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Dottorato di Ricerca in Medicina sperimentale: Nutrizione in Oncologia

SINGLE-CENTER OBSERVATIONAL STUDY ON CHANGES IN BODY COMPOSITION IN PATIENTS WITH RESECTABLE GASTRIC CANCER CHEMOTREATED WITH THE FLOT PERIOPERATIVE REGIMEN.

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1. INTRODUCTION TO GASTRIC CANCER

1.1 Epidemiology and etiology

According to the most updated epidemiological data provided by the Global Cancer Observatory (GCO), gastric cancer ranks sixth in incidence and fifth in mortality among the worldwide population, including all age groups and both sexes. The highest prevalence rates for this malignancy are recorded in Asia, where Helicobacter pylori infection, a known risk factor for gastric cancer, is diffused. In Europe and Italy, however, gastric cancer has an intermediate incidence, with about 135,000 and 14,000 new cases/year, respectively. [1]

Regarding etiology, gastric cancer, like most cancers, has a multifactorial origin involving dietary, environmental, infectious and genetic factors. First of all, there is scientific evidence that high consumption of salty and smoked foods, especially when combined with low fruit and vegetable intake, increases the risk of gastric cancer. The formation of nitrous compounds, which these foods are rich in, may be responsible for the malignant transformation of the gastric mucosa. Other risk factors include cigarette smoking, excessive alcohol consumption and obesity.

Helicobacter pylori infection, widespread in developing countries, is recognized as a major risk factor for gastric cancer. Indeed, if left untreated, this infection can lead, through a series of clinicopathological changes (chronic gastritis, multifocal atrophic gastritis, Barrett's intestinal metaplasia and dysplasia) to the final development of gastric cancer.

There are also well-defined pathological conditions that predispose to a higher risk of gastric cancer, such as gastroesophageal reflux disease (GERD), Menetrier's syndrome and previous gastric resection. GERD is an increasingly common disease in the Western world, closely associated with obesity and unhealthy diet, which can cause gastric cancer, predominantly in the proximal regions of the organ (the cardias and the esophagogastric junction); these parts, not surprisingly, are the areas most affected by acid reflux. Menetrier's syndrome is a chronic hypertrophic gastritis in which the constant inflammatory state of the gastric mucosa can induce to oncological alterations. After gastrectomy, especially if the reconstructive technique used was the Billroth II, chronic reflux of bile salts can lead to the malignant transformation of gastric epithelium.

Regarding genetic factors, it should be noted immediately that the majority of gastric cancers occur sporadically without any hereditary predisposition. In approximately 10% of cases, a hereditary-familial pattern can be observed, in which, however, the genetic susceptibility

alterations are not fully known. In a very small percentage of cases, gastric cancer occurs in diffuse familial form, due to specific mutations in the E-cadherin gene. [2]

1.2 Histopathological and biomolecular classifications

The World Health Organization (WHO) histopathological classification divides gastric cancer into two main types: adenocarcinomas, which account for 95% of all diagnoses, and other histological forms, which account for the remaining 5%. Gastric adenocarcinomas, in turn, present in five variants: classic, papillary, tubular, mucinous and signet ring cell. Other histological forms mainly include squamous cell carcinoma, undifferentiated carcinoma, GIST, MALT lymphoma and leiomyosarcoma. [3]

In the histopatology of gastric cancer, two classifications are of historical importance: the Lauren classification and the Ming classification. The first divides gastric adenocarcinomas into two forms: intestinal type (differentiated carcinoma with a tendency to form glands) and diffuse type (undifferentiated carcinoma with poorly cohesive cells). The second classification, that of Ming, divides gastric cancer into an expansive form (carcinomas with exophytic development) and an infiltrative form (carcinomas which penetrate through the gastric layers). [4], [5]

In 2014, The Cancer Genome Atlas (TCGA) classification was presented; this system identifies four types of gastric cancer: EBV-related, microsatellite unstable (MSI), genomically stable (GS) and chromosomal unstable (CIN). [6]

Finally, there is the biomolecular classification which, according to the most updated national and international guidelines, recommends classifying gastric cancer based on the expression of the following biomarkers: HER-2, MMR/MSI, PD-L1 and Claudin-18. This classification has a predictive role in the selection of personalized systemic oncological treatment. [7], [8]

