



Selecting esophageal cancer patients for lymphadenectomy after neoadjuvant chemoradiotherapy: a modeling study

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ABSTRACT

Objectives Two-thirds of patients do not harbor lymph node (LN) metastases after neoadjuvant chemoradiotherapy (nCRT). Our aim was to explore under which circumstances a selective lymph node dissection (LND) strategy, which selects patients for LND based on the restaging results after nCRT, has added value compared with standard LND in esophageal cancer.

Design A decision tree with state-transition model was developed. Input data on short-term and long-term consequences were derived from literature. Sensitivity analyses were conducted to assess promising scenarios and uncertainty.

Setting Dutch healthcare system.

Participants Hypothetical cohort of esophageal cancer patients who have already received nCRT and are scheduled for esophagectomy.

Interventions A standard LND cohort was compared with a cohort of patients that received selective LND based on the restaging results after nCRT.

Main outcome measures Quality-adjusted life years (QALYs), residual LN metastases and LND-related complications.

Results Selective LND could have short-term benefits, that is, a decrease in the number of performed LNDs and LND-related complications. However, this may not outweigh a slight increase in residual LN metastases which negatively impacts QALYs in the long-term.

To accomplish equal QALYs as with standard LND, a new surgical strategy should have the same or higher treatment success rate as standard LND, that is, should show equal or less recurrences due to residual LN metastases.

Conclusions The reduction in LND-related complications that is accomplished by selecting patients for LND based on restaging results after nCRT seems not to outweigh a QALY loss in the long-term due to residual LN metastases. Despite the short-term advantages of selective LND, this strategy can only match long-term QALYs of standard LND when its success rate equals the success rate of standard LND.

INTRODUCTION

Primary treatment of resectable esophageal cancer consists of neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection of the esophagus including the regional

Key messages

What is already known about this subject?

► As many as 65% of esophageal cancer patients do not harbor lymphnode (LN) metastases after neoadjuvant chemoradiotherapy (nCRT), which challenges the need for lymphadenectomy in a substantial part of patients. Ideally, only patients who harbor LN metastases after nCRT would undergo lymphnode dissection (LND), but the added value of such a selective LND approach is currently unknown.

What are the new findings?

► Our modeling study shows that selecting patients for LND based on restaging results after nCRT could reduce LND-related complications, but this beneficial effect seems not to outweigh a loss in quality of life in the long-term due to a slight expected increase in patients with residual LN metastases.

How might these results affect future research or surgical practice?

► The consequences of having residual LN metastases are far more serious than those of short-term complications. Despite the short-term advantages of selective LND based on restaging results after nCRT, this strategy can only match long-term QALYs of standard LND when its success rate equals the success rate of standard LND.

lymph nodes (LNs).^{1–3} However, only 31% to 38% of patients harbor LN metastases after nCRT.^{1 4 5} This implies that in up to 69% of patients the lymph node dissection (LND) and its associated morbidity is needless. If we would adopt a new surgical strategy in which the restaging results after nCRT are used to select patients suspicious for harboring locoregional LN metastases, part of surgery-related complications could possibly be avoided.⁶ Our hypothesis is that by reducing the number of unnecessary LNDs, unnecessary morbidity could be prevented.

Ideally, consequences (eg, therapeutic consequences, quality of life (QoL) and survival) and relevant uncertainties of new

surgical strategies should be evaluated in an early stage of development, for example, in the pre-IDEAL stage (framework that describes the stages of innovation in surgery: Idea, Development, Exploration, Assessment, Long-term study). In that way, research and development of new surgical strategies can be steered in a way that they add most value to patients, healthcare and society. Therefore, we have previously conducted an expert case vignette survey in which we collected opinions from esophageal surgeons worldwide (n=89) via case presentations.⁶ In this paper, we describe the results of a modeling study based on scientific literature and the results of the expert case vignette survey, in which we compare standard LND practice with a hypothetical new selective LND strategy in which the restaging results after nCRT are used to select patients for LND. The model analyses the short-term and long-term consequences of both strategies and explores promising scenarios.

