CHAPTER 3

Impact of pretreatment nodal staging on response evaluation to neoadjuvant chemoradiotherapy and prognosis in esophageal cancer

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ABSTRACT

Background and objectives

Clinical lymph node (cN) staging in esophageal cancer (EC) remains difficult. We evaluated the reliability of pretreatment nodal staging and the effect on disease-free survival (DFS) after neoadjuvant chemoradiotherapy (nCRT) and esophagectomy related to primary surgery.

Methods

Three-hundred-ninety-five EC patients who underwent curative intended surgery with or without nCRT between 2000 and 2015, were included. A surgery-alone and nCRT group (each n = 135) were formed by propensity score matching on clinical tumor and nodal stage, and histopathology. Pretreatment staging consisted of PET and CT or PET-CT, and EUS. Clinical and pathological N-stage (pN) was scored as correct (c*N*=pN), downstaged (cN>pN) or upstaged (cN<pN). Prognostic impact on 5-year DFS was assessed with multivariate Cox regression analysis (factors with P value < 0.1 on univariate analysis).

Results

The surgery-alone and nCRT group differed in correct (31.9% vs. 28.1%), nodal up (43.0% vs. 16.3%) and downstaging (25.2% vs. 55.6%), respectively (P < 0.001). Nodal up-staging was common in cT3/T4a tumors and adenocarcinomas. Prognostic factors for DFS were pN (P = 0.002) and lymph-angioinvasion (P = 0.016) in the surgery-alone v.s. upper abdominal cN metastases (P = 0.012) and lymph-node ratio (P = 0.034) in the nCRT group.

Conclusions

Incorrect lymph node staging is common and might impede determination of response and prognosis after nCRT.

INTRODUCTION

Accurate pretreatment staging of the primary tumor and lymph nodes (LNs) is crucial for proper treatment decision-making, prediction of response to neoadjuvant therapy, and for prognostication in patients with esophageal cancer (EC) [1-4]. Clinical staging commonly consists of endoscopic ultrasonography (EUS) with fine needle aspiration (FNA), multi-row detector computed tomography (CT), and 18-F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) or integrated PET-CT [5, 6]. In patients treated with surgery-alone "inadequate" clinical nodal staging is high which may pursue after neoadjuvant chemoradiotherapy (nCRT) [6-11]. The main effect of nCRT is downstaging of the primary tumor and metastatic LNs, with nodal downstaging (clinical (c) N_{stage}> pathological (p)N_{stage}) being present in 45%-69% of the patients treated with nCRT [12, 13]. However, due to underestimation of nodal involvement (30%- 63%) in patients treated with surgery-alone, a clinical "nodal downstaging effect" is commonly reported as well [7, 9, 10]. This implicates that the amount of patients with lymph node response after nCRT is overestimated, as pathologically negative nodes after nCRT include both patients initially staged as node negative (cN0=pN0) and sterilized nodes (cN+ to pN0). On the other hand, patients falsely assessed as clinically node negative (cN0=pN+) might not be treated with nCRT or might receive an inadequate radiotherapy dosage on metastatic lymph nodes. Furthermore, the impact of site-specific localized LN metastases on survival remains unclear. In surgery-alone patients with proven LN metastases on both diaphragmatic sides, Talsma et al. found a detrimental survival [3]. However, others failed to prove prognostic importance of cN-positive localization in EC patients after nCRT [13].

Aim of this study was to evaluate the rate of nodal up- and downstaging in EC patients treated with primary surgery and with nCRT followed by surgery, and its presuming effect on pathologic response to nCRT. In addition, we determined the prognostic impact of LN localization and nodal up- and downstaging on the 5-year disease-free survival.

MATERIALS AND METHODS

Study population

Data of patients with locally advanced adenocarcinoma (AC) and squamous cell carcinoma (SCC) of the esophagus (cT2-4aN0-3M0/cT1N1-3M0) who underwent esophagectomy with curative intent between 2000 and 2015 (n = 419), were collected from a prospectively managed database. From 2004-2009 nCRT was given in the randomized controlled CROSS trial and as standard in the same patients' categories from 2009 onwards. 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 were treated with surgery-alone and 173 with nCRT and surgery. After propensity score matching on clinical T-stage (cT) / N-stage (cN) and histopathologic tumor type, both groups consisted of 135 patients (Table 1). This study was performed according to the National Health Care guidelines with approval of our Institutional Ethical Board.

