Does Radical Lymphadenectomy Improve Survival in Esophageal and Gastroesophageal Junction Cancer?

Mahesh Mani Adhikari[1], Binay Thakur[1], Sun Zhengqing[2], Sagar Khatiwada[1], Shashank Shrestha[1], Ashish Kharel[1], Manoj Tiwari[1], Shachee Bhattarai[1],

[1]Department of Surgical Oncology. BP Koirala Memorial Cancer Hospital, Bharatpur, Nepal.

[2]Thoracic Department of the Affiliated Hospital of Hebei University, China

Abstract

Background: Esophageal carcinoma is one of the deadliest cancer in gastrointestinal system with 5-years survival of only 24%. Lymphnode metastasis has been associated with worse outcome. But the extent of lymphnode dissection has been a debate among surgeons worldwide. This study aimed to compare the overall survival of patients undergoing radical and non-radical lymphadenectomy in a tertiary referral cancer hospital in Nepal.

Methodology: This study included 634 patients of esophageal and gastroesophageal junction cancer who underwent surgical resection at our institution over a period of 2001- 2019. The patients were divided into 2 groups; radical lymphadenectomy (RLN) and non-radical lymphadenectomy (NRLN) groups. RLN group underwent two-field or three field lymphadenectomy for esophageal cancer and D2 or D2 + lower mediastinal lymphadenectomy for GEJ cancer. NRLN group underwent nodal sampling or D1 dissection.

Results: RLN was performed in 85.9%. NRLN was done in 14.1%. Surgery alone was performed in 47.1% and multimodality approach in 52.9% cases. Median survival for RLN and NRLN groups was 34 and 15 months, respectively ($p < .001$).

Conclusion: Improved median survival has been observed after radical lymphadenectomy for esophageal and GEJ cancer.

Keyword: Esophageal Neoplasms, Esophagogastric Junction, Lymph Node Excision

Introduction

According to estimates from International Agency for Research on Cancer (IARC) in 2022, there were approximately 20 million new cases of cancer globally.[1] The Global Cancer Observatory report of 2022 reported 510716 recorded case of Esophageal cancer with 445129 deaths due to esophageal cancer.[1]

The two most common histological subtypes of Esophageal carcinoma (EC) are Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), with ESCC accounting for about 80% of EC cases globally.[2] Currently, there

Correspondence

Dr Mahesh Mani Adhikari. Dept. of Surgical Oncology (Thoracic Unit). BP Koirala Memorial Cancer Hospital. Bharatpur, Nepal. Email: adhikarimmani1@gmail.com Phone: +9779865402464

has been an increasing trend of EAC and Gastroesophageal junction Adenocarcinoma (GEJC) in the developed nations.[3] Patients are generally diagnosed in locally advanced stages which require multimodality therapy consisting of neo-adjuvant or perioperative chemo(radio)therapy followed by a radical surgical resection of the primary tumor and a 2-field lymphadenectomy(2FND) or 3-field lymphadenectomy (3FND) is considered.[4] In Nepal, the 5 year overall survival has been estimated to be 24% with median survival of 30 months in patients receiving treatment.[5]

Extent of lymphadenectomy has always been an important parameter in determining long term outcome in patients undergoing esophagectomy for carcinoma esophagus. The prevalence of nodal metastases varies from 28.6% in T1 lesions to as high as 81.4% in T2 – 3 lesions.[6] This indicates the importance of radical lymphadenectomy to be mandatory for submucosal cancers and for cancers with deeper invasion.[6]

The optimal extent of lymphadenectomy is still controversial depending upon the surgeon's philosophy – radical or simple sampling.[4] This study aims to assess the characteristics and overall survival of the patients with EC and GEJC who underwent surgical treatment in one of the tertiary cancer centers of Nepal depending upon the extent of lymphadenectomy.

Methods

This study included all the 634 patients of esophageal carcinoma and gastroesophageal carcinoma who underwent surgical resection at our institution over a period of 2001-2019.