MATERIALS AND METHODS

Model development

We developed a model to evaluate complications, QoL and survival associated with standard LND for the diagnosis and treatment of LN metastases in patients with resectable distal esophageal cancer, and compared this to a hypothetical new strategy in which the restaging results after nCRT are used to select patients for LND. We assumed patients were 60 years old, the mean age at which esophageal cancer is diagnosed.¹ Furthermore, we assumed all patients had already received nCRT, had no distant metastases and were eligible for both strategies. The model consisted of a decision tree to model the primary treatment, and a state-transition model for the long-term follow-up of patients (figures 1 and 2). Based on clinical guidelines and expert interviews, the model was designed to resemble the clinical situation. The model was validated in accordance with the AdViSHE

checklist (Assessment of the Validation Status of Health-Economic decision models), by means of consulting clinical experts, cross-validation with relevant literature, and extreme value and subunit testing.⁷ Consequences of the hypothetical new test strategy were based on a worldwide case vignette study among esophageal surgeons.⁶

Decision tree

For each strategy, patients could either have locoregional LN metastases or no locoregional LN metastases after nCRT. In the standard LND strategy, all patients received routine esophagectomy with LND.¹ In the selective LND strategy, patients were selected for LND based on the restaging results after nCRT. Patients with low suspicion of LN metastases received esophagectomy without LND, while patients with high suspicion of LN metastases received esophagectomy with LND. As a result, four groups of patients can be distinguished: first, patients with low suspicion of LN metastases, in whom LN metastases were not present. Those patients benefited from the esophagectomy only. Second, patients with low suspicion of LN metastases, in whom LN metastases turned out to be present. Those patients were falsely treated with esophagectomy only and have residual LN metastases as a result. Third, patients with high suspicion of LN metastases, in whom LN metastases were indeed present. Those patients were successfully treated with esophagectomy and LND. Last, patients with high suspicion of LN metastases, in whom LN metastases were not present. Those patients received unnecessary LND. Furthermore, we assumed that in patients selected for LND who harbor LN metastases, these were always included in the LND.

In our model, we included complications that could potentially be avoided if LND is omitted. International experts of a previous case vignette survey determined that the number of pneumonias, chyle leakages and recurrent laryngeal nerve pareses would decrease when LND would be omitted.⁶

