REVIEW

Nutritional support management in resectable gastric cancer

Francesco Serra¹, Paolo Pedrazzoli¹, Silvia Brugnatelli¹, Anna Pagani¹, Salvatore Corallo¹, Giovanni Rosti¹, Riccardo Caccialanza², Jacopo Viganò³, Ornella Carminati⁴

¹Medical Oncology Unit, IRCCS Policlinico San Matteo, Department of Internal Medicine and Medical Therapy, University of Pavia, Pavia, Italy; ²Clinical Nutrition and Dietetics Unit, IRCCS Policlinico San Matteo, Pavia, Italy; ³General Surgery Unit, IRCCS Policlinico San Matteo, Pavia, Italy; ⁴Medical Oncology Unit, AUSL della Romagna, Rimini Hospital, Rimini, Italy

Abstract

Gastric cancer is the sixth most common malignancy in the world. However, its mortality has been decreasing in the last years thanks to improvement in diagnostics and therapeutics. Nevertheless, the high rate of malnutrition in patients with gastric cancer still has a major impact on the overall survival and quality of life of patients. The narrative review presents the most recent data on nutritional support in the resectable stages of gastric cancer, with a particular focus on perioperative strategies, and discusses malnutrition in gastric cancer, nutritional support before and after surgery, and the relationship between nutritional support and chemotherapy. Despite the predominantly methodological limitations related to the difficulty of performing randomized controlled trials on nutritional support in cancer patients, this review highlights important points. Nutritional counselling is essential starting from diagnosis. In limited or locally advanced forms (about 40% of cases), the therapeutic cornerstone is represented by gastric surgery. In most of these cases, perioperative chemotherapy is also indicated. Of note, nutritional support varies before and after surgery. In the preoperative period, the goal is to

prepare the body for surgery, with available evidence recommending the prescription of immunonutrition (both oral and artificial, as appropriate). In the postoperative period, on the other hand, the objective is to facilitate recovery and adaptation to the new anatomy; an early and combined strategy (oral and enteral) seems to be the most suitable to pursue this. Unfortunately, rigorous data on the relationship between nutritional support and chemotherapy treatments used in resectable gastric cancer are not available. In the absence of strong scientific evidence, it may be useful to adopt a personalized multidisciplinary strategy for each patient wherein the chemotherapy programme is modulated based on nutritional status.

Keywords: gastric cancer, malnutrition, nutritional support, patient survival, quality of life.

Citation

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Introduction

Gastric cancer is the sixth most common malignancy in the world. However, its mortality has been decreasing in recent years thanks to improvements in diagnostics and therapeutics. Nevertheless, the high rate of malnutrition in patients with gastric cancer still has a major impact on their overall survival and quality of life; the prevalence of malnutrition in these patients is of ~75% and increases with disease stage.¹²

A first epidemiological division of gastric cancer concerns the practical distinction between early or resectable

stages and advanced or unresectable stages; in ~40% of cases, gastric cancer occurs in a limited stage with a 5-year survival of 70% whilst, in the remaining 60% of cases, oncological disease occurs in an advanced stage with a decrease in survival to 30%.³ This narrative review presents the most recent data on nutritional support in the resectable stages of gastric cancer, with a particular focus on perioperative strategies.

Methods

This narrative review discusses malnutrition in gastric cancer, nutritional support before and after surgery,

and the relationship between nutritional support and chemotherapy. The literature search was conducted using the keywords "gastric cancer", "malnutrition" and "nutritional support" using on PubMed. The inclusion of studies in this narrative review was at the discretion of the authors, favouring those with greater statistical impact in order to offer readers useful, updated and evidence-based information.

Review

Malnutrition in gastric cancer

After pancreatic cancer, gastric cancer is the cancer second most likely type of cancer to cause malnutrition.^{4,5} The process leading to malnutrition is multifactorial because it involves factors related to the oncological disease, to the treatments performed and to psychosocial issues relating to the patient.⁶

There are several definitions of malnutrition; our work was based on two of these. The first is that provided by WHO, which defines malnutrition as "a condition of imbalance, in deficiency or in excess, of an individual's energy needs".7 Gastric cancer thus promotes a negative imbalance in nutritional status. The second definition is that provided by the Global Leadership Initiative on Malnutrition, which recommends diagnosing malnutrition with two essential criteria: phenotypic (loss of body weight, low BMI, loss of muscle mass) and aetiological (reduced dietary intake, malabsorption, state of systemic inflammation, pre-existing diseases). The nutritional deterioration typically seen in gastric cancer also satisfies this definition of malnutrition.⁸ Whilst the definition of WHO is general, the Global Leadership Initiative on Malnutrition is more detailed due to its origin in a consensus conference, which established objective criteria for the diagnosis of malnutrition in clinical contexts.

