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RESEARCH ARTICLE

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Totally minimally invasive esophagectomy after neoadjuvant chemoradiotherapy: Long-term oncologic outcomes

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Background and Objectives: Minimally invasive esophagectomy is emerging with comparable short-term outcomes as open esophagectomies. Neoadjuvant chemoradiotherapy followed by surgery is considered standard of care in the Netherlands for patients with esophageal cancer. The aim of this study was to analyze the long-term oncologic outcome after neoadjuvant chemoradiotherapy followed by totally minimally invasive esophagectomy.

Methods: Neoadjuvant carboplatin and paclitaxel based chemotherapy was concomitantly given with 41.4 Gy radiotherapy. Six weeks after neoadjuvant treatment, totally minimally invasive esophagectomy was performed.

Results: From December 2010 until December 2015 161 patients received this combination of treatment. In 128 male and 33 female patients with median age of 65 years (58-71), 88 minimally invasive esophagectomies with intrathoracic anastomosis and 73 minimally invasive esophagectomies with cervical anastomosis were carried out. Radical (R0) resection was confirmed in 156 patients (97%). In hospital mortality occurred in 6 patients (3.7%). Overall survival was 79% and 51% at 1 and 5 years, respectively, with a median follow-up of 24.5 months (13-38). Disease-free survival was, respectively, 76% and 55%.

Conclusions: Totally minimally invasive esophagectomy after neoadjuvant chemoradiotherapy for esophageal cancer is a safe treatment with low postoperative mortality rates and favorable overall and disease-free survival.

KEYWORDS
esophageal cancer, minimally invasive esophagectomy, neoadjuvant chemoradiotherapy, survival

1 | INTRODUCTION

Every year, over 440 000 patients die from esophageal cancer worldwide, despite improved diagnostic and treatment modalities. Globally, esophageal cancer ranked ninth for cancer incidence and sixth for cancer mortality in 2013. Besides that, incidence is still rising, especially due to an aging and growing population.[1]

Esophagectomy is the cornerstone of curative treatment of esophageal cancer. However, despite the curative intent of the surgery, radical resection (R0)-rates vary between 59% and 92% and overall 5-year survival rates are poor, ranging from 34% to 41%.[2–4]

Several studies described improved oncologic results and higher survival rates when patients were treated with a combination of neoadjuvant chemoradiotherapy (nCRT) followed by surgery.[2,5,6] The CROSS trial, published in 2012, showed in a randomized controlled setting that nCRT prior to surgery for resectable esophageal cancer is advantageous compared to surgery alone. Neoadjuvant therapy increased R0-rates from 69% to 92% and significantly improved both disease-free and overall survival, without increased postoperative morbidity and mortality rates.[2] As a result of this study, the standard treatment of cT2-4N0-3M0 esophageal cancer in the Netherlands is multimodality treatment of nCRT followed by surgery.

However, all trials which showed positive results after embedding nCRT in the treatment of esophageal cancer were conducted in the era of open esophagectomies. In recent years, several research groups have shown that totally minimally invasive esophagectomy (tMIE) is safe with comparable or even better short-term morbidity and mortality rates. The TIME trial that compared open esophagectomies with tMIE, showed significantly lower postoperative morbidity rates after tMIE, without deteriorations in short-term oncologic outcome.[7] Furthermore, Luketich et al showed that tMIE is safe in the largest cohort study published so far, with low postoperative morbidity rates and a 30-day mortality rate of 1.7%. The R0-rates and the amount of yielded lymph nodes were similar to open procedures. However, only 31% of these patients received nCRT before surgery.[8]

Until now, the combination of nCRT and tMIE as treatment for esophageal cancer has rarely been described in the literature. Publications on long-term oncologic outcomes after the combination of these treatment modalities are even scarcer.

This study evaluated the long-term oncologic results of nCRT and tMIE as curative treatment for patients with esophageal cancer in a large consecutive cohort.

