Impact of Neoadjuvant Chemoradiation on Lymph Node Status in Esophageal Cancer

Post hoc Analysis of a Randomized Controlled Trial

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Objective: The study objectives were to analyze the impact of the number of lymph nodes (LNs) reported as resected (NLNr) and the number of LNs invaded (NLNi) on the prognosis of esophageal cancer (EC) after neoadjuvant chemoradiotherapy.

Background: Pathological LN status is a major disease prognostic factor and marker of surgical quality. The impact of neoadjuvant chemoradiation (nCRT) on LN status remains poorly studied in EC.

Methods: Post hoc analysis from a phase III randomized controlled trial comparing nCRT and surgery (group nCRT) to surgery alone (group S) in stage I and II EC (NCT00047112). Only patients who underwent surgical resection were considered (n = 170).

Results: nCRT resulted in tumoral downstaging (pT0, 40.7% vs 1.1%, $P < 0.001$), LN downstaging (pN0, 69.1% vs 47.2%, $P = 0.016$), and reduction in the median NLNr [16.0 (range, 0–47.0) vs 22.0 (range, 3.0–58.0), $P = 0.001$] and NLNi [0 (range, 0–25) vs 1.0 (range, 0–25), $P = 0.001$]. A good histological response (TRG1/2) in the resected esophageal specimen correlated with reduced median NLNi [0 (range, 0–10) vs 1.0 (range, 0–4), $P = 0.007$]. After adjustment by treatment, NLNi [hazards ratio (HR) (1–3 vs 0) 3.5, 95% confidence interval (CI): 2.3–5.5, and HR (>3 vs 0) 3.5, 95% CI: 2.0–6.2, $P < 0.001$] correlated with prognosis, whereas NLNr [HR (<15 vs ≥15) 0.95, 95% CI: 0.6–1.4, $P = 0.807$ and HR (<23 vs ≥23) 1.4, 95% CI: 0.9–2.0, $P = 0.131$] did not. In Poisson regression analysis, nCRT was an independent predictive variable for reduced NLNr [exp(coefficient) 0.80, 95% CI: 0.66–0.96, $P = 0.018$].

Conclusions: nCRT is not only responsible for disease downstaging but also predicts fewer LNs being identified after surgical resection for EC. This has implications for the current quality criteria for surgical resection.

Keywords: chemoradiation, esophageal cancer, lymph node, randomized trial, surgery, survival

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The outlook for most patients with esophageal cancer (EC) remains bleak. This fact is largely due to the aggressive spread of disease through the lymphatic system at an early stage. Increasingly, evidence has suggested that after esophagectomy both the number of lymph nodes (LNs) reported as having been resected (NLNr)[1–4] and the number of LNs invaded (NLNi)[2,5,6] are predictive of survival. These data derive from retrospective series that have systematically excluded patients receiving neoadjuvant treatments, to avoid the bias of its potential downstaging effects, and have not controlled for the quality of the surgical resections performed.

Adjuvant therapies in EC have not shown survival benefits,[7] and today most patients require neoadjuvant treatment. For locally advanced tumors, neoadjuvant chemoradiation (nCRT) is the treatment of choice with the most recent meta-analysis,[8] and the results of the CROSS trial,[9] supporting such a strategy. The data from rectal cancer suggest that nCRT reduces the NLNr[10–12] and NLNi found in the resected mesorectum,[12] suggesting that reduced LN numbers may reflect a good response to treatment and be an indicator of improved prognosis.[12] This finding challenges the current surgical dogma that NLNr both reflects the quality of surgical lymphadenectomy and correlates with survival after nCRT.

To date, the effect of nCRT on LN status after resection for EC has been poorly studied. In 2009, the Fédération Francophone de Cancérologie Digestive (FFCD) completed a multicenter randomized controlled phase III trial comparing nCRT followed by surgery with surgery alone in patients with localized (stage I or II) EC.[13] Such a trial, in which the surgical lymphadenectomy was comparable between the groups, provides the ideal opportunity to evaluate LN status after nCRT for EC. This study comprises a post hoc analysis of LN data from this trial, evaluating how the NLNr and the NLNi are affected by nCRT and their consequent impact on survival.

