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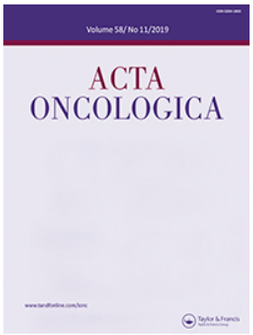

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ORIGINAL ARTICLE

Reliability of clinical nodal status regarding response to neoadjuvant chemoradiotherapy compared with surgery alone and prognosis in esophageal cancer patients

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ABSTRACT

Background: Clinical nodal (cN) staging is a key element in treatment decisions in patients with esophageal cancer (EC). The reliability of cN status regarding the effect on response and survival after neoadjuvant chemoradiotherapy (nCRT) with esophagectomy was evaluated in determining the up- and downstaged pathological nodal (pN) status after surgery alone.

Material and methods: From a prospective database, we included all 395 EC patients who had surgery with curative intent with or without nCRT between 2000 and 2015. All patients were staged by a standard pretreatment protocol: 16-64 mdCT, 18 F-FDG-PET or 18 F-FDG-PET/CT and EUS ± FNA. After propensity score matching on baseline clinical tumor and nodal (cT/N) stage and histopathology, a surgery-alone and nCRT group (each $N = 135$) were formed. Clinical and pathological N stage was scored as equal (cN = pN), downstaged (cN > pN) or upstaged (cN < pN). Prognostic impact on disease free survival (DFS) was assessed with multivariable Cox regression analysis (factors with p value <.1 on univariable analysis).

Results: The surgery-alone and nCRT group did not differ in cT/N status. Pathologic examination revealed equal staging (32 vs. 27%), nodal up (43 vs. 16%) and downstaging (25 vs. 56%), respectively ($p < .001$). Nodal up-staging was common in cT3-4a tumors and adenocarcinomas in the surgery-alone group, while nodal downstaging was found in half of cT1-2 and cT3-4 regardless of tumortype after nCRT. Prognostic factors for DFS were pN ($p = .002$) and lymph-angioinvasion ($p = .016$) in surgery-alone, and upper abdominal cN metastases ($p = .012$) and lymph node ratio ($p = .034$) in the nCRT group.

Conclusions: Despite modern staging methods, correct cN staging remains difficult in EC. Nodal over-staging (cN > pN) occurred more often than understaging impeding an adequate assessment of pathologic complete response and prognosis after nCRT.

SYNOPSIS

Preoperative assessment of true nodal response after nCRT in EC remains difficult with clinical nodal upstaging (16% vs. 43%) and downstaging (56% vs. 25%) after nCRT and surgery alone, respectively.

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Introduction

Accurate staging of lymph nodes (LNs) is crucial in treatment decision making, prediction of true response to neoadjuvant chemoradiotherapy (nCRT) and prognosis in patients with esophageal cancer (EC) [1–4]. Clinical nodal (cN) staging commonly consists of computed tomography (CT), 18-F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) or integrated PET-CT and endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) [5,6]. The reliability of cN staging is shown at pathologic examination in EC patients after surgery alone, and may proceed after nCRT [5–12]. While pathological nodal (pN) status is a strong prognostic

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Supplemental data for this article can be accessed here.

factor, the impact of nCRT to the veracity of the N status is poorly studied [10].

In patients with EC, nodal downstaging after nCRT (cN > ypN stage) is described in 45–69% [10,13]. Besides pathologic complete response (pCR), pN status, both after nCRT (ypN) as after surgery alone (pN), is one of the most important prognostic factors in EC [2,3,10,14]. However, a substantial part of nodal downstaging is associated with overestimation of cN involvement, as reported in 30–63% after surgery alone [6,9,15]. This implicates an overestimation of nodal response, as pathologic negative nodes after nCRT (ypN0) include both true node negative (cN0 = ypN0) and sterilized nodes (cN+ to ypN0). On the other hand, falsely assessed clinical node negativity (cN0 = pN+) might withhold patients from nCRT or adequate radiotherapy dosage on true metastatic LNs.

Furthermore, the impact of locations of LN metastases on survival remains unclear. LN metastases on both diaphragmatic sides had a detrimental effect on survival after surgery alone, although others failed to prove prognostic impact of localization after nCRT [3,13].

The aim of this study was to evaluate the impact of the reliability of cN status after primary surgery and the presumed effect on pCR to nCRT in a propensity matched group of EC patients, in determining the discordance between clinical and pN staging in both groups. In addition, we determined the prognostic impact of nodal up- or downstaging of site-specific LN metastases.

Material and methods

Study population

Data were collected from a prospectively managed database of 419 consecutive patients with locally advanced EC ($cT_{2\text{-}4a}N_{0\text{-}3}M_0$ or $cT_1N_{1\text{-}3}M_0$) who underwent an esophagectomy with curative intent between 2000 and 2015.