Clinical staging

All patients were clinically staged before treatment by 16-64 CT thorax-abdomen (2mm slices) and PET or PET-CT with EUS FNA by two experienced GI-endoscopists in our high-volume institute. EUS was performed with (n=48:17.8%) or without FNA (n = 222:82.2%) and endobronchoscopic ultrasonography (EBUS; n = 5: 1.9%) with FNA on indication. Before 2009, patients received a PET scan (n = 145: 53.7%), thereafter patients received an integrated PET-CT scan (n = 125: 46.3%). Patients were staged according to the 7th TNM system of the American Joint Committee on Cancer (AJCC) [14]. LNs were considered clinically positive (cN+) if highly suspected (≥1cm on short axis) on CT, EUS/ EBUS, if FNA proven, or with increased FDG-uptake on PET-CT.

Treatment and pathology

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 and perigastric) lymph nodes by 3 experienced surgeons. High paratracheal nodes (AJCC LN station 2) were usually dissected when indicated [14]. Neoadjuvant chemoradiotherapy consisted of carboplatin (area under curve of 2 mg/min) and paclitaxel (50 mg/ m2) and 41.4 Gy/ 23 fractions of 1.8 Gy (the CROSS regimen) for five weeks, followed by surgical resection within 6-10 weeks [15]. All patients received full radiotherapy doses and over 75% completed nCRT, while 23% had 4 of the 5 cycles of chemotherapy. Pathological examination was performed by two experienced upper-GI pathologists using our standard pathologic protocol [16]. Tumor response was scored according to Mandard tumor regression grade (TRG) ranging from pathologic complete response (TRG 1) to non-response (TRG 5) [17]. None of the patients received adjuvant therapy.

Clinical versus pathological nodal staging

Pretreatment i.e. clinical nodal staging was correlated with pathological staging. Nodal staging was scored as either correct in node negative (cN0=pN0) and node positive (cN1-3=pN1-3) patients, as nodal downstaging (cN>pN), or as upstaging

(cN<pN). The outcome of clinical nodal staging in the surgery-alone group was compared with the outcome of clinical nodal staging in the nCRT group. In the surgery-alone group the accuracy, sensitivity, specificity, positive and negative predictive value of clinical staging were determined. These analyses could not be performed after nCRT, because of genuine downstaging effect by sterilizing of nCRT. We assumed the hypothetic impact of nodal response to nCRT by comparing the clinical and pathologic nodal classification after nCRT to the findings after primary surgery. Nodal response cannot be assumed adequately if cN0-status altered to pN+, while cN0 to pN0 evaluation may be based on incorrect assessment as cN0 (false treatment response) or on potential sterilized effect of nCRT (true treatment response). In both groups, nodal misstaging was based on up- and downstaging and assessed by histologic type and clinical T-stage.

Site-specific LN metastases and prognostic value on DFS

LN regions were marked prospectively according to a standard pathologic protocol, including the AJCC node map [14]. We determined the effect of nodal up-/downstaging in patients (surgery-alone: n = 124, nCRT: n = 122) with adequately recorded suspected clinical lymph node locations. Lymph nodes were scored in 3 regions: upper mediastinal (paratracheal/para-aortic; station 2-6), low mediastinal (para-esophageal/subcarinal/pulmonary ligament: station 7-9 and 15), and upper abdominal (station 16-20). Thereafter, we determined the prognostic value of involvement of these nodal locations of DFS. Potential prognostic factors in the univariate analyses included clinical and pathological supra- (mediastinal and para-esophageal) and sub-diaphragmatic LNs, and the variable nodal up- and downstaging.

Follow-up

Patients received follow-up every 3, 4 and 6 months during the first, second and third year, respectively and yearly thereafter. Recurrences were determined with radiological imaging, endoscopy and/or histocytologic examination. DFS was measured from the date of treatment until recurrence or end of follow-up.

Statistical analysis

Chi-square test and likelihood ratio were used to determine differences in LN involvement and location. DFS was displayed with Kaplan-Meier curves. Factors with P value < 0.10 on univariate regression analysis were included in a multivariate Cox regression analysis for DFS with P value < 0.05 as significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.).