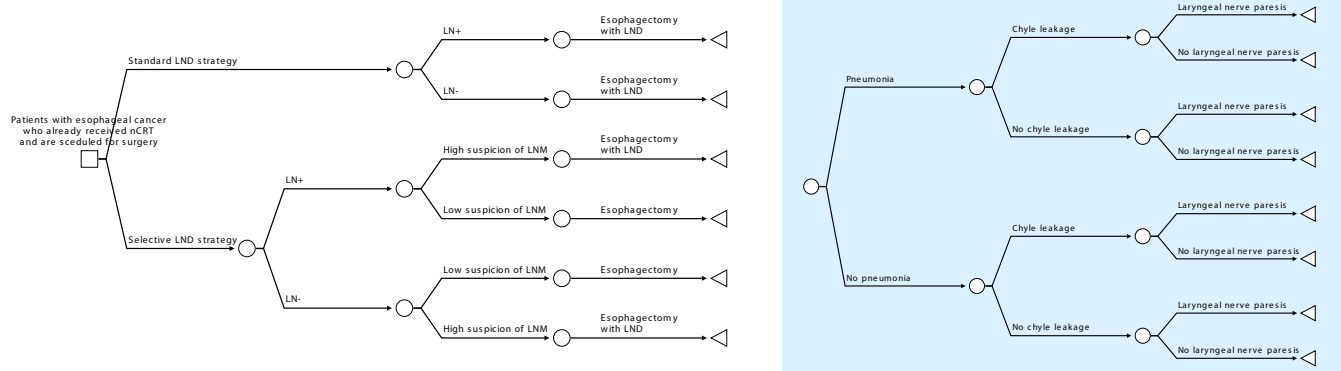


Figure 1 Decision tree of diagnosis and initial treatment. In the standard LND strategy, patients with esophageal cancer receive esophagectomy with LND regardless of their LN status. In the selective LND strategy, the restaging results after nCRT determine what treatment is given. In case of high suspicion for LNM, the patient receives esophagectomy with LND, while in case low suspicion for LN metastases, the patient receives esophagectomy. Each terminal node (triangle) is followed by the complications decision tree displayed in the blue box. LN, lymph node; LND, lymph node dissection; LNM, lymph node metastases; nCRT, neoadjuvant chemoradiotherapy.

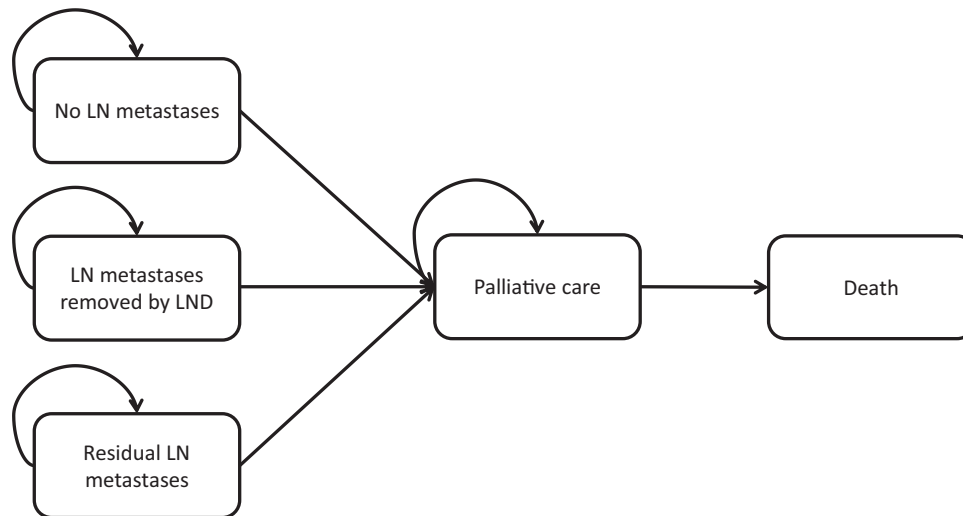


Figure 2 State-transition model of long-term follow-up. After initial treatment patients could have had no lymph node metastases and transit to the ‘no LN metastases’ health state. Patients with lymph node metastases could be successfully treated for their LN metastases and transit to the ‘LN metastases removed by LND’ health state. Patients who received no or unsuccessful treatment for their LN metastases transited to the ‘residual LN metastases’ health state. Patients could transit to the ‘palliative care’ health state in case recurrent disease was detected and from ‘palliative care’ to ‘death’. Patients could die in every state due to non-cancer-related causes, this is not displayed. LN, lymph node; LND, lymph node dissection.

State-transition model

To simulate the long-term follow-up of patients after treatment, the decision tree was followed by a state-transition model with lifetime horizon. The health states in this model were ‘no LN metastases’, ‘LN metastases removed by LND’, ‘residual LN metastases’, ‘palliative care’, and ‘death’. After the decision tree, we assumed patients without LN metastases transit to the ‘no LN metastases’ state with a relatively low chance of extraregional progression.⁸ Patients with LN metastases could be successfully treated for their metastases and transit to the ‘LN metastases removed by LND’ with the possibility of extraregional progression.⁹ In case restaging results falsely indicated low suspicion of LN metastases, LND was falsely omitted. Therefore, these patients transit to the ‘residual LN metastases’ state. We assumed these patients would receive palliative care after 6 months.