The extent of lymphadenectomy was classified according to the definitions as per Japanese Classification of Esophageal Cancer, 12th Edition: Part I, as:[7]Two-field nodal dissection (2FND) is classified into three types:

1. Standard: In the thorax: Infra-carinal 107, 108, 109, 110, 111, 112and 113. In the abdomen: D2 lymphadenectomy- 9, 8, 11, 3, 7 and 12.
2. Extended: Standard 2FND and 106R, 106recR along the right recurrent laryngeal nerve in addition to D2 lymphadenectomy.
3. Total: Extended 2FND with 106L, 106recL in addition to D2 lymphadenectomy

Three-field nodal dissection (3FND): is characterized by nodal dissection in the abdominal, mediastinal and cervical compartments.

1. Lymph node stations 101 and 104 in the neck bilaterally in addition to Total 2FND.
2. For GEJ carcinoma:
   2.1 D1: Lymph node dissection of No. 1, 2, 3a, and 7.
   2.2 D1+ : Lymph node dissection of No. 1, 2, 3a, 7, 8a, 9, and 11p.
   2.3 D2: Lymph node dissection of No. 1, 2, 3a, 7, 8a, 9, 11p, 19, 20 and 110.

In our study, radical lymphadenectomy (RL) for EC included those with 3FND, 2FND and non-radical lymphadenectomy (NRL) for EC included those with Sampling. Similarly, for GEC, RL included those with at least a complete D2 lymphadenectomy, D2 combined with lower mediastinal lymphadenectomy,

whereas NRL included those with D1 or D1+ lymphadenectomy.

Patient characteristics were assessed, modalities of treatment received by the patients were also categorized. Overall survival was calculated using Kaplan-Meir curve and survival differences were compared using Log rank test. P value <0.05 was considered to be significant. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS 26).

Results

A total of 634 patients were included in the study. Basic characteristics and treatment received by the patients are mentioned in Table 1. Most of the patients were treated with upfront surgery. The extent of lymphnode dissection are shown in the Table 2. Two-FND was the most commonly performed extent of lymphadenectomy in the EC patients and abdominal D2 lymphadenectomy was more commonly performed in GEC patients.

In this study, there was significant difference in the overall survival of the patients with median survival for RLN: 34 months and for NRL: 15 months (p<.001).

Overall survival of the two groups of patients has been shown using the Kaplan-Meier curve in the Fig 1.

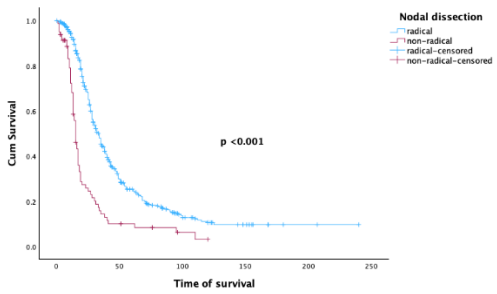

Figure 1. Kaplan-Meier curve showing the overall survival of the patients.

Table 1. Basic parameters and treatments received by patients in the study.

Mean age (in years)	58	
Male	394	(62.15%)
Female	240	(37.85%)
Total	634	(100.00%)
Treatment modalities		
Upfront surgery	299	(47.16%)
Neoadjuvant Chemoradiation followed by surgery	107	(16.88%)
Preop- or perioperative chemotherapy and surgery	96	(15.14%)
Surgery followed by chemotherapy or chemoradiation	132	(20.82%)
Total	634	(100.00%)

Table 2 Extent of lymphadenectomy performed.

Radical Lymphadenectomy (RL)	545	(85.96%)
2 FND	293	(46.21%)
Extended 2FND	13	(2.05%)
Total 2 FND	33	(5.21%)
3FND	28	(4.42%)
Abdominal D2 with lower mediastinal lymphnode dissection	77	(12.15%)
Abdominal D2 nodal dissection	101	(15.93%)
Non-radical lymphadenectomy(NLR)	89	(14.04%)
Abdominal D1 dissection	8	(1.26%)
Nodal sampling	81	(12.78%)
Total	634	(100.00%)

Discussion

The extent of lymphnode metastasis in EC and its relation with overall survival of the patients have been studied in great details

by several studies. In Akiyama's series, cervical nodes metastases were found in 46.3%, 29.2% and 27.2% for upper, middle and lower EC, respectively. In the same study, mediastinal nodal metastases were seen in 56.1%, 53% and 58% for upper, middle and lower EC, respectively. Similarly, abdominal nodal metastases were noted in 12.2%, 39.9% and 74.1% of upper, middle and lower EC, respectively.[6]

