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Locoregional Residual Esophageal Cancer after Neo-adjuvant Chemoradiotherapy and Surgery Regarding Anatomic Site and Radiation Target Fields: A Histopathologic Evaluation Study

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Objective: Neoadjuvant chemoradiotherapy followed by surgery establishes a considerable pathologic complete response (pCR) in EC. The aim was to determine site of residual tumor and its prognostic impact.

Summary Background Data: High rates of residual tumor in the adventitial region even inside the radiation fields will influence current decision-making.

Methods: We evaluated resection specimens with marked target fields from 151 consecutive EC patients treated with carboplatin/paclitaxel and 41.4Gy between 2009 and 2018.

Results: In radically resected (R0) specimens 19.8% (27/136) had a pCR (ypT0N0) and 14% nearly no response (tumor regression grade: tumor regression grade 4-5). Residual tumor commonly extended in or restricted to the adventitia (43.1%; 47/109), whereas 7.3% was in the mucosa (ypT1a), 16.5% in the submucosa (ypT1b) and 6.4% only in lymph nodes (ypT0N+). Macroscopic residues in R0-specimens of partial responders (tumor regression grade 2-3: N = 90) were found in- and outside the gross tumor volume (GTV) in 33.3% and 8.9%, and only microscopic in- and outside the clinical target volume in 58.9% and 1.1%, respectively. Residual nodal disease was observed proximally and distally to the clinical target volume in 2 and 5 patients, respectively. Disease Free Survival decreased significantly if macroscopic tumor was outside the GTV and in ypT2-4aN+.

Conclusions: After neoadjuvant chemoradiotherapy, pCR and ypT1aN0 were seen in a limited number of R0 resected specimens (19.8% and 7.3%, respectively), whereas 6.4% had only nodal disease (yT0N+). Disease Free Survival decreased significantly if macroscopic residue was outside the GTV and in responders with only nodal disease. Therefore, we should be cautious in applying wait and see strategies.

Keywords: esophageal cancer, neoadjuvant CRT, site residual tumor

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Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is common treatment in patients with potentially curable locally advanced esophageal cancer (EC), which improves survival by increased surgical radical resectability (R0) and reduced locoregional recurrences.[1,2] Several studies have shown a significant higher survival after pathologic complete response (pCR) in the resected specimens.[3–6]

In complete responders surgery might be less beneficial as it is associated with considerable morbidity and mortality.[7–9] For good decision-making accurate preoperative selection is essential to identify these patients.[10,11] However, the accuracy of restaging by endoscopic ultrasonography (EUS) and ^{18}F-FDG-positron emission and computed tomography (PET/CT) is not sufficient enough, whereas additional improvements of magnetic resonance imaging in predicting response are still investigated.[11–13] Pathologic examination remains the gold standard to assess complete response after nCRT, but a comprehensive definition is still missing and the inter-observer consistency lacking.[10,15] In our previously described institutional method, which allows adequate evaluation of residual EC regarding radiotherapy target volumes, microscopic residues were found outside these target fields in 14%.[16]

The aim of this study was to evaluate the anatomical site of residual cancer after nCRT in the esophageal wall layers in relation with radiation tumor volumes at pathologic examination to get more insight in the clinical impact on patients' outcome.

METHODS

Patients and Treatment

For this retrospective study, we included 151 of 386 patients in a prospectively maintained database with potentially resectable locally advanced (T1N+/T2-T4aN0-3/M0) EC in patients who were treated with nCRT followed by surgery with curative intent at the University Medical Center Groningen between October 2009 and March 2018. All included patients had a complete restaging, for example, EUS with fine needle aspiration biopsy and uniform 18F-FDG-PET/CT and underwent pre and intraoperative tumor marking according to the previously described institutional protocol with demarcations of the radiotherapy target volumes on the surgical specimen at pathologic evaluation.[16] Excluded were those with incomplete nCRT (<4 of the 5 courses), interval progression of disease, stopped or delayed treatment (>10 weeks after nCRT) due to deteriorated condition, surgery at another hospital or if opted for wait and see policy.