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PATIENTS AND METHODS

Patients

In June 2000, the FFCD began a multicenter randomized controlled phase III trial comparing nCRT followed by surgery with surgery alone in patients with stage I and II EC (FFCD9901). The trial design is registered on the ClinicalTrials.gov Web site under the identifying number NCT00047112, and the detailed methodology has been reported elsewhere.[13] Briefly, the patients included were younger than 75 years, had a World Health Organization (WHO) performance status 0 or 1, and were judged to be suitable for curative surgical resection with clinical stage I and II (cT1-T2 N0 or N+, cT3N0) thoracic epidermoid or glandular EC. Baseline clinical examination, routine laboratory blood analyses, endoscopy with tumor biopsy, indirect laryngoscopy, bronchoscopy, respiratory function testing, and electrocardiogram were standard for all patients. Selected patients also underwent cervical ultrasound examination and positron emission tomographic scanning. The clinical stage of the disease was assessed by systematic endoscopic ultrasound using the classification of Tio et al[14] combined with computerized tomographic scans using the modified classification proposed by Bosset et al.[15]

Treatment

Neoadjuvant Chemoradiation (Group nCRT)

Chemotherapy was delivered concomitantly with radiotherapy and comprised 2 cycles of 5-fluorouracil and cisplatin; 5-fluorouracil, 800 mg/m^2/24 h, was administered as a continuous infusion from days 1 through 4 and from days 29 through to 32. Cisplatin, 75 mg/m^2, was delivered by infusion (1 mg/min) on days 1 or 2 and then on day 29 or 30. Alternatively, it was delivered as an infusion at a dose of 15 mg/m^2 for 5 consecutive days from days 1 to 5 and from days 29 to 33. All patients in the nCRT group were scheduled for treatment by radiotherapy and received a total dose of 45 Gy, which was delivered in 25 fractions (5 fractions per week) over a period of 5 weeks. For tumors with a proximal margin of more than 30 cm from the dental arch inclusion of the celiac nodes in the clinical target volume was obligatory.

Surgery (Group S)

All patients in the nCRT group had a clinical reevaluation 4 to 6 weeks after finishing neoadjuvant CRT to verify the absence of metastatic progression and confirm resectability. Surgery was performed 4 to 8 weeks after the completion of nCRT and within 4 weeks of random assignment to group S. The surgical technique and lymphadenectomy were performed according to the French National Guidelines.[16] All patients had an esophageal resection via open thoracotomy, mainly through an Ivor-Lewis procedure. A 3-stage operation was performed with cervical anastomosis for tumors with a proximal margin above the carina. A 2-field lymphadenectomy was standard and no transhiatal resections were performed. Cervical lymphadenectomy was not undertaken.

Study Population

From June 2000 until June 2009, 195 patients from 30 French centers were randomly assigned to either the nCRT followed by surgery group (group nCRT, n = 98) or the surgery alone group (group S, n = 97). Recruitment to this trial was limited by its restriction to patients with early-stage tumors, which continues to be an uncommon presentation in the French population. Only patients who proceeded to EC resection were included in this post hoc analysis, corresponding to 81 of 98 (82.7%) in group nCRT and 89 of 97 (91.8%) in group S. The 2 groups were comparable in terms of their demographic and clinical tumoral data (Table 1). The male to female ratio was 9:1, and the median age was 57.8 years (range, 40.1–76.4). There was a predominance of epidermoid subcarinal tumors in both treatment groups, a feature that is particular to the French population. Before treatment, 45 patients (26.5%) were identified with cN1 disease, of whom 23 were in the nCRT group and 22 were in the S group.

Pathological Assessment of Lymphadenectomy and Tumor Response

In accordance with evidence of increased nodal yields,[2,3] it was recommended that the surgeon separately dissect all nodal material from the specimen at the end of each procedure. There was no procedure for monitoring the techniques of pathological analysis used in each center. The specimens were analyzed according to the National guidelines of the Japanese Society for Esophageal Diseases.[2,17] The histologic staging was based on the sixth UICC/TNM classification.[18] The pathological response to nCRT was defined by tumor regression grade (TRG) according to the Mandard classification as follows: TRG1 represented complete tumoral regression, TRG2 represented rare residual cancer cells scattered through fibrosis, TRG3 represented an increased number of residual cancer cells with fibrosis still predominating, TRG4 represented residual cancer outgrowing fibrosis, and TRG5 represented the absence of regressive changes.[19] All specimens were examined locally by dedicated gastrointestinal pathologists using routine pathological procedures without any fat-clearing solutions.

