Gastric Cancer (2014) 17:478–488
DOI 10.1007/s10120-013-0296-0

ORIGINAL ARTICLE

Interim endoscopy results during neoadjuvant therapy for gastric cancer correlate with histopathological response and prognosis

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Received: 18 April 2013 / Accepted: 14 August 2013 / Published online: 1 September 2013

Abstract
Background Neoadjuvant chemotherapy for locally advanced gastric cancer leads to major histopathological response in less than 30 % of patients. Data on interim endoscopic response assessment do not exist. This exploratory prospective study evaluates early endoscopy after 50 % of the chemotherapy as predictor for later response and prognosis.
Methods Forty-seven consecutive patients were included (45 resected; 33 R0 resections). All patients received baseline endoscopy and CT scans, after 50 % of their chemotherapy (EGD-1, CT-1) and after completion of chemotherapy (EGD-2, CT-2). Interim endoscopic response (EGD-1) was assessed after having received 50 % (6 weeks) of the planned 12 weeks of neoadjuvant chemotherapy. Post-chemotherapy response was clinically assessed by a combination of CT scan (CT-2) and endoscopy (EGD-2). Histopathological response was determined by a standardized scoring system (Becker criteria). Endoscopic response was defined as a reduction of >75 % of the tumor mass.
Results Twelve patients were responders at EGD-1 and 13 at EGD-2. Nine patients (19.1 %) were clinical responders and 7 patients (15.6 %) were histopathological responders after chemotherapy. Specificity, accuracy, and negative predictive value of the interim EGD-1 for subsequent histopathological response were 31/38 (82 %), 36/47 (76 %), and 31/33 (93 %); and for recurrence or death, 28/30 (93.3 %), 38/47 (80.9 %), and 28/35 (80.0 %). Response at EGD-1 was significantly associated with histopathological response ($p = 0.010$), survival ($p < 0.001$), and recurrence-free survival ($p = 0.009$).
Conclusions Interim endoscopy after 6 weeks predicts response and prognosis. Therefore, tailoring treatment

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according to interim endoscopic assessment could be feasible, but the findings of this study should be validated in a larger patient cohort.

Keywords Gastric cancer · Neoadjuvant therapy · Early response evaluation · Endoscopy · Prognosis

Introduction

Neoadjuvant therapy is nowadays established as the standard of care in the treatment of locally advanced gastric cancer in Europe [1–3]. However, an objective histopathological response with less than 10 % residual tumor cells after preoperative chemotherapy can be found in only 20–30 % of the patients suffering from gastric cancer at the time of resection [4]. Histopathological regression is accepted to be strongly associated with prognosis in gastric cancer [4, 5], although 30 % of those patients will present with recurrence subsequently [6]. Histopathological classification of regression is considered the gold standard for response assessment; nevertheless, it seems to have several limitations. Despite an objective quantification of residual tumor cells, it remains dependent on the standard of histopathological workup and the experience of the pathologist. Furthermore, its evaluation after resection allows only for modification of postoperative adjuvant treatment. The prognostic impact of response to neoadjuvant therapy was first published by Lowy et al. [7], including both histopathological and clinical response. Since then most studies have been based on histopathological response because it was estimated to be more objective than the evaluation of clinical response by endoscopy, endoluminal ultrasound, and computed tomography (CT) scan [2, 8, 9]. However, data of clinical response after the end of neoadjuvant treatment also appear promising in respect to association with histopathological response as well as prognosis [10–14]. In all phase II trials conducted by our group, an early clinical response evaluation by endoscopy and CT scan between the first and second cycle of neoadjuvant chemotherapy regimen (usually 6 weeks) was included [10, 12, 15–21], but the value of early endoscopic response has not been reported in regard to an association with definitive clinical and histopathological response and prognosis. Because most patients do not achieve a major response during the preoperative period of chemotherapy, lasting up to 3 months depending on the regimen applied [1, 2, 5, 10, 16, 22], an early evaluation during neoadjuvant treatment would be of utmost interest to tailor therapy according to the individual response. Data on tailoring treatment based on response early during preoperative treatment are so far only available for adenocarcinomas of the esophagogastric junction type I and II according to Siewert's classification based on metabolic response assessment after 2 weeks of chemotherapy [23, 24]. However, 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) seems not to be informative for early response in true gastric cancer [21]. For clinical reasons, the early and correct identification of nonresponding patients would be of interest to avoid a relatively long-lasting, toxic, and ineffective chemotherapy [18, 19, 23].

