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 subdivided 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, 2004).

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The preoperative prognostic impact of HGC in patients with EC can only be accurately determined by post-operative histological tumour stage, lymph node invasion and metastasis (TNM) can be expanded by DTC status and four HGC prognostic groups were defined. Table 1 depicts details of HGC classification.

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).

**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≥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 \(\chi^2\)-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 \(P < 0.05\).

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

| Variables       | HGC I | HGC II | HGC III | HGC IV |
|-----------------|-------|--------|---------|--------|
| DTC status      | Neg.  | Neg.   | Pos.    | Pos.   |
| CRP (mg l\(^{-1}\)) | <10   | ≥10    | >10     | >10    |
| Albumin (g l\(^{-1}\)) | ≥35 or <35 | ≥35 | <35 and >35 | or <35 and ≤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)      |              |              |              |              |              |         |
| <60              | 155 (47.5)   | 79 (49.7)    | 17 (40.5)    | 44 (46.3)    | 15 (50.0)    | 0.738   |
| >60              | 171 (52.5)   | 80 (50.3)    | 25 (59.5)    | 51 (53.7)    | 15 (50.0)    |         |
| Sex              |              |              |              |              |              |         |
| Male             | 260 (78.8)   | 127 (79.9)   | 33 (78.6)    | 79 (83.2)    | 21 (70.0)    | 0.478   |
| Female           | 66 (20.2)    | 32 (20.1)    | 9 (21.4)     | 16 (16.8)    | 9 (30.0)     |         |
| Tumour stage     |              |              |              |              |              |         |
| pT1              | 69 (21.2)    | 39 (24.5)    | 9 (21.4)     | 18 (18.9)    | 3 (10.0)     | 0.147   |
| 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   |
| pN1              | 191 (58.6)   | 81 (50.9)    | 25 (59.5)    | 62 (65.3)    | 23 (76.7)    |         |
| pN2              | 83 (25.5)    | 36 (22.6)    | 13 (31.0)    | 27 (28.4)    | 7 (23.3)     |         |
| pN3              | 58 (17.8)    | 26 (16.4)    | 4 (9.5)      | 20 (21.1)    | 8 (26.7)     |         |
| UICC pTNM        |              |              |              |              |              |         |
| I A/B            | 87 (26.7)    | 54 (34.0)    | 10 (23.8)    | 20 (21.1)    | 3 (10.0)     | 0.001   |
| 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        |              |              |              |              |              |         |
| AC               | 154 (47.2)   | 75 (47.2)    | 21 (50.0)    | 49 (51.6)    | 9 (30.0)     | 0.219   |
| SCC              | 172 (52.8)   | 84 (52.8)    | 21 (50.0)    | 46 (48.4)    | 21 (70.0)    |         |
| Grading          |              |              |              |              |              |         |
| G1               | 13 (4.0)     | 7 (4.4)      | 2 (4.8)      | 3 (3.2)      | 1 (3.3)      | 0.446   |
| 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 |          |              |              |              |              |         |
| Transhiatal      | 156 (49.2)   | 83 (54.6)    | 20 (47.6)    | 41 (44.1)    | 12 (40.0)    | 0.283   |
| Thoracabdominal  | 161 (50.8)   | 69 (45.4)    | 22 (52.4)    | 52 (55.9)    | 18 (60.0)    |         |
| Recurrence       |              |              |              |              |              |         |
| Negative         | 150 (46.0)   | 90 (56.6)    | 20 (47.6)    | 32 (33.7)    | 8 (26.7)     | 0.001   |
| 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 $\chi^2$-test.
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
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; Cumulative overall survival and Disease-free survival for 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

| Variables | Overall survival | Disease-free survival |
|-----------|-----------------|----------------------|
|           | HR  | 95% CI | P-value* | HR  | 95% CI | P-value* |
| 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 | 1.064–3.156 | 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 | 2.338 | 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. *Indicates significance according to Cox regression analysis comparing the specified variables.
The authors declare no conflict of interest.

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CONFLICT OF INTEREST

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