RESULTS

Patients and tumor characteristics

After propensity score matching ($n = 270$), the groups differed in age ($P = 0.013$), pT-stage and pN-stage ($P < 0.001$), lymph-angioinvasion ($P = 0.003$), and LN ratio >0.2 ($P < 0.001$) (Table 1). The median (IQR) number of resected LNs was higher in the nCRT group (15 (IQR 12.0-22.0) compared to 14 (IQR 12.0-18.8) after surgery-alone.

Pathologic Response

Complete pathologic response of the primary tumor (ypT0) after nCRT was 20.7% ($n = 28$), while pathologic complete response (pCR: ypT0N0), including nodal response was seen in 15.6% ($n = 21$). A significant higher pCR rate was seen in SCC (8/22 (36.4%) vs 13/113 (12%) with AC; $P = 0.007$).

Table 1. Patient and tumor related characteristics in the surgery-alone vs. nCRT group

	Surgery-alone ($n = 135$), n (%)	**nCRT ($n = 135$), n (%)**	***P* value**
Male	114 (84.4%)	106 (78.5%)	$P = 0.210^a$
Age in years; median (IQR)	65 (57-71)	63 (57-68)	$P = 0.013^b$
Histology			$P = 0.737^a$
Adenocarcinoma	115 (85.2%)	113 (83.7%)	
Squamous cell carcinoma	20 (14.8%)	22 (16.3%)	
Tumor location			$P = 0.988^a$
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)	$P = 0.786^b$
cT-stage			$P = 0.527^c$
T1	3 (2.2%)	1 (0.7%)	
T2	18 (13.3%)	21 (15.6%)	
T3&T4a	114 (84.4%)	113 (83.7%)	
cN-stage			$P = 0.984^c$
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%)	

pT-stage			$P < 0.001^a$
pCR (ypT0N0)	-	21 (15.6%)	
T0	0 (0.0%)	28 (20.7%)	
T1	11 (8.1%)	20 (14.8%)	
T2	27 (20.0%)	24 (17.8%)	
T3&T4	97 (71.8%)	63 (46.7%)	
pN-stage			$P < 0.001^a$
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%)	
Perineural growth	40 (29.9%)	28 (21.1%)	$P = 0.099^a$
Lymph-angioinvasion	51 (38.3%)	29 (21.8%)	$P = 0.003^a$
Number of resected LN; median (IQR)	14.0 (9.0-18.8)	15.0 (12.0-22.0)	$P = 0.009^b$
Lymph node ratio >0.2	60 (44.8%)	12 (8.9%)	$P < 0.001^a$
Follow-up in months; median (IQR)	22.6 (11.6-51.6)	22.3 (11.2-42.6)	$P = 0.551^b$
R1-resection	16 (11.9%)	7 (5.2%)	$P = 0.050^a$

Abbreviations: 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. [a] = chi-Square test, [b] = Mann-Whitney U test, and [c] = likelihood ratio.

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

	Equal nodal staging (cN_{stage}=pN_{stage})		Nodal up-staging (cN_{stage}< pN_{stage})	Nodal down-staging (cN_{stage}> pN_{stage})	*P* value
	Node negative (cN0=pN0)	Node positive (cN1-3=pN1-3)			
Surgery alone (*n*=135), *n*%	15 (11.1%)	28 (20.7%)	58 (43.0%)	34 (25.2%)	$P < 0.001^a$
nCRT (*n*=135), *n*%	22 (16.3%)	16 (11.9%)	22 (16.3%)	75 (55.6%)	
Surgery-alone group					
Adenocarcinoma (*n*=115)	12 (10.4%)	25 (21.7%)	54 (47.0%)	24 (20.9%)	$P = 0.031^b$
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%)	$P = 0.002^b$
cT3/4a tumors (*n*=114)	8 (7.0%)	24 (21.1%)	55 (48.2%)	27 (23.7%)	
nCRT group					
Adenocarcinoma (*n*=113)	17 (15.0%)	12 (10.6%)	22 (19.5%)	62 (54.9%)	$P = 0.026^b$
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%)	$P = 0.037^b$
cT3/4a tumors (*n*=113)	14 (12.4%)	14 (12.4%)	21 (18.6%)	64 (56.6%)	
Mediastinal lymph nodes					
Surgery alone (*n*=124)	102 (82.3%)	2 (1.6%)	5 (4.0%)	15 (12.1%)	$P = 0.022^b$
nCRT (*n*=122)	101 (82.8%)	0 (0.0%)	0 (0.0%)	21 (17.2%)	
Para-esophageal nodes					
Surgery alone (*n*=124)	31 (25.0%)	41 (33.1%)	24 (19.4%)	28 (22.6%)	$P < 0.001^a$
nCRT (*n*=122)	46 (37.7%)	9 (7.4%)	11 (9.0%)	56 (45.9%)	
Upper abdominal nodes					$P < 0.001^a$
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%)	

Abbreviations: nCRT = neoadjuvant chemoradiotherapy, cN = clinical nodal stage, pN = pathological nodal stage, cT = clinical tumor stage. [a] = Pearson chi-square, [b] = likelihood ratio.