The study was approved by the Institutional Ethical Board (METc Nr 201800658).

All patients were treated according to the ChemoRadiotherapy for esophageal cancer followed by surgery study (CROSS) regimen after staging corresponding to the 7th TNM classification system, based on CT and/or 18-F-FDG-PET/CT and EUS with eventually fine needle aspiration biopsy.[17] Treatment consisted of 5 weekly cycles of paclitaxel (50 mg/m^2) and Indeed carboplatin (AUC = 2), combined with 41.4 Gy radiotherapy in daily fractions of 1.8 Gy, 5 times per week. Surgery consisted of a transthoracic open or minimally invasive esophagectomy with 2- field lymphadenectomy 6 to 10 weeks

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after completion of nCRT.[2,3] In the resection specimens of the 151 eligible patients, the radiation target volumes were marked intra-operatively using anatomical reference points to provide more accurate information regarding tumor location at pathologic evaluation.[16] Gross tumor volume (GTV) containing the primary tumor and clinical pathologic lymph nodes (LN), was delineated by experienced radiation oncologists on a planning CT scan, using all available diagnostic information (EUS/PET/CT).[16,18] Since 2011 an internal target volume was generated encompassing the target volume in all breathing phases, to account for breathing movements. The clinical target volume (CTV) was obtained by adding 1 cm margin in the transversal and 3.5 cm margin in the cranio-caudal direction (2.5 cm margin if the tumor expanded into the stomach until 2014; afterwards 3.5 cm) to the primary tumor, adjusted to anatomical structures, with a minimal margin of 5 mm. For pathologic LNs, one cm margin was used. The planning target volume (PTV) was generated by expanding the CTV with 5 mm margin to account for setup uncertainties. The radiotherapy treatment field borders (GTV and CTV) were demarcated, during surgery on the in-vivo esophageal specimen defined just before definitive dissection related to noted intra-operative reference measure points.[16]

Histopathologic Examination and Follow up

After careful fixation and inking of the resected specimen, which was directly pinned ex-vivo to a foam board to minimalize shrinkage, the specimen was sliced and the tissue sections were evaluated with hematoxylin and eosin stain. Presence of macroscopic tumor outside the GTV was confirmed microscopically. If microscopic tumor was within 1 mm of the surgical margins, the resection was considered as R1 according to the Royal College of Pathologists (RCP).[19,20] Tumor response to nCRT was evaluated using the Mandard tumor regression grade (TRG) system.[19] Pathologic evaluation was performed by 2 experienced gastrointestinal pathologists and if doubtful by specimen revision. Pathologic complete response (pCR, ie, ypT0N0) was defined as absence of tumor cells in the resected specimen. Data was extracted from revised pathology reports including presence of positive resection margins, macroscopic and /or microscopic residual tumor outside the GTV and CTV related to target volumes, nodal involvement and tumor invasion in surrounding tissue, including lymph-angio invasion.

Follow-up after surgery was performed every 3 months in the first year, every 4 months in the second year and yearly thereafter. If there was any suspicion of recurrence, it was commonly confirmed by CT or PET-CT.

Statistics

Survival curves were estimated using the Kaplan–Meier curves. The log-rank test was used for comparing disease free survival (DFS), defined as the time from the start of nCRT till the date of recurrence or death. Patients were censored at the last point of known contact during follow-up without acquiring the outcomes of interest. In addition, patients who died within 90 days after surgery were excluded from the survival analysis. Statistical analysis was performed using SPSS 23.0 software (SPSS Inc, Chicago, IL).

RESULTS

Patients and Histopathological Characteristics

Table 1 shows the relevant patient and tumor characteristics after nCRT. Most patients were males (78.8%) and the median age was 66 years. Microscopic radical resection (R0) was achieved in 90% (136/151) and pathologic complete response (ypT0N0), that is, Mandard TRG1 in 17.9% (27/151). In the R0 resection specimens pCR was seen in 19.8% (27/136), whereas 14% (19/136) had nearly no response (pNR; TRG 4-5). Tumor residue was more frequently seen in the deeper adventitial layer (37.7%: 57/151) and limited to the superficial layers in 17.2% (26/151).

