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ypT0N+ status in oesophageal cancer patients: Location of residual metastatic lymph nodes with regard to the neoadjuvant radiation field

B. Schurink [a, b, *], M.F.J. Seesing [b], L. Goense [b, c], S. Mook [c], L.A.A. Brosens [d], N. Haj Mohammad [e], J.P. Ruurda [b], T.A.P. Roeling [a], R.L.A.W. Bleys [a], R. van Hillegersberg [b, **]

[a] Department of Anatomy, University Medical Center Utrecht, the Netherlands
[b] Department of Surgery, University Medical Center Utrecht, the Netherlands
[c] Department of Radiation Oncology, University Medical Center Utrecht, the Netherlands
[d] Department of Pathology, University Medical Center Utrecht, the Netherlands
[e] Department of Medical Oncology, University Medical Center Utrecht, the Netherlands

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ABSTRACT

Introduction: A subset of oesophageal cancer patients has residual nodal disease despite complete pathologic response of the primary tumour after neoadjuvant chemoradiation and resection. The aim of this study was to determine the exact location of metastatic nodes with regard to the neoadjuvant radiation field and to assess progression-free (PFS) and overall survival (OS) in this group of patients.
Materials and methods: From January 2010 to January 2017, complete tumour responders (ypT0) after neoadjuvant chemoradiotherapy and oesophagectomy were identified from a prospective database and grouped according to residual nodal disease (ypT0N + or ypT0N0). Radiation fields were analysed for location of the metastatic nodes and PFS and OS were determined.
Results: In a total of 192 patients, 53 complete responders (ypT0) were identified. Of those, 11 patients (20.8%) were ypT0N+ with a total of 12 metastatic nodes: 8 (66.7%) located within the neoadjuvant radiation field and 4 (33.3%) located outside this field. Although not statistically significant, 1- and 2-year PFS were worse in ypT0N + patients (ypT0N+ 64.3% vs. ypT0N0 84.4%; ypT0N+ 48.2% vs. ypT0N0 80.7%, respectively; p = 0.051), just as 1- and 2-year OS rates, however, to a lesser extent (ypT0N+ 75.0% vs. ypT0N0 76.3%; ypT0N+ 75.0% vs. ypT0N0 72.9%, respectively; p = 0.956).
Conclusion: Most ypT0N + lymph nodes are located within the neoadjuvant radiation field. Although a small heterogeneous population was included, this might be due to an inadequate response to neoadjuvant chemoradiotherapy leading to a trend towards worse PFS and OS in ypT0N + patients. Larger studies need to validate our findings.

Introduction

Neoadjuvant chemoradiation (nCRT) followed by oesophagectomy is the treatment with curative intent for resectable oesophageal cancer [1]. Complete pathologic response (pCR) of the primary tumour after nCRT and surgery is associated with improved 5-year survival [2–4]. However, in a subset of patients residual nodal disease is found despite complete pathologic response of the primary tumour (ypT0N+). In previous studies, prevalence of ypT0N + varied between 3% and 22% after nCRT and surgery [5–8]. Data regarding the effect of residual nodal disease on progression-free survival (PFS) and overall survival (OS) are contradictory and limited to mostly retrospective studies [6,7,9]. Another important limitation of all previously conducted studies is the lack of information regarding location of metastatic nodes

* Corresponding author. Department of Anatomy, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG, Utrecht, the Netherlands.
** Corresponding author. Department of Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CG, Utrecht, the Netherlands
E-mail addresses: b.schurink@umcutrecht.nl (B. Schurink), r.vanhillegersberg@umcutrecht.nl (R. van Hillegersberg).

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relative to the neoadjuvant radiation fields. This information could lead to better insight into tumour biology and provide ways to optimize treatment of both the primary tumour and metastatic lymph nodes. The aims of this study were to determine the location of metastatic lymph nodes with regard to the radiation field in patients with ypT0N + disease after nCRT followed by oesophagectomy, and to compare PFS and OS between ypT0N0 and ypT0N + patients.

