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Prognostic value of histopathological regression in 850 neoadjuvantly treated oesophagogastric adenocarcinomas

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Background: Recently, histopathological tumour regression, prevalence of signet ring cells, and localisation were reported as prognostic factors in neoadjuvantly treated oesophagogastric (junctional and gastric) cancer. This exploratory retrospective study analyses independent prognostic factors within a large patient cohort after preoperative chemotherapy including clinical and histopathological factors.

Methods: In all, 850 patients presenting with oesophagogastric cancer staged cT3/4 Nany cM0/x were treated with neoadjuvant chemotherapy followed by resection in two academic centres. Patient data were documented in a prospective database and retrospectively analysed.

Results: Of all factors prognostic on univariate analysis, only clinical response, complications, ypTNM stage, and R category were independently prognostic ($P<0.01$) on multivariate analysis. Tumour localisation and signet ring cells were independently prognostic only when investigator-dependent clinical response evaluation was excluded from the multivariate model. Histopathological tumour regression correlates with tumour grading, Laurén classification, clinical response, ypT, ypN, and R categories but was not identified as an independent prognostic factor. Within R0-resected patients only surgical complications and ypTNM stage were independent prognostic factors.

Conclusions: Only established prognostic factors like ypTNM stage, R category, and complications were identified as independent prognostic factors in resected patients after neoadjuvant chemotherapy. In contrast, histopathological tumour regression was not found as an independent prognostic marker.

Perioperative chemotherapy for locally advanced oesophagogastric cancer is a recommended standard of care in Europe (Cunningham *et al*, 2006, 2008; Ychou *et al*, 2011; Lutz *et al*, 2012). For adenocarcinomas of the oesophagogastric junction (AEG), neoadjuvant chemoradiotherapy has been suggested to further improve response rates and prognosis (Stahl *et al*, 2009; Burmeister *et al*, 2011; Sjoquist *et al*, 2011; van Hagen *et al*, 2012), although the 5-year survival gain reported in the CROSS study is in the same range as in the MAGIC (Cunningham *et al*, 2006) and FFCD (Ychou *et al*, 2011) perioperative chemotherapy studies. However,

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the histopathological complete response rates of the CROSS study and the results in the surgery alone arm were excellent and similar rates were reached in only a few other randomised controlled multicentre studies (Hulscher *et al*, 2002).

The evaluation of prognostic factors within neoadjuvantly treated patients was mainly performed retrospectively within phase II studies with limited patient numbers (Lowy *et al*, 1999; Becker *et al*, 2003; Mansour *et al*, 2007; Fujitani *et al*, 2012; Lorenzen *et al*, 2012; Koh *et al*, 2013). The reliability of these reports is limited by the relatively small sample size of most of the studies, and by heterogeneity with regard to the patient cohorts, to neoadjuvant treatment, response evaluation and histopathological regression (HPR) scoring systems. The factors included in the respective multivariate analysis strongly affect the study results and are difficult to compare. Often, ypT category, ypN category, Laurén classification, tumour localisation, tumour differentiation, perineural or vascular invasion, and response were selected by Cox regression (Lowy *et al*, 1999; Becker *et al*, 2003; Mansour *et al*, 2007; Fujitani *et al*, 2012; Lorenzen *et al*, 2012; Koh *et al*, 2013).

Larger series mostly focussed on single prognostic factors of interest. Special attention was recently paid to three factors: localisation (Kunz *et al*, 2012; Lorenzen *et al*, 2012; Reim *et al*, 2012), HPR (Langer *et al*, 2009; Becker *et al*, 2011), and signet ring cell cancer (SRC) (Messager *et al*, 2011; Kunz *et al*, 2012; Taghavi *et al*, 2012). However, most of these factors were not even used for stratification within clinical trials, because they were judged to be too weak or too difficult to assess on a standardised basis to enable stratification to be performed.

Response to neoadjuvant treatment is an important clinical readout for tumour biology and was first described by Lowy *et al.* for gastric adenocarcinomas (Lowy *et al*, 1999). The focus of this study is the histopathological tumour regression after chemotherapy, which was found to be an independent prognostic factor in a large series with gastric cancer (GC) (Becker *et al*, 2011). Despite being considered as the gold standard for response evaluation, histopathological response is still not clearly defined and several competing scoring systems associated with prognosis exist (Kurihara and Aiko, 2001; Mansour *et al*, 2007; Becker *et al*, 2011). Most often, patients with $<10\%$ residual tumour are classified as responder (Schneider *et al*, 2008; Becker *et al*, 2011; Lorenzen *et al*, 2012). But it needs to be noted that about 30% of patients with an obvious HPR of the primary tumour still die due to recurrence (Fields *et al*, 2011; Ott *et al*, 2013). HPR assessment is not free of bias and it depends on the experience of the respective pathologist and the processing of the resection specimens. Given these limitations, the significance of HPR as an independent prognostic factor remains unclear. The value of HPR as a prognostic factor needs to be analysed alongside clinical response, as clinical response was shown to be prognostic by our group and others (Lowy *et al*, 1999; Ott *et al*, 2003; Weber *et al*, 2003), but was deemed to be investigator dependent by other groups (Schneider *et al*, 2008).

