BMJ Surgery, Interventions, & Health Technologies

Extent and consequences of lymphadenectomy in oesophageal cancer surgery: case vignette survey

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To cite: de Gouw DJJM, Scholte M, Gisbertz SS, *et al*. Extent and consequences of lymphadenectomy in oesophageal cancer surgery: case vignette survey. *BMJ Surg Interv Health Technologies* 2020;**2**:e000026. doi:10.1136/bmjsit-2019-000026

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjsit-2019-000026).

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Received 08 October 2019
Revised 02 March 2020
Accepted 14 March 2020

Check for updates

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ABSTRACT

Objectives Lymph node dissection (LND) is part of the standard operating procedure in patients with resectable oesophageal cancer after neoadjuvant chemoradiotherapy regardless of lymph node (LN) status. The aims of this case vignette survey were to acquire expert opinions on the current practice of LND and to determine potential consequences of non-invasive LN staging on the extent of LND and postoperative morbidity.

Design An online survey including five short clinical cases (case vignettes) was sent to 272 oesophageal surgeons worldwide.

Participants 86 oesophageal surgeons (median experience in oesophageal surgery of 15 years) participated in the survey (response rate 32%).

Main outcome measures Extent of standard LND, potential changes in LND based on accurate LN staging and consequences for postoperative morbidity were evaluated.

Results Standard LND varied considerably between experts; for example, pulmonary ligament, splenic artery, aortopulmonary window and paratracheal LNs are routinely dissected in less than 60%. The omission of (parts of) LND is expected to decrease the number of chyle leakages, pneumonias, and laryngeal nerve pareses and to reduce operating time. In order to guide surgical treatment decisions, a diagnostic test for LN staging after neoadjuvant therapy requires a minimum sensitivity of 92% and a specificity of 90%.

Conclusions This expert case vignette survey study shows that there is no consensus on the extent of standard LND. Oesophageal surgeons seem more willing to extend LND rather than omit LND, based on accurate LN staging. The majority of surgeons expect that less extensive LND can reduce postoperative morbidity.

Key messages

What is already known about this subject?

► As many as 65% of patients with oesophageal cancer do not harbour lymph node metastases after neoadjuvant chemoradiotherapy, which challenges the need for lymph node dissection (LND) in a substantial part of patients. New techniques that select patients for LND could impact the extent of LND and possibly postoperative complications.

What are the new findings?

► This expert case vignette survey study shows that there is no consensus on the extent of routine LND, but omitting LND could have advantages in terms of fewer complications and shorter OR time. Surgeons seem more willing to expand instead of omit LND in case of accurately being informed regarding LN status prior to surgery.

How might these results affect future research or surgical practice?

► LND comparability and accuracy is currently limited, as routine two-field LND recommended in the American Joint Committee on Cancer guidelines is not routinely performed by all experts. This could hamper the implementation of new diagnostic techniques for stratifying patients for LND.

INTRODUCTION

Standard primary treatment of resectable distal oesophageal cancer (cT1b-4aN0-3M0) may consist of neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection of the oesophagus, including the regional lymph nodes (LNs).[1] After nCRT, on average, 31%–38% of patients harbour LN metastases.[2–4] This implies that in up to 69% of patients, a lymph node dissection (LND) may be superfluous.

At present, the imaging modalities used for staging of oesophageal cancer, including CT, fluorodeoxyglucose positron emission tomography/computed tomography and endoscopic ultrasound, have low diagnostic accuracy for the detection of LN metastases.[3 5 6] Therefore, international guidelines recommend formal LND in all patients.[7 8] However, new modalities and more accurate techniques for detection of LN metastases are being developed and might improve detection of LN metastases after nCRT.[9–11]

Application of a new diagnostic technique that is able to accurately detect the number and location of LN metastases prior to surgery could have an impact on the extent of LND and subsequently on postoperative complications. However, due to variation in clinical practice of LND and different behaviours towards innovation, it is unclear whether surgical practice will change after developing and implementing such a new diagnostic imaging technique. Therefore, the aim of this case vignette survey was to acquire expert opinions on the current practice of LND after nCRT, and the potential consequences of accurate LN staging on the extent of LND and postoperative morbidity in patients with resectable oesophageal cancer.