Materials and methods

Institutional Review Board (IRB) approval was obtained and the requirement for informed consent was waived. Patients who underwent oesophagectomy for T1N + or T2-4aN_x oesophageal cancer after nCRT in the University Medical Center (UMC) Utrecht between January 2010 and January 2017 were selected. Prospectively collected data were reviewed and included patient demographics and related characteristics, tumour-related variables, treatment related variables, and follow-up.

Clinical staging

Diagnostic work-up included endoscopy with biopsy, endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) or integrated 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET)/CT scanning. Patients were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system [10]. Follow-up was planned 6 weeks, 3 and 6 months, and yearly up to 5 years after surgery according to the national guidelines. If deemed clinically necessary during follow-up, a (PET)-CT scan was done to evaluate the presence of recurrent disease.

Chemoradiotherapy

Patients received nCRT followed by oesophagectomy [11]. Chemoradiation consisted of 5 cycles of intravenous carboplatin (targeted at an area under the curve of 2 mg/mL per min)/paclitaxel (50 mg/m2 of body-surface area) and with a total concurrent radiation dose of 41.4 Gy (23 × 1.8Gy). Patients were treated using Intensity-modulated radiotherapy (IMRT), Volumetric Intensity modulated radiotherapy (VMAT) or 3D conformal radiotherapy (3D-CRT). A radiation oncologist (SM) retrospectively delineated the location of the metastatic lymph node on the planning CT, blinded for the original treatment planning and assessed mean radiation dose, and location of metastatic lymph nodes relative to the clinical target volume (CTV) and planning treatment volume (PTV).

Surgery

Type of surgical resection was determined based on tumour location and surgeon's preferences: a transthoracic (Ivor Lewis or McKeown) or a transhiatal (Orringer) procedure either via an open or minimally invasive approach. A two-field lymph node dissection was routinely performed during the transthoracic procedures. Some patients were treated with a three-field lymphadenectomy as part of a study investigating the feasibility of this approach in patients with oesophageal cancer and proven cervical lymph node metastases.

Pathology

Patients with a pathologic complete response of the primary tumour were selected, defined as Mandard grade I upon histological evaluation [12], and categorized into patients with (ypT0N+) and without (ypT0N0) nodal metastases.

Paratracheal, para-oesophageal lymph node stations and the left gastric artery were marked on all surgically resected specimens (Fig. 1) in the operating room before transport to the Pathology Department. Thus, the location of (metastatic) lymph nodes with reference to the labelled landmarks could be extracted from the pathology report. Pathology sections from lymph nodes from the resection specimen were revised by a dedicated GE pathologist (LB) and checked for the presence of regressional lymph node changes (such as fibrosis, necrosis, and foreign body giant cell reactions) to identify ypT0N0 patients with lymph nodes showing complete pathological response to nCRT. These patients were compared to ypT0N + patients regarding time from completion of nCRT to date of surgery to evaluate the contribution of time to surgery to lymph node status.

Statistical analyses

Statistical analyses were performed with SPSS 21.0 (IBM Corporation, Armonk, NY, USA). Categorical data were presented as frequencies (%) and compared using Chi-squared tests and Fisher exact tests, depending on the cell count. Continuous data were described as medians with an interquartile range (IQR) and analysed with a Mann Whitney *U* test. Median time of follow-up (95% CI) was calculated using a reversed Kaplan-Meier method [13]. PFS and OS were calculated from the date of oesophagectomy to date of diagnosis of progression of disease (loco-regional or distant metastasis) or last follow-up, or the date of death or last follow-up, respectively. Patients classified as Clavien Dindo grade V for an oesophagectomy related complication were excluded from analyses. PFS and OS were assessed using the Kaplan-Meier method and log-rank test, and specified for 1- and 2- years of follow-up. Subgroup analyses were done according to tumour histology and in ypT0N0 patients according to regressional nodal changes. Shapiro et al. showed improved survival in patients without nodal involvement compared to patients that became node negative after nCRT [14]. A two-sided P- value < 0.05 was considered statistically significant.