1.3 Diagnosis and staging

For the diagnosis of gastric cancer, the gold standard is esophagogastroduodenoscopy (EGDS), which allows for a macroscopic description of the lesion and, more importantly, biopsies for histological examination. All patients over 50 years of age who present to medical care with worsening symptoms characterized by loss of appetite, fatigue, weight loss, digestive disorders and anemia should undergo to endoscopic examinations to exclude

a possible gastrointestinal cancer. Among tumor markers, despite their diagnostic limitations, CEA and CA 19.9 levels can be considered useful as a general framework.
To stage gastric cancer, a contrast-enhanced CT scan of the chest and abdomen is required. Gastric cancer is then divided into four stages according to the standard international TNM classification of the American Joint Committee on Cancer (AJCC). [9]
In high-incidence countries, such as Asian countries, there are screening protocols for the early diagnosis of gastric cancer. Indeed, periodic EGDS is recommended to identify malignant gastric lesions in their early stages. These protocols are not validated in Europe and the rest of the world. [10]

1.4 Treatment

The therapeutic management of gastric cancer must be multidisciplinary to offer the patient the best personalized strategy. [11]
Gastric cancer presents in limited form in only 20% of cases. In these cases, surgery remains the only potentially curative weapon. However, given the high risk of recurrence, increasing evidence suggests that perioperative chemotherapy should also be considered in this patients setting. This therapeutic approach, which consists of a preoperative and a postoperative phase, would allow for better oncological radicality, recurrences reduction and improved survival outcomes. [12]
In still early forms, such as early gastric cancer, a lesion limited to the mucosa or submucosa, the standard of care is endoscopic resection. [13]
In 80% of cases, gastric cancer is locally advanced or metastatic. Treatment of locally advanced forms has been revolutionized by the advent of the FLOT chemotherapy, which has been shown to significantly increase patient overall survival. This regimen has therefore become the standard of care for these forms of gastric cancer. [14]
In metastatic disease, a thorough assessment of the patient is essential to determine whether they are suitable for systemic oncological treatment or best supportive care (BSC). To make the most appropriate decision, the patient's assessment must be comprehensive and therefore address general clinical conditions, age, non-oncological comorbidities, autonomy in daily activities (e.g., hygiene and personal care), family and social support. For patients considered fit for systemic treatment, this is selected based on the tumor's molecular biology. There are several options which essentially involve the combination of platinum- and fluorouracil-

based chemotherapy with biological drugs such as trastuzumab and zolbetuximab, or immunotherapy drugs such as nivolumab. [7], [8]

1.5 Focus on resectable stages

In oncology, the TNM staging of cancers is commonly simplified into three classes of oncological disease: limited disease, locally advanced disease and metastatic disease. [15]

The TNM staging of gastric cancer is quite complex and escapes this simplification because gastric cancer, even if localized to the organ wall, tends to produce early involvement of the lymphatic structures. For this reason, lymph node parameter is crucial for correctly staging all forms of gastric cancer. A significant proportion of tumors which seem in limited stage are actually locally advanced due to involvement of the loco-regional lymphatic network. [16]

Limited and locally advanced forms are resectable. Limited stages can be treated immediately with surgery while locally advanced ones must be treated with perioperative chemotherapy. It's important to note that most resectable gastric cancers are locally advanced. [17]

Until the 2000s, resectable gastric cancer was conventionally treated with neoadjuvant fluoropyrimidine-based chemotherapy followed by surgery. This strategy ensured overall good surgical results but it did not significant impact on patient prognosis. [18]

In the early 2000s, the treatment of resectable gastric cancer began to change with the advent of the perioperative medical strategy: the prognostic importance of both pre- and post-operative chemotherapy phases was thus understood and maked systematic. Over the years, several chemotherapy regimens have been developed up to what still represents the standard of care today: the FLOT regimen; this scheme is composed of three drugs: 5FU, Oxaliplatin and Docetaxel; it is structured in 4 pre-operative and 4 post-operative chemotherapy cycles, administered every 14 days. [19] [14]

The MATTERHORN study was recently published demonstrating increased benefit from adding the immunotherapy drug Durvalumab to the FLOT regimen. [20]

At the time of writing of this PhD Thesis, the new chemo-immunotherapy regimen is under discussion at European and Italian regulatory authorities.