Study Objectives

The primary objective is to analyze the effects of nCRT on the pN status, NLNr, and NLNi in the resected specimen. The secondary objectives include assessing (i) the correlation between tumoral response and the NLNr and NLNi, (ii) the impact of NLNr and NLNi on overall survival, and (iii) the identification of predictive factors for the NLNr at surgery.

Statistical Analysis

The data were described using frequencies (percentage), means (standard deviation), or medians (range). Continuous data were compared by the Wilcoxon test, and qualitative data were compared by the χ^2 test. The analysis of the overall survival of operated patients, depending on NLNi and NLNr, was estimated using the Kaplan-Meier method, and the log-rank test was used for comparison by treatment group. Cox models were used to identify whether NLNi or NLNr were independent prognostic factors. The cutoff values of 15 and 23 LNs were chosen according to studies that associated 15[2] and 23[3] LNs with surgical quality and optimal staging in EC. Regarding the center volume, the cutoff value of 5 was arbitrarily defined on the basis of the median number of patients included per center. A univariate analysis of the factors associated with NLNr was performed using a Poisson regression model. Poisson multivariate analysis was then performed using a threshold value of 0.2 to enter the variables into the model.

RESULTS

The primary evaluation of this trial has already been reported.[13] Briefly, after a median follow-up of 93.6 months, the overall survival was not significantly different between the groups [hazards ratio (HR) group nCRT vs group S, 0.99; 95% confidence interval (CI): 0.69–1.40, $P = 0.94$]. This result, in conjunction with an in-hospital postoperative mortality that was significantly higher in the nCRT group than surgery alone (11.1% vs 3.4%, $P = 0.049$), meant that the trial was halted on the basis of futility and led to the conclusion that nCRT does not provide a survival benefit in stage I and II EC.

TABLE 1. Patient and Tumor Characteristics of 170 Patients Undergoing EC Resection

	Resected Population (n = 170)		nCRT Group (n = 89)		S Group (n = 81)		
Variables	**No.**	**%**	**No.**	**%**	**No.**	**%**	***P***
Age, median (range)	57.8 (36.9–76.4)		57.8 (40.1–76.4)		57.6 (36.9–74.3)		0.813
Sex							
Male	146	85.9	73	90.1	73	82.0	0.130
Female	24	14.1	8	9.9	16	18.0	
Tumor histology							
Epidermoid	121	71.2	57	70.4	64	71.9	0.795
Glandular	48	28.2	23	28.4	25	28.1	
Undifferentiated	1	0.6	1	1.2	0	0.0	
Tumor location							
Above carina	15	8.8	5	6.2	10	11.2	0.245
Below carina	155	91.2	76	93.8	79	88.8	
WHO performance index							
0	127	74.7	61	75.3	66	74.2	1.00
1	41	24.1	20	24.7	21	23.6	
2	1	0.6	0	0.0	1	1.1	
Unknown	1	0.6	0	0.0	1	1.1	
Weight loss							
<10%	158	92.9	74	91.4	84	94.4	0.199
≥10%	10	5.9	7	8.6	3	3.4	
Unknown	2	1.2	0	0.0	2	2.2	
cT stage							
cT1	42	24.7	21	25.9	21	23.6	0.770
cT2	97	57.1	47	58.0	50	56.2	
cT3	31	18.2	13	16.1	18	20.2	
cN stage							
cN0	125	73.5	58	71.6	67	75.3	0.587
cN1	45	26.5	23	28.4	22	24.7	
Stage cTNM							
I	33	19.4	15	18.5	18	20.2	0.856
IIa	92	54.1	43	53.1	49	55.1	
IIb	45	26.5	23	28.4	22	24.7	

NLNr and NLNi

The global median NLNr was 19.5 (range, 0–58) and was significantly lower in group nCRT than it was in group S [16.0 (range, 0–47.0) vs 22.0 (range, 3.0–58.0), $P = 0.001$]. Concerning pathology, node-positive disease was diagnosed in 25 of the 81 patients (30.9%) in group nCRT and in 47 of the 89 patients (52.8%) in group S (Table 2), with an odds ratio of pN0 versus pN+ disease of 2.5 (95% CI: 1.3–4.7, $P = 0.004$) in favor of group nCRT. The global median NLNi was 0 (range, 0–10) and was significantly reduced in group nCRT compared with group S [0 (range, 0–25) vs 1.0 (range, 0–25), $P = 0.001$]. Whether surgery was performed before or after 6 weeks from the completion of nCRT affected neither the NLNr ($P = 0.73$) nor the NLNi ($P = 0.30$) in group nCRT.