To enable integration of a simple interim clinical response assessment by endoscopy in future clinical trials, we tested the efficacy of an interim endoscopy after 50 % of chemotherapy dose (here mostly after 6 weeks of therapy) regarding its association with subsequent histopathological response and prognosis in a well-defined neoadjuvantly treated gastric cancer cohort [21] with long-term follow-up. Further aims were evaluation of the association of interim endoscopy with other staging examinations at the respective time points, and post-therapeutic clinical response by the combination of CT scan and endoscopy.

Patients and methods

Population

Forty-seven consecutive patients with histologically proven locally advanced gastric cancer diagnosed between January 2006 and February 2007 were included (Tables 1, 2; Fig. 1). Forty-five of these patients have been the subject of previously reported studies with a shorter follow-up under the aspect of FDG/FLT response evaluation in gastric cancer [21]. Two patients who were integrated in the intention-to-treat analysis did not undergo the initial 3-[F-18]fluoro-3-deoxythymidine (FLT)-PET, so that they were not included in the FDG/FLT analysis but were included in this study. All patients gave written informed consent and the study received approval by the local ethics committee of the Technische Universität München.

Chemotherapy (CTx)

All patients had a Karnofsky performance status of >80. Most patients received two cycles of platinum, 5-FU, and leucovorin-based chemotherapy [10] with or without the addition of paclitaxel [12] lasting 36 days each with a 2-week interval between the two cycles. One patient had an additional aggressive B-cell non-Hodgkin lymphoma and therefore received rituximab/CHOP. Detailed chemotherapy regimens and reasons for discontinuation are shown in Table 1.

Endoscopy (EGD) and computed tomography (CT)

Staging endoscopy was performed by an experienced endoscopist before the start of neoadjuvant treatment. All patients received a CT scan of the thorax and abdomen at

Table 1 Patient characteristics

Characteristic	Number	Percent (%)
Age (years)		
Median	64	
Range	36–77	
Sex		
Male	32	68.1
Female	15	31.9
Localization		
Proximal	30	63.8
Middle	9	19.1
Distal	8	17.0
Grading		
G2 (moderately differentiated)	11	23.4
G3/4 (poorly differentiated)	36	74.5
Laurén classification		
Intestinal	16	34.0
Diffuse	19	40.4
Mixed	12	25.5
cTNM		
T3N0M0	2	4.3
T3N1M0/x	45	95.7
Chemotherapy regimens		
Capecitabine/oxaliplatin	1	2.1
EOX	1	2.1
OLF	7	14.9
PLF	27	57.4
PLF/OLF	1	2.1
Rituximab/CHOP	1	2.1
Cetuximab/oxaliplatin/5-FU/ folinic acid	1	2.1
Taxol/PLF	8	17.0
Discontinuation of chemotherapy		
No	33	70.2
Yes	14 (1 during second cycle)	29.8
Reasons for discontinuation of chemotherapy		
Non-response	5	10.6
Non-response + toxicity	5	10.6
Toxicity	2 (1 during second cycle)	4.3
Patient refusal	1	2.1

baseline. CT (CT-1) and endoscopy (EGD-1) were repeated after the first 6 weeks of chemotherapy (50 % of the projected chemotherapy duration) and after completion of chemotherapy (CT-2 and EGD-2). Data were prospectively documented. The written results of all endoscopies including the data of video sequences and CT scans are available from the authors.

Table 2 Response rates

Assessment	Number	Percent (%)
EGD-1[a]		
Partial response	12	25.5
Minor response	27	57.4
No change	6	12.8
Progressive disease	2	4.3
Total responders	12	25.5
Total nonresponders	35	74.5
EGD-2[a]		
Partial response	13	38.2
Minor response	17	50
No change	2	5.9
Progressive disease	2	5.9
Total responders	13	38.2
Total nonresponders	21	61.8
CT-1[b]		
Partial response	12	25.5
Minor response	15	31.9
No change	19	40.4
Progressive disease	1	2.1
Total responders	12	25.5
Total nonresponders	35	74.5
CT-2[b]		
Partial response	9	26.5
Minor response	9	26.5
No change	14	41.2
Progressive disease	2	5.9
Total responders	9	26.5
Total nonresponders	25	73.5

[a] Esophagoduodenoscopy (EGD) after 50 % (EGD-1) and completed (EGD-2) neoadjuvant chemotherapy

[b] Computed tomography after after 50 % (CT-1) and completed (CT-2) neoadjuvant chemotherapy

Endoscopic response evaluation

Response assessment by endoscopy was performed as interim analysis after 6 weeks (EGD-1) and after the completion of chemotherapy after 12 weeks (EGD-2). Criteria for endoscopic response were similar to those of the Japanese guidelines [25], which define endoscopic response as a dramatic regression such as flattening, corresponding to about a 75 % decrease in our study. Detailed criteria are shown in Table 3. All endoscopies were video endoscopies and were presented at the interdisciplinary tumor board.