Results

General characteristics

Between January 2010 and January 2017 192 patients were selected who underwent nCRT followed by oesophagectomy in the UMC Utrecht, of which 53 (27.6%) had a pathologic complete response of the primary tumour (ypT0): 21 (39.6%) with adenocarcinoma and 32 (60.4%) with squamous cell carcinoma. A total of 11/53 (20.8%) were ypT0N+. Demographics and clinical characteristics are summarized in Table 1. Median age was 67.2 years (IQR 61.3–72.6); ypT0N + patients were younger than ypT0N0 patients, 59.5 (IQR 55.1–67.9) and 68.5 (IQR 63.5–73.0; $p = 0.048$), respectively. No other significant differences were seen between groups.

Radiation field

Pathological evaluation identified 11 ypT0N + patients with 12 residual metastatic lymph nodes. All completed radiotherapy, however, 3/11 patients (27.3%) did not complete chemotherapy (no difference between ypT0N+ and ypT0N0 patients ($p = 0.678$)).

Location of residual metastatic nodes was widespread (Fig. 1; Table 2). A total of 8/12 (66.7%) metastatic nodes were located within the neoadjuvant radiation field, either delineated separately during neoadjuvant treatment planning and therefore located within the GTV ($n = 5$, 62.5%), or situated in the PTV-CTV ($n = 3$, 37.5%) resulting in a planned radiation dose >40 Gy (Table 2).

