



# Nutritional interventions in elderly gastrointestinal cancer patients: the evidence from randomized controlled trials

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## Abstract

Literature concerning nutritional interventions in elderly patients with gastrointestinal cancer, with special reference to randomized clinical trials, has been critically reviewed. This segment of oncologic population was found to be penalized by a high prevalence of malnutrition and sarcopenia which translated in an increased rate of toxicity from chemotherapy, poor compliance with oncologic treatments, and, finally, with a poor prognosis. Attempts to reverse this condition included a potentiation of nutrients intake which should sequentially proceed through the use of dietary counseling and administration of standard or  $\omega$ -3 fatty acid-enriched oral supplements to finally come to enteral or parenteral nutrition. Randomized clinical trials investigating the effects of simple dietary advice and use of standard oral supplements were disappointing as regards long-term compliance and results. Nutritional and clinical benefits were reported with the use of  $\omega$ -3 fatty acid-enriched oral supplements and especially with long-term supplemental parenteral nutrition. Despite the general recommendation of the scientific community that emphasizes the use of the enteral route, whenever possible, for delivering the nutritional support, it appears from the literature that more consistent benefits can be achieved, especially in the long-term nutritional support, when an insufficient oral nutrition is partnered with intravenous nutrition.

**Keywords** Gastrointestinal cancer · Elderly cancer patients · Malnutrition of cancer patients · Sarcopenia in cancer patients · Supplemental parenteral nutrition · Nutritional interventions in elderly cancer patients

## Introduction

Although malignancies occur at all ages, cancer disproportionately strikes individuals in the age group 65 years and older. Data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program report that 56% of all newly diagnosed cancer patients and 71% of cancer deaths are confined to this age group. Median ages of cancer patients at death for the major tumors common to both sex and all races (colorectal, pancreas, stomach, and other) range from 71 to 77 years [1]. Furthermore, the incidence rate for patients older than 65 years is increasing consistently, and demographic projections would indicate that in the USA the number of persons 65-year old and older will double from the current estimate of 35 million to a projected 70 million persons by 2030 [2]. Since

aging is characterized by a decrease in genome integrity and an increased risk of cancer, which coincide with clonal dominance of expanded mutant stem and progenitor cell populations in aging tissues, such as the intestinal epithelium, we could expect an increased incidence of gastrointestinal (GI) cancer in the next future. An estimate of 2013 reported that GI cancer incidence accounts for almost 30% of global tumor incidence, and 32% of cancer deaths worldwide are due to GI malignancies [3].

It is well known that the aging process per se is associated with malnutrition, sarcopenia, loss of functional reserve of multiple organ systems, and increased vulnerability to frailty [4]. According to a recent French observational multicenter cross-sectional study of malnutrition in elderly patients with cancer, weight loss and malnutrition were significantly more reported in the elderly than in younger patients reaching a value of 73.6% and 44.9% respectively [5].

Hence, in the elderly GI cancer population, the oncologists face a dangerous variety of factors including old age, presence of cancer, and alteration of an apparatus involved in the intake, digestion, and absorption of nutrients, which, alone or

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combined together, are capable to adversely affect the outcome of the patient.

The aim of this critical literature review is to update the oncologists on the impact of malnutrition on the prognosis of elderly GI cancer patients and to update them about the potential benefits of the nutritional support on compliance with oncologic therapy and on the final outcome.

For the purpose of this narrative review, only series including (exclusively or for the major part) 65-year old or older patients affected (exclusively or for the major part) by GI tumors were considered. The search was limited to the English language and publications from 2000 onwards mainly using first MEDLINE and then EMBASE and CINAHL. The following broad search terms were used to identify relevant papers: elderly cancer patients, nutritional intervention, dietary counseling, oral nutritional supplements, and parenteral and enteral nutrition. A manual search of references of key articles was also carried out. The results of comparative studies on the use and effects of nutritional interventions were considered only if based on randomized clinical trials.

