Received: 26 December 2016 | Accepted: 1 May 2017
DOI: 10.1002/jso.24689

RESEARCH ARTICLE

WILEY Journal of SURGICAL ONCOLOGY

Sterilization of tumor-positive lymph nodes of esophageal cancer by neo-adjuvant treatment is associated with worse survival compared to tumor-negative lymph nodes treated with surgery first

Styliani Mantziari MD[1] | Pierre Allemann MD[1] | Michael Winiker MD[1] | Christine Sempoux MD, PhD[2] | Nicolas Demartines MD, FACS, FRCS[1] | Markus Schäfer MD, FACS[1]

[1] Department of Visceral Surgery, University Hospital CHUV, Lausanne, Switzerland

[2] Institute of Pathology, University of Lausanne, Lausanne, Switzerland

Correspondence
Markus Schäfer, MD, FACS, Department of Visceral Surgery, University Hospital CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland.
Email: markus.schafer@chuv.ch

Background and Objectives: Lymph node (LN) involvement by esophageal cancer is associated with compromised long-term prognosis. This study assessed whether LN downstaging by neoadjuvant treatment (NAT) might offer a survival benefit compared to patients with a priori negative LN.

Methods: Patients undergoing esophagectomy for cancer between 2005 and 2014 were screened for inclusion. Group 1 included cN0 patients confirmed as pN0 who were treated with surgery first, whereas group 2 included patients initially cN+ and down-staged to ypN0 after NAT. Survival analysis was performed with the Kaplan-Meier and Cox regression methods.

Results: Fifty-seven patients were included in our study, 24 in group 1 and 33 in group 2. Group 2 patients had more locally advanced lesions compared to a priori negative patients, and despite complete LN sterilization by NAT they still had worse long-term survival. Overall 3-year survival was 86.8% for a priori LN negative versus 63.3% for downstaged patients ($P = 0.013$), while disease-free survival was 79.6% and 57.9%, respectively ($P = 0.021$). Tumor recurrence was also earlier and more disseminated for the down-staged group.

Conclusions: Downstaged LN, despite the systemic effect of NAT, still inherit an increased risk for early tumor recurrence and worse long-term survival compared to a priori negative LN.

KEYWORDS
downstaging, esophageal cancer, esophagectomY, lymph node metastasis, neoadjuvant treatment

Abbreviations: CT, computerized tomography; DFS, disease-free survival; EUS, endoscopic ultrasound; FDG-PET/CT, 18-fluoroxyglucose positron emission tomography-computerized tomography; GEJ, gastroesophageal junction; HR, hazard ratio; LOS, length of stay; NAT, neoadjuvant treatment; OS, overall survival.

This paper has been presented in parts during the 100th Annual Congress of the Swiss Surgical Society, Bern, 2013.

1 | INTRODUCTION

Esophageal cancer remains one of the most lethal gastrointestinal malignancies with an increasing incidence, caused by the rising

frequency of adenocarcinoma of the distal esophagus and gastro-esophageal junction in the western world.[1,2] For advanced cancer stages, a multimodal approach of preoperative radiochemo- or chemotherapy and radical esophagectomy with regional lymph node (LN) resection offers the best long-term survival.[3–6] However, 5-year survival rates are still dismal, estimated at 15-30% for surgery alone and 45% after neoadjuvant treatment (NAT) followed by surgery.[3,7]

Lymphatic tumor spread is an early event during esophageal cancer growth, and tumor-positive LN can be detected in initial stages, for example, up to 40% of patients with submucosal (T1b) tumors.[8,9] Taking into account the prognostic relevance of nodal status great emphasis is given to its assessment during preoperative workup, as regional and distant LN invasion modifies treatment strategy and prognosis.[10–12] In terms of biological behavior, scarce published data exist upon whether patients with down-staged lymph nodes after NAT (cN+ to ypN0) will have the same long-term outcome as those with a priori tumor-negative lymph nodes (cN0 to pN0). Rice et al[10] have suggested that long-term survival is significantly worse for patients with affected LN, especially in those with a poor response to NAT. In a more recent publication Shapiro et al assessed the prognostic value of preoperative tumor extent in esophageal cancer. Truly negative preoperative LNs had the best prognosis compared to initially positive down-staged LNs, as well as positive LNs that remained positive after NAT.[13] While main tumor stage and other biological parameters also play an important role on patients' oncologic outcome, LN response to treatment is of particular interest. Affected LNs may not be included in the resection specimen, or micro-metastases might already be present by the time of surgery, which might explain why esophageal cancer recurrence and death are often related to lymph node dissemination.[11,12]

The present study aimed to determine whether the survival of patients with a priori tumor-negative LN (cN0 and pN0) treated with surgery first was comparable to patients with down-staged LN (cN+ to ypN0) treated with NAT and oncological esophagectomy.