Tumor Regression Grade With NLNr and NLNi

TRG data were available for 76 of the 81 patients who were treated with nCRT and proceeded to resection. A complete pathological response (ypT0N0) was observed in 27 patients (33.3%), and 33 patients (40.7%) had a complete tumoral response after nCRT. The patients were grouped into those exhibiting evidence of good treatment response (TRG1/2, 56 patients) and those with poor treatment response (TRG3-5, 20 patients). After nCRT, no difference was noted in the median NLNr on the basis of the tumor response [median NLNr TRG1/2, 16.5 (range, 4–39) vs TRG3–5, 20.5 (range, 8–33), $P = 0.230$]. However, patients with a good tumor response to therapy had a significantly reduced median NLNi compared with those who had a poor histological response to treatment [median NLNi TRG1/2, 0 (range, 0–10) vs TRG3–5, 1.0 (range, 0–4), $P = 0.007$].

NLNi and Overall Survival

Because NLNi has been established as a strong predictor of survival in patients undergoing primary resection for EC,[8] we aimed to evaluate its prognostic impact after nCRT. In the population of patients who underwent EC resection, the NLNi was analyzed for 3 groups (NLNi = 0, NLNi = 1–3, and NLNi > 3) because the threshold values of 1 and 3 NLNi are used as discriminating values in the seventh AJCC (American Joint Committee on Cancer) classification.[27] In univariate analysis, after adjustment by treatment arm, NLNi [HR (1–3 vs 0) 3.5, 95% CI: 2.3–5.5, and HR (>3 vs 0) 3.5, 95% CI: 2.0–6.2, $P < 0.001$] was associated with poor prognosis. A multivariate analysis, considering NLNi, treatment arm, WHO performance status, pTNM stage, and weight loss at randomization, revealed NLNi to be an independent predictor of poor prognosis in EC resected patients [HR (1–3 vs 0) 4.1, 95% CI: 2.2–7.8, and HR (>3 vs 0) 4.1, 95% CI: 1.9–8.5, $P < 0.001$], in group nCRT [HR (1–3 vs 0) 4.7, 95% CI: 1.9–11.7 and HR (>3 vs 0) 5.5, 95% CI: 1.5–20.0, $P = 0.003$] and in group S [HR (1–3 vs 0) 3.1, 95% CI: 1.3–7.3 and HR (>3 vs 0) 3.2, 95% CI: 1.3–8.0, $P = 0.026$]. We thus conclude that the well-known prognostic role of NLNi after primary surgery is maintained after nCRT for EC.

TABLE 2. Surgery and Pathological Staging

	Resected Population (n = 170)		nCRT Group (n = 81)		S Group (n = 89)		
	n	%	n	%	n	%	*P*
Time—randomization to resection—median (range), d	29.0 (1–200)		102.0 (13–200)		15.0 (1–85)		—
Level of anastomosis							
Intrathoracic	158	92.9	77	95.1	81	91.0	0.303
Cervical	12	7.1	4	4.9	8	9.0	
pT stage							
pT0	34	20.0	33	40.7	1	1.1	<0.001
pT1	49	28.8	21	25.9	28	31.5	
pT2	32	18.8	12	14.8	20	22.5	
pT3	43	25.3	13	16.1	30	33.7	
pT4	12	7.0	2	2.5	10	11.2	
PN Stage							
N0	98	57.7	56	69.1	42	47.2	0.016
N1	38	22.4	15	18.5	23	25.8	
N2	22	12.9	8	9.9	14	15.7	
N3	12	7.1	2	2.5	10	11.2	
pTNM Stage							
0	31	18.2	29	35.8	2	2.3	<0.001
I	38	22.4	14	17.3	24	27.0	
II	56	32.9	28	34.6	28	31.5	
III	45	26.5	10	12.4	35	39.3	
R0 Resection							
Yes	158	92.9	76	93.8	82	92.1	0.749
No	10	5.9	4	4.9	6	6.7	
Unknown	2	1.1	1	1.2	1	1.1	
No. LNs invaded (NLNi)							
0	97	57.1	56	69.1	41	46.1	0.001
1–3	47	27.6	21	25.9	26	29.2	
>3	24	14.1	4	5.0	20	22.5	
Unknown	2	1.2	0	0.00	2	2.2	
No. LNs resected (NLNr)							
≥15	114	67.0	48	59.3	66	74.2	0.021
<15	54	31.8	33	40.7	21	23.6	
Unknown	2	1.2	0	0.0	2	2.2	
≥23	67	39.4	25	30.9	42	47.2	0.021
<23	101	59.4	56	69.1	45	50.6	
Unknown	2	1.2	0	0.0	2	2.2	