Clinical response evaluation

Clinical response was defined by the interdisciplinary tumor board of the Technische Universität München based

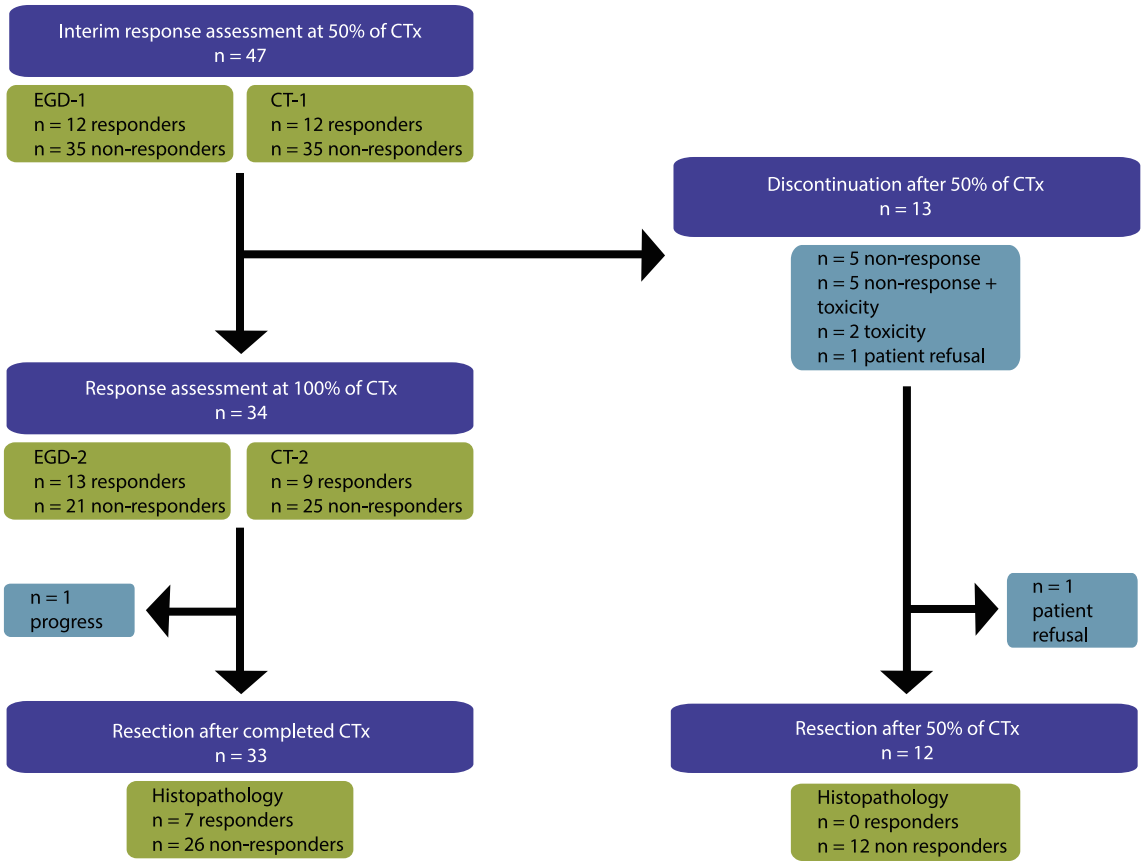

Fig. 1 Patients, response, and treatment. *EGD* esophagogastroduodenoscopy, *CTx* chemotherapy; EGD-1 and CT-1, after one cycle (6 weeks) of neoadjuvant therapy; EGD-2 and CT-2, after two cycles (12 weeks)