The aim of our retrospective exploratory study from two academic centres was the analysis of independent prognostic factors with special emphasis on influence of HPR, but also including other factors like clinical response, signet ring cells, and localisation within a large series of resected oesophagogastric adenocarcinomas treated with preoperative chemotherapy.

PATIENTS AND METHODS

This retrospective exploratory study includes 850 (of a total of 952) patients ($n=675$ Department of Surgery, Klinikum Rechts der Isar, TU München and $n=175$ Department of General, Visceral and Transplantation Surgery, University of Heidelberg) with histologically proven locally advanced stage ($cT_{3/4}$ and cN_{any}) AEG and GC after neoadjuvant chemotherapy followed by surgical resection (Figure 1).

Preoperative staging, neoadjuvant chemotherapy, and surgical therapy. The staging procedures before initiation of chemotherapy included endoscopy and computed tomography of the chest and the abdomen. Staging was repeated before resection to determine clinical response and to exclude distant metastases. The neoadjuvant chemotherapy was mostly platinum based. Patients underwent established chemotherapy regimens, including combinations of platinum (cis- or oxaliplatin) with 5-fluorouracil (or capecitabine) either or not combined with anthracyclines (epirubicin) or taxanes (paclitaxel or docetaxel) (Lim *et al*, 2003; Bader *et al*, 2008; Blank *et al*, 2013) (Supplementary Table S1).

Surgery. Resection was according to tumour localisation and local standards (Bader *et al*, 2008; Ott *et al*, 2008, 2009; Blank *et al*, 2013; Sisic *et al*, 2013). Tumours of the oesophagogastric junction were treated by transhiatal extended gastrectomy, abdomino-thoracic oesophagectomy, or transhiatal oesophagectomy. Gastric cancers of the middle and distal gastric third were treated with total or subtotal gastrectomy. All surgical approaches included an abdominal D2 lymphadenectomy.

Histopathological workup and response assessment. The histopathological workup was classified and staged according to the recommendations by the Union for International Cancer Control (UICC), 7th edition (UICC, 2010). Histopathological response was graded according to Becker *et al* (2003, 2011). Grade 1 response indicates complete or subtotal regression with 1a complete regression and 1b $<10\%$ residual tumour tissue. Grade 2 response indicated partial tumour regression with 10–50% residual tumour and grade 3 minimal or no tumour regression ($>50\%$ residual tumour).

Clinical response evaluation. Clinical response was defined by the interdisciplinary tumour board based on a combination of

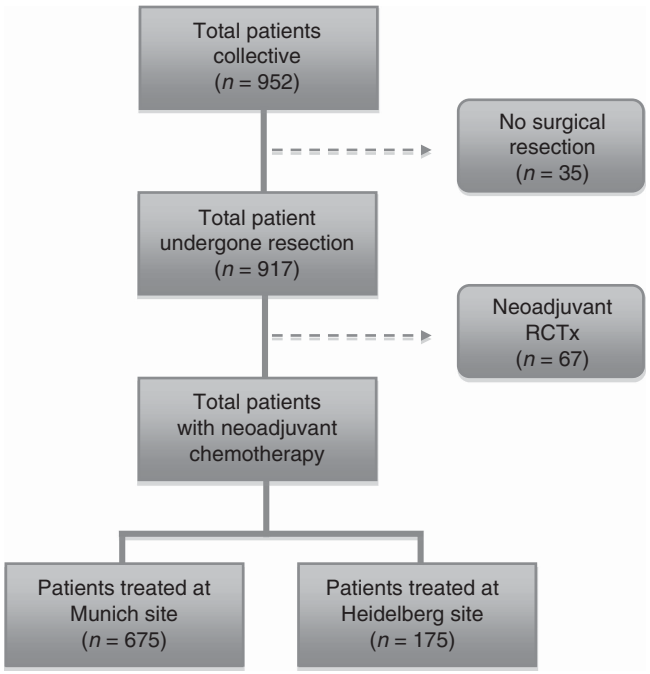


Figure 1. Patient collective. Flowchart describing the composition of the patient collective included in this study.

endoscopy and CT scan after neoadjuvant treatment before resection without the knowledge of the histopathological workup. Responders were defined with at least a partial response (PR) to both endoscopy (<75% residual tumour) and CT scan (decrease of >50% in the wall diameter) (Ott *et al*, 2003).

Patient follow-up. The patients were followed up routinely on an outpatient basis according to a standard protocol with visits q3 month in the first year, q6 month in the second and third year and yearly afterwards until the end of the fifth year. Patients who did not participate in this programme were contacted by telephone to obtain follow-up data.