NLNr and Overall Survival

Improved survival for patients undergoing surgery alone, based on the NLNr, has been established in the literature, with a threshold value of 15 resected LNs generally associated with high surgical quality and optimal staging.[8] We thus examined the prognostic impact of NLNr on overall survival in a population of patients treated by nCRT. Adjusted by treatment arm, the NLNr (≥15 vs <15) was not found to be associated with survival for the population as a whole (HR 0.95, 95% CI: 0.6–1.4, $P = 0.807$) or after nCRT (HR 1.1, 95% CI: 0.6–1.9, $P = 0.791$). In our analysis, we did not replicate others' findings of better survival in patients treated with surgery alone and having 15 of more LNs resected (HR 0.8, 95% CI: 0.5–1.5, $P = 0.50$). As a threshold of 23 resected LNs has also been associated with surgical quality and optimal staging,[3] we investigated the prognostic role of NLNr (≥23 vs <23) as an exploratory analysis. NLNr (≥23 vs <23) was not found to be associated with survival (HR 1.4, 95% CI: 0.9–2.0, $P = 0.131$) or identified as a prognostic factor in the multivariate model. As such, the well-known prognostic role of NLNr after primary surgery may not be maintained after nCRT for EC.

Factors Predictive of NLNr

Variables associated with NLNr in the whole population were identified by uni- and multivariate analysis (Table 3). Univariate analysis revealed that patients receiving nCRT ($P < 0.001$) and patients with a WHO performance status of 1 or greater ($P = 0.036$) resulted in a reduced NLNr. Conversely, patients with a glandular rather than epidermoid carcinomas ($P = 0.042$) and centers including more than 5 patients ($P = 0.003$) were found to be associated with increased NLNr. No correlation between NLNr and the following factors were observed: weight loss ($P = 0.151$), age ($P = 0.695$), sex ($P = 0.382$), tumor location ($P = 0.596$), cT stage ($P = 0.274$), cN stage ($P = 0.302$), and cTNM stage ($P = 0.906$). Multivariate analysis identified nCRT ($P = 0.018$) and patient performance status ($P = 0.044$) as independent predictive factors of reduced NLNr (Table 3). Patients with preoperative weight loss of 10% or more ($P = 0.037$) and centers contributing 5 or more patients to the study ($P = 0.004$) were both found to be independently predictive of increased NLNr. We thus conclude that nCRT is responsible for reduced NLNr after EC surgery.

TABLE 3. Poisson Regression—Univariate and Multivariate Analyses of Factors Predictive of the Total Number of Resected LNs in Total Study Population

Univariable Analysis	Exp (coefficient)	95% CI	*P*
Treatment			
Group nCRT vs Group S	0.76	0.65–0.88	<0.001
Age, >60 vs ≤60 yrs	0.97	0.82–1.14	0.695
Sex, female vs male	1.10	0.88–1.38	0.382
Histology, glandular vs epidermoid	1.19	1.01–1.42	0.042
Tumor location, above vs below carina	0.93	0.71–1.22	0.596
WHO performance status, ≥1 vs 0	0.81	0.67–0.99	0.036
Weight loss at inclusion, ≥10% vs <10%	1.25	0.92–1.70	0.151
No. patients by center, ≥5 vs <5	1.39	1.12–1.73	0.003
Tumor differentiation			
Well—moderately vs no tumor	1.40	1.12–1.76	0.010
Poor—undifferentiated vs no tumor	1.34	1.00–1.78	
cT stage			
3 vs 1	0.90	0.69–1.16	0.274
2 vs 1	1.07	0.88–1.30	
cN stage			
1 vs 0	1.10	0.92–1.31	0.302
cTNM stage			
II vs I	0.99	0.81–1.21	0.906
Multivariate analysis			
Treatment			
Group nCRT vs Group S	0.80	0.66–0.96	0.018
Histology, glandular vs epidermoid	1.16	0.98–1.38	0.080
WHO performance status, ≥1 vs 0	0.81	0.66–1.00	0.044
Weight loss at randomization, ≥10% vs <10%	1.41	1.04–1.93	0.037
No. patients by center, ≥5 vs <5	1.38	1.10–1.74	0.004
Tumor differentiation			
Well-moderately vs no tumor	1.25	0.97–1.59	0.152
Poor-undifferentiated vs no tumor	1.13	0.81–1.55	

S indicates surgery.

