



An Editorial on Lymphadenectomy in Esophagectomy for Cancer

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In esophageal cancer patients, the entire peri-esophageal lymph node network is at risk for lymph node metastases and therefore lymphadenectomy is a traditional part of esophagectomy, aiming to maximize survival.¹ The extent of lymphadenectomy is a continuous topic of debate, especially in the current era of neoadjuvant treatment. Neoadjuvant chemoradiotherapy (nCRT) according to the CROSS regimen (5 cycles of carboplatin/paclitaxel combined with 41.4 Gy radiation in 23 fractions) achieves complete pathological response in almost 50% of patients with squamous cell carcinoma and in 16–20% of patients with adenocarcinoma of the esophagus.³ Furthermore, primarily irresectable tumors can in some cases be downstaged by administering a prolonged CROSS regimen (6 cycles of carboplatin/paclitaxel combined with 50.4 Gy radiation in 28 cycles), allowing esophagectomy with a reported radicality rate of 92%.⁴ After observing these positive effects of nCRT on pathological tumor and nodal status, the need for extended thoracic lymphadenectomy has been questioned for patients who undergo nCRT prior to esophagectomy for cancer. Less aggressive lymphadenectomy could reduce the risk of iatrogenic injury to structures such as the recurrent laryngeal nerves and thoracic duct. This might be especially relevant for the increasing group of patients undergoing salvage esophagectomy after definitive chemoradiotherapy (dCRT), as lymph node dissection can be challenging due to extensive post-radiation fibrosis. The study by Mayanagi et al. retrospectively evaluated the overall survival of a selected population who underwent dCRT followed by

salvage esophagectomy with selective dissection of clinically positive lymph nodes based on PET-CT (i.e., node picking), showing an overall 3-year survival of 60% and overall postoperative morbidity rate that was comparable to patients who underwent standard chemoradiotherapy followed by esophagectomy with 3-field lymphadenectomy.⁵ Although these results seem promising, the study was not designed to evaluate whether selective lymphadenectomy is oncologically non-inferior to extended lymphadenectomy during salvage esophagectomy in terms of survival.

In the debate on the optimal extent of lymphadenectomy in esophageal resection, esophageal adenocarcinoma and squamous cell carcinoma should be regarded as distinct entities with different responses to nCRT. Although literature is scarce regarding salvage esophagectomy, more evidence has emerged on the impact of lymph node yield in ‘standard’ planned esophagectomy after nCRT. While a side-study of the CROSS trial suggested that patients with esophageal adenocarcinoma may not benefit from an extended thoracic lymphadenectomy after nCRT,⁶ a large population-based study showed that increased lymph node yield (i.e., ≥ 15 nodes) is associated with improved overall survival following esophagectomy for esophageal adenocarcinoma, even after nCRT.^{7,8} This association was less evident for a smaller group of patients with squamous cell carcinoma, which might be explained by better response to nCRT and therefore less need for extended lymphadenectomy.⁸ These findings illustrate that the discussion on this topic is still open, which also seems to be true for patients undergoing salvage esophagectomy following dCRT. While the observational findings by Mayanagi et al. suggest that salvage esophagectomy with selective lymphadenectomy for squamous cell carcinoma could yield an acceptable survival rate, another study demonstrated that the retrieval of ≥ 15 lymph nodes significantly improves overall survival in that same patient population.⁹

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More studies are warranted to evaluate the role of extended lymphadenectomy in both planned and salvage esophagectomy following CRT.

Ideally, lymph node dissection is limited to lymph nodes that are truly metastasized. The challenge remains, however, in how to adequately identify lymph node metastases during the preoperative workup. The reliability of clinical lymph node staging is limited, particularly due to the poor sensitivity of PET/CT scanning for the detection of esophageal lymph node metastases [34–74%].¹⁰ This means that lymph node metastases are frequently missed in clinical staging, which precludes any solid strategies for targeted lymph node dissection and leads most Western surgeons to prefer a two-field lymphadenectomy as a routine part of esophagectomy.¹¹ This concept probably applies to both patients undergoing planned esophagectomy after nCRT and patients undergoing salvage esophagectomy after dCRT. Yet, it remains unclear exactly which lymph node stations should be part of this standard two-field lymphadenectomy.¹² Particular disagreement exists on the necessity of dissecting the high mediastinal paratracheal lymph nodes in patients with distal esophageal tumors. Comparable to the rationale of surgeons performing selective lymphadenectomy in salvage esophagectomy,⁵ some surgeons only perform paratracheal lymphadenectomy in cases with preoperatively identified tumor-positive nodes in that region, as they are concerned about iatrogenic injury to the recurrent laryngeal nerves. However, in light of the limitations of current staging techniques and the additional fact that paratracheal lymph node metastases are found in up to 10% of patients who undergo esophagectomy for cancer of the distal esophagus or gastro-esophageal junction,^{1,13,14} routine paratracheal lymphadenectomy may be justified from an oncological perspective.