2 | PATIENTS AND METHODS

2.1 | Patients

Our institutional prospectively maintained database was screened for patients operated between 2005 and 2014 for esophageal cancer, to identify those with negative lymph nodes confirmed by final histopathological analysis (pN0). These patients were further categorized in 2 groups: group 1 with a priori node-negative patients (cN0 and pN0), and group 2 with those preoperatively identified as node-positive (cN+), but down-staged to ypN0 by NAT.

As exclusion criteria were defined in-hospital mortality, unknown lymph node status, or incomplete dataset, patients cN0/pN0 who received NAT and patients cN+/pN0 who did not receive NAT. Indeed, cN0/pN0 patients having received NAT could be a confounder because of systemic impact of chemotherapy, and cN+/pN0 patients without NAT could correspond to false positives during preoperative staging. The patient selection is shown in Fig. 1. The study was

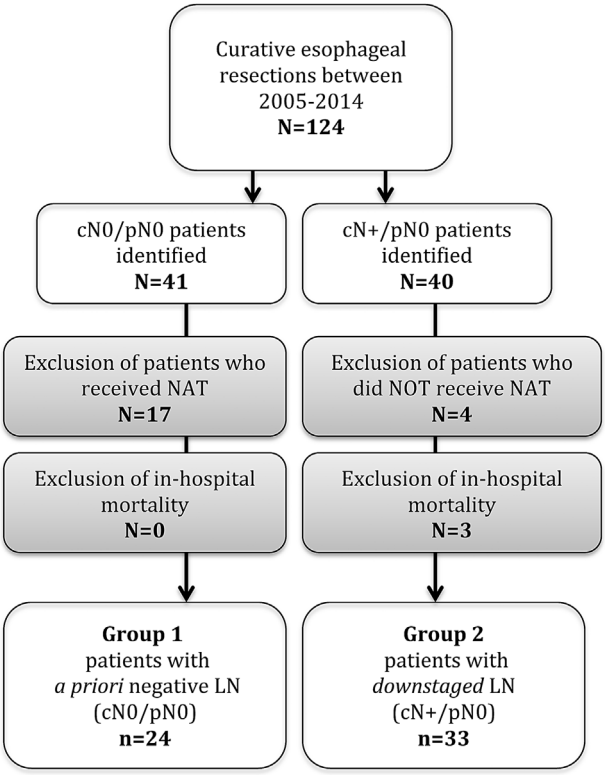

FIGURE 1 Flowchart of patient selection

conducted according to the code of Ethics of the World Medical Association (declaration of Helsinki) and approved by the internal Institutional Review Board.

2.2 | Preoperative tumor and lymph node assessment

Tumor staging was performed according to the 7th TNM classification.[14] Preoperative workup included endoscopy with ultrasound (EUS), thoraco-abdominal CT scan, and whole body ^{18}FDG-PET/CT. Lymph nodes were assessed by the combination of ^{18}FDG-PET/CT and EUS, which provides the most reliable preoperative appreciation of lymph node invasion (uN) in expert hands.[15,16] Morphologically, LN were considered to be tumor positive if their major axis was ≥1 cm, or in presence of a central hypodensity, peripheral rim enhancement, conglomeration of ≥3 lymph nodes despite normal size, or metabolic hypercaptation in ^{18}FDG-PET/CT.[17] In case of inconclusive imaging, preoperative biopsy (EUS-or image-guided) was performed to assess lymph node invasion.

2.3 | Neoadjuvant treatment and surgery

NAT was administered for locally advanced (>T2 and/or N+) tumors[4,5,7,18]; 5FU/cisplatine or taxotere/carboplatin were the basic chemotherapy regimens, both with a proven efficacy in esophageal cancer, to which cetuximab was associated in case of inclusion in the Swiss Group of Clinical Cancer Research protocol.[19] External beam radiation of 41.4, 45, or 50.4 Gy was administered preoperatively with

locoregional lymph nodes included in the radiation field, and surgical resection was performed 6-8 weeks after the end of NAT.

The standard operative technique for patients with tumors of the distal esophagus and gastroesophageal junction was an Ivor Lewis approach with abdominal laparoscopic access and right thoracotomy. For tumors located more proximally, a McKeown's resection was performed, with a manual cervical end-to-side esophago-gastrostomy. Transhiatal resection was reserved for patients with a contra-indication to thoracotomy. In all cases, a two-field lymphadenectomy (abdominal and mediastinal) was performed. During the whole study period, only three senior surgeons were involved in all operations.

2.4 | Histological analysis of lymph nodes and tumor response to treatment

According to current guidelines, at least six lymph nodes were analyzed to formally determine pN0 status.[14] The pathologist dissected the specimen for lymph nodes, if not resected separately during the intervention. To be considered as ypN0, resected lymph nodes had to reveal a complete absence of viable tumor cells. For the primary tumor, response to NAT was determined by means of the Mandard score,[20] a 5-point scale based on the presence of residual cancer cells and the degree of fibrosis; it ranges from complete tumor regression grade (TRG 1) to TRG 5, representing no regression at all.