METHODS

Participants

Invitations for the English web-based survey were send to 236 surgical members of the International Society for Diseases of the Oesophagus (ISDE) and 36 members of the minimally invasive oesophageal cancer think tank group from around 15 European high volume centres.

Survey mailings

In July 2018, participants were invited via email to participate in an online survey. A total of three reminders (August, September and October) were sent, and participants who had not responded after these reminders were classified as non-responders. The questionnaires were analysed anonymously. The survey was constructed using Castor Electronic Data Capture.[12]

LN staging

For the purpose of this study, the eighth edition of the American Joint Committee on Cancer (AJCC) staging and the 11th edition of the Japanese Classification of Oesophageal Cancer staging for LN stations were combined to classify abdominal, thoracic and cervical LN metastases.[1 13–15] The superficial cervical, cervical paraoesophageal, deep cervical, peripharyngeal and supraclavicular LN stations were considered to be part of a cervical LND (1–5). The upper and lower paratracheal, aortopulmonary window, subcarinal, mediastinal paraoesophageal (upper, middle and lower) and pulmonary ligament LN stations were part of thoracic LND (6–13), and the paracardial, left gastric artery, coeliac trunk, splenic artery and splenic hilum, common hepatic artery and hepatoduodenal ligament LN stations were considered part of abdominal LN stations.[14 15 15–19]

Case vignette

In this case vignette study, we proposed a hypothetical diagnostic imaging test that is able to predict preoperative LN status 100% accurately. We used a hypothetical test since there is currently no diagnostic test that is able to accurately detect LN metastases after nCRT.

Participants were asked about their experience in oesophagectomy and routine surgical approach, including the extent of LND. Thereafter, a case of a 65-year-old, previously healthy man with a primary resectable distal oesophageal carcinoma (cT2-3) was presented. This patient underwent nCRT under the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) regimen, intravenous carboplatin and intravenous paclitaxel with concurrent radiotherapy, and is now scheduled for oesophagectomy.[2] In this survey, we used five case vignettes in which we varied the LN involvement within the abovementioned patient. In case 1, no LN metastases were detected by the proposed imaging test. In case 2, only thoracic LN metastases were detected; in case 3, only abdominal LN metastases were detected; and in case 4, both thoracic and abdominal LN metastases were detected by the proposed preoperative imaging test. A fifth case with only one cervical LN metastasis according to the preoperative imaging test was presented. Participants were invited to determine the preferred surgical approach for each case. Finally, participants were asked to determine the minimally required diagnostic accuracy for a preoperative imaging test that detects LN metastases, to justify a change in the extent of surgical resection.

In the last part of the survey, participants were asked about the expected effects on postoperative complications (anastomotic leakage, chyle leakage, pneumonia, tracheal injury, laryngeal nerve paresis and postoperative bleeding), intensive care unit (ICU) length of stay, total length of stay and mortality when LND was omitted or minimised. If no change was expected, the literature-based complication rate was used as expected complication rate. The entire content of the questionnaire is shown in online supplementary file 1.

Statistical analysis

Statistical analysis was performed using R (V.3.2.4) and consisted of descriptive statistics: proportions, medians and IQRs. We calculated relative risks (RRs) for the expected changes in complications. In case of missing data, the data of this participant were still used in the analyses, except for the missing values.

RESULTS

Participant characteristics

We obtained 272 email addresses from six different continents. The overall response rate was 33% (n=89) from 29 different countries and 6 different continents (figure 1). The members of the ISDE had a response rate of 26% (n=62), and the members of the minimally invasive oesophageal cancer think tank group had a response rate of 75% (n=27). Three participants did not meet the inclusion criteria as they were not performing oesophageal surgery. Eighty participants completed the survey. Surgeons had a median experience of 15 years (IQR 10–20) regarding oesophageal surgery and performed a median of 30 (IQR 20–50) oesophagectomies annually. All baseline characteristics are summarised in table 1.

