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TITLE PAGE

Sarcopenia remaining after intensive nutritional prehabilitation could be a criterion for the selection of patients for surgery for oesogastric junction adenocarcinoma

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HIGHLIGHTS

- Sarcopenia is recognized as a negative prognostic factor in several cancers.
- Prehabilitation with nutritional support with feeding jejunostomy is a protective factor for sarcopenia occurrence in patients with esogastric junction adenocarcinoma.
- Sarcopenia occurrence was an independent risk factor for overall survival in patients who underwent surgery.
- Overall survival was similar between sarcopenic patients after nutritional prehabilitation with a FJ and patients excluded from surgery in palliative situations.
- The persistence of sarcopenia despite renutrition program could be a selection factor for surgery.

Author statement

PdM, SM, JBD, AV, SR, CB, CG, BR: Conceptualization, Methodology, Software. PdM, SM, BR: Data curation, Writing- Original draft preparation. PdM, SM, BR: Visualization, Investigation. SR, CB, BR, CG: Supervision.: CB, CG, BR: Software, Validation.: PdM, SM, AV, JBD, BR: Writing- Reviewing and Editing,

ABSTRACT

Background: Sarcopenia is recognized as a negative prognostic factor in several cancers. The exact causes are still debated, and no cure has yet been recognized. The aim of this study was to investigate the impact of nutritional prehabilitation with feeding jejunostomy (FJ) on the occurrence of sarcopenia and how it may affect postoperative short-term outcomes and long-term survival outcomes in patients undergoing esophagectomy for oesogastric junction adenocarcinoma (OJA) after neoadjuvant chemoradiotherapy.

Methods: Patients with OJA were included. The presence of sarcopenia was determined using cutoff values of the total cross-sectional muscle tissue measured on CT scan (axial plane, level of the third lumbar vertebra). We analyzed risk factors for sarcopenia occurrence and the impact of preoperative sarcopenia on postoperative results, overall survival and disease-free survival.

Results: A total of 124 patients were eligible for analysis. Ninety-one patients underwent surgery after chemotherapy, and 72 of them received preoperative feeding jejunostomy. Among the 91 patients, 21 patients (23.0%) were sarcopenic after preoperative chemotherapy. Multivariate analysis showed that feeding jejunostomy is a protective factor against sarcopenia occurrence. Overall survival was significantly different between sarcopenic and nonsarcopenic patients (median survival = 33.7 vs. 58.6 months, respectively, $p=0.04$), and sarcopenia occurrence was an independent risk factor for overall survival in patients who underwent surgery (HR = 3.02; CI 95% 1.55-5.9; $p<0.005$). Subgroup analyses showed no differences in overall survival between patients who presented sarcopenia despite nutritional prehabilitation with a feeding jejunostomy and patients excluded from surgery in palliative situations (median survival = 21.9 vs. 17.2 months, respectively, $p=0.46$).

Conclusion: The persistence of sarcopenia after preoperative chemotherapy despite renutrition with FJ could be a selection factor to propose curative surgery for OJA.

KEYWORDS

Sarcopenia, Esophagectomy, Jejunostomy, Prehabilitation, Esogastric junction adenocarcinoma

TEXT OF MANUSCRIPT

1.1 Introduction

Management of oesogastric junction adenocarcinoma (OJA) remains challenging, even with various advances in surgery, chemotherapy, targeted therapy and immunotherapy. Overall survival of OJA remains poor, with a 5-year survival rate below 30%. Oesogastric junction malignancy is among the diseases with the highest association with cancer-related malnutrition (1). This state of malnutrition can be explained by tumor-induced anorexia and by an obstructive mechanism, which may lead to dysphagia and further deteriorate the nutritional status (2). Furthermore, in advanced OJA, aggressive combined chemotherapies involving cytotoxic agents (e.g., cisplatin, 5-fluorouracil, epirubicin) are known to be associated with gastrointestinal side effects and may worsen an already deteriorated nutritional condition.

Nutritional management is crucial for patient care. Preoperative feeding jejunostomy (FJ) is frequently used when denutrition is diagnosed or in cases of dysphagia, as it allows more patients to complete all cycles of preoperative chemotherapy (3,4). Additionally, the main goal of nutritional management is to prevent the onset of sarcopenia, which is characterized by a progressive and generalized loss of skeletal muscle mass and strength (1).