Nodal staging: clinical versus pathological N-stage

After nCRT the rate of positive nodes differed considerably compared to surgery alone (31.9% vs 72.6%), with a remarkable reduction in N2/N3 stages (10.3% vs 42.3%: Table 1). Table 2 depicts the nodal up- and downstaging in both groups and in regard to lymph node locations.

Overall, clinical and pathological N-stage were equal (c*N*=pN) in 81 (30.0%) patients. In surgery-alone patients, 43 (31.9%) were staged adequately (15 cN0=pN0 and 28 cN1-3=pN1-3), with an overall accuracy of 31.9%. Nodal upstaging occurred in 58 (43.0%) and downstaging in 34 (25.2%) patients after primary surgery. In comparison, the accuracy of clinical N+ detection (cN0=pN0/cN+=pN+) was 68.1%.

In the nCRT group, 38 (28.1%) patients had equal cN/pN-stages (22 cN0=pN0 and 16 cN1-3=pN1-3) with nodal up- and downstaging in 22 (16.3%) and 75 (55.6%) patients, respectively, which differed significantly in surgery-alone patients ($P< 0.001$). A significant difference in the surgery-alone ($P = 0.031$) and nCRT (0.026)) groups was seen in regard to histologic type, with relatively more upstaging in AC and more downstaging in SCC (Table 2). Nodal up- and downstaging also differed between cT1/T2 and cT3/T4a tumors in the surgery-alone ($P = 0.002$) and nCRT group ($P < 0.037$) with a higher rate of nodal upstaging in locally advanced (cT3/T4a) tumors (Table 2). Nodal downstaging was common in cT1/T2 (33.3%: $n = 7$) after surgery-alone, but was more or less equal after nCRT in both, cT1/T2 (50%: $n = 11$) and cT3/T4a (56,6%: $n = 64$). Equal nodal cN/pN staging was often seen in cT1/T2 tumors in the surgery-alone (52,4%: $n = 11$) and nCRT group (45,5%: $n = 10$).

Clinical and pathological location of LN metastases

Nodal up-/downstaging differed significantly between the locational subgroups: upper mediastinal, low mediastinal and upper abdominal LN's (Table 2). Figure 1 displays the distribution and number 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 mediastinal and upper abdominal (87.2% and 83.4%) lymph nodes, but lower in low-mediastinal nodes (52.5%, Figure 1).

After nCRT, no upper mediastinal LN metastases were detected. Upper abdominal LN metastases were commonly understaged in the surgery-along group, particularly in the distal/GEJ tumors, while downstaging frequently occurred