## Prevalence of malnutrition

Prevalence of malnutrition assessed through different methods, ranging from the simple weight loss to more composite tools as the Nutritional Risk Index [6] or the Mini Nutritional Assessment [7] are reported in Table 1. Depending on the cutoff value, the authors chose to define malnutrition, the prevalence changes. If we accept a  $\geq 10\%$  weight loss as a time-honored value which was deemed clinically significant in oncologic patients [15, 16] and was recently included in the criteria to define malnutrition endorsed by ESPEN [17], the prevalence of malnutrition was 20–32%, a value rather close to the percentage of patients with a low

MNA score or a severe NRI. With lower thresholds, the prevalence can double.

Interestingly, patients undergoing palliative chemotherapy had a higher prevalence of malnutrition as compared with patients on curative chemotherapy [13], an expected finding since this group of patients were in a more advanced stage of disease.

## Impact of sarcopenia on tolerance to chemotherapy

Whereas, there are several publications reporting an excess of toxicity in an unselected population of malnourished adult patients on oncologic treatments [18–26], these data are lacking when referring to elderly cancer patients.

On the contrary, there are a few papers investigating the correlation between muscle mass depletion and poor compliance and toxicity from chemotherapy. Sarcopenia is defined as muscle mass two standard deviations below the mean muscle mass of healthy younger adults. The most common way to estimate the muscle mass in the clinical practice is through a CT-defined cross-sectional image analysis, using the third lumbar vertebra (L3) as a standard bony landmark. At this vertebral level, the cross-sectional areas are linearly related to whole-body muscle mass ( $r^2 = 0.86$ ). Two different L3 skeletal muscle index cut points for sarcopenia have been published; the first provides only sex-specific L3 skeletal muscle index cut points [27]. The updated L3 skeletal muscle index cut points classify sarcopenia based on both sex and body mass index (BMI) [28]. Table 2 reports the relative increase of toxicity from chemotherapy when sarcopenic patients are compared with non-sarcopenic ones. Some authors [8, 29, 30] used the sex-specific cutoffs for defining sarcopenia as  $55.4 \text{ cm}^2/\text{m}^2$  for males and  $38.9 \text{ cm}^2/\text{m}^2$  for

**Table 1** Prevalence of malnutrition

Author (year)	N patients/primary	Assessment parameter	Prevalence
Barret et al. (2011) [8]	114/colon-rectum	> 10% weight loss	32.5%
		NRI moderate (83.5–95.7)	45.6%
		NRI severe (< 83.5)	19.3%
Sanchez-Lara et al. (2013) [9]	53/GI	$\geq 10\%$ weight loss	20%
Barret et al. (2014) [10]	51/GI	$\geq 10\%$ weight loss	33%
Vagnilhaugh et al. (2017) [11]	21/GI inpatients 64/GI outpatients	International consensus classification	61%
			42%
Fonck et al. (2011) [12]	40/stomach	MNA 0–16.9	20%
		MNA 17–23.5	55%
Aaldriks et al. (2013) [13]	143/colon-rectum	MNA > 23.5	20%, curative chemotherapy patients 33%, palliative chemotherapy patients
Paillaud et al. (2014) [14]	519/GI	MNA 0–16.9	29%
		MNA 17–23.5	46%

*NRI* (nutritional risk index):  $1.519 \times \text{sALB} + 0.417 \times \text{current BW/basic BW} \times 100$ ; *MNA*, mini nutritional assessment

**Table 2** Impact of sarcopenia on chemotherapy toxicity

Author (year)	N patients/primary	Therapy	Outcome
Barret et al. (2014) [8]	51/colon-rectum	Fluoropyrimidine, irinotecan, oxaliplatin	13.5↑ grade III-IV toxicity
Tan et al. (2015) [29]	89/esophagus, stomach	Epirubicin, cisplatin, capecitabine, oxaliplatin	2.9↑ dose-limiting toxicity
Anandavadivelan et al. (2016) [30]	72/esophagus, stomach	Cisplatin, 5-FU	5.5 ↑ dose-limiting toxicity in obese sarcopenic patients
Palmela et al. (2017) [31]	48/esophagus, stomach	Epirubicin, cisplatin, capecitabine, oxaliplatin	4.2↑ early termination

↑ means increase

women, and others [31] defined sarcopenia as skeletal muscle index lower than 41 cm<sup>2</sup>/m<sup>2</sup> in women or lower than 43 cm<sup>2</sup>/m<sup>2</sup> in men with BMI < 25 kg/m<sup>2</sup> and < 53 cm<sup>2</sup>/m<sup>2</sup> in men with BMI > 25 kg/m<sup>2</sup>, respectively.