Sarcopenia is a recognized negative prognostic factor after colorectal, pancreatic, hepatic and gastric surgeries (5–8). Furthermore, in patients with gastric cancer, its presence at diagnosis is associated with significantly lower overall survival. Moreover, sarcopenia seems to influence postoperative outcomes. For instance, studies have shown that changes in body composition secondary to neoadjuvant chemotherapy for esophageal cancer could correlate with the occurrence of

1 complications after esophagectomy (9). However, the exact origin of sarcopenia remains debated, as
2 it cannot be reverted with complementary feeding (10) and can be induced by anticancer drugs
3 (11,12). Interestingly, some studies point toward particular tumors markers or gene variation in cancer
4 patients that correlates with sarcopenia, suggesting that the tumor itself or the patients' genetic
5 background may play a role (13). Therefore, the question remains whether sarcopenia is caused by
6 malnutrition, anticancer treatment and/or the tumor itself. Similarly, the molecular mechanisms
7 leading to sarcopenia are complex and involve multiple steps, including the activity of transcription
8 factors that regulate the expression of muscle catabolic enzymes, such as TAP63-TRIM63 cascades
9 (14). This complexity and the lack of understanding of the etiology of sarcopenia may explain why, thus
10 far, no efficient cure has been established against the loss of skeletal muscle mass, despite some
11 preclinical attempts (15).
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26 We previously showed that prehabilitative feeding using FJ helps to prevent sarcopenia following
27 perioperative chemotherapy (16). The main objective of this study was to investigate the impact of
28 sarcopenia, despite a renutrition program, on patients with OJA.
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38 **2. Patients and Methods**

39 **2.1 Study Setting and Selection of Participants**

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41 This is a single-center retrospective analysis of a prospective database that included
42 consecutive patients diagnosed with OJA from January 2007 to December 2017 at Strasbourg
43 University Hospital (Tertiary center). The Ethics Committee of our institution approved the study, and
44 all patients gave their written consent for their participation in this study. Patients presenting with
45 nonmetastatic OJA, with WHO scores of 0–2, treated with a perioperative chemotherapy protocol
46 were included in our study. All patients underwent a routine abdominal computed tomography (CT)
47 scan before and after chemotherapy. The exclusion criteria were as follows: patients with WHO scores
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3-4, patients with missing follow-up or imaging (CT) data either before and/or after preoperative chemotherapy; patients with confirmed metastatic disease at diagnosis, assessed by preoperative imaging; and patients with positive macroscopic peritoneal carcinomatosis or positive peritoneal cytology in staging exploratory laparoscopy. Patients with progressive disease during chemotherapy were used as a comparative group.

All patients were classified by age, sex, BMI at diagnosis, tumor histology, presence or absence of a preoperative feeding jejunostomy before chemotherapy and type of surgery performed. Management and treatment modalities for each patient were discussed in multidisciplinary meetings. All patients underwent a complete chemotherapy regimen including EOX (epirubicin, oxaliplatin and capecitabine), ECX (epirubicin, cisplatin, capecitabine), FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) and FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel).

Surgical placement of a feeding jejunostomy was performed during the staging exploratory laparoscopy after multidisciplinary assessment. This was only performed after 2010 according to the evolution of the local practice; after 2010, every patient with dysphagia or insufficient oral intake and/or nutritional risk index (NRI) score < 97.5 benefited from FJ. All patients with preoperative feeding jejunostomy had nutritional support from neoadjuvant period until weight stabilisation after surgery.

Surgical resections were performed according to the tumor location after the completion of preoperative chemotherapy. The surgical procedures included total gastrectomy, transhiatal extended gastrectomy and superior polar oesophagogastrectomy (Ivor Lewis esophagectomy), which were all followed by Roux-en-Y reconstruction. Lymphadenectomy was performed according to international standards. Pathology examination was performed in all patients, allowing for classification according to histopathologic findings (i.e., well differentiated, moderately differentiated, isolated cells). Surgery was not performed when there was metastatic disease at diagnosis or appearing during chemotherapy. Patients were classified by ypTNM stage groups (I-IV; AJCC/UICC 8th edition).

2.2 Evaluation of sarcopenia

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3 The evaluation of sarcopenia was performed prospectively according to the literature
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5 guidelines on axial abdominal CT images acquired before (T0) and after (T1) chemotherapy for each
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7 patient. The third lumbar vertebrae (L3) served as a reference landmark to measure cross-sectional
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9 areas of muscles reflecting sarcopenia: the psoas muscle, paraspinal muscles and abdominal wall
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11 muscles. Muscles were identified using quantification thresholds from -30 to +110 Housefield units
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13 (HU). Muscle areas were assessed using ImageJ VR software. The muscles' cross-sectional areas were
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15 automatically segmented, with manual corrections if needed. The muscle surface was defined as the
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17 sum of the cross-sectional areas of all these muscles for each patient. The surface muscular index (SMI)
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19 in cm^2/m^2 was obtained by dividing the muscular surface value by the normalized stature body-surface
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21 area. The body surface area was calculated using the Mosteller formula [body surface area (m^2) =
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23 (height (cm) * weight (kg)/3600) * 0.5] (17). We used literature-based cutoff values for sarcopenia
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25 (guidelines by Prado et al.: L3 skeletal SMI < 38.5 cm^2/m^2 for women and < 52.4 cm^2/m^2 for men) (18).
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2.3 Postoperative outcomes and follow-up