Gastric cancer produces, in particular, a state of malnutrition through three interrelated conditions: anorexia/ cachexia syndrome, sarcopenia and myosteatosis. The anorexia/cachexia syndrome is a complex medical condition that includes low food intake, weight loss, sarcopenia and metabolic alterations such as hypoalbuminaemia. The syndrome is complex and involves the release of proinflammatory cytokines that modify the regulatory mechanisms of appetite and body composition, finally resulting in the loss of lean mass.9 There are three main stages of cachexia: precachexia, cachexia and refractory cachexia. In precachexia, the metabolic alterations precede clinically detectable weight loss and, in this phase, the nutritional intervention must be as early and efficacious as possible. In the cachexia stage, there is significant weight loss, more or less associated with sarcopenia; in this phase, the nutritional intervention

should be more intensive to allow the recovery of body weight and, in particular, of muscle mass. Refractory cachexia is an irreversible stage, correlated to a state of progressive oncological disease no longer susceptible to oncological treatments. In this phase, the costs and risks of the nutritional intervention, usually artificial, exceed the expected benefits.¹⁰

Sarcopenia is characterized by the loss of muscle mass and strength. It is a process due not only to oncological disease but also to age and other chronic diseases, often contextual to active cancer. Sarcopenia represents a negative prognostic factor affecting both medical and surgical outcomes. As a pathogenic mechanism, we have the modification of muscle fibres in terms of atrophy, infiltration by fibrous or non-muscular cells with consequent reduction of the patient functional status. Sarcopenia in patients with gastric cancer becomes more pronounced in the group of elderly patients; ageing, as is well known, unbalances body metabolism towards catabolic processes and consequently towards a greater risk of muscle mass loss. Therefore, the European Working Group on Sarcopenia in Older People, over the years, developed recommendations addressed to clinicians for the prompt recognition of this pathological condition and for better management.^{11,12}

Another important condition, the subject of recent studies, is myosteatosis, which can be defined as a reduction in the radiodensity of muscle tissue due to infiltration by fat cells. It is therefore associated with obesity, which is a well-known oncological risk factor in general and particularly for gastrointestinal malignancies.¹³ It is important to note that sarcopenia and myosteatosis are two interrelated alterations in the modification of muscle tissue: the first determines a reduction in muscle volume (quantity) whilst the second leads to a change in muscle radiodensity (quality).¹⁴

An interesting study, published in 2021, established that myosteatosis, together with sarcopenia and visceral obesity, is a potential factor for the development of postsurgical complications and for an increase in hospitalization time.¹⁵

Nutritional screening tools

Nutritional screening of patients with gastric cancer is an important stage in the planning of specialist treatment and makes use of various tools, which can be grouped into six main categories: conventional anthropometric parameters, validated questionnaires, biochemical assessments, functional tests, instrumental examinations and specialist tests.

The most routine anthropometric parameter in clinical settings is the BMI, which remains an essential tool for initial screening. It is necessary to remember that BMI does not provide information on body composition and therefore does not distinguish between fat mass and lean mass.¹⁶ Furthermore, in patients with gastric cancer, malnutrition is often associated with obesity and consequentially with a high BMI. It is therefore important to overcome the false belief that malnutrition only affects patients who are underweight and should be sought and treated in the presence of a low BMI.¹⁷

The validated questionnaires are tools that extract information related to dietary habits, physical activity, preexisting diseases and the timing of weight loss, amongst others. The tools suggested by the European guidelines and most used in clinical practice are the Nutrition Risk Screening tool, Malnutrition Universal Screening Tool, Mini Nutritional Assessment Short Form, and Short Nutritional Assessment Questionnaire.^{18,19}

Several biochemical evaluation tools, are available, including the Prognostic Nutritional Index, Glasgow Prognostic Score, Neutrophil to Lymphocyte Ratio, COntrol NUTritional Score and Geriatric Nutritional Risk Index.²⁰

The calculation of Prognostic Nutritional Index is based on albumin levels and lymphocyte count in peripheral blood. The Glasgow Prognostic Score is calculated with serum albumin and C-reactive protein levels; it appears to be highly appropriate and is widely used because the impact of C-reactive protein is greater than that of albumin alterations alone. The Neutrophil to Lymphocyte Ratio evaluates, as the name suggests, the ratio between the two classes of white blood cells. The COntrol NUTritional Score is calculated using lymphocyte count as well as albumin and total cholesterol levels. Finally, the Geriatric Nutritional Risk Index is a tool based on albumin levels, the patient's current weight and their ideal weight. All these tools demonstrate usefulness in providing a recent picture of nutritional status.²⁰ From their definitions, it is clear how albumin plays a key role in the evaluation of malnutrition. Nevertheless, albumin levels are affected by many variables, from physical activity to previous trauma as well as from acute inflammation and liver disease, which are common in cancer, especially in the perioperative setting. Therefore, the use of transthyretin, otherwise called prealbumin, is increasing in clinical practice.²⁶ It is a small protein with a short half-life of about 3 days, which best describes the protein turnover and nutritional dynamics. Thus, both albumin and prealbumin can provide useful information only when included in a multiparameter assessment and never alone.21-26

The most used functional tests are the handgrip strength, the Gait Speed test and the forced expiratory

volume test. An update of the guidelines of the European Working Group on Sarcopenia in Older People published in 2019 stated that sarcopenia is formally recognized as a real muscle disease and criteria for diagnosis were established.28 In clinical practice, the suspicion of sarcopenia must arise whenever a patient reports typical symptoms or signs of sarcopenia, including falls, a sense of weakness, slow walking, difficulty getting up from a chair, weight loss and muscle atrophy. The handgrip test is a simple and inexpensive test that uses a calibrated palm dynamometer that allows measurement of the maximum isometric force by the forearm muscles and is moderately correlated to overall body strength; if this test cannot be performed due to disability of the hand (e.g. in the case of advanced arthritis or stroke), the strength of the lower limbs is measured.