Routine extent of LND

The routine extent of LND is shown in figure 2. The majority of surgeons (>80%) dissect the subcarinal (9),

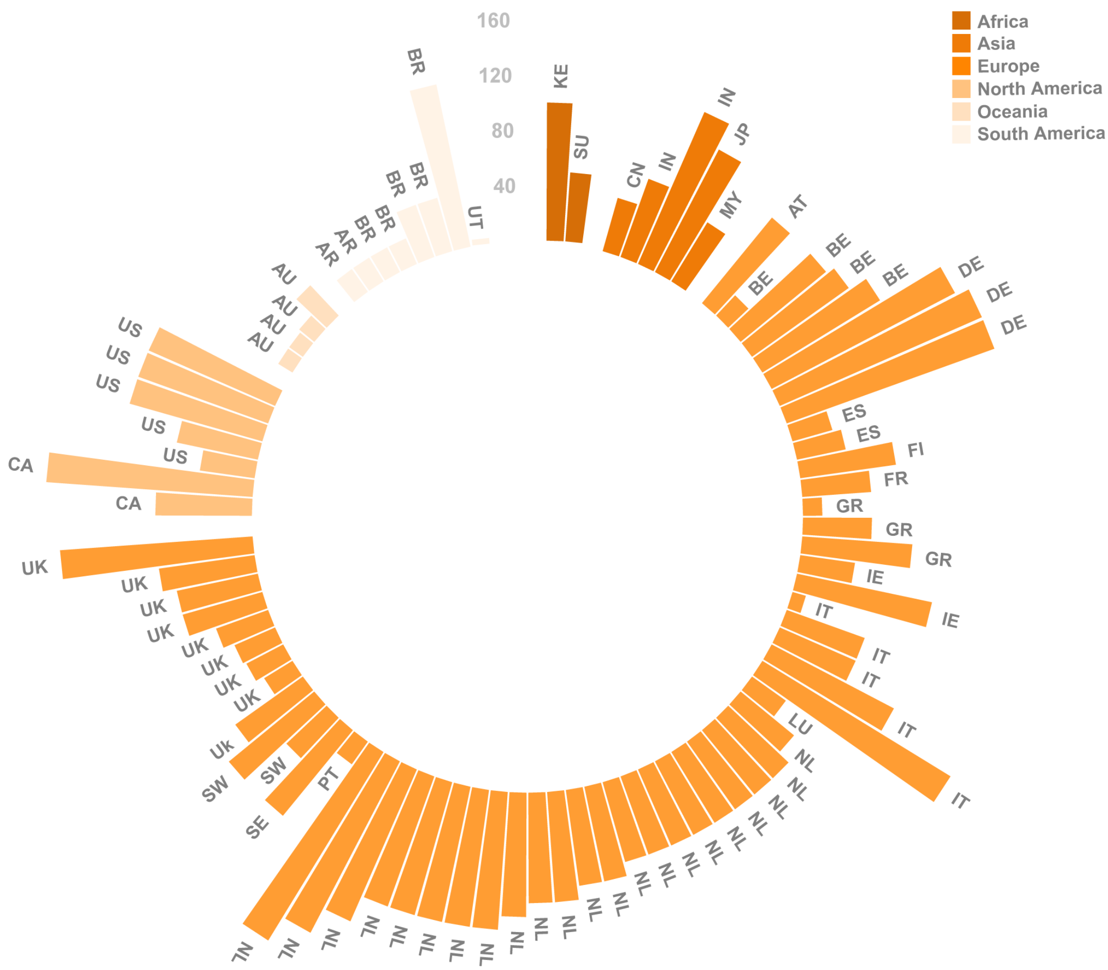


Figure 1 Characteristics of the participants. Participants are grouped per continent and country. The height of the bar indicates the performed number of oesophagectomies per year.

middle and lower mediastinal paraoesophageal (11 and 12), pulmonary ligament (13), paracardial (14), left gastric artery (15), coeliac trunk (16) and the common hepatic artery LN stations (18). In case LN metastases were found in a field outside the routine LND field, the upper paratracheal LNs (increase of 40%), the cervical paraoesophageal LNs (increase of 34%) and the lower paratracheal LNs (increase of 33%) would most frequently be added to the routine LND (figure 2). Results of the routine extent of LND for adenocarcinoma and squamous cell carcinoma are shown in online supplementary file 2.

Case vignette results

Seventy per cent of the participants would continue to perform thoracic and abdominal LND despite 100% certainty that no LN metastases were present, as detected by the hypothetical imaging test. Twenty-eight per cent of the participants would omit LND and 2% would only perform thoracic LND. A similar trend was observed in the other cases, where approximately one-third of participants would adapt their LND based on the imaging results (figure 3). In case only a cervical LN metastasis was detected by the proposed imaging test, 48% of the participants would perform cervical, thoracic and abdominal LNDs; 21% would solely perform a cervical LND; 2% would perform oesophagectomy without LND; and 29% would not perform surgery at all.