Table 3 Response definitions

Clinical response	Endoscopy	CT scan
CR = complete response	No residual tumor confirmation after 6 weeks	No residual tumor
PR = partial response	Decrease of intraluminal tumor >75 %	>50 % decrease of wall thickness
MR = minor response	Decrease of intraluminal tumor 75–25 %	50–25 % decrease of wall thickness
NC = no change	25 % decrease to 25 % increase of intraluminal tumor	25 % decrease to 25 % increase of wall thickness
PD = progressive disease	Increase >25 % of intraluminal tumor	Increase >25 % of wall thickness or distant metastases

CR complete response, *PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease

on a combination of endoscopy and CT scan at interim evaluation (clinical response-1) after 6 weeks, and after neoadjuvant treatment before resection (clinical response-2) at 12 weeks without knowledge of the histopathological workup. Responders were defined by at least a partial response to both endoscopy (<75 % residual tumor) and CT scan (decrease >50 % in wall diameter). Detailed criteria for clinical response evaluation are shown in Table 3.

Histopathological response evaluation

Resected specimens were worked up in a highly standardized manner and analyzed histopathologically by two experienced pathologists (K.B., R.L). ypTNM staging was performed according to UICC, 6th edition. The scoring system of Becker et al. [26] was applied. Patients with less than 10 % residual tumor were classified as responders.

Surgery

Resections were performed according to tumor localization and local standard: tumors located at the esophagogastric junction were treated by transhiatal extended gastrectomy and extended D2 lymphadenectomy including left retroperitoneal lymphadenectomy [10, 21], or abdominothoracic esophageal resection with gastric pull-up and intrathoracic

anastomosis [20]. Tumors of the middle and distal gastric third were treated with total or subtotal gastrectomy and D2 lymphadenectomy [5, 10]. No adjuvant chemotherapy regimen was administered.

Follow-up

Patient follow-up for monitoring of recurrence was conducted by spiral CT scan of the chest and abdomen, and endoscopy every 3 months during the first year, every 6 months during the second and third year, and subsequently every 12 months on an outpatient basis. One patient was lost to follow-up after 6.3 months.

Statistical analysis

For reasons of the explorative and retrospective nature of this trial, no regular sample-size calculation was performed. Statistical analyses were performed using PASW Statistics software (version 18.0; SPSS, Chicago, IL, USA). Quantitative values are expressed as mean ± standard deviation, median, and range. Survival curves were estimated according to the Kaplan–Meier method. Fisher's exact test or the χ^{TM} χ^2 test was used for comparison of frequencies, and Spearman correlation coefficients were calculated to quantify bivariate correlations. All statistical tests were conducted two sided, and a p value less than 0.05 was considered to indicate statistical significance. Overall survival was calculated from diagnosis to death, recurrence-free survival from resection to recurrence, and event-free survival from diagnosis to recurrence, progression, or death. No imputation of missing data was planned; the analysis was done at the full cases population.

Results

A total of 47 neoadjuvantly treated patients with locally advanced gastric cancer (clinical stage T3 or 4 N0 or N+) were analyzed: 24 patients are alive, 7 with recurrence. The median follow-up for the surviving patients is 65.8 (6.3–82.5) months; median survival is 28.5 months. Patient characteristics are shown in Tables 1, 2.

Interim endoscopy (EGD-1) after 50 % of chemotherapy in comparison with clinical and histopathological response

All patients underwent EGD-1 and CT-1. Twelve (25.5 %) of the patients were judged to be endoscopic responders (Table 2). In the combination of both examinations, 11 (23.4 %) were classified as clinical responders and 36 (76.6 %) as nonresponders. In 13 patients, chemotherapy was discontinued after 50 % of the projected chemotherapy dose: all were endoscopic and clinical nonresponders (Fig. 1). Twelve of these patients underwent resection and all showed histopathological non-response; 1 patient refused the operation. Thirty-four patients continued with chemotherapy and had preoperative restaging with EGD-2 and CT-2 (Table 2). Preoperative endoscopy classified 13 (27.7 %) as responders. Eventually, 9 (19.1 %) patients were classified in combination with CT criteria as clinical responders and 38 (80.9 %) as nonresponders, including the 13 nonresponding patients who discontinued chemotherapy. One patient was excluded from resection because of progression with peritoneal carcinomatosis, and of the other 33 patients, 7 were histopathological responders and 26 nonresponders (Fig. 1). Analyzing only the 24 resected clinical nonresponders after complete chemotherapy, 22 (91.9 %) were also histopathological nonresponders. Histopathological response showed a trend toward improved survival ($p = 0.068$), whereas clinical response after