The Gait Speed test is predictive of negative outcomes related to sarcopenia such as disability, cognitive impairment and risk of falls. Usually, the time it takes the patients to walk 4 m at a normal pace is measured; this test is considered an indicator of severe sarcopenia with a single measurement ≤0.8 m/s.

Sarcopenia also affects the muscles involved in breathing; the forced expiratory volume test, normally used in spirometric tests and described as the maximal expiration rate after a complete inhalation, is reduced in people with sarcopenia. This reduction is often related to the reduction in peripheral muscle strength, measured with the handgrip test.²⁷⁻²⁹

The instrumental examinations applied for nutritional purposes are used to define the body composition and, in particular, lean mass. There are three main investigations: dual-energy X-ray absorptiometry, MRI and CT. Dual-energy X-ray absorptiometry is based on the difference in attenuation of an X-ray beam as it passes through body tissues; the technique therefore allows estimation of the percentage of fat mass and lean mass but has the disadvantages of the high cost of the device, long execution times, exposure to radiation (albeit lower than CT scan) and providing only a rough estimate of muscle mass.³⁰

MRI allows better study of the various compartments of the body by differentiating their composition between muscle tissue and adipose tissue. In this sense, MRI is a very accurate examination for the diagnosis of myosteatosis. Nevertheless, MRI is generally a second-level examination used after initial examination, such as CT scan and also requires costs and specialized training of the operators; therefore, it cannot currently be considered a routine method for the definition of a patient's body composition.³¹ CT is the *de facto* gold standard, both because it can provide a reliable estimate of muscle mass and because it is a routine investigation in oncology. To evaluate muscle mass, the muscle area around the L3 vertebra is quantified and divided by the patient's height squared, providing the Skeletal Muscle Index, a parameter that reflects the total skeletal muscle mass of the whole body, normalized for stature.³²

The most used specialist test in clinical nutrition for defining a patient's body composition is bioimpedance analysis. This test is based on the human body offering different resistance to the passage of an alternating electric current at low intensity in relation to its composition; lean mass conducts a greater electric current than fat mass because it contains a greater quantity of water and electrolytes. The final result therefore provides an estimate of lean and fat mass.³³

Nutritional interventions

In patients with gastric cancer, nutritional support varies depending on the level of malnutrition and the integrity of the digestive system. There are three different types of nutritional intervention, which can also be combined: oral nutrition (ON), enteral nutrition (EN) and parenteral nutrition (PN).

ON includes free diet, dietary indications provided by nutritional counselling and any ON supplements. This is the natural way of food intake and should be used as first line, where possible. EN is the administration of nutrients through a tube (nasogastric, naso-jejunal, percutaneous gastrostomy or jejunostomy tubes) into the gastrointestinal tract; it is generally used in patients with poor appetite, dysphagia, gastroparesis or with a stenosis of the proximal digestive system but who have a functioning small intestine for absorption purposes. PN consists of the intravenous administration of nutrients, via central or peripheral access, and is used when the dysfunction of the digestive system, usually due to occlusive problems, is such as to compromise the intestinal absorption of nutrients.³⁴ Both artificial nutritional interventions, and especially PN, are burdened by the risk of infections.

Considering that most patients receiving artificial nutrition are bedridden, the most frequent infections are those related to muscle weakness and prolonged immobilization, such as lung infections and phlebitis. Severe infections, such as sepsis, which are often caused by an infection of the access devices (venous catheters or tubes), are generally comparable between the two types of artificial nutrition, with a moderately higher rate for PN (15%) than for EN (13%).³⁵ Therefore, their use must always take place within the general asepsis recommendations, both by the medicalnursing staff and by the patient and their caregiver, who must be properly educated on the management of these devices.³⁶

In the management of artificial nutrition, mechanical complications, such as obstruction or removal of devices, are also an issue as are other problems like diarrhoea, hyperglycaemia or refeeding syndrome. Particular attention should be given to refeeding syndrome, which occurs with important biochemical alterations, such as hypophosphataemia, hypokalaemia, hypomagnesaemia and thiamine deficiency that, if not adequately corrected, can be potentially fatal.^{37,38}

Nutritional support before gastric surgery

In about 40% of cases, gastric cancer occurs in a limited or locally advanced form, which is potentially resectable. The early stages are candidates for endoscopic resection whilst those later in the TNM classification, up to stage III, are candidates for gastrectomy associated with D2-lymphadenectomy.³⁹

In the latter setting, national and international guidelines suggest perioperative chemotherapy, preoperatively and postoperatively. Since 2019, the standard of care has been represented by the FLOT regimen (fluorouracil, leucovorin, oxaliplatin and docetaxel), administered for four cycles before surgery and four cycles after surgery.⁴⁰

We must not forget that gastroresection is the therapeutic cornerstone in these oncological stages. Nevertheless, surgical stress induces a metabolic response characterized by systemic inflammation and protein catabolism that can further aggravate the patient's condition, who often presents with malnutrition before surgery. Therefore, it is essential to prepare the patient's body for surgery with different objectives and methods of nutritional support depending on the preoperative and postoperative periods.⁴¹

The main purposes of preoperative nutritional support are to avoid weight loss, correct any nutritional deficiencies, preserve the intestinal microbiome and improve the patient's functional status.⁴² If the patient does not have significant deficits, the recommended nutritional support in this phase is ON whilst, in malnourished patients, based on the individual case's severity, artificial nutrition may be added (preferably EN).⁴³