From 2004 to 2009, nCRT was given in the randomized controlled ChemoRadiotherapy for Esophageal Cancer followed by Surgery Study (CROSS trial). From 2009 onwards, the same nCRT regimen was given as standard treatment in all patients with locally advanced EC [1,16]. Excluded were patients with concurrent malignancies ($N = 5$), missing data ($N = 12$), salvage surgery or preceding endoscopic mucosal resection ($N = 7$). Of the remaining 395 patients, 222 underwent surgery alone and 173 nCRT plus surgery (Table S1). After propensity score matching on clinical T stage (cT), N stage (cN), and histopathologic tumor type, both groups consisted of 135 patients. This study was performed according to the National Health Care guidelines with approval of our Institutional Ethical Board.

Clinical staging

During the whole study period, the preoperative workup in all patients consisted of 16–64 multidetector CT thorax-abdomen (2 mm slices) and 18 F-FDG-PET or FDG-PET/CT followed by EUS with FNA of suspected LN's on EUS and/or PET/PET-CT. EUS was commonly performed after PET/PET-CT for the best possible FNA-guidance by two experienced GI-endoscopists in our high-volume institute, according to the 7th TNM/AJCC system [17–20]. LN involvement was considered clinical positive (cN+) if highly suspected (≥1cm on short axis on PET/CT and/or correlated with cortical thickening and increased FDG-uptake), or on EUS by size, shape, echoic pattern, and border sharpness. FNA was performed in suspected LNs when relevant in determining the extent of radiation fields and/or nodal dissection. LNs were negative if a representative FNA was without tumor cells, as described earlier [19,20]. To prevent false positivity, nodal FNA was not performed if the needle had to pass the primary tumor.

Before 2009, a FDG-PET scan was followed after CT ($N = 145$; 53.7%). After 2009 patients underwent an integrated FDG-PET/CT scan ($N = 125$; 46.3%). EUS was performed with ($N = 48$;17.8%) or without FNA ($N = 222$;82.2%). Endobronchoscopic ultrasonography (EBUS) with FNA was performed in suspected high paratracheal level 2 LNs ($N = 5$; 1.9%). Staging of all patients was also discussed in a multidisciplinary gastro-esophageal tumor board.

Treatment and pathology

All patients underwent a transthoracic open or minimally invasive esophagectomy with standard 2-field dissection of mediastinal, para-esophageal, and upper abdominal (along splenic, common hepatic, celiac artery) LNs, and high paratracheal LNs (station 2) when indicated [21,22]. Neoadjuvant CRT consisted of carboplatin (area under curve of 2 mg/ml/min) and paclitaxel (50 mg/m^2 body surface) with concurrent radiotherapy of 41.4 Gy (23 fractions of 1.8 Gy) for 5 weeks, followed by surgical resection within 6–10 weeks [16]. Pathologic examination of the resection specimen was performed according to a standard institutional protocol by two experienced upper-GI pathologists [23]. Tumor response was scored at microscopic level using the Mandard tumor regression grading (TRG) system from pCR (ypT0N0; TRG 1) to absence of regressive changes (TRG 5) [24]. The presence of viable tumor cells within LNs was considered as nodal involvement (ypN+).

Clinical versus pN staging

cN staging was compared with pathological staging and scored equal stage (cN = pN) in either node negative (cN0 = pN0) and node positive (cN1-3 = pN1-3), and as nodal downstaging (cN > pN), or upstaging (cN < pN). Accuracy, sensitivity, specificity, positive and negative predictive value of cN staging, in which correct dichotomous nodal staging was defined as true node negative [cN0 = pN0] or true node positive [cN+ = pN+; regardless of stage]), were calculated in the surgery-alone group. We did not perform this in the nCRT group, because the analyses after nCRT are biased by the potential sterilizing nodal downstaging effect. Therefore, we intended to assess the nodal downstaging effect of nCRT by comparing nodal downstaging after nCRT with the changed nodal status at pathologic examination after surgery

alone. Nodal downstaging from cN+ to ypN0 can only be considered as potential sterilized effect of nCRT (true treatment response), but this may lead to a false treatment response in the true cN0 group (cN0 = ypN0), which is partially based on incorrect assessment. This concept of nodal misstaging based on up- and downstaging is also influenced by histologic type and clinical T stage [25].