Table 4 Association of EGD-1 with other examinations at different time points

	EGD-1[a]			
	NR	R	p	Spearman
CT-1[b]				
NR	34	1	<0.001	0.888
R	1	11		
Clin Resp-1[c]				
NR	35	11	<0.001	0.944
R	0	1		
EGD-2[a]				
NR	19	2	<0.001	0.685
R	3	10		
CT-2[b]				
NR	21	4	<0.001	0.673
R	1	8		
Clin Resp-2[c]				
NR	34	4	<0.001	0.707
R	1	8		
Histopathological response				
NR	31	7	0.010	0.434
R	2	5		

[a] Esophagoduodenoscopy after 50 % (EGD-1) and completed (EGD-2) neoadjuvant chemotherapy

[b] Computed tomography after 50 % (CT-1) and completed (CT-2) neoadjuvant chemotherapy

[c] Clinical response after 50 % (Clin Resp-1) and completed (Clin Resp-2) neoadjuvant chemotherapy

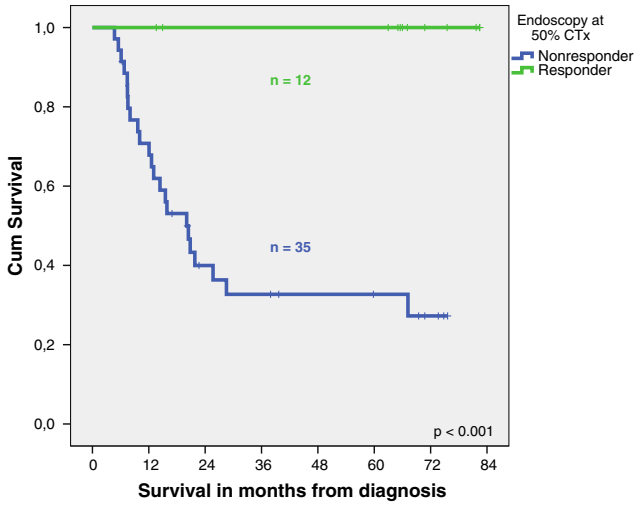

Fig. 2 Overall survival based on log-rank test. *CTx* chemotherapy, *Cum* cumulative

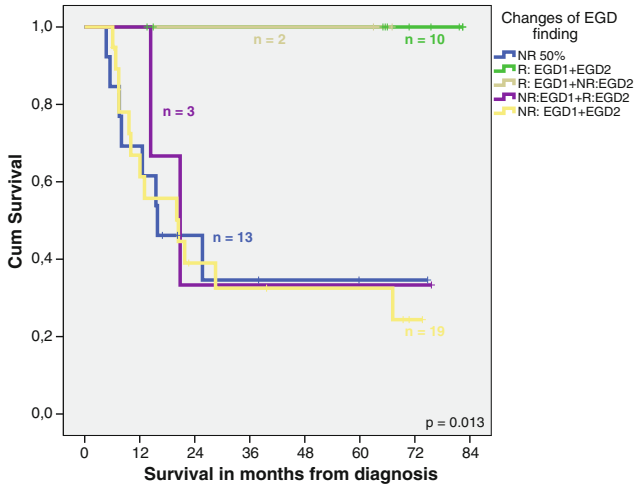

Fig. 3 Patient survival according to detailed response based on the combination of EGD-1 and EGD-2. Results are shown as Kaplan–Meier curves. *p* value based on log-rank test. NR 50 % = nonresponders who discontinued chemotherapy after 6 weeks, *EGD* esophagogastroduodenoscopy, *R* responders, *NR* nonresponders, *1* after one cycle, *2* after completion

neoadjuvant treatment was significantly associated with survival ($p = 0.014$).

Changes from EGD-1 to EGD-2 were relatively rare. Five of the patients changed in their endoscopic response: two (4.3 %) shifted to endoscopic non-response and three (6.4 %) shifted to endoscopic response. The response evaluation in EGD-1 was significantly associated with the other staging examinations at different time points as well as clinical and histopathological response evaluation (Table 4).