### Impact of malnutrition or sarcopenia on survival

Both malnutrition (evaluated according to the Mini Nutritional Assessment or the bioimpedance analysis) and sarcopenia are associated with poor survival (Tables 3 and 4). It is noteworthy that this effect which concerns the overall and the disease-free survival as well as the incidence of local recurrences was reported in a variety of GI tumors in patients undergoing different oncologic treatments (chemotherapy, surgery, radiofrequency ablation).

### Therapeutic approach to malnutrition

The therapeutic approach to malnutrition follows the general rules of a good clinical practice which have been recently defined by the guidelines on nutrition in cancer patients on behalf of the European Society for Clinical Nutrition and Metabolism [39]. These guidelines state that the nutritional approach:

- (1) should follow a sequence from the less invasive route of feeding (dietary counseling and oral supplementation) to the more demanding procedures as the home parenteral nutrition (HPN) and

- (2) should privilege the oral/enteral route (whenever possible) versus the intravenous route because is considered a safer and cheaper way of nutritional support.

### Dietary counseling

There are two systematic reviews and meta-analysis on dietary counseling with or without oral nutritional supplements in the management of malnourished patients: the first one [40], involving a total of 2123 patients (from 24 RCTs), failed to reveal any differences in mortality, weight change, and energy intake between fed and comparator groups, even when clinical background and age were taken into account. The second paper [41] included 1414 malnourished cancer patients from 13 RCTs and reached similar conclusions: oral nutritional intervention were effective at increasing nutritional intake and improving some aspects of quality of life but all differences disappeared when removing all sources of heterogeneity.

If we focus on elderly GI cancer patients, we can identify three RCTs evaluating the effects of an oral supplementation [42–44] (Table 5). These studies reported minimal (if any) benefit and have several limitations: the Persson's study disclaimed some errors in the dietary assessment, and at 12 and 24 months, about half of the patients did not reach 75% of the energy intake recommended. The Baldwin's RCT [43] was underpowered and required the addition of lung cancer patients to improve the accrual of the sample. In addition, the percentage of weight loss at the randomization was not reported, the allocation of the patients was not blinded to the dietitians involved in the study and, finally, the compliance to take supplements was very low and there was the possibility of some contamination by the control group. The study of

**Table 3** Impact of malnutrition on survival

Author	N patients/primary	Therapy	Assessment	Outcome
Lecleire et al. (2006) [32]	120/esophagus	Stent insertion	BMI < 18	↓ 1.9 survival
Aaldriks et al. (2013) [13]	143/colon-rectum	Palliative capecitabine, oxaliplatin, folfox	MNA < 24	↓ 2.7 survival
Barao et al. (2017) [33]	250/colon-rectum	Chemotherapy or FU	PG-SGA C Phase angle ≤ 5°	↓ 12 survival ↓ 0.5 survival

MNA, Mini Nutritional Assessment; PG-SGA, Patient-generated Subjective Global Assessment; ↑ means increase, ↓ means decrease

**Table 4** Impact of sarcopenia on survival

Author	Author	Therapy	Therapy
Palmela et al. (2017) [31]	48/esophagus, stomach	Epirubicin, oxaliplatin, 5-FU, capecetabine, docetaxel	4↓ median OS
Miyamoto et al. (2015) [34]	215/colon-rectum	Oxaliplatin, irinotecan, bevacizumab	Median DSF: 9 vs 10.3 months ( $P = 0.02$ )
Fujiwara et al. (2016) [35]	1257/HCC	Miscellaneous treatments in 38% of patients	1.8↓ 5-year OS
Iritani et al. (2015) [36]	217/HCC	Miscellaneous	1.5↓ 5-year OS
Kamachi et al. (2015) [37]	92/HCC	Curative surgery/RFA	1.4↓ 5-year OS, 1.6 ↑1-yr recurrence
Van Vledder et al. (2012) [38]	196/colorectal liver metastases	Resection	1.8↓ 1-year DFS, 2.5↓3-year OS

DFS, disease-free survival; OS, overall survival; RFA, radiofrequency ablation; ↑ means increase, ↓ means decrease

Bourdel-Marschasson [44] was also penalized by the poor compliance and by the enrolment of non-malnourished patients.