Required diagnostic accuracy of new diagnostic test

The median minimally required sensitivity to minimise LND was 92% (IQR 85–98), and the median minimum specificity was 90% (IQR 84–98) according to the participants.

Expected change in complications

Participants expected a reduction in postoperative chyle leakage, pneumonia and laryngeal nerve palsy if LND was omitted compared with complication rates of oesophagectomy with LND dissection (online supplementary file 3). Chyle leakage rate was expected to decrease from 7.6% with LND to 2.1% without LND (RR: 0.28)[16]; pneumonia was expected to decrease from 43.8% to 30.2% (RR: 0.69)[16]; and laryngeal nerve paresis was expected to decrease from 6.5% to 2.8% (RR: 0.43).[17] The participants expected no change in the percentage of anastomotic leakages, tracheal injury, postoperative bleeding, length of stay (including ICU) and deaths (figure 4). In case of omitting abdominal LND, no decrease in complications was expected, while omitting thoracic LND would result in a decrease in

Table 1 Participant characteristics

	All participants (n=86), n (%)	European participants (n=58), n (%)
Neoadjuvant therapy		
No CRT	2 (2)	1 (2)
Chemotherapy	17 (20)	12 (21)
Chemoradiotherapy other CROSS	8 (9)	3 (5)
Chemoradiotherapy CROSS	59 (69)	42 (72)
Surgical approach		
Abdominal and transhiatal approach	3 (3)	1 (2)
Abdominal and transthoracic approach	81 (94)	57 (98)
Other	2 (2)	0 (0)
Location of anastomoses		
Intrathoracic anastomosis	60 (70)	52 (89)
Cervical anastomosis	21 (24)	6 (11)
Other	5 (6)	0 (0)
Surgical technique		
Open surgery	20 (23)	11 (19)
Minimally invasive surgery	54 (63)	36 (62)
Hybrid surgery	21 (24)	14 (24)
Robot surgery	5 (6)	3 (5)

Based on the routine approach for treatment of T2–3 resectable distal oesophageal cancer. This scheme includes intravenous carboplatin and intravenous paclitaxel with concurrent radiotherapy followed by surgery. According to CRT scheme used in the CROSS trial (ref).
CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (ref); CRT, chemoradiotherapy.

the abovementioned complications. If LND is omitted, participants expected to save a median of 60 min per procedure (IQR 50–100).

Subgroup analysis

No differences between European participants and all participants were found.

DISCUSSION

The results of this case vignette survey showed that the routine extent of LND varies considerably between experts worldwide. Guidelines for LND are not always followed; especially the aortopulmonary window LNs and paratracheal LNs are not routinely dissected. Furthermore, the majority of participants would still perform thoracic and abdominal LND even if it is assumed that a hypothetical 100% accurate imaging test did not detect any LN metastases. If LND was omitted, a change in the percentage of chyle leakage, pneumonia and laryngeal nerve paresis was expected, as well as a 60 min shorter operative time. If a diagnostic imaging test was available that could detect the presence of LN metastases after nCRT, a minimum sensitivity of 92% and a specificity of 90% were recommended to personalise LND based on the diagnostic test.

Strength and limitations

This is the first study investigating the routine extent of standard LND and additionally resected LN stations in case of suspicious LN metastases. Based on worldwide expert opinion, we provided an overview of the implications of personalising LND in oesophageal cancer surgery. Some potential limitations should also be mentioned. First, the response rate was limited for some continents, especially Africa and Oceania, and the results of this survey might therefore not reflect a broader view from these geographical areas. Second, we provided information about the presence of thoracic or abdominal LN metastases in the cases, but the precise location, subtype (adenocarcinoma or squamous cell carcinoma) and number of these metastases was not specified. This might have resulted in different interpretations and answers, since experts could have envisioned the case differently (eg, only one LN metastasis vs multiple LN metastases). However, in this way, we were able to provide an overview of the expert opinion on omitting LND, while differences in practice had little influence on our results. Third, some questions would not likely occur in clinical practice. On the other hand, these theoretical cases provide useful information about adherence to the guidelines for the purpose of policy decisions.

