Original Article

Impact of anaemia in oesophago-gastric cancer patients undergoing curative treatment by means of neoadjuvant chemotherapy and surgery

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Highlights:

- Pre-neoadjuvant chemotherapy and pre-operative anaemia was associated with poorer overall survival.
- Normocytic anaemia was most prevalent, suggesting a multifactorial aetiology.
- Targeting anaemia at this point in treatment may reduce blood transfusion and improve outcomes.

Abstract

Background: The present study investigated factors associated with pre-neoadjuvant chemotherapy (NAC), and pre-operative anaemia, and examined their impact on outcomes in patients with oesophago-gastric cancer treated with curative intent.

Methods: Patients diagnosed with oesophago-gastric cancer (January 2010 to December 2015) and treated with curative intent by NAC then surgery at a tertiary centre were included. Patients were grouped by the presence of anaemia (haemoglobin <130 mg/L in males and <120 mg/L in females) and into microcytic (MCV <80 fL), normocytic (80-100 fL) and macrocytic (>100 fL) subgroups. Categorical data were analysed by chi-squared test and overall survival by univariate and multivariate Cox regression.

Results: 99/295 (34%) patients who received NAC were diagnosed with pre-NAC anaemia, and 157/268 (59%) of patients who subsequently underwent surgery were diagnosed with pre-operative anaemia. Normocytic anaemia was the most common, with 76 (26%) in pre-NAC and 107 (40%) in pre-operative groups. Pre-NAC

anaemia was associated with increasing clinical N stage (p=0.022), higher modified Glasgow Prognostic Score (mGPS) (p=0.006), and a higher rate of intra-operative transfusion (p = 0.030). Pre-operative anaemia was associated with pre-NAC anaemia (p=0.004), increasing age (p = 0.026), higher pre-operative mGPS (p=0.021), and a higher rate of intra-operative transfusion (p=0.021). Anaemia before NAC and surgery was associated with poorer overall survival in patient following R0 resection, independent of stage (HR 1.26, 95% CI 1.02-1.54, p = 0.030).

Conclusion: Anaemia was associated with poorer overall survival and greater requirement for intra-operative blood transfusion in oesophago-gastric cancer patients undergoing treatment with curative intent.

1. Introduction

Pre-operative anaemia is common in gastrointestinal (GI) disease[1]. Recent studies have suggested that 35-40% of colorectal cancer patients are anaemic at presentation[2,3]. In cancer patients undergoing chemotherapy, the occurrence of anaemia can be as high as 75%[2]. It has been previously thought that anaemia in the oesophago-gastric cancer population is mainly due to iron-deficiency caused by a mix of chronic occult GI blood loss and inadequate oral iron intake, leading to insufficient iron stores (absolute iron deficiency)[4], and it is usually associated with microcytosis[5]. However, a recent study has suggested that normocytic anaemia is the most common type of anaemia seen in GI cancer patients[6]. It has also been suggested that systemic inflammation is associated with pre-operative normocytic anaemia in colorectal cancer patients[3]. Therefore, the cause of pre-operative anaemia in GI cancer patients remains uncertain. It can often be complex and multifactorial, with chronic blood loss, nutritional deficiencies, oncologic treatment and a chronic inflammatory state being contributing factors.

Pre-operative anaemia has been found to be associated with poorer post-operative outcomes, including increased length of stay[7], complications[8], and mortality[9]. It is also the strongest indicator of requirement of allogenic blood transfusion[2], with its associated risk of transfusion reaction, adverse cardiovascular events[10], and increased mortality and serious morbidity[11].

Transfusion is also associated with shorter disease-free survival and overall survival in patients after cancer resection[12]. Therefore, it is imperative that strategies are developed to recognise and treat anaemia in oesophago-gastric cancer patients at an early stage to minimise the use of blood transfusions in the peri-operative period.

The aim of this study therefore was to identify and compare factors associated with pre-chemotherapy anaemia and pre-operative anaemia, together with their effect upon short term treatment and postoperative outcomes, and overall survival in oesophago-gastric cancer patients undergoing radical treatment by means of neoadjuvant chemotherapy (NAC) and surgery.