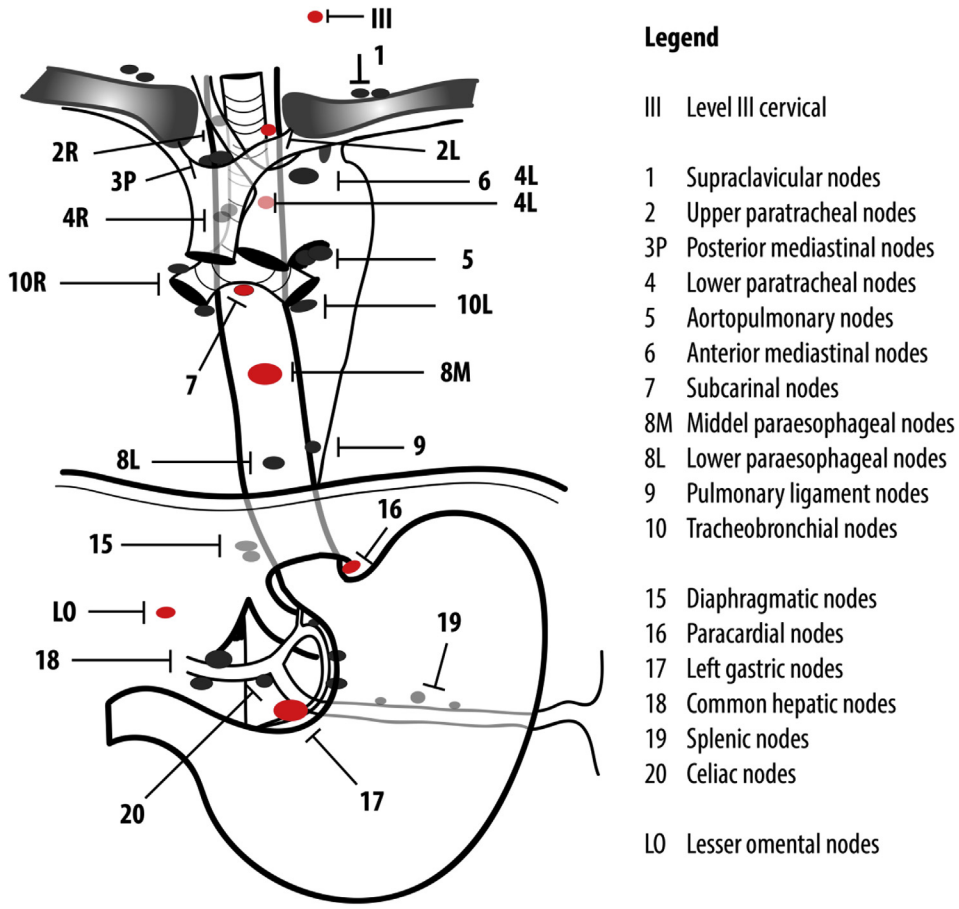

Fig. 1. Lymph node station classification according to the AJCC staging system (7th edition) with the addition of lymph nodes at Level III cervical (III) and in the lesser omentum (LO) as a possible location for lymph node metastasis. Lymph node stations that contained metastasis upon pathologic evaluation are depicted in red; the larger the lymph node, the more ypT0N + patients had metastatic nodes at this location.

However, 4/12 (33.3%) metastatic nodes were located outside the neoadjuvant radiation field. During clinical staging these were either interpreted as enlarged due to benign disease (n = 1) or not identified as metastatic nodes (n = 3).

Histology

Of the 42 ypT0N0 patients, 12 (28.6%) showed pathological signs of nodal involvement before nCRT. The other 30 (71.4%) showed no regressional changes in the resected lymph nodes. Median lymph node yield in this group was 21.0 (IQR 15.8–31.0). In the 11 ypT0N + patients, an almost complete regression was seen in 8/12 lymph nodes (66.7%). The other 4/12 residual metastatic nodes (33.3%) did not show any regressional changes. In one of these patients, the metastatic lymph node was not included in the radiation field and 2 patients did not complete neoadjuvant chemotherapy. Despite completion of nCRT and a location within the neoadjuvant radiation field, one patient still had a lymph node with residual metastasis that did not show any response to nCRT. In ypT0N + patients a median lymph node yield of 19.0 (IQR 13.0–33.0) was reached (Table 1).

Median time to surgery did not differ between ypT0N0 patients with nodal regressional changes and ypT0N + patients (8.5 (IQR 5.9–9.6) weeks and 8.2 (IQR 6.7–10.1) weeks, respectively).

Overall survival and progression-free survival

In total, 16 patients (30.2%) died during follow-up. Two (3.8%), were classified as Clavien Dindo grade V and died due to mediastinitis following anastomotic leakage (n = 1) or fulminant sepsis based on an aspiration pneumonia (n = 1). Of the remaining 14 patients (26.4%), 7 patients (13.2%) died due to disease progression, 4 (7.5%) due to other causes: pneumonia, a head and neck tumour, subdural hematoma or cardiac sepsis. In 3 patients (5.7%) cause of death was unknown.

Median time of follow-up was 24.1 months (95% CI 19.5–28.7 months). Although not statistically significant, a trend towards worse 1- and 2- year PFS was seen in ypT0N + patients (Fig. 2). At 1-year of follow-up, disease did not recur in 84.4% of ypT0N0 patients, versus 64.3% of ypT0N + patients; at 2-years of follow-up PFS was 80.7% and 48.2%, respectively (p = 0.051). This difference between both groups was also seen for OS, but to a much lesser extent (Fig. 3). OS at 1-year was 76.3% for ypT0N0 patients and 75.0% for ypT0N + patients; 2-year OS was 72.9% and 75.0%, respectively (p = 0.956).

Subgroup analyses

In the 31 patients with squamous cell carcinoma, a trend towards worse PFS was seen. PFS at 1-year of follow-up was 79.7% for ypT0N0 patients versus 75.0% for ypT0N + patients; at 2-years this was 74.0% versus 37.5% (p = 0.175). This was also the case for OS, although to a much lesser extent. At 1-year of follow-up 73.1% of ypT0N0 patients was alive versus 66.7% of ypT0N + patients; at 2-years of follow-up, this was 63.0% versus 66.7% (p = 0.439). In ypT0N + patients with adenocarcinoma a trend towards worse PFS

Table 1
Demographics and clinical characteristics.