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38 Postoperative complications were prospectively recorded according to the Clavien–Dindo
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40 classification and Comprehensive Complications Index (CCI) (19,20). The CCI was calculated as the sum
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42 of all complications, weighted for their severity, and ranked based on the severity of any combination
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44 of complications from 0 to 100 in a single patient. Major complications were defined as any
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46 complication with a Clavien–Dindo grade ≥ 3 . Postoperative stay was also determined for all patients.
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48 Follow-up took place every 3 to 6 months, according to French surgical society (SFCD) guidelines. The
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50 diagnosis of recurrence was based on postoperative examination, which included imaging, tumor
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52 markers and/or biopsy. Overall survival and disease-free survival rates were calculated for all patients.
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57 The date of initial diagnosis, which was confirmed by the histological examination performed on the
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endoscopic biopsy of the tumor, was considered the baseline. Follow-up ended for each patient either at the date of death, last follow-up date or at the end of the study.

3. Statistical Analysis

Statistical calculations were performed using SPSS 10.0 (SPSS Inc., Chicago, IL) and Python Software (version 3). Categorical variables are described as frequencies and percentages, while continuous variables are expressed as the mean and its standard deviation.

Chi-square and Fisher's exact tests were used as appropriate to determine the association between categorical variables. Student's t test and Wilcoxon-rank sum test were used to evaluate differences in means between two groups of continuous variables. ANOVA and logistic regression were used for univariate and multivariate analyses.

Kaplan–Meier survival analysis was used to analyze survival data. Differences were tested with univariate and multivariate Cox proportional hazards regression analyses and the log-rank test. All tests were two-sided, and a difference was considered significant when the p value was < 0.05.

4. Results

4.1 Risk factors for sarcopenia occurrence

Data from 156 patients diagnosed with OJA were reviewed. Among them, 32 (21%) patients with missing follow-up or imaging data were excluded, and the remaining 124 patients were analyzed. The experimental group was composed of 91/124 patients (74%) who underwent surgery after preoperative chemotherapy. The remaining 33/124 patients (26%) with metastatic disease at the time of diagnosis or with disease progression during neoadjuvant therapy served as controls. In the experimental group, 72/91 patients (79%) underwent a feeding jejunostomy (FJ) before OJA surgical resection. (Fig. 1) Sarcopenic status of all patients before and after surgery and according to the presence or absence of a preoperative feeding jejunostomy are reported in Table A.1 et Table A.2.

1 Before preoperative chemotherapy, 13 patients from the experimental group (14.3%) were
2 sarcopenic. Among them, 11/13 patients underwent FJ (vs. 2/13; $p=0.603$). After preoperative
3
4 chemotherapy, 21 patients from the experimental group (23%) were sarcopenic (13 with FJ [61.9%]
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6 and 8 without FJ [38.1%], $p=0.026$), while 70 patients (77%) were not.
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10 The demographic and physical characteristics of both sarcopenic and nonsarcopenic
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12 populations after preoperative chemotherapy are presented in Table 1. Sex distribution was not
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14 significantly different between sarcopenic and nonsarcopenic patients (19 men [90.5%] and 2 women
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16 [9.5%] vs. 55 men [78.5%] and 15 women [21.4%], respectively, $p= 0.364$). Sarcopenic patients
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18 presented a significantly smaller mean SMI than nonsarcopenic patients ($45.3 \pm 5.4 \text{ cm}^2/\text{m}^2$ vs. $61.1 \pm$
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20 $9.9 \text{ cm}^2/\text{m}^2$, $p < 0.001$). Sarcopenic patients were significantly older than nonsarcopenic patients (mean
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22 age 68.6 ± 6.1 years vs. 60.3 ± 12.2 years, $p < 0.001$) and presented a significantly different mean BMI
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24 than nonsarcopenic patients ($29.5 \pm 5.3 \text{ kg}/\text{m}^2$ vs. $26.5 \pm 5.0 \text{ kg}/\text{m}^2$ respectively, $p= 0.024$). According
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26 to ESPEN guidelines, 39/91 patients (42.9%) were malnourished after preoperative chemotherapy
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28 (21). Feeding jejunostomy during chemotherapy does not improve mean BMI (27.4 ± 5.6 before
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30 chemotherapy vs. 27.0 ± 5.1 after chemotherapy, $p= 0.502$).
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37 There were no significant differences between sarcopenic and nonsarcopenic patients
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39 regarding the type of surgical resection, histopathology, ypT stages, ypN stages and yp stage
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41 (AJCC/UICC) ($p = 0.136$, $p=0.301$, $p= 0.106$, $p= 0.441$, $p = 0.080$, respectively).
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45 In the multivariate analysis of factors related to sarcopenia occurrence, age > 65 years old, BMI
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47 ≥ 25 and preoperative feeding jejunostomy were independent risk factors ($p = 0.01$, $p < 0.001$, $p=0.03$,
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49 respectively, Table 2).
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55 **4.2 Preoperative sarcopenia and postoperative results**