2 | MATERIALS AND METHODS

2.1 | Data collection

From December 2010 until December 2015 all patients treated with curative intent for esophageal cancer with nCRT prior to tMIE in Hospital Group Twente (ZGT) Almelo, the Netherlands were included. ZGT is a high-volume-tertiary referral center for patients with esophageal cancer in the Netherlands.[9] This retrospective study was part of an Institutional Review Board-approved protocol for ongoing assessment of esophagectomy outcomes. As a consequence, patient consent was not necessary.

2.2 | Staging

Each patient with esophageal cancer was diagnosed and completely staged upon referral. Esophago-gastro-duodenal endoscopy with biopsies described tumor location and histological characteristics. A CT-scan of the neck, chest, and abdomen was used for appropriate staging according to the TNM 7 classification system.[10] Until 2014 a PET-CT-scan was applied on indication. From 2014 onward a PET-CT-scan was routinely made according to the renewed Dutch Guidelines of Surgical Oncology. Endoscopic ultrasonography (EUS) and endoscopic bronchial ultrasound (EBUS) with fine needle aspiration were performed on clinical indication.

2.3 | Neoadjuvant chemoradiotherapy

After staging, all patients with tumor stage 1b or higher received nCRT. Chemotherapy consisted of carboplatin and paclitaxel via infusion at day 1, 8, 15, 22, and 29 of the chemoradiation cycles. Single doses of carboplatin were calculated by the following formula: (GFR in mL/min + 25) × 2 mg. Single doses of paclitaxel existed of 50 mg/m^2 body surface. Concomitantly a total dose of 41.4 Gy-radiotherapy was administered in 23 daily fractions of 1.8 Gy.

After nCRT a recovery period of minimally 6 weeks was given to decrease tumor volume and to improve the patients' condition. In this waiting period, a CT-neck-thorax-abdomen was used for restaging on indication.

2.4 | Surgery

After the recovery period patients underwent tMIE, either with an intrathoracic anastomosis as described by Ivor Lewis (ILE) or a cervical anastomosis as described by McKeown (MKE). From December 2010 until December 2012 all patients went for MKE. Since December 2012 the type of anastomosis was selected depending on the tumor location.

All patients with distal tumors close to the cardia up to the level of the tracheal bifurcation underwent ILE. First, the stomach was mobilized laparoscopically and the gastric conduit was created with the patient in supine position. The second part was the thoracoscopic mobilization and resection of the esophagus with the formation of an intrathoracic anastomosis in prone position. A feeding jejunostomy was placed laparoscopically. Two-field lymph node dissection was performed; all lymph nodes up to the level of the carina were dissected, the high paratracheal lymph nodes were dissected on indication.

MKE was performed for tumors proximal to the tracheal bifurcation. First the patient was placed in prone position and via thoracoscopic approach the esophagus was mobilized. After that, the patient was turned in supine position, the stomach was mobilized and the gastric conduit was created laparoscopically. Finally, the gastric conduit was pulled upwards to the neck and cervical anastomosis was made. Two-field lymph node dissection was performed and a feeding jejunostomy was placed laparoscopically. All lymph nodes up to the level of the carina together with the high paratracheal lymph nodes were dissected.

2.5 | Postoperative complications

Pneumonia, anastomotic leakage, laryngeal nerve palsy, delirium, chylothorax, and cardiac complications were scored. The Esophageal Complication Consensus Group guidelines (ECCG) were used to define anastomotic leakage and chylothorax.[11] Pneumonia was defined using the Uniform Pneumonia Scale.[12]

2.6 | Histopathologic analysis

Histopathologic analysis was performed according to the TNM 7 classification.[10] Resection margins were analyzed and scored; in R0-resection, the proximal, distal, and circumferential resection margins were free of tumor and in R1-resection microscopic tumor invasion had been occurred in one or more resection margins. R2-resection was a macroscopically non-radical resection. The total amount of lymph nodes yielded and the amount of lymph nodes with metastasis were examined as well.

2.7 | Follow-up

After discharge all patients were regularly seen at the outpatient clinic. In the first year, follow-up consisted of evaluations every 3 months. In the second and third year, follow-up took place every 6 months and annual visits were held during the fourth and fifth year. Vitamin status was checked every 6 months and imaging studies were only performed on indication during follow-up.

