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ORIGINAL ARTICLE

Factors predicting prognosis and recurrence in patients with esophago-gastric adenocarcinoma and histopathological response with less than 10 % residual tumor

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Abstract
Purpose Neoadjuvant treatment is an accepted standard approach for treating locally advanced esophago-gastric adenocarcinomas. Despite a response of the primary tumor, a significant percentage dies from tumor recurrence. The aim of this retrospective exploratory study from two academic centers was to identify predictors of survival and recurrence in histopathologically responding patients.
Methods Two hundred thirty one patients with adenocarcinomas (esophagus: $n=185$, stomach: $n=46$, cT3/4, cN0/+, cM0) treated with preoperative chemotherapy ($n=212$) or chemoradiotherapy ($n=19$) followed by resection achieved a histopathological response (regression 1a: no residual tumor ($n=58$), and regression 1b<10 % residual tumor ($n=173$)).
Results The estimated median overall survival was 92.4 months (5-year survival, 56.6 %) for all patients. For patients with regression 1a, median survival is not reached (5-year survival, 71.6 %) compared to patients with regression 1b with 75.3 months median (5-year survival, 52.2 %) ($p=0.031$). Patients with a regression 1a had lymph node metastases in 19.0 versus 33.7 % in regression 1b. The ypT-category ($p<0.001$), the M-category ($p=0.005$), and the type of treatment ($p=0.04$) were found to be independent prognostic factors in R0-resected patients. The recurrence rate was 31.7 % ($n=66$) (local, 39.4 %; peritoneal carcinomatosis, 25.7 %; distant metastases, 50 %). Recurrence was predicted by female gender ($p=0.013$), ypT-category ($p=0.007$), and M-category ($p=0.003$) in multivariate analysis.
Conclusion Response of the primary tumor does not guarantee recurrence-free long-term survival, but histopathological complete responders have better prognosis compared to partial responders. Established prognostic factors strongly influence the outcome, which could, in the future, be used for stratification of adjuvant treatment approaches. Increasing the rate of histopathological complete responders is a valid endpoint for future clinical trials investigating new drugs.

Keywords Histopathological response · Esophago-gastric adenocarcinoma · Prognostic factors · Patterns of recurrence

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Introduction

Pre- or perioperative treatment is nowadays a standard for locally advanced adenocarcinomas of the esophagus or

stomach in Europe [1–3]. In gastric cancer, a perioperative chemotherapy is generally preferred [1, 2], whereas in adenocarcinomas of the esophagus, often radiation is added to increase local response rates [4–6]. However, a recently published metaanalysis does not prove that chemoradiotherapy is superior to chemotherapy for the treatment of adenocarcinomas of the esophagus [5]. Neoadjuvant treatment followed by surgery increases long-term survival about 13 % compared to surgery alone [1, 2, 6, 7]. The reported 5-year survival rates for resected patients with additional chemotherapy are 36 % in the MAGIC trial including 25 % adenocarcinomas of the esophago-gastric junctions (AEGs) I–III, 38 % in the FFCD9703 trial including 66 % AEGs I–III [1, 2], and the 2-year survival rate in the EORTC 40954 trial is 73 % including 50 % AEG II/III [3].

For more than 10 years, it has been generally accepted that patients with response of the primary tumor have a significant improved prognosis compared to patients who do not respond [8]. Three different types of response evaluation exist with varying acceptance. A metabolic response evaluation can be performed early during or after treatment [9–15], a clinical response evaluation by endoscopy, endoluminal ultrasound and CT scans after the end of neoadjuvant treatment [16–18], and histopathological response evaluation after resection [4, 19, 20]. However, the histopathological response evaluation is judged to be a gold standard [4, 20]. A recent study on 480 neoadjuvant-treated resected gastric cancer patients proved that histopathological tumor regression provides objective and highly valuable prognostic information and should be implemented in the pathology report [20]. Also in AEG, histopathological response is strongly associated with prognosis [4, 21, 22]. However, the definition of histopathological response still varies from a complete histopathological regression (pCR) up to 50 % residual tumor [4, 19, 20, 23, 24]. In most studies, either a pCR [22, 23, 25] or less than 10 % residual tumor is used as the threshold of defining response [4, 20]. The percentage of histopathologically responding patients ranges from 21.2 % after neoadjuvant chemotherapy [20] up to 40.5 % after neoadjuvant radiochemotherapy [4, 23]. The consequences of a histopathological response have been poorly understood until now because the value of the existing data is limited due to the relatively low response rates leading to small sample sizes in single center trials. A relevant percentage of patients die from tumor recurrence despite a histopathological response of the primary tumor [22, 23]. The only multicenter trial including 299 patients with complete histopathological remission after esophagectomy shows a 5-year survival of 55 % and provides only age as a predictor of survival [22].