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Seventy-one patients out of 91 (78%) presented at least one complication (all severities included) after surgery (Table 3). A major complication (i.e., Clavien–Dindo ≥ 3) occurred in 6/21 (28.6%) sarcopenic patients vs. 27/70 (38.6%) nonsarcopenic patients ($p = 0.564$). The mean CCI was not significantly different between sarcopenic and nonsarcopenic patients (27.8 ± 29.0 vs. 23.8 ± 21.4 , $p = 0.558$, respectively). The mean length of stay for sarcopenic and nonsarcopenic patients was not significantly different (21.3 ± 14.3 days vs. 21.3 ± 13.4 days, respectively, $p = 0.994$).

4.3 Impact of preoperative sarcopenia on overall survival and disease-free survival

The mean time of follow-up was 37 months [1-131]. Sarcopenia after preoperative chemotherapy was identified as a risk factor for lower survival rates in the Cox regression analysis (HR = 3.02; 95% CI [1.55-5.90], $p < 0.005$). Cancer staging was also identified as a negative risk factor for survival (HR = 5.03; 95% CI [2.48-10.20], $p < 0.005$). Age > 65 , sex, and BMI ≥ 25 had no significant influence on survival in the univariate and multivariate Cox regression analyses ($p = 0.93$, $p = 0.90$, $p = 0.14$, respectively, Table 4).

Patients with sarcopenia had a significantly shorter median overall survival duration than nonsarcopenic patients (33.7 months [95% CI, 18.0-56.5] vs. 58.6 months [95% CI, 31.7-108.2], $p = 0.04$). (Fig. 2a, part 1). There was no statistically significant difference in disease-free survival between sarcopenic and nonsarcopenic patients, although nonsarcopenic patients had a tendency toward longer disease-free survival (20.4 months [95% CI, 12.2-54.8] vs. 55.2 months [95% CI, 27.4-106.6], $p = 0.08$) (Fig. 2b, A and B).

4.4 Overall survival of sarcopenic patients with or without feeding jejunostomy vs. patients with palliative status

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There were no significant differences in the overall survival between sarcopenic patients after a preoperative feeding jejunostomy and patients with progressive or metastatic disease (21.9 months [95% CI, 10.7-48.3] vs. 17.2 months [95% CI, 14.4-22.3], $p = 0.46$) (Fig. 2, C and D). The causes of death among the 13 sarcopenic patients with FJ were pneumopathy in the postoperative period ($n=1$) and cancer recurrence ($n=7$). Five patients were still alive at the end of the follow-up period.

5. Discussion

Our results showed that 23% of the patients who were eligible for OJA surgery were sarcopenic after their preoperative chemotherapy, according to the CT-based definition of sarcopenia. Age > 65 years old and BMI ≥ 25 kg/m² were identified as independent risk factors for sarcopenia occurrence. Nutrition prehabilitation with a feeding jejunostomy, performed in 79% of the patients, was a significant protective factor against preoperative sarcopenia occurrence. Sarcopenia status negatively influenced overall survival, but its impact on disease-free survival was less obvious, and it did not appear to impact the occurrence of postoperative complications. Overall survival of sarcopenic patients after nutritional prehabilitation with a feeding jejunostomy was not significantly different compared to the overall survival of the control group of patients with a palliative status.

Sarcopenia is more frequently associated with specific types of cancer, notably OJA cancers. The prevalence of sarcopenia, as defined by Prado's criteria, was 23% in our cohort, which is lower than the reported overall prevalence of 38% of sarcopenic patients in a Caucasian population with oesogastric junction adenocarcinoma in a meta-analysis by Boshier et al. (2). Additionally, sarcopenia is defined as an age-related decline in muscle mass. This association between age and sarcopenia is well described in the literature. Before its importance was considered in the field of oncology, sarcopenia was first described in elderly patients and represented an important element in geriatric care (22). Indeed, in this study, patients with sarcopenia were significantly older than nonsarcopenic patients. Nevertheless, age was not an independent predictive factor for survival in our Cox regression

