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Impact of response evaluation for resectable esophageal adenocarcinoma — A retrospective cohort study

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HIGHLIGHTS

- Multimodal therapy has become a corner stone for treatment in locally advanced esophageal cancer.
- However, methods of response evaluation and guidance of treatment are still controversial.
- This manuscript provides an analysis of response evaluation and subsequent oncological outcome.
- Analysis of the existing literature comparing response prediction and oncological outcome.

ARTICLE INFO

ABSTRACT

Introduction: The standard treatment concept in patients with locally advanced adenocarcinoma of the esophagogastric junction is neoadjuvant chemotherapy, followed by tumor resection in curative intent. Response evaluation of neoadjuvant chemotherapy using histopathological tumor regression grade (TRG) has been shown to be a prognostic factor in patients with esophageal cancer. **Methods**: We assessed the impact of the various methods of response control and their value in correlation to established prognostic factors in a cohort of patients with adenocarcinoma at the gastroesophageal junction treated by neoadjuvant chemotherapy. **Results**: After neoadjuvant chemotherapy, in 56 consecutive patients with locally advanced (T2/3/4 and/or N0/N1) esophageal adenocarcinoma an oncologic tumor resection for curative intent was performed. Median follow-up was 44 months. Histopathological tumor stages were stage 0 in 10.7%, stage I in 17.9%, stage II in 21.4%, stage III in 41.1% and stage IV 8.9%. The 3-year overall survival (OS) rate was 30.3%. In univariate analysis, ypN-status, histopathological tumor stage and tumor regression grade correlated significantly with overall survival ($p = 0.022$, $p = 0.001$, $p = 0.035$ respectively). Clinical response evaluation could not predict response and overall survival ($p = 0.556$, $p = 0.254$ respectively). **Conclusion**: After preoperative chemotherapy, outcomes of esophageal carcinoma are best predicted utilizing pathological tumor stage and histologic tumor regression. Clinical response assessments were not useful for guidance of treatment.

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1. Introduction

The incidence of the adenocarcinoma of the esophagogastric junction (AEG) is growing rapidly in Western countries [1]. At diagnosis, the majority of patients have locally advanced disease with tumor penetration into the muscular wall or lymph node metastases with consecutive poor 5-year survival rate of 30% [2–4].

AEG is divided into three subtypes: type I, adenocarcinoma of the distal esophagus with the center located within 1 cm above and 5 cm above the anatomic esophagogastric junction (EGJ); type II, carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ; type III, subcardial carcinoma with the tumor center between 2 cm and 5 cm below EGJ, which infiltrates the EGJ and distal esophagus from below [5].

Treatment is performed stage dependent, in locally advanced stages usually in a multimodality treatment concept. Hereby, surgical resection remains the basis of cure: Beside R0-resection, additional factors are favoring the outcome especially a complete

histopathologic response to neoadjuvant chemotherapy indicated by improved five-year survival [6]. For early identification of non-response to neoadjuvant chemotherapy next to computed tomography (CT), esophagogastroscopy and endoscopic ultrasound (EUS) the additional response evaluation with [^{18}F] FDG–PET–CT has been introduced to identify patients without benefit from multi-modality therapy. In this regard, recent studies showed contradictionary results using PET–CT for response evaluation [7,8].

Therefore, we retrospectively evaluated the efficacy of the neoadjuvant chemotherapy aiming to explore the value of morphologic tumor regression in prediction of histopathologic response, overall (OS)- and disease-free (DFS) survival after neoadjuvant chemotherapy for locally advanced carcinoma of the esophagogastric junction.

2. Materials and methods

2.1. Patients

Criteria for inclusion in this study were the following: (1) unifocal adenocarcinoma of the esophagogastric junction; (2) tumors without metastasis and either with or without lymph node involvement on CT scan (cT3–4, cN0, M0 or cT1–4, cN1, M0); (3) tumors deemed to be resectable as a curative attempt and (4) performed neoadjuvant chemotherapy. Between 2006 and 2011, 56 consecutive patients met the inclusion criteria and their medical charts were reviewed. All included patients underwent surgery with curative intent after neoadjuvant chemotherapy for locally advanced disease at the Division of General and Visceral Surgery at the University hospital Tübingen.

2.2. Staging

According to the national guidelines, resectability was determined through thoracoabdominal computed tomography scans and esophageal endoscopic ultrasonography (EUS). The tumor size in the computed tomography scans was documented before and after chemotherapy as well as the size of enlarged peritumoral lymph nodes.

