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Hamburg-Glasgow classification: preoperative staging by combination of disseminated tumour load and systemic inflammation in oesophageal carcinoma

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Background: The aim of this study was to establish a new preoperative staging classification and evaluate its comparability to the post-operative tumour stage, lymph node invasion and metastasis (TNM) classification. To date, adequate, preoperative staging in patients with oesophageal carcinoma (EC) is still missing but urgently needed. Systemic inflammation and disseminated tumour load have a pivotal role in recurrence and oncological outcome. To improve the clinical staging, we merged the Glasgow Prognostic Score (GPS) and disseminated tumour cells (DTC) into a new sufficient preoperative staging classification, the Hamburg-Glasgow classification (HGC).

Methods: In this prospective, single-centre study, 326 patients following curative oesophagectomy were included. From all patients preoperative bone marrow was aspirated from the iliac crest to detect DTCs by immunostaining with the pan-keratin antibody A45-B/B3. HGC was subdefined into four prognostic groups on the basis of C-reactive protein (CRP), albumin and DTC. The three prognostic groups of the GPS were supplemented by DTC detection status. Results were correlated with clinicopathological parameters and clinical outcome.

Results: Increasing HGC significantly correlated with lymph node invasion ($P=0.022$), post-operative pathohistological TNM staging ($P=0.001$) and tumour recurrence ($P=0.001$). The four HGC prognostic groups displayed a gradual decrease in overall as well as disease-free survival ($P<0.001$, each). Hamburg-Glasgow classification was a strong, significant independent predictor of overall survival and disease-free survival ($P<0.001$, both) in multivariate analysis.

Conclusions: Hamburg-Glasgow classification seems to be a promising preoperative additive staging classification for accurate and simple outcome stratification.

Oesophageal cancer (EC) is an aggressive disease and the sixth most frequent cause of cancer death worldwide (Siegel *et al*, 2015). Five-year survival rates following curative oesophagectomy in a multimodal treatment approach have increased but locoregional recurrence and distant metastasis remain a significant problem even in node-negative patients (Hulscher *et al*, 2002; Allum *et al*,

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2009). Neoadjuvant treatment regimes have been introduced for improving long-term locoregional as well as systemic tumour control (Cunningham *et al*, 2006; Sjoquist *et al*, 2011; van Hagen *et al*, 2012). However, indication for neoadjuvant therapy is based on insufficient preoperative staging tools like computed tomography (CT) and endoscopic ultrasound (EUS) with poor sensitivities and significant proportion of under- and over-staging (Kutup *et al*, 2007; Allum *et al*, 2011). Disseminated tumour load and systemic inflammation have a pivotal role in cancer progression and tumour recurrence (O'Sullivan *et al*, 1999; Pantel *et al*, 2008). Oesophageal adenocarcinoma is an exemplar model of an inflammation-associated cancer (O'Sullivan *et al*, 2014). Several studies and our own previous work have shown a significant prognostic impact and clinical significance of disseminated tumour cells (DTC) in the bone marrow of patients with EC (Thorban *et al*, 2000; Macadam *et al*, 2003; Vashist *et al*, 2012). In addition, systemic inflammation (SI) also correlates to cancer progression but the interaction between tumour cells and host inflammatory response is still poorly understood (Zhang *et al*, 2007; Boffetta, 2010; Sgambato and Cittadini, 2010; Terzic *et al*, 2010). The Glasgow Prognostic Score (GPS) based on two acute phase proteins albumin and C-reactive protein (CRP), represents an indicator of SI and is a useful tool for risk stratification in cancer patients (O'Gorman *et al*, 1999; McMillan, 2009). Several studies and our own work validated the GPS in several tumour entities including EC (Brown *et al*, 2007; Ishizuka *et al*, 2007, 2009; Kobayashi *et al*, 2008; Sharma *et al*, 2008; Roxburgh *et al*, 2009; Vashist *et al*, 2011).

We merged GPS and DTC status to a new sufficient preoperative staging classification (Hamburg-Glasgow classification (HGC)) substratifying four preoperative prognostic groups. HGC is based on three preoperatively, easily available and objective parameters, whereas the routinely used variables like tumour stage, lymph node invasion and metastasis (TNM) can only be accurately determined by post-operative histological analysis.

The aim of this prospective investigation was to evaluate the preoperative prognostic impact of HGC in patients with EC.

MATERIALS AND METHODS

Patients characteristics. The study was approved by the Medical Ethical Committee, Hamburg, Germany. All patients enrolled in this study underwent oesophageal resection at the Department of General, Visceral and Thoracic surgery at the University Medical Center Hamburg-Eppendorf. Informed consent was obtained from all patients before study inclusion.

Routine workup of patients included patient's history, physical examination, routine blood tests, studies of tumour markers (carcinoembryonic antigen and CA 19-9), abdominal ultrasonography, endoscopy and thoracic and abdominal CT scans as well as PET scans in selected cases from 2006 forward.

The database included 605 patients. 360 patients had available DTC and GPS status. Only patients without neoadjuvant therapy and histologically proven EC as well as tumour-free resection margins and without distant metastasis (M0) with complete follow up data were included in the study ($N = 326$).

Disseminated tumour cell detection. Bone marrow was aspirated from the right upper iliac crest before primary oesophageal cancer surgery. Mononuclear cells were enriched using the Ficoll-Hypaque gradient. Bone marrow samples were immunocytochemically assessed for DTC using the monoclonal anticytokeratin antibody A45-B/B3 (mouse IgG1; AS Diagnostics, Hückeswagen, Germany). The A45-B/B3 antibody has been established for disseminated tumour cell detection in EC earlier (Izbicki *et al*, 1997). As an isotype-specific negative control the MOPC-21 monoclonal antibody (Sigma Chemical, St Louis, MO, USA), lacking any known reactivity for epithelial cells or bone marrow cells, was used at the same concentration as the A45-B/B3. This immunocytochemical assay for DTC in bone marrow is state-of-the-art and has a false-positive rate of maximum 1% in control cases (Braun *et al*, 2000). Criteria applied for the disseminated tumour cell analysis were extensively analyzed by Fehm *et al* (2006). Disseminated tumour cells detection, staining and interpretation were performed in the same way as described before (Vashist *et al*, 2012).

Hamburg-Glasgow classification. For evaluation of the HGC blood test results containing albumin and CRP from the day before surgery or test results not older than 1 week before surgery were used. Abnormalities were defined as follows: DTC status positive (DTC $\geqslant 1$), elevated CRP ($>10\,g\,l^{-1}$) and hypoalbuminemia ($<35\,g\,l^{-1}$). Glasgow Prognostic Score prognostic groups were expanded by DTC status and four HGC prognostic groups were defined. Table 1 depicts details of HGC classification.

Statistical analysis. For statistical analysis, SPSS 20.0 (Chicago, IL, USA) was used. Descriptive statistics were used to describe patient baseline characteristics. To evaluate a potential association between the HGC and clinicopathological parameters, the χ^2-test was applied. Survival curves for disease-free and overall survivals of the patients were plotted using the Kaplan–Meier method and analyzed using the log-rank test. Results are presented as median survival in months with 95% confidence interval (CI) and number of patients at risk. Post-operative follow-up was conducted at 3-month intervals for the first 2 years, including physical examination, plain chest radiography, abdominal ultrasonography, endoscopy, endoscopic ultrasonography and computed tomography of the chest and abdomen. Studies of tumour markers (carcinoembryonic antigen and cancer antigen 19-9) and bone scans were also performed. The overall survival was computed as the time period from the date of surgery to either the date of death or last follow-up, whichever occurred first. The disease-free survival was defined as the time period from the date of surgery to the date of recurrence, last follow-up or date of death, whichever occurred first. Patients alive without recurrence at the last follow-up dates were censored. Cox regression hazard model was used for multivariate analysis to assess the independent influence of HGC and other covariates on tumour recurrence and overall survival. Results are presented as hazard ratio (HR) with 95% CI. Significant statements refer to P-values of two-tailed tests that were $P<0.05$.

Table 1. Definition of the Hamburg-Glasgow classification (HGC)

Variables	HGC I	HGC II	HGC III			HGC IV
DTC status	Neg.	Neg.	Neg.	Pos.	Pos.	Pos.
CRP ($mg\,l^{-1}$)	<10	$\geqslant 10$	$\geqslant 10$	<10	$\geqslant 10$	$\geqslant 10$
Albumin ($g\,l^{-1}$)	and >35	or $\leqslant 35$	and $\leqslant 35$	and >35	or $\leqslant 35$	and $\leqslant 35$

Abbreviations: CRP = C-reactive protein; DTC = disseminated tumour cell.

RESULTS

Patient characteristics and HGC correlations. Three hundred and twenty six patients following curative oesophagectomy with tumour-free resection and preoperative available DTC, albumin and CRP status were finally included. There were 154 patients with adenocarcinomas (AC) and 172 patients with squamous cell carcinomas (SCC). Of the 326 patients, 260 were men and 66 were women, and their median age was 61 years (range 34–83 years). Ninety-day mortality rate was 3.3%. None of the patients received adjuvant treatment.

We assessed the correlation of HGC with gender, age and the following histopathological parameters: tumour depth, lymph node stage, post-operative Union for International Cancer Control (UICC) TNM classification, histological type, tumour grading, surgical approach and tumour recurrence. No correlations were found between HGC stages and gender, age, tumour depth, histological type, tumour grading and surgical approach (P = n.s.). Hamburg-Glasgow classification was significantly correlated with the presence of lymph node invasion ($P = 0.022$), post-operative TNM classification ($P = 0.001$) and tumour recurrence ($P = 0.001$). Table 2 depicts the tumour-specific patient characteristics and the results of the correlation analysis. Further, we analyzed the positive predictive value, negative predictive value as well as accuracy concerning lymph node metastasis. The results were 68%, 47.3% and 55.2%, respectively.

Univariate survival analysis. The median follow-up time of surviving patients was 60 months. The median survival time was 21.97 months (95% CI, 18.05–25.89 months). Hamburg-Glasgow classification showed significant preoperative risk stratification between the four prognostic groups for overall as well as disease-free survival ($P < 0.001$, each) (Figure 1). Hamburg-Glasgow classification showed significant overall survival stratification for SCC and AC subgroup analyses ($P < 0.001$, each). These results were comparable to the significant survival stratification of the post-operative UICC TNM classification ($P < 0.001$, each) (Figure 1). Pairwise log rank analyses showed significant survival stratification by each HGC stage as well as pTN stages. In a subgroup analysis including only pT1–2 N0 patients ($N = 129$), HGC groups III/IV showed significant shorter overall as well as disease-free survival in comparison to HGC groups I/II ($P < 0.001$, each) (Figure 2).

Multivariate survival analysis. We analyzed the independent prognostic impact of the HGC on overall and disease-free survival by multivariate stratified analysis including age, gender, post-operative UICC TNM classification, tumour grading and histological type. The HGC prognostic groups were identified as strong independent prognostic markers for overall survival ($P < 0.001$; HR 3.19, 95% CI, 2.06–4.93) and disease-free survival ($P < 0.001$; HR 2.24, 95% CI, 1.36–3.68; Table 3).

Table 2. Patient characteristics and correlation between Hamburg-Glasgow classification (HGC) and clinicopathological parameters

Variables	All	HGC I	HGC II	HGC III	HGC IV	*P*-value
Total	326 (100)	159 (48.8)	42 (12.9)	95 (29.1)	30 (9.2)	
Age (years)						0.738
⩽60	155 (47.5)	79 (49.7)	17 (40.5)	44 (46.3)	15 (50.0)	
>60	171 (52.5)	80 (50.3)	25 (59.5)	51 (53.7)	15 (50.0)	
Sex						0.478
Male	260 (78.8)	127 (79.9)	33 (78.6)	79 (83.2)	21 (70.0)	
Female	66 (20.2)	32 (20.1)	9 (21.4)	16 (16.8)	9 (30.0)	
Tumour stage						0.147
pT1	69 (21.2)	39 (24.5)	9 (21.4)	18 (18.9)	3 (10.0)	
pT2	100 (30.7)	54 (34.0)	14 (33.3)	25 (26.3)	7 (23.3)	
pT3	141 (43.3)	62 (39.0)	16 (38.1)	44 (46.3)	19 (63.3)	
pT4	16 (4.9)	4 (2.5)	3 (7.1)	8 (8.4)	1 (3.3)	
Lymph node stage						
pN0	135 (41.4)	78 (49.1)	17 (40.5)	33 (34.7)	7 (23.3)	0.022
pN positive	191 (58.6)	81 (50.9)	25 (59.5)	62 (65.3)	23 (76.7)	
pN1	83 (25.5)	36 (22.6)	13 (31.0)	27 (28.4)	7 (23.3)	0.097
pN2	58 (17.8)	26 (16.4)	4 (9.5)	20 (21.1)	8 (26.7)	
pN3	50 (15.3)	19 (11.9)	8 (19.0)	15 (15.8)	8 (26.7)	
UICC pTNM						0.001
I A/B	87 (26.7)	54 (34.0)	10 (23.8)	20 (21.1)	3 (10.0)	
II A/B	80 (24.5)	43 (27.0)	14 (33.3)	19 (20.0)	4 (13.3)	
III A/B/C	159 (48.8)	62 (39.0)	18 (42.9)	56 (58.9)	23 (76.7)	
Histology						0.219
AC	154 (47.2)	75 (47.2)	21 (50.0)	49 (51.6)	9 (30.0)	
SCC	172 (52.8)	84 (52.8)	21 (50.0)	46 (48.4)	21 (70.0)	
Grading						0.446
G1	13 (4.0)	7 (4.4)	2 (4.8)	3 (3.2)	1 (3.3)	
G2	181 (55.5)	93 (58.5)	27 (64.3)	48 (50.5)	13 (43.3)	
G3	132 (40.5)	59 (37.1)	13 (31.0)	44 (46.3)	16 (53.3)	
Operating technique						0.283
Transhiatal	156 (49.2)	83 (54.6)	20 (47.6)	41 (44.1)	12 (40.0)	
Thoracoabdominal	161 (50.8)	69 (45.4)	22 (52.4)	52 (55.9)	18 (60.0)	
Recurrence						0.001
Negative	150 (46.0)	90 (56.6)	20 (47.6)	32 (33.7)	8 (26.7)	
Positive	176 (54.0)	69 (43.4)	22 (52.4)	63 (66.3)	22 (73.3)	

Abbreviations: AC = adenocarcinoma; SCC = squamous cell carcinoma; Percentages are shown in parentheses; *P*-value indicates significance according to χ^2-test.

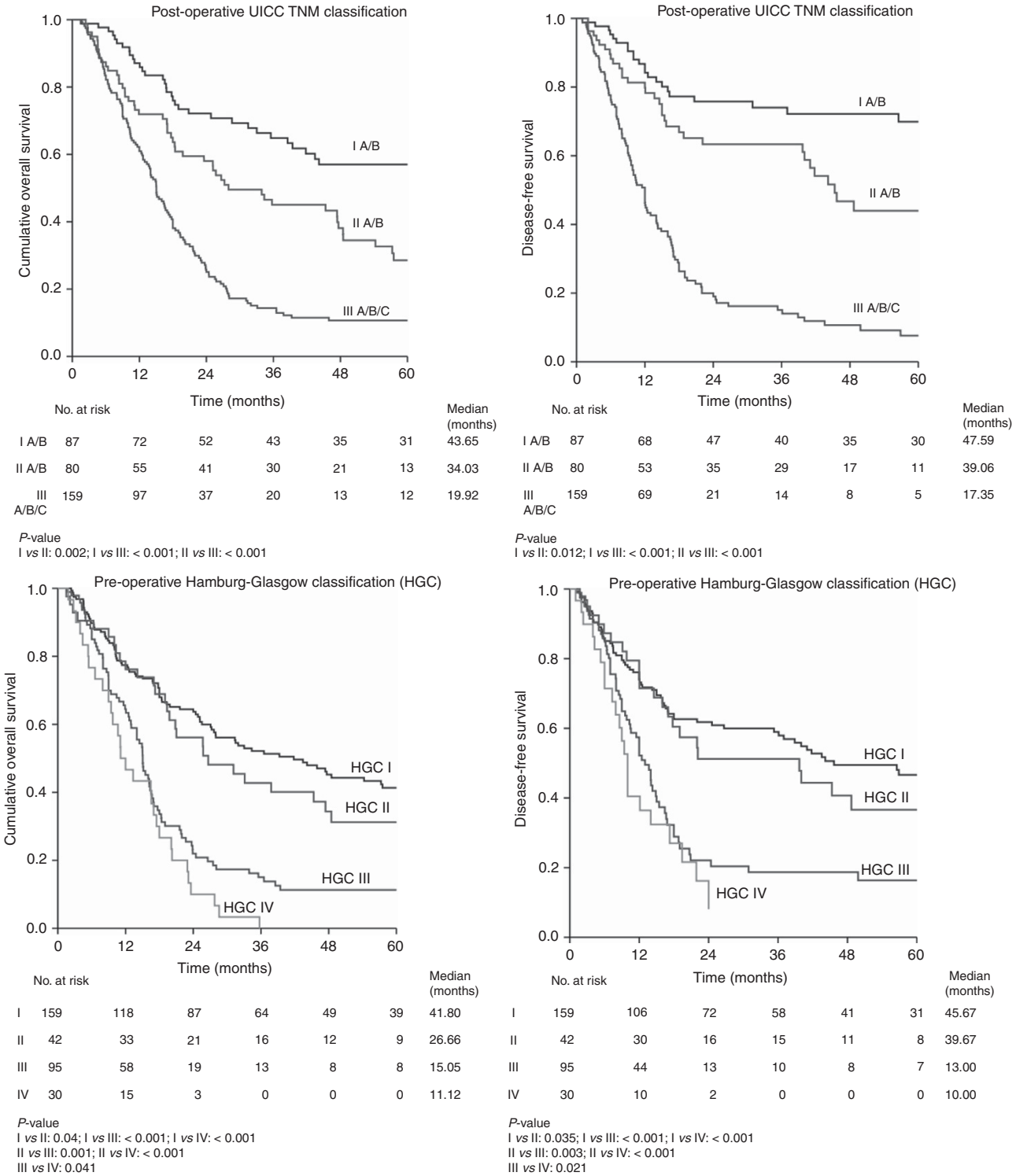

Figure 1. Comparison of the current UICC TNM classification and the HGC in regard to overall and disease-free survival.

DISCUSSION

The results of the present study show for the first time that the preoperative combination of disseminated tumour load in bone marrow indicated by DTC and systemic inflammation evaluated by GPS are associated with poor overall survival and disease-free survival after potentially curative resection in EC. Furthermore, the new defined preoperative HGC is a strong predictor of oncological outcome of patients with EC and showed comparable survival stratification to the post-operative UICC TNM classification. The HGC has several advantages compared with conventional preoperative TNM staging (Sobin and Compton, 2010; Allum *et al*, 2011). Based on the primary staging an interdisciplinary planning and therapy decision making is mandatory in EC patients. Several multicentric randomised studies showed that surgery alone in patients with advanced disease (T3 N+) results in poor survival rates (Cunningham *et al*, 2006; Allum *et al*, 2009; Sjoquist *et al*, 2011; Ychou *et al*, 2011; van Hagen *et al*, 2012). These patients need neoadjuvant chemotherapy or