Statistical analysis. Overall survival was evaluated in months from time of diagnosis until death or until the most recent follow-up using the Kaplan–Meier method. Differences in the survival curves were evaluated by log-rank test for significance. Quantitative values are expressed as mean ± standard deviation, median, and range, and categorical values with absolute and relative frequencies (count and percent). χ^2 test was used for comparison of frequencies, and Spearman correlation coefficients were calculated to quantify bivariate correlation. Stepwise Cox proportional hazard regression was performed as multivariate analysis with forward and backward regression models. A *P*-value of smaller than 0.05 was considered as statistically significant and all statistical tests were conducted two-sided. IBM SPSS Version 20 (Ehningen, Germany) was used for analysis.

RESULTS

Patients. The patients had a median age of 57.5 years (range 17–80) and were predominantly male ($n = 687$ (79.8%)). The tumour was localised at the oesophagogastric junction (junctional cancer) in 610 and in the stomach in 240 patients. Further patients' characteristics are presented in detail in Table 1. Clinical response was evaluated in 824 of the 850 patients. In all, 28.6% (236) were classified as responder (Table 2). The surgical procedures and postoperative complications are also listed in Table 2. Chemotherapy-associated tumour regression was evaluated according to the tumour regression system of Becker. In all, 215 tumours (25.2%) showed a histopathological response of grade 1a (5.6%) or 1b (19.6%), whereas the remainder showed minor or no response (Table 2).

The median survival was 37.1 months (95% CI: 31.2–43.0 months). The 30-day mortality rate was 3.2% and the in-hospital mortality rate 7.9%. Analysing the data according to the time point of diagnosis, no significant survival differences were observed within the different time intervals (1: 1987–12/1995; 2: 01/1996–12/2000; 3: 01/2001–12/2005; and 4: 01/2006–12/2010) (Supplementary Figure S1). The distribution of the surgical procedures remained similar over the study period, with the only difference that in earlier time points transhiatal oesophageal resection was favoured over abdomino-thoracic oesophageal resection (Supplementary Table S2A). The number of resected/analysed lymph nodes was higher at earlier time points (Supplementary Table S2B)

Prognostic factors. Kaplan–Meier curves analysed by log-rank test revealed tumour grading, Laurén classification, SRC (according to WHO definition), clinical response, total complications, surgical complications, resection status (R0 *vs* R1/2), ypTNM stage and HPR (grade 1a/b *vs* grade 2/3) and detailed HPR (all grades separately) (total and surgical complications $P = 0.005$, all others $P < 0.001$) as prognostic factors by univariate analysis in all included patients. On the other side, completion of the full planned chemotherapy regimen, site of treatment (Munich *vs* Heidelberg), or chemotherapy regimen (anthracycline-containing *vs* taxane-containing *vs* non-anthracycline-non-taxane-containing) were not found to be a prognostic factor.

Table 1. Pretreatment clinicopathologic characteristics of the study population ($n = 850$)

	n (%)
Gender	
Male	678 (79.8)
Female	172 (20.2)
Localisation	
Oesophagus	610 (71.8)
AEG I	241 (28.4)
AEG II	254 (29.9)
AEG III	115 (13.5)
Gastric	240 (28.2)
Gastric body	94 (11.1)
Gastric antrum	94 (11.1)
Total gastric carcinoma	52 (6.1)
Grading[a]	
G1/2	217 (25.9)
G3/4	621 (74.1)
Laurén classification[a]	
Intestinal type	436 (52.3)
Non-intestinal type	397 (47.7)
Signet ring cell cancer[a]	
Yes	221 (30.0)
No	516 (70.0)

Abbreviation: AEG = adenocarcinomas of the oesophagogastric junction.
[a]Missing data in some cases.

Histopathological regression as a prognostic factor. Histopathological regression grade was found to be strongly associated with survival. Patients with tumour regression grade 1 (1a + 1b) had a median survival of 92.2 months (CI: median survival not reached). For patients without regression, median survival was 27.9 months (95% CI: 24.2–31.6 months) (Figure 2A) ($P < 0.001$). Histopathological regression based on the four groups (grades 1a, 1b, 2, and 3) did also significantly discriminate the patients' prognosis ($P < 0.001$) (Figure 2B). Histopathological response was significantly associated with the preoperative grading ($P = 0.001$) and Laurén classification of the tumour ($P = 0.002$). Histopathological response was correlated with clinical response ($P < 0.001$), but not with discontinuation of chemotherapy. The postoperative parameters of ypT, ypN, and R categories were associated with HPR ($P < 0.001$), whereas the M category not (Supplementary Table S3). A more detailed analysis showed that in patients with a histopathological response of the primary tumour, lymph-node metastases are relatively frequent in the pathological specimens. In all, 20.9% (10 out of 48) of the patients with regression grade 1a and 41.6% (67 out of 161) (Table 3) with grade 1b had lymph-node metastases as well as distant metastases in 8.3% (4 out of 48) *vs* 21.1% (34 out of 161) (Supplementary Table S4). In all, 55.7% (93 out of 161) of the responders with grade 1b had an advanced T category with yT3 and yT4 and 13.8% (23 out of 167) of those had tumour infiltration of the surgical resection margins (R1/R2) (Supplementary Table S4).