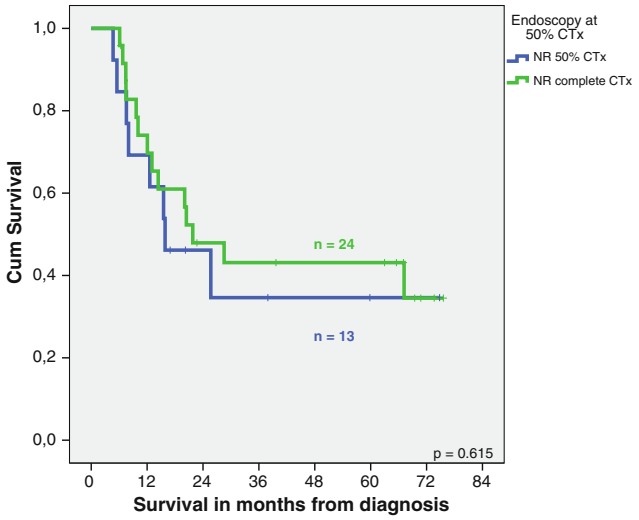

Fig. 4 Survival of nonresponders according to chemotherapy dose. Results are shown as Kaplan–Meier curves. *p* values based on log-rank test. NR 50 % = nonresponders who discontinued chemotherapy after 6 weeks, *NR* nonresponders with complete chemotherapy

Sensitivity, specificity, accuracy, PPV, and NPV of interim endoscopy (EGD-1)

Sensitivity of EGD-1 to predict later histopathological response was 5/7 (71.4 %), specificity was 31/38 (81.6 %), accuracy was 36/47 (76.0 %), positive predictive value (PPV) was 5/12 (41.7 %), and negative predictive value (NPV) was 31/33 (93.9 %).

EGD-1 was associated with a later event (recurrence, progression, or death) with a sensitivity of 10/17 (58.8 %), a specificity of 28/30 (93.3 %), an accuracy of 38/47 (80.9 %), a PPV of 10/12 (83.3 %), and an NPV of 28/35 (80.0 %).

Prognosis

Response at interim endoscopy (EGD-1) was significantly associated with prognosis ($p < 0.001$) (Fig. 2). Furthermore, early response evaluation in CT-1 ($p = 0.004$) and clinical response evaluation by a combination of EGD-1 and CT-1 after 50 % of the projected chemotherapy ($p = 0.001$) were associated with prognosis. The analysis of the changes of endoscopic response from EGD-1 to EGD-2 shows that all patients with response at EGD-1 are still alive, whereas two of three patients with secondary endoscopic response have already died. The differences between the groups are statistically significant ($p = 0.013$) (Fig. 3), but have to be interpreted with caution because the sample sizes are very small.

The prognosis of the 13 patients who discontinued chemotherapy after the interim assessment was not inferior

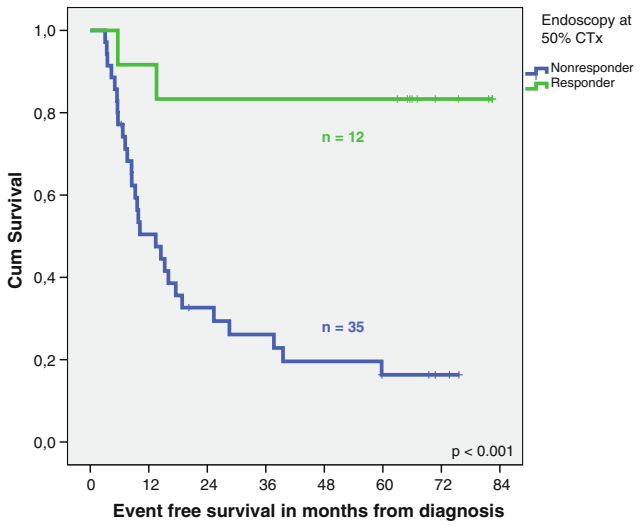

Fig. 5 Event-free survival based on log rank test. *CTx* chemotherapy

compared with the 24 patients with clinical non-response completing the preoperative chemotherapy ($p = 0.615$) (Fig. 4).

Analyzing only the completely resected patients, response at interim endoscopy (EGD-1) remained statistically significant with respect to overall survival ($p = 0.004$). Additionally, response at EGD-1 remained prognostically relevant, analyzing event-free survival for all patients ($p < 0.001$) (Fig. 5), event-free survival for the completely resected patients ($p = 0.008$), and recurrence-free survival for the completely resected patients ($p = 0.009$).

The prognostic influence of the interim endoscopy (EGD-1) was lost in tumors localized in the middle and distal third and with G1/G2 and reduced in tumors with intestinal Laurén classification (Table 5).