Variable	Total (N = 53)[a]	ypT0N+ (N = 11)[b]	ypT0N0 (N = 42)[b]	P-value
Age, years	67.2 (61.3–72.6)	59.5 (55.1–67.9)	68.5 (63.5–73.0)	0.048
Gender				
Male	37 (69.8)	9 (24.3)	28 (75.7)	0.471
Female	16 (30.2)	2 (12.5)	14 (87.5)	
BMI, kg/m^2	24.1 (21.9–26.8)	24.0 (23.1–26.8)	24.5 (21.9–27.0)	0.809
ASA score				
1	11 (20.8)	2 (18.2)	9 (81.8)	0.432
2	30 (56.6)	8 (26.7)	22 (73.3)	
3	12 (22.6)	1 (8.3)	11 (91.7)	
Comorbidity, yes	40 (75.5)	8 (20.0)	32 (80.0)	0.999
nCRT in UMC Utrecht	46 (86.8)	11 (23.9)	35 (76.1)	0.322
nCRT completed	42 (79.2)	8 (19.0)	34 (81.0)	0.678
Time from completion nCRT to surgery (weeks)	8.3 (6.6–10.1)	8.4 (6.4–10.2)	7.9 (6.7–10.1)	0.629
Clinical T stage				
T1	4 (7.5)	1 (25.0)	3 (75.0)	0.703
T2	10 (18.9)	3 (30.0)	7 (70.0)	
T3	38 (71.7)	7 (18.4)	31 (81.6)	
T4a	1 (1.9)	0 (0.0)	1 (100)	
T4b	0 (0.0)	0 (0.0)	0 (0.0)	
Clinical N stage				
N0	13 (24.5)	1 (7.7)	12 (92.3)	0.828
N1	22 (41.5)	7 (31.8)	15 (68.2)	
N2	17 (32.1)	3 (17.6)	14 (82.4)	
N3	1 (1.9)	0(0.0)	1 (100)	
Tumour location				
Proximal	1 (1.9)	0 (0.0)	1 (100)	0.602
Middle	20 (37.7)	3 (15.0)	17 (85.5)	
Distal	32 (60.4)	8 (25.0)	24 (75.0)	
Histology				
AC	21 (39.6)	7 (33.3)	14 (66.7)	0.090
SCC	32 (60.4)	4 (12.5)	28 (87.5)	
Lymph node yield	21.0 (14.5–31.0)	19.0 (13.0–33.0)	21.0 (15.8–31.0)	0.818
Type of surgery				
Transthoracic	48 (90.6)	10 (20.8)	38 (79.2)	0.999
Transhiatal	5 (9.4)	1 (20.0)	4 (80.0)	

Categorical data are shown as number (%), continuous data as median (IQR).
Abbreviations. ACA = adenocarcinoma; BMI = body mass index; DLN = dissected lymph nodes; nCRT = neoadjuvant chemoradiotherapy according to CROSS; nCRT in UMC Utrecht = neoadjuvant chemoradiation was given in the UMC Utrecht; SCC = squamous cell carcinoma; Transhiatal = Orringer approach, Transthoracic = Ivor-Lewis oesophagectomy (open or minimally invasive) or McKeown (open or minimally invasive); ypT0N0 = complete pathologic response in tumour without residual nodal disease; ypT0N+ = complete pathologic response in tumour with residual nodal disease.
[a] Percentages are presented as column percentages.
[b] Percentages are presented as row percentages.

Table 2
Location of metastatic lymph nodes relative to radiation fields in ypT0N + patients.