Stiles et al., showed patients with T3 or more advanced GEC had a greater probability of subcarinal nodal disease as compared to patients with early lesions, as there were no patients with subcarinal nodal metastasis, disease free after 3 years.[8]

Hence it is rational to perform 3FND. But, the optimal extent of lymphadenectomy for EC and GEC has always been a debatable topic among surgeons. The lymph node ratio is shown to be a major factor determining prognosis and survival of the EC and GEC patients. The 5-year survival rate for node-negative patients was found to be 88%, compared with 33% for patients with positive nodal metastases ($p = 0.0007$).[9] Altorki et al, noted that there can be unsuspected nodal metastasis to recurrent laryngeal and/or cervical nodes in upto 36% of patients with esophageal carcinoma, regardless of the histological type of location of the cancer in the esophagus, and advocated the need for more extensive lymphadenectomy.[9] D'Journo et al. showed that standard 2FND would result in inadequate nodal staging and incomplete resection in as much as 25% of all patients and in more than 35% of the node-positive patients, supporting the need of 3FND.[10] The need of 3 FND is also shown by our previous study, which has shown significant survival benefit in the patients who had undergone radical lymphadenectomy, be it either EC or GEC.[11,12]

However, there are differences in the guidelines regarding treatment protocols of esophageal carcinoma in different regions of the world. This indicates the lack of a common consensus among surgeons around the world. Japanese guidelines state the curative therapy of esophageal cancer involving preoperative triplet chemotherapy with docetaxel, cisplatin plus 5-fluorouracil followed by an esophagectomy with a 3FND or tailored lymphadenectomy in case of a thoracic ESCC (stage II and III).[13,14] In China, for mid-lower thoracic esophageal carcinoma, neoadjuvant chemoradiotherapy is followed by an esophagectomy with a total mediastinal 2FND, and a 3-FND in suspected cervical lymph nodes metastasis or in case of upper thoracic cancer.[15] The current ESMO (European Society of Medical Oncology) and NCCN guidelines are similar in terms of extent of lymphadenectomy in EC. These guidelines suggest for either a standard 2FND or a en-bloc 2FND (extended 2FND) for fit patients following neoadjuvant chemoradiotherapy or perioperative chemotherapy.[16,17]

Studies have shown that an extended lymphadenectomy (3FND) improves the accuracy of staging and the prognosis of the tumor, locoregional disease control and survival in EC and GEC.[9,18] However, Orringer et al. demonstrated that more extensive nodal dissection sometimes results in stage migration; surgical morbidity and mortality rates are increased and a real benefit in long-term survival has not been well demonstrated.[19] A Swedish study revealed survival in esophageal cancer was not improved by extensive

lymphadenectomy, but resection of a moderate number (20–30) of nodes was prognostically beneficial for patients with advanced T-stages (T3/T4) and those not receiving neoadjuvant therapy.[20]

Although, overall survival was shown to be better with 3FND in advanced disease, there were major morbidity associated with 3FND which were essentially avoided in lesser lymphadenectomy. Even in Japan where 3FND is frequently performed, overall hospital mortality rate of 4%.[21] In western countries it can vary from 1% in Lerut's series up to 5% in Altorky's series.[9,22] Septic complications in 26.8%, followed by pulmonary complications in 21.3%; the rate of recurrent laryngeal nerve injury was seen in more than 50% of patients in study by Tachibana et al.[23] A study by Yasuda et al. observed insufficient laryngeal elevation after 3FND, this increased the incidence of aspiration in these patients.[24]

In Siewert's study of 1602 GEJC(adenocarcinoma) cases, only 5% had the risk of having lymph node involvement above the level of the carina; therefore, more than 60% of patients with Siewert type I GEC underwent a transhiatal resection. However, by this approach it is impossible to perform a formal nodal dissection above the carinal region.[25]

GEJC have been managed according to two main approaches: Limited Transhiatal esophagectomy(THE) and Transthoracic esophagectomy(TTE). THE, as by Orringer in 1984 was designed to minimize the postoperative morbidity/mortality.[19] The purpose of TTE with a more extended nodal dissection (2FND) is to improve completeness of the resection and to increase locoregional tumor control.