Discussion

This study shows that response assessed by an interim endoscopy during neoadjuvant chemotherapy has a significant predictive and prognostic value in locally advanced gastric gastric cancer treated by neoadjuvant chemotherapy.

Interim endoscopic response evaluation showed very promising results with respect to an association with all other staging investigations as well as clinical and histopathological response evaluation. The respective specificity and negative predictive value of the early endoscopic evaluation after half the treatment was completed was more than 80 % for their association with subsequent histopathological response and recurrence or death. Thus, the likelihood to withhold effective treatment is relatively low. Furthermore, the prognostic value of this early endoscopic evaluation seems to be promising. However, although prospectively evaluated, the small patient number must always be considered to not interpret our data too optimistically.

In the past, the relatively long duration of up to 3 months of the preoperative part of chemotherapy was never questioned, because according to the oncologists'

Table 5 Prognostic influence of response at EGD-1 stratified by factors known to influence outcome of neoadjuvant chemotherapy

Factor	Localization		Laurén classification		Signet ring cells		Grading	
	Proximal	Nonproximal	Intestinal	Nonintestinal	Yes	No	G1/2	G3/4
Preoperative factors								
Number	30	17	16	31	28	19	11	36
Response EGD-1[a] *p* OS	<0.001	0.234	0.062	0.004	0.006	0.036	0.176	0.003
Response EGD-1[a] *p* EFS	0.001	0.114	0.084	0.003	0.001	0.169	0.187	0.003

Factor	yLaurén classification		ySignet ring cells		yGrading	
	Intestinal	Nonintestinal	Yes	No	G1/2	G3/4
Postoperative factors						
Number	16	28	22	23	10	34
Response EGD-1[a] *p* OS	0.081	0.009	0.028	0.017	0.162	0.005
Response EGD-1[a] *p* EFS	0.031	0.013	0.008	0.039	0.617	0.001

OS overall survival, *EFS* event-free survival

[a] Esophagoduodenoscopy after 50 % of neoadjuvant chemotherapy

experience the patients needed this time to gain sufficient local and systemic effect of chemotherapy [15, 27, 28], and the influence of response on prognosis was first published in 1999 [7]. Indeed, opinions have been revised during recent past years. Regimens tended to be shorter by about 2 months but have remained effective [1, 29]. Clinical experience showed us that a relief of clinical symptoms [30], such as an improved swallowing function in proximal gastric cancer, occurs early during treatment if patients respond. Additionally, there is evidence that nonresponders are not likely to profit from the completion of preoperative chemotherapy [5, 23, 31, 32]. We do not want to correctly predict a complete histopathological response in contrast to other published studies, which mostly failed [33]. Although many phase II studies [10, 12, 15–21] included sequential endoscopy and CT scans pretherapeutically, after 50 % of the projected chemotherapy dose, and preoperatively, data on interim response evaluation based on these examinations after half the treatment are not available in the literature so far. Generally, there are few studies dedicated to clinical response evaluation by endoscopy, endoluminal ultrasound, and CT scan and combinations of those methods [33–43]. Most of them were retrospective and, apart from three studies [33, 36, 44] with small patient numbers, were mainly focused on esophageal cancer: these included evaluation with different tools at different time points after chemo- and chemoradiotherapy, which finally ended with inconclusive results. The majority compared clinical response after the end of the treatment with postoperative histopathological response and survival [33, 34, 45] and found a significant association of the clinical response with subsequent histopathological response and prognosis [34–36, 45]. We put special emphasis on the evaluation of endoscopy, as many other centers do not perform an interim response assessment between the two cycles because of high costs and uncertain clinical relevance. The integration of an additional endoscopy between two cycles of chemotherapy seems more easily feasible within clinical routine than that of a CT scan because of lower cost, availability, and no radiation exposure.

In our study, clinical and endoscopic response evaluation is superior to histopathological response evaluation, similarly to results of Jost et al. [36], which measured maximal tumor thickness by endoscopic ultrasound (EUS) after chemoradiotherapy in esophageal carcinoma with better correlation with prognosis than histopathological regression. The lack of significance of the histopathological response evaluation in our series can easily be explained by the low patient numbers, because in large series in gastric cancer it is an accepted independent prognostic factor [4]. Further influencing factors might also be the relatively high percentage of nonproximal gastric cancer, of non-intestinal Lauren classification, and signet ring cell-containing tumor. These factors are judged to influence response and prognosis in patients with neoadjuvantly treated gastric cancer [13]. A detailed analysis revealed a decreasing value of EGD-1 in highly differentiated tumors and more distant localizations. Both results are influenced by the small sample size ($n = 11$ and $n = 17$), respectively. However, the lower value of EGD-1 in more distant tumors might also be a result of different growth pattern with more intramural tumor, which makes endoscopic interpretation more difficult.