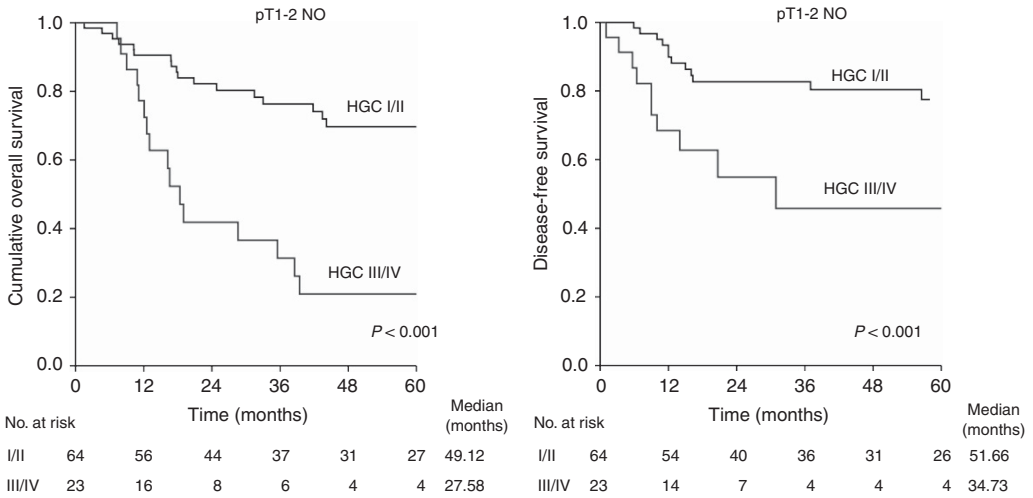

Figure 2. Outcomes of EC patients with pT1–2 N0 stratified by HGC groups I/II and III/IV in regard to overall and disease-free survival.

Table 3. Multivariate analyses of overall survival and disease-free survival

	Overall survival			Disease-free survival		
Variables	**HR**	**95% CI**	***P*-value[a]**	**HR**	**95% CI**	***P*-value[a]**
Age						
⩽60 *vs* >60 years	0.996	0.764–1.299	0.978	0.992	0.737–1.334	0.957
Sex						
Female *vs* male	1.211	0.859–1.707	0.275	1.275	0.862–1.887	0.224
HGC						
I *vs* II	1.301	0.845–2.004	0.033	1.210	0.745–1.965	0.041
I *vs* III	2.312	1.698–3.148	<0.001	1.929	1.362–2.732	<0.001
I *vs* IV	3.187	2.061–4.928	<0.001	2.241	1.364–3.680	<0.001
UICC pTNM						
I *vs* II	1.846	1.183–2.881	0.007	1.835	1.064–3.165	0.029
I *vs* III	3.337	2.246–4.958	<0.001	5.114	3.187–8.206	<0.001
Grade						
G1 *vs* G2/3	2.538	1.037–6.210	0.041	2.126	0.781–5.789	0.140
Histotype						
AC *vs* SCC	1.100	0.841–1.439	0.488	1.096	0.811–1.481	0.552

Abbreviations: AC = adenocarcinomas; CI = confidence interval; HGC = Hamburg-Glasgow classification; HR = hazard ratio; SCC = squamous cell carcinomas.
[a]Indicates significance according to Cox regression analysis comparing the specified variables.

radiochemotherapy which lead to prolonged survival in comparison to surgery as monotherapy. Therefore, accurate preoperative diagnosis and prognostic staging are imperative before multimodal treatment. Indication for neoadjuvant treatment regime is still only based on the commonly used diagnostic techniques, computed tomography, endoscopy and endoscopic ultrasound (Stahl *et al*, 2010; Allum *et al*, 2011). Sensitivities of N-staging which is the most important prognostic parameter are given between 42–68% for EUS and between 33 and 35% for CT that results in under but also overstaging in a significant number of patients (Kelly *et al*, 2001; Lowe *et al*, 2005; Kutup *et al*, 2007; van Vliet *et al*, 2008; Takizawa *et al*, 2009; Choi *et al*, 2010; Pech *et al*, 2010; Konieczny *et al*, 2013). Thus, accurate pretreatment staging remains inconsistent. However, an improvement of the current staging system by adding other significant and objective prognosticators like disseminated tumour load and SI inherit the potential for defining adequate treatments regimes based on better risk-stratification in patients with EC.