Clinical response, localisation, and signet ring cell carcinoma. The analysis of clinical response showed a significantly better prognosis for clinical responders *vs* non-responders (Figure 3A) ($P < 0.001$). Subgroup analysis showed a significant survival

Table 2. Post-treatment-related clinical characteristics of the study population ($n = 850$)

	n (%)
Clinical response	
Responder	236 (28.6)
Non-responder	590 (71.4)
Minor response	298 (36.1)
No change	267 (32.3)
Progressive disease	25 (3.0)
Surgical procedure	
Abdomino-thoracic oesophageal resection	201 (23.6)
Transmediastinal oesophageal resection	88 (10.4)
Oesophago-gastrectomy	9 (1.1)
Transhiatal extended gastrectomy	295 (34.7)
Total gastrectomy	208 (24.5)
Subtotal gastrectomy	35 (4.1)
Others	14 (1.6)
Complications	
Yes	352 (41.5)
Surgical	135 (15.9)
Medical	282 (33.2)
ypT category	
ypT0	48 (5.6)
ypT1	62 (7.3)
ypT2	101 (11.9)
ypT3	505 (59.4)
ypT4	134 (15.8)
ypN category	
ypN0	314 (37.3)
ypN1	147 (17.5)
ypN2	146 (17.3)
ypN3	235 (27.9)
M category	
M0	674 (79.3)
M1	176 (20.7)
R category	
R0	637 (74.9)
R1	177 (20.8)
R2	36 (4.2)
HPR	
Grade 1a	48 (5.6)
Grade 1b	167 (19.6)
Grade 2	208 (24.5)
Grade 3	427 (50.2)

Abbreviations: HPR = histopathological regression; UICC = Union for International Cancer Control. TNM classification according to UICC 7th edition.

difference for patients with a PR (median survival: not reached), minor response (MR) (median survival: 29.1 months, 95% CI: 22.1–36.1 months), no change (NC) (median survival: 27.1 months, 95% CI: 23.0–32.2 months), and progressive disease (PD) (median survival: 10.5 months, 95% CI: 9.1–11.9 months) (Figure 3B).

Also the tumour localisation was found to be a significant prognostic marker. Patients with a carcinoma involving the entire stomach had a worse prognosis, whereas all other localisations had a similar survival (Figure 3C).

When analysing the patients for signet ring cell carcinoma *vs* non-signet ring cell carcinoma, it was found that patients with signet ring cell carcinoma (median survival: 26.7 months, 95% CI: 22.1–31.4 months) had a significantly worse survival than non-signet ring cell type carcinoma patients (median survival: 46.6 months, 95% CI: 37.9–55.2 months) (Figure 3D, $P < 0.001$).

Analysing only the 637 R0-resected patients by log-rank tests revealed comparable results for prognostic factors with significant differences for tumour location, tumour grading, Laurén classification, SRC, clinical response, total complications, surgical complications, ypTNM, and HPR (grade 1a/b *vs* grade 2/3).

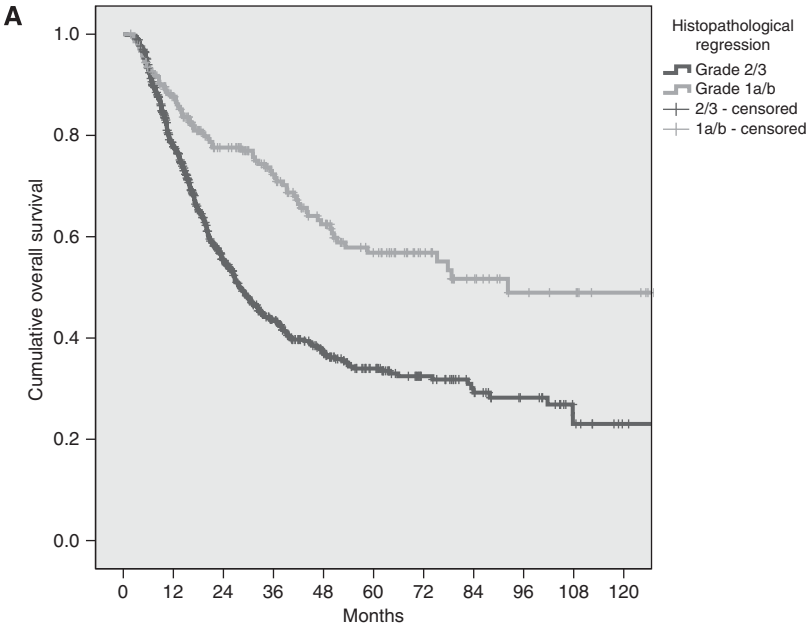
Independent prognostic factors. Multivariate analysis with Cox forward and backward regression revealed clinical response, total complications, and ypT and ypN categories as independent prognostic factors. M and R categories were independent prognostic factors in Cox forward regression, but not confirmed in backward regression. HPR was not confirmed as an independent prognostic factor neither included as parameter responder *vs* non-responder nor with the detailed regression classification (Table 4A). In the next step clinical response was deleted, because it is not a generally accepted prognostic factor within all working groups, because it is judged to be investigator dependent. Without clinical response Cox regression revealed tumour location, SRC, total complications, and ypTNM and R categories as independent prognostic markers in forward and backward Cox regression, again not HPR (Table 4B). Despite tumour localisation was statistically significant, the survival curves are crossing (Figure 3C). Therefore, this parameter was deleted from further analysis. Then in multivariate analysis, total complications, and ypTNM and R categories remained as independent prognostic factors (Table 4C).