2. MALNUTRITION IN GASTRIC CANCER

2.1 The size of the problem

Gastric cancer is a malignancy associated with a very high rate of malnutrition; the prevalence of malnutrition in gastric cancer patients is estimated to be approximately 75% and this percentage tends to further increase with the disease stage.

The process which leads to malnutrition is multifactorial because it includes both factors intrinsically linked to the oncological disease and factors related to the medical and surgical treatments to which patients are subjected. [21]

There are various definitions of the concept of malnutrition; for this work, we selected the one formulated by the Global Leadership Initiative on Malnutrition (GLIM), which identifies malnutrition through two essential diagnostic criteria: a phenotypic one (weight loss, low body mass index, loss of lean mass) and an etiological one (reduced food intake, malabsorption, systemic inflammation, pre-existing diseases). The nutritional deterioration which is often observed in patients with gastric cancer clearly satisfies this definition. [22]

2.2 Screening and nutritional support

Nutritional screening of gastric cancer patients is an important step in the multidisciplinary planning of the treatment program and uses various tools that can be grouped into six main categories: conventional anthropometric parameters (weight, height and body mass index); questionnaires validated by the international scientific community (for example NRS); biochemical assessments and scores (such as the NRI); functional tests (such as the Handgrip test); instrumental tests (CT and MRI); finally specialized tests (such as bioimpedance analysis).

Once malnutrition has been diagnosed, the best nutritional support for the patient is determined. There are three different types of nutritional intervention, which can also be combined: oral nutrition (ON), enteral nutrition (EN) and parenteral nutrition (PN).

In gastric cancer, nutritional support must be provided early, starting from diagnosis and regardless of the disease stage. In resectable stages, in particular, nutritional support varies depending on the pre-operative and post-operative phases in order to maintain optimal nutritional status throughout all steps of the care program. [23]

2.3 FLOT chemotherapy and impact on body composition

The FLOT regimen is currently the standard perioperative chemotherapy for patients with resectable gastric cancer. In addition to its clinical and oncological effects, it has a significant impact on body composition, which is increasingly recognized as a prognostic factor. [24]

Several observational studies have shown that during FLOT chemotherapy, skeletal muscle wasting occurs, assessed by CT index. Sarcopenia is associated with increased toxicity, chemotherapy reduction, delays or discontinuation and worse outcomes. In patients already sarcopenic before starting treatment, the overall prognosis is less favorable. The same studies have shown that fat mass (visceral and subcutaneous) is also reduced, but to a lesser extent than muscle mass, thus indicating greater protein catabolism. [25]

Dynamic assessment of body composition through imaging index (such as the Skeletal Muscle Index – SMI) is an emerging tool to monitor the patient's skeletal mass throughout the treatment process and prevent excessive loss. [26]

Nutritional interventions and early exercise programs are increasingly being studied to reduce the negative effects of sarcopenia. [27]

3. DESIGN AND PURPOSE OF THE STUDY

For this PhD Thesis we decided to conduct an observational and single-center study aimed at evaluating the changes in body composition of patients with resectable gastric cancer chemotreated with the FLOT regimen.
The overall purpose of this study is to contribute to a subject of recent interest in oncology: the impact of nutritional status on the prognosis of cancer patients.
The specific purposes are detailed in the study endpoints.

The primary endpoint is the dynamic evaluation of body composition parameters in relation to early nutritional support.
The secondary endpoints are represented by the survival outcomes (DFS and OS), always in relation to early nutritional support.

4. PATIENTS AND METHODS

4.1 Patients selection

For the purpose of our study, 87 patients with resectable gastric cancer, chemotreated with perioperative FLOT regimen, attending the Oncological department of the "Policlinico San Matteo" Hospital in Pavia (Italy), were selected between January 2012 and August 2025.

Patient data was obtained from the medical records and outpatient reports available at our hospital and patient selection was performed according to the inclusion and exclusion criteria reported below.

Inclusion criteria:

- Histological diagnosis of gastric or gastroesophageal junction adenocarcinoma;
- TNM stages I-III
- Be eligible for perioperative chemotherapy treatment.

Exclusion criteria:

- Other histological diagnoses;
- TNM stage IV;
- Having undergone up-front gastrectomy.

4.2 Data collection

Once the patients were selected, their clinical data were entered into a database. The database contains each patient's oncological history, distributed across five different areas.