THE with limited lymphadenectomy and TTE with extended lymphadenectomy were compared in a prospective randomized controlled trial for adenocarcinoma of the esophagus and GEJ, and no difference was found in postoperative mortality nor in overall oncological results ($p = 0.45$); 5-year survival rates were 34 and 36%, respectively ($p = 0.71$), but intraoperative blood loss and short-term outcome were significantly better in the THE arm.[26] In Patients with distal esophageal cancer or Siewert type I cancer, a better long-term survival was obtained in the TTE group, especially in those patients with a limited number of positive nodes, but this survival benefit was not shown for patients with Siewert type II tumors of the GEJ.[27]

To the best our knowledge this is the first study from Nepal exploring the results of lymphadenectomy in large number of patients. Our study emphasizes the need for a radical dissection as it carries better median survival of 34 months vs 15 months ($p<0.001$). The higher survival of the patients who underwent radical lymphadenectomy in our study is in line previously published reports regarding EC and GEC treatment trends in Nepal.[12,5] Therefore, it appears for esophageal SCC, radical lymphadenectomy in amount of either 2-FND or 3-FND should be a standard practice in Nepalese context. Similarly, for GEJC, D2 +/- lower mediastinal adenectomy should be considered.

Limitations

This study has compared the overall survival in patient undergoing RL and NRL in EC and GEC. But, the specific postoperative outcomes, complications and quality of life associated with different

types of radical lymphadenectomy has not been evaluated and warrants further investigations. Moreover, it is a retrospective study coming from a single center in a long span of 18 years with changing pattern of treatment modalities.

Conclusion

All these observations related to improved overall survival in the patients who undergo more extensive lymphnode dissection as compared to the lesser extent or NRL dissection, since nodal involvement has been associated with worse outcome in patients with EC and GEC. It is clear with this study as well that a more formal lymphadenectomy confers better overall survival to our patients as very few patients present in the early stages of the disease which may be attributable to lack of access to efficient health facilities in this country.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2024;74(3):229–63.

2. Uhlenhopp DJ, Then EO, Sunkara T, Gaduputi V. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. Clin J Gastroenterol. 2020;13(6):1010–21.

3. Agarwal S, Bell MG, Dhaliwal L, Codipilly DC, Dierkhising RA, Lansing R, et al. Population Based Time Trends in the Epidemiology and Mortality of Gastroesophageal Junction and Esophageal Adenocarcinoma. Dig Dis Sci. 2024;69(1):246–53.

4. Schuring N, van Berge Henegouwen MI, Gisbertz SS. History and evidence for state of the art of lymphadenectomy in esophageal cancer surgery. Diseases of the Esophagus. 2024;37(4):1–16.

5. Thakur B, Devkota M, Thapa A. Trends in Surgical Management of Esophageal Cancer. J Nepal Health Res Counc. 2022;20(57):868–74.

6. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg. 1994;220(3):364–73.

7. Mine S, Tanaka K, Kawachi H, Shirakawa Y, Kitagawa Y, Toh Y, et al. Japanese Classification of Esophageal Cancer, 12th Edition: Part I. Esophagus. 2024: 1-37.

8. Stiles ZE, Brady M, Hochwald SN, Kukar M. Relevance of Subcarinal Lymph Node Dissection for Gastroesophageal Junction Adenocarcinoma. Journal of Surgical Research. 2023;290:2–8.

9. Altorki N, Kent M, Ferrara C, Port J. Three-Field Lymph Node Dissection for Squamous Cell and Adenocarcinoma of the Esophagus: Annals of Surgery. 2002;236(2):177–83.

10. D'Journo XB, Doddoli C, Michelet P, Loundou A, Trousse D, Giudicelli R, et al. Transthoracic esophagectomy for adenocarcinoma of the oesophagus: standard versus extended two-field mediastinal lymphadenectomy?. European Journal of Cardio-Thoracic Surgery. 2005;27(4):697–704.