By multivariate Cox regression analysis (forward and backward regression), surgical complications and ypTNM categories were identified as independent prognostic factors (all $P < 0.005$) in the completely resected patients (Table 4D). As expected distant metastasis (M1 status) was a prognostic factor, therefore Cox regression analysis was also performed for all patients without distant metastasis (M0) (Supplementary Table S5A) and all curatively resected patients with complete resection (R0) and without distant metastasis (M0) (Supplementary Table S5B). In these patient groups, localisation, clinical response, and ypTN categories remained as independent prognostic factors, whereas HPR was not found to be statistically significant.

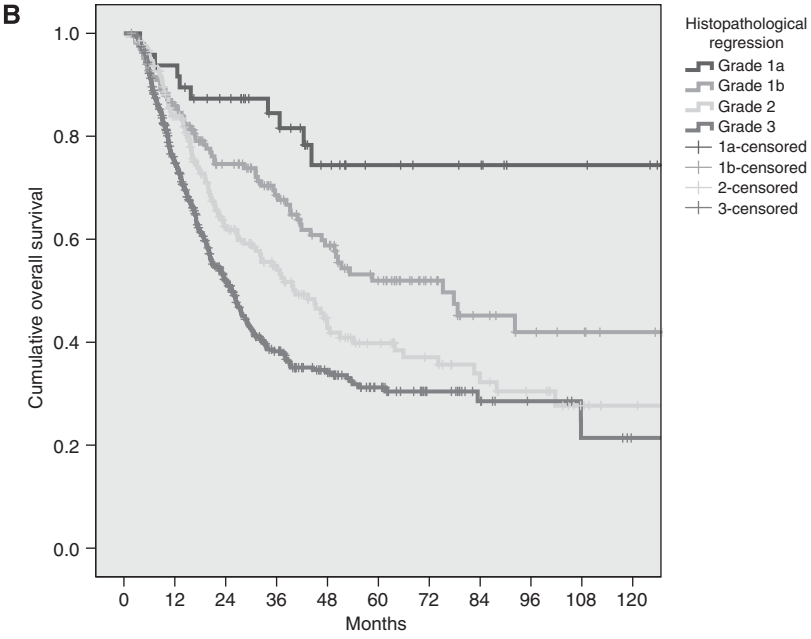
DISCUSSION

This study shows that established prognostic factors like ypTNM and R categories, as well as complications, are independent prognostic factors in neoadjuvant treated oesophagogastric adenocarcinomas. Hence, similar factors were also revealed to be prognostically relevant for primary resected tumours. Chemotherapy-associated characteristics such as histopathological response scoring were shown to be less important. Even patients with a good response in their primary tumour often have high T categories and lymph-node metastases, which may be responsible for the lower relevance of the tumour regression score in multivariate analysis. Only one localisation influences outcome in our analysis: carcinomas of the entire stomach have a disastrous prognosis compared with all other localisations (Messager *et al*, 2011; Lorenzen *et al*, 2012).

Limitations in other studies are usually related to the inclusion of only a few preselected parameters. Additionally, differences in survival over the study period can be observed (Kunz *et al*, 2012). In general, it needs to be noted that only a few prospective randomised



	Months										
Pts at risk	0	12	24	36	48	60	72	84	96	108	120
Responder	209	165	123	96	68	46	33	22	16	13	6
Non-resp.	612	422	247	156	100	66	44	30	20	9	3



	Months										
Pts at risk	0	12	24	36	48	60	72	84	96	108	120
Grade 1a	48	42	34	25	15	11	10	7	5	4	2
Grade 1b	161	123	89	71	53	35	23	15	11	9	4
Grade 2	200	148	90	65	41	31	24	17	11	4	1
Grade 3	412	274	157	91	49	35	20	13	9	5	2

Figure 2. Prognostic value of the histopathological regression. Kaplan–Meier plots for overall survival of (**A**) histopathological regression grading grouped grade 1a/b and group 2/3 and (**B**) histopathological regression by subgrades ($n=850$, $P<0.001$). The tables show the number of patients at risk at the indicated time points.

phase III studies exist (Cunningham *et al*, 2006; Schuhmacher *et al*, 2010; Ychou *et al*, 2011) and that the evaluation of prognostic factors is not a primary objective of phase III studies. Hence, there are currently some questions that can only be answered retrospectively (Messager *et al*, 2011; Kunz *et al*, 2012), but results must be interpreted with caution and with the awareness of this limitation.