Based on biannual follow-up, a cycle time of 6 months was chosen with a lifelong time horizon. A discount rate was applied to effects, to adjust future effects to present values. A discount rate of 1.5% was applied to quality-adjusted life years (QALYs), according to Dutch guidelines.¹⁰

Transition probabilities

Transition probabilities were derived from literature or expert opinion (table 1). A probability of 31% to have N+disease after nCRT was used, based on van Hagen *et al.*¹ The percentage of LNDs in which all LN metastases are successfully removed is unknown and may vary per surgeon. We therefore assumed a 94% probability

of treatment success for LND (ie, 6% of patients with residual LN metastases), which was based on the number of early locoregional recurrences after surgery with LND in van Hagen *et al.*¹ Frequencies of LND-related complications were derived from the Dutch Upper Gastrointestinal Cancer Audit database.¹¹ Sixty-four per cent of patients had either pulmonary complications, chyle leakage or recurrent laryngeal nerve paresis, or a combination of complications (online supplementary figure 1). The other 36% of patients had no complications or complications that would not be influenced by LND.

In the case vignette study among esophageal surgeons, experts were asked to determine the minimally required diagnostic accuracy of a new diagnostic test to omit LND, and this resulted in a median sensitivity of 92% and specificity of 90%.⁶ We used these values for accuracy of the restaging results after nCRT in our model. Currently, LND is never omitted in clinical practice, therefore the percentage of complications that could be avoided when LND is omitted is unknown. In the case vignette survey, experts expected a 31% decrease in pneumonia, 72% decrease in chyle leakage, and a 57% decrease in laryngeal nerve paresis when LND is omitted (online supplementary figure 1).⁶

Outcome measures

Effectiveness was measured through QALYs, which is a combination of QoL (utility) and survival (table 2). A utility reflects QoL on a 0 to 1 scale, with 0 representing death and 1 representing full health. Utility scores were obtained from a cross-sectional study in esophageal cancer

**Table 1** Transition probabilities

Parameter	Probability*	Source
Decision tree		
N0 after nCRT	0.689 ($\alpha=111$; $\beta=50$)	van Hagen <i>et al</i> ¹
Treatment success rate standard LND	0.938 ($\alpha=167$; $\beta=11$)	van Hagen <i>et al</i> ¹
Treatment success rate of selective LND	0.92	de Gouw <i>et al</i> ⁶
Unnecessary LND rate of selective LND	0.10	de Gouw <i>et al</i> ⁶
Chance of pneumonia	0.523 ($\alpha=1120$; $\beta=1023$)	DUCA database ¹¹
Chance of chyle leakage	0.150 ($\alpha=153$; $\beta=870$)	DUCA database ¹¹
Chance of laryngeal nerve paresis	0.123 ($\alpha=99$; $\beta=708$)	DUCA database ¹¹
Chance of chyle leakage when pneumonia is present	0.099 ($\alpha=111$; $\beta=1009$)	DUCA database ¹¹
Chance of laryngeal nerve paresis when pneumonia is present	0.067 ($\alpha=65$; $\beta=899$)	DUCA database ¹¹
Chance of laryngeal nerve paresis when chyle leakage is present	0.049 ($\alpha=7$; $\beta=135$)	DUCA database ¹¹
Chance of laryngeal nerve paresis when pneumonia and chyle leakage are present	0.119 ($\alpha=12$; $\beta=89$)	DUCA database ¹¹
Relative risk of pneumonia without LND	0.689 (IQR 0.457–1)†	de Gouw <i>et al</i> ⁶
Relative risk of chyle leakage without LND	0.276 (IQR 0.065–0.526)†	de Gouw <i>et al</i> ⁶
Relative risk of laryngeal nerve paresis without LND	0.431 (IQR 0.154–1)†	de Gouw <i>et al</i> ⁶
Remaining OR time without LND	0.800 (IQR 0.667–0.833)†	de Gouw <i>et al</i> ⁶
State-transition model		
Chance of recurrence in patients with N0 after nCRT	0.475 ($\alpha=28$; $\beta=31$) over 7 years‡	Shapiro <i>et al</i> ⁸
Chance of recurrence in patients with N1 after nCRT	0.690 ($\alpha=80$; $\beta=36$) over 7 years‡	Shapiro <i>et al</i> ⁸
Chance of palliative care in patients with residual LN metastases	1.00	Assumption
Standard death rate	Age dependent mortality rates	Statistics Netherlands ¹⁸
Cancer related death ('palliative treatment' to 'death')	0.930 ($\alpha=159$; $\beta=12$) over 2 years‡	Parry <i>et al</i> ¹⁹