The first area concerns personal data, the date of the oncological diagnosis, the gastric location of cancer, the histological diagnosis and the clinical TNM stage (cTNM).

The second area collects data relating to perioperative chemotherapy including the drug regimens used, the total number of cycles performed, the theoretical planned and actual doses administered and finally the recording of toxicities.

The third area concerns the surgical procedure and reports the date of surgery, the type of gastrectomy performed (total or subtotal) and the post-chemotherapy TNM stage (ypTNM).

The fourth area contains data on the timing evolution of the oncological disease and therefore the date and locations of any pre-surgery disease progression, any post-surgery relapse, the date of the last follow-up check or the date of the patient's death.

The fifth area is the most important because it represents the heart of the data collection and is therefore transversal to all the areas; it reports the anthropometric and body composition

parameters of each patient in 3 key timepoints: at diagnosis, before surgery (after neoadjuvant chemotherapy) and finally after surgery (before adjuvant chemotherapy).

4.3 Statistical analysis

Statistical analysis of the collected data was performed using Excel (Microsoft Office) and SPSS. Continuous variables are presented as mean, median, minimum value, maximum value and standard deviation while categorical variables are presented as absolute frequencies and percentages. Survival parameters, in particular, were developed using the log-rank test for subgroup comparisons and are graphically represented by Kaplan-Meier curves. The statistical significance of the results obtained was assessed using the standard cut-off of a p-value equal to or less than 0.05.

5. RESULTS

5.1 General overview

All selected patients were first analyzed according to 8 variables: sex, age, gastric cancer location, histological diagnosis, TNM stage, perioperative chemotherapy regimen, early nutritional support and BMI. **Table 1.**

PATIENTS' FEATURES	N=87 (%)
SEX	
Male	63 (72.4%)
Female	24 (27.6%)
AGE	
Median	62.7
<70 years	63 (72.4%)
>= 70 years	24 (27.6%)
GASTRIC LOCATION	
Gastro-oesophageal junction	31 (35.6%)
Corpus/fundus	36 (41.4%)
Antrus	20 (23%)
HISTOTYPE	
Intestinal	30 (34.5%)
Diffuse	28 (32.2%)
Mixed	8 (9.2%)
Poor differentiated	12 (13.8%)
Not available	9 (10.3%)
TNM STAGE	
II	25 (29.4%)
III	60 (70.6%)
Missing data	2 (2.3%)
CHEMOTHERAPY REGIMEN	
FLOT	60 (69%)
XELOX	3 (3.4%)
FOLFOX	10 (11.5%)
CISPLATIN-5FU	12 (13.8%)
CISPLATIN-DOCETAXEL-5FU	2 (2.3%)
EPIRUBICIN-CISPLATIN-CAPECITABINE	2 (2.3%)
EARLY NUTRITIONAL ASSESSMENT	
Yes	49 (56.3%)
No	38 (43.7%)
BMI AT DIAGNOSIS	
Underweight	1 (1.1%)
Normal weight	40 (46.0%)
Over weight	39 (44.8%)
Obese	7 (8.0%)
Missing data	2 (2.3%)

Table 1

A further preliminary analysis concerns body composition parameters: these are 13 indexes that involve muscle mass and adipose mass (subcutaneous and visceral). These indexes are SMA (Skeletal Mass Area), VAT (Visceral Adipose Tissue), SAT (Subcutaneous Adipose Tissue), IMAT (InterMuscular Adipose Tissue), VSR (Visceral-Subcutaneous fat Ratio), SMI (Skeletal Muscle Index), VATI (Visceral Adipose Tissue Index), SATI (Subcutaneous Adipose Tissue Index), IMATI (Inter-Muscular Adipose Tissue Index), Muscle density, VAT density, SAT density and IMAT density. All these parameters are calculated starting from the area of muscle and adipose tissue at the L3 vertebra (considered the international standard) in patient CT scans. The difference between muscle and adipose tissue is called segmentation and is performed by analyzing the HU (Hounsfield Units) density thresholds. The total area is then normalized by height to allow for correct data comparison. [28] **Table 2.**