2. Methods

2.1 Patient population

All patients diagnosed with oesophageal, junctional or gastric cancer who underwent NAC with a plan for surgery with curative intent were included in this study. Patients who underwent chemotherapy in National Health Service Greater Glasgow and Clyde (NHS GGC) or National Health Service Forth Valley (NHS FV) between January 2010 and December 2015 (determined by date of first attendance of chemotherapy) were identified from the Beatson Oncology Centre Chemocare database. Patients operated in Glasgow Royal Infirmary (GRI) with curative intent within the same time period (defined by date of surgery) were identified from a prospectively collected Clinical Outcomes Audit database maintained within the Upper GI unit at GRI.

All patients received NAC in either NHSGGC and those who proceeded to surgery were operated on in a single tertiary referral teaching hospital (Glasgow Royal Infirmary). All NAC regimens used included a combination of a platinum-based drug plus 5-fluorouracil or capecitabine, and also Epirubicin where tolerated, with a median 8 weeks between the end of treatment and surgery during which re-staging occurred.

During the study period, there was no specific policy or protocol in place for the treatment of anaemia either before NAC or surgery, with blood transfusions or otherwise.

Datasets were merged and patient details were then extracted from NHS GGC clinical portal, which is prospectively maintained, using Community Health Index (CHI) number. Patients with metastatic disease at time of diagnosis, patients that underwent radical primary chemoradiotherapy without plan for surgery, and patients that underwent palliative intervention as first line treatment were excluded. Patients that underwent direct primary surgery without NAC were also excluded.

This study was approved by the local Caldicott Guardian and Research Ethics Committee (19/SC/0653).

2.2 Study design

Demographics, clinical information regarding physical status and comorbidities, pathological variables including laboratory results and staging according to seventh edition of the TNM Classification of Malignant Tumours by Union for International Cancer Control (UICC), as well as data on treatment outcomes were extracted to form a database.

Patients were then categorised by the presence of anaemia according to the World Health Organisation guideline (haemoglobin < 130 mg/L for male and < 120 mg/L for female)[13]. Pre-chemotherapy anaemia was defined by haemoglobin level below these values recorded

between date of endoscopic diagnosis and date of first attendance for NAC. Pre-operative anaemia was defined by a haemoglobin level below these values between last attendance of NAC and date of surgery. Anaemic patients were further subdivided based on mean corpuscular volume (MCV) into microcytic (MCV < 80 fL), normocytic (MCV 80-100 fL) and macrocytic (MCV > 100 fL) groups using standard criteria[14]. Iron status of patients were also collected and intended to identify deficiencies, but data were only available in a minority of patients and so were not included in this study.

2.3 Statistical analysis

Categorical variables including 30-day mortality, surgical complications and peri-operative blood transfusion were recorded, and frequencies were found by cross-tabulations. Analysis on association between different factors and either pre-chemotherapy or pre-operative anaemia was carried out by chi-squared tests; Pearson's chi-squared test was used for 2x2 tables, and chi-squared test for linear trend was used for multiple categorical data. Multivariate binary logistic regression with backward conditional model was then performed on variables associated with anaemia in univariate regression with significance level of $p < 0.05$.

Survival analysis was conducted by first using Kaplan-Meier curves and log-rank test to

examine the differences in overall survival between groups with and without pre-chemotherapy and pre-operative anaemia. Patients who did not proceed to surgery, who did not have an R0 resection, who died within 30 days of surgery, and who were lost to follow up were excluded from survival analysis. Overall survival was defined as time from date of diagnosis by endoscopy to date of death by any cause or date of censoring (14 March 2019). Multivariate survival analysis was performed using Cox regression with a backward conditional model including those variables found to be associated with overall survival at a univariate significance of $p<0.1$. Two-sided p values <0.05 were considered statistically significant.

Statistical analysis was performed using SPSS Statistics software (IBM SPSS Statistics Version 24, Chicago, USA).

3. Results

3.1 Patients characteristics

A total of 429 patients were identified as undergoing radical treatment for oesophago-gastric cancer incorporating NAC and planned surgical resection between 2010 and 2015. 92 patients proceeded straight to surgery and so were excluded. 337 patients were therefore available for analysis. 301 (89%) of these patients proceeded to surgery following NAC, with a median wait of 8 weeks, of which 270 (90%) had the tumour resected, while 31 (10%) had an inoperable tumour (Figure 1).