* β -distributions were assigned to the parameters for use in the probabilistic sensitivity analysis. The characteristics of the β -distribution are presented between brackets, as an α and β value (where α represents the number of events in a sample and β the number of non-events).

†Data was sampled from the original study data.

‡Probabilities were converted to bi-annual probabilities using the formulas: $r = -\log(1-p)$ and $p = 1 - e^{(-r)}$.²⁰

DUCA, Dutch Upper Gastrointestinal Cancer Audit; LN, lymph node; LND, lymph node dissection; N0, no lymph node metastases; N1, presence of lymph node metastases; nCRT, neoadjuvant chemotherapy; OR, operating room.

patients which measured EuroQol-5D utilities during surveillance, progressive disease and palliative care.¹² Utility scores for the first 6 months after surgery were calculated from a multicenter randomized controlled trial that investigated open versus minimally invasive esophagectomy.¹³ We calculated the utility for having no or LND-unrelated complications and disutilities for developing a pneumonia, chyle leakage or recurrent laryngeal nerve paresis. We assumed that the disutility for developing a complication would influence QoL in the first 6 months. ShortForm-36 values from Biere *et al* were converted to EuroQol-5D utilities by the algorithm of Ara *et al*.^{13 14}

Analysis

A hypothetical cohort of patients was sent through the model to evaluate short-term and long-term consequences.

Short-term consequences of both strategies included percentages of patients that received LND, number of complications and the percentage of early locoregional recurrences. Long-term consequences included QALYs and survival.

Threshold analyses

We assumed that using the restaging results after nCRT to select patients for LND would result in 92% treatment success, that is, no recurrence due to residual LN metastases, and in 10% unnecessary LNDs, that is, LND performed while no LN metastases were present, based on the expert case vignette survey. However, using the restaging results could potentially have different results. We determined which combinations of treatment success and unnecessary LNDs resulted in equal QoL (ie, QALYs) for both strategies.

Table 2 Utilities

Parameter	Utility*	Source
Disutility for experiencing a pneumonia	0.079	Biere <i>et al</i> ¹³
Disutility for experiencing a chyle leakage†	0	Biere <i>et al</i> ¹³
Disutility for experiencing laryngeal nerve paresis†	0	Biere <i>et al</i> ¹³
Utility in the first 6 months in the no evidence of disease state	0.729 (SD=0.259; n=32)	Biere <i>et al</i> ¹³
Utility after the first 6 months in the no evidence of disease state	0.800 (SD=0.21; n=75)	Doherty <i>et al</i> ¹²
Utility in the residual LN metastases state	0.780 (SD=0.2; n=30)	Doherty <i>et al</i> ¹²
Utility in the palliative care state	0.740 (SD=0.19; n=26)	Doherty <i>et al</i> ¹²

* β -distributions were assigned to the parameters for use in the probabilistic sensitivity analysis. The characteristics of the β -distribution are presented between brackets, as an SD and n.

†Patients with chyle leakage and laryngeal nerve paresis had a higher utility than patients without complications, therefore the disutility was zero.

.LN, lymph node.

Routine LND practice varied considerably in extent and in the specific LN stations that are dissected. It is therefore likely that this influences the treatment success of LND. In the base case analysis, we assumed treatment success in 94% of patients (ie, 6% residual LN metastases). In case treatment success of LND is higher or lower than expected, the effectiveness of both strategies will change. We determined at which point both strategies result in equal QoL.