1 analysis. Similarly, patients with sarcopenia had a significantly higher mean BMI than nonsarcopenic
2 patients, which classified them as overweight. We also reported that BMI >25 was associated with
3 sarcopenia. This result hints at sarcopenic obesity which has been demonstrated to be the highest risk
4 factor for poor survival in other studies (18,22,23,24). However, our cohort is too small to highlight
5 this result with only 8/21 sarcopenic obese patients (BMI >30). This result highlights the need to pay
6 particular attention to obese or overweight patients and to screen them for sarcopenia.
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14 In the literature, sarcopenia has been shown to be a poor prognostic factor, but unfortunately,
15 there are no clinical standards thus far to treat such patients. Several mechanisms of sarcopenia have
16 been described, mostly pointing toward an impact of chemotherapy on the muscles, the production
17 of chemokines by the tumors, malnutrition (which would be an obvious reason) and/or mechanical
18 obstructive tumors that induce anorexia and dysphagia. Nutritional support by feeding jejunostomy
19 may prevent the occurrence of sarcopenia during neoadjuvant chemotherapy and could be especially
20 helpful in cases of obstructive disease with dysphagia (3). In this study, a feeding jejunostomy was
21 placed in 84.3% of nonsarcopenic patients who underwent surgery, and the multivariate analysis
22 suggests that it could protect them from becoming sarcopenic. This result is important because it
23 highlights the possibility that for some patients, attentive feeding could prevent chemotherapy-
24 induced sarcopenia.
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41 In the multivariate analysis, the occurrence of sarcopenia after preoperative chemotherapy
42 and tumor staging were independent predictors of survival. The occurrence of sarcopenia appears to
43 significantly influence overall survival, with no impact on the postoperative complication rate and
44 disease-free survival rate. This result on the disease-free survival may explained by a lack of power of
45 our study which does not allow to highlight a significant difference (55.2 months for sarcopenic
46 patients vs 20.4 months for nonsarcopenic patients).
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56 Sarcopenia was identified as a poor prognostic factor in other cancers and has been shown to
57 negatively impact survival in locally advanced pancreatic adenocarcinoma (5), gastric cancer (8) and
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1 postoperative complications after laparoscopic surgery for colon cancer (25). However, it was not
2 identified as a pejorative factor for survival in colon cancer (25,26). This difference in the impact of
3 sarcopenia may be explained by the greater malnutrition immediately resulting from dysphagia related
4 to OJA. Hence, FJ appears to be an interesting approach to improve patients' care and overall survival.
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6 However, our results also showed that some patients appear resistant to FJ and will still develop
7 sarcopenia. This highlights the influence of other factors (in addition to malnutrition) also involved in
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9 sarcopenia occurrence.
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17 Some authors have distinguished outcomes according to the histological type of cancer,
18 namely, oesogastric junction adenocarcinoma, squamous cell cancer, or both, but the negative effect
19 on the overall survival of patients undergoing oesophagectomy for OJA has been described in several
20 studies (27–31). However, Grotenhuis et al. did not find any difference in survival according to
21 sarcopenic status (32). In contrast, Reisinger et al. showed that the amount of muscle mass lost during
22 neoadjuvant CRT was predictive of postoperative mortality in a subgroup of patients presenting with
23 stage 3-4 esophageal tumors (33). We did not find significant differences in the global score of
24 complications according to sarcopenic status. This finding is supported by some studies (32,34) but
25 appears to contradict other studies that found a higher incidence of postoperative global
26 complications in sarcopenic patients (27,31,35,36), especially pulmonary ones (28,34,37).
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41 We performed subgroup analyses to assess overall survival in sarcopenic patients despite a
42 feeding jejunostomy and patients who did not undergo surgical cancer resection due to metastatic or
43 progressive disease. This comparison suggests that survival between these two groups was similar.
44 Mortality in sarcopenic patients is common and comparable to patients with advanced stages of
45 disease, even though intensive nutrition therapy was performed. These data suggest that sarcopenic
46 patients, despite FJ, do not benefit from curative surgical resection. Persistent sarcopenia despite
47 active renutrition during preoperative chemotherapy could be a key factor in selecting patients who
48 would not benefit from curative surgical intent.
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2 Our study has several limitations, including a retrospective design and a limited cohort of
3 patients from a single institution. The main limit and potential source of bias remains the
4 interpretation of the sarcopenic status by means of a radiologic assessment alone as proposed by
5 Prado et al., however extensively used by many; it could be interesting to use other means to define
6 sarcopenia, such as bioelectrical impedance analysis and/or dual-energy X-ray absorptiometry (2). This
7 could account for the conflicting results with other previously published studies.
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18 **6. CONCLUSION**

