoadjuvant chemoradiotherapy for carcinoma esophagus-impact on lymph node yield and hemodynamic parameters. J Gastrointest Cancer 2019;50:230-5.

13. Collard JM, Romagnoli R, Goncette L, Otte JB, Kestens PJ. Terminalized semimechanical side-to-side suture technique for cervical esophagogastrostomy. Ann Thorac Surg 1998;65:814-7.

14. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, Djoumbo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015;262:286-94.

15. Cunha BA. Pneumonia Essentials. 3rd ed. Royal Oak, Michigan: Physicians Press; 2010.

16. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A 3rd. AJCC Cancer Staging Manual. 7th ed. New York: Springer-Verlag; 2010.

17. Tang H, Zheng H, Tan L, Shen Y, Wang H, Lin M, et al. Neoadjuvant chemoradiotherapy followed by minimally invasive esophagectomy: Is it a superior approach for locally advanced resectable esophageal squamous cell carcinoma? J Thorac Dis 2018;10:963-72.

18. Nabavizadeh N, Shukla R, Elliott DA, Mitin T, Vaceiro GM, Dolan JP, et al. Preoperative carboplatin and paclitaxel-based chemoradiotherapy for esophageal carcinoma: Results of a modified CROSS regimen utilizing radiation doses greater than 41.4 Gy. Dis Esophagus 2016;29:614-20.

19. Koen Talsma A, Shapiro J, Looman CW, van Hagen P, Steyerberg EW, van der Gaast A, et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: Prognostic and therapeutic impact on survival. Ann Surg 2014;260:786-92.

20. Miyata H, Yamasaki M, Makino T, Miyazaki Y, Takahashi T, Kurokawa Y, et al. Therapeutic value of lymph node dissection for esophageal squamous cell carcinoma after neoadjuvant chemotherapy. J Surg Oncol 2015;112:60-5.

21. Miyata H, Sugimura K, Yamasaki M, Makino T, Tanaka K, Morii E, et al. Clinical impact of the location of lymph node metastases after neoadjuvant chemoradiation for middle and lower thoracic esophageal cancer. Ann Surg Oncol 2014;21:200-8.

22. Warner S, Chang YH, Paripati H, Ross H, Ashman J, Harold K, et al. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. Ann Surg Oncol 2010;17:1159-67.

23. Meredith KL, Weber JM, Turaga KK, Siegel EM, McLoughlin J, Hoffe S. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. Ann Surg Oncol 2014;21:439-45.

24. Li ZG, Zhang XB, Wen YW, Liu YH, Chao YK. Incidence and Predictors of unsuspected recurrent laryngeal nerve lymph node metastasis after neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma. World J Surg 2018;42:2485-92.