Site-specific LN metastases and prognostic value

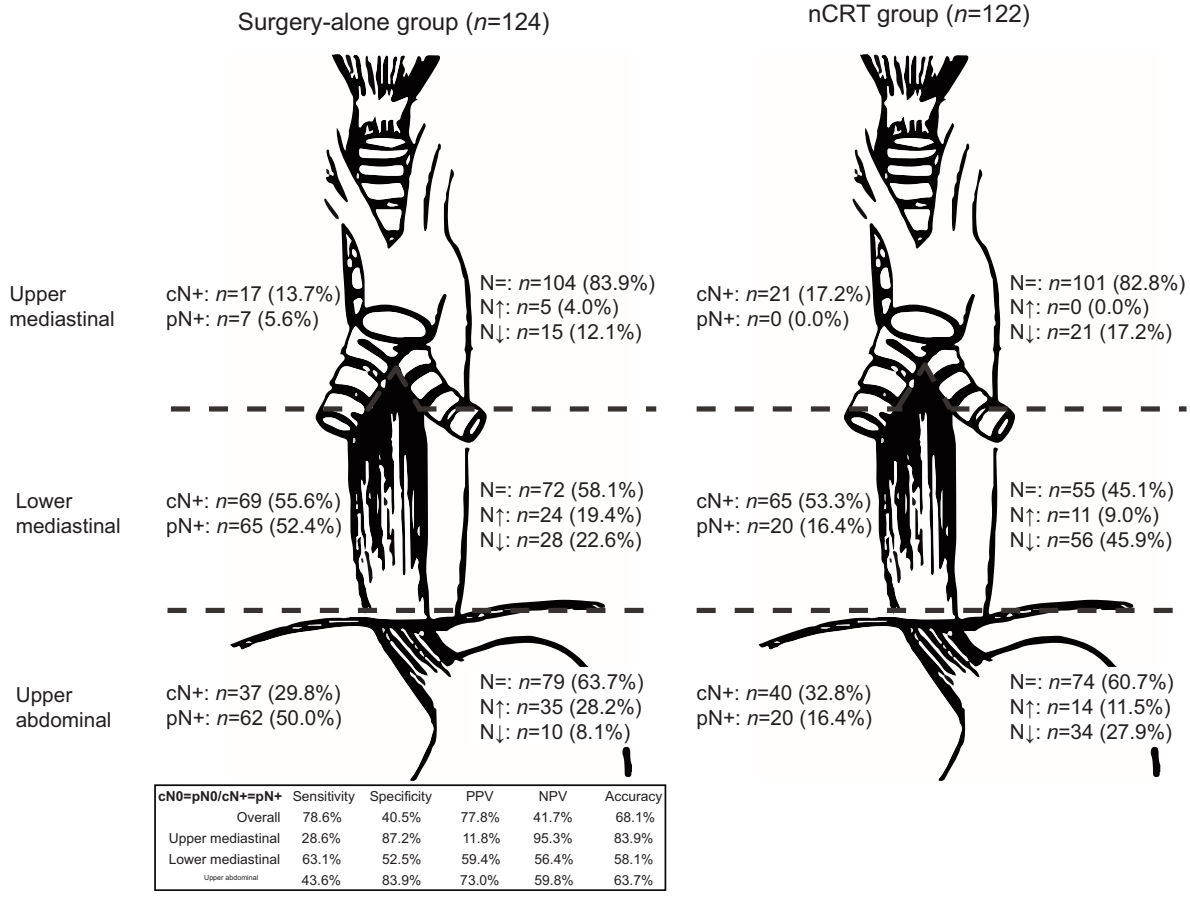
LN regions were marked prospectively according to a standard pathologic protocol, including the AJCC node mapping [17,22]. We determined the effect of nodal up-/downstaging in patients adequately by recording clinically suspected node locations, if known (surgery-alone: $N = 124$; nCRT: $N = 122$) and the prognostic value of these locations on DFS. LNs were scored in 3 regions: upper mediastinal (paratracheal/para-aortic; station 2–6), lower mediastinal (para-esophageal/subcarinal/pulmonary ligament: station 7–9 and 15), and upper abdominal (station 16-20) (Figure 1).

Follow-up

Patients were followed at 4 weeks postoperatively and every 3, 4 and 6 months during the first, second and third year, respectively, and yearly thereafter. Recurrences were detected with radiological imaging (CT or PET/CT), endoscopy and/or histo/cytologic examination. DFS was measured from the date of treatment until recurrence or end of follow-up.

Statistical analysis

Patient and tumor characteristics, and details on HER2 testing were displayed with counts and percentages, means and standard deviations (SDs), or medians and interquartile ranges (IQRs). Chi-square tests and likelihood ratios were used to determine differences in LN involvement and location. Potential prognostic factors in the univariable analyses, including clinical and pathological upper/lower mediastinal and upper abdominal LNs, and the variable nodal up- and downstaging, with p value $<.10$ on univariable regression analysis were included in a multivariable Cox regression analysis for DFS. p value $<.05$ was regarded as statistically



cN0=pN0/cN+=pN+	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall	78.6%	40.5%	77.8%	41.7%	68.1%
Upper mediastinal	28.6%	87.2%	11.8%	95.3%	83.9%
Lower mediastinal	63.1%	52.5%	59.4%	56.4%	58.1%
Upper abdominal	43.6%	83.9%	73.0%	59.8%	63.7%