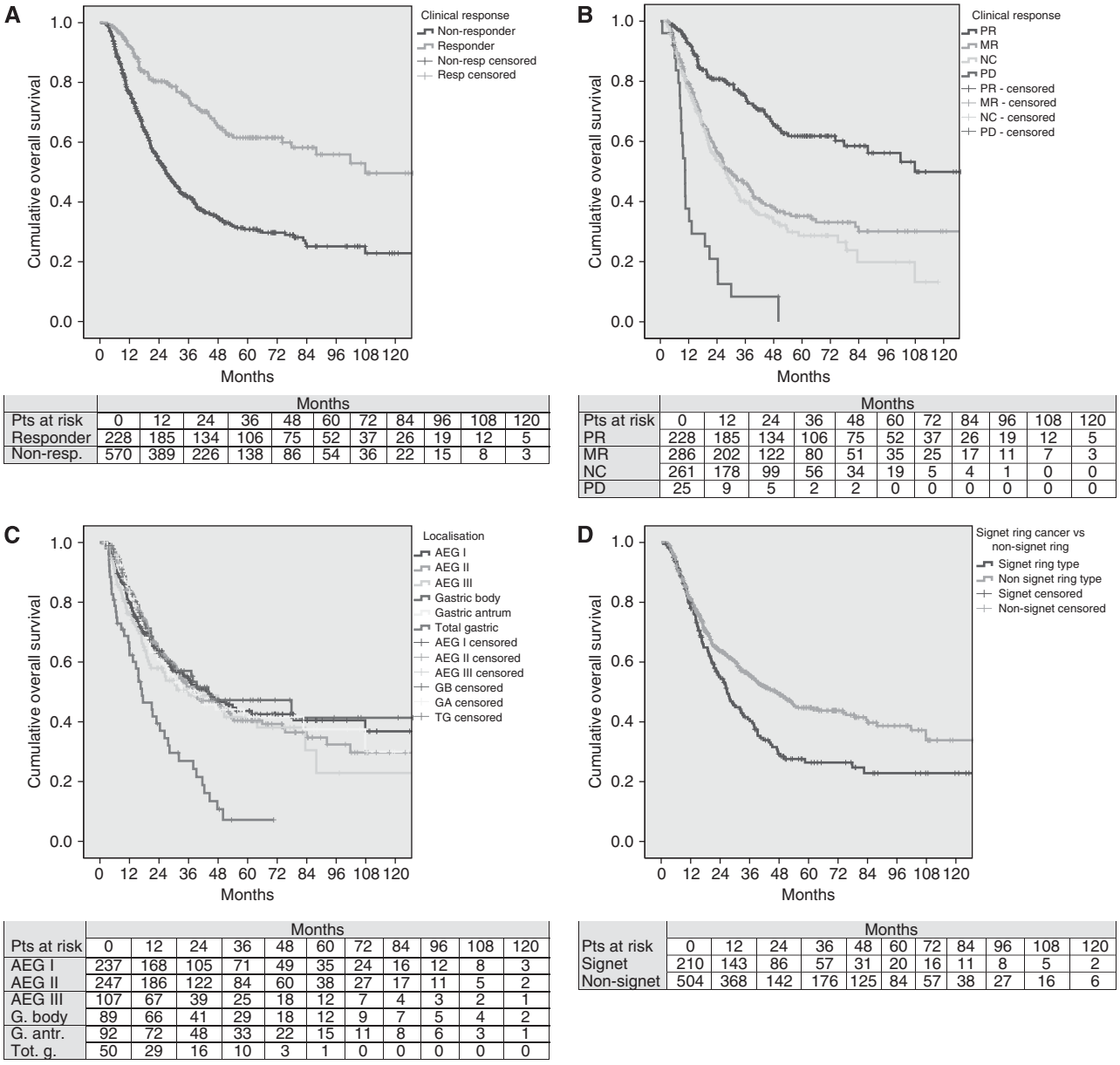
Considering these limitations, the analysis of our data is more comprehensive compared with many other published series. We included a multiplicity of factors such as Laurén classification, grading, clinical response, HPR, and SRC classification according to the WHO. In addition, the clinical information including the type and conduct of preoperative chemotherapy and intraoperative

Table 3. Lymph-node metastasis according to histopathological regression

	Histopathological regression			
Lymph-node metastasis	**1a**	**1b**	**2**	**3**
Negative	38 (79.2%)	94 (58.4%)	76 (36.7%)	106 (24.9%)
Positive	10 (20.8%)	67 (41.6%)	131 (53.3%)	310 (75.1%)

The table indicates the number of patients with lymph-node metastasis according to histopathological regression (HPR) as well as the percentage of patients with lymph-node metastasis for each specific HPR grade.

and postoperative complications was available. Some other interesting information, like initial pretherapeutic cTNM (Messager *et al*, 2011; Reim *et al*, 2012), was not completely recorded in our database and therefore was not included (Blank *et al*, 2012). Furthermore, no detailed information on pretherapeutic performance status or nutritional status was available (Messager *et al*, 2011), but all of our patients who were selected for multimodal treatment had to have a Karnofsky performance status of >80. Despite prospective meticulous documentation of many factors, some prognostically relevant factors like lymphangiosis (von Rahden *et al*, 2005), perineural or vascular invasion (Mansour *et al*, 2007), or tumour regression within the lymph nodes (Bollschweiler *et al*, 2011) were only recorded for small subgroups and were not included in our analysis. As overall survival did not