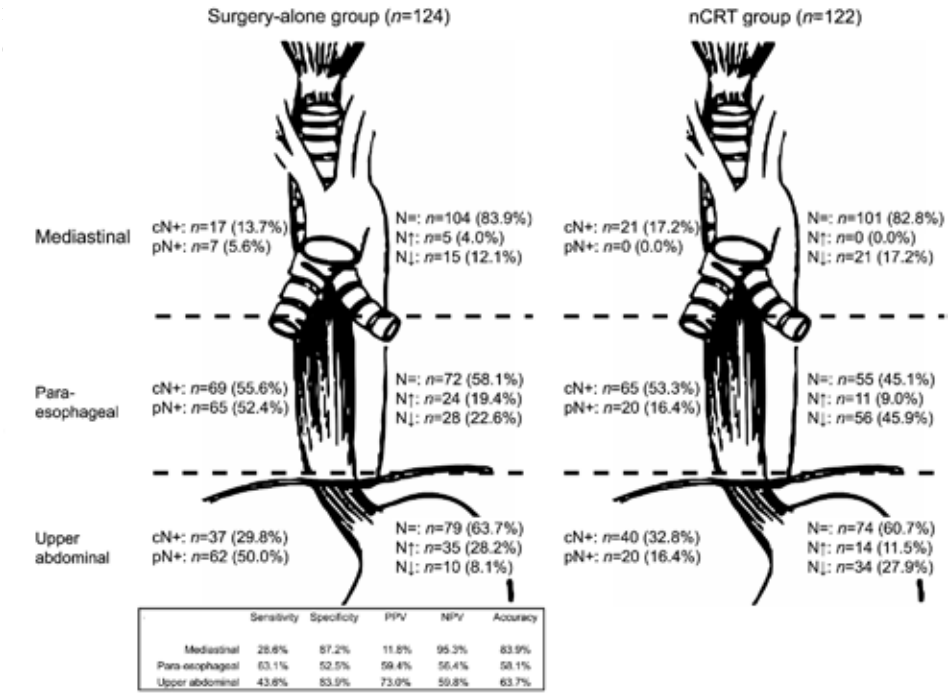

Figure 1. Distribution of clinical and pathological lymph node involvement in the surgery-alone and nCRT group.
Abbreviations: nCRT = neoadjuvant chemoradiotherapy, cN+ = clinical node positive, pN+ = pathologic node positive, *N*= = equal nodal staging, N↑ = nodal upstaging, N↓ = nodal downstaging, cN0 = clinical node negative, pN0 = pathologic node negative PPV = positive predictive value, NPV = negative predictive value.

Prognostic value of LN metastases location related to nodal up-/downstaging

Figure 2 displays the 5-year DFS of nodal up- and downstaging, which differed significantly in both the surgery-alone ($P < 0.001$) and nCRT group ($P = 0.014$). Independent prognostic factors for 5-year DFS were pathological N-stage ($P < 0.002$) and lymph-angioinvasion ($P = 0.016$) in the surgery-alone group. In the nCRT group, clinical upper abdominal LN metastases ($P = 0.012$) and lymph node ratio >0.2 ($P = 0.034$) were most prognostic (Table 3).

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

Univariate Cox regression analyses						
	Surgery-alone			nCRT		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Squamous cell carcinoma			NS	0.43	0.18 – 1.02	0.054
cN+ upper abdominal			NS	2.38	1.36 – 4.16	0.002
pT0	-		-	1.00		0.095#
pT1-2	1.00		0.001#	2.85	1.07 – 7.60	0.036
pT3-4	2.82	1.51 – 5.27		2.71	1.04 – 7.08	0.042
pN0	1.00		0.000#	1.00		0.022#
pN1	3.46	1.62 – 7.37	0.001	1.28	0.62 – 2.67	0.506
pN2	4.80	2.23 – 10.30	0.000	3.38	1.19 – 9.64	0.023
pN3	6.78	3.11 – 14.79	0.000	5.46	1.29 – 23.19	0.021
pN+ above diaphragm	2.71	1.65 – 4.44	0.000	2.10	1.07 – 4.11	0.030
pN+ abdominal	3.14	1.89 – 5.21	0.000	2.00	1.00 – 4.02	0.051
Lymph-angioinvasion	2.64	1.63 – 4.29	0.000			NS
Lymph node ratio >0.2	3.28	2.02 – 5.35	0.000			0.002
R1-resection	3.54	1.78 – 7.04	0.000	4.81	1.68 – 13.82	0.004
Equal nodal staging (c*N*=pN)	1.00		0.000#			NS
Nodal downstaging (cN>pN)	0.62	0.30 – 1.30	0.204			
Nodal upstaging (cN<pN)	2.77	1.61 – 4.78	0.000			

Multivariate Cox regression analysis							
	Surgery-alone				nCRT		
	HR	95% CI	*P* value		HR	95% CI	*P* value
pT0	-		-	pT0	1.00		0.143#
pT1-2	1.00		0.066#	pT1-2	2.69	1.01 – 7.18	0.049*
pT3-4	1.83	0.96 – 3.48		pT3-4	2.22	0.83 – 5.93	0.111
pN0	1.00		0.002*#	cN+ upper abdominal	1.91	1.05 – 3.47	0.012*
pN1	3.04	1.41 – 6.55	0.004*				
pN2	3.64	1.65 – 8.04	0.001*				
pN3	4.54	2.03 – 10.19	0.000*				
Lymph-angioinvasion	1.89	1.13 – 3.18	0.016*	Lymph node ratio >0.2	4.09	1.39 – 12.04	0.034*

Abbreviations: 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, *NS* = not significant, # = overall *P*-value of the categorical variables, * = significant ($P < 0.05$).