TABLE 1. Patient and pathological characteristics (n = 151)

	N (%)
Age (median/range) yr	66.2 (44–86) yr
Sex	
Male	119 (78.8)
Female	32 (21.2)
Histology	
Adenocarcinoma	128 (84.5)
Squamous cell carcinoma	23 (15.2)
Localization	
Middle	8 (5.3)
Distal	143 (94.7)
Pathologic (yp) TN stage	
T0N0	27 (17.9)
T0N+	7 (4.6)
T+N0	70 (46.4)
T+N+	47 (31.1)
Deepest anatomical layers	
Muscularis mucosae	8 (5.3)
Submucosa	18 (11.9)
Muscularis propria	22 (14.6)
Adventitia	57 (37.7)
Outside esophageal wall	12 (7.9)
None (ypT0)	34 (22.5)
Responses / radicality R0 vs R1	
R0	136 (90)
pCR	27 (19.8)
pPR	90 (66.2)
pNR	19 (14.0)
R1	15 (10)
pPR	9 (60)
pNR	6 (40)

pCR indicates pathological complete response; pNR, pathological non-response; pPR, pathological partial response; R0, microscopic radical resection; R1, irradical resection.

Anatomical Site of Residual Cancer

Table 2 depicts the residual tumor distribution regarding response in the esophageal wall and GTV/CTV in the R0 group. Pathologic partial response (pPR: TRG 2-3) was seen in 82.6% (90/109). In these patients, residual tumor was only found in the esophageal wall (ypT+N0) in 58.9% or in lymph nodes (ypT0N+)) in 7.8%. Residual tumor in pPR was limited to the superficial layers, for example, muscularis mucosae (ypT1a) and submucosa (ypT1b) in 7.8% and 18.9%, respectively. The most common anatomical site of residual cancer in R0 specimens was in the adventitia (43.1%), of which 38.9% were pPR.

In patients with an initially cT3-T4a tumor (n = 119) a substantial reduction (29.4%; n = 35) to ypT1/T2 was achieved in the resection specimens (R0+R1) (supplementary Table 1, http://links.lww.com/SLA/C350).

Site of Residual Cancer With Regard to the Radiation Fields

Among the 109 R0 resection specimens, histopathologically confirmed, macroscopic residual tumor, macroscopic residue was found inside the GTV in 34.9% (n = 38) and outside the GTV in 11.9% (n = 13). Microscopic residual tumor deposits were seen inside the CTV in 70 (64.2%) and also outside the CTV margins in 18 (16.5%), whereas it was observed only outside the CTV margins in 1 specimen (0.9%) (Tables 2 and 3).

TABLE 2. Pathological Characteristics of Specimens With Partial and Nonresponse in R0 Resection

Characteristics	Total (n = 109) N (%)	Partial Responders (n = 90) N (%)	Nonresponders (n = 19) N (%)
ypTN			
T0N+	7 (6.4)	7 (7.8)	—
T+N0	63 (57.8)	53 (58.9)	10 (52.6)
T+N+	39 (35.8)	30 (33.3)	9 (47.4)
ypT			
T0	7 (6.4)	7 (7.8)	—
T1a	8 (7.3)	7 (7.8)	1 (5.3)
T1b	18 (16.5)	17 (18.9)	1 (5.3)
T2	21 (19.3)	18 (20.0)	3 (15.8)
T3	54 (49.5)	41 (45.5)	13 (68.4)
T4a	1 (0.9)	—	1 (5.3)
Deepest involved esophageal layer			
None (ypT0)	7 (6.4)	7 (7.8)	—
Muscularis mucosa	8 (7.3)	7 (7.8)	1 (5.3)
Submucosa	18 (16.5)	17 (18.9)	1 (5.3)
Muscularis propria	21 (19.3)	18 (20)	3 (15.8)
Adventitia	47 (43.1)	35 (38.9)	12 (63.2)
Outside the esophageal wall	8 (7.3)	6 (6.7)	2 (10.5)
Macroscopic tumor outside GTV	13 (11.9)	8 (8.9)	5 (26.3)
Microscopic tumor within CTV	70 (64.2)	53 (58.9)	17 (89.5)
Microscopic tumor outside CTV	18 (16.5)	15 (16.7)	3 (15.8)
Microscopic tumor outside CTV only	1 (0.9)	1 (1.1)	—

CTV indicates clinical target volume; GTV, gross tumor volume; T1a, muscularis mucosa; T1b, submucosa.