DISCUSSION

Retrospective studies of patients treated with primary surgery have revealed that failure to examine 15 to 30 LNs is predictive of poor survival in EC.[1–4] Consequently, NLNr is considered an indicator of surgical quality and allows for optimal staging. Despite the vast majority of patients receiving neoadjuvant treatment, mainly nCRT, no strong evidence is available regarding the impact of nCRT on LN status in EC. The current analysis, derived from a multicenter randomized controlled trial of nRCT plus surgery versus surgery alone, establishes that NLNr is significantly lower after nCRT ($P = 0.001$), with a 27% reduction in the mean number of nodes examined. Similarly, NLNi is significantly reduced after nCRT and patients exhibiting a better tumor response have a significantly reduced median NLNi. Although the prognostic value of NLNi remains no matter whether patients do or do not receive nCRT, the prognostic value of NLNr may not persist after nCRT. Finally, nCRT was an independent predictor for fewer LNs being resected in EC.

Pathological LN assessment is important in EC because both increasing numbers of metastatic nodes and the extent of lymphadenectomy have both been shown to predict patient survival.[1–4,20] In accordance with the sixth edition of the AJCC staging manual[18], the resection of 15 LNs has commonly been used as the minimum required for adequate staging.[2] More recently, the analysis of Peyre et al[3] established that the survival benefit is optimized by removing the threshold of 23 LNs.[3] As studies that have sought to establish a threshold for the number of LNs to be resected in EC have systematically excluded patients undergoing neoadjuvant therapy, to avoid the bias of its potential nodal downstaging effects, their applicability to all patients is limited.

A retrospective analysis of a cohort of resectable patients from our group previously suggested that nCRT for EC decreases both NLNr and NLNi.[2] Similar findings have been reported after preoperative radiotherapy in the setting of rectal cancers,[21,22] where it appears that NLNr loses its prognostic value after nCRT[23] and that the 5-year survival may not be associated with NLNr.[22] Our analysis in EC suggests that the prognostic value of NLNr may also be lost after nCRT, with no difference observed in overall survival in patients in group nCRT, regardless of whether they had either <15/≥15 or <23/≥23 LNs retrieved.

Evidently, the quality of surgical resection and pathological examination dictate the reported NLNr, and these factors are well controlled for in the setting of a randomized controlled trial. Nodal size may impact nodal identification by the pathologist and studies in both rectal cancer[24] and EC[25] have suggested a significant reduction in nodal size after nCRT. Ionizing radiation causes significant lymphocyte depletion at lower doses and atrophy and fibrosis of the stroma at higher doses.[26] With many nodes in the surgical specimen being as small as 1 to 2 mm in diameter, the need for an exacting pathological examination is clear.

The concept of a pN classification that incorporates levels of LN involvement, as described in the seventh edition of the TNM staging system for EC, seems logical because our findings consistently demonstrated the prognostic value of the NLNi, regardless of whether the patients received nCRT.[27] Nodal downstaging after

nCRT was clear, with an odds ratio of pN0 versus pN+ disease of 2.5 ($P = 0.004$) in favor of group nCRT. Furthermore, pN0 disease was significantly associated with better survival. Despite some degree of downstaging, nCRT failed to offer a survival benefit in this trial, an outcome that may be explained by several factors. These include the higher postoperative mortality rate after nCRT, the better baseline prognosis for stage I and II tumors compared to patients with stage III tumors, the fact that some patients did not respond favorably to nCRT, and finally, evidence of the high surgical quality in this trial, as shown by the low postoperative mortality rate, high NLNr, and high R0 resection rate in group S. The combination of these variables may lead to a benefit and risk balance that does not favor nCRT in early EC, as opposed to locally advanced EC.[13]