The turning point in preoperative nutritional recommendations is certainly the advent of immunonutrition (IN).^{44,45} This new approach consists of the oral or artificial

administration of nutrients capable of modulating the immune system in favour of anabolic processes, protein synthesis, and cell regeneration and against excessive inflammation. Although several substances have been tested, the main evidence is for the association of L-arginine, nucleotides and omega-3 fatty acids. L-Arginine is an important amino acid capable of improving the nitrogen balance, activating collagen synthesis and stimulating the activity of immune system cells. Nucleotides are the monomers needed for DNA and RNA synthesis, crucial in any cell division process. They are essential both for the proliferation of immune cells and for the repair of tissues subjected to surgery. They also reduce the production of IL-2, which is a potent proinflammatory cytokine. Finally, omega-3 fatty acids are essential constituents of cell membranes and reduce the proinflammatory response.⁴⁶ Some studies have shown that IN reduces postoperative complications and length of hospital stay but higher-level experimental trials are needed to define its usefulness in oncology, with reference to both nutritional and survival patient outcomes. A particularly controversial point is the duration of this specific nutritional support; the studies available so far suggest 5-7 days before surgery but scientific and large-scale confirmation is not yet available.47 Despite the mixed results, the ASPEN and ESPEN guidelines support the use of IN in the preoperative period in patients who are candidates for gastric surgery.48,49

An interesting topic on nutritional support in this setting is the role of carbohydrate loading before surgery. This method is recommended by the ERAS programme with the aim of reducing insulin resistance and tissue glycosylation but its role remains to be clarified.50 The principle behind carbohydrate loading is to counteract the impact of surgery-induced insulin resistance. Any surgical stress causes a systemic metabolic condition of insulin resistance that leads to a series of complications: generalized state of inflammation, delay in the healing of surgical wounds, and an increase in morbidity and mortality of patients. Several studies demonstrated that preoperative carbohydrate loading produces an insulin release capable of opposing insulin resistance induced by surgery, thus promoting the bioutilization of glucose by tissues and the normalization of body metabolism during surgery and immediately postoperatively.⁵¹

Nutritional support after gastric surgery

After any surgery, the patient undergoes metabolic stress characterized by an increase in catabolic processes and systemic inflammation. This condition produces weight loss, in particular of lean mass, which can be harmful especially in patients who do not have adequate reserves before surgery, causing slow wound healing, a reduction in immune responses, an alteration of barrier function of the gastrointestinal mucosa and a reduction in the overall functional status.⁵²

Gastrectomy, in particular, induces, through the alteration of mucosal permeability, a state of dysbiosis that leads to a new composition of the microbiome; specifically, there is an increase in typical bacteria of the upper digestive tract, the facultative aerobes and those capable of metabolizing substances such as bile. However, this dysbiotic condition can cause various intestinal problems such as chronic intestinal inflammation, small intestinal bacterial overgrowth and an increased risk of colorectal cancer.⁵³

Nutritional support in this phase must be aimed at the physical recovery of the patient and adaptation to the newly altered anatomy. The surgical technique varies depending on the location of the gastric cancer: for tumours located in the extremities of the stomach (the cardias and antrum), the operative choice is partial or subtotal gastrectomy, in which only the part of the organ that contains the tumour is removed, whilst tumours located in the centre of the stomach or those that give an extensive involvement of the gastric walls are treated with total gastrectomy, in which the entire stomach is removed. In both cases, the surgeon completes the surgery by restoring the continuity of the digestive tract. The new anatomy following gastroresection can lead to various problems, of greater intensity in patients who have undergone a total gastrectomy because, in these patients, the stomach is completely missing.54

Whenever possible, the ideal nutritional support remains ON but, in most cases, it is necessary to add artificial nutritional support, possibly enteral with percutaneous jejunostomy, to ensure caloric and nutrient intake adequate to the patient's needs. Of note, during this period, the small intestine undergoes a transient and paraphysiological dysfunction, which impairs nutrient absorption. The available evidence recommends starting EN 6 hours after surgery, which is the interval needed to allow the small intestine to resume its function. ON remains essential in this setting because it stimulates the natural function of the digestive system. It is possible to resume oral fluid intake early in the first postoperative day regardless of the type of surgery; in the following days, it is recommended to follow dietary regimens introducing foods with increasing density up to normal solid foods.55

Several studies suggest that early oral feeding is associated with a reduction in postoperative complications and in average hospitalization times; other studies, on the other hand, confirm the reduction in hospital length of stay but not the impact on postoperative complications.⁵⁶

Nutrition counselling does not have to end in the hospital setting. The patient should have periodic nutritional checks even after hospital discharge for long-term nutritional support. Gastroresection surgery leads to a new anatomical condition that can be complicated by various diseases, such as gastric stasis, small intestinal bacterial overgrowth, dumping syndrome and nutritional deficiencies. Therefore, it is essential to continue nutritional checks by providing dietary recommendations for patients undergoing gastroresected in the clinical nutrition service of the cancer centre where they are being treated. National and international guidelines prescribe eating small and frequent meals, slow chewing, avoiding processed foods, such as hyperosmolar drinks, and correcting nutritional deficiencies with particular reference to vitamin B12, iron, calcium and vitamin D.^{57,58}

In patients who have not obtained a satisfactory nutritional status during hospitalization, it is highly recommended to continue artificial nutritional support even at home trying to wean them as soon as possible from artificial devices.⁵⁹