Variation in current practice

The results show considerable variation in current extent of LND as performed by oesophageal surgeons worldwide. Routine two-field LND as recommended in the AJCC guidelines is not routinely performed by all experts, which could limit LND accuracy. Experts indicate multiple reasons for omitting particular LN stations, for example, because of technical difficulties, increased morbidity or a low risk of LN metastases in a particular area.[18] Despite a few studies describing the pattern of LN metastases in oesophageal carcinoma,[19–21] the distribution of LN metastases has not yet been described in large series. Moreover, it is known that nCRT significantly modifies location and distribution of LN metastases.[22] The balance between oncological value (accuracy of LND) and morbidity is therefore unclear. Currently, a worldwide prospective study (TIGER study, distribution of LN metastases in oesophageal carcinoma)[15] evaluates the distribution of LN metastases in patients with resectable oesophageal carcinoma. This may lead to new global guidelines for LND.

Besides variation in routine LND, participants seem more willing to extend the LND in case LN metastases are found than to omit LND in case no LN metastases are present according to the hypothetical test. In case of a cervical LN metastases, approximately half of the experts would perform a cervical, thoracic and abdominal LND. This is a surprising result, since the cervical LN stations are not part of routine clinical practice for the majority of

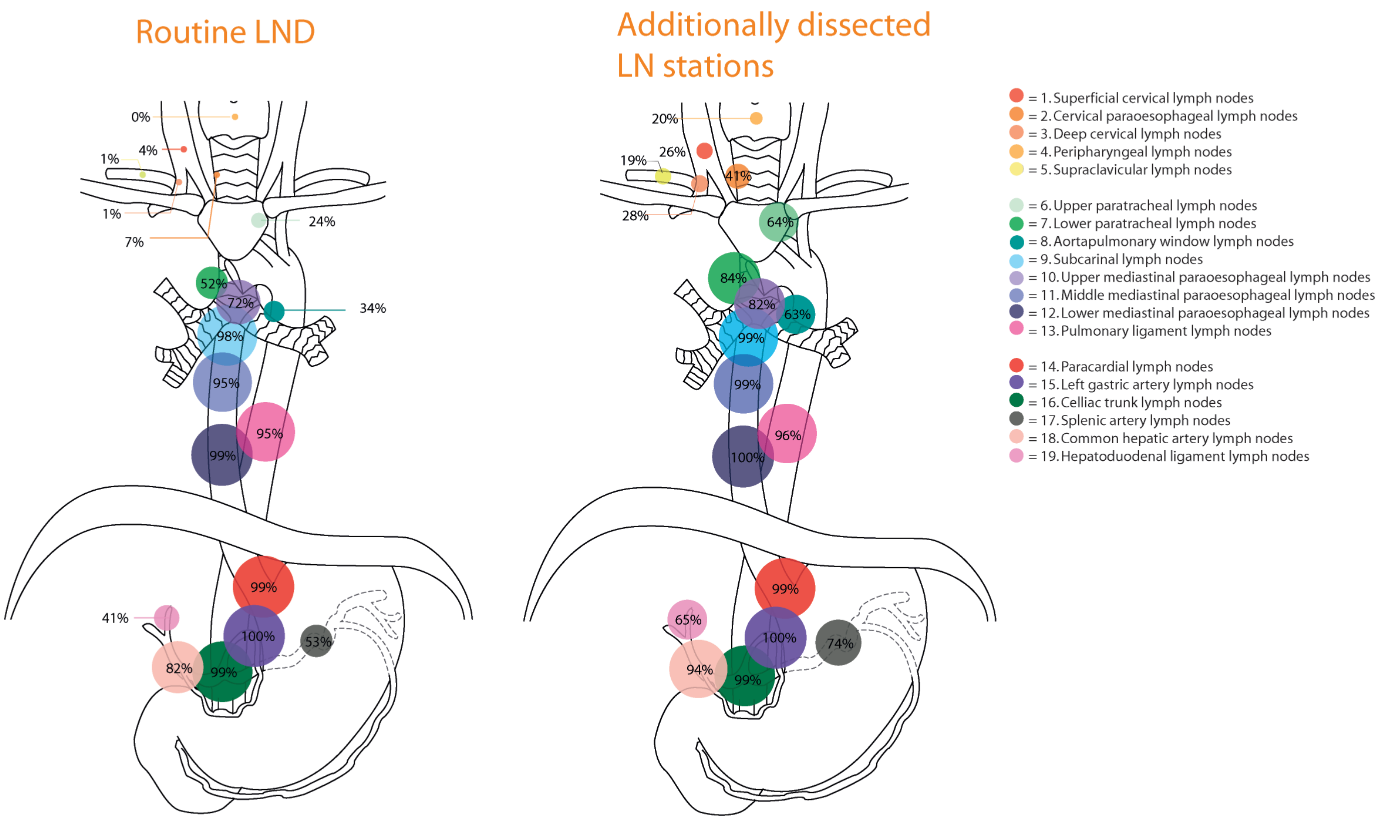


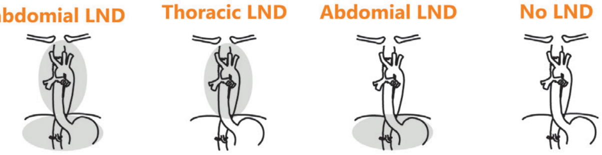