Pts at risk	0	12	24	36	48	60	72	84	96	108	120
Responder	228	185	134	106	75	52	37	26	19	12	5
Non-resp.	570	389	226	138	86	54	36	22	15	8	3

Pts at risk	0	12	24	36	48	60	72	84	96	108	120
PR	228	185	134	106	75	52	37	26	19	12	5
MR	286	202	122	80	51	35	25	17	11	7	3
NC	261	178	99	56	34	19	5	4	1	0	0
PD	25	9	5	2	2	0	0	0	0	0	0

Pts at risk	0	12	24	36	48	60	72	84	96	108	120
AEG I	237	168	105	71	49	35	24	16	12	8	3
AEG II	247	186	122	84	60	38	27	17	11	5	2
AEG III	107	67	39	25	18	12	7	4	3	2	1
G. body	89	66	41	29	18	12	9	7	5	4	2
G. antr.	92	72	48	33	22	15	11	8	6	3	1
Tot. g.	50	29	16	10	3	1	0	0	0	0	0

Pts at risk	0	12	24	36	48	60	72	84	96	108	120
Signet	210	143	86	57	31	20	16	11	8	5	2
Non-signet	504	368	142	176	125	84	57	38	27	16	6

Figure 3. Clinical response, localisation, and signet ring cell carcinoma as prognostic factors. Kaplan–Meier plots for overall survival of (**A**) clinical response grouped by responders and non-responders, (**B**) clinical response of partial response (PR), minor response (MR), no change (NC), progressive disease (PD) and (**C**) according to tumour localisation of the primary tumour. (**A**–**C**, $n=850$, $P<0.001$) (**D**) according to tumour type, signet ring cell cancer *vs* non-signet ring cell cancer ($n=737$, $P<0.001$). The tables show the number of patients at risk at the indicated time points.

Table 4. Significant prognostic factors in multivariate analyses

	P-value	RR	95% CI
(A) (included: localisation, grading, Laurén classification, signet ring cell cancer, clinical response, complications, surgical complications, ypTNM, R status, and histopathological regression)			
Clinical response[a]	0.004	1.53	1.14–2.05
Complications[a]	0.001	0.70	0.57–0.87
ypT category[a]	0.002		
ypT0	0.009	0.31	0.13–0.75
ypT1	0.039	0.51	0.27–0.97
ypT2	<0.001	0.42	0.26–0.68
ypT3	0.140	0.81	0.61–1.07
ypN category[a]	<0.001		
ypN0	<0.001	0.45	0.33–0.63
ypN1	0.010	0.65	0.47–0.90
ypN2	0.003	0.66	0.48–0.68
M category	<0.001	0.55	0.42–0.73
R category	0.014		
R0	0.018	0.55	0.34–0.91
R1	0.240	0.75	0.47–1.21
(B) (clinical response excluded) (included: localisation, grading, Laurén classification, signet ring cell cancer, complications, surgical complications, ypTNM, R status, and histopathological regression)			
Localisation[a]	0.006		
Signet cell type cancer[a]	0.033	1.32	1.02–1.70
Complications[a]	0.004	0.73	0.58–0.90
ypT category[a]	<0.001		
ypT0	<0.001	0.19	0.08–0.47
ypT1	0.006	0.39	0.20–0.76
ypT2	<0.001	0.38	0.23–0.64
ypT3	0.075	0.73	0.52–1.03
ypN category[a]	<0.001		
ypN0	<0.001	0.40	0.29–0.56
ypN1	0.001	0.57	0.41–0.79
ypN2	<0.001	0.60	0.45–0.80
M category[a]	<0.001	0.53	0.40–0.70
R category[a]	0.009		
R0	0.004	0.48	0.29–0.79
R1	0.041	0.60	0.37–0.98
(C) (clinical response + localisation excluded) (included: grading, Laurén classification, signet ring cell cancer, complications, surgical complications, ypTNM, R status, and histopathological regression)			
Complications[a]	<0.001	0.69	0.56–0.85
ypT category[a]	<0.001		
ypT0	0.001	0.23	0.10–0.55
ypT1	0.008	0.42	0.23–0.80
ypT2	<0.001	0.40	0.28–0.72
ypT3	0.198	0.84	0.64–1.1
ypN category[a]	<0.001		
ypN0	<0.001	0.43	0.32–0.59
ypN1	0.003	0.61	0.44–0.85
ypN2	0.002	0.63	0.47–0.84
M category[a]	<0.001	0.55	0.42–0.72
R category[a]	0.006		
R0	0.011	0.53	0.33–0.86
R1	0.212	0.74	0.46–1.19

Table 4. (Continued)

	P-value	RR	95% CI
(D) (R0 completely resected patients) (included: grading, Laurén classification, signet ring cell cancer, clinical response, complications, surgical complications, ypTNM, and histopathological regression)			
Surgical complications[a]	0.004	0.68	0.52–0.89
ypT category[a]	<0.001		
ypT0	0.002	0.25	0.10–0.61
ypT1	0.011	0.40	0.19–0.81
ypT2	<0.001	0.36	0.21–0.63
ypT3	0.318	0.922	0.56–1.21
ypN category[a]	<0.001		
ypN0	<0.001	0.39	0.27–0.57
ypN1	0.006	0.58	0.39–0.85
ypN2	0.006	0.59	0.41–0.86
M category [a]	<0.001	0.47	0.33–0.67

Abbreviations: CI = confidence interval; RR = relative risk.
[a]Confirmation by Cox backward regression analysis.
Results of Cox forward regression analysis.

change significantly over the study period, inclusion of all patients over this long time period remains justified.