During the follow up period there were 203 deaths (60%), with 183 of these deaths caused by oesophago-gastric cancer. The median survival of the cohort as a whole was 37 months (95% CI 25-48 months). The median follow up of those alive at the time of censoring was 69 months (range 44-114 months).

3.2 Pre-neoadjuvant chemotherapy anaemia and its association with patient characteristics and outcomes

295 (87%) of the 337 NAC patients had haemoglobin measured between diagnosis and first attendance of chemotherapy, of which 99 (34%) met the diagnostic criteria of anaemia

(Supplementary Figure 1). 19 (6%) had microcytic anaemia, 76 (26%) had normocytic anaemia, and 4 (1%) had macrocytic anaemia. In this group, the majority were male (208, 71%), aged ≥ 65 (152, 53%), had a junctional tumour (185, 63%) and with clinical staging of T3 (142, 63%).

When patients with pre-neoadjuvant chemotherapy anaemia were compared with patients without anaemia (

Table 1), clinical N stage (p = 0.015) and pre-chemotherapy mGPS (p = 0.001) showed a significant difference, with a higher nodal staging and greater extent of systemic inflammation shown in anaemic patients. At multivariate level (Supplementary Table 1), both higher clinical N stage (p = 0.022) and pre-chemotherapy mGPS (p = 0.006) remained independently associated with pre-neoadjuvant chemotherapy. Patients with different subtypes of anaemia were also compared with patients without anaemia (Supplementary Table 2), at which increasing age (p = 0.037) and lower oxygen uptake (VO_2) at peak exercise (p = 0.017) were also found to be significantly associated with pre-neoadjuvant chemotherapy anaemia.

Pre-neoadjuvant chemotherapy anaemia was associated with a significantly higher rate of intraoperative blood transfusion (15% vs 6%, p = 0.030), but a lower rate of postoperative blood transfusion (16% vs. 29%, p = 0.044), and there was no association with preoperative blood transfusion (Table 2).

3.3 Pre-operative anaemia and its association with patient characteristics and outcomes

268 (99%) of the 270 resected patients had haemoglobin measured before surgery, of which 157 (59%) were diagnosed with anaemia. No patient had microcytic anaemia, 107 (40%) had normocytic anaemia, and 50 (19%) had macrocytic anaemia.

When patients who underwent surgical resection with and without pre-operative anaemia were compared (Table 33), significant differences were noted in age ($p = 0.006$), VO_2 peak ($p = 0.045$), pre-neoadjuvant chemotherapy anaemia ($p < 0.001$), and pre-operative mGPS ($p = 0.014$). Preoperative anaemia (0.004), increasing age ($p = 0.026$), lower VO_2 peak ($p = 0.077$) and higher pre-operative mGPS ($p = 0.021$) all remained independently associated with pre-operative anaemia in multivariate binary logistic regression (Supplementary Table 3). When different subtypes of anaemia were considered (Supplementary Table 4), male sex ($p = 0.048$), tumour site ($p = 0.039$) and cell type of cancer ($p = 0.047$) were also shown to be statistically significant.

Pre-operative anaemia was significantly associated (Table 4) with a higher proportion of patients requiring intra-operative blood transfusion (11% vs. 4%, $p = 0.021$). However, there was no significant association between pre-operative anaemia, post-operative complications or death within 30 days of surgery.

3.4 Relationship between anaemia, blood transfusion, and overall survival

Of the 270 patients who underwent resection, margin free (R0) resection was confirmed in 215 patients. After exclusion of patients who died within 30 days of surgery (n=7), those who were lost to follow up (n=6), or who had missing anaemia or transfusion data (n=28), overall survival data were available for 174 patients. In this groups there 71 were events with 63 of these deaths due to oesophageal cancer, and a median follow up of 69 months for those alive at censoring (range 44-114 months).

Anaemia was significantly associated ($p = 0.034$) with poorer overall survival, with anaemia at both the pre-neoadjuvant chemotherapy and pre-operative stages associated with the poorest outcome (Figure 2). There was no association between perioperative blood transfusion and overall survival ($p = 0.723$). At multivariate analysis (Table 5), anaemia categorised by its absence, or its presence at each time point, remained independently associated with poorer overall survival (HR 1.26, 95% CI 1.02-1.54, $p = 0.030$).