2.5 | Postoperative outcomes and long-term follow-up

Postoperative complications were graded according to the Clavien classification.[21] Complications I-IIIa were considered as minor, while grades IIIb-IVb as severe. Grade V represents in-hospital mortality, and is reported in the study although these patients were excluded from survival analysis. Long-term follow-up was carried out clinically and with regular CT scans, as well as symptom-directed additional imaging if needed. Patients not followed in our institution were contacted by phone on a yearly basis, and radiological reports and images were obtained from their treating physician.

2.6 | Statistical analysis

Categorical data are presented as numbers with percentages, and compared with the chi-square or Fisher's exact test where appropriate. Numerical variables are presented as medians with interquartile ranges [IQR], compared with non-parametrical Mann-Whitney *U*-test. Overall and disease-free survival rates were illustrated by Kaplan-Meier curves and differences were compared with the log-rank test. Overall survival and time to recurrence were calculated in months from the index operation. Median follow-up was calculated by means of the reverse Kaplan-Meier method for all patients. To adjust for confounding in survival analysis, a multivariable Cox regression model was built, including one co-variable for every 10 events. Parameters with a *P*-value <0.05 in univariable analysis were included in a stepwise backward elimination process to find the model with the best fit. Cox regression results were expressed as HR (95%CI). In all tests, *P*-value <0.05 was the significance threshold.

Data analysis was performed with MedCalc Software (Version 12.4.0, Ostend, Belgium) and RStudio (Integrated Development for R. RStudio Team 2015, Boston).

3 | RESULTS

3.1 | Patient demographics

The main patient and tumor characteristics are illustrated in Table 1. Group 1 included 24 patients with a priori negative LN and group 2, 33 patients with down-staged LN. There were no significant differences in terms of age, gender, ASA class or BMI. However, group 1 had more patients with Barrett's metaplasia of the lower esophagus (58% vs 24%, $P = 0.009$) and group 2 had significantly more patients with dysphagia (79% vs 29%, $P = 0.0002$).

Tumor localization was equally distributed in both groups, but median tumor length was significantly longer in group 2 (5 vs 3 cm, $P = 0.002$). Preoperative T stage (cT) presented significant differences between the two groups, with 92% T1-T2 tumors in group 1 and 81% T3-T4 tumors in group 2 ($P < 0.0001$). In group 1, all patients were by definition cN0, but group 2 included 82% N1 and 18% N2 patients and had also 2 patients with isolated resectable metastasis upon diagnosis (cM1). One of them had one hypermetabolic inter-aortico-caval lymph node, resected during the intervention with viable tumor cells found upon histopathologic analysis; this patient had, however, complete tumor regression (TRG1) of the primary tumor and received extensive locoregional lymph node dissection, with no other positive LNs among the 24 retrieved (0/24). The second patient had hypermetabolic supra-clavicular LNs in the preoperative workup, which were included in the radiation field and resected with no viable tumor cells found.

3.2 | Operative characteristics

The surgical approach was similar in both groups; the majority of patients underwent transthoracic resection with intrathoracic end-to-side esophago-gastrostomy (88% group 1 and 85% group 2), whereby the abdominal part was performed laparoscopically in >50% of cases in both groups, and the thoracic part by right-sided thoracotomy. Two patients in group 1 underwent transhiatal resection. The median operative time was similar, with 350 min [IQR 141] in group 1 and 357 min [IQR 134] in group 2 ($P = 0.63$), respectively. Estimated blood loss was also comparable, with a median of 450 mL [IQR 250] and 300 mL [IQR 225] in groups 1 and 2, respectively ($P = 0.11$) (Table 1).

3.3 | Postoperative outcomes

Thirty-eight percent of group 1 and 34% of group 2 patients had no adverse postoperative outcome at all. Occurrence of minor (24% vs 39%) and major complications (38% vs 27%) was similar in both groups

TABLE 1 Patient demographics, tumor, and operative characteristics for patients with a priori negative (group 1) and downstaged lymph nodes (group 2)

	Group 1, cN0/pN0, *n* = 24	Group 2, cN+/ypN0, *n* = 33	*P*-value
Gender, male	17 (71)	22 (67)	0.74
Median age, years [IQR]	65 [14]	63 [8]	0.45
ASA			0.61
I/II	19 (79)	26 (79)	
III/IV	5 (21)	7 (21)	
Median BMI, kg/m^2 [IQR]	27 [4]	25 [6]	0.13
Preoperative dysphagia	7 (29)	26 (79)	0.0002
Barrett's metaplasia	14 (58)	8 (24)	0.009
Tumor localization			0.49
Middle third	9 (38)	14 (42)	
Lower third	10 (42)	10 (30)	
GE Junction	5 (21)	9 (27)	
Median endoscopic tumor length, cm [IQR]	3 [3]	5 [3]	0.002
cT stage			<0.0001
T1	13 (54)	1 (3)	
T2	9 (38)	6 (18)	
T3	1 (4)	24 (72)	
T4	0	3 (9)	
cN stage			<0.0001
N0	24	0	
N1	0	27 (82)	
N2	0	6 (18)	
cM1 stage	0	2 (6)	0.25
Operative technique			0.13
Thoracoabdominal approach (Lewis)	21 (88)	28 (85)	
Thoracoabdominal resection, cervical anastomosis (McKeown)	1 (4)	5 (15)	
Transhiatal resection	2 (8)	0	
Laparoscopic approach	14 (58)	17 (52)	0.61
Median estimated blood loss (mL) [IQR]	450 [250]	300 [225]	0.11
Median operative time, min [IQR]	350 [141]	357 [134]	0.63

Data are shown as frequencies *n* (%) or median [IQR].
LN, lymph nodes; ASA, American Society of Anesthesiologists; BMI, body mass index.

(*P* = 0.63). Of note, mortality rate in this series was 2.4% (*n* = 3), but these 3 patients were excluded from analysis as described in the methods section (Fig. 1). Median length of hospital stay (LOS) was 19 days for both groups (Table 2).

3.4 | Tumor histology, lymph node harvesting, and response to NAT

There was a non-significant higher prevalence of adenocarcinoma in group 1, (63% vs 27%, *P* = 0.085). Differentiation grades (G1-3) were equally distributed in both groups, while pathological T stage (pT) showed some significant differences. Group 1 had more pT1 (68% of all), no pT4 and 2 pT0 patients, who actually had in situ carcinoma and high-grade dysplasia, respectively. Group 2 had more ypT0 tumors (43% of all), and one ypT4 patient who did not respond well to NAT (TRG 4) (Table 2).

The extent of lymph node harvest was comparable in both groups, with a median of 18 LN [IQR 9 and 13, respectively]. Similarly, negative resection margins (R0) were achieved in 88% of group 1, and 100% of group 2 patients (*P* = 0.07). There were no R2 resections.

In group 2, 42% of patients (*n* = 14) had primary tumor complete response to NAT (Mandard TRG 1), whereas 49% (*n* = 16) had TRG 2-3, a moderate to good response. Only one patient had poor response (TRG 4) and no patient had complete absence of response to treatment (TRG 5).

3.5 | Overall survival (OS), disease-free survival (DFS), and tumor recurrence

Overall survival was significantly better for patients within group 1, with a 3-year survival rate of 86.8% versus 63.3% for group 2 (*P* = 0.013). Median overall survival was 97 months (95%CI 38.1-155.8 months) for all patients and 46 months (95%CI 34.7-57) for group 2, whereas it could not be assessed for group 1 patients as >50% of them were alive at the time of the last follow-up.

Disease-free survival (DFS) at 3-years was estimated at 79.6% for group 1 and 57.9% for group 2 (*P* = 0.021). Median DFS was 39 months (95% CI 4.1-73.9) for group 2, but again, it was not calculated for group 1 as >50% of patients had not relapsed by the time of the last follow-up. Kaplan-Meier curves for overall survival (OS) and disease-free survival (DFS) are shown in Figs. 2 and 3, illustrating significantly better OS and DFS for group 1 (a priori negative LN) patients.

In this series, 29% of group 1 and 55% of group 2 patients presented tumor recurrence during follow-up (*P* = 0.10) (Table 2). Two patients from group 1 and one patient from group 2 had isolated loco-regional recurrence (*P* = 0.57), whereas no patient in group 1 and 9 patients (27%) in group 2 developed distant metastatic recurrence (*P* = 0.007). Median time to recurrence was 25 months (range 6-42 months) in group 1 and 10 months (range 4-68 months) in group 2 (*P* = 0.021). Median follow-up was 40 months (95%CI 28.8-51.2 months) for the whole population, 42 months (95%CI 21.2-62.8 months) for group 1 and 31 months (95%CI 11.9-50.0 months) for group 2.

3.6 | Cox regression analysis of survival

Through a stepwise backward elimination process, two co-variates remained in the final multivariable Cox regression model: LN

TABLE 2 Tumor histology, postoperative and long-term outcomes for patients with a priori negative (group 1) and downstaged lymph nodes (group 2)

	Group 1, cN0/pN0, *n* = 24	Group 2, cN+/ypN0, *n* = 33	*P*-value
Postoperative complications (%)			0.63
None	9 (38)	11 (34)	
Minor (I-IIIa)	6 (24)	13 (39)	
Major (IIIb/IVa/IVb)	9 (38)	9 (27)	
Median LOS, days [IQR]	19 [42]	19 [12]	0.83
Adjuvant (postoperative) treatment (%)	1 (4)	3 (9)	0.63
Histological type			0.085
Adenocarcinoma	15 (63)	9 (27)	
Squamous cell carcinoma	13 (54)	20 (61)	
Grading (%)			0.30
G1	6 (25)	3 (9)	
G2	10 (42)	8 (24)	
G3	6 (25)	10 (30)	
Histopathologic T stage (%)			0.0004
pT0	2 (8)	14 (43)	
pT1	16 (68)	5 (15)	
pT2	4 (16)	5 (15)	
pT3	2 (8)	8 (24)	
pT4	0	1 (3)	
Pathological tumor length, cm, median [IQR]	1 [1]	1 [3]	0.94
Harvested LN, median [IQR]	18 [9]	18 [13]	0.94
Resection margins (%)			0.07
R0	21 (88)	33 (100)	
R1	3 (13)	0	
Recurrence during follow-up (%)	7 (29)	18 (55)	0.10
Locoregional recurrence (%)	2 (8)	1 (3)	0.57
Distant metastases (%)	0	9 (27)	0.007
Mixed (locoregional & distant) (%)	2 (8)	4 (12)	1.00
Unknown site of metastasis (%)	3 (13)	4 (13)	1.00
Median time to recurrence, months [range]	25 [6-42]	10 [4-68]	

LOS, length of stay; IQR, interquartile range; LN, lymph nodes.

down-staging and the presence of distant metastases upon diagnosis (cM+). As illustrated in Table 3, LN down-staging was significantly associated with an increased hazard of death compared to a priori negative LN (HR 3.84, 95%CI 1.07-11.29, $P = 0.037$). A trend for higher HR was observed for cM+ status (HR 3.16, 95%CI 0.86-11.51, $P = 0.082$). The final multivariate Cox regression model had an AIC value of 117.86, and a good overall fit to the data (likelihood ratio test *P*-value = 0.0091).

4 | DISCUSSION

The present study found that patients with sterilized lymph nodes after NAT and surgery had a significantly worse overall and disease free survival than patients with a priori negative lymph nodes treated with surgery alone. This poor long-term prognosis was associated with distant metastatic relapse, significantly higher in the down-staged group.

4.1 | Lymph node harvesting and its prognostic value in esophageal cancer

Cancer positive LN have a negative impact on overall and disease-free survival, and both rapidly drop <50% even in early-stage tumors.[12,22] There is increasing evidence that larger number of metastatic LNs (>3-4) and higher ratio of LN affected/resected (>0.2) are major negative prognostic factors.[23] Controversy still exists upon the optimal extent of lymphadenectomy needed to improve survival.[12,24,25] As in most centers, transthoracic esophagectomy with a two-field lymphadenectomy is the standard approach; upper mediastinal or cervical dissection are only selectively performed in case of suspected invaded LNs. Both groups in the present series had a median number of 18 resected LNs, in accordance with current standards to obtain correct staging and expected survival benefit.[25,26]

Esophageal cancer is associated with skip LN metastases, meaning positive distant LNs while peritumoral nodes are not affected,[27] as well as micro-metastases that can be detected only by immunohistochemical analyses not yet integrated in current practice, and therefore, not performed in our study. The latter have been described in up to 15-20% of cases considered as pN0 in standard pathologic examination.[8,12,28,29] Hence, lymphatic spread carries a significant metastatic potential, as even with aggressive surgical lymphadenectomy there is a high risk to leave behind tumor-positive LN or micrometastases. If those lymph nodes could be sterilized by NAT, a curative approach could still be considered after surgery.

Our current analysis showed a significant overall survival benefit for a priori LN negative patients (3-year survival of 86.8% vs 63.3% for group 2, $P = 0.013$) even though none of them had any systemic preoperative treatment. This survival benefit remained significant in multivariable analysis in favor of the a priori negative LN group. Indeed, group 1 had a particularly long survival in our study, with

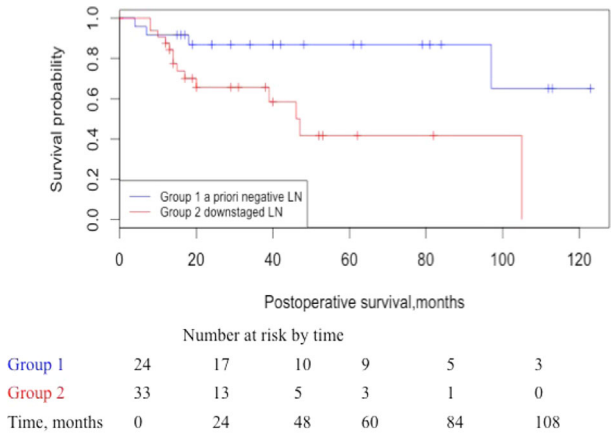

FIGURE 2 Kaplan-Meier curves of Overall Survival for group 1 (a priori negative LN) and group 2 (down-staged LN). Group 1 had a significantly better overall survival, with a 3-year survival rate of 86.8% versus 63.3% for group 2 ($P = 0.013$). LN, lymph nodes