In the partial responders (TRG 2-3), macroscopic residual tumor was within and outside the GTV in 33.3% (n = 30) and 8.9% (n = 8), respectively, whereas microscopic residue was within and outside the CTV in 53 (58.9%) and 15 (16.7%), respectively (Table 3A). Among the nonresponders (TRG 4-5; n = 19) the rates of residual disease were high with macroscopic tumor within the GTV in 42.1% (n = 8) and microscopic tumor within the CTV in 89.5% (n = 17), whereas microscopic residue was even outside CTV in 3 (15.8%) patients (Table 3B).

The distribution of the nodal residual disease in respect to the different parts of the target volumes and N-stages are shown in Table 4A/B. Residual nodal tumor (ypT0N+/ypT+N+) was observed in 46 (42.2%) R0 specimens of which 37 (41%) in the TRG2-3. In these partial responders 72.9% (n = 27) were staged as ypN1 and 24.3% as ypN2. In R0 specimens seven (6.4%) had nodal residue outside the CTV. In 2 (2.2%) of the TRG2-3 specimens this residue was cranial and in five (5.5%) caudal of the CTV margin. Of the 24 adequately localized residual nodes in the TRG 2-3 specimens,

TABLE 3. Residual tumor regarding the primary tumor (pT) stage and radiation fields in R0 resection specimen (n = 109)

3A: Within the Esophageal Wall Regarding the TRG 2-3 (n = 90).

Layer	Macroscopic Tumor Within GTV n = 30 N (%)	Macroscopic Tumor Outside GTV n = 8 N (%)	Microscopic Tumor Within CTV n = 53 N (%)	Microscopic Tumor Outside CTV n = 15 N (%)
Muscularis mucosa	2 (6.7)	—	3 (5.7)	1 (6.7)
Submucosa	5 (16.7)	2 (25.0)	10 (18.9)	2 (13.3)
Muscularis propria	6 (20.0)	1 (12.5)	9 (16.9)	2 (13.3)
Adventitia	13 (43.3)	4 (50.0)	25 (47.2)	9 (60)
Outside the esophageal wall	4 (13.3)	1 (12.5)	6 (11.3)	1 (6.7)
No layer	—	—	—	—

3B: Within the Esophageal Wall Regarding the TRG 4-5 (n = 19).

Layer	Macroscopic Tumor Within GTV n = 8 N (%)	Macroscopic Tumor Outside GTV n = 5 N (%)	Microscopic Tumor Within CTV n = 17 N (%)	Microscopic Tumor Outside CTV n = 3 N (%)
Muscularis mucosa	—	—	1 (5.9)	—
Submucosa	—	—	1 (5.9)	—
Muscularis propria	1 (12.5)	1 (20.0)	2 (11.8)	1 (33.3)
Adventitia	6 (75.0)	3 (60.0)	11 (64.7)	2 (66.7)
Outside the esophageal wall	1 (12.5)	1 (20.0)	2 (11.8)	—
No layer	—	—	—	—

CTV indicates clinical target volume; GTV, gross tumor volume; TRG, tumor regression grade.

TABLE 4. Residual Tumor Regarding the Nodal (pN) Stage and Radiation Fields in R0 Resection Specimen (n = 109)

4A: According to the TRG 2-3 (n = 90).

Lymph nodes	No Positive LN n = 53 N (%)	Cranially of CTV n = 2 N (%)	Upper Part of CTV n = 3 N (%)	Within GTV n = 9 N (%)	Lower Part of CTV n = 5 N (%)	Caudally of CTV n = 5 N (%)	Unknown n = 13 N (%)
N0	53 (100.0)		—	—	—	—	—
N1	—	2 (100.0)	3 (100.0)	6 (66.7)	4 (80.0)	5 (100.0)	7 (53.8)
N2	—	—	—	3 (33.3)	1 (20.0)	—	5 (38.5)
N3	—	—	—	—	—	—	1 (7.7)

4B: According to the TRG 4-5 (n = 19).