			Location metastatic lymph nodes				Radiotherapy	
ypT0N + patient	cTN stage	Tumour location	Histology	CT	E(B)US	PET-CT	Within field	Dose (Gy)
1	T3N2	Distal	8M	8M, 20	7, 20	8, 20	CTV	41.7
			17				CTV	42.0
2	T3N2	Mid	8M	2L, 4R + L, 8M, 20	10	2L, 4R + L, 8M, 20	No	1.1
3	T2N0	Distal	8M	–	NP	–	No	0.7
4	T1N1	Mid	2R	2R	NP	2R	CTV	41.4
5	T3N1	Distal	16	20	20	20	PTV	40.9
6	T3N1	Distal	17	20	20	–	CTV	41.3
7	T3N2	Distal	4R/L	7	4,7,20[a]	7, 15	No	1.1
8	T3N1	Distal	Level III cervical	1	NP	1	CTV	41.3
9	T2N1	Distal	LO	8	8M	–	PTV	42.4
10	T3N1	Mid	17	16/17	NP	NP	CTV	41.5
11	T2N1	Distal	7	17	NP	17	No	2.0

Mid = middle 1/3 oesophagus; Distal = distal 1/3 oesophagus.
- = metastatic nodes not identified.
[a] FNA: N4 = no tumour cells detected, N7 = tumour positive node; NP = examination not performed.

was seen as well. PFS at 1-year and 2-years of follow-up was 91.7% for ypT0N0 patients versus 60.0% for ypT0N + patients (p = 0.086). OS also differed between ypT0N0 and ypT0N + patients with adenocarcinoma, but not statistically significantly. At 1-year and 2-years of follow-up 91.7% of ypT0N0 patients was still alive versus 80.0% of ypT0N + patients (p = 0.468).

In ypT0N0 patients, no differences in PFS (p = 0.350) and OS (p = 0.881) were seen between patients with and without regressional nodal changes.

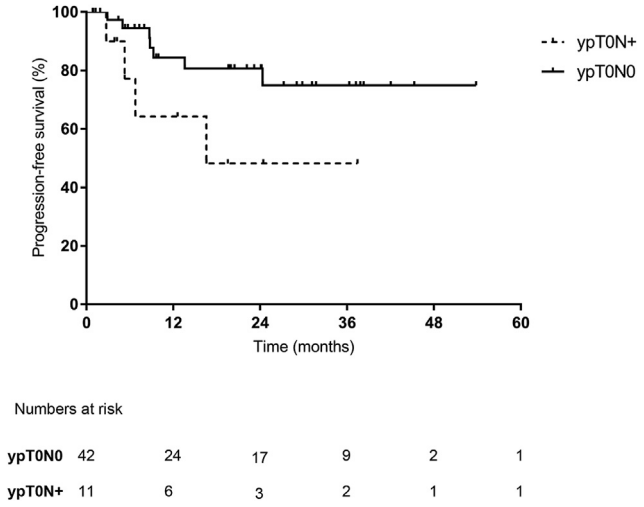

Fig. 2. Progression-free survival (PFS) in ypT0N0 and ypT0N + patients (p = 0.075).

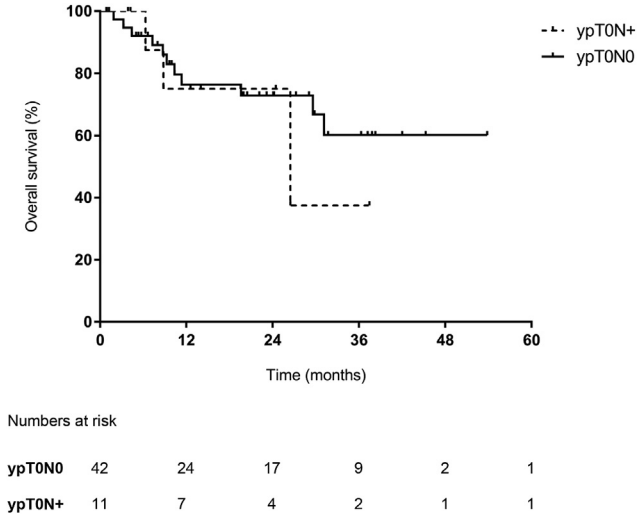

Fig. 3. Overall survival (OS) in ypT0N0 and ypT0N + patients (p = 0.648).