In patients with major histological responses to therapy (TRG1/2), we found a significant reduction in NLNi. This is consistent with previous reports of significantly reduced pN1 disease after a good response to neoadjuvant therapy and rates of pN1 disease after minimal tumor response similar to patients having no neoadjuvant therapy.[25] This correlation between LN and tumoral response raises the question concerning whether extensive lymphadenectomy is necessary in every case. Asking this question is especially pertinent if the prognostic role of NLNr is indeed also lost after nCRT. Solomon et al[28] presented an analysis of SEER (Surveillance, Epidemiology, and End Results) data for 4224 patients undergoing surgery with curative intent for glandular EC using the analysis stratified by the administration of radiotherapy and adequate ($\geq$18 LNs) or inadequate ($<$18LNs) lymphadenectomy. They found that in node-positive patients who received neoadjuvant radiotherapy, adequate lymphadenectomy significantly prolonged survival (32 vs 19 months, $P = 0.036$) compared with inadequate lymphadenectomy. For node-positive patients who did not receive neoadjuvant treatment, adequate lymphadenectomy also prolonged survival ($P = 0.021$). The greatest survival advantage was observed in patients receiving both neoadjuvant treatment and adequate LN dissection, suggesting a cooperative survival benefit for neoadjuvant radiation and adequate lymphadenectomy. In patients who undergo surgery after nCRT there is currently no justification for the modification of surgical lymphadenectomy based on tumoral response to treatment. It should be kept in mind that tumoral response is a postoperative diagnosis and lacks any currently available modality for its accurate prediction. In addition, inadequate lymphadenectomy may lead to positive nodes being missed and patients being erroneously classified as ypN0.

In addition to identifying nCRT as a strong predictor of fewer LNs being resected, the multivariate analysis revealed that a weight loss of 10% or more of body mass at presentation was predictive of higher nodal yields in the population as a whole. The reasons underlying this observation are unclear. Reduction in the fat content of the meso-esophagus may lead to easier node identification, and we hypothesize that malnutrition may diminish LN responsiveness to neoadjuvant therapy, as may be the case for primary tumors.[29] Poorer WHO performance status was independently predictive of fewer LNs being resected and may reflect the poor immunological response of the host to the tumor burden.

Multivariate analysis revealed that the most significant factor that was predictive of NLNr was centers contributing 5 or more patients to the trial ($P = 0.004$), suggesting that center resection volume acts as a surrogate marker for the quality of surgical lymphadenectomy. This finding adds further impetus to the arguments for the centralization of esophageal resections in high-volume centers.

This study has some limitations. First, the retrospective nature of the study may have incurred some bias. However, the randomization guarantees that major prognostic variables are well balanced between groups nCRT and S. Second, the early closure of recruitment to this trial after an interim analysis meant fewer patients than anticipated were included. However, because the correlations between nCRT and both NLNr and NLNi are significant, more patients would not have provided additional value. Third, including only patients with stage I and II, EC may limit our conclusions to these stages. However, because stage III tumors are exposed to more extensive LN involvement and, consequently, are exposed more commonly to neoadjuvant treatment, it is reasonable to think that our results may be amplified in stage III tumors. Finally, although we found that centers contributing more than 5 patients to this trial were predictive of an increased NLNr, our data do not allow us to definitively correlate number of patients contributed with resection volume or, hence, to rule out the possibility of a cluster effect related to a volume bias. Our study's strength is that for the first time, we have provided an analysis, of the impact of nCRT on LN status, derived from a prospective, randomized, controlled trial in the setting of EC. In this context, the arguments that decreased NLNr and NLNi may represent disease understaging after inadequate dissection are not valid. Instead, the decreased NLNr and NLNi after nCRT are confirmed to be treatment-related disease downstaging and reflect the impact of treatment. We established that after nCRT and appropriate surgical resection, caution must be exercised in labeling a patient as inadequately staged based on the NLNr. In addition, our findings must not be used to justify less radical surgical resection or a less rigorous search for LNs during pathological examination. In particular, standard pathological techniques may need to be revised after nCRT, and the use of fat clearing solutions could potentially impact on the number of nodes identified in this setting.[24]

In summary, using the current standards of specimen analysis, a decreased NLNr and NLNi can be expected in patients undergoing esophagectomy after nCRT. Patients with a good tumor response to therapy also exhibit a significantly better nodal response. Staging systems must evolve to accurately reflect nCRT nodal downstaging.

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