Nutritional support and chemotherapy

The relationship among malnutrition, tolerance to chemotherapy and patient outcomes is well known and evidence based. Klute et al. demonstrated, in patients with gastrointestinal malignancies, that the malnutrition state was significantly correlated to the need for dose reduction of chemotherapy drugs.⁶⁰ One of the hypotheses studied is that sarcopenia reduces tolerance to chemotherapy treatments due to an altered distribution of drugs in the body compartments; the dosage of cytotoxic drugs is commonly determined with the body surface area (BSA), though patients with the same BSA can have extremely different body compositions, which impacts the relative dose received due to differential distribution of drugs in various body tissues. Furthermore, drug metabolism is usually renal or hepatic and the calculation of the BSA is not an indicator of their functionality.61

Unfortunately, we do not have rigorous studies on the association of nutritional support and chemotherapy treatments; the information we have is derived from exploratory studies.⁶²

As we have already said, the reference chemotherapy regimen in the resectable stages of gastric cancer is the FLOT regimen; within this scheme, the most important drug is fluorouracil. It has been shown that fluorouracil increases the risk of muscle mass loss and that patients with excessive toxicity were often exposed to excessive doses when body weight was corrected for lean mass.⁶³ This fact unequivocally suggests that the chemotherapy dosage should be calculated, not only on body weight but also with consideration for body composition. Nevertheless, there is no study that introduced a more accurate method for calculating the dosage of cancer drugs.

Some researchers raised the hypothesis that BSA calculated using the current method in patients with obesity may expose the same patients to greater drug toxicity. It is reasonable to think that adipose tissue, for pharmacokinetic reasons, can trap intermediate metabolites with lipophilic properties, altering the processes of drug distribution and elimination. Therefore, some oncologists propose calculation of the dosage of chemotherapy drugs in patients with obesity following empirical rules that are based on a BSA cut-off established as the maximum value or on the use of ideal weight and not real weight.⁶⁴

Despite the soundness of the clinical reasoning, none of these intuitions found confirmation in evidence-based medicine. In the future, it would be desirable to improve the method of calculating oncological drug dosages in order to provide patients treatment that is as personalized as possible in terms of weight, body composition and hepatorenal function. Looking forward to this progress, clinical judgment remains crucial; each patient must be evaluated as a whole, considering not only BSA but also performance status, nutritional status and biochemical assessments.⁶⁵

Chemotherapy of resectable gastric cancer, namely fluorouracil-based regimens both in the neoadjuvant and adjuvant settings, can therefore worsen the patient's nutritional status. Thus, it is essential to match chemotherapy plans with nutritional counselling so that the patient can start any chemotherapy with an optimal nutritional status and avoid weight and muscle mass loss during oncological treatment.⁶⁶

Regarding malnutrition during the FLOT regimen, a study published in 2021 showed that the nutritional status of patients worsened during the treatment course albeit without interfering with the overall chemotherapy toxicity and on the short-term outcome of completion of all phases of this perioperative treatment (neoadjuvant phase, surgical intervention and adjuvant phase).⁶⁷

Discussion

Studying the relationship between nutrition and gastric cancer is a major challenge. Nevertheless, it is extremely complex because nutritional status is multifactorial, often difficult to interpret and translate into scientific evidence. Despite the evidence provided herein, a methodological limitation must be acknowledged, namely that the data were retrieved from simple studies, usually monocentric and exploratory, based on the scientific evidence hierarchy. There remains a lack of large-scale, reproducible, controlled and randomized clinical trials mainly due to the complexity of conducting clinical studies in the nutrition field.⁶⁸

Another important limitation concerns the lack of discussion of the relationship between malnutrition and gastric cancer histotypes; there are preliminary studies, for example, that suggest higher rates of malnutrition in patients with poorly differentiated and signet ring cell gastric cancer.⁶⁹ However, data are scarce in the medical literature despite its practical implications; an unfavourable histology with a high risk of malnutrition could be indicated for closer nutritional counselling.⁷⁰

A separate topic is that of clinicians neglecting nutritional support. This is due to the lack of specific nutritional guidelines, the lack of time and the lack of interest for the subject. For example, in a national exploratory survey addressed to Italian oncologists on the link between malnutrition and cancer, only 5.7% of the 2375 members of the Italian Association for Medical Oncology participated in the initiative. These data unfortunately lead us to consider the partial awareness of the problem amongst many oncologists: "malnutrition exists but it is not within my competence", "the prognosis is affected primarily by the treatment" or "we will think about malnutrition later on".⁷¹

Despite these limitations, the work we produced leads us to conclude the following statements. Nutritional coun-

selling is essential right from diagnosis. In fact, nutritional support allows the patient to be prepared for any oncological treatment, both medical and surgical.

In limited or locally advanced forms (about 40% of cases), the therapeutic cornerstone is represented by gastric surgery. In most of these cases, perioperative chemotherapy is also indicated. In this regard, it should be noted that nutritional support varies before and after surgery. In the preoperative period, the goal is to prepare the body for surgery, and the evidence available so far recommends prescribing immunonutrition (both oral and artificial, as appropriate). In the postoperative period, on the other hand, the objective is to facilitate recovery and adaptation to the new anatomy; an early and combined strategy (oral and enteral) seems to be the most suitable to pursue this. Long-term nutritional support includes continuing nutritional follow-up and applying the general recommendations provided by national and international guidelines on diet for patients undergoing gastroresection.