>50% of patients being still alive and recurrence-free up to the last follow-up. Median follow-up was of 42 months (95%CI 21.2-62.8 months) for this group and 31 months (95%CI 11.9-50.0 months) for group 2, which represents a long enough time frame to draw conclusions from, despite the small number of patients in each group. Our results are in line with Rice[10] who described similar effects of lymph node involvement on survival. They observed the best 5-year survival (69%) in cN0/pN0 patients undergoing surgery alone, and the worst survival in cN1/pN1 patients without NAT (12%); down-staged patients (cN1/pN0) after NAT had a 5-year survival of 37%. In a more recent study, Shapiro et al assessed the predictive value of pre-treatment N stage, based on the presence of residual tumor cells and the degree of fibrosis, in comparison to cN and ypN stage.[13] They report a worse survival for pretreatment N+ patients down-staged to ypN0, compared to those with a priori

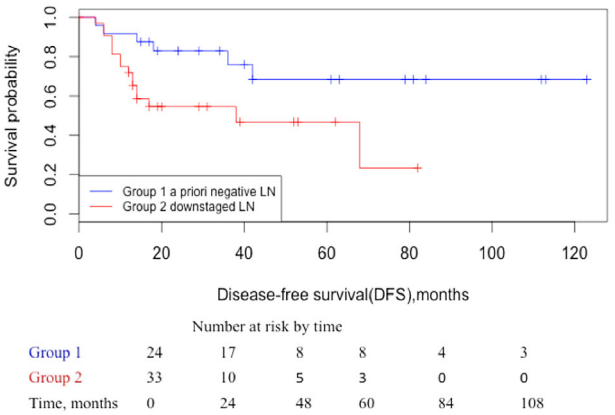

FIGURE 3 Kaplan-Meier curves of disease-free survival for group 1 (a priori negative LN) and group 2 (down-staged LN). Group 1 had significantly better disease-free survival (DFS), with a 3-year survival rate of 79.6% versus 57.9% for group 2 ($P = 0.021$). DFS, disease-free survival; LN, lymph nodes

negative LNs (5-year survival 51% vs 68%, $P = 0.019$), demonstrating thus, a strong predictive value of preoperative N status on survival. Our results are perfectly in line with this observation and reinforce the decisional role of pre-treatment N stage on long-term outcomes. Initially positive LNs, even sterilized by NAT, seem to remain a poor prognostic factor for the patient, probably suggesting early extended lymphatic dissemination, which might be the source of distant metastases and recurrence.

Indeed, recurrence patterns are of particular interest; 29% of group 1 and 55% of group 2 patients presented tumor recurrence during follow-up. Distant metastases occurred exclusively in down-staged patients (0 vs 9 patients, $P = 0.07$), while loco-regional and mixed recurrence rates were similar in both groups. Both groups of this series had similar postoperative adverse outcomes, with 62% and 66% overall morbidity, whereby 38% and 27% were severe complications for groups 1 and 2, respectively. It has been suggested that severe postoperative complications might affect long-term survival,[30] however, this could not be observed in our series.

4.2 | Effects of NAT on primary tumor

Although the role of lymph node metastases in esophageal cancer remains critical, the primary tumor cannot be overlooked. One important point to consider is the lack of accuracy in preoperative staging, as illustrated both by Shapiro[13] and by Crabtree et al for cT2N0 tumors.[31] The latter study reports a high percentage of cT2N0 tumors (47%) treated with surgery first actually being pT3-4 or pN+ upon resection, which might lead to inappropriate treatment strategies, and thus, worse long-term outcomes. In the present study, significantly higher T-stages, longer endoscopic tumor lengths and more preoperative dysphagia were observed in group 2, reflecting an increased tumor burden. In the same group, pathological complete response was observed in 42% of patients after NAT, which correlates with recently published data.[32,33] Group 1 had more R1 resections compared to group 2 (3 vs 0 patients, $P = 0.07$); this is also in accordance with recent literature suggesting that NAT increases downsizing and R0 resection rates.[6] Although the more advanced T stages in the "down-staged" group might be looked upon as a potential source of confounding, this should be given some further reflection. Group 2 patients had indeed more advanced tumors upon diagnosis, as they had by definition a positive cN status and thus, not surprisingly, also a more advanced cT status. They were, however, excellent responders to NAT as they were all LN negative after treatment. In our attempt to compare survival between more advanced tumors with lymphatic dissemination who respond well to NAT versus earlier stages who did not receive NAT at all, we did not confirm a survival benefit for the "down-staged" group compared to their "a priori negative" counterparts. Along with Rice[10] and Shapiro,[13] our study adds to the growing body of evidence suggesting preoperative N+ status as a poor prognostic factor even in the era of efficient NAT. This might help identify cN+ as high-risk patients, for whom reinforced follow-up programs or