Figure 2 Routine extent of LND. The diameter of the circle indicates the percentage of surgeons that dissect the station with routine LND (left) and based on suspicious LN metastases (right). Anatomical figure was adapted from the TIGER study protocol with permission of the authors.[15] LN, lymph node; LND, lymph node dissection.

surgeons (figure 2). In the most recent AJCC guidelines, however, the lower cervical paratracheal, cervical perioesophageal level VI and VII LN stations are also considered to be locoregional LN stations, thereby justifying extension of the LND for the presence of cervical LNs in these particular stations.

Clinical implications

Experts indicate that omitting LND could have advantages in terms of fewer complications and shorter OR time, thereby improving quality of life and reducing costs. Currently, it is unknown if these advantages will weigh up to the possible risks of omitting LND when a diagnostic test is not 100% accurate. Recently, two phase III trials were initiated where watchful waiting is compared with standard surgery for patients with complete response of the tumour and LNs after nCRT.[23 24] In these trials, the importance of an accurate diagnostic test after nCRT is crucial as patients with (micro) LN metastases could easily be missed, resulting in unjustified omission of surgery. Results of these trials

Preferred extent of LND with different locations of LN metastases



	Thoracic and abdominal LND	Thoracic LND	Abdominal LND	No LND
Case 1 - No LN metastases	70%	2%	0%	28%
Case 2 - Only thoracic LN metastases	72%	28%	0%	0%
Case 3 - Only abdominal LN metastases	71%	0%	29%	0%
Case 4 - Both thoracic and abdominal metastases	99%	1%	0%	0%

Figure 3 Results of the case vignettes (short clinical cases). LN, lymph node; LND, lymph node dissection.