Lymph nodes	No positive LN n = 10 N (%)	Cranially of CTV n = 0 N (%)	Upper Part of CTV n = 2 N (%)	Within GTV n = 3 N (%)	Lower Part of CTV n = 2 N (%)	Caudally of CTV n = 0 N (%)	Unknown n = 2 N (%)
N0	10 (100.0)		—	—	—	—	—
N1	—	—	1 (50.0)	2 (66.7)	1 (50.0)	—	1 (50.0)
N2	—	—	1 (50.0)	1 (33.3)	1 (50.0)	—	1 (50.0)
N3	—	—	–	–	–	—	—

CTV indicates clinical target volume; GTV, gross tumor volume; LN, lymph nodes; TRG, tumor regression grade.

37.5% (n = 9) were in the GTV and 33.3% (n = 8) in the CTV. In the 15 TRG 4-5 specimens residual nodal disease was more or less equally distributed between the CTV and GTV (Table 4B).

Among the 15 R1 resection specimens, macroscopic residual tumor was found outside the GTV in 20.0% (n = 3), whereas 9 (60%) had microscopic residual tumor cells outside the CTV (*data not shown*).

Outcome

The median DFS of the whole group (R0 and R1 resections), who were alive >90 days after surgery was 33 (20–45) months. Patients with superficial residual disease (ypT0-1N+ (44 months) or ypT1-4aN0 (33 months)) had a better median DFS than patients with deeper located residue (ypT2-4aN+ (18 months)) ($P = 0.002$) (Fig. 1). DFS was also related with residues in the anatomical layer