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21 Intensive nutritional prehabilitation with feeding jejunostomy was a protective factor against
22 preoperative sarcopenia occurrence in patients who were eligible for surgery for oesogastric junction
23 adenocarcinoma. Sarcopenia was an independent poor prognostic factor for overall survival after
24 surgery. Moreover, there was no significant difference in the long-term outcomes between sarcopenic
25 patients who underwent surgery after optimal nutritional care with a feeding jejunostomy and patients
26 without surgery due to metastatic or progressive disease. This result suggests that the response of the
27 patient to nutritional prehabilitation management with a feeding jejunostomy could have a place in
28 patient selection before surgery for oesogastric junction adenocarcinoma.
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8 **Figure 1.** Flow diagram
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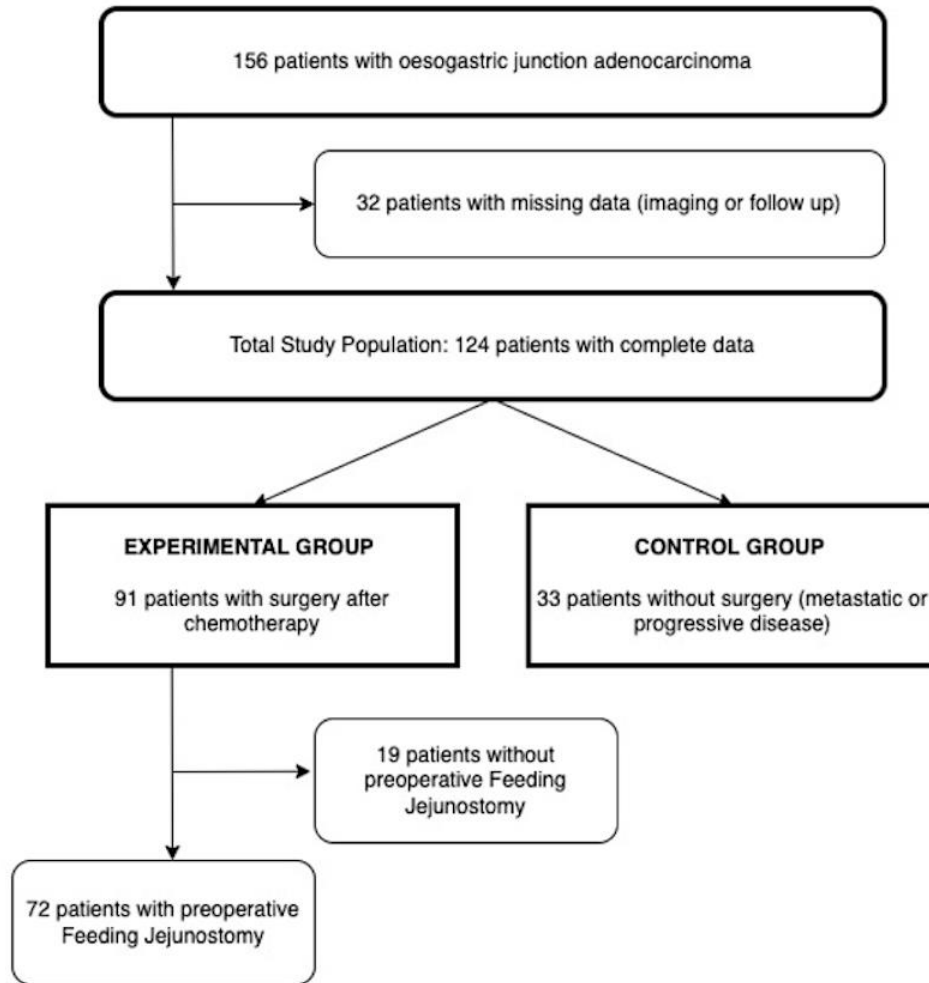
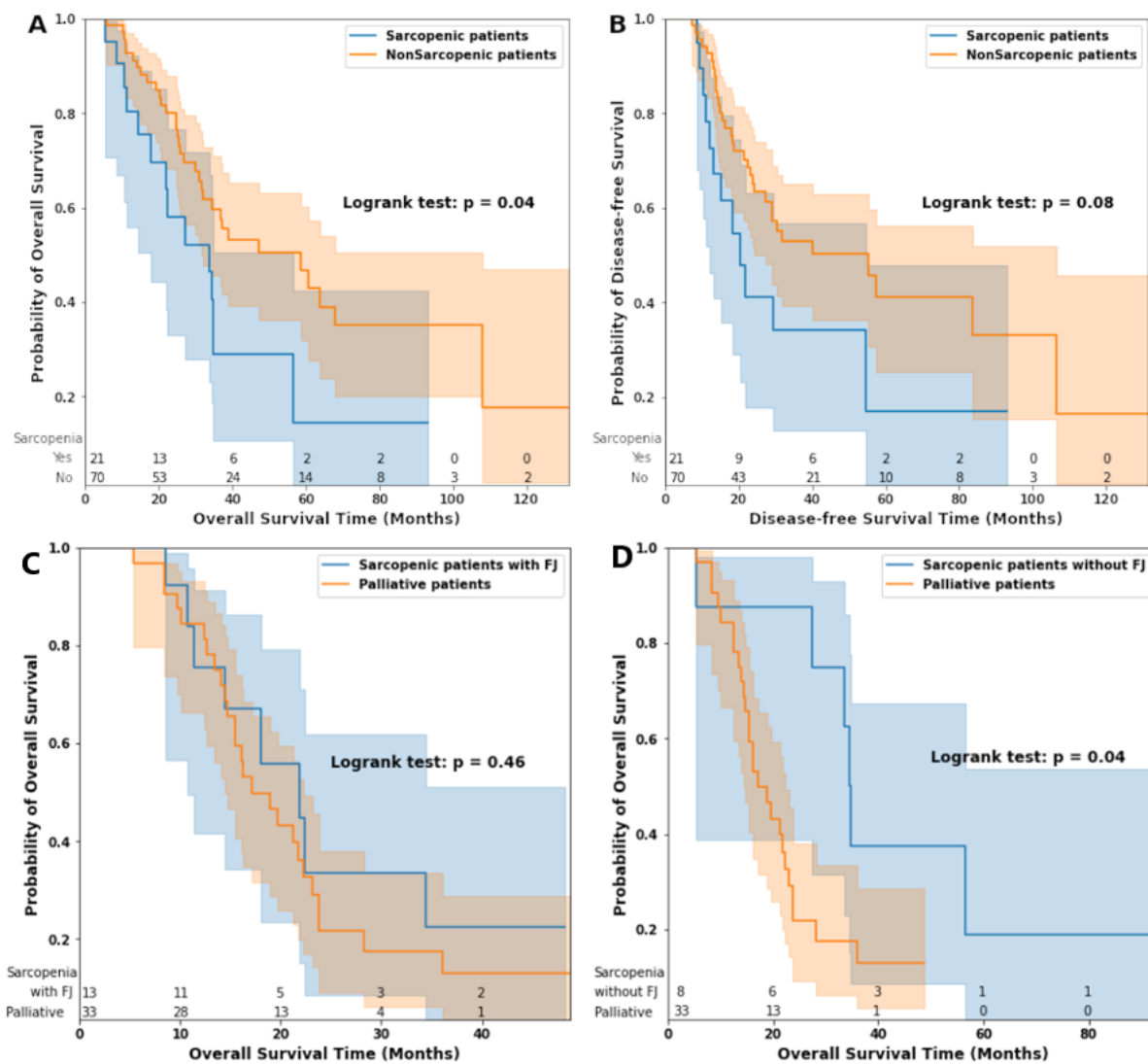