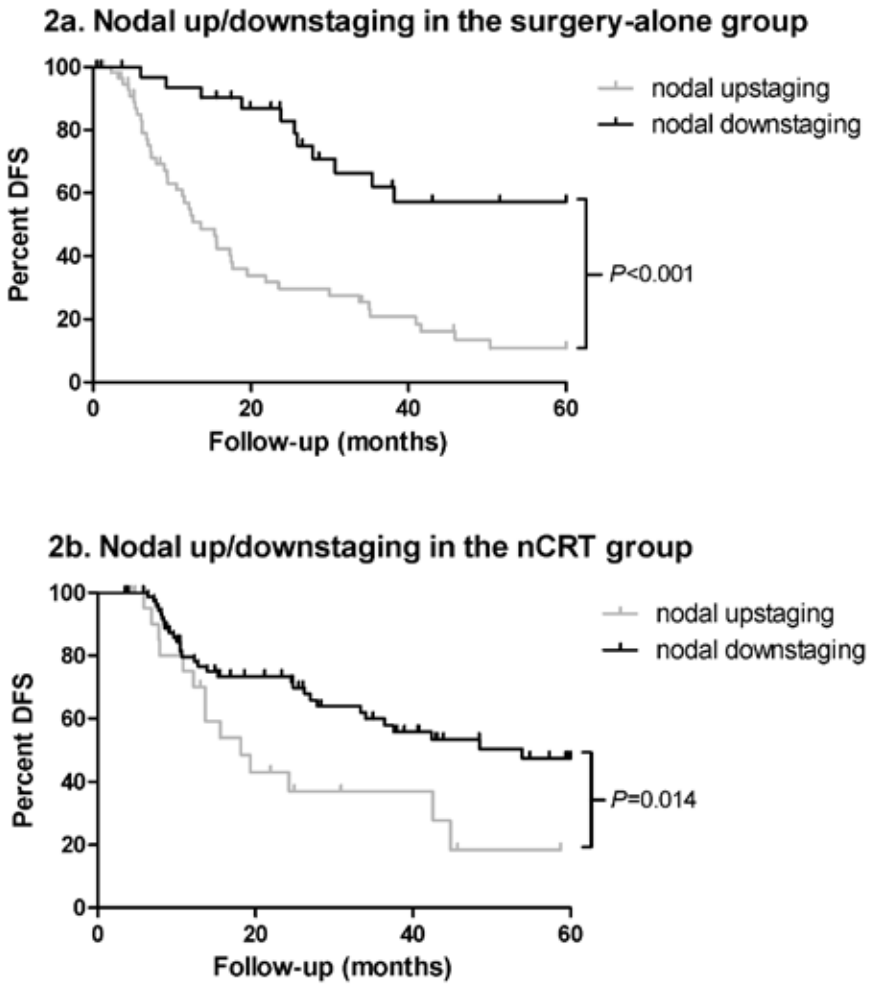

Figure 2. Kaplan Meier curves for 5-year disease-free survival in nodal up- and downstaging in the surgery-alone and nCRT group.

DISCUSSION

Adequate detection of LN metastases in EC is a strong prognostic parameter and essential in accurate delineation of radiotherapy tumor volumes and extent of radical nodal dissection. Moreover, it can make a difference in treatment decision making in cT1/T2 tumors between surgery alone or surgery preceded by nCRT. Unfortunately, inappropriate preoperative LN staging is still common in EC, even with current sophisticated methods [6, 7]. Not surprisingly nCRT

leads to nodal downstaging of 55.6% in this study. However, the low accuracy of nodal staging with >25% downstaging in patients treated with surgery alone indicates that a considerable part of post-nCRT downstaging is in fact caused by inadequate staging rather than genuine response. Inaccurate staging therefore impedes determination of complete response and prognosis after nCRT.