The strong prognostic influence of an endoscopic response evaluation has been shown for metastatic gastric cancer in univariate and multivariate analysis [44]. In contrast to our data, the correlation of CT scan with endoscopy was low, which can be explained by the different time points chosen for response evaluation: endoscopic response was measured after three cycles of chemotherapy, and CT response was defined as the best response of all assessments done during the three cycles. In contrast, in our study endoscopy and CT scan were performed at the same time. The response rates in this study [44] (about 30 %) were similar to ours, with 26 %.

A clear weakness of our study is the small patient number, which can be explained by the complexity of the study design including sequential FDG and FLT examinations [21]. Still, the data on interim endoscopic response yield such remarkable prognostic significance that they might appear implausible at first glance. However, the prospectively evaluated data set on clinical response after treatment consisting of a combination of endoscopy and CT scan was already reported in our former paper on virtually the same patient cohort [21] with shorter follow-up, which clearly demonstrates that the data were prospectively documented and available unmodified previously. Furthermore, the prognostic value of the combined clinical response of CT scan and endoscopy using identical criteria was shown by all other phase II studies from our group [2, 10, 15, 19, 21]. Criteria for clinical response evaluation remained unchanged since the first phase II study [15], but are admittedly not completely corresponding to published official criteria [25, 46, 47], although quite similar. To achieve comparability of the data within the respective academic center, we continued with the old classification, which is consistent with the WHO definition of response for CT [46] and very similar to the Japanese endoscopic criteria [25], defining partial response as a dramatic regression such as flattening, roughly corresponding to at least 50 % decrease in tumor size, whereas we defined more restrictively at about 75 % decrease. This difference highlights well the dilemma of an endoscopic response evaluation. It is a perfect tool in experienced hands, but the excellent data will never be reproduced by inexperienced endoscopists having no experience with neoadjuvant

treatment. Therefore, it is realistic to assume that in gastric cancer endoscopic response evaluation will never be based on measureable calculated data only but requires also the experience of the investigator. In our series the examinations were done by five experienced endoscopists, all of them surgeons with more than 5 years experience in neoadjuvantly treated gastric cancer. The strong predictive value of an interim endoscopy after 50 % of the chemotherapy dose strengthens the hypothesis that changes in the case of an objective response occur early, as already shown by a decrease of the metabolic activity [17, 19], and also that the transient tissue reactions are less than after chemoradiotherapy; this might explain the poor predictive value of post-therapeutic clinical response for histopathological response and prognosis after chemoradiotherapy [33, 48]. As clinical response evaluation seems not to be feasible by CT scan after 2 weeks, as shown by Beer et al. [49], and data for endoscopy after 2 weeks were never presented in the literature, 4–6 weeks after the beginning of chemotherapy seems to be adequate for clinical response evaluation according to our data. The respective sensitivity, specificity, accuracy, PPV, and NPV of an early endoscopy are similar to those of the FDG-PET response evaluation after 2 weeks [18, 19]. This understanding was successfully used to tailor treatment in adenocarcinomas of the esophagogastric junction type I and II [23, 24]. The comparison of survival data of the nonresponding patients completing chemotherapy and those discontinuing after 2 weeks showed that an early discontinuation of chemotherapy seems not to harm the latter [18, 23], and this also is in line with our data.

Conclusion

We showed that interim endoscopy is a simple tool to predict response and prognosis in experienced hands. We also observed that endoscopic nonresponders who discontinued chemotherapy after 6 weeks do not have a worse survival than patients who completed chemotherapy despite early endoscopic non-response. Limitations of the study are the small sample size and the unscheduled discontinuation of chemotherapy in individual patients. Therefore, tailoring treatment according to early endoscopic assessment could be feasible, but the findings of this study need to be validated in a larger patient cohort.

Acknowledgments The authors thank Dr. Catherine Bernaciak for revising the manuscript. K.H. was supported by the collaborative research center SFB 824, TP B1, German Research Foundation (DFG) "Imaging for Selection, Monitoring and Individualization of Cancer Therapies."

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