11. Thakur B, Zhang CS, Meng XL, Bhaktaman S, Bhurtel S, Khakural P. Eight-year experience in esophageal cancer surgery. Indian Journal of Cancer. 2011;48(1):34–9.

12. Thakur B, Li H, Devkota M. Results of management of esophageal and GE junction malignancies in Nepalese context. J Thorac Dis. 2013;5(2):123–8.

13. Kitagawa Y, Ishihara R, Ishikawa H, Ito Y, Oyama T, Oyama T, et al. Esophageal cancer practice guidelines 2022 edited by the Japan esophageal society: part 1. Esophagus. 2023;20(3):343–72.

14. Kitagawa Y, Ishihara R, Ishikawa H, Ito Y, Oyama T, Oyama T, et al. Esophageal cancer practice guidelines 2022 edited by the Japan

Esophageal Society: part 2. Esophagus. 2023;20(3):373–89.

15. Health Commission of the People's Republic of China N. National guidelines for diagnosis and treatment of esophageal carcinoma 2022 in China (English version). Chin J Cancer Res. 2022;34(4):309–34.

16. Obermannová R, Alsina M, Cervantes A, Leong T, Lordick F, Nilsson M, et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2022;33(10):992–1004.

17. Ajani JA, Barthel JS, Bentrem DJ, D'Amico TA, Das P, Denlinger CS, et al. Esophageal and Esophagogastric Junction Cancers (Version 3. 2024). J Natl Compr Canc Netw. 2024.

18. Lerut T, Nafteux P, Moons J, Coosemans W, Decker G, De Leyn P, et al. Three-Field Lymphadenectomy for Carcinoma of the Esophagus and Gastroesophageal Junction in 174 R0 Resections: Impact on Staging, Disease-Free Survival, and Outcome: A Plea for Adaptation of TNM Classification in Upper-Half Esophageal Carcinoma. Annals of Surgery. 2004;240(6):962–74.

19. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two Thousand Transhiatal Esophagectomies: Changing Trends, Lessons Learned. Annals of Surgery. 2007;246(3):363–74.

20. Gottlieb-Vedi E, Kauppila JH, Mattsson F, Hedberg J, Johansson J, Edholm D, et al. Extent of Lymphadenectomy and Long-term Survival in Esophageal Cancer. Annals of Surgery. 2023;277(3):429–36.

21. Udagawa H, Ueno M, Shinohara H, Haruta S, Kaida S, Nakagawa M, et al. The importance of grouping of lymph node stations and rationale of three-field lymphoadenectomy for thoracic esophageal cancer. Journal of Surgical Oncology. 2012;106(6):742–7.

22. Lerut T, Moons J, Fieuws S. Extracapsular lymph node involvement in esophageal cancer and number of involved nodes. The Journal of Thoracic and Cardiovascular Surgery. 2004;127(6):1855–6.

23. Tachibana M, Kinugasa S, Yoshimura H, Dhar DK, Nagasue N. Extended Esophagectomy With 3-Field Lymph Node Dissection for Esophageal Cancer. Archives of Surgery. 2003 Dec 1;138(12):1383–9.

24. Yasuda T, Yano M, Miyata H, Yamasaki M, Takiguchi S, Fujiwara Y, et al. Evaluation of Dysphagia and Diminished Airway Protection after Three-Field Esophagectomy and a Remedy. World Journal of Surgery. 2013;37(2):416–23.

25. Feith M, Stein HJ, Siewert JR. Adenocarcinoma of the Esophagogastric Junction: Surgical Therapy Based on 1602 Consecutive Resected Patients. Surgical Oncology Clinics of North America. 2006;15(4):751–64.

26. Omloo JMT, Lagarde SM, Hulscher JBF, Reitsma JB, Fockens P, van Dekken H, et al. Extended Transthoracic Resection Compared With Limited Transhiatal Resection for Adenocarcinoma of the Mid/Distal Esophagus: Five-Year Survival of a Randomized Clinical Trial. Annals of Surgery. 2007;246(6):992.

27. Hulscher JBF, van Lanschot JJB. Individualised Surgical Treatment of Patients with an Adenocarcinoma of the Distal Oesophagus or Gastro-Oesophageal Junction. Digestive Surgery. 2005;22(3):130–4.