Sensitivity analysis

We determined the influence of uncertainty in treatment success of LND, the percentage of patients with N0 after nCRT, and the disutilities assigned to complications on QoL outcomes. Disutilities were varied from 0 (0 days of full health lost) to 0.5 (183 days of full health lost), treatment success was varied from 80% to 100% and N0 after nCRT was varied from 50% to 95%. The results are displayed in a tornado diagram.

To investigate sampling uncertainty concerning the different parameters in the model, a probabilistic sensitivity analysis with 10,000 simulations was performed. Distributions were estimated for all uncertain parameters

in the model, except for assumptions, characteristics of the new test and disutilities which were incorporated in threshold analyses and tornado diagrams. Parameters based on the worldwide case vignette survey were sampled from the original data and 95% CIs were calculated using the percentile method and displayed between brackets.

RESULTS

Using a selective LND approach based on restaging results after nCRT, with an assumed treatment success rate of 92% and 10% unnecessary LNDs, could potentially result in a 65% (59% to 70%) decrease in LNDs. Due to the decrease in number of performed LNDs, a 10.6%, 4.9% and 2.8% decrease in pneumonias, chyle leakages and in recurrent laryngeal nerve paresis might be accomplished (table 3). On the other hand, there seems a slight increase in patients with residual LN metastases of 0.6% (−0.7% to 1.6%), which has a huge impact on the quality of life of these patients. Although uncertain, the long-term effectiveness in QALYs seems lower, as the decrease in complications appears not to outweigh

Table 3 Outcomes

	Standard LND strategy	Selective LND strategy	Increment
Short-term			
Percentage of LNDs (95% CI)	100 (100 to 100)	35.4 (29.7 to 41.5)	−64.6 (−70.3 to −58.5)
Percentage of patients with residual LN metastases (95% CI)	1.9 (0.9 to 3.3)	2.5 (1.9 to 3.1)	0.6 (−0.7 to 1.6)
Percentage of pneumonias (95% CI)	52.3 (50.2 to 54.4)	41.7 (21.8 to 53.9)	−10.6 (−30.4 to 0)
Percentage of chyle leakages (95% CI)	12.3 (11.0 to 13.7)	7.4 (3.9 to 13.8)	−4.9 (−8.6 to 1.1)
Percentage of laryngeal nerve paresis (95% CI)	9.1 (7.9 to 10.4)	6.4 (2.9 to 10.9)	−2.8 (−6.3 to 1.5)
Long-term			
Survival, years (95% CI)	8.19 (6.86 to 9.67)	8.16 (6.83 to 9.65)	−0.03 (−0.08 to 0.03)
QALYs (95% CI)	6.44 (5.35 to 7.68)	6.42 (5.34 to 7.67)	−0.02 (−0.06 to 0.03)

LN, lymph node; LND, lymph node dissection; QALYs, quality-adjusted life years.

the downside of an increase in residual LN metastases, that is, the expected QALY loss was 0.02 (0.06 QALY lost to 0.03 QALY gained).

Threshold analyses

In the base case analysis, the selective LND strategy results on average in less QoL (QALYs). To be equally effective as the standard LND strategy, the selective LND strategy should have at least 94% treatment success. In other words, the treatment success rate of selective LND should be equal to the treatment success rate of standard LND, resulting in an equal amount (1.9%) of residual LN metastases in both strategies. The influence of unnecessary LNDs is too small to influence QoL outcomes. Residual LN metastases have therefore a larger impact on QoL than short-term complications.

Conversely, a surgical strategy with 92% treatment success and 10% unnecessary LNDs will result in equal QoL in both strategies when standard LND has a treatment success of 92%. In this case, both standard LND and selective LND treat 92% of patients in the correct way and have an equal number of patients with residual LN metastases (2.5%), while selective LND also decreases the amount of unnecessary complications.

Sensitivity analyses

We determined the influence of our assumptions on QoL outcomes. Treatment success rate of standard LND was the main determinant, while an increase or decrease in either the percentage of patients with N0 after nCRT or severity of complications had lower impact on quality of life (figure 3).