4. Discussion

Anaemia was common in oesophago-gastric cancer patients, with a prevalence of 34% before NAC and 59% before surgery, similar to figures reported in previous studies[3]. When anaemia was subcategorised, normocytic anaemia was most prevalent, found in 26% of patients before NAC and in 40% of patients prior to surgery. Anaemia was associated with the need for perioperative blood transfusion but transfusion itself was not associated with survival in this cohort. In contrast, anaemia was associated with poorer overall survival, and in particular, patients who were anaemic both before NAC and before surgery appeared to have the poorest long term outcome.

The small proportion of patients with microcytic anaemia suggests that pre-chemotherapy and pre-operative anaemia are unlikely to be simply caused by chronic occult GI blood loss[15]. However, most patients in this study did not have their ferritin levels, transferrin saturation or total body iron storage measured, hence some patients with normocytic anaemia could have had low iron stores which were unrecognised. Comparing pre-chemotherapy anaemia and pre-operative anaemia, a major difference in the prevalence of macrocytic anaemia was noted, while no patients were found to have microcytic anaemia following NAC. This change may be due to the chemotherapeutic drugs used, which were mainly epirubicin, cisplatin, 5-fluorouracil combination (ECF) or cisplatin, 5-fluorouracil combination (CISP/5-FU) in line

with the MAGIC[16] and OEO2 trials[17]. Since 5-fluorouracil has been found to be associated with macrocytosis induction[18], the use of chemotherapeutic drugs may mask the effect of microcytosis due to chronic blood loss and show seemingly normocytic anaemia even if absolute iron deficiency is a major contributor to anaemic state.

Another possibility is that the host innate systemic inflammatory response to cancer is associated with the observed normocytic anaemia[3]. In this study, pre-chemotherapy and pre-operative anaemia were shown to be independently associated with mGPS, which may support the view that anaemia is a consequence of inflammation in oesophago-gastric cancer[19]. The underlying mechanisms are multiple, including suppression of erythropoiesis, reduced erythrocyte lifespan, and an increase in hepcidin synthesis by the liver resulting in ferroportin internalisation. This decreases iron absorption in the duodenum and iron release from spleen, hence reducing plasma concentrations of iron[20]. The unavailability of iron despite the presence of sufficient iron stores is known as functional iron deficiency.

Another factor associated with pre-neoadjuvant chemotherapy anaemia in this cohort, disease stage, is also thought to relate to inflammation, supported by findings that nodal metastasis may be driven by inflammatory cytokines in other tumour types such as malignant melanoma[21]. In addition, the efficacy of chemotherapeutic drugs, especially cisplatin and 5-fluorouracil, have been shown to vary with increased inflammatory markers[22].

These multiple aetiologies make the management of peri-treatment and preoperative anaemia more challenging in terms of evaluation and suitable selection of treatment. In light of the possible masking of absolute iron deficiency and the coexistence of absolute and functional iron deficiency, we suggest that haematinic studies should be included in routine pre-chemotherapy and pre-operative assessment to identify the actual cause of anaemia. We do however recognise that almost all of the measures of iron status commonly used in clinical practice are affected by the presence of inflammation, making the accurate determination of iron status potentially difficult in this group of patients[23]. A recent study demonstrated that intravenous iron infusion is effective in reversing anaemic condition in patients with low ferritin levels, but it failed to increase haemoglobin concentration in patients with ferritin levels above threshold[24,25]. If absolute iron deficiency is confirmed, iron therapy in form of oral tablets or intravenous infusion can be prescribed to correct the underlying deficit, reducing the requirement for blood transfusion, although the treatment of inflammation related anaemia is less clear[25,26].

The present study reported no association between anaemia before NAC or surgery and either complications or immediate post-surgical deaths. There was a strong association with intra-operative allogenic blood transfusion, as in a previous study of similar patients[2]. Blood transfusion was also the most common treatment for pre-operative anaemia in our patient

group[27]. Although no association was found between blood transfusion and survival in the present study, it is widely hypothesised that blood transfusion is associated with postoperative morbidity and poorer survival [10,12], and that these risks increase with the number of units packed red cells transfused[11]. As a result, there is a significant push toward employing restrictive transfusion strategies[28] and Patient Blood Management (PBM) protocols[29]. Until recently there was little evidence that normalising pre-operative haemoglobin concentration was associated with improved mortality or morbidity[30], however, the long term follow up of the IVICA trial hints that such strategies might be beneficial.[31] As such, consideration must be given to multimodal patient blood management plans,[32] to reduce the need for allogeneic blood transfusion.