This study provides important insights into the outcome of neoadjuvantly treated patients. As a fundamental finding, TNM classification seems to be the strongest prognostic factor in neoadjuvantly treated patients, despite being based on the data from primary resected patients (Gertler *et al*, 2011; Reim *et al*, 2013). The prognostic relevance of complications is known in oesophagogastric adenocarcinoma (Ott *et al*, 2009; Messager *et al*, 2011), and was confirmed in our study. Interestingly, for both groups, the resected and completely (R0) resected patients, the same prognostic factors were revealed to be significant. Therapy-associated variables, for example, discontinuation of chemotherapy or the type of cytotoxic drug combinations applied, were not statistically relevant or meaningful because of small subgroups and crossing survival curves.

The inclusion of different localisations of adenocarcinomas as stratification criterion in studies is a matter of debate because, according to centres and standards, the associated treatment strategies might differ significantly. Since our study is focussed on patients with chemotherapy only, all treated adenocarcinomas were included according to the MAGIC and FFCD study results (Cunningham *et al*, 2006; Ychou *et al*, 2011). There is an ongoing discussion regarding whether in AEG I, or even in AEG II and III, preoperative chemoradiotherapy should be performed (Sjoquist *et al*, 2011; van Hagen *et al*, 2012). In our centres, we mostly used chemotherapy alone due to the reduced immunosuppression after chemotherapy compared with radiochemotherapy (Heidecke *et al*, 2002) and due to the good local resectability of adenocarcinomas in most cases (Siewert and Ott, 2007). Whether the significantly higher rates of complete histopathological responses after chemoradiotherapy compared with chemotherapy are also translated into an improved survival remains unclear so far (Vallbohmer *et al*, 2010; Fields *et al*, 2011; Ott *et al*, 2013), as only limited prospectively controlled randomised data addressing this issue exist (Stahl *et al*, 2009; Burmeister *et al*, 2011). In contrast to primary resected AEG (Siewert *et al*, 2001), in this study all localisations have a similar prognosis with only cancers of the entire stomach having a significantly worse prognosis. This supports our combined analysis of adenocarcinomas in the upper GI after chemotherapy.

The most remarkable and debatable finding of our retrospective study was the lack of independent prognostic relevance of the

tumour regression score. It was previously shown that about 30% of patients classified as histopathological responders die due to recurrence, mostly occurring as distant metastases (Fields *et al*, 2011; Ott *et al*, 2013). Here, we found that a relevant percentage of patients with <10% residual tumour have advanced tumour categories and/or lymph-node metastases. Although the findings from the largest series for GC support tumour regression as an independent prognostic factor (Becker *et al*, 2011), there are also other studies in the literature that contradict this finding and thus support our data (Mansour *et al*, 2007; Fujitani *et al*, 2012). We integrated all pre- and postoperative relevant parameters, including clinical and histopathological information, as Cox regression analysis is dependent on the chosen factors. None of the performed analyses revealed tumour regression as an independent prognostic factor. Interestingly, clinical response was an independent prognostic factor, but it was excluded from further analysis, because it is judged to be investigator dependent.

Despite the lack of significance in multivariate analysis, HPR remains an important piece of information after preoperative chemotherapy, because it represents an *in vivo* testing of the chemosensitivity of the tumour and may serve as a stratification criterion for tailored postoperative treatment in future studies. Its clinical relevance must be interpreted with caution, as there are several classification systems available in the literature (Becker *et al*, 2003, 2011; Fujitani *et al*, 2012), with classification of responders varying from a complete HPR to <50% residual tumour (Becker *et al*, 2003; Mansour *et al*, 2007; Fujitani *et al*, 2012). A homogenisation of scoring systems, a standardisation resection specimen processing, and a consensus definition of a histopathological response after chemotherapy are strongly warranted to make study results comparable in the future.

In conclusion, in neoadjuvantly treated oesophagogastric adenocarcinomas, only established factors such as ypTNM categories and total complications, and no chemotherapy related factors, are revealed as independent prognostic factors in our series. Specifically, HPR was not an independent prognostic factor. Advanced tumour categories and lymph-node metastases in >40% of patients with <10% residual tumour might be one reason. Therefore, since no generally accepted scoring systems exist, HPR should be interpreted with caution and might be used for postoperative treatment decisions only in combination with the established prognostic factors.

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