Figure 2. Kaplan-Meier analyses of overall survival (A) and disease-free survival (B) of Sarcopenic vs. Nonsarcopenic patients. Kaplan-Meier analyses of overall survival (C) and disease-free survival (D) of patients without surgery due to progressive or metastatic disease vs. Sarcopenic patients with a Feeding Jejunostomy.



9. TABLES

Table 1. Demographics of the study population

	All n = 91 (%)	Sarcopenic n = 21 (23.0%)	Nonsarcopenic n = 70 (77.0%)	p-value
Age, mean, years ±SD	62.2 ±11.6	68.6 ±6.1	60.3 ±12.2	<0.001
Gender, No. (%)				0.364
Male	74 (81.3)	19 (90.5)	55 (78.6)	
Female	17 (18.7)	2 (9.5)	15 (21.4)	
BMI, mean, kg/m² ±SD	27.2 ±5.2	29.5±5.3	26.5 ±5.0	0.024
SMI, mean, cm²/m² ±SD	57.5 ±11.2	45.3±5.4	61.1±9.9	<0.001
Surgery, No. (%)				0.136
Total Gastrectomy	20 (22.0)	2 (9.5)	18 (25.7)	
Extended Gastrectomy	16 (17.6)	5 (23.8)	11(15.7)	
Ivor Lewis Esophagectomy	55 (60.4)	14 (66.7)	41 (58.6)	
Histopathology, No. (%)				0.301
Well differentiated	52 (57.1)	15 (71.4)	37 (52.9)	
Poorly differentiated	16 (17.6)	2 (9.5)	14 (20.0)	
Isolated cells	23 (25.3)	4 (19.1)	19 (27.1)	
ypT stage, No. (%)				0.106
T0	14 (15.4)	7 (33.3)	7 (10.0)	
T1	16 (17.6)	3 (14.3)	13 (18.6)	
T2	9 (9.9)	1 (4.8)	8 (11.4)	
T3	42 (46.1)	9 (42.8)	33 (47.1)	
T4	10 (11.0)	1 (4.8)	9 (12.9)	
ypN stage, No. (%)				0.441
N0	43 (47.2)	13 (61.9)	30 (42.9)	
N1	26 (28.6)	5 (23.8)	21 (30.0)	
N2	12 (13.2)	2 (9.5)	10 (14.2)	
N3	10 (11.0)	1 (4.8)	9 (12.9)	
ypStage (AJCC/UICC), No. (%)				0.080
0	14 (15.4)	7 (33.4)	7 (10.0)	
1	12 (13.1)	2 (9.5)	10 (14.3)	