The main limitation of this study is the lack of data on patient iron status, which causes an inability to distinguish between absolute and functional iron deficiency, particularly in the normocytic anaemia group. Further investigation of iron status in the context of inflammation in these patients might help guide treatment of anaemia in this patient group in the future. Another limitation is the small number of patients with a preoperative mGPS of 1 or 2, partly due to missing data and partly due to disease and treatment. A larger sample size might show a more definitive association between inflammation and anaemia in oesophago-gastric cancer patients, although published data from this cohort has already

shown the prognostic utility of inflammation in patients undergoing NAC then surgery.[33] Finally, the reason for blood transfusion in our patients could not be ascertained due to the retrospective nature of this study and no formal transfusion protocol was in place during the study period.

In conclusion, this study reports that in patients with oesophago-gastric cancer undergoing curative treatment with NAC and surgery, anaemia was associated with higher rates of perioperative blood transfusion and poorer overall survival. In this patient group normocytic anaemia was the major subtype of anaemia before NAC and before surgery, rather than the anticipated microcytic anaemia classically associated with GI cancers. At both time points anaemia was significantly associated with the presence of an innate systemic inflammatory response. Due to the multifactorial nature of anaemia in such patients, it will be important to recognise and subcategorise anaemia by aetiology, to allow effective management before and during treatment while minimising potentially harmful blood transfusions.

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6. Tables and footnotes

Table 1 – Pre-neoadjuvant chemotherapy variables of patients with oesophago-gastric cancer classified by the presence of anaemia

Pre-chemotherapy Anaemia	No	Yes	P-value
n = 295	196 (66%)	99 (34%)	
Demographics			
Sex			
Male	137 (70%)	71 (72%)	0.746
Female	59 (30%)	28 (28%)	
Age			
< 65	96 (50%)	38 (41%)	
65-75	87 (45%)	45 (48%)	0.064
> 75	10 (5%)	10 (11%)	
Body mass index (BMI)			
< 20	6 (3%)	5 (5%)	
20-24	60 (32%)	36 (39%)	0.112
25-29	76 (41%)	36 (39%)	
> 29	43 (23%)	16 (17%)	
Smoking			
Non-smoker	61 (32%)	34 (36%)	
Ex-smoker	85 (45%)	42 (44%)	0.538
Current smoker	42 (22%)	19 (20%)	
Physical status			
ASA physical status			
1	89 (47%)	36 (38%)	
2	68 (36%)	36 (38%)	0.115
≥ 3	34 (18%)	23 (24%)	
VO2 anaerobic threshold			
< 11	51 (34%)	30 (42%)	0.252
≥ 11	100 (66%)	42 (58%)	
VO2 peak			
< 19	55 (46%)	37 (60%)	0.069
≥ 19	66 (54%)	25 (40%)	
Pathological			
Tumour site			

Oesophageal	58 (30%)	26 (27%)	
Junctional	122 (63%)	63 (64%)	0.450
Gastric	14 (7%)	9 (9%)	
Clinical T stage			
≤ 2	72 (37%)	33 (33%)	0.565
≥ 3	124 (63%)	66 (67%)	
Clinical N stage			
0	85 (45%)	28 (30%)	**0.015**
≥ 1	105 (55%)	66 (70%)	
Systemic inflammation			
Pre-chemotherapy NLR			
< 5	180 (92%)	84 (85%)	0.065
≥ 5	16 (8%)	15 (15%)	
Pre-chemotherapy mGPS			
0	125 (78%)	50 (63%)	
1	25 (16%)	13 (16%)	**0.001**
2	10 (6%)	17 (21%)	

Notes: VO2 refers to oxygen uptake;

NLR refers to neutrophil to lymphocyte level;

mGPS refers to modified Glasgow Prognostic Score;

Anaemia refers to haemoglobin < 130 mg/L in male and < 120 mg/L in female.

Table 2 – Treatment outcomes of patients with oesophago-gastric cancer undergoing surgical resection classified by presence of pre-chemotherapy anaemia

Pre-chemotherapy Anaemia	No	Yes	P-value
n = 233	160 (69%)	73 (31%)	
Blood transfusion			
Peri-operative transfusion			
Yes	59 (37%)	23 (31%)	0.427
No	101 (63%)	50 (69%)	
Pre-operative transfusion			
Yes	16 (10%)	7 (10%)	0.922
No	144 (90%)	66 (90%)	
Intra-operative transfusion			
Yes	10 (6%)	11 (15%)	**0.030**
No	150 (94%)	62 (85%)	
Post-operative transfusion			
Yes	46 (29%)	12 (16%)	**0.044**
No	114 (71%)	61 (84%)	
Complication			
Any complication			
Yes	107 (67%)	48 (66%)	0.867
No	53 (33%)	25 (34%)	
Major complication			
CD grading ≥ 3	38 (24%)	19 (26%)	0.685
No	121 (76%)	53 (74%)	
Death within 30 days			
Yes	7 (4%)	2 (3%)	0.549
No	153 (96%)	71 (97%)	

Notes: CD grading refers to Clavien-Dindo system for grading of surgical complication;
Anaemia refers to haemoglobin < 130 mg/L in male and < 120 mg/L in female;

Table 3 – Preoperative variables of patients with oesophago-gastric cancer undergoing neoadjuvant chemotherapy, classified by the presence of preoperative anaemia

Pre-operative Anaemia	No	Yes	P-value
n = 268	111 (41%)	157 (59%)	
Demographics			
Sex			
Male	72 (65%)	119 (76%)	0.052
Female	39 (35%)	38 (24%)	
Age			
< 65	64 (58%)	60 (38%)	
65-75	38 (34%)	80 (51%)	**0.006**
> 75	9 (8%)	17 (11%)	
Body mass index (BMI)			
< 20	8 (8%)	3 (2%)	
20-24	34 (33%)	53 (35%)	0.344
25-29	40 (39%)	64 (42%)	
> 29	22 (21%)	33 (22%)	
Smoking			
Non-smoker	30 (29%)	54 (35%)	
Ex-smoker	49 (47%)	77 (50%)	0.082
Current smoker	26 (25%)	24 (15%)	
Physical status			
ASA physical status			
1	52 (49%)	65 (42%)	
2	37 (35%)	57 (37%)	0.245
≥ 3	18 (17%)	33 (21%)	
VO2 anaerobic threshold			
< 11	23 (27%)	47 (38%)	0.085
≥ 11	63 (73%)	76 (62%)	
VO2 peak			
< 19	27 (40%)	55 (56%)	**0.045**
≥ 19	41 (60%)	44 (44%)	
Pre-chemotherapy anaemia			
Yes	8 (9%)	64 (45%)	**< 0.001**
No	83 (91%)	77 (55%)	
Pathological			

Tumour site			
Oesophageal	36 (34%)	39 (25%)	
Junctional	63 (60%)	96 (63%)	0.068
Gastric	7 (7%)	18 (12%)	
Pathological T stage			
0	8 (7%)	14 (9%)	
1/ 2	33 (30%)	45 (29%)	0.791
≥ 3	68 (62%)	96 (62%)	
Pathological N stage			
0	52 (48%)	72 (46%)	0.841
≥ 1	57 (52%)	83 (54%)	
Cell type of cancer			
Adenocarcinoma	97 (89%)	147 (95%)	0.078
Squamous cell carcinoma	12 (11%)	8 (5%)	
Differentiation			
Well/ Moderate	46 (42%)	81 (52%)	0.108
Poor	63 (58%)	74 (48%)	
Resection margin			
Clear	83 (76%)	124 (81%)	0.338
Not clear	26 (24%)	29 (19%)	
Venous invasion			
Yes	54 (52%)	75 (51%)	0.870
No	49 (48%)	71 (49%)	
Systemic inflammation			
Pre-operative NLR			
< 5	101 (91%)	143 (91%)	0.979
≥ 5	10 (9%)	14 (9%)	
Pre-operative mGPS			
0	105 (96%)	135 (90%)	
1	4 (4%)	5 (3%)	**0.014**
2	0 (0%)	10 (7%)	

Notes: VO2 refers to oxygen uptake;

NLR refers to neutrophil to lymphocyte level;

mGPS refers to modified Glasgow Prognostic Score;

Anaemia refers to haemoglobin < 130 mg/L in male and < 120 mg/L in female.

Table 4 – Treatment outcomes of patients with oesophago-gastric cancer undergoing surgical resection classified by presence of pre-operative anaemia

Pre-operative Anaemia	No	Yes	P-value
n = 268	111 (41%)	157 (59%)	
Blood transfusion			
Peri-operative transfusion			
Yes	39 (35%)	55 (35%)	0.986
No	72 (65%)	102 (65%)	
Pre-operative transfusion			
Yes	11 (10%)	15 (10%)	0.923
No	100 (90%)	142 (90%)	
Intra-operative transfusion			
Yes	4 (4%)	18 (11%)	**0.021**
No	107 (96%)	139 (89%)	
Post-operative transfusion			
Yes	30 (27%)	38 (24%)	0.602
No	81 (73%)	119 (76%)	
Complication			
Any complication			
Yes	80 (72%)	101 (64%)	0.183
No	31 (28%)	56 (36%)	
Major complication			
CD grading ≥ 3	27 (24%)	38 (24%)	0.971
No	84 (76%)	117 (76%)	
Death within 30 days			
Yes	2 (2%)	7 (5%)	0.235
No	109 (98%)	150 (95%)	

Notes: CD grading refers to Clavien-Dindo system for grading of surgical complication;
Anaemia refers to haemoglobin < 130 mg/L in male and < 120 mg/L in female;

Table 5 – Overall survival following R0 resection of oesophago-gastric cancer – univariate and multivariate Cox regression

Variable	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age (<65/65-75/>75, years)	1.19 (0.85-1.65)	0.312	-	-
Male Sex	1.89 (1.10-3.26)	0.022	1.83 (0.99-3.36)	0.053
ASA (1/2/3)	1.26 (0.96-1.65)	0.103	-	-
VO2 peak (<19/>19, ml/kg/min)	1.13 (0.66-1.93)	0.653	-	-
pTNM stage (0-2/3-4A)	1.75 (1.43-2.15)	<0.001	1.70 (1.36-2.12)	<0.001
Pre-op mGPS (0/1/2)	1.69 (0.87-3.28)	0.121	-	-
Anaemia (None/pre-chemo/pre-op/both)	1.28 (1.05-1.57)	0.015	1.26 (1.02-1.54)	0.030
BMI (<20/20-24/25-29/>29, kg/m^2)	0.79 (0.61-1.02)	0.065	-	0.548
Postoperative complication (no/yes)	1.12 (0.71-1.77)	0.621	-	-
Perioperative blood transfusion (no/yes)	0.82 (0.51-1.31)	0.398	-	-

Notes: VO2 refers to oxygen uptake;
NLR refers to neutrophil to lymphocyte level;
mGPS refers to modified Glasgow Prognostic Score;
Anaemia refers to haemoglobin < 130 mg/L in male and < 120 mg/L in female;
HR refers to hazard ratio
CI refers to confidence interval
BMI refers to body mass index

7. Figures and legends

Figure 1 – Flowchart of patient inclusion

Figure 2 – Kaplan Meier curves of overall survival in patients with R0 resection grouped by (A) anaemia before neoadjuvant chemotherapy or surgery (p=0.034), and (B) perioperative allogeneic blood transfusion (p=0.723)

8. Supplementary Files

Supplementary Figure 1 –Boxplots of haemoglobin concentrations (mg/L) by sex (A) before neoadjuvant chemotherapy and (B) before surgery for oesophago-gastric cancer

Supplementary Table 1 – Multivariate binary logistic regression of factors associated with pre-neoadjuvant chemotherapy anaemia

Supplementary Table 2 – Pre-chemotherapy variables of patients with oesophago-gastric cancer classified by different types of anaemia

Supplementary Table 3 – Multivariate binary logistic regression of factors associated with pre-operative anaemia

Supplementary Table 3 – Pre-operative variables of patients with oesophago-gastric cancer that underwent neoadjuvant chemotherapy classified by different types of anaemia

9. References

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