DISCUSSION

Summary of main findings

After nCRT, only one-third of esophageal cancer patients harbor positive locoregional LN metastases.

Our hypothesis before modeling was that by selecting patients for LND, the number of unnecessary LNDs could be reduced and unnecessary morbidity could be saved. Results of our decision analytical model show that a selective LND strategy with 92% treatment success and 10% unnecessary LNDs could have short-term benefits, that is, a decrease in the number of performed LNDs and LND-related complications. However, it may also result in a slight increase in residual locoregional LN metastases, which impacts the quality of life tremendously. Although uncertain, the long-term effectiveness in QALYs of selective LND seems lower. Furthermore, the potential added value of such a new surgical strategy is highly dependent on the treatment success rate of standard LND, which is currently unknown and will vary between surgeons. Residual LN metastases have a larger impact on QoL than short-term complications, and new surgical strategies should therefore have a treatment success rate at least equal to the treatment success rate of standard LND.

Strengths and limitations

This study showed the value of decision analytical modeling prior to surgical innovation, that is, in the pre-IDEAL stage. Our hypothesis was that by selecting patients for LND, the number of unnecessary LNDs could be reduced and unnecessary morbidity could be saved. We showed that this is not necessarily the case, therefore modeling could inform the decision whether it is worthwhile to invest in research and development of this surgical innovation. Furthermore, in case research is initiated, modeling showed the circumstances under which this surgical innovation would have added value. It can therefore serve as guidance to monitor surgical innovation. Also, this study highlighted important information gaps in current clinical practice, for example, treatment success rate of standard LND, which can now be included in research.

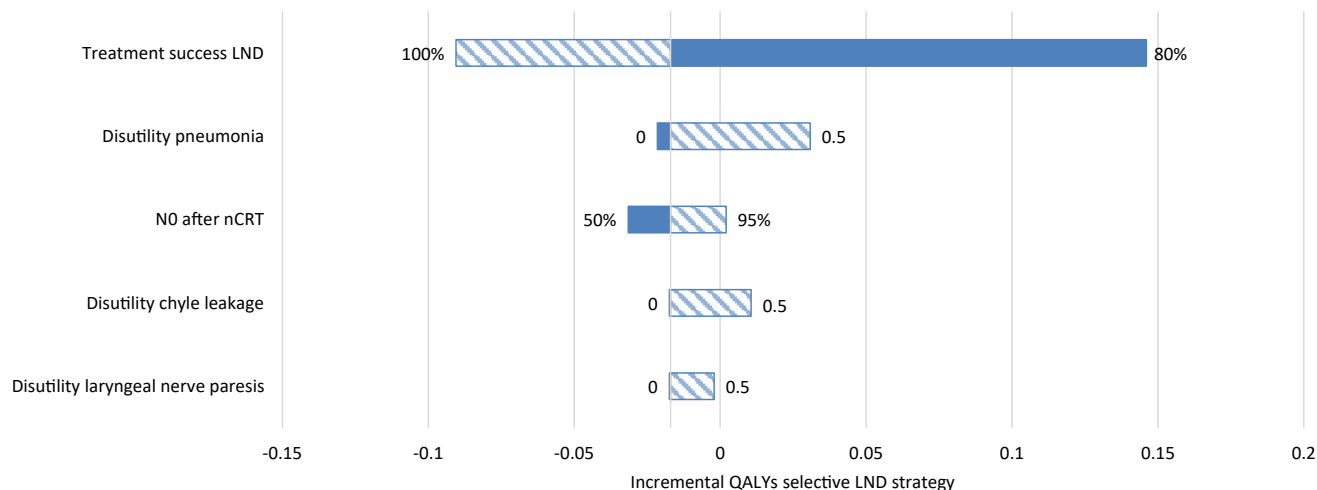


Figure 3 Tornado diagram showing the incremental QoL (QALYs) for different treatment success rates of LND, percentage of patients with N0 after nCRT, and complication-related disutilities. Value ranges are indicated in the chart. A disutility of 0.5 equals 183 days in full health that are lost. LND, lymph node dissection; nCRT, neoadjuvantchemoradiotherapy; N0, no lymph node metastases; QALYs, quality-adjusted life years; QoL, quality of life.

Some potential limitations should also be mentioned. First, we had to make assumptions about the consequences of omitting LND, as LND is currently never omitted in esophageal cancer surgery. To inform these assumptions, we conducted a case vignette study which provided estimates of the consequences of omitting LND determined by 89 esophageal surgeons.⁶

Second, there was little evidence about utility values for specific complications. We were able to use real world data to construct these utilities, however this resulted in small patient groups for specific complications.¹³ The utility values are therefore uncertain and should be researched in more detail in future studies.

Third, it is important to note that we assumed that in the selective LND strategy, all LN metastases were always included in the LND. Although preoperative localization of LN metastases might improve results of LND, treatment success of LND might still be lower than 100% as LND success rates are highly dependent on local operative protocols.^{6,15} Moreover, it is unknown if complete LND, including all metastatic lymph nodes, leads to better survival.

Fourth, some probabilities are based on Dutch healthcare data and may therefore slightly differ from other countries. However, we expect small differences but similar trends in effectiveness. Given the detailed presentation of the model, those interested can assess the transferability of the results to their specific situation/country.

Implications for clinical practice and further research

Our results show that the consequences of having residual LN metastases are far more serious than those of short-term complications. Only when the number of patients with residual LN metastases is equal or lower than with standard LND, a new surgical strategy that selects patients for LND based on restaging results after nCRT will be more effective than standard LND. However, standard LND practice varies considerably in extent and in the specific LN stations that are dissected.^{6,15} Therefore, the treatment success rate of standard LND will likely vary per surgeon, hospital and country. Since the treatment success rate is the most important determinant for the effectiveness of selective LND strategies, this should be researched in more detail to determine the real value of developing and implementing new surgical strategies. In case the treatment success rate of standard LND is lower than assumed, positive outcomes for selective LND strategies seem more likely. Once positive outcomes seem likely, other consequences of a new surgical strategy, such as its price, potential cost savings and logistic issues, should also be researched during development.

In this study we compared standard esophagectomy with standard LND to a new strategy in which LND was omitted in patients with low suspicion of LN metastases after nCRT. As esophagectomy is still performed while LND is omitted, only a limited amount of morbidity could be prevented. To increase the effectiveness of a selective LND strategy, less invasive surgical techniques such as local endoscopic resection might be an alternative approach.¹⁶ Furthermore, active surveillance for patients with a complete response (no

evidence of the primary tumor or metastases after nCRT) is currently studied in two phase 3 trials.¹⁷ The already completed preSANO trial showed favorable outcomes for this treatment strategy.⁹ This shows that the treatment of esophageal cancer is transforming towards more personalized treatment strategies with an increasing need for personalized surgical strategies. Our model provides important guidance in the development of these strategies, and can easily be updated to assess the added value of promising surgical strategies or specific techniques for the detection of LN metastases.

CONCLUSIONS

Decision analytical modeling showed that the reduction in LND-related complications that is accomplished by selecting patients for LND seems not to outweigh a QALY loss in the long-term due to residual LN metastases. Despite the short-term advantages of selective LND based on restaging results after nCRT, this strategy can only match long-term QALYs of standard LND when its success rate equals the success rate of standard LND.

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Contributors MMR, CR, DJJMdG, JG, BRK and MS conceived and designed the study. BRK and CR critically reviewed the outcomes from a clinical point of view. DJJMdG and MS acquired the data and performed the analyses with supervision of JG and MMR. DJJMdG and MS drafted the manuscript. All authors critically reviewed the manuscript and approved the final submitted version.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement 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 its supplementary materials. The model is available from the corresponding author, MS, upon reasonable request.

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