BODY COMPOSITION PARAMETERS	OVERALL (N=87)	MALES (N=63)	FEMALES (N=24)
SMA (cm^2)			
Median	140,00	152,80	99,05
Mean (SD)	139,10 (30,88)	154,15 (21,02)	99,60 (11,20)
VAT (cm^2)			
Median	119,05	129,50	54,02
Mean (SD)	119,55 (83,65)	137,84 (84,73)	72,30 (59,91)
SAT (cm^2)			
Median	138,25	135,60	146,10
Mean (SD)	151,80 (88,89)	146,96 (88,14)	164,32 (91,47)
IMAT (cm^2)			
Median	8,42	8,50	7,78
Mean (SD)	11,02 (9,46)	10,56 (7,99)	12,23 (12,66)
VSR			
Median	0,64	0,87	0,40
Mean (SD)	0,83 (0,54)	0,98 (0,54)	0,45 (0,33)
SMI (cm^2/m^2)			
Median	48,58	51,30	40,48
Mean (SD)	49,04 (8,43)	52,11 (7,16)	41,01 (5,87)
VATI (cm^2/m^2)			
Median	39,74	44,35	22,45
Mean (SD)	42,10 (28,93)	46,79 (29,17)	29,99 (24,97)
SATI (cm^2/m^2)			
Median	47,41	43,60	62,90
Mean (SD)	54,46 (32,37)	49,18 (27,63)	68,08 (39,70)
IMATI (cm^2/m^2)			
Median	2,92	2,90	2,99
Mean (SD)	4,01 (3,70)	3,59 (2,68)	5,15 (5,46)
Muscle density (HU)			
Median	45,43	45,43	45,62
Mean (SD)	44,71 (8,82)	45,19 (7,66)	43,43 (11,43)
VAT density (HU)			
Median	-90,44	-91,35	-85,51
Mean (SD)	-88,53 (8,59)	-89,24 (8,91)	-86,71 (7,56)
SAT density (HU)			
Median	-95,38	-95,20	-96,81
Mean (SD)	-92,20 (11,56)	-90,70 (12,41)	-96,09 (7,96)
IMAT density (HU)			
Median	-60,86	-60,85	-62,18
Mean (SD)	-61,50 (5,91)	-61,00 (6,28)	-62,81 (4,70)

Table 2

The final analysis therefore focused on 60 patients (69% of total) who received the standard of care FLOT as their perioperative chemotherapy regimen. Of these 60 patients admitted to the statistical analysis, 28 (46,7%) received early nutritional support and 32 (53,3%) did not. These two groups conceptually represent the two comparison arms of our observational study.

5.2 Primary endpoint

First of all we identified 3 essentials timepoints of the patient's oncological pathway: the condition at diagnosis, before surgery (after neoadjuvant FLOT) and after surgery (before adjuvant FLOT). Of the 13 body composition indexes we specifically analyzed the most important and most widely used in the scientific field: the SMI, the VATI and the SATI.

The primary endpoint is the dynamic evaluation of changes in body composition in relation to early nutritional support; so we analyzed the trend of the average SMI, VATI and SATI values at the 3 timepoints of the oncology pathway.

These values are reported in **Table 3** with their respective standard deviations and confidence intervals.

Measure	nutritional support prescribed (Y/N)	timepoints	Mean	Std. Error	95% Confidence Interval	
					Lower Bound	Upper Bound
SMI	N	1	49,391	1,380	46,621	52,161
		2	48,566	1,159	46,241	50,892
		3	46,741	1,294	44,145	49,337
	Y	1	49,214	1,874	45,454	52,973
		2	47,698	1,573	44,542	50,854
		3	47,146	1,756	43,622	50,669
VATI	N	1	40,026	4,552	30,893	49,160
		2	39,405	4,148	31,082	47,728
		3	21,238	2,641	15,938	26,537
	Y	1	30,125	6,178	17,728	42,522
		2	32,860	5,630	21,564	44,157
		3	20,212	3,584	13,020	27,405
SATI	N	1	61,213	5,887	49,400	73,026
		2	57,974	5,079	47,783	68,166
		3	45,551	4,842	35,835	55,267
	Y	1	44,498	7,990	28,465	60,530
		2	45,607	6,893	31,775	59,439
		3	40,894	6,572	27,707	54,081

Table 3

In both study arms (patients with early nutritional support and patients who did not receive it), the SMI decreased during the oncological pathway, but the curve of patients who did not receive nutritional support was steeper and reached a lower mean at the final timepoint than the control group (patients with early nutritional support). In other words, the curve of patients receiving early nutritional support has a lower slope, especially in the transition from the pre-surgery to the post-surgery timepoint. **Figure 1.**

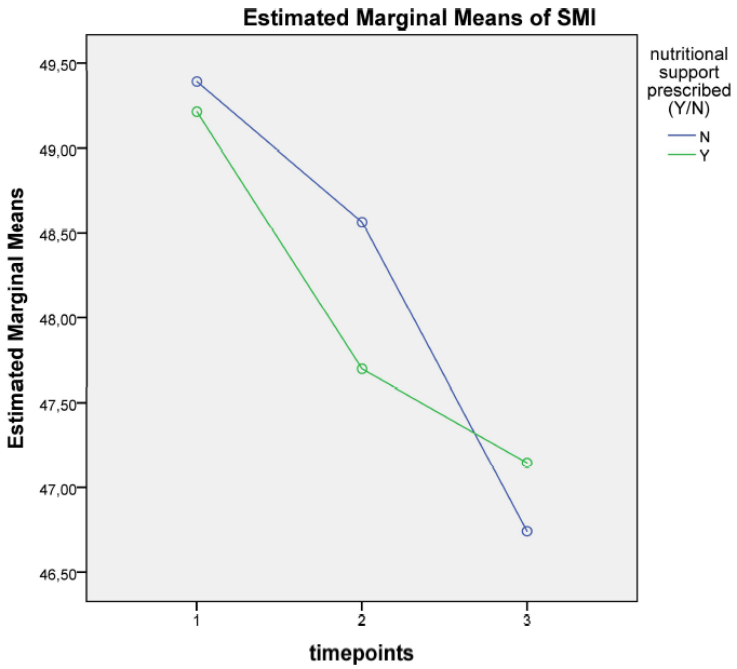

Figure 1

As regards the VATI, the two curves behave differently: in patients who did not receive early nutritional support, we have an initial phase of slight decline (almost a plateau) between the condition at diagnosis and the pre-surgical moment, subsequently we have a steep decline until the post-surgical timepoint. Conversely, in patients who received early nutritional support, we have an initial phase of rising curve between the first two timepoints and subsequently a phase of steep decline. **Figure 2.**

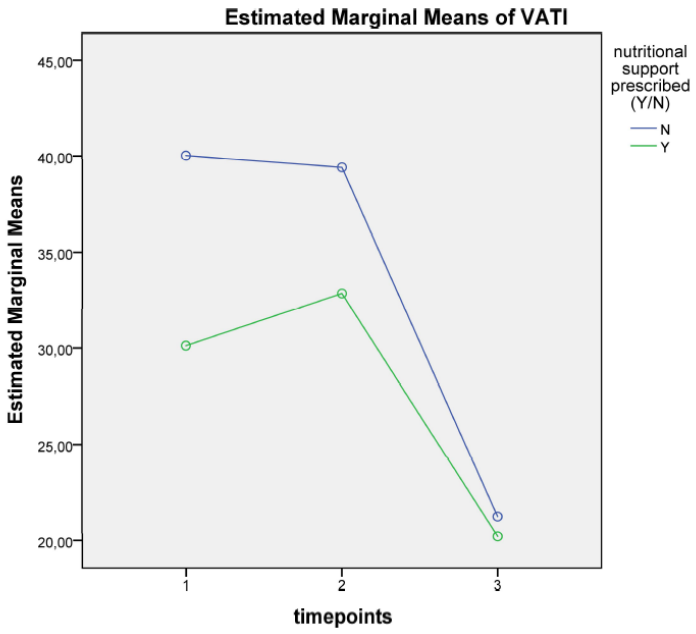

Figure 2

Also for the SATI, the curves have a similar morphology to the VATI but with a lower slope in both comparison groups. **Figure 3.**

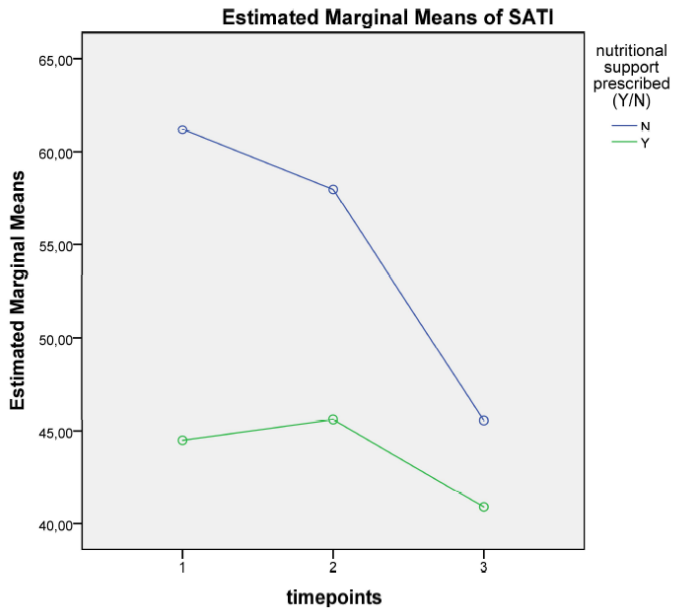

Figure 3

5.3 Secondary endpoints

The secondary endpoints are DFS and OS. DFS was 67,7 months versus 47,5 (p value 0,038), respectively between patients without early nutritional support and patient with early nutritional support.

OS was 69,3 months versus 68,1 (p value 0,603), between the two respective comparison arms (no early nutritional support and patients with early nutritional support).

While the DFS curves faithfully reflect the reported means, the OS curves, after an initial advantage for patients who did not receive nutritional support, invert, showing a clear benefit for the group of patients who received nutritional support**. Figures 4 and 5**.

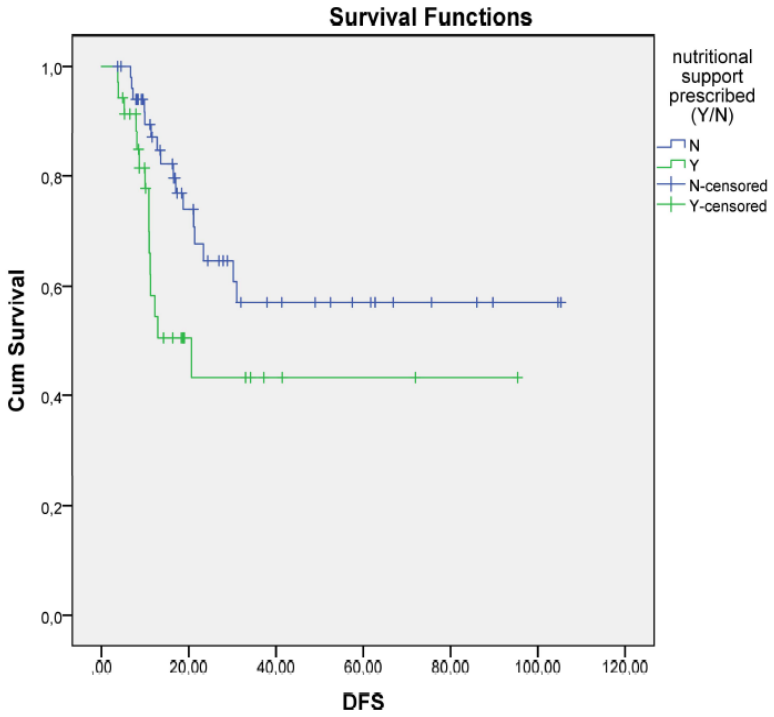

Figure 4

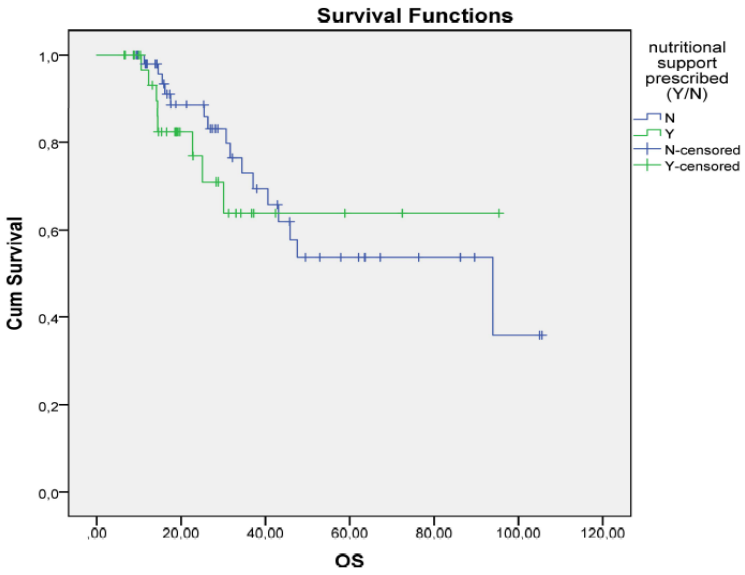
Survival Functions
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
20,00
40,00
60,00
80,00
100,00
120,00
OS
nutritional support prescribed (Y/N)
N
Y
N-censored
Y-censored

Figure 5

6. DISCUSSION AND CONCLUSION

The prognosis of resectable gastric cancer has improved significantly in recent years thanks to the advent of perioperative chemotherapy and, more specifically, the FLOT regimen. [29]

Nevertheless, we know that malnutrition in these patients negatively affects prognosis, at all disease stage. Recently, oncology research has focused on the role of nutritional support in gastric cancer patients suggesting that adequate support could facilitate tolerance to oncology treatments, ensure continuity of treatment, reduce toxicities and overall improve prognosis. In this sense, national and international guidelines recommend performing universal nutritional screening at diagnosis and not only targeting malnourished patients. [21][30], [31]

As already explained in the study design and purpose section, the general aim of this work is to contribute to the oncology literature regarding the positive impact of nutritional support on the prognosis of patients with resectable gastric cancer.

A critical discussion of the results obtained for each endpoint analyzed, net of statistical significance levels, leads us to conclude that early nutritional support has a very modest impact on the maintenance of muscle mass in patients and their survival. Nevertheless, to interpret these results as a whole, it is necessary to recognize the strengths and weaknesses of the study.

As for the weaknesses, these are represented by the methodological limitations of the study; we identified four: the sample size, the complexity of performing a statistical analysis across a complex treatment pathway (neoadjuvant chemotherapy, surgery and adjuvant chemotherapy), the difficulty in processing data regarding patients' nutritional status and finally the lack of universal nutritional screening.

This last point is extremely important and deserves more detailed discussion; the division of patients into two study groups was indeed based on an incorrect approach to providing nutritional support, which nevertheless remains a widespread practice in current clinical activity: that of activating early nutritional support only for patients who are malnourished at diagnosis, whereas the guidelines, as mentioned, recommend universal screening. This point explains how body composition parameters, at diagnosis, differed between the two study groups: muscle mass indexes were quite similar between the two groups while fat mass indexes were higher in patients who did not receive nutritional support (see Table 3). This explanation suggests that early nutritional support was

provided only to patients who were supposedly malnourished or with risk of weight loss at diagnosis, and not to all; it is correct to say supposedly because the nutritional screening was not done by immediately analyzing body composition (a rather long investigation, the data for which were obtained retrospectively thanks to our analysis) but on the basis of BMI: therefore, underweight and normal-weight patients are typically referred for early nutritional support while overweight and obese patients are not.

The division of the two comparison groups, if we want too approxiamte, brings with it a preliminary disadvantage to the analysis of the results: the patients receiving early nutritional support were considered malnourished or at such risk and therefore began the oncological pathway from a disadvantaged condition compared to the control arm (non-malnourished patients with no need for early nutritional support). This disadvantage is essentially linked to the lower weight compared to the control group, a lower fat reserve and a greater tendency to lose weight during oncological treatments.

Nevertheless, a closer look at this crucial point reveals that nutritional support has a positive effect: patients who received it experienced weight gain (more fat than muscle), especially during the transition from the diagnosis to the pre-surgery timepoint. The predominant increase in adipose tissue compared to muscle is consistent with literature studies. [32]

Furthermore, the OS curves also show a reversal of the trend in favor of patients who received early nutritional support, demonstrating that the final benefit in prognosis is achieved in the medium-long term thanks to the slow but effective changes in the body's metabolism. [33]

Regarding the study's strengths, we identified three: its real-life nature, the importance of delving deeper into the subject of nutrition in active oncology and the originality of examining body composition parameters in their entirety. Most studies similar to ours focus only on skeletal muscle mass and its loss, whereas our work examines 13 body composition parameters that also include fat mass.

Despite the stated limitations, our study allows us to reach some key considerations: nutrition plays a central role in oncology demonstrating to be not only a risk/protective factor but also a factor modulating treatment adherence and patients prognosis. Early nutritional support slows muscle loss. Finally, it seems to have a modest impact on survival

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