2.8 | Statistical analysis

Analyses were performed using the Statistical Package for the Social Sciences version 22 (SPSS Inc., Chicago, IL) and statistical significance was set at $P < 0.05$ (two-tailed). Descriptive statistics were applied for the patient characteristics, postoperative complications, and pathology. Categorical variables were described as number with corresponding percentage; continuous variables were described as median with interquartile range (IQR). Kaplan-Meier survival analyses were used to calculate overall and disease-free survival. Disease-free survival by pathologic stage was calculated using Kaplan-Meier survival analyses as well; log-rank test and cox-regression analyses were used to compare the disease-free survival of these pathologic stages.

3 | RESULTS

A total of 175 consecutive patients underwent tMIE esophagectomy in the period December 2010 until December 2015. Fourteen patients did not receive nCRT; five patients due to high age (78-84 years) and five patients were considered too fragile for nCRT due to extensive (psychiatric) medical history. The remaining four patients had tumor stage 1a so nCRT was not indicated. In total 161 patients were treated with nCRT prior to tMIE and this group constitutes the cohort described hereafter.

Basic characteristics of these patients are presented in Table 1. Median (IQR) age was 65 years (58-71), 80% was male and 82% had ASA-classification 1 or 2. The majority of patients had cT2-3N+ disease; one young patient who presented with a synchronous single resectable liver metastasis was intentionally treated in curative setting.

All patients received tMIE; 88 patients (55%) underwent ILE and 73 patients (45%) MKE.

TABLE 1 Characteristics of patients

Characteristics	Patients (n = 161)
Age, median (IQR)	65 (58-71)
Gender	
Male	128 (80)
Female	33 (20)
ASA classification	
1	25 (15)
2	107 (67)
3	28 (17)
4	1 (1)
WHO performance status[13]	
0	87 (54)
1	28 (17)
2	3 (2)
Missing	43 (27)
PET CT scan	91 (57)
cT classification	
cT2	40 (25)
cT3	117 (73)
cT4	4 (2)
cN classification	
cN0	70 (44)
cN1	67 (42)
cN2	21 (13)
cN3	3 (1)
cM classification	
cM0	160 (99)
cM1	1 (1)
Neoadjuvant chemoradiotherapy	161 (100)
Type of surgery	
Ivor Lewis	88 (55)
McKeown	73 (45)
Pathology	
Adenocarcinoma	129 (80)
Squamouscell carcinoma	27 (17)
Adenosquamous	5 (3)

Values are presented as n (%) unless stated otherwise.

3.1 | Postoperative complications

Postoperative complications are highlighted in Table 2. Uncomplicated recovery was seen in 58 patients (36%). Postoperatively, 50 patients (31%) developed pneumonia and 38 patients (24%) developed anastomotic leakage. When differentiating between ILE and MKE, 23 patients (26%) developed anastomotic leakage after ILE, respectively, 15 patients (21%) after MKE.

Of all patients who developed an anastomotic leak, 6 patients (16%) were successfully treated with antibiotics only, 29 patients

TABLE 2 Postoperative complications

Complications	Patients (*n* = 161)
Uncomplicated recovery	58 (36)
Pneumonia	50 (31)
Aspiration	6 (4)
Anastomotic leakage	38 (24)
Ivor Lewis	23 (26)
McKeown	15 (21)
Laryngeal nerve palsy	3 (2)
Delirium	21 (13)
Cardiac	40 (25)
Atrial fibrillation	37 (22)
Asystole	3 (2)
Cardiac asthma	1 (1)
Myocardial infarction	1 (1)
Chylothorax	7 (4)
In hospital mortality	6 (3.7)
30-day mortality	5 (3.1)
Cause of mortality	
Anastomotic leakage	3 (1.9)
Refusal to treat complications	1 (0.6)
Pulmonary failure	1 (0.6)
Cardiac failure	2 (1.2)
Discharge from the hospital	
Home	150 (97)
Rehabilitation center	5 (3)

Values are presented as *n* (%).