Conclusion

Fluorouracil-based chemotherapy, which is the medical standard of care for the treatment of gastric cancer, can worsen a patient's nutritional status; therefore, it is essential to combine chemotherapy programmes with nutritional counselling. In the event of deterioration of the patient's nutritional and functional status, a combined strategy of reducing pharmacological dosages and a more aggressive nutritional intervention could be the appropriate strategy to promote the achievement of the main objectives of cancer care: treatment continuity, quality of life and long-term survival.

References

- 1. International Agency for Research on Cancer (IARC). Global Cancer Observatory. https://gco.iarc.fr/. Accessed March 1, 2022.
- Baracos VE. Cancer-associated malnutrition. Eur J Clin Nutr. 2018;72(9):1255–1259. https://doi.org/10.1038/s41430-018-0245-4
- American Society of Clinical Oncology. Stomach cancer: statistics. https://www.cancer.net/cancer-types/stomach-cancer/statistics. Accessed March 1, 2022.
- 4. DeWys WD. Nutritional care of the cancer patient. *JAMA*. 1980;244(4):374–376. https://doi.org/10.1001/jama.1980.03310040056033
- 5. Bozzetti F. Nutritional support in patients with oesophageal cancer. Support Care Cancer. 2010;18(Suppl. 2):S41–S50. https://doi.org/10.1007/s00520-009-0664-9
- Aapro M, Arends J, Bozzetti F, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol. 2014;25(8):1492–1499. https://doi.org/10.1093/annonc/mdu085
- World Health Organization (WHO). Malnutrition definition. https://www.who.int/health-topics/malnutrition#tab=tab_1. Accessed March 1, 2022.

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Correspondence: Francesco Serra, Medical Oncology Unit, IRCCS Policlinico San Matteo, Department of Internal Medicine and Medical Therapy, University of Pavia, 19 Viale Camillo Golgi, Pavia, Italy. Email: francesco.serra03@ universitadipavia.it

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- 8. Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. *Clin Nutr.* 2019;38(1):1–9. https://doi.org/10.1016/j.clnu.2018.08.002
- 9. Li H, Li Y, Liu Y, et al. The incidence and impact of weight loss with cachexia in gastric cancer patients. *J Clin Oncol.* 2015;33:15. https://doi.org/10.1200/jco.2015.33.15_suppl.e20644
- Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–495. https://doi.org/10.1016/S1470-2045(10)70218-7
- 11. Ongaro E, Buoro V, Cinausero M, et al. Sarcopenia in gastric cancer: when the loss costs too much. *Gastric Cancer*. 2017;20(4):563–572. https://doi.org/10.1007/s10120-017-0722-9
- Martone AM, Marzetti E, Salini S, et al. Sarcopenia identified according to the EWGSOP2 definition in communityliving people: prevalence and clinical features. J Am Med Dir Assoc. 2020;21(10):1470–1474. https://doi.org/10.1016/j.jamda.2020.03.007