Discussion

To the best of our knowledge, this is the first study to report on the location of lymph nodes with residual metastatic disease relative to neoadjuvant radiation fields in patients with a complete pathologic response of the primary tumour. The majority of metastatic nodes (66.7%) were located within the neoadjuvant radiation field possibly indicating a difference in radiosensitivity between the primary tumour and nodal metastases but also between lymph nodes. Both the primary tumour and metastases are biologically heterogeneous [15], and oesophageal cancer is moderately sensitive to radiation [16]. Radiation exerts its anticancer effect via the induction of double strand breaks (DSB) that lead to cell apoptosis [17]. Radiation-resistance is influenced by a number of factors that affect the ability to repair these DSB. Changes in expression profiles of tumour suppressors and proto-oncogenes in metastatic tumour cells can affect the ability to repair these DSB [18–20], which could explain the presence of metastatic cells in lymph nodes despite being irradiated with 41.4Gy. Potential differences in radiation sensitivity between the primary tumour and metastatic lymph nodes could provide an argument to increase the radiation dose on metastatic lymph nodes to decrease the number of ypT0N + patients, especially since ypT0N + status seems to be associated with worse PFS in this study. A total of 4 (33.3%) residual metastatic nodes were located outside the neoadjuvant radiation field. They were not identified as metastatic during clinical staging and therefore did not receive an appropriate radiation dose. It is known that current staging methods do not adequately detect nodal metastasis, which is also dependent on location of metastatic nodes [21,22]. This highlights the need for a careful mediastinal and abdominal lymph node dissection during surgery and indicates that lymph node detection during initial clinical staging can be improved.

Although not statistically significant, a trend was seen towards worse PFS and to a lesser extent worse OS for ypT0N + patients in this study. This was the case for both patients with adenocarcinoma and squamous cell carcinoma. These findings were supported by a study by Wang et al., who also showed a lower PFS in ypT0N + patients [19]. Lower OS in ypT0N + patients was seen in several studies, which also identified remnant nodal disease as an important prognostic factor [6,8,23,24]. The fact that only a trend and no significant difference was seen in PFS and OS between ypT0N+ and ypT0N0 patients in this study could be due to the small number of included patients. This might also be the explanation for the fact that no difference was seen in survival between ypT0N0 patients with pre-treatment nodal involvement who became node negative after nCRT compared to patients without pre-treatment nodal involvement. Other studies show that pre-treatment nodal status is an important prognostic factor [14,25]. In the current study, no difference was seen in time from completion of nCRT to surgery between ypT0N0 patients with nodal regressional changes and ypT0N + patients. Therefore, it is not likely that this parameter has influenced nodal status.

An important limitation is the small number of included ypT0N + patients. No adequate adjustment for potential confounders could be done; previous studies showed that neoadjuvant therapy results in higher pathologic complete response rates in squamous cell carcinoma compared to adenocarcinoma [26]. Despite the small number of patients, it is clear that there is a difference in response to neoadjuvant radiation between the primary tumour and metastatic lymph nodes. Larger prospective studies are needed to validate our results. Secondly, radiation fields of other hospitals than the UMC Utrecht were unknown. However, these were all ypT0N0 patients and therefore this did not influence the results. Thirdly, transhiatal resections were included possibly resulting in an underestimation of the number of ypT0N + patients, as the thoracic lymphadenectomy in this procedure is limited [27,28]. As a consequence, the difference in PFS and OS between ypT0N0 and ypT0N + patients could have been underestimated.

Conclusions

In conclusion, in the majority of included ypT0N + patients metastatic lymph nodes were located within the neoadjuvant radiation field but still contained metastasis upon pathologic evaluation. Although a small heterogeneous population was included, this might be due to an inadequate response to neoadjuvant chemoradiation, leading to a trend towards worse PFS and OS in ypT0N + patients. However, larger studies are needed to validate our findings.

Declarations of interest

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