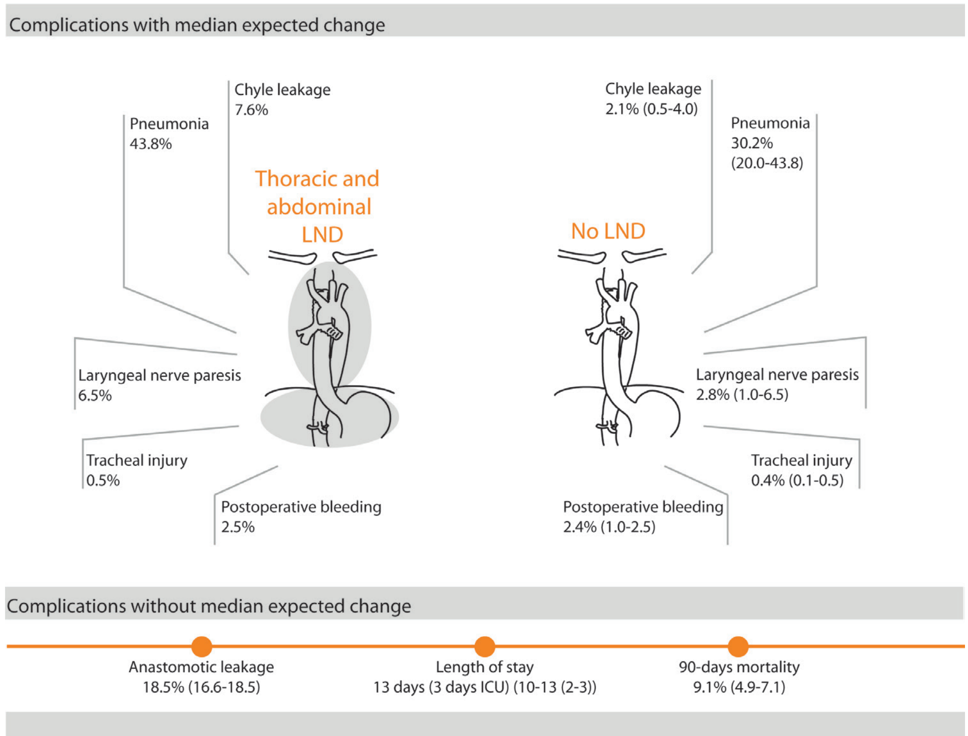


Figure 4 Expected change in complications when LND is omitted. The percentage for thoracic and abdominal LNDs are based on literature (online supplementary file 3). For no LND, the expected percentages of complications are displayed. The median percentages are displayed with IQRs. ICU, intensive care unit; LND, lymph node dissection.

are therefore of high interest to evaluate the consequences of unjustified omission of surgery.

The implications of accurate LN staging after nCRT will likely have a greater impact than solely omitting LND. For example, surgical approaches with a limited LND, for example, transhiatal oesophagectomy, might be more beneficial in patients without mediastinal LN metastases, given the lower risk of postoperative pulmonary complications. Furthermore, less invasive surgical techniques might prevent even more (functional) morbidity, for example, active surveillance in complete responders after nCRT.

This survey showed reluctance to omit LND despite the absence of LN metastases according to the hypothetical test. Experts mentioned disbelief in the accuracy of the test to detect micrometastases and missing the opportunity to perform LND (as reoperation is often not an option) as reasons not to omit LND. This is not surprising, since current imaging techniques have a relatively low accuracy and a recent meta-analysis showed a higher number of LN dissected during oesophagectomy resulted in better overall survival in this patient group.[5 6 25 26] Therefore, further explorative studies to assess the potential impacts of selecting patients for LND, as well as studies into promising diagnostic tests that could accurately detect LN metastases, are crucial to eventually, in case of encouraging results, translate surgical practice into a more personalised approach.

In conclusion, there is no consensus on the extent of LND after nCRT. Oesophageal surgeons seem more willing to extend LND if LN metastases are found rather than omit LND in case no LN metastases are identified. The majority of oesophageal surgeons expect to reduce morbidity and OR time when LND is omitted.

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Acknowledgements We are very grateful to the oesophageal surgeons who participated in this study.

Collaborators J Berg, M van Berge Henegouwen, L Bonavina, T Bright, A Charalampopoulos, M Chaudry, L Chen, E Cheong, F Daams, G Darling, A Davies, G Decker, J Dekker, L Depyere, M van Det, D Devriendt, X Djourno, F Duarte Sabino, W Eshuis, B Etten, M Ferguson, L Ferri, O Filho, J Freire, F Fumagalli Romario, P Grimminger, M Guglielmetti, R Gurunathan, C Gutschow, H Hartgrink, J Haveman, J Hayden, D Heineman, J Heisterkamp, A Hoelscher, P Jiang, I Karavokyros, G Kohn, E Kouwenhoven, J van Lanschot, T Liakakos, B Louie, C Loureiro Gonzalez, L Loviscek, D Low, J Luttikhold, M Luyer, S Mahdi, R Matthijsen, S de Meester, S Mercer, S Mine, K Moorthy, C Morse, M Muhinga, K Murthy, P Nafteux, G Nieuwenhuijzen, M Nilsson, D van der Peet, J Pierie, K Raja, J Räsänen, N Ravi, U Ribeiro, R Rosati, A Sanchez-Pernaute, S Santi, M Schafer, D Schizas, S Schoppmann, W Schröder, B Sgromo, M Smithers, S Szachnowics, F Takeda, R Taruselli morencio, D Tong, H van Veer, N Velasco Hernandez, E Wassenaar, D Watson, J Whiting, F van den Wildenberg.

Contributors DJJMdG, MS, BRK, CR conceived and designed the study. SSG and BW critically reviewed the survey. DJJMdG and MS acquired the data and performed the analyses with supervision of MMR. DJJMdG and MS drafted the manuscript. All authors critically reviewed the manuscript and approved the final submitted version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. The authors confirm that the data supporting the findings of this study are available within the article and are available from the corresponding author (DG), upon reasonable request.

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