Figure 1. Distribution of clinical and pathological lymph node involvement in the surgery-alone and nCRT group. Comparison of clinical and pathological nodal staging in the surgery-alone and neoadjuvant chemoradiotherapy groups, displayed per lymph node location. Accuracy, sensitivity, specificity, positive and negative predictive value of cN staging (correct nodal negative [cN0 = pN0] or correct nodal positive cN+ = pN+]) is calculated in the surgery-alone group. True positive (TP), false positive (FP), true negative (TN), and false negative (FN) clinical node stage were used to determine overall accuracy ((TP + TN)/(TP + FP + FN + TN)) of correct dichotomous (positive vs. negative) nodal staging (cN0 = pN0 and cN+ = pN+, regardless of which cN+/pN + stage), as well as sensitivity (TP/(TP + FN)), specificity (TN/(TN + FP)), positive predictive value (PPV: TP/(TP + FP)), and negative predictive value (NPV: TN/(TN + FN)). The nodal downstaging effect due to neoadjuvant chemoradiotherapy is expressed by the lower proportion of patients with pN + stage in all locations, and by the percentage of patients that had nodal downstaging in all three locations. nCRT: neoadjuvant chemoradiotherapy; cN+: clinical node positive; pN+: pathologic node positive; N=: equal nodal staging; N↑: nodal upstaging; N↓: nodal downstaging; cN0: clinical node negative; pN0: pathologic node negative PPV: positive predictive value; NPV: negative predictive value.

significant. DFS in patients with nodal up- and downstaging in both groups was displayed with Kaplan–Meier curves and tested using the log rank test. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.).

Results

Patients and tumor characteristics in the nCRT and surgery-alone group

Baseline characteristic of all patients can be found in Table S1. After propensity score matching, the groups did not differ in cT stage, cN stage and histology, but only in age and the known effects of nCRT including radicality (R0), pathological T and N stages, lymph-angioinvasion, median number of positive resected LNs, and the ratio of positive/all retrieved LNs (LN ratio >0.2), as well as period of resection (Table 1). All patients in the nCRT group received full radiotherapy doses and >75% completed chemotherapy (98% had ≥4 cycles). The pathologic complete response (pCR) of the primary tumor (ypT0) after nCRT was 20.7% ($N = 28$), while pCR rate including histologically negative nodes (ypT0N0) was 15.6% ($N = 21$). Higher pCR rates (ypT0N0) were seen in SCC (36.4 vs. 11.5% in AC; $p = .007$).

Nodal staging: clinical versus pathological N stage and impact of nCRT

In the surgery-alone group, 21 of the 36 (58.3%) cN0 patients were upstaged and 22 of the 37 patients with pN0 were downstaged cN+ patients (59.5%). In the nCRT group, 14 of 36 (38.9%) cN0 patients were upstaged and 70 of 92 ypN0

Table 1. Patient and tumor-related characteristics in the surgery-alone and nCRT group after propensity score matching in EC patients treated between 2000 and 2015.

	Surgery-alone ($n = 135$), no. (%)	nCRT ($n = 135$), no. (%)	p value
Male	114 (84.4)	106 (78.5)	.210[a]
Age (years), median (IQR)	65 (57–71)	63 (57–68)	.013[b]
Histology			.737[a]
Adenocarcinoma	115 (85.2)	113 (83.7)	
Squamous cell carcinoma	20 (14.8)	22 (16.3)	
Tumor location			.988[a]
Middle esophagus	13 (9.6)	13 (9.6)	
Distal esophagus	96 (71.1)	97 (71.9)	
GEJ	26 (19.3)	25 (18.5)	
Tumor length (cm), median (IQR)	5 (3–7)	5 (3–7)	.786[b]
cT-stage			.527[c]
T1	3 (2.2)	1 (0.7)	
T2	18 (13.3)	21 (15.6)	
T3/T4a	114 (84.4)	113 (83.7)	
cN-stage			.984[c]
N0	36 (26.7)	36 (26.7)	
N1	67 (49.6)	67 (49.6)	
N2	28 (20.7)	29 (21.5)	
N3	4 (3.0)	3 (2.2)	
Period of resection			<.001[a]
2000–2005	62 (45.9)	0 (0.0)	
2006–2010	60 (44.4)	31 (23.0)	
2011–2015	13 (4.8)	104 (77.0)	
pT-stage			<.001[a]
T0	0 (0.0)	28 (20.72)	
T1	11 (8.1)	20 (14.8)	
T2	27 (20.0)	24 (17.8)	
T3/T4	97 (71.8)	63 (46.7)	
pN-stage			<.001[a]
N0	37 (27.4)	92 (68.1)	
N1	41 (30.4)	29 (21.5)	
N2	31 (23.0)	11 (8.1)	
N3	26 (19.3)	3 (2.2)	
pCR (ypT0N0)	–	21 (15.6)	–
Adenocarcinoma	–	13/113 (11.5)	
Squamous cell carcinoma	–	8/22 (36.4)	.007[a*]
R1-resection	16 (11.9)	7 (5.2)	.050[a]
Perineural growth	40 (29.9)	28 (21.1)	.099[a]
Lymph-angioinvasion	51 (38.3)	29 (21.8)	.003[a]
Number of resected LN, median (IQR)	14 (9–19)	15 (12–22)	.009[b]
Number of positive LN, median (IQR)	2 (2–5)	0 (0–1)	<.001[b]
Lymph node ratio >0.2	60 (44.8)	12 (8.9)	<.001[a]
Postoperative (30-day) mortality	7 (5.2)	2 (1.5)	.172[d]
Follow-up (months), median (IQR)	22.6 (11.6–51.6)	22.3 (11.2–42.6)	.551[b]