TABLE 3 Simple and multiple Cox regression analysis of survival

	Unadjusted HR	95%CI	*P*-value[a]	Adjusted HR	95%CI	*P*-value[a]
Downstaged LN	4.04	1.29-12.65	0.016	3.84	1.07-11.29	0.037
cM+ stage[b]	4.98	1.41-17.61	0.013	3.16	0.86-11.51	0.082
Gender						
Male	1	1	1			
Female	0.76	0.27-2.13	0.596	–	–	–
Age	1.02	0.97-1.07	0.529			
ASA class						
I	1	1				
II	0.38	0.05-3.04	0.365	–	–	–
III	0.86	0.10-7.42	0.891			
Severe postoperative complications [21]	1.19	0.41-3.43	0.753	–	–	–
cT stage[b]						
cT1	1	1	1			
cT2	0.65	0.11-3.96	0.646			
cT3-4	3.35	0.93-12.10	0.064	–	–	–
Tumor differentiation						
G1	1	1	1			
G2	4.38	0.52-36.82	0.173	–	–	–
G3	5.98	0.71-50.25	0.099			
pT stage[b]						
pT0	1	1	1			
pT1	0.31	0.07-1.25	0.100	–	–	–
pT2	0.50	0.10-2.52	0.403			
pT3-4	2.42	0.76-7.66	0.134			
Number of harvested LN	1.00	0.96-1.05	0.911	–	–	–
R+ resection	0.68	0.09-5.15	0.707	–	–	–

HR, hazard ratio; 95%CI, 95th percentile confidence intervals; ASA, American Society of Anesthesiologists; LN, lymph nodes.
Downstaged LN remained independently associated with an increased death hazard compared to a priori negative LN.
[a]Wald test.
[b]7th TNM edition.[14]

even adjuvant treatment with novel biological agents might have a potential interest.

4.3 | Limitations of the study

This study has some shortcomings and limitations that must be addressed. By means of our exclusion criteria, we aimed to obtain a maximal homogeneity in the context of a retrospective, real-life study. However, because of the limited number of patients, it was not possible to perform separate subgroup analyses for squamous cell carcinoma and adenocarcinoma to identify potential variations in response to NAT and survival; moreover as the difference in histological type between the groups was not significant, we did not consider this as a source of confounding. Some staging differences between the groups, mostly in cT, cM, and pT stage are also present in our series; to overcome this, multivariable Cox analysis was performed, allowing to adjust for these potential confounders.

When assessing lymph node harvesting, some inherent limitations also need to be mentioned. Positive lymph nodes may have been missed during surgical lymphadenectomy and also, false-positive pretreatment staging could have been registered in active smokers or patients with smoking history or with other pulmonary diseases, who often reveal enlarged and irregularly shaped lymph nodes.[34,35] Of course, dissociated response of tumor and LN or distant metastases is a described phenomenon.[23,36] even in absence of staging errors; although the exact mechanism remains unclear, and different histologic response to treatment might be encountered between tumor and lymph nodes. Finally, as tumor response is not routinely assessed in the LN and this was not done in our study either, it is difficult to actually prove that individual LNs were actually "sterilized" by NAT.

In conclusion, patients with initially positive, down-staged lymph nodes still seem to have a worse long-term outcome compared to patients with a priori negative lymph nodes, despite the systemic impact of NAT. So far, there is no data to support limited lymphadenectomy even in presence of excellent response to NAT.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

REFERENCES

1. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst*. 2008;100:1184–1187.
2. Gatenby PAC, Hainsworth A, Caygill C, Watson A, Winslet M. Projections for oesophageal cancer incidence in England to 2033. *Eur J Cancer Prev*. 2011;20:283–286.
3. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16:1090–1098.
4. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v50–v57.
5. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–2084.
6. Gronnier C, Tréchot B, Duhamel A, et al. Impact of neoadjuvant chemoradiotherapy on postoperative outcomes after esophageal cancer resection: results of a European multicenter study. *Ann Surg*. 2014;260:764–770.
7. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol*. 2009;27:5062–5067.
8. Prenzel KL, Hölscher AH, Drebber U, Agavonova M, Gutschow CA, Bollschweiler E. Prognostic impact of nodal micrometastasis in early esophageal cancer. *Eur J Surg Oncol*. 2012;38:314–318.
9. Bollschweiler E, Baldus SE, Schröder W, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. *Endoscopy*. 2006;38:149–156.
10. Rice TW, Blackstone EH, Adelstein DJ, et al. N1 esophageal carcinoma: the importance of staging and downstaging. *J Thorac Cardiovasc Surg*. 2001;121:454–464.
11. Schneider PM, Baldus SE, Metzger R, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. *Ann Surg*. 2005;242: 684–692.
12. Kayani B, Zacharakis E, Ahmed K, Hanna GB. Lymph node metastases and prognosis in oesophageal carcinoma—a systematic review. *Eur J Surg Oncol*. 2011;37:747–753.
13. Shapiro J, Biermann K, van Klaveren D, et al. Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. *Ann Surg*. 2017;265:356–362.
14. Sobin L, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours* (7th ed.). Wiley; 2011 E-book ISBN: 978-1-4443-5896-4.
15. Foley KG, Lewis WG, Fielding P, et al. N-staging of oesophageal and junctional carcinoma: is there still a role for EUS in patients staged N0 at PET/CT? *Clin Radiol*. 2014;69:959–964.
16. Blackshaw G, Lewis WG, Hopper AN, et al. Prospective comparison of endosonography, computed tomography, and histopathological stage of junctional oesophagogastric cancer. *Clin Radiol*. 2008;63:1092–1098.
17. Sarvanan K, Bapuraj JR, Sharma SC, Radotra BD, Khandelwal N, Suri S. Computed tomography and ultrasonographic evaluation of metastatic cervical lymph nodes with surgicoclinicopathologic correlation. *J Laryngol Otol*. 2002;116:194–199.
18. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet* 2016;381:400–412.
19. Ruhstaller T, Pless M, Dietrich D, et al. Cetuximab in combination with chemoradiotherapy before surgery in patients with resectable, locally advanced esophageal carcinoma: a prospective, multicenter phase IB/II trial (SAKK 75/06). *J Clin Oncol*. 2011;29:626–631.
20. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: clinicopathologic correlations. *Cancer*. 1994;73:2680–2686.
21. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
22. Waterman TA, Hagen JA, Peters JH, DeMeester SR, Taylor CR, DeMeester TR. The prognostic importance of immunohistochemically detected node metastases in resected esophageal adenocarcinoma. *Ann Thorac Surg*. 2004;78:1161–1169.
23. Mariette C, Piessen G, Briez TJ. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg*. 2008;247:365–371.
24. Mariette C, Piessen G. Oesophageal cancer: how radical should surgery be? *Eur J Surg Oncol*. 2012;38:210–213.
25. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. *Ann Surg*. 2010;251:46–50.
26. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. *Cancer*. 2008;112:1239–1246.
27. Nigro JJ, Hagen JA, Demeester TR, et al. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. *J Thorac Cardiovasc Surg*. 1999;117:16–25.
28. Grotenhuis BA, VanHeijl M, Wijnhoven BPL, et al. Lymphatic micrometastases in patients with early esophageal adenocarcinoma. *J Surg Oncol*. 2010;102:863–867.
29. Marjanovic G, Schricker M, Walch A, et al. Detection of lymph node involvement by cytokeratin immunohistochemistry is an independent prognostic factor after curative resection of esophageal cancer. *J Gastrointest Surg*. 2011;15:29–37.
30. van Heijl M, Sprangers MAG, de Boer AGEM, et al. Preoperative and early postoperative quality of life predict survival in potentially curable patients with esophageal cancer. *Ann Surg Oncol*. 2010;17:23–30.
31. Crabtree TD, Kosinski AS, Puri V, et al. Evaluation of the reliability of clinical staging of T2 N0 esophageal cancer: a review of the Society of Thoracic Surgeons database. *Ann Thorac Surg*. 2013;96:382–390.
32. Siddiqui F, Atkins KM, Diggs BS, Thomas CR, Hunter JG, Dolan JP. Overall survival analysis of neoadjuvant chemoradiotherapy and esophagectomy for esophageal cancer. *J Gastrointest Oncol*. 2014;5:86–91.
33. Pasini F, de Manzoni G, Zanoni A, et al. Neoadjuvant therapy with weekly docetaxel and cisplatin, 5-fluorouracil continuous infusion, and concurrent radiotherapy in patients with locally advanced esophageal cancer produced a high percentage of long-lasting pathological complete response: a phase. *Cancer*. 2013;119:939–945.

34. Misra S, Choi M, Livingstone AS, Franceschi D. The role of endoscopic ultrasound in assessing tumor response and staging after neoadjuvant chemotherapy for esophageal cancer. *Surg Endosc Other Interv Tech*. 2012;26:518–522.
35. Napier KJ, Scheerer M, Misra S. Esophageal cancer: a review of epidemiology, pathogenesis, staging workup and treatment modalities. *World J Gastrointest Oncol*. 2014;6:112–120.
36. Hölscher AH, Drebber U, Schmidt H, Bollschweiler E. Prognostic classification of histopathologic response to neoadjuvant therapy in esophageal adenocarcinoma. *Ann Surg*. 2014;260:779–785.

How to cite this article: Mantziari S, Allemann P, Winiker M, Sempoux C, Demartines N, Schäfer M. Sterilization of tumor-positive lymph nodes of esophageal cancer by neo-adjuvant treatment is associated with worse survival compared to tumor-negative lymph nodes treated with surgery first. *J Surg Oncol*. 2017;116:524–532. https://doi.org/10.1002/jso.24689