- 13. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2020;145:102839. https://doi.org/10.1016/j.critrevonc.2019.102839
- Zhuang C-L, Shen X, Huang Y-Y, et al. Myosteatosis predicts prognosis after radical gastrectomy for gastric cancer: a propensity score-matched analysis from a large-scale cohort. Surgery. 2019;166(3):297–304. https://doi.org/10.1016/j.surg.2019.03.020
- Murnane LC, Forsyth AK, Koukounaras J, et al. Myosteatosis predicts higher complications and reduced overall survival following radical oesophageal and gastric cancer surgery. *Eur J Surg Oncol.* 2021;47(9):2295–2303. https://doi.org/10.1016/j.ejso.2021.02.008
- 16. Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. *Nutr Today*. 2015;50(3):117–128. https://doi.org/10.1097/NT.0000000000092
- 17. Kim YM, Kim JH, Baik SJ, Chun J, Youn YH, Park H. Sarcopenia and sarcopenic obesity as novel risk factors for gastric carcinogenesis: a health checkup cohort study. *Front Oncol.* 2019;9:1249. https://doi.org/10.3389/fonc.2019.01249
- 18. Academy of Nutrition and Dietetics. Nutrition screening adults. https://www.andeal.org/. Accessed April 1, 2022.
- 19. Arends J, Strasser F, Gonella S, et al. Cancer cachexia in adult patients: ESMO clinical practice guidelines. *ESMO Open*. 2021;6(3):100092. https://doi.org/10.1016/j.esmoop.2021.100092
- 20. Keller U. Nutritional laboratory markers in malnutrition. J Clin Med. 2019;8(6):775. https://doi.org/10.3390/jcm8060775
- 21. Migita K, Takayama T, Saeki K, et al. The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. *Ann Surg Oncol.* 2013;20(8):2647–2654. https://doi.org/10.1245/s10434-013-2926-5
- 22. Hirahara N, Matsubara T, Kaji S, et al. Glasgow prognostic score is a better predictor of the long-term survival in patients with gastric cancer, compared to the modified Glasgow prognostic score or high-sensitivity modified Glasgow prognostic score. *Oncotarget*. 2020;11(45):4169–4177. https://doi.org/10.18632/oncotarget.27796
- Miyamoto R, Inagawa S, Sano N, Tadano S, Adachi S, Yamamoto M. The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients. *Eur J Surg Oncol.* 2018;44(5):607–612. https://doi.org/10.1016/j.ejso.2018.02.003
- 24. Kuroda D, Sawayama H, Kurashige J, et al. Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. *Gastric Cancer*. 2018;21(2):204–212. https://doi.org/10.1007/s10120-017-0744-3
- 25. Hirahara N, Matsubara T, Fujii Y, et al. Preoperative geriatric nutritional risk index is a useful prognostic indicator in elderly patients with gastric cancer. *Oncotarget*. 2020;11(24):2345–2356. https://doi.org/10.18632/oncotarget.27635
- 26. Shimura T, Shibata M, Gonda K, et al. Serum transthyretin level is associated with prognosis of patients with gastric cancer. *J Surg Res.* 2018;227:145–150. https://doi.org/10.1016/j.jss.2018.02.035
- 27. Russell MK. Functional assessment of nutrition status. *Nutr Clin Pract*. 2015;30(2):211–218. https://doi.org/10.1177/0884533615570094
- 28. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16–31. https://doi.org/10.1093/ageing/afy169
- 29. Nagano A, Wakabayashi H, Maeda K, et al. Respiratory sarcopenia and sarcopenic respiratory disability: concepts, diagnosis, and treatment. *J Nutr Health Aging*. 2021;25(4):507–515. https://doi.org/10.1007/s12603-021-1587-5
- 30. Andreoli A, Scalzo G, Masala S, Tarantino U, Guglielmi G. Body composition assessment by dual-energy X-ray absorptiometry (DXA). *Radiol Med*. 2009;114(2):286–300. English, Italian. https://doi.org/10.1007/s11547-009-0369-7
- Huber FA, Del Grande F, Rizzo S, Guglielmi G, Guggenberger R. MRI in the assessment of adipose tissues and muscle composition: how to use it. *Quant Imaging Med Surg.* 2020;10(8):1636–1649. https://doi.org/10.21037/qims.2020.02.06
- Tolonen A, Pakarinen T, Sassi A, et al. Methodology, clinical applications, and future directions of body composition analysis using computed tomography (CT) images: a review. *Eur J Radiol*. 2021;145:109943. https://doi.org/10.1016/j.ejrad.2021.109943
- 33. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Battaglini CL, Williams GR. Bioelectrical impedance analysis for the assessment of sarcopenia in patients with cancer: a systematic review. *Oncologist*. 2020;25(2):170–182. https://doi.org/10.1634/theoncologist.2019-0600
- 34. Serra F, Lobascio F, Pagani A, et al. Gastric cancer and nutritional support: a binomial which should become dogmatic. *Supportive Palliative Cancer Care*. 2020;5:1–9.
- 35. Wu GH, Liu ZH, Wu ZH, Wu ZG. Perioperative artificial nutrition in malnourished gastrointestinal cancer patients. *World J Gastroenterol.* 2006;12(15):2441–2444. https://doi.org/10.3748/wjg.v12.i15.2441
- 36. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr.* 2001;74(4):534–542. https://doi.org/10.1093/ajcn/74.4.534

- 37. Blumenstein I, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. *World J Gastroenterol.* 2014;20(26):8505–8524. https://doi.org/10.3748/wjg.v20.i26.8505
- 38. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ*. 2008;336(7659):1495–1498. https://doi.org/10.1136/bmj.a301
- 39. Smyth EC, Verheij M, Allum W, et al. ESMO gastric cancer: clinical practice guidelines for diagnosis, treatment and follow-up. ESMO Guidelines Committee. *Ann Oncol.* 2016;27(Suppl. 5):v38–v49. https://doi.org/10.1093/annonc/mdw350
- 40. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1
- 41. Rosania R, Chiapponi C, Malfertheiner P, Venerito M. Nutrition in patients with gastric cancer: an update. *Gastrointest Tumors*. 2016;2(4):178–187. https://doi.org/10.1159/000445188
- 42. Ding D, Feng Y, Song B, Gao S, Zhao J. Effects of preoperative and postoperative enteral nutrition on postoperative nutritional status and immune function of gastric cancer patients. *Turk J Gastroenterol.* 2015;26:181185. https://doi.org/10.5152/tjg.2015.3993
- 43. Choi WJ, Kim J. Nutritional care of gastric cancer patients with clinical outcomes and complications: a review. *Clin Nutr Res.* 2016;5(2):65–78. https://doi.org/10.7762/cnr.2016.5.2.65
- 44. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA*. 2001;286:944–953. https://doi.org/10.1001/jama.286.8.944
- 45. Cerantola Y, Hübner M, Grass F, Demartines N, Schäfer M. Immunonutrition in gastrointestinal surgery. *Br J Surg.* 2011;98:37–48. https://doi.org/10.1002/bjs.7273
- 46. Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. *Gastroenterology*. 2002;122(7):1763–1770. https://doi.org/10.1053/gast.2002.33587
- 47. Kubota T, Shoda K, Konishi H, Okamoto K, Otsuji E. Nutrition update in gastric cancer surgery. *Ann Gastroenterol Surg.* 2020;4(4):360–368. https://doi.org/10.1002/ags3.12351
- 48. August DA, Huhmann MB; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr. 2009;33:472–500. https://doi.org/10.1177/0148607109341804
- 49. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr.* 2017;36(1):11–48. https://doi.org/10.1016/j.clnu.2016.07.015
- 50. Mariette C. Role of the nutritional support in the ERAS programme. *J Visc Surg.* 2015;152(Suppl. 1):S18–S20. https://doi.org/10.1016/S1878-7886(15)30006-0
- 51. Makuuchi R, Sugisawa N, Kaji S, et al. Enhanced recovery after surgery for gastric cancer and an assessment of preoperative carbohydrate loading. *Eur J Surg Oncol.* 2017;43(1):210–217. https://doi.org/10.1016/j.ejso.2016.07.140
- 52. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013;37(Suppl. 5):21S–29S. https://doi.org/10.1177/0148607113496117
- 53. Maksimaityte V, Bausys A, Kryzauskas M, et al. Gastrectomy impact on the gut microbiome in patients with gastric cancer: a comprehensive review. *World J Gastrointest Surg.* 2021;13(7):678–688. https://doi.org/10.4240/wjgs.v13.i7.678
- 54. Weledji EP. The principles of the surgical management of gastric cancer. *Int J Surg Oncol.* 2017;2(7):e11. https://doi.org/10.1097/IJ9.000000000000011
- 55. Desiderio J, Trastulli S, D'Andrea V, Parisi A. Enhanced recovery after surgery for gastric cancer (ERAS-GC). Optimizing patient outcome. *Transl Gastroenterol Hepatol.* 2020;5:1–7. https://doi.org/10.21037/tgh.2019.10.04
- 56. Liu X, Wang D, Zheng L, Mou T, Liu H, Li G. Is early oral feeding after gastric cancer surgery feasible? A systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014;9(11):e112062. https://doi.org/10.1371/journal.pone.0112062
- 57. Caccialanza R, Pedrazzoli P, Cereda E, et al. Nutritional support in cancer patients: a position paper from the Italian Society of Medical Oncology (AIOM) and the Italian Society of Artificial Nutrition and Metabolism (SINPE). *J Cancer*. 2016;7(2):131–135. https://doi.org/10.7150/jca.13818
- 58. Weimann A, Braga M, Carli F, et al. ESPEN guideline: clinical nutrition in surgery. *Clin Nutr.* 2017;36(3):623–650. https://doi.org/10.1016/j.clnu.2017.02.013
- 59. MSKCC. General diet guidelines after gastrectomy. https://www.mskcc.org/cancer-care/patient-education/eating-after-your-gastrectomy#section-1. Accessed April 1, 2022.