[a]Chi-square test.
[b]Mann–Whitney U test.
[c]Likelihood ratio.
[d]Fisher's exact test.
*Difference in pCR between adenocarcinoma and squamous cell carcinoma.
nCRT: neoadjuvant chemoradiotherapy; IQR: interquartile range; GEJ: gastroesophageal junction, pretreatment staging; cT: clinical tumor stage; cN: clinical nodal stage; pT: pathological tumor stage; pCR: pathologic complete response; pN: pathological nodal stage; LN: lymph node; R1: microscopic positive resection margin.

Table 2. N-stage pattern in surgery-alone and nCRT group and regarding location of positive lymph nodes.

	Equal nodal staging (cNstage = pNstage: $n = 81$)				
	Node negative (cN0 = pN0)	Node positive (cN1-3 = pN1-3)	Nodal upstaging (cNstage < pNstage)	Nodal downstaging (cNstage > pNstage)	p value
All patients ($N = 270$)					
Surgery alone (n=135), n (%)	15 (11.1)	28 (20.7)	58 (43.0)	34 (25.2)	<.001[a*]
nCRT (n=135), n (%)	22 (16.3)	16 (11.9)	22 (16.3)	75 (55.6)	
Surgery-alone group ($N = 135$)					
Adenocarcinoma ($n = 115$)	12 (10.4%)	25 (21.7%)	54 (47.0%)	24 (20.9%)	.031[b]
Squamous cell carcinoma ($n = 20$)	3 (15.0%)	3 (15.0%)	4 (20.0%)	10 (50.0%)	
cT1/2 tumors ($n = 21$)	7 (33.3%)	4 (19.0%)	3 (14.3%)	7 (33.3%)	.002[b]
cT3/4a tumors ($n = 114$)	8 (7.0%)	24 (21.1%)	55 (48.2%)	27 (23.7%)	
nCRT group ($N = 135$)					
Adenocarcinoma ($n = 113$)	17 (15.0%)	12 (10.6%)	22 (19.5%)	62 (54.9%)	.026[b]
Squamous cell carcinoma ($n = 22$)	5 (22.7%)	4 (18.2%)	0 (0.0%)	13 (59.1%)	
cT1/2 tumors ($n = 22$)	8 (36.4%)	2 (9.1%)	1 (4.5%)	11 (50.0%)	.037[b]
cT3/4a tumors ($n = 113$)	14 (12.4%)	14 (12.4%)	21 (18.6%)	64 (56.6%)	
Patients with known lymph node locations ($n = 146$)					
Upper mediastinal lymph nodes					.022[b]
Surgery alone ($n = 124$)	102 (82.3%)	2 (1.6%)	5 (4.0%)	15 (12.1%)	
nCRT ($n = 122$)	101 (82.8%)	0 (0.0%)	0 (0.0%)	21 (17.2%)	
Lower mediastinal lymph nodes					<.001[a]
Surgery alone ($n = 124$)	31 (25.0%)	41 (33.1%)	24 (19.4%)	28 (22.6%)	
nCRT ($n = 122$)	46 (37.7%)	9 (7.4%)	11 (9.0%)	56 (45.9%)	
Upper abdominal nodes					<.001[a]
Surgery alone ($n = 124$)	52 (41.9%)	27 (21.8%)	35 (28.2%)	10 (8.1%)	
nCRT ($n = 122$)	68 (55.7%)	6 (4.9%)	14 (11.5%)	34 (27.9%)	

[a]Chi-square test.
[b]Likelihood ratio.
*Surgery-alone versus nCRT group.
nCRT: neoadjuvant chemoradiotherapy; cN: clinical nodal stage; pN: pathological nodal stage; cT: clinical tumor stage.

(76.1%) downstaged cN+ patients. The rate of positive nodes differed considerably in the nCRT (31.9%) compared to surgery-alone (72.6%) group, with a remarkable reduction in (y)pN2-3 stages (from 71.8 to 46.7%; Table 1).

Table 2 depicts nodal up- and downstaging in both groups, and subdivided for LN locations. In the surgery-alone group, 43 (31.9%, of whom 15 cN0 = pN0 and 28 cN1-3 = pN1-3) patients were staged adequately. Nodal upstaging occurred in 58 (43.0%) and downstaging in 34 (25.2%) patients after primary surgery, whereas the accuracy of cN detection (cN0 = pN0 or cN+ = pN+) was 68.1% (Figure 1). Significant differences were seen pertaining the histologic type, with relatively more upstaging in AC and more downstaging in SCC (Table 2). Nodal upstaging occurred more often in cT3/T4a compared to cT1/T2 tumors in the surgery-alone group ($p = .002$), while nodal downstaging occurred in one third of the cT1/T2 ($N = 7$; 33.3%) compared with 23.7% ($N = 27$) of cT3/4a tumors.