2.3. Classification

For tumor classification the known definition of Siewert et al. was used [9,10]. Using this classification there were 20 patients with an AEG I, 21 patients with an AEG II and 15 with a tumor classification AEG III.

2.4. Chemotherapy

Patients were treated with neoadjuvant chemotherapy with 35 patients receiving 5-fluorouracil/leucovorin–oxaliplatin–docetaxel (FLOT), 10 patients receiving Cisplatin–5-FU–leucovorin (PLF), 3 patients receiving Oxaliplatin–leucovorin–5-FU (FOLFOX), 3 patients receiving epirubicin–oxaliplatin–cabecitabine (EOX), 3 patients receiving epirubicin–cisplatin–fluorouracil (ECF), and 2 patients receiving a docetaxel–cisplatin–fluorouracil (DCF) combination. In the postoperative setting all patients got adjuvant chemotherapy.

2.5. Surgical treatment

If the majority of tumor was in the distal esophagus (Siewert I/II), the operation was carried out as a two-phase abdominal and right chest approach for enbloc subtotal esophagectomy followed by a double-stapled esophagogastric anastomosis. Extended D1

Table 1
Shows the characteristics of 56 patients with adenocarcinoma of the esophagus.

Parameter	No. (%) of patients
Median age (lower/upper quartile)	61 (54/71)
Gender	
Male	51 (91.1)
female	5 (8.9)
Localization	
AEG I	20 (35.7)
AEG II	21 (37.5)
AEG III	15 (26.8)
cT category	
cT2	10 (17.9)
cT3	43 (76.8)
cT4	3 (5.4)
cN category	
cN0	13 (23.2)
cN+	43 (76.8)
Grading (bei ED)	
G1	1 (1.8)
G2	30 (53.6)
G3	25 (44.6)
pT category	
yp stage 0	6 (10.7)
yp stage I	10 (17.9)
yp stage II	12 (21.4)
yp stage III	23 (41.1)
yp stage IV	5 (8.9)

resection with dissection of the celiac nodes was performed. If the majority of tumor was in the stomach (Siewerts type III), a gastrectomy was performed along with the esophagectomy through an abdominal incision. The proximal jejune intestine was used as conduit and anastomosed side-to-end to the remaining esophagus. The distal anastomosis was done as a Roux-en-y reconstruction.

2.6. Image analysis according to RECIST

Unidimensional measurements of the long axis of tumors on coronal CT images were performed using a caliper on the monitor, with reference to multiplanar reconstruction images (axial, coronal, and sagittal imaging) and enhanced CT images. Objective therapeutic responses according to RECIST 1.1 [11] were as follows: complete response (CR) was disappearance of tumor foci for at least 4 wk; partial response (PR) was a decline of at least 30% in tumor diameter for at least 4 wk; stable disease was neither PR nor progressive disease (PD); and PD was at least a 20% increase in tumor diameter for at least 4 wk.

2.7. Histomorphologic staging and grading of tumor regression

Two independent pathologists from the Department of Pathology at the University of Tübingen confirmed the histological diagnosis of the resected tissue. The results were classified according to the TNM-classification, including the grade of regression as described before [12]: Complete tumor regression (regression grade 1a); marked regression (less than 10% viable tumor, regression grade Ib); regression to 10–50% remaining viable tumor (regression grade II) and bad regression (more than 50% viable tumor remaining, regression grade III).

2.8. Statistical analysis

Statistical analysis was done using SPSS software, version 21 (SPSS Inc., Chicago, IL, USA). Results are reported as median and lower and upper quartiles. Survival curves were calculated using Kaplan–Meier analysis and the log rank test. For testing significant

differences between the examined groups, Student's *t*-test and the Mann–Whitney *U* test was used. A significance level <0.05 was defined.

3. Results

3.1. Study population

Between January 2006 and April 2011 fifty-six patients with an esophageal adenocarcinoma underwent tumor resection with curative intent after a preoperative chemotherapy, 51 males (91%) and 5 females (9%). Median age was 61 years. In 20 patients we found AEG I, in 21 patients AEG II and in 15 patients AEG III. Initial clinical tumor staging showed 10 patients with cT2, 43 patients with cT3 and 3 patients with cT4. Nodalpositivity (cN+) was seen in 43 patients (76.8%). In the postoperative tumor staging, 6 patients showed yp-stage 0, 10 patients showed yp-stage I, 12 patients showed yp-stage II, 23 patients showed yp-stage III and 5 patients showed yp-stage IV. Table 1 shows the patients' characteristics in detail.