TABLE 3 Pathology

Characteristics	Patients (*n* = 161)
pT classification	
pT0	46 (29)
pT1	26 (16)
pT2	36 (22)
pT3	51 (32)
pT4	2 (1)
pN classification	
pN0	102 (63)
pN1	37 (23)
pN2	15 (10)
pN3	7 (4)
pTNM stage	
ypT0N0	33 (21)
ypT0N+	13 (8)
1	43 (27)
2	37 (23)
3	31 (19)
4	4 (2)
Resection	
R0	156 (97)
R1	5 (3)
Lymph nodes	19 (15-25)
Positive lymph nodes	0 (0-1)
Follow-up in months	24.5 (13-38)

Values are presented as *n* (%) or median (IQR).

(76%) received endoscopic treatment (stent, clipping, suction-drainage), and 17 patients (45%) underwent thoracoscopic surgery. Reoperation included removal of the gastric conduit and esophageal diversion due to conduit necrosis (3 patients), suture repair of a small perforation (1 patient), and drainage of empyema (13 patients).

Recurrent laryngeal nerve palsy and chylothorax rates were low; 2% and 4%, respectively.

Six patients died in hospital (3.7%), five patients passed away within 30 days after surgery (3.1%). Of these, three patients (1.9%) died as a consequence of an anastomotic leakage.

3.2 | Histopathologic analysis

The results of pathologic analyses are summarized in Table 3. R0-resection was achieved in 156 patients (97%) and a median of 19 lymph nodes (15-25) was yielded. Pathologic complete response after nCRT was seen in 33 patients (21%) and complete pathologic response to the primary tumor with persisting lymph nodes metastases (ypT0N1-3) was observed in 13 patients (8%). Median follow-up was 24.5 months (13-38).

3.3 | Mortality and survival

Kaplan-Meier survival analyses (Table 4 and Figure 1) showed an overall survival after 1 and 5 years of 79% and 51%, respectively; disease-free survival after 1 and 5 years was 76% and 55%, respectively (Figure 2). Figure 3 shows Kaplan-Meier disease-free survival curves by pathologic stage. Disease-free survival of ypT0N0, stage 1-disease, and stage-2 disease were similar (Table 5; 5-year disease-free survival was approximately 70%. Disease-free 5-year survival of ypT0N+ was 40%. Cox-regression analyses showed a significant higher risk of recurrence in stage 3 and stage 4-disease compared to ypT0N0, $P = 0.002$ and $P < 0.001$, respectively (Table 5). Log-rank test showed a significant difference in the time to recurrence of disease between these groups ($P < 0.001$).

3.4 | Recurrence

Recurrence of disease was seen in 60 patients (37%). Of these, three patients (5%) developed regional recurrence only. Distant metastases only were observed in 50 patients (83%); 7 patients (12%) developed concurrent locoregional and distant relapses. The vast majority of the recurrences occurred in the first 2 years after esophagectomy.

TABLE 4 Survival

Survival	Percentage (*n* = 161)
Overall survival	
1 year	79 (73-85)
3 year	57 (49-65)
5 year	51 (41-61)
Disease-free survival	
1 year	76 (70-82)
3 year	57 (49-65)
5 year	55 (45-65)

Values are presented as % (95%CI).

4 | DISCUSSION

Globally, there is a growing tendency towards the use of chemo-radiotherapy prior to surgery in patients with esophageal cancer since studies showed improved long-term survival after this trimodality treatment.[6,14–16] To mention in particular, the ChemoRadiotherapy for oesophageal cancer followed by Surgery Study (CROSS) demonstrated statistically significant improvement in long-term survival after induction chemoradiotherapy compared to surgery alone for both squamous cell carcinoma and adenocarcinoma subtypes.[17]

Although not revealed in the CROSS study, concerns about increased postoperative complications after nCRT have been addressed in a nationwide trial in France, comparing surgery after induction chemoradiotherapy to surgical resection alone. This study was terminated early due to a significantly higher postoperative mortality rate after trimodality treatment compared to patients receiving surgery alone.[3]