The aim of this retrospective exploratory study from two major academic centers is the analysis of predictors of survival and recurrence in the subgroup of responding patients with less than 10 % residual tumor cells.

Patients and methods

This retrospective exploratory study includes 231 histopathologically responding patients (n=195—Department of Surgery, Klinikum rechts der Isar, TUM, 1987–2005 and n=36—Department of Surgery, University of Heidelberg, 2002–2011) (<10 % residual tumor) with initially histologically proven, locally advanced esophago-gastric adenocarcinomas (cT3/4, cN0/+, cM0), who underwent neoadjuvant treatment followed by resection. One hundred ninety five (28.0 %) of 696 neoadjuvant-treated patients from the surgical department in Munich and 36 (18.3 %) of 213 neoadjuvant-treated patients from the surgical department of the University of Heidelberg presented with less than 10 % residual tumor (Fig. 1).

Staging

Staging including endoscopy and CT scan was performed before preoperative treatment and repeated after the end of neoadjuvant treatment before surgery for all patients in both institutions.

Neoadjuvant treatment

Neoadjuvant chemotherapy was performed in 219 patients on outpatient basis with established chemotherapy regimens [12, 26–29]. For simplification, we combined the regimens as followed: Platin/5-FU/Leucovorin based (n=119), Adriamycine/epirubicine based (n=53), and taxane-containing regimens (n=40). In 19 patients, radiotherapy in addition to chemotherapy was delivered. Most patients received 45 Gy.

Surgery

Tumor resection was scheduled 2–3 weeks after chemotherapy or 4–6 weeks after chemoradiotherapy was completed. In patients with adenocarcinomas of the esophagus, either an abdominothoracic approach [28] (Ivor Lewis procedure) or a transhiatal esophagectomy [29] with two-field lymphadenectomy was performed. Proximal gastric cancer was treated by a transhiatal extended gastrectomy and an extended D2-lymphadenectomy (resection of the lymph node groups 1 and 2 according to the Japanese Research Society for Gastric Cancer); a left retroperitoneal lymphadenectomy was also performed. For patients with tumor localization in the middle or distal third, a total gastrectomy with D2-lymphadenectomy was performed [27, 28]. Patients with distal gastric cancer underwent a subtotal gastrectomy with D2-lymphadenectomy.

Histopathological evaluation

Histopathological evaluation was done by standardized protocols including the pTNM categories, grading, tumor

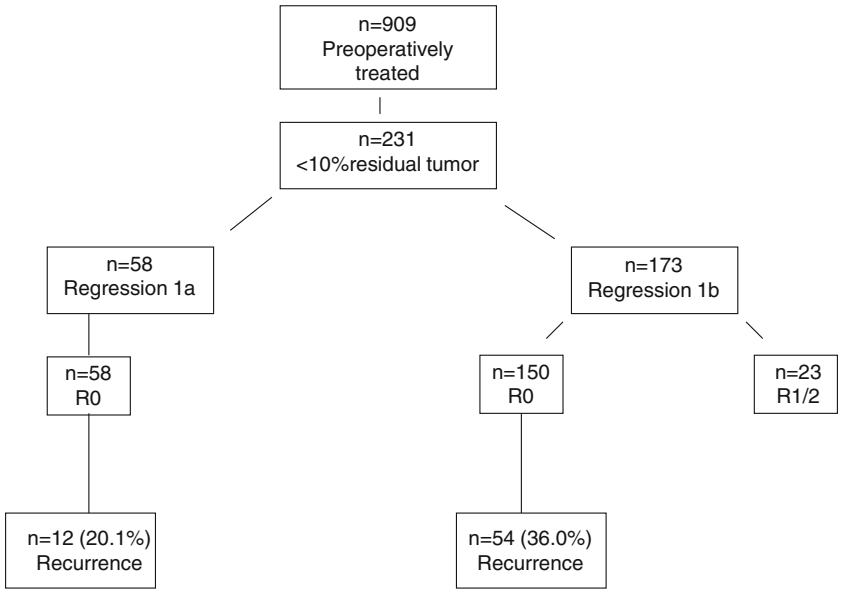


Fig. 1 Patient study group, R-category, and recurrence. *R* R-category, *n* number

localization, subtype according to Laurén classification, and R-category including proximal, distal, and deep resection margins, as demanded in the guidelines of the UICC seventh edition.

Tumor regression analyses of the primary tumors were performed by four experienced pathologists (K.B. and R.L. (TU Munich), W.W. and W.R. (University of Heidelberg)) using an accepted scoring system (Becker score) [20]. For the purpose of this study, all patients with less than 10 % residual tumor cells in the primary tumor (score 1a: complete response, score 1b: subtotal response) were chosen.

Adjuvant treatment

No patients from Munich received postoperative adjuvant chemo- or radiochemotherapy. From the 36 patients included from Heidelberg, 14 received postoperative treatment. No patients received chemoradiation. Seven patients were treated with EOX, two with FLO, one with ECX (stopped after one cycle), one with Taxol-PLF, one with PLF, and two with unknown regimens.

Patient follow-up

The patients were generally followed on an outpatient basis according to standard protocols with visits every 3 months during the first year, then every 6 months during the second and third years and once yearly thereafter until the fifth year. Those patients who were not included in these programs were contacted by telephone to obtain follow-up data. No patient was lost to follow-up.

Statistical analysis

Associations between the clinical or pathological parameters were assessed by the χ^2 test or the Fisher's exact test. The Kaplan–Meier method was used for calculation of survival times, and the comparison of the survival curves was carried out by the log-rank test. Univariate analysis was used to evaluate prognostic factors, followed by multivariate analysis using stepwise Cox proportional hazard regression modeling. With the significant prognostic factors obtained in multivariate analysis, the hazard ratio was calculated for each patient.

A two-sided significance test with a P value <0.05 was considered significant; all statistic calculation were done by SPSS 17.0 (SPSS Inc, Chicago, IL, USA).

Results

Two hundred thirty one patients from both centers had <10 % residual tumor. Fifty eight (25.1 %) patients had a complete histopathological response (Fig. 1). Despite a pCR of the primary tumor, 11 patients (19.0 %) still had lymph node metastases (ypN1 (n=8), ypN2 (n=3)). Seventy six (32.9 %) patients died; 155 (73.1 %) are alive. The median follow-up for the surviving patients is 47.7 months. Thirty-day mortality was 2.6 %, and in-hospital mortality was 6.9 %. Furthermore, the patient's characteristics are shown in Table 1.

The estimated overall survival is 92.4 months median for all responders (1-year overall survival [OS], 88.7 %; 3-year OS, 72.5 %; 5-year OS, 56.6 %). The prognosis of all responders (p=0.84) and the R0 responders (p=0.77) is not different for the patients from both centers.

Table 1 Patient's characteristics

Age 57.10+12.01 (18.9–78.5)		
	Number	Percent
Gender		
Female	37	16.0 %
Male	194	84.0 %
Localization		
Esophageal cancer (UICC 7th)	185	80.1 %
Gastric cancer (UICC 7th)	46	19.9 %
Esophageal cancer (UICC 6th)	77	33.3 %
Gastric cancer (UICC 6th)	154	66.7 %
Lauren classification		
Intestinal	135	58.4 %
Nonintestinal	84	36.4 %
Missing	12	5.2 %
Grading		
G1/2	82	35.5 %
G3/4	142	61.5 %
Missing	7	3.0 %
Type of chemotherapy		
PLF/OLF/EPLF/MPLF	119	51.5 %
EAP/ECF/EOX	53	22.9 %
Taxol-PLF/Taxotere	40	17.3 %
Chemoradiotherapy	19	8.2 %
Discontinuation of chemotherapy		
Yes	41	17.7 %
No	189	81.8 %
Missing	1	0.4 %
Type of resection		
Subtotal gastrectomy	7	3.0 %
Total gastrectomy	39	16.9 %
Transhiatal extended gastrectomy	91	39.4 %
Transhiatal esophagectomy	23	9.9 %
Transthoracic esophagectomy	62	26.9 %
Missing	9	3.9 %
Complications		
Medical	30	15.6 %
Surgical	76	32.9 %
ypT-category (UICC 7th)		
ypT0	58	25.1 %
ypT1	39	16.9 %
ypT2	40	17.3 %
ypT3	74	32.0 %
ypT4	20	8.7 %
Number of lymphnodes removed	28.9±15.1 (1–107)	
ypN-category (UICC 7th)		
ypN0	147	63.6 %
ypN1	25	10.8 %
ypN2	25	10.8 %
ypN3	28	12.1 %
Missing	6	2.0 %
M-category		
M0	193	83.5 %
M1	38	16.5 %
Localization M1		
Peritoneal carcinomatosis	12	
Liver metastases	5	
Distant lymph node metastases	4	
Spleen	4	
Esophagus	2	
Colon	1	
Pancreas	1	
Combinations	10	
+Peritoneal carcinomatosis	10/10	
+Distant lymph nodes	5/10	
R-category		
R0	208	90.0 %
R1	23	10.0 %
Regression		
1a: complete remission	58	25.1 %
1b: (<10 %) subtotal regression	173	74.9 %
30-day mortality	6	2.6 %
In-hospital mortality	16	6.9 %

The separate analysis of AEGs I, II, III, and gastric cancer showed significant survival differences between the respective tumor entities ($p=0.019$) (Fig. 2), therapy regimens applied ($p<0.001$) (Table 2), and probability of histopathological regression ($p<0.001$) (Table 2).

For patients with regression 1a, median survival is not reached (1-year OS, 94.8 %; 3-year OS, 78.1 %; 5-year OS, 71.6 %) compared to patients with regression 1b who had a median survival of 75.3 months (1-year OS, 86.6 %; 3-year OS, 70.5 %; 5-year OS, 52.2 %) ($p=0.031$) (Fig. 3). Multivariate analysis including the significant prognostic factors (gender, localization UICC seventh ed., type of CTx, Lauren classification, grading, ypTNMR-categories, and regression) identified Lauren classification ($p=0.007$) and ypT-category ($p<0.001$) as independent predictors of survival (Table 3).

For the R0 responders ($n=208$), median survival is not reached (1-year OS, 90.9 %; 3-year OS, 75.5 %; 5-year OS, 61.6 %). Basically, the same factors are of prognostic impact as in the group of all resected responder, only gender, grading, and grade of regression lose their prognostic relevance (Table 4). Independent prognostic factors are the ypT-category ($p<0.001$), the M-category ($p=0.005$), and the type of treatment ($p=0.04$) (Fig. 4) (Table 4).

The recurrence rate is 31.7 % ($n=66$). Sites of recurrence were local recurrence in 26 patients (39.4 %), peritoneal

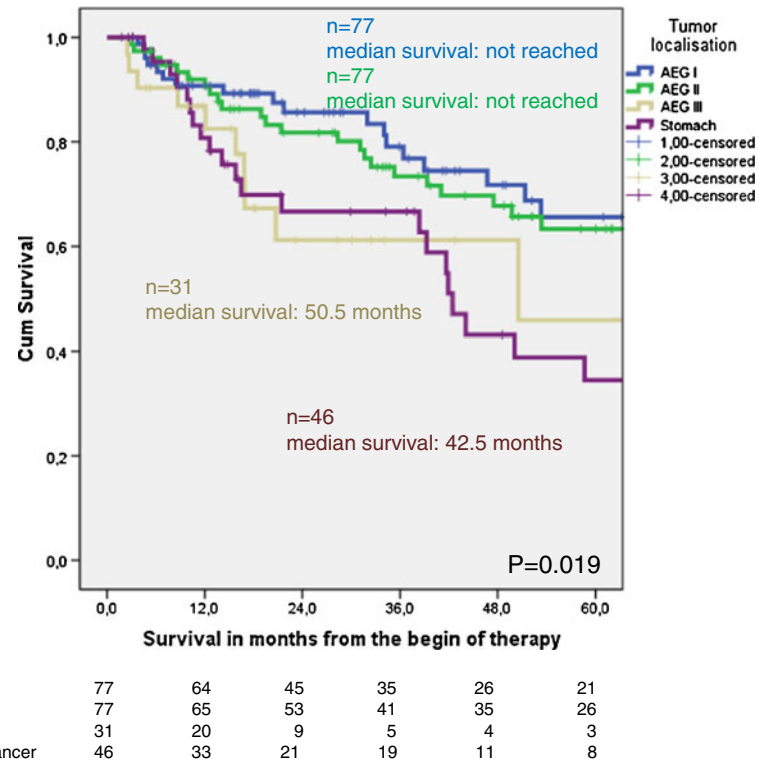


Fig. 2 Kaplan–Meier estimates of overall survival stratified by tumor localization (AEG I versus II versus III versus gastric cancer) in all included patients. Statistical comparisons were determined using the log-rank test

carcinomatosis in 17 patients (25.7 %), and distant metastases in 33 patients (50.0 %). The first documented sites of recurrence are shown in detail in Table 5. Recurrence is significantly associated with gender (females 47. 1 % versus male 28.7 %, p=0.04), grade of regression (1a 20.7 % versus 1b 36.0 %, p=0.046), ypT-category (ypT0 20.7 % versus ypT1 23.1 % versus ypT2 23.7 % versus ypT3 51.6 % versus pT4 36.4 %, p=0.002), ypN-category (ypN0 23.2 % versus ypN1 41.7 % versus ypN2 57.9 % versus ypN3 57.9 %, p<0.001), and M-category (M0 27.9 % versus M1 60.0 %, p=0.002).

The median recurrence-free survival (RFS) is not yet reached (1-year RFS, 81.0 %; 3-year RFS, 64.0 %; 5-year RFS, 58.9 %). Patients with complete remission (median not reached, 1-year RFS, 82.5 %; 3-year RFS, 75.4 %; 5-year RFS, 75.4 %) have a significant improved recurrence-free survival (median, 68.1 months; 1-year RFS, 80.3 %; 3-year RFS, 59.7 %; 5-year RFS, 53.1 %) compared to patients with subtotal regression (p=0.049). Factors predicting recurrence are gender (p=0.013), ypT-category (p=0.007), and M-category (p=0.003) in multivariate analysis (Table 6).

Table 2 Chemotherapy regimens, histopathological response, and survival in respect of the different tumor localizations

	AEG I	AEG II	AEG III	GC	p
	Number	Number	Number	Number	
Chemotherapy regimens					
PLF/OLF/EPLF/MPLF	28	51	14	26	<0.001*
EAP/ECF/EOX	12	15	11	15	
Taxol-PLF/Taxotere	22	9	4	5	
+RCTx	15	2	2	0	
Histopathological response					
Regression 1a	36	12	3	7	<0.001**
Regression 1b	41	65	28	39	
Survival Data					
Median survival (months)	n.r.	n.r.	50.5	42.5	0.019***
3-year survival (%)	79.1 %	73.4 %	61.2 %	66.7 %	
5-year survival (%)	65.6 %	63.4 %	45.9 %	34.5 %	

AEG adenocarcinoma of the esophago-gastric junction, *GC* gastric cancer, *n.r.* not reached
*p evaluated by χ^2 test, **p evaluated by Fisher's exact test, ***p evaluated by log-rank test

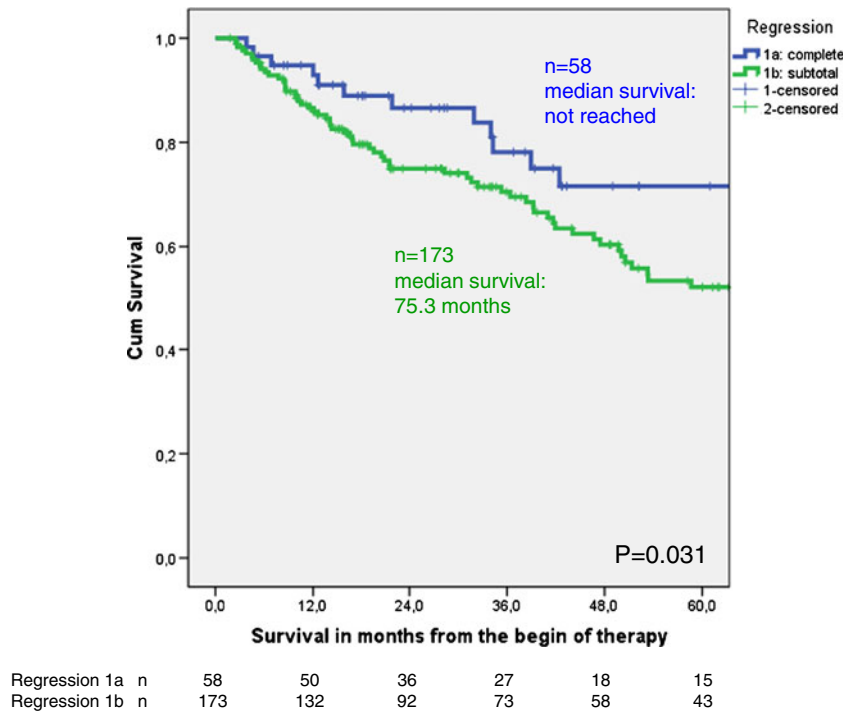


Fig. 3 Kaplan–Meier estimates of overall survival stratified by histopathological regression 1a (no residual tumor) versus regression 1b (less than 10 % residual tumor) in all included patients. Statistical comparisons between 1a and 1b were determined using the log-rank test

Table 3 Prognostic factors in all responding patients (n=76/231 died) based on overall survival

Factor	p (Kaplan–Meier)	p (univariate)		p (multivariate)	RR	95 % CI
Center	0.840					
Gender	0.047	0.063				
Esophagus (UICC 6th) vs. rest	0.073					
Esophagus (UICC 7th) vs. rest	0.008	0.017				
Type of chemotherapy	0.002	0.004				
Integration of radiation	0.292					
Discontinuation of chemotherapy	0.274					
Lauren classification (int. vs. rest)	<0.001	<0.001				
			Diff/mix		1	
			Intest	0.007	0.501	0.303–0.829
Grading (G1/2 vs. G3/4)	0.016	0.023				
Type of resection	0.432					
Complications yes vs. no	0.422					
Surgical complications yes vs. no	0.608					
ypT-category (UICC 7th)	<0.001	<0.001				
			ypT4	0.001	1	
			ypT0	<0.001	0.116	0.047–0.291
			ypT1	<0.001	0.121	0.044–0.333
			ypT2	<0.001	0.105	0.038–0.289
			ypT3	0.006	0.386	0.196–0.761
ypN-category (UICC 7th)	<0.001	<0.001				
M-category	<0.001	<0.001				
R-category	<0.001	<0.001				
Regression 1a vs. 1b	0.031	0.021				

Table 4 Prognostic factors in R0-responding patients (n=60/208 died) based on overall survival

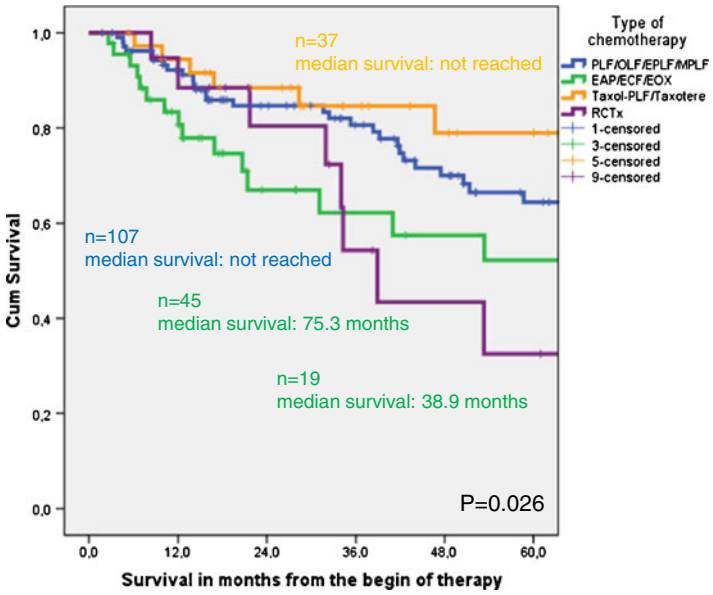
Factor	p (Kaplan–Meier)	p (univariate)		p (multivariate)	RR	95 % CI
Center	0.767					
Gender	0.065	0.086				
Esophagus (UICC 6th) vs. rest	0.163					
Esophagus (UICC 7th) vs. rest	0.011	0.011				
Type of chemotherapy	0.026	0.070				
			+RTX	0.041	1	
			+PLF	0.029	0.272	0.085–0.875
			+Epi/Platin	0.228	0.469	0.137–1.605
			+Taxan	0.017	0.187	0.047–0.745
Integration of radiation	0.115					
Discontinuation of chemotherapy	0.455					
Lauren classification (int. vs. rest)	0.003					
Grading (G1/2 vs. G3/4)	0.103					
Type of resection	0.419					
Complications yes vs. no	0.428					
Surgical complications yes vs. no	0.616					
ypT-category (UICC 7th)	<0.001	<0.001				
			ypT4	<0.001	1	
			ypT0	0.002	0.142	0.042–0.483
			ypT1	0.012	0.202	0.058–0.703
			ypT2	0.001	0.111	0.028–0.430
			ypT3	0.241	0.550	0.262–1,495
ypN-category (UICC 7th)	0.001	<0.001				
M-category	<0.001	<0.001				
			M1		1	
			M0	0.005	0.391	0.204–0.748
Regression 1a vs. 1b	0.146	0.055				

Discussion

Histopathological responders with esophago-gastric adenocarcinomas with less than 10 % residual tumor have a good long-term prognosis with a 5-year survival of 56.6 %, which corresponds to the only multicenter trial including only histopathological complete responders after esophagectomy with a 5-year survival of 55 % including both adenocarcinomas and squamous cell carcinomas [22]. A complete histopathological remission in this study was significantly associated with an improved 5-year survival of 71.6 % and a 5-year recurrence-free survival of 75.4 %, which is far better than reported in unselected patients until now [4, 22, 23]. In contrast to a recently published multicenter trial [22], in which only age had a prognostic impact, several factors predicting the outcome of responding patients could be identified in our study. Both the established prognostic factors ypT- and M-categories were independent predictors for overall and recurrence-free survival; additionally, overall survival was determined by the type of the chemotherapy regimen, and, interestingly, recurrence-free survival showed a gender difference.

Of note, more than 40 % of the patients with less than 10 % residual tumor present with ypT3/4 categories showing that an excellent histopathological response of the primary tumors does not necessarily lead to low ypT-categories. The established prognostic factor ypN-category did not show prognostic significance in the multivariate analysis in the subgroup of histopathological responder. Additionally, in 19 % of the patients, a mixed response was found with persisting lymphnodes metastases despite a complete regression of the primary tumor.

The relatively low rates of 25.4 % (231/909) for a complete or subtotal regression and 6.4 % (58/909) for a complete regression in our study are not astonishing because in 92.8 %, only chemotherapy was delivered. The data are in line with the published data with 21.2 % complete or subtotal regression for gastric cancer and 4–7 % complete regression 1a for adenocarcinomas of the esophagus or stomach after preoperative chemotherapy only [19, 20].



PLF/OLF/EPLF/MPLF	107	89	68	57	44	32
EAP/ECF/EOX	45	31	16	13	11	10
Taxol-PLF/Taxotere	37	33	26	18	14	12
+RCTx	19	15	10	6	4	3

Fig. 4 Kaplan–Meier estimates of overall survival stratified by chemotherapy regimen applied in the subgroup of R0-resected patients. Statistical comparisons between 1a and 1b were determined using the log-rank test

The lower probability of merely 18 % regressions 1a or b of the patients from Heidelberg might be associated with the treatment of less AEG tumors in this center [30]. The other clinical and pathological factors were well balanced in both institutions [31]. The combination of AEG and gastric cancer in one analysis seemed to be justified because often identical preoperative regimens are used and randomized studies exist combining these entities; however, we performed a separate analysis for AEG and gastric cancer according to the two available UICC classifications (sixth and seventh editions), which showed no independent prognostic impact for localization. However, a detailed analysis of the four different tumor localizations AEGs I, II, III, and gastric cancer, which is not integrated in any "official classification," showed a significant different overall survival and a different probability of regression, which might suggest a similar biological behavior of AEGs I and II in contrast to AEG III and gastric cancer, which is neither represented by the sixth nor the seventh edition of the UICC classification. So the problem of the belonging of the junctional adenocarcinomas, either to esophageal or gastric cancer seems not to be solved by the seventh edition of the UICC classification, in which all AEG with extension to the esophagus are classified identically as esophageal cancer despite of their different biological behavior.

The addition of radiotherapy increases response rates up to 40 % [4, 23]. In contrast to our study, in the recently published multicenter trial, only 5.0 % of the complete responders had chemotherapy, while the vast majority had preoperative chemoradiotherapy [22]. In a single center study from the Sloan Kettering including patients with AEGs II and III analyzing 60 patients with a pCR compared to those with residual tumor, 46 % were preoperatively treated with chemotherapy only and 54 % with combined chemoradiotheray. The pCR rate was significantly higher in the chemoradiotherapy group, but the rate of recurrence was slightly, however, not statistically significant, higher after chemoradiotherapy with 26 % compared to 15 % after chemotherapy only [22]. This suggests that despite a higher histopathological regression rate observed during radiochemotherapy, the control of systemic disease is of crucial importance.

We used less than 10 % residual tumor as a criterion for response and not only a pCR because it has been shown to be associated with excellent prognosis following chemotherapy alone [4, 8, 20] and increases the percentage of patients with histopathological response because the incidence of a pCR after chemotherapy only is very rare [19, 20, 32]. The 5-year survival rate of 56.6 % observed in our study is comparable to outcomes seen in two studies with 55 % [22] and 60 % [32] including patients with a pCR only. Our very similar survival data justify the definition of patients with less than 10 % residual tumor and not only patients with histopathological complete regression as responders after preoperative chemotherapy.

In our study, the cisplatin/5-FU-based chemotherapy [27] and taxol-based regimens [29] are superior to the etoposide-, doxorubicin-, or epirubicin-containing [26, 33] regimens. The addition of taxanes to cisplatin/5-FU-based regimen might increase the response rates even after chemotherapy only [34, 35]. The worse survival of the etoposide- and doxorubicine-containing regimens in our study might be

Table 5 Sites of first documented recurrence based on tumor regression

	Regression 1a*n*=58		Regression 1b*n*=150 R0		Responder
	No. of sites	No. of patients	No. of sites	No. of patients	No. of patients
Recurrence		*n*=12[a] (20.7 %)		*n*=54[a] (36.0 %)	*n*=66 (31.7 %)
Site of recurrence					
Distant metatases					
Distant lymph nodes	3		16		
Liver	5		5		
Lung	4		4		
CNS	–		3		
Bone	–		2		
Adrenal gland	–		1		
	12	8 (66.7 %)	31	25 (44.4 %)	33 (50 %)
Local					
Endoluminal	2		4		
Extraluminal	–		11		
Local lymp nodes	–		9		
	2	2 (16.7 %)	24	24 (46.3 %)	26 (39.4 %)
Carcinomatosis					
Pleura carcinomatosis	2		1		
Peritoneal carcinomatosis	–		12		
Krukenberg tumor	–		3		
	2	2 (16.7 %)	16	15 (27.8 %)	17 (25.8 %)

[a] In one patient of each group, the site of recurrence is unknown, both died of metastatic disease; one patient with regression 1a had two different sites of recurrence, and 11 patients with regression 1b.

caused by the relatively poor outcome of the patients treated with EAP due to far-advanced tumor categories and resections often including the spleen and the pancreatic tail [26, 33].

Despite a relevant histopathological regression of the primary tumor, at least one third of patients suffer a recurrence. Therefore, we have to be aware that a histopathological response is merely a surrogate parameter for a favorable

Table 6 Factors predicting recurrence (*n*=66/208 relapsed) based on recurrence-free survival. The same factors as in Tables 3 and 4 were tested, but only the significant factors are mentioned

Factor	*p* (Kaplan–Meier)	*p* (univariate)		*p* (multivariate)	RR	95 % CI
Gender	0.007	0.006				
			Female		1	
			Male	0.013	0.471	0.260–0.853
ypT-category (UICC 7th)	<0.001	<0.001				
			ypT4	0.007	1	
			ypT0	0.025	0.263	0.082–0.844
			ypT1	0.040	0.271	0.078–0.942
			ypT2	0.018	0.226	0.066–0.776
			ypT3	0.385	0.620	0.212–1.820
ypN-category (UICC 7th)	0.001	<0.001				
M-category	<0.001	<0.001				
			M1	1		
			M0	0.003	0.391	0.204–0.748
Regression 1a vs. 1b	0.049	0.049				

outcome but does not guarantee long-term recurrence-free survival. The reason for this might be the persisting influence of the relevant prognostic factors like ypT- and M-categories as shown for the first time in this analysis. The higher risk of recurrence in females might be explained by their special tumor characteristics (significantly more often gastric cancer, a non-intestinal Lauren classification, a lower differentiation, and, most importantly, less frequent pCR [$p=0.006$] compared to men) which are associated with impaired prognosis and resulting often in a peritoneal carcinomatosis as the first site of failure. Our overall recurrence rate of 31.7 % is higher compared to the 23.4 % [22] and 23 % [32] of the two other studies including only histopathological complete responders. However, the recurrence rate of 20.7 % for the complete histopathological responder is nearly identical. Distant metastases as first sites of recurrence (50–86 %)[26,45] are predominant in all studies. The local recurrence rate for histopathological complete responder ranges from 14.3 % [22] for histopathological complete responders after chemoradiotherapy followed by resection up to 43 %[45] after chemotherapy followed by complete resection. In contrast to the data presented from the MSKCC [22], our study shows a significant association of recurrence rate and grade of regression.

In summary, patients with a less than 10 % residual primary tumor have a good prognosis with a 5-year survival rate of 56.6 %, patients with a pCR even of 71.6 %; therefore, increasing the rate of pCR must be one goal of the future. Nevertheless, ypT-, ypM-, and type of chemotherapy are independent prognostic factors patients and could be used for the modification of adjuvant treatment and follow-up but should be validated in independent patients' populations. Despite a histopathological response, 31.7 % of the patients relapsed, most often with distant metastases. Risk factors for recurrence are advanced ypT- and M1-categories and female gender. This highlights the demand for a more effective adjuvant therapy.

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