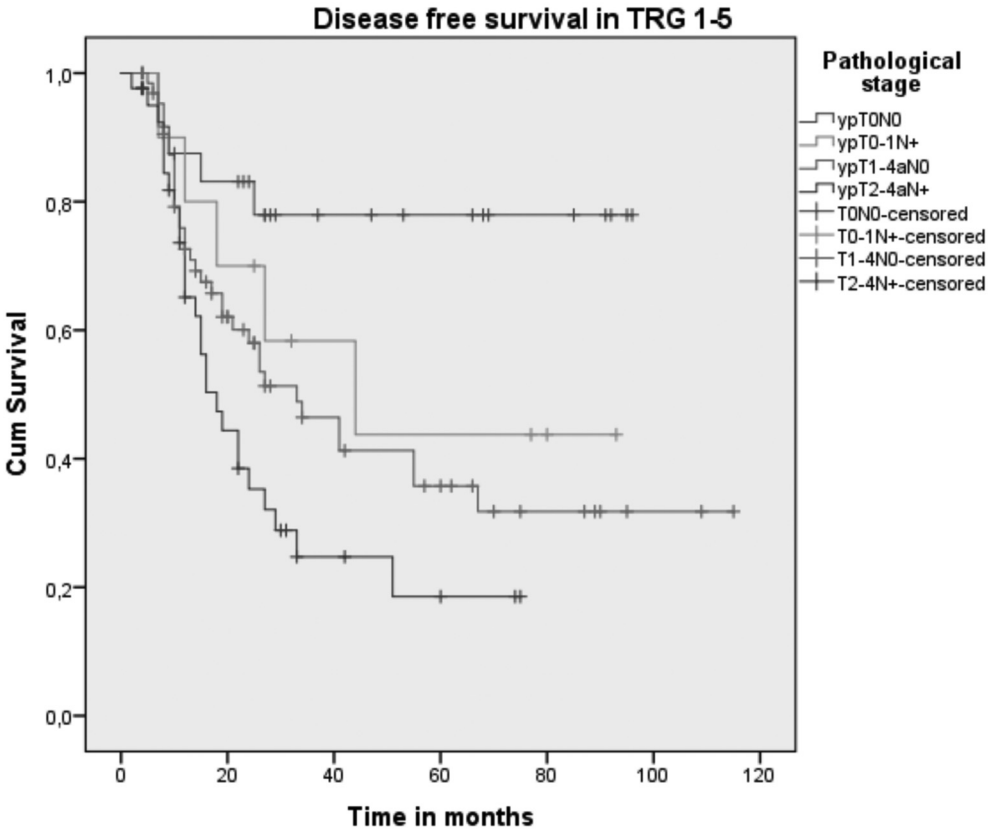

FIGURE 1. Disease free survival in whole group patients (n = 143) regarding residual tumor in superficial (ypT0-1N+) and deeper layers (ypT1-4aN0, ypT2-4aN+) ($P = 0.002$).

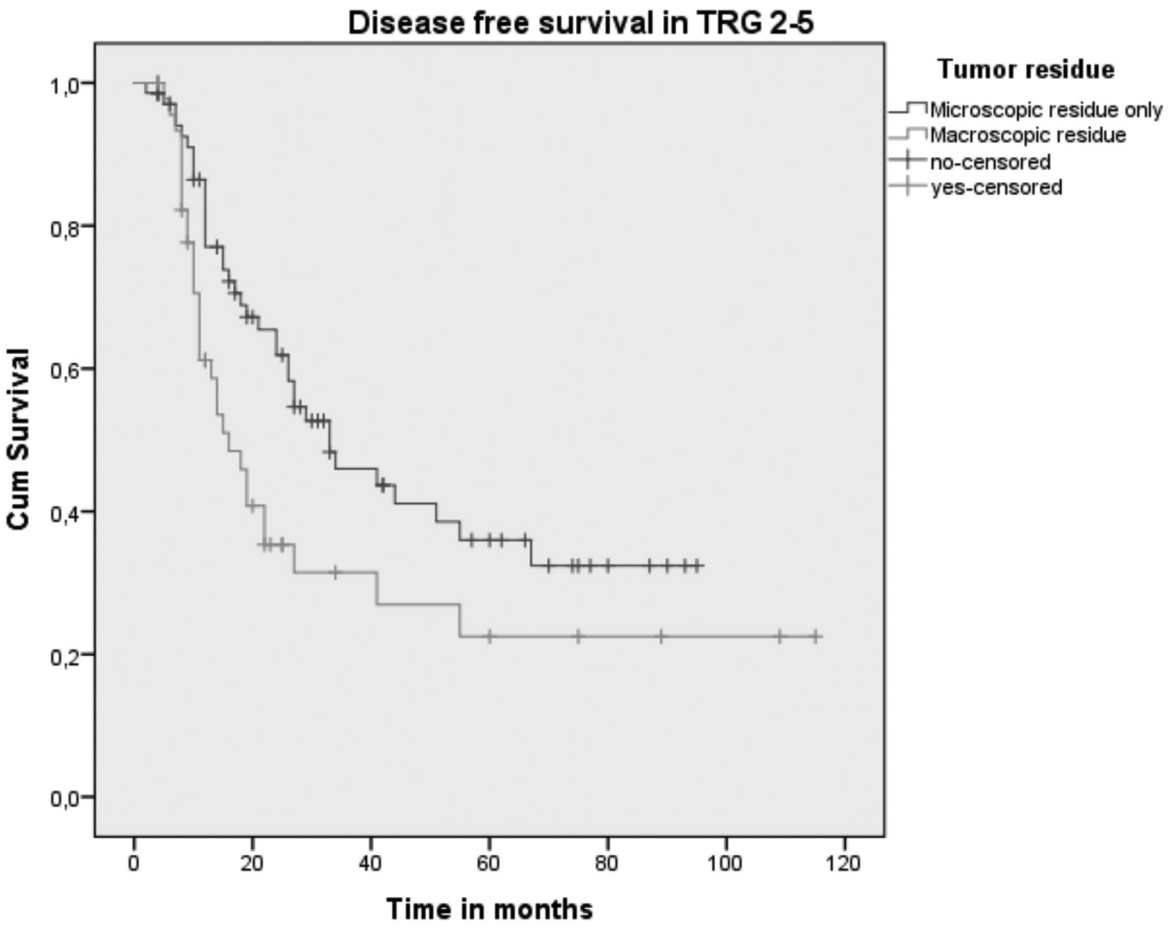

FIGURE 2. Disease free survival in months among patients with tumor regression grade 2-5 (n = 118) between microscopic residual tumor only and macroscopic residual tumor ($P = 0.022$).