Notwithstanding, a large meta-analysis of nCRT prior to esophagectomy could not find a significant negative impact on postoperative complications.[18]

In the same decade these studies on the effect of neoadjuvant therapy were performed, a minimally invasive technique for esophageal surgery was evolved by Cuschieri.[19] In the largest tMIE cohort to date, Luketich et al showed that tMIE is safe with low postoperative morbidity rates and a low 30-day postoperative mortality rate of 1.7%.[8] In a randomized setting, the TIME-trial demonstrated superiority of tMIE over open esophagectomy on patients' outcomes, with significantly fewer postoperative pulmonary infections and shorter hospital stay.[7]

Postoperative morbidity and mortality rates in our cohort are similar to the literature. However, pneumonia and anastomotic leakage rates are widely spread in the literature, ranging from 12% to 34% and 12% to 24%, respectively. Pneumonia and anastomotic leakage rates in our study are in the upper limit.[2,7,20–22]

The TIME-trial used a strict definition of pneumonia which required radiologic confirmation in combination with a positive sputum culture. However, in our present study, the Uniform Pneumonia Scale was used as definition for pneumonia; a less stringent definition in which a positive sputum culture was not required for diagnosis and as a consequence, higher pneumonia rates were observed.[12]

The relatively high anastomotic leakage rates could be a result of the daily testing of drain amylase.[23] Elevated drain amylase levels led to additional diagnostic tests, even when patients were asymptomatic. As a result of this aggressive approach, non-clinical leakages were also diagnosed and treated. Fortunately, this strategy resulted in relatively low mortality rates among patients with an anastomotic leak, expressed in a failure to rescue rate of 7.9%.

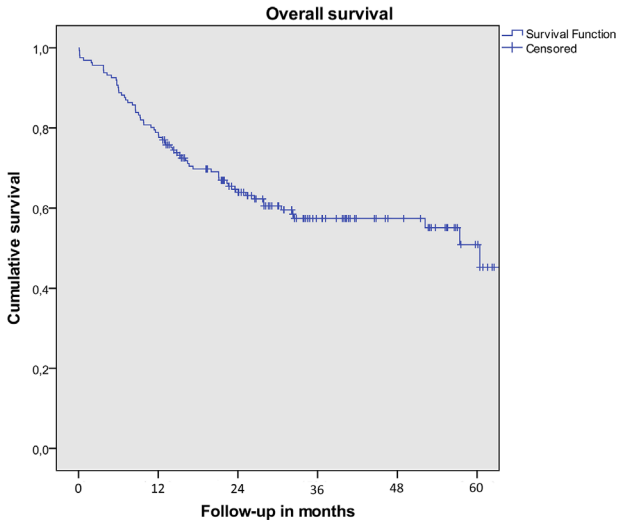

FIGURE 1

Kaplan-Meier survival curve, overall survival

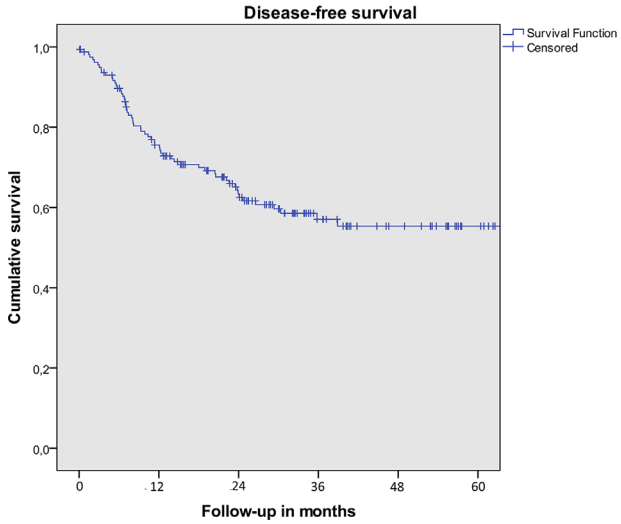

FIGURE 2

Kaplan-Meier survival curve, disease-free survival

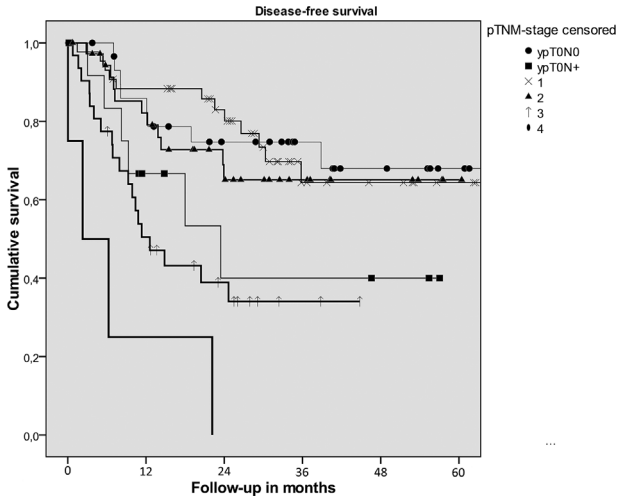

FIGURE 3

Kaplan-Meier survival curve, disease-free survival by pathologic stage. The pathologic stage predicts significant differences in disease-free survival (log-rank < 0.001)

TABLE 5 Cox-regression analysis disease-free survival by pathologic stage

			95%CI for Exp(B)	
pTNM-stage	*P*-value	Hazard ratio (HR)	Lower	Upper
ypT0N0[a]	0.000			
ypT0N+	0.092	2.489	0.862	7.192
Stage 1	0.983	1.010	0.412	2.472
Stage 2	0.594	1.282	0.515	3.188
Stage 3	0.002	3.683	1.601	8.476
Stage 4	0.000	12.486	3.697	7.192

[a]Reference category.

In the short term, the oncologic efficacy after tMIE defined by the completeness of resection and number of dissected lymph nodes outperforms open esophagectomies, as shown in a recent meta-analysis.[24] In our present cohort median lymph node retrieval of 19 and radical resection rate of 97% is in concordance with MIE-literature.[7,8,22] Data regarding the long-term oncologic outcome after tMIE combined with induction chemoradiotherapy are less clear to interpret though. Since many minimally invasive esophagectomy-centers introduced the neoadjuvant therapy at a later stage, most MIE-studies report a mix of surgery alone and multimodality treatment; outcomes have not been split up according to treatment modality. Furthermore, the percentage of the trimodality groups is small and varies from 31% to 63% or is not clearly specified.[8,20,22,25,26]

Although two retrospective cohort studies comparing long-term outcome after tMIE and open esophagectomies demonstrated improved survival after tMIE, the heterogeneity between the two groups in terms of neoadjuvant treatment, pathologic stage and choice for traditional or MI-surgery, obscure definite knowledge about the oncologic long-term outcome of MIE after induction therapy.[22,27] Additionally, in the beginning of the minimally invasive era teams used different regimens (chemotherapy, radiotherapy, combined chemo-radiotherapy) thereby unintentionally muddling insight in outcomes of one regimen.[20,26,28] For instance Van der Sluis et al demonstrated in their series of 130 patients a 3-year overall survival of 50%, in which 36% of the patients received surgery alone, 57% neoadjuvant chemotherapy, 7% nCRT, and 1% neoadjuvant radiotherapy.[20]

To the best of our knowledge, this study is the largest series focusing on long-term oncologic outcomes of tMIE combined with nCRT, showing overall survival of 51% after 5 years. Some small tMIE-studies focused on long-term survival after one neoadjuvant regimen as well. Spector et al showed 5-year overall survival rate of 49% in 69 patients with pathologic stage 0-2 disease who underwent tMIE MKE after nCRT.[25] Recently, Tapias et al demonstrated similar 5-year survival rates (49.6%) in 56 patients who underwent tMIE ILE after induction therapy.[28] Our larger series strengthens the 5-year outcomes of these relative small series. More importantly, 5-year overall survival rate observed in our present study is similar to the results of open procedures after induction therapy in the CROSS trial (47%).[17]

Despite studies on the surgical treatment of esophageal cancer have shown that a greater extend of lymphadenectomy has been associated with increased survival.[29,30] Talsma et al revealed that this relationship is less clear after induction chemoradiotherapy.[31] Our standard two-field lymphadenectomy yielded a median of 19 lymph nodes and is comparable to other groups who performed tMIE after induction therapy.[22,25,28] Noteworthy, this surpasses the median number of 14 lymph nodes yielded in the CROSS chemoradiotherapy group, in which both patients with a transhiatal and transthoracic approach were included. Nevertheless, the clinical relevance of a transthoracic two-field lymph node dissection after induction chemo-radiotherapy has recently been called into question.[32]

Research has shown that the risk of disease recurrence and the associated mortality is at its greatest during the first 2 years after surgery; the overall survival curve as well as the disease-free survival curve stabilize 2 years postoperative.[17,33,34]

Nowadays isolated local recurrence is sparse due to high radical resection-rates after multimodality treatment. Five percent of the patients in our cohort developed recurrence of disease only within the original radiation field which corresponds to other published series.[35]

In our series, patients with stage 3 and 4 disease had a significantly poorer outcome with lower disease-free survival rates compared to patients with a complete response after nCRT, $P = 0.002$ and $P < 0.001$, respectively. Survival of patients with stage 1 or 2 disease and a complete response were very similar in our cohort, 65-70%. Woodard et al showed similar 5-year disease-free survival rates for patients with a complete pathologic response. In spite of this, 5-year disease-free survival for patients with stage I disease stabilized at approximately 85%,

whereas in our study this was approximately 70%. This difference in survival is probably explained by the fact that Woodard et al included patients with carcinoma in situ in stage 1. However, these patients did not receive nCRT and, therefore, were not included in our present study. Woodard et al revealed a significantly lower disease-free survival in patients with stage 3 and 4 disease as well, similar to the results of our cohort. However, patients with ypT0N+ disease were not mentioned in their studies.[26] Spector et al revealed poorer 5-year overall survival rates; 50% for ypT0N0, 76% for stage 1 disease and 22% for stage 2 disease. A possible explanation is the relative low radical resection-rate of 92% with a median of 16 (3-35) yielded lymph nodes.[25]

Pathologic complete response (ypT0N0) was seen in 21% of the patients in our series. Remarkably, 28% of the patients with a complete pathologic tumor response had residual nodal disease (ypT0N+). Other studies seldom described this phenomenon.[25] Our finding could reflect either more included advanced cancers, standard two-field lymphadenectomy or a less extensive radiation field.

Despite complete regression of the primary tumor, 5-year disease-free survival was disappointing and approached the disease-free survival of patients with stage 3 disease. These results suggest that present lymph nodes metastases have a more determinative prognostic impact on long-term survival than the tumor-stage. Recently, Talsma et al demonstrated that lymph node positivity is a strong negative prognostic factor for overall survival, especially if persistent after nCRT.[31]

A limitation of this study is its retrospective and descriptive character. Since the minimally invasive technique and the trimodality treatment were adopted in our hospital in the same year, there is neither a control-group with patients receiving tMIE without nCRT, nor a group of patients who underwent open esophagectomy after nCRT. However, several studies in the recent past have shown that neoadjuvant treatment in combination with surgery is superior in the area of survival compared to surgery alone and, therefore, nCRT is incorporated in national guidelines as standard care.[2,3,5,6]

The strength of our study is the homogeneity of the group; all patients received nCRT, which was in all cases the same regimen. Contrary to design of prospective trials with defined inclusion and exclusion criteria, like age and frailty, a cohort study in a single institution might more reliably reflect the patient population of daily practice.

5 | CONCLUSIONS

In conclusion, totally minimally invasive esophagectomy after neoadjuvant chemoradiotherapy is a safe treatment with a low postoperative mortality rate and favorable overall and disease-free long-term survival. Furthermore, present lymph node metastases after nCRT seem to have a more determinative prognostic impact on long-term survival than tumor-stage.

CONFLICTS OF INTEREST

None.

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