3.2. Surgical results

In 44 patients an abdomino-thoracic subtotal esophagectomy with an esophagojejunostomy to restore gastrointestinal continuity and lymphadenectomy was performed; in 12 patients a transhiatal extended total gastrectomy was done, including a radical lymph node resection followed by an esophagojejunostomy. 47 patients (83.9%) showed R0-resection, 8 patients (14.3%) showed microscopical residual tumor (R1-resection) and 1 patient had macroscopical residual tumor (R2-resection). There was no perioperative death documented (Table 2).

3.3. Treatment response assessments

3.3.1. Downstaging of tumor and lymph nodes

In the ypT-category complete tumor response was seen in 6 patients (10.7%), ypT1 in 3 patients (5.4%), ypT2 in 19 patients (34%), ypT3 in 26 patients (46.4%) and ypT4 in 2 patients (3.6%). In the ypN-category nodalpositivity was seen in 32 patients (57.1%) and nodalnegativity in 24 patients (42.9%). Histomorphologic tumor regression grading showed major response (Becker I) in 13

patients (23.2%), intermediate response (Becker II) in 7 patients (12.5%) and non-response (Becker III) in 36 patients (64.3%) (Table 2).

3.3.2. Histological

With 8 patients (40%) from AEG I, 4 patients (19%) from AEG II and 1 patient (6.7%) from AEG III showing major histopathological response, tumor localization did not affect histological outcome (Table 3).

3.3.3. CT and PET–CT (Table 4)

Used staging modalities for response monitoring of neoadjuvant chemotherapy were heterogenous: In 18 patients PET–CT was used, in 54 patients CT-scan was performed. In CT-staging and restaging after neoadjuvant chemotherapy tumor partial response was seen in 35 (64.8%) patients, no change was seen in 16 (29.6%) patients and progression of disease was seen in 3 (5.6%) patients; regarding lymph node status, partial response was seen in 31 (57.4%) patients, no change in 20 (37.0%) patients and progression of disease was seen in 3 (5.6%) patients. In PET/CT-staging and restaging after neoadjuvant chemotherapy tumor response was seen in 12 (66.67%) patients, no change was seen in 3 (16.67%) patients and progression of disease was seen in 3 (16.67%) patients; regarding lymph node, response was seen in 9 (50.0%) patients, no change in 8 (44.4%) patients and progression of disease was seen in 1 (5.56%) patient. Imaging modalities taken together showed in 38 patients (67.9%) partial response, in 8 patients (14.3%) no change and progression of disease in 8 patients (14.3%).

The imaging modalities showed no clearly predictable response in comparison to the final histological results ($p = 0.556$) (Table 4).

3.4. Survival and relapse patterns

During the study period, 26 (46.4%) patients died. 31 (55.4%) patients experienced recurrence. The overall median survival was 44 month with 3-years survival rates of 30.3% ($N = 15$) (Fig. 1). Univariate analysis of survival showed no statistical influence of clinical tumor (cT) or lymph node (cN) status ($p = 0.810$, $p = 0.114$). The pathological tumor (ypT) status after neoadjuvant chemotherapy showed as well no statistically relevant influence with a clear trend to improved survival the lower the tumor status ($p = 0.077$). Resection status (R-category) ($p = 0.001$), grade of histomorphologic tumor regression ($p = 0.035$) (Figs. 3 and 4), pathological lymph node (ypN) status ($p = 0.022$) and pathological stage (UICC) ($p = 0.001$) (Fig. 2) had significant influence on survival (Table 5).

The prevalence of tumor recurrence was clearly predictable classifying into major (grade Ia/b) and minor histomorphologic (II, III) regression ($p = 0.004$). The regression grade has a significant influence on the incidence of tumor recurrence after tumor resection (Table 6).

4. Discussion

The presented study shows the methods of staging, the evaluation of histopathological response and the outcome of patients

Table 2
Shows the surgical treatment and the response to treatment.

Parameter	No. (%)of patients
Operation:	
- Abdomino-thoracic esophagectomy	44 (78.9)
- Transhiatal extended total gastrectomy	12 (21.1)
Resection	
R0	47 (83.9)
R1	8 (14.3)
R2	1 (1.8)
ypT category	
ypT0	6 (10.7)
ypT1	3 (5.4)
ypT2	19 (34)
ypT3	26 (46.4)
ypT4	2 (3.6)
ypN category	
ypN0	24 (42.9)
ypN+	32 (57.1)
Classification of histomorphologic tumor regression	
I (1a/b)	13 (23.2)
II	7 (12.5)
III	36 (64.3)

Table 3
Shows the tumor localization in correlation to the histopathological therapy response.

Tumor type	Becker 1a/b N (%)	Becker 2/3 N (%)
AEG I	8 (40)	12 (60)
AEG II	4 (19)	17 (81)
AEG III	1 (6.7)	14 (93.3)

Table 4
Shows the apparative response evaluation in correlation to the histomorphological response evaluation.

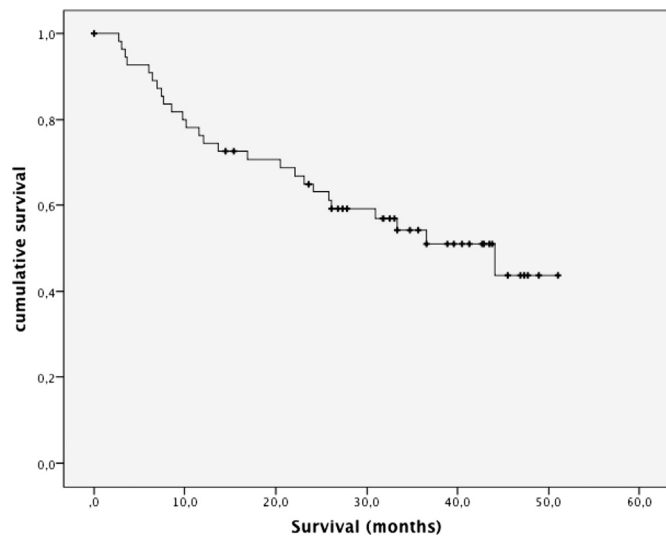| Parameter			N (%)	p-value
CT-scan	T		PR 35 (64.8)	0.616
			NC 16 (29.6)	
			PD 3 (5.6)	
	N		PR 31 (57.4)	0.533
			NC 20 (37.0)	
			PD 3 (5.6)	
PET–CT	T		PR 12 (66.67)	0.442
			NC 3 (16.67)	
			PD 3 (16.67)	
	N		PR 9 (50)	0.613
			NC 8 (44.4)	
			PD 1 (5.6)	
CT-scan and/or PET–CT	T and/or N		PR 38 (70.4)	0.556
			NC 8 (14.8)	
			PD 8 (14.8)	

Fig. 1. Shows the overall survival of all patients ($n = 56$). The overall median survival was 44 month with 3-years survival rates of 30.3% ($N = 15$).
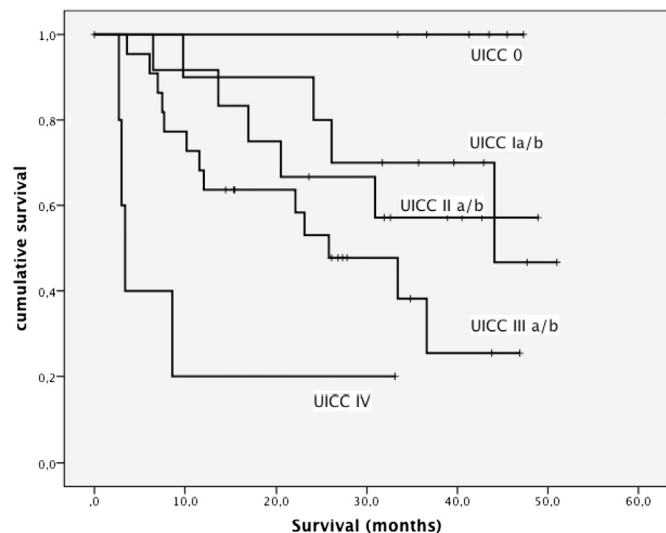
undergoing neoadjuvant chemotherapy for resectable adenocarcinoma at the gastroesophageal junction and delivers three main results: Firstly, clinical response evaluation is not highly associated with pathological response. Secondly, in addition to radical resection, histopathological response and nodalnegativity in the histological workup were indicators of improved survival. Finally, the analyzation of histopathological tumor response in comparison to outcome showed two main streams with better outcome in patients with 'major tumor regression' and worse outcome in patients with 'minor tumor regression'.

The limited number of patients has to be acknowledged. Furthermore, the accuracy of PET–CT-evaluation is limited due to the small number of patients out of this subgroup.

The main step in the multimodal treatment concept for cure of adenocarcinoma at the esophagogastric junction remains surgical resection with lymph node dissection. Transhiatal or combined thoracoabdominal esophagectomy is traditionally regarded as standard treatment for patients with locally advanced esophageal cancer in combination with neoadjuvant chemotherapy [13]. For further improvement of survival in multimodality treatment approach, the introduction of early response evaluation using PET–CT was introduced. The feasibility of [18F] FDG–PET–CT in predicting response to neoadjuvant chemotherapy in esophageal adenocarcinoma, was presented in the MUNICON II trial by Lordick et al. [14]. They showed that regression of tumor FDG metabolism during neoadjuvant chemotherapy could serve to guide patients into either a neoadjuvant and surgery-, or a surgery-only group.

Otherwise, the German Advanced Surgical Treatment Study Group stated that there is currently no universally accepted, reproducible, and reliable method for response assessment after neoadjuvant treatment of esophageal carcinoma. This is due in part to differing neoadjuvant therapy regimens, differing methods for response assessment, e.g., CT scan, endoscopy, endoscopic ultrasound or PET–CT, and differing time frames for response control, which leads to varying definitions of "response" and "nonresponse" [15].

This is a retrospective single institution analysis of 56 consecutive patients with locally advanced esophageal carcinoma treated with neoadjuvant chemotherapy. In this retrospective evaluation, we investigated the outcome of patients with adenocarcinoma at the gastroesophageal junction and the impact of response evaluation after neoadjuvant chemotherapy followed by surgical
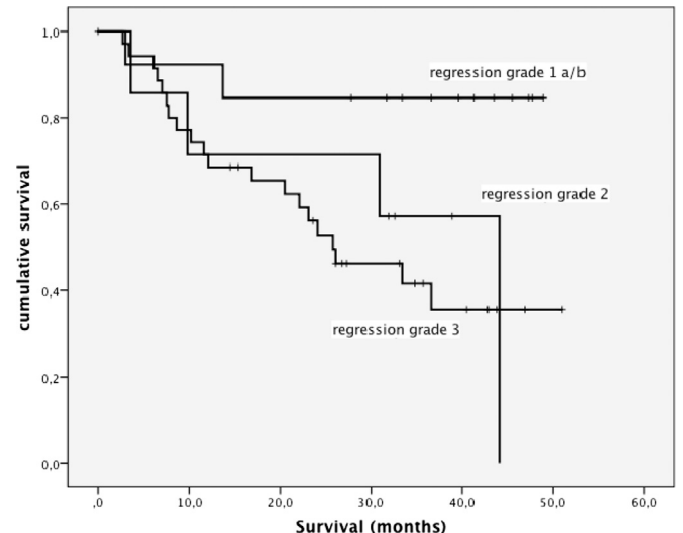

Fig. 2. Shows the survival in correlation to the pathological tumor stage UICC.

Fig. 3. Shows the survival in correlation to the histopathological tumor regression.
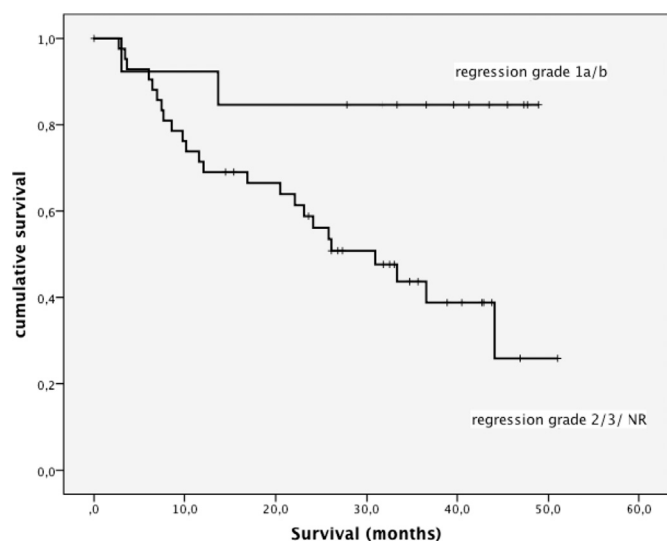
Fig. 4. Shows the survival in correlation to major (Ia/b) and minor (II, III) histopathological tumor regression.

resection. To evaluate prognostic factors for patients with locally advanced esophageal carcinoma, we reviewed several clinical and histological parameters. There are different staging modalities and methods of response evaluation: The combination of CT, endoscopy

Table 5
Shows the univariate cox regression analysis of survival in month.

Parameter	No.(%) of patients	Median survival (month)	p-value
Clinical T status			0.810
cT1-2	—	—	
cT2	10 (17.9)	44	
cT3	43 (76.8)	33	
cT4	3 (5.4)	37	
Clinical N status			0.114
cN0	13 (23.2)	44	
cN+	43 (76.8)	33	
Classification of histomorphologic tumor regression			0.035
Ia/b	13 (23.2)	43 (Mean survival)	
II	7 (12.5)	44	
III	35 (64.3)	26	
ypT-category			
ypT0	6 (10.7)	—	
ypT1	3 (5.4)	—	0.077
ypT2	19 (34)	26	
ypT3	26 (46.4)	33	
ypT4	2 (3.6)	23	
ypN category			
ypN0	24 (42.9)	42 (Mean survival)	0.022
ypN+	31 (57.1)	23	
Pathological stage (UICC)			
ypStage 0	6 (10.7)	—	0.001
ypStage I	10 (17.9)	44	
ypStage II	12 (21.4)	36	
ypStage III	23 (41.1)	26	
ypStage IV	5 (8.9)	3	
R category			
R0	46 (83.9)	44	0.000
R1	8 (14.3)	6	
R2	1 (1.8)	—	

R category, residual tumor category according to UICC; grade Ia complete response (pCR, ypT0); grade Ib) nearly complete response (NCR) with 10% VRTCs, grade II: 10%–50% VRTCs (partial response), grade III 50% vital residual tumor cells (VRTCs). ypT/ypN, histopathologic tumor/lymph node categories following neoadjuvant treatment according to UICC.

Table 6
Shows the major and minor histomorphological response and prevalence of tumor recurrence.

Grade of regression	No tumor recurrence N [%]	Tumor recurrence N [%]	P value
I a/b	14 (73.7)	5 (26.3)	0.004
II and III	12 (32.4)	25 (67.6)	

and endoscopic ultrasound (EUS) for preoperative staging is considered as best preoperative clinical work-up. More ambiguous are the methods of consecutive response evaluation. Numerous reports showed conflicting results with various studies showing PET/CT-improved prediction possibility of response and survival [16], and others without [8]. Regarding response evaluation, in our study the histopathological effect could not be concluded by radiological methods.

Main factors for survival in our study were surgical resection status, histopathological regression grading and pathological tumor stage. Complete remission in primary tumor and lymph nodes (ypT0 ypN0) was the best possible pathological outcome of chemotherapy. The observed percentage of patients with a pathological complete response was 10.7%. The prevalence of tumor recurrence was clearly predictable classifying into major (grade Ia/b) and minor histomorphologic (II, III) regression ($p = 0.004$). Major response was seen in 23.2% of patients. The rate of histopathologic non-responder was 64%. In these patients the overall survival was significantly reduced.

In locally advanced esophageal carcinoma multimodality treatment approach shows significant better survival. As response to preoperative treatment is the most important prognostic factor future therapy should optimize preoperative treatment. Whether esophagogastric-junction adenocarcinomas should be treated by perioperative chemotherapy or preoperative chemoradiotherapy is under debate. The actual treatment concept using perioperative chemotherapy is based on the results of the MAGIC [6] and ACCORD [17] trial. Contrary showed the POET trial including patients with esophageal and esophagogastric-junction adenocarcinomas and randomizing into preoperative chemotherapy or chemoradiotherapy [18]. In this study a clear trend towards survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy was shown.

5. Conclusion

1) Clinical response evaluation is not highly associated with pathological response and should not be used for clinical decision making on delaying/avoiding surgery.
2) Evaluation of histopathological tumor response should classify all patients into 'major tumor regression' and 'minor tumor regression'.
3) In addition to radical resection, histopathological response and nodalnegativity in the histological workup were indicators of improved survival.

Ethical approval

Not necessary because of the study design.

Author contribution

RB: conceived and designed the study, collated the information, analyzed and interpreted the data, searched the literature, wrote the paper, approved the final version of the manuscript.

JB: did statistical evaluation, helped in literature search and preparing the manuscript, provided critical revisions, approved the final version of the manuscript.

AH: collected and analyzed the data, approved the final version of the manuscript.

JS: provided critical revisions, approved the final version of the manuscript.

GS: provided critical revisions, approved the final version of the manuscript.

AK: provided critical revisions, approved the final version of the manuscript.

RL: analyzed and interpreted the data, provided critical revisions that were important for the intellectual content, approved the final version of the manuscript.

Competing interests

All authors read and approved the final version of the manuscript. The authors declare that they have no competing interests. No funding.

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