in TRG 1-5 (n = 143) specimens, including muscularis mucosae, submucosa, muscularis propria, and adventitia (median DFS: 16–29 months; $P = 0.028$). Among the TRG 2-3 group (n = 118), the median DFS was 26 (19–32) months. Patients with macroscopic residual tumor had a significantly worse DFS compared to patients with microscopic tumor alone (16 vs 33 months; $P = 0.022$) (Fig. 2). No significant difference in DFS was seen in patients with ypT1, ypT2 and > ypT2-4a (median DFS: 22 to 33 months; $P = 0.4$). However, R0 patients with macroscopic residual tumor in the adventitia had a significant lower DFS compared to patients with only microscopic residue in the adventitia (mean DFS: 14 vs 51 months; $P = 0.039$). Patients with TRG 2-5 (n = 118) with histopathologically confirmed macroscopic tumor outside the GTV (n = 15) had a lower DFS (9 vs 27 months; $P = 0.009$).

DISCUSSION

In this retrospective study we analyzed the site of residual tumor regarding the anatomical esophageal wall layers and the radiation target fields in locally advanced EC patients treated with nCRT according to the CROSS regimen. Among patients with microscopic radical resection (R0) after nCRT, 19.8% had a pCR (ypT0/N0), whereas 7.3% had a ypT1aN0 and 16.5% a ypT1bN0. In the R0 group, 7.8% of the partial responders with ypT0 had residual tumor in regional LNs and approximately 18% had residual tumor outside the CTV. Of the R0 resections with residual tumor, the residue was commonly located in the deeper layers (65.6%) and most frequently in the adventitia (45.6%).

The reported pCR rates, defined as ypT0N0 commonly ranged between 20% to 35%, whereas another 20% did not respond to nCRT and residual disease is found in the remaining 55% to 60%.[3–5] Based on this substantial proportion of pCR after nCRT, an organ preserving ''watch-and-wait'' approach is currently considered and evaluated by some investigators in absence of residual tumor at clinical restaging imaging after nCRT.[22] This is obviously relevant as EC patients with a pCR seem to have a better long-term outcome with lower rates of local recurrences than those with residual tumor.[23] However, it remains difficult to reliably identify clinical complete response with current staging methods as a surrogate for pCR to avoid esophageal resection safely.[15,23,24] The up to date imaging techniques, EUS-FNA and CT or PET-CT are not sufficient enough for a proper selection in the restaged EC patients after nCRT.[14] The proposed bite to bite biopsies at EUS before surgery may contribute to improved results, but their value is controversial with a sensitivity of less than 35%.[25,26] These disappointing results seem to be in concordance with our findings that residual tumor is more frequently beyond the muscular layer, which is probably also related to the histological tumor type. In concordance with our results, another study has reported a preference of residual tumor beyond the muscular layer and adventitia in adenocarcinoma in contrast to the superficial layers in squamous cell carcinoma.[21]

Our results show only superficially located residual primary tumor in 8% to 18% of the resected ypN0 specimens. In these patients the question arises whether organ preservation using an endoscopic mucosal resection or endoscopic submucosal dissection could be an effective organ sparing approach. Though this approach was found to be feasible in a recent meta-analysis, diagnostic accuracy remains mandatory to perform these individualized treatment procedures safely.[27]

Of particular interest is the negative impact on survival in patients with ypT0N+ which seems to be determined by the N-category including the numbers of positive LNs. In line with the literature (2.9%–14%),[28,29] we found a relatively high incidence (6.4%; n = 7) of nodal metastasis in patients who seemed to have CR in the esophageal wall (ypT0N+). The residues were even within >2 positive LNs (10%), which had a significant deteriorated effect on the DFS (Fig. 1 and Table 4). Moreover, in five of the seven patients with ypT0N+, the positive LNs were within the CTV. In 3 patients there was also a discrepancy between the pathological and clinical N stage, with progression in one patient (supplementary Table 3, http://links.lww.com/SLA/C350). In addition, residual tumor was found in 14 of 15 patients with a R1 resection in or beyond the adventitia with even involved LNs (ypT+N+) in >50% (n = 8). This poor response suggests a more aggressive biological behavior in this group.

Noticeable, is the reported low rate of 3% ypT0N+ presented as isolated residues alone in single cells after CROSS in the study of Shapiro et al.[29] Moreover, the rates of positive LNs after nCRT seemed to be higher in squamous cell carcinoma patients with ypT0 (14%) as observed by Chao et al.[23,28] Schurink et al found positive LNs even in the majority of ypT0N+ patients within the radiation target fields and in one third outside the radiation field.[30] A recently performed meta-analysis of 8 studies (n = 837) in ypT0N+ EC patients showed a high rate of recurrences, both locoregional and distant with a pooled odds ratio of 4.52 and 2.65, respectively. Moreover, a significant declined 3-year and 5-year DFS and overall survival (OS) were observed with pooled odds ratio (3.90 and 517) and (3.08 and 4.27), respectively (31).

As pathologic response after nCRT is an important indicator for survival benefit, it is interesting whether additional surgery will prolong survival in approximately 60% of the EC patients with residual tumor or partial responses.[5,6] Meredith et al found lower R0 resections in the non and partial response groups (87.5% and 94.7%: $P = 0.02$) with higher rates of recurrences (28.8% and 23.7% vs 14.2%: $P = 0.04$). Moreover, both the 5-years DFS and OS increased with response level (19% and 22% vs 36% and 38% vs 52% and 52%: $P < 0.0001$).[5] A recent systematic review of Scheer et al also showed a significant decreased OS in residual tumor at 2, 3, and 5 years with 36.8%, 29%, and 22.6% compared to 93.1%, 75%, and 50% in pCR.[6] Based on these and our results additional surgery is still warranted to improve local control and survival in the partially responding patients.

In present study, less than 12% of the R0 specimens had a histologically confirmed macroscopic tumor outside the GTV and only microscopic tumor in 16.5% outside the CTV. Even after caudal expansion of the target area by 1 cm since 2014, there was no significant decrease in the incidence of microscopic residue outside the target volumes, suggesting the presence of treatment resistance or even progression due to poor tumor biology. This was also shown by the significant worse DFS in patients with macroscopic residual tumor versus only microscopic residue in the adventitia. In concordance with other studies we likewise found a worse prognosis in ypT0N+ compared with ypT0N0 patients (Fig. 2), indicating the need for potential useful biomarkers to select patients better with improved treatment options taking into account the differences in histological types.[31–33]

This study also showed that we need more innovative and protocol-based information of both pretreatment imaging and examination of the pathological specimens. Promising is the image quantification with radiomics as a potential future tool in predicting nCRT response after EC treatment.[34] Moreover, magnetic resonance imaging which is increasingly used may improve clinical staging due to technical advantages of diffusion-weighted imaging with a higher specificity for T stage end sensitivity to detect lymph node involvement.

Future efforts will improve the outcome in delivery of RT more accurately by reducing in-field relapses and better systemic treatment regimens.[35,36] Besides better imaging methods in optimizing staging, more accurate delineation of target volumes is necessary in reducing the chance of residual disease. Future use of proton radiotherapy could allow for dose escalation, aiming at less residual tumor.

CONCLUSIONS

After nCRT, 19.8% of the R0 resected specimens showed a pCR and 7.3% a ypT1aN0. In patients with ypT0, about 6.4% had nodal disease. Therefore, we should be reluctant with wait and see strategies, and aim for optimal response prediction of both primary tumor and lymph nodes. Response to nCRT significantly affected the DFS, which was significantly lower if histopathologically confirmed macroscopic tumor was detected outside the GTV and in responders with residual nodal disease.

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