Disseminated tumour cells are described to be an early event in tumour progression which is independent of tumour depth and lymph node invasion (Pantel *et al*, 2008). Tumour recurrence and metastasis supposedly result from clinically occult, minimal residual disease like DTC (Pantel *et al*, 2008). In this context, several studies reported a prognostic value of DTC in patients with EC (Thorban *et al*, 2000; Macadam *et al*, 2003; Vashist *et al*, 2012). The advantage of this tool is the easily accessibility preoperatively in contrast to lymph nodes or other distant sites. Thus, we included DTC as a significant prognostic biomarker in the new defined, preoperative HGC. Further, we included the acute phase proteins CRP and albumin based GPS as a well-known parameter for systemic inflammation (O'Gorman *et al*, 1999; McMillan, 2009). The underlining mechanisms of SI leading to aggressive tumour biology and decreased survival are only partially understood. Elevated CRP levels are associated with proangiogenic environment based on increased levels of vascular growth factors (Krzystek-Korpacka *et al*, 2008; McMillan, 2009). Furthermore, impaired lymphocyte function correlates to elevated CRP and poor survival in several tumour entities (Jain *et al*, 2009). In addition, several studies postulated the association between increasing CRP and poor survival in various tumour types (Crumley *et al*, 2006;

Glen *et al*, 2006; Brown *et al*, 2007; McMillan *et al*, 2007; Ramsey *et al*, 2007). A decrease in albumin level was verified in several tumour entities. Hypoalbuminemia is a well-known negative prognosticator in cancer patients and is a surrogate parameter for SI (Forrest *et al*, 2003; McMillan, 2008). Several studies reported on prognostic significance of GPS on survival in various cancers including EC (Crumley *et al*, 2006; Glen *et al*, 2006; McMillan *et al*, 2007; Vashist *et al*, 2011).

Due to the prognostic significance of DTC, CRP and albumin, we constructed the HGC as a new and promising preoperative staging classification which should be additionally used in staging of patients with EC. Hamburg-Glasgow classification seems to be an objective, easily available and significant prognosticator for survival of patients with EC. Even in patients with pT1–2 N0-tumours, HGC showed significant survival stratification between the groups I/II and III/IV. The patients of the prognostic groups HGC III/IV had similar survival as patients with pT3/4 N+. In consequence, these patients (pT1–2 N0 and HGC III/IV) should have been treated by neoadjuvant treatment, which underlines the urgent need of improvement of the current TNM staging system. We could show that the HGC is independent of the TNM system. However, the HGC measures other relevant biological parameters with significant clinical impact in contrast to the TNM staging system. The implementation of the HGC into standard clinical preoperative staging might add significant information of tumour biology to the TNM classification. This have to be evaluated, prospective designed studies should evaluate the prognostic value and its role in neoadjuvant treated patients.

Although we were able to present a new and promising staging classification, our study is biased by the lack of comparative data, for example, preoperative clinical TNM stages or ASA score. However, we report on a homogenous and large study population which underwent surgery alone for EC and neither DTC status nor SI were affected by neoadjuvant systemic therapy. However, this aspect opens another future issue to be evaluated whether HGC could be used for response prediction after neoadjuvant therapy.

In conclusion, HGC is a new and promising preoperative staging classification which showed significant risk stratification for overall survival and disease-free survival in patients with non-metastatic EC. Our results suggest that HGC can enable accurate preoperative staging in addition to the TNM classification which might improve treatment of patients with EC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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