In the nCRT group, 38 (28.1%, of whom 22 cN0 = ypN0 and 16 cN1-3 = ypN1-3) patients had equal cN/ypN stages with nodal up- and downstaging in 22 (16.3%) and 75 (55.6%) patients, respectively. Nodal downstaging occurred in about half of the patients after nCRT in both cT1/T2 and cT3/T4a, and in more than half of both AC (54.9%) and SCC (59.1%) tumors. Nodal upstaging occurred in none of SCC tumors treated with nCRT.

Clinical and pathological location of LN metastases

Figure 1 displays the distribution of cN+ and pN+ per LN location. In the surgery-alone group, the sensitivity in detecting low mediastinal LN metastases (63.1%) was higher than in the upper abdominal (43.6%) and upper mediastinal (28.6%) stations. The specificity was high in upper mediastinal (87.2%) and abdominal (83.4%) LNs, and lower in lower mediastinal nodes (52.5%; Figure 1).

After nCRT, no upper mediastinal LN metastases were detected. Upstaging occurred often in upper abdominal LNs in the surgery-alone group, while downstaging frequently occurred in lower mediastinal nodes (45.9%).

Nodal up-, down- and correct staging differed significantly in upper mediastinal, lower mediastinal and upper abdominal LNs between the surgery-alone and nCRT groups ($p = .022$, $p < .001$, and $p < .001$, respectively; Table 2).

Nodal up-/downstaging, LN locations and disease-free survival

Five-year DFS of nodal up- and downstaging differed significantly in both groups in univariable analyses (Figure 2). Independent prognostic for 5-year DFS were pN stage ($p = .007$) and lymph-angioinvasion ($p = .019$) in the surgery-alone group, and cN metastases in the upper abdominal region ($p = .049$) in the nCRT group (Table 3).

Discussion

Adequate clinical detection of LN metastases is a useful prognostic indicator and essential in delineation of radiation tumor volumes and extent of nodal dissection in EC [1]. In absence of any reliable clinical assessment tool, the definitive diagnosis

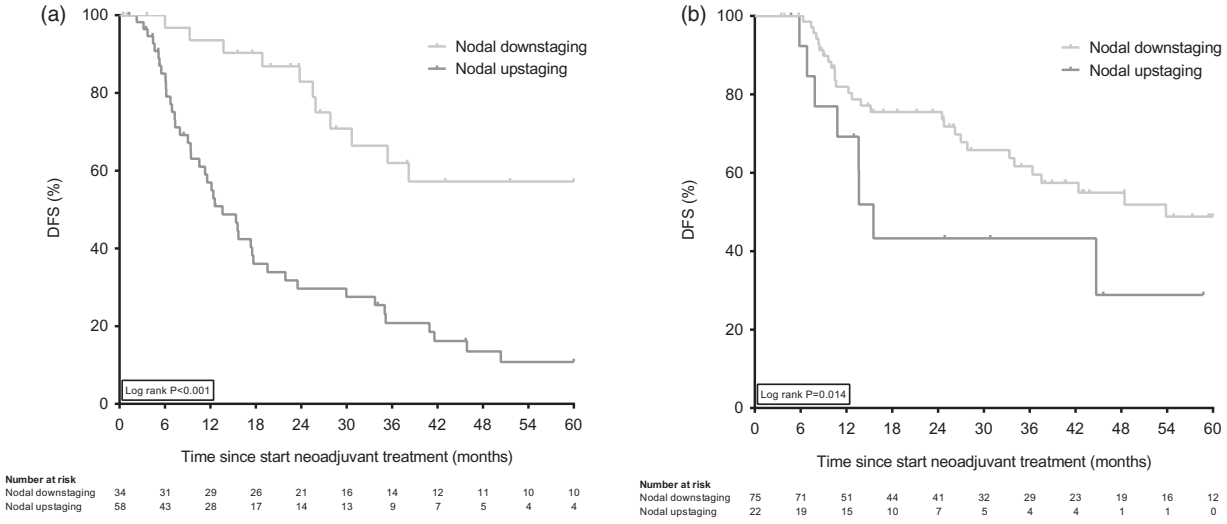


Figure 2. Kaplan–Meier curves for 5-year disease-free survival in nodal up- and downstaging in the surgery-alone and nCRT group. Disease-free survival in patients treated with surgery alone (a) and patients treated with neoadjuvant chemoradiotherapy and surgery (b), with nodal upstaging and downstaging. Patients with equal nodal clinical and pathological stage are not displayed. DFS: disease-free survival; nCRT: neoadjuvant chemoradiotherapy.