- 60. Klute KA, Brouwer J, Jhawer M, et al. Chemotherapy dose intensity predicted by baseline nutrition assessment in gastrointestinal malignancies: a multicentre analysis. *Eur J Cancer*. 2016;63:189–200. https://doi.org/10.1016/j.ejca.2016.05.011
- 61. Antoun S, Borget I, Lanoy E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. *Curr Opin Support Palliat Care*. 2013;7(4):383–389. https://doi.org/10.1097/SPC.000000000000011
- 62. Mulazzani GEG, Corti F, Della Valle S, Di Bartolomeo M. Nutritional support indications in gastroesophageal cancer patients: from perioperative to palliative systemic therapy. A comprehensive review of the last decade. *Nutrients*. 2021;13(8):2766. https://doi.org/10.3390/nu13082766
- 63. Williams GR, Deal AM, Shachar SS, et al. The impact of skeletal muscle on the pharmacokinetics and toxicity of 5-fluorouracil in colorectal cancer. *Cancer Chemother Pharmacol.* 2018;81(2):413–417. https://doi.org/10.1007/s00280-017-3487-2
- 64. Silvestris N, Argentiero A, Natalicchio A, et al. Antineoplastic dosing in overweight and obese cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper. ESMO Open. 2021;6(3):100153. https://doi.org/10.1016/j.esmoop.2021.100153
- 65. Griggs JJ, Bohlke K, Balaban EP, et al. Appropriate systemic therapy dosing for obese adult patients with cancer: ASCO guideline update. *J Clin Oncol.* 2021;39(18):2037–2048. https://doi.org/10.1200/JCO.21.00471
- 66. Kaegi-Braun N, Schuetz P, Mueller B, Kutz A. Association of nutritional support with clinical outcomes in malnourished cancer patients: a population-based matched cohort study. *Front Nutr.* 2021;7:603370. https://doi.org/10.3389/fnut.2020.603370
- 67. Rinninella E, Strippoli A, Cintoni M, et al. Body composition changes in gastric cancer patients during preoperative FLOT therapy: preliminary results of an Italian cohort study. *Nutrients*. 2021;13:960. https://doi.org/10.3390/nu13030960
- 68. Cotogni P, Pedrazzoli P, De Waele E, et al. Nutritional therapy in cancer patients receiving chemoradiotherapy: should we need stronger recommendations to act for improving outcomes? *J Cancer*. 2019;10(18):4318–4325. https://doi.org/10.7150/jca.31611
- 69. Messager M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. *Ann Surg.* 2011;254(5):684–693; discussion 693. https://doi.org/10.1097/SLA.0b013e3182352647
- 70. Voron T, Messager M, Duhamel A, et al. Is signet-ring cell carcinoma a specific entity among gastric cancers? *Gastric Cancer*. 2016;19(4):1027–1040. https://doi.org/10.1007/s10120-015-0564-2
- 71. Caccialanza R, Cereda E, Pinto C, et al. Awareness and consideration of malnutrition among oncologists: insights from an exploratory survey. *Nutrition*. 2016;32(9):1028–1032. https://doi.org/10.1016/j.nut.2016.02.005