2	17 (18.7)	5 (23.8)	12 (17.1)
3	33 (36.3)	5 (23.8)	28 (40.0)
4	15 (16.5)	2 (9.5)	13 (18.6)

Abbreviations: AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer

Control; BMI, body mass index; SMI, surface muscular index.

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Table 2. Risks factors of sarcopenia occurrence: Multivariate analysis

	Sarcopenic patients n = 21 (23.0%)	Nonsarcopenic patients n = 70 (77.0%)	Regression coefficient (log-odds)	p-value
Age, years, No. (%)			1,70	0.01
>65	16 (76.2)	29 (41.4)		
<65	5 (23.8)	41 (58.6)		
BMI, kg/m², No. (%)			2,17	<0.001
≥25	18 (85.7)	34 (48.6)		
<25	3 (14.3)	36 (51.4)		
Feeding Jejunostomy, No. (%)			-1,41	0.03
Yes	13 (61.9)	59 (84.3)		
No	8 (38.1)	11 (15.7)		

Abbreviation: BMI, body mass index

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Table 3. Postoperative complications. Sarcopenic and non-Sarcopenic patients

	All	Sarcopenic	NonSarcopenic	p-value
	n = 91	n = 21 (23.0%)	n = 70 (77.0%)	
Complication, No (%)	71 (78.0)	18 (85.7)	53 (75.7)	0.503
Major Complication^a, No (%)	33 (36.3)	6 (28.6)	27 (38.6)	0.564
CCI, mean, (%) ±SD	24.7±23.3	27.8 ±29.0	23.8±21.4	0.558
Postoperative Stay, mean, days ±SD	21.3±13.6	21.3±14.3	21.3±13.4	0.994

Abbreviations: CCI, Comprehensive Complications Index; CD

^a Major complication is defined as a complication ranked greater than to 2 in the Clavien-Dindo classification of postoperative complications.

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Table 4. Risk factors for Overall Survival (Univariate and Multivariate Cox regression analysis)

Univariate analysis				
	Hazard ratio	CI 95% Lower	CI 95% Upper	p-value
Age (\leq/$>$65)	1.03	0.57	1.83	0.93
Gender (Male/Female)	0.95	0.46	1.98	0.90
BMI ($<$/\geq 25)	1.57	0.86	2.86	0.14
Sarcopenia	1.93	1.02	3.64	0.04
ypStage (AJCC/UICC) (0-2/3-4)	3.94	2.00	7.76	<0.005
Multivariate analysis				
Sarcopenia	3.02	1.55	5.90	<0.005
ypStage (AJCC/UICC) (0-2/3-4)	5.03	2.48	10.20	<0.005

Abbreviations: AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer

Control; BMI, body mass index

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10. APPENDICES A

Table A.1. Sarcopenic status of all patients before and after surgery and according to the presence or absence of a preoperative feeding jejunostomy.

	Before chemotherapy		After chemotherapy	
Total Population	Sarcopenic	13 (14,3%)	Sarcopenic	8 (61.5%)
			Nonsarcopenic	5 (38.5%)
	Nonsarcopenic	78 (85,7%)	Sarcopenic	13 (16.7%)
			Nonsarcopenic	65 (83.3%)
Patient with preoperative FJ	Sarcopenic	11 (15,3%)	Sarcopenic	7 (63.6%)
			Nonsarcopenic	4 (36.4%)
	Nonsarcopenic	61 (84,7%)	Sarcopenic	6 (9.8%)
			Nonsarcopenic	55 (90.2%)
Patients without preoperative FJ	Sarcopenic	2 (10,5%)	Sarcopenic	1 (50.0%)
			Nonsarcopenic	1 (50.0%)
	Nonsarcopenic	17 (89,5%)	Sarcopenic	7 (41.2%)
			Nonsarcopenic	10 (58.9%)

Table A.2. Characteristics of sarcopenic patients without FJ and patients with progressive or metastatic disease.

	Sarcopenic patients without FJ n = 13	Progressive disease or metastatic patients n = 33	p-value
Gender			0.292
Male	12 (92.3%)	24 (72.7%)	
Female	1 (7.7%)	9 (27.3%)	
BMI ± STD	29.5 ± 5.2	24.1 ± 3.7	<0.05
Age ± STD	69.5 ± 5.5	64.8 ± 8.2	0.067

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: