Short-term and long-term outcomes of oesophagogastric surgery for cancer in obese and normal weight patients

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Introduction
Prevalence of overweight and obesity is increasing in the western society and is associated with serious medical, social, and economic problems. Overweight is generally considered to be a risk factor for poor surgical outcome. Impaired wound healing and other comorbidities as well as hindered surgical conditions predispose the patient for perioperative complications. Recent register studies from the USA and Asia show an increased morbidity and mortality for morbidly obese patients after major surgical resections for cancer, but comparable results for the moderately overweight population compared with patients of normal weight. Furthermore, obesity was described to be associated with impaired long-term results and decreased survival, for example in colorectal surgery. In a literature review, this effect does not seem to apply to patients undergoing surgery for oesophagogastric cancer. The data from Europe and Northern America are very limited, but no association between pre-therapeutic body mass index (BMI) and increased perioperative morbidity and mortality or impaired oncological results could be shown for this collective in several retrospective database analyses.

Patients with oesophagogastric cancer undergoing curative surgery are in a peculiar situation. Pre-therapeutic weight loss is regularly associated with oesophagogastric cancer due to dysphagia. Perioperative weight loss and low BMI are for their part likewise suspected to be associated with increased perioperative complication rate and inferior overall survival. Studies consistently show impaired short- and long-term results for cachectic patients with oesophageal cancer with a pre-therapeutic BMI of 18.5 or lower, but the impact of pre-therapeutic BMI in normal weight, overweight and obese patients with oesophagogastric cancer on perioperative outcome and long-term survival is controversially discussed.

We conducted this study to review the surgical and oncological results in overweight and obese patients undergoing surgery in curative intent for oesophagogastric cancer.

Abstract
Background: Obesity is generally considered to be associated with worse surgical outcome and impaired oncological prognosis. The impact of pre-therapeutic body mass index (BMI) in patients with oesophagogastric cancer on the surgical outcome is controversially discussed.

Methods: We retrospectively examined 730 patients who had undergone curative treatment for oesophagogastric cancer at the Medical Center of the University of Freiburg (1996–2015). Patients were divided in groups according to pre-therapeutic BMI (underweight (UW): <18.5 kg/m²; normal weight (NW): 18.5–25 kg/m²; overweight (OW): 25–30 kg/m²; and obese (OB): >30 kg/m²). Pre-therapeutic BMI was significantly associated with 5-year survival (UW: 22%, NW: 37%, OW: 51%, OB: 50%, P < 0.001). Multivariate analysis identified UW/NW (BMI <25 kg/m²) as an independent risk factor for poor survival (relative risk 1.38, P = 0.001) among high American Society of Anesthesiologists score, old age, positive resection margin and high cancer stage according to the Union Internationale Contre le Cancer (UICC).

Conclusion: In oesophagogastric cancer, OW and OB patients can be treated surgically without impaired perioperative outcome and expect improved long-term survival compared to patients with a BMI <25 kg/m².
Methods
This study evaluates the outcome of 730 consecutive patients with oesophago-gastric cancer, who underwent oesophagectomy or gastrectomy between January 1996 and December 2015 at the Medical Centre of the University of Freiburg (MCUF). Pre-therapeutic BMI was not available for four patients. Informed consent was obtained from all patients before their inclusion in the cancer registry. The study was approved by the Medical Ethics Committee of the University of Freiburg. Patients were divided in four groups: underweight (UW, BMI <18.5 kg/m²), normal weight (NW, BMI 18.5–25 kg/m²), overweight (OW, BMI 25–30 kg/m²) and obese (OB, BMI >30 kg/m²).

Pre-therapeutic work-up
Patients were initially seen in the MCUF cancer centre in the outpatient setting. Comorbidities and nutritional status were recorded, and pulmonary and cardiac check-up were routinely performed in risk patients. Pre-therapeutic diagnostics included endoscopy with biopsies and thoraco-abdominal computerized tomography in all patients. Endoscopic ultrasound was applied routinely for staging at all cancer locations if possible. PET scans and staging laparoscopy were only used in selected cases. The classification of the UICC tumour stage was made retrospectively according to the eighth edition of the classification. Beginning in 2006 all patients were discussed in our interdisciplinary cancer conference, where the decision for neoadjuvant treatment was made.

Neoadjuvant chemoradiation was performed for squamous cell tumours and adenocarcinoma of the oesophagus without infiltration of the cardia. Perioperative chemotherapy has been performed for adenocarcinoma of the distal oesophagus, oesophagogastric junction and stomach initially according to the protocol suggested by Cunningham et al., which was replaced by the FLOT (chemotherapy with 5-FU, leucovorin, docetaxel and oxaliplatin) Protocol after 2009.

Surgical therapy
Before surgery or start of neoadjuvant therapy, body weight and body height were recorded (for BMI calculation). The operative procedure was chosen according to tumour location. Patients with oesophageal cancer were operated by an Ivor-Lewis thoraco-abdominal approach or underwent oesophagectomy by a transhiatal approach with cervical anastomosis. Reconstruction was routinely performed by a gastric tube or by colonic interposition in a few cases. Two-field lymphadenectomy was routinely performed in patients with a thoraco-abdominal approach. In patients with a transhiatal approach, lymphadenectomy was limited to the lower mediastinum and abdominal compartment. Patients with junctional adenocarcinoma alternatively underwent transthiatal extended gastrectomy with lower mediastinal and modified D2-lymphadenectomy. Tumours of the corpus and antrum were treated with total or subtotal gastrectomy plus modified D2-lymphadenectomy. Reconstruction after gastrectomy was routinely performed by a Y-Roux construction.

Perioperative nutritional management
Patients did not routinely receive pre-operative additional nutrition. Pre-operative parenteral or enteral supplements were limited to individual cases. The majority of patients undergoing oesophagectomy received a jejunostomy catheter for post-operative enteral feeding. Enteral feeding via jejunostomy catheter was started 6 h after surgery and was continued till patients were able to consume sufficient solid food (usually by post-operative day 7). Patients without a jejunostomy catheter received total parenteral nutrition instead. Patients were restricted to fluids until post-operative day 5 and started on solids after a routine contrast oesophagogram ruled out anastomotic leak or stenosis. In rare case of significant weight loss during the first 4 weeks post-operatively, feeding was restarted.

All patients undergoing gastrectomy received post-operative enteral feeding via nasogastric tube until they were started on solid food (routinely on post-operative day 4).

Follow-up
Peri-operative complications were recorded up to 90 days after surgery and were graded according to Clavien–Dindo classification. Major surgical and pulmonary complications were defined according to the criteria of the Esophagectomy Complications Consensus Group. The survival data were systematically obtained from the cancer registry of the MCUF cancer centre.

Statistical analysis
The results of our study were gained by retrospective analysis of our prospective oesophageal and gastric cancer (GC) databases. SPSS for Windows was used for statistical analysis (SPSS, Chicago, IL, USA).

Categorical variables were given in absolute and relative frequencies; differences were evaluated by chi-squared test or Fisher’s exact test, as applicable. Quantitative values were expressed as mean ± standard deviation and medians with range, as appropriate, and differences were measured using the Kruskal–Wallis test. A Mann–Whitney U test was added to compare groups. A P-value <0.05 was considered statistically significant. Survival was univariately analysed by the Kaplan–Meier method with a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed by the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic) including the report of relative risks and their 95% confidential intervals.

Results
Patients, tumours and treatment
The majority of patients were male (73%) with a median age of 64 years (range 28–90). Median BMI was 24.7 kg/m² with a range from 13.8 to 46.2 kg/m². Most patients were NW (n = 337) or OW (n = 263). UW (n = 42) or OB (n = 84) were present only in a minority of patients.

In the analysis, 19% of the patients had an oesophageal squamous cell carcinoma (SCC), 40% oesophageal or junctional adenocarcinoma (OJAC) and 41% had GC. All clinical and pathological factors were not evenly distributed among the groups. OW/OB
Table 1: Association of pre-operative body mass index (BMI) with demographic factors and surgical outcome

|                               | All, n = 726 | UW, BMI <18.5, n = 42 | NW, BMI 18.5–25, n = 337 | OW, BMI 25–30, n = 263 | OB, BMI >30, n = 84 | P-value |
|-------------------------------|-------------|-----------------------|--------------------------|-----------------------|-------------------|---------|
| Male sex, n (%)              | 527 (73)    | 22 (62)               | 233 (69)                 | 207 (79)              | 65 (77)           | 0.001†  |
| Age (years), median (range)  | 64 (28–90)  | 58 (36–83)            | 64 (28–89)               | 64 (36–90)            | 62 (43–79)        | 0.016‡  |
| ASA score, n (%)             |             |                       |                          |                       |                   |         |
| 1                             | 43 (6)      | 1 (2)                 | 25 (7)                   | 15 (6)                | 2 (2)             | 0.252†  |
| 2                             | 390 (54)    | 20 (48)               | 175 (52)                 | 148 (56)              | 47 (56)           |         |
| 3                             | 276 (38)    | 20 (48)               | 130 (39)                 | 90 (34)               | 36 (42)           |         |
| 4                             | 18 (3)      | 1 (2)                 | 7 (2)                    | 10 (4)                | 0                 |         |
| Tumour type, n (%)           |             |                       |                          |                       |                   |         |
| ESCC                          | 139 (19)    | 13 (31)               | 82 (24)                  | 32 (12)               | 12 (14)           | <0.001† |
| OJAC                          | 292 (40)    | 8 (19)                | 113 (34)                 | 128 (49)              | 43 (51)           |         |
| GAC                           | 295 (41)    | 21 (50)               | 142 (42)                 | 103 (39)              | 29 (35)           |         |
| pUICC stage, n (%)           |             |                       |                          |                       |                   |         |
| 1                             | 277 (38)    | 12 (29)               | 109 (32)                 | 114 (43)              | 42 (50)           | 0.025†  |
| 2                             | 234 (32)    | 17 (41)               | 123 (37)                 | 70 (27)               | 24 (29)           |         |
| 3                             | 130 (18)    | 6 (14)                | 65 (19)                  | 46 (18)               | 13 (15)           |         |
| 4                             | 85 (12)     | 7 (17)                | 40 (12)                  | 33 (13)               | 5 (6)             |         |
| Neoadjuvant therapy, n (%)    |             |                       |                          |                       |                   |         |
| None                          | 327 (45)    | 16 (38)               | 152 (45)                 | 123 (47)              | 36 (43)           | 0.012†  |
| RCTX                          | 190 (26)    | 17 (41)               | 102 (30)                 | 53 (20)               | 18 (21)           |         |
| CTX                           | 209 (29)    | 9 (21)                | 83 (25)                  | 87 (33)               | 30 (36)           |         |
| Surgical approach, n (%)     |             |                       |                          |                       |                   |         |
| Gastrectomy                   | 393 (54)    | 23 (55)               | 177 (53)                 | 147 (56)              | 46 (55)           | 0.873†  |
| Oesophagectomy                | 333 (46)    | 19 (45)               | 160 (47)                 | 116 (44)              | 38 (45)           |         |
| Resection margin, n (%)       |             |                       |                          |                       |                   |         |
| R0                            | 622 (86)    | 31 (73)               | 282 (64)                 | 232 (88)              | 77 (82)           | 0.021†  |
| R+                            | 104 (14)    | 11 (26)               | 55 (16)                  | 31 (12)               | 7 (8)             |         |
| In-hospital mortality, n (%)  | 44 (6)      | 3 (7)                 | 22 (6)                   | 11 (4)                | 8 (9)             | 0.306†  |
| Post-operative morbidity, n (%)| 437 (60)    | 22 (52)               | 208 (61)                 | 151 (57)              | 56 (67)           | 0.294†  |
| Severity of complications§, n (%)| 149 (21)    | 7 (17)                | 70 (21)                  | 58 (22)               | 14 (17)           | 0.124†  |
| Grade I/II                    | 281 (25)    | 7 (17)                | 89 (26)                  | 64 (24)               | 21 (25)           |         |
| Grade III                     | 107 (15)    | 8 (19)                | 49 (15)                  | 29 (11)               | 21 (25)           |         |
| Grade IV/V                    | 356 (49)    | 8 (19)                | 250 (69)                 | 114 (43)              | 36 (43)           |         |
| Operating time (min), median (range) | 6 (1–227) | 5 (1–77)             | 6 (1–227)               | 6 (1–91)             | 7 (1–121)       | 0.081†  |
| ICU stay, median (range)      | 20 (3–235)  | 22 (11–99)            | 21 (3–235)               | 19 (4–150)            | 20 (7–144)       | 0.169†  |

Bold values denote statistical significance. †Chi-squared test. ‡Kruskal–Wallis test. §Complications were graded according to Clavien–Dindo classification. ASA, American Society of Anesthesiologists; CTX, perioperative chemotherapy; ESCC, oesophageal squamous cell carcinoma; GAC, gastric adenocarcinoma; ICU, intensive care unit; NW, normal weight; OB, obese; OJAC, oesophageal or junctional adenocarcinoma; OW, overweight; pUICC, pathological staging according to the Union Internationale Contre le Cancer; RCTX, neoadjuvant chemoradiation; UW, underweight.

**Fig. 1.** Overall survival of 726 resected patients with oesophagogastric cancer grouped by pre-therapeutic body mass index (BMI) in (a) two groups (BMI <25 kg/m² and BMI ≥25 kg/m²) and (b) four groups (BMI <18.5 kg/m²; BMI 18.5–25 kg/m²; BMI 25–30 kg/m²; BMI >30 kg/m²).
patients had less SCC than UW/NW patients and more UICC stage 1 tumours. Furthermore the UW group consisted of more stage 4 tumours and was less likely to have negative resection margins. All characteristics are displayed in Table 1.

Impact of pre-therapeutic BMI on perioperative complication rate

Analysis of perioperative morbidity and mortality revealed perioperative morbidity (any surgical or medical complication) of 60%, and an in-hospital mortality of 6% (Table 1).

Subgroup analysis of the UW, NW, OW and OB patients showed very similar results for all groups without statistically significant deviations for post-operative morbidity ($P = 0.294$), severity of complications ($P = 0.124$) and in-hospital mortality ($P = 0.306$). Also, there was no difference among the groups in operating time ($P = 0.408$) and length of intensive care unit ($P = 0.081$) and hospital stay ($P = 0.169$).

Comparison of the 84 obese patients with all other patients (UW/NW/OW) indicated a statistically not significantly increased relative risk for those patients regarding in-hospital mortality of 1.70 (95% confidence interval 0.82–3.53). The increase applies to morbidly obese patients (BMI $>35$ kg/m$^2$, n = 22), with an in-hospital mortality of 23%, compared to 5% for patients with a BMI between 30 and 35 kg/m$^2$ (n = 62) and 6% for all other patients (UW/NW, n = 642), equalling a relative risk of 4.10 (95% confidence interval 1.79–9.40) not surviving their hospital stay for patients with a BMI $>35$ kg/m$^2$. This subset was made up of three SCCs, 10 OJACs and nine gastric adenocarcinomas (GACs). Thirteen patients received a gastrectomy and nine an oesophagectomy. Five of 22 patients in the group deceased in hospital, three patients due to anastomotic complications, one due pneumonia and one due to a post-operative bleeding from the splenic artery.

The relative risk of developing any post-operative complication is only marginally increased for OB patients (1.12; 95% confidence interval 0.95–1.32) compared to UW/NW/OW patients and even for the morbidly obese patients (1.14; 95% confidence interval 0.85–1.52) compared to all other patients.

Separate evaluation of cachectic patients (UW) showed no substantial deviation in relative risk regarding in-hospital mortality (1.19; 95% confidence interval 0.39–3.79) and post-operative morbidity (0.86; 95% confidence interval 0.64–1.16).

Association of low or normal pre-therapeutic BMI and impaired long-term survival

Median follow-up was 3.8 years, 29 patients were lost to follow-up. At the time of the last follow-up, 279 patients were alive and 447 were deceased. Mean 5-year survival among all patients was 43%. Patients with a BMI of 25 or higher had a significantly improved 5-year survival with 51% compared to 36% ($P < 0.001$, Fig. 1a). The benefit affected both OW (51%) and OB (50%) patients, who had an advantage compared to NW (37%, $P > 0.001$) patients. UW patients had an even worse life expectancy with a 5-year survival of only 22% (Fig. 1b), while the 5-year-survival of the small subset of patients with a BMI $>35$ kg/m$^2$ was comparable to the OW and OB groups (47%).

Table 2 Analysis of survival

| Predictor | n | 5-year survival (%) | P-value |
|-----------|---|---------------------|---------|
| Sex       |   |                     |         |
| Male      | 201 | 42                  | 0.433   |
| Female    | 529 | 45                  |         |
| Age       |   |                     |         |
| <65 years | 379 | 47                  | <0.001  |
| ≥65 years | 351 | 38                  |         |
| Pre-therapeutic BMI |   |                    |         |
| <18.5     | 42  | 22                  | <0.001  |
| 18.5–25   | 337 | 37                  |         |
| 25–30     | 263 | 51                  |         |
| >30       | 84  | 50                  |         |
| ASA score |   |                     |         |
| 1         | 43  | 44                  | <0.001  |
| 2         | 392 | 49                  |         |
| 3         | 277 | 34                  |         |
| 4         | 18  | 30                  |         |
| Tumour location |    |                   |         |
| Oesophageal squamous cell carcinoma | 139 | 41 | 0.437 |
| Oesophageal and junctional adenocarcinoma | 295 | 47 | |
| Gastric cancer | 296 | 39 | |
| Neoadjuvant therapy |   |                |         |
| None      | 331 | 40                  | 0.131   |
| RCTX      | 190 | 42                  |         |
| CTX       | 209 | 48                  |         |
| Operation |   |                     |         |
| Gastrectomy | 395 | 40 | 0.505 |
| Oesophagectomy | 335 | 45 | |
| UICC stage |   |                    |         |
| 1         | 279 | 66                  | <0.001  |
| 2         | 235 | 40                  |         |
| 3         | 131 | 16                  |         |
| 4         | 85  | 10                  |         |
| Resection margin | R0  | 625 | 49 | <0.001 |
| R+        | 105 | 6                   |         |

(B) Multivariate analysis

| Parameter | RR | 95% CI | P-value |
|-----------|----|-------|---------|
| ASA score (3–4 versus 1–2) | 1.32 | 1.09–1.60 | 0.004 |
| Age (≥65 versus <65) | 1.33 | 1.10–1.61 | 0.004 |
| Pre-therapeutic BMI (UW/NW versus OW/OB) | 1.38 | 1.14–1.67 | 0.001 |
| Resection margin (R+ versus R0) | 2.56 | 1.97–3.31 | <0.001 |
| UICC stage (3–4 versus 1–2) | 2.64 | 2.13–3.28 | <0.001 |

Bold values denote statistical significance. ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; CTX, perioperative chemotherapy; NW, normal weight; OB, obese; OW, overweight; RCTX, neoadjuvant chemoradiation; RR, relative risk; UICC, pathological staging according to the Union Internationale Contre le Cancer; UW, underweight.

Prognostic factors for overall survival

Univariate analysis of overall survival identified other prognostic factors besides pre-therapeutic BMI. Age and American Society of Anesthesiologists score were both associated with overall survival (Table 2). Advanced UICC stage was associated with a poor prognosis as well: 5-year survival was 66% for stage 1 and 40% for stage 2 and rapidly decreased for stage 3 and 4 (16% and 10%,
respectively, $P < 0.001$). The worst prognosis awaited patients with a margin-positive resection (5-year survival: 6% versus 49%, $P < 0.001$). In the analysed collective with various tumour stages included and the different treatment protocols, neoadjuvant treatment had no impact on survival ($P = 0.0131$).

As shown in Table 1, pre-therapeutic BMI was associated with several factors like positive resection margins or UICC stage, which themselves were associated with overall survival. To specify the observed effect, we performed a multivariate analysis and subgroup breakdown.

**Subgroup breakdown and multivariate analysis**

Among UW and NW patients, there was a higher percentage of patients with an SCC, while fewer patients had an OJAC. Subgroup analysis according to tumour entity demonstrates that BMI has no impact on survival for patients with an SCC, while 5-year survival is significantly higher for OW/OB patients compared to UW/NW patients in the OJAC and GAC groups (Fig. 2).

To eliminate falsification of the observed association between BMI and survival by multicollinearity of low pre-therapeutic BMI with advanced malignant disease, we divided our collective by UICC stages. OW/OB patients have a survival benefit over UW/NW patients in limited stages (61% versus 48%, $P = 0.007$) as well as advanced tumour stages (23% versus 7%, $P = 0.005$).

Multivariate analysis, including pre-therapeutic BMI, American Society of Anesthesiologists score, age, resection margin and UICC stage confirmed the impression suggested by the subgroup breakdown: OW/OB patients had an independent survival benefit over UW/NW patients with a hazard ratio of 1.38 and a 95% confidence interval of 1.14–1.67. All other risk factors identified in the univariate analysis were likewise confirmed as independent prognosticators of overall survival (Table 2).

**Discussion**

Our study in context with other recent analyses demonstrates that UW, NW, OW and OB patients can be resected with comparable complication rates by oesophagectomy or gastrectomy.

The data of the small subset of morbidly obese patients (BMI $\geq 35$ kg/m$^2$) show an increased perioperative mortality, with comparable oncological results to the other groups, as was shown before. While post-operative complications are not more frequent in this subgroup, severe complications are much harder to manage and therefore put the patient at a higher mortality risk.

Independent of tumour stage and resection status, pre-therapeutic BMI was identified as an independent prognosticator of overall survival. This effect is limited to the OJAC and GAC groups and does not apply to oesophageal SCC in our analysis.

Derived from other tumour entities, the initiators of the first studies dealing with BMI and oesophagogastric cancer expected obese patients to face a worse prognosis compared to NW patients but were proven wrong. In 2013, an Italian study in 278 patients was the first to demonstrate a survival benefit for overweight and obese patients after oesophagectomy for cancer, which was not significant after adjusting for tumour stage.

This study was followed by several reports from Asian countries confirming these results for oesophageal and gastric adenocarcinoma, and GC, but reporting discordant results for oesophageal SCC.

Several factors are being discussed in the literature to explain the inconsistency of these results. The significance of pre-therapeutic overweight and obesity seems to be largely dependent on the population studied and can certainly not be compared between Asia and western countries. The analysed time period, the predominant histological type of tumour, the use and type of multimodal treatment and the prevalence of obesity in the studied population determine whether a correlation between pre-therapeutic BMI and improved overall survival can be observed. The discrepancy between

![Fig. 2](https://example.com/fig2.png)

**Fig. 2.** Subgroup analysis of overall survival of 726 resected patients with oesophagogastric cancer grouped by pre-therapeutic body mass index (BMI) in two groups (BMI <25 kg/m$^2$ and BMI $\geq$25 kg/m$^2$). Patients were subdivided by tumour entity: oesophageal squamous cell cancer (SCC; $n = 139$), oesophageal and junctional adenocarcinoma (OJAC; $n = 292$) and gastric adenocarcinoma (GAC; $n = 295$).
adenocarcinoma and SCC has been scarcely discussed in the literature so far. Our data demonstrate that the prevalence of overweight and obesity is much lower in the group of patients with a SCC compared to patients with oesophageal adenocarcinoma. This fact and the different multimodal protocols used, as well as a different tumour biology, might contribute to the observed effect.

Our study is the largest study so far analysing the association between pre-therapeutic BMI and surgical and oncological outcome after surgery for oesophagogastric cancer in a western population. The study conclusively demonstrates an acceptable perioperative risk for all subgroups. Additionally, an association between pre-therapeutic BMI and overall survival was shown for GC and oesophageal adenocarcinoma. Yet our study has several limitations: Our study summarizes a heterogeneous patient collective over a period of 20 years. Several confounding factors are present in our data and could only be partially eliminated by subgroup and multivariate analysis. The uneven distribution of tumour and patient characteristics, especially the high rate of stage 4 cancer and positive resection margins in the UW group as well as the long observation period represent a potential bias. Over the last 20 years oncological and surgical management has undergone several alterations so far. Our data demonstrate that the prevalence of overweight and obesity among patients with oesophagogastric adenocarcinoma can be operated with comparable perioperative outcome and expect improved long-term survival compared with patients of normal weight independent of tumour stage and resection status.

Conclusion

From our data, we draw the conclusion that OW and OB patients with oesophagogastric adenocarcinoma can be operated with comparable perioperative outcome and expect improved long-term survival compared with patients of normal weight independent of tumour stage and resection status.

Conflicts of interest

None declared.

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