Table 3. Univariable and multivariable Cox regression analysis for 5-year disease-free survival in the surgery-alone and nCRT group.

	Surgery-alone group				nCRT group		
	HR	95% CI	*p* value		HR	95% CI	*p* value
Univariable Cox regression analyses							
Squamous cell carcinoma	0.78	0.38–1.56	.473	Squamous cell carcinoma	**0.43**	**0.18–1.02**	**.054**
cN + upper/lower mediastinal	1.15	0.71–1.86	.583	cN + upper/lower mediastinal	0.73	0.41–1.27	.263
cN + upper abdominal	0.93	0.56–1.56	.791	cN + upper abdominal[&]	2.38	1.36–4.16	**.002**
pT0	–		–	pT0	1.00		**.095**[#]
pT1&pT2	1.00		**<.001**[#]	pT1&pT2	2.85	1.07–7.60	**.036**
pT3&pT4	2.82	1.51–5.27		pT3&pT4	2.71	1.04–7.08	**.042**
pN0	1.00		**<.001**[#]	pN0[&]	1.00		**.022**[#]
pN1	3.46	1.62–7.37	**<.001**	pN1	1.28	0.62–2.67	**.506**
pN2	4.80	2.23 –10.30	**<.001**	pN2	3.38	1.19–9.64	**.023**
pN3	6.78	3.11–14.79	**<.001**	pN3	5.46	1.29–23.19	**.021**
pN + upper/lower mediastinal[&]	2.71	1.65–4.44	**<.001**	pN + upper/lower mediastinal[&]	2.10	1.07–4.11	**.030**
pN + upper abdominal[&]	3.14	1.89–5.21	**<.001**	pN + upper abdominal[&]	2.00	1.00–4.02	**.051**
Lymph-angioinvasion	2.64	1.63–4.29	**<.001**	Lymph-angioinvasion	1.67	0.90–3.11	.104
Lymph node ratio >0.2[&]	3.28	2.02–5.35	**<.001**	Lymph node ratio >0.2	6.57	2.51–17.22	**<.001**
R1-resection	3.54	1.78–7.04	**<.001**	R1-resection	4.81	1.68–13.82	**.004**
Equal nodal staging (cN = pN)[&]	1.00		**<.001**[#]	Equal nodal staging (cN = pN)	1.00		.205
Nodal downstaging (cN > pN)	0.62	0.30–1.30	**.204**	Nodal downstaging (cN > pN)	0.75	0.40–1.44	.390
Nodal upstaging (cN < pN)	2.77	1.61–4.78	**<.001**	Nodal upstaging (cN < pN)	1.51	0.63–3.62	.350
Multivariable Cox regression analysis							
				Squamous cell carcinoma	0.74	0.29–1.90	.534
pT0	–		–	pT0	1.00		.268[#]
pT1&pT2	1.00		.080[#]	pT1&pT2	2.38	0.84–6.76	.105*
pT3&pT4	1.79	0.94–3.41		pT3&pT4	1.99	0.71–5.53	.189
pN0	1.00		**.007***[#]	cN + upper abdominal	1.85	1.00–3.40	**.049***
pN1	3.10	1.45–6.64	**.004***				
pN2	3.46	1.56–7.67	**.002***				
pN3	3.85	1.65–9.00	**.002***				
Lymph-angioinvasion	1.87	1.11–3.15	**.019***	Lymph node ratio >0.2	2.84	0.67–12.10	.157
R1 resection	1.91	0.91–4.00	.087	R1 resection	1.82	0.41–8.18	.434

[#]Overall *p*-value of the categorical variables.
*Statistically significant ($p < .05$).
[&]These variables were not added to multivariable analyses to avoid multicollinearity.
nCRT: neoadjuvant chemoradiotherapy; HR: hazard ratio; CI: confidence interval; cN+: positive clinical nodal stage; pT: pathological tumor stage; pCR: pathologic complete response; pN: pathological nodal stage; pN+: positive pathological nodal stage; R1: microscopic positive resection margin; cN: clinical nodal stage.
The bold values represent the statistically significant *p* values.

for pCR can only be made by pathologic examination of the resected specimen . Even with current sophisticated diagnostic methods, preoperative LN staging remains uncertain with considerable high false negative rates [5,6]. In this study we found a nodal downstaged ratio of 56% after nCRT, including a 'true' downstaging due to the neoadjuvant treatment and the so-called 'natural' nodal downstaging through overestimation of cN stage [25]. Surgery alone provided a nodal downstaging of 25%, indicating that a substantial part of the post-nCRT nodal downstaging attributes to the inadequacy of pretreatment

staging rather than to treatment responses. This relative high discordance in cN staging has a serious impact on prognosis with a wide variation of pCR, hampering a proper selection of patients who might benefit from a non-surgical wait-and-see approach [26].

The nodal upstaging of 43% in the surgery-alone group is comparable with the 44% in Crabtree study, despite they only included T2 tumors [6]. However, the 16% upstaging in our nCRT group was considerably lower than the 37% they reported, probably because about 60% of their patients received preoperative chemotherapy alone. Even with an extensive staging, the accuracy of nodal staging was slightly lower in our group (68 vs. 74%) [6]. Combined with an overestimated nodal involvement, as expressed by a 25% nodal downstaging in the surgery-alone group, a substantial inaccuracy rate might be expected after nCRT. The downstaging effect was even higher in cT1/T2 tumors (50%), but comparable to the nodal up and downstaging in cT3/T4 after nCRT, suggesting a generally high nodal overstaging and probably less CRT sensitivity in these advanced tumors. This potential overestimation of response might contribute to the reported large variety (25–42%) of complete responses [16,25,27].

Patients with pCR including a node-negative status (ypT0N0), have a lower recurrence risk and higher survival. While omission of surgery and a wait-and-see strategy have been suggested, predicting prognosis in clinical complete responders remains difficult, as ypT0N0 patients with nodal downstaging (cN+ to ypN0) appeared to have a lower survival compared with true equal staged (cN0 = ypN0) patients [25,28]. This was also expressed in our study by a significant better prognosis of patients with nodal downstaging than those with nodal upstaging in both groups, probably due to true nodal negative tumors (Figure 2).

Moreover, diagnostic inaccuracy has been indirectly expressed by the fact that pN rather than cN stage has found to be independent prognostic for overall survival [10]. Inferior survival in patients with ypN0 after nCRT versus patients with pN0 after primary surgery was reported earlier, suggesting a negative prognostic impact in case of sterilized cN+ nodes (cN+ to ypN0) [29]. On the other hand, patients with cN0 may benefit less from nCRT [30].

Interestingly, downstaging and pCR were more frequently seen in patients with SCC compared to AC treated with nCRT [16,31]. However, 50% nodal downstaging in SCC patients in our surgery-alone group was considerably higher than the reported 15% by Park et al. (Table 2) [32].

After propensity score matching, we found a higher median number of resected LNs in the nCRT group compared with the surgery-alone group (15 vs. 14 LNs, respectively; Table 1). This is probably due to a slight difference in the pathologic examination by introducing the intraoperative marking of the radiation target volumes during surgery just before the final esophagectomy, as nCRT was given from 2005 onwards. Moreover, the effect of nCRT on regression of pathologic nodes particularly around the celiac axis may lead to a higher resectability rate with a possible effect on the number of resected nodes in these cases.

Nodal inaccuracy seemed to be T stage dependent in the surgery-alone group (Table 2), expressed by a higher rate of nodal upstaging in advanced tumor (T3/T4) stages. Others also reported a disputable reliance of EUS in assessing cN+ with even higher rates (80%) of overstaging in pN0 tumors [11,33]. In the surgery-alone group, nodal upstaging was more common in the upper abdominal region (28%), probably related to incomplete EUS staging by more severe stenosis [34]. Since the presence of clinical abdominal LN metastases in the upper abdominal region was independently associated with DFS in the nCRT group, detection of these metastases is important. Although EUS is the preferred method to assess pathological abdominal LNs, PET-CT should be performed in case of stenosis, since the accuracy of PET-CT in detecting abdominal LNs is rather high [35]. Other possible explanations for difficult nodal staging are the complexity of longitudinal lymphatic drainage with skip metastases and large number (>50%) of small LN metastases (<5 mm) in EC [32,36]. Improvement of PET-CT with diffusion-weighted magnetic resonance imaging (DWI-MRI) with gadofosveset might increase the adequacy in detecting LN metastases, even in small nodes [37]. Also promising is the elastography-enhanced EUS measuring ultrasonic waves generated when light is absorbed in the examined tissues with potential clinical use in assessing regional LN involvement [38].

Certain limitations should be considered in interpreting the results of this study. The integrated FDG-PET/CT was only available after 2008, whereas CT followed by FDG-PET was used between 2000 and 2009. The relatively long inclusion period (2000–2015) could have a possible effect on the accuracy of staging, using the next generation of staging techniques over time in the nCRT group, as these patients were diagnosed after 2005. Next, the accuracy of EUS might be higher if FNA could be applied to more distinct LNs, whereas it was performed selectively in clinically suspected LNs considered as relevant in determining the extent of radiation fields and/or nodal resection. Moreover, these data were based on a single institution rather than a desirable multicenter study.

In conclusion, nodal up- and downstaging (43 and 25%) are frequently found in EC patients after surgery alone and more often in upper abdominal and lower mediastinal LNs, respectively. The observed discordancy with a substantial overstaging (cN > pN) and inaccuracy in cN staging in the primary surgery group has an impact on the prognostic strength of ypN after nCRT. Improvement of current preoperative nodal staging in assessing the genuine effect of nCRT is important to optimize future individualized treatment options, including the feasibility of a wait-and-see approach in clinical complete responders.

Disclosure statement

No potential conflict of interest was reported by the authors.

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