Even though we included all patients (T1-T4a), the 43% clinical nodal upstaging in the surgery-alone group was comparable with the 44.4% in Crabtree study with only T2 tumors [7]. However, the 16.3% upstaging in our nCRT group is considerably lower than the 36.9% in Crabtree group, probably because approximately 60% of their patients was treated with only preoperative chemotherapy. Even with our extensive staging (CT and PET or PET-CT, and EUS if possible), the accuracy (cN0=pN0/cN+=pN+) of 68.1% was slightly lower than the 74.4% in Crabtree group [7]. The inaccuracy seems to be T-stage based on EUS, as shown in the primary surgery group (Table 2), which implies a higher rate of pN upstaging in the more advanced T3/T4 stages. Others also reported a disputable reliance of EUS in assessing cN with even higher overstaging rates of pN0 tumors [6, 8]. Combined with overestimation of nodal involvement, as expressed by 25.2% nodal downstaging in the surgery-alone and 55.6% in the nCRT group (Table 2), a substantial inaccuracy rate might be expected after neoadjuvant treatment. If accurate staged it would have led to a change in the radiation fields with fewer regions to be targeted. Moreover, the downstaging effect was even higher in the cT1/T2 tumors (50%), but comparable to the nodal up and downstaging of cT3/T4 in the neoadjuvant group, which suggests a generally high nodal overstaging with probably less nodal CRT sensitivity. This potential overestimation of response to nCRT might contribute to the large variety of 25% to 42% complete response in the literature [15, 18, 19].

It is important to predict prognosis in complete responders, since ypT0N0 patients with nodal downstaging (ypN0) appeared to have a worse survival compared with true equal staged cN0=pN0 patients [20]. This was also expressed in a significant better prognosis of patients with nodal downstaging (cN>pN) than those with nodal up-staging in both groups ($P < 0.001$ surgery-alone vs. $P = 0.014$ nCRT), probably caused by true N negative tumors (Figure 2).

Nieman et al found survival to be less in patients with pN0 after neoadjuvant therapy vs. patients with pN0 after primary surgery and suggested a negative prognostic impact in case of sterilized involved nodes [21]. Currently the standard of pathologic LN evaluation in the resected specimen is based on presence or absence of viable tumor cells. Others suggests that nodal collagen fibrosis or necrosis may be useful in determining evidence of prior nodal involvement, but they are still not considered in most pathologic reports as it may be difficult to differentiate some of these changes from radiation induced effects [21].

Interestingly, downstaging and pCR were more frequently in SCC patients treated with nCRT compared to patients with AC, which supports earlier findings [15, 22]. However, 50% nodal downstaging in SCC patients in our surgery-alone group is considerably higher than 15.4% reported by Park et al., and was also more frequently in surgically treated cT1/T2 patients (n = 7: 33.3%, Table 2) [23]. Possible explanations for difficult nodal staging might be the complexity of longitudinal esophageal lymphatic drainage with skip metastases, and a large number (>50%) of small LN metastases (<5 mm) in EC, impeding clinical detection [23, 24].

Another problem is the relatively high rate of LN metastases in the upper abdominal region, which is prognostic in the nCRT group (P = 0.012) [25]. We identified nodal up-staging more commonly in the upper abdominal region in the surgery-alone group (28%), which is probably related to incomplete EUS staging by severe stenosis in 20-36% [26]. In line with tumor positive LN location, Talsma et al. found a worse prognosis in distal EC patients with suspected LN on EUS at both diaphragmatic sides, and suggested a combined staging system including distribution of LN related to the diaphragm [3].

Improvement of PET-CT and recently the application of diffusion-weighted magnetic resonance imaging, eventually with nodal contrast agents (gadofosveset or iron nanoparticles), might increase the adequacy of detecting LN metastases in future studies [27, 28].

A limitation of this study might be the use of integrated PET-CT combined with a diagnostic CT after 2009, versus CT and PET between 2000-2009. Furthermore, the accuracy of EUS might be higher if FNA could be applied to more distinct lymph nodes. In our center, FNA was performed in patients with clinically suspected LNs (n = 48:17.7%) considered relevant in determining the extent of radiation fields and/or nodal resection.

In conclusion, treatment decision-making in EC strongly depends on adequate clinical LN staging. Nodal up- and downstaging was frequently found in patients treated with surgery alone (43% and 25%, respectively). This inaccuracy rate in LN staging has an impact on prognosis to nCRT, especially pertaining advanced tumors and upper abdominal nodes. It might also influence radiotherapy target volume delineation with increased risk of locoregional recurrence or overtreatment with inappropriate administration or unnecessary chemoradiation which may induce (cardiopulmonary) toxicity. Furthermore, it is important to acknowledge imperfections of current preoperative nodal staging in assessing the genuine effect of nCRT to optimize future individualized treatment options, including a possible wait-and-see strategy in future EC patients with a clinical complete response to nCRT.

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