True tailoring of lymphadenectomy may become a realistic possibility as our understanding of the spread patterns of different esophageal tumors improves. The Japan Esophageal Society (JES) and Japanese Gastric Cancer Association (JGCA) recently collaborated to perform a prospective nationwide study investigating the incidence of lymph node metastases for each separate abdominal and mediastinal lymph node station in patients with cancer of the gastro-esophageal junction, suggesting that lymphadenectomy might be restricted to only the abdominal field in cases where esophageal involvement is limited (< 4 cm).¹⁵ The TIGER study is currently investigating this topic on a global scale and is expected to provide more valuable insights.¹⁶ Furthermore, in the future, intraoperative targeting of lymph nodes might become realistic with the aid of indocyanine green (ICG) imaging techniques.

In conclusion, current staging techniques alone are probably not sufficient to guide a targeted lymph node dissection in (salvage) esophagectomy, and further research is required to gain insight into the balance between oncological merits and clinical risks of extended lymphadenectomy in esophageal cancer patients. As highlighted by the results of Mayanagi et al.⁵, this discussion is also highly relevant for the growing number of patients undergoing salvage esophagectomy following dCRT.

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REFERENCES

1. Parry K, Haverkamp L, Bruijnen RC, et al. Staging of adenocarcinoma of the gastroesophageal junction. *Eur J Surg Oncol.* 2016;42(3):400–6.
2. Reynolds JV, Preston SR, O'Neill B, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 39 (15_suppl) (2021).
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366(22):2074–84.
4. Defize IL, van der Horst S, Bulbul M, et al. Salvage Robot-Assisted Minimally Invasive Esophagectomy (RAMIE) for T4b Esophageal Cancer After Definitive Chemoradiotherapy. *Ann Surg Oncol.* 2021;28(5):2730–8.
5. Mayanagi S, Haneda R, Inoue M, Ishii K, Tsubosa Y. Selective Lymphadenectomy for Salvage Esophagectomy in Patients with Esophageal Squamous Cell Carcinoma. *Ann Surg Oncol.* 2022. <https://doi.org/10.1245/s10434-022-11625-x>.
6. Noordman BJ, van Klaveren D, van Berge Henegouwen MI, et al. Impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy. *Ann Surg.* 2018;267(5):892–7.
7. Visser E, Markar SR, Ruurda JP, Hanna GB, van Hillegersberg R. Prognostic value of lymph node yield on overall survival in esophageal cancer patients: a systematic review and meta-analysis. *Ann Surg.* 2019;269(2):261–8.
8. Visser E, van Rossum PSN, Ruurda JP, van Hillegersberg R. Impact of lymph node yield on overall survival in patients treated with neoadjuvant chemoradiotherapy followed by esophagectomy for cancer: a population-based cohort study in the Netherlands. *Ann Surg.* 2017;266(5):863–9.
9. Wang S, Tachimori Y, Hokamura N, Igaki H, Nakazato H, Kishino T. Prognostic analysis of salvage esophagectomy after definitive chemoradiotherapy for esophageal squamous cell carcinoma: the importance of lymphadenectomy. *J Thorac Cardiovasc Surg.* 2014;147(6):1805–11.
10. Shi W, Wang W, Wang J, Cheng H, Huo X. Meta-analysis of 18FDG PET-CT for nodal staging in patients with esophageal cancer. *Surg Oncol.* 2013;22(2):112–6.
11. Haverkamp L, Seesing MF, Ruurda JP, Boone J, Hillegersberg VR. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. *Dis Esophagus.* 2017;30(1):1–7.

12. Hagens ERC, van Berge Henegouwen MI, Cuesta MA, Gisbertz SS. The extent of lymphadenectomy in esophageal resection for cancer should be standardized. *J Thorac Dis.* 2017;9(Suppl 8):S713–23.
13. Sepesi B, Schmidt HE, Lada M, et al. Survival in Patients With Esophageal Adenocarcinoma Undergoing Trimodality Therapy Is Independent of Regional Lymph Node Location. *Ann Thorac Surg.* 101(3): 1075–80; Discussion 1080 (2016).
14. Gantxegi A, Kingma BF, Ruurda JP, Nieuwenhuijzen GAP, Luyer MDP, van Hillegersberg R. The value of paratracheal lymphadenectomy in esophagectomy for adenocarcinoma of the esophagus or gastroesophageal junction: a systematic review of the literature. *Ann Surg Oncol.* 2022;29(2):1347–56.
15. Kurokawa Y, Takeuchi H, Doki Y, et al. Mapping of lymph node metastasis from esophagogastric junction tumors: a prospective nationwide multicenter study. *Ann Surg.* 2021;274(1):120–7.
16. Hagens ERC, van Berge Henegouwen MI, van Sandick JW, et al. Distribution of lymph node metastases in esophageal carcinoma [TIGER study]: study protocol of a multinational observational study. *BMC Cancer.* 2019;19(1):662–719.

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