### Oral special formulations

The results on the nutritional status and on the clinical outcome may be different when considering the use of oral nutritional supplements (ONS) which are enriched in nutrients which have special metabolic or immune-modulatory effects.

A small study [45] on 35 hepatitis-related HCC showed that patients randomized to receive 42 g BCAA/day had a lower respiratory quotient and better quality of life score at 1 year as compared to the control group. However, the sample size was very small and quality of life was not a primary endpoint of the study. There is a more extensive experience with RCT using  $\omega$ -3 fatty acids-enriched ONS (Table 6). These studies show that  $\omega$ -3 fatty acids-enriched ONS are capable, when adequately taken by mouth [46, 48], to have positive nutritional/metabolic effects [46, 47, 49] and to achieve a longer survival in selected groups of patients.

### Parenteral nutrition

There are two papers which are scientifically noteworthy. In the first one [50], the authors tested a “supplemental”

HPN (sHPN) in 309 weight-losing patients with an expected survival of at least 6–12 months or longer using a multimodal palliation which included COX inhibitors (usually indomethacin, 50 mg twice daily), erythropoietin (15–40,000 units per week), and insulin (0.11 units/kg/day). They showed that, on an intention-to-treat basis, patients randomized to receive nocturnal sHPN (20–25 kcal/kg/day; 0.10–0.15 g nitrogen/kg/day) had a statistically significant improvement in energy balance and the as-treated analysis demonstrated in these patients receiving nutrition a prolonged survival, improved energy balance, increased body fat, and a greater maximum exercise capacity. In a further analysis of a subset of patients [51], the authors reported that insulin treatment improved metabolic efficiency during exercise, but did not increase maximum exercise capacity and spontaneous physical activity. Interestingly, the authors also found that tumor markers in blood (CEA, CA-125, CA 19-9) did not indicate the stimulation of tumor growth by insulin; a conclusion also supported by improved survival of insulin-treated patients ( $P < 0.03$ ). A recent RCT [52] compared in cachectic incurable GI cancer patients on palliative chemotherapy the effects of a sHPN for 6 months to the best practice nutritional care, and reported that sHPN can maintain/increase fat-free mass and improve QoL evaluated through the EORTC-QLQ-C15-PAL. These two studies show that a

**Table 5** RCT on oral supplementation

Author	N pts/primary	Therapy	Intervention	Outcome
Perrson et al. (2002) [42]	137/stomach, colon-rectum	Unspecified	I arm: individual nutritional supplementation ± rehabilitation II arm: rehabilitation + standard care	I arm: better weight gain at 12–24 months, no difference in QoL between the arms
Baldwin et al. (2011) [43]	277/GI	Chemotherapy	Dietary advice or supplements or both versus standard treatment for 6 weeks	No difference in body weight, QoL, and survival at 6 months
Bourdel-Marschasson et al. (2014) [44]	136/GI	Chemotherapy	30 kcal + 1.2 g protein/kg/d versus standard treatment × 6 months	Increase in nutrient intake with dietary advice. No difference in 2-year survival

**Table 6** RCT on  $\Omega$ -3 fatty acid-enriched ONS

Author (year)	N pts/primary	Therapy	Outcome
Fearon et al. (2003) [46]	200/pancreas	620 kcal, 29 g protein $\pm$ 2.2 g EPA $\times$ 2 months	No difference in BW or LBM change but in EPA group correlation between EPA intake (and its blood level) with BW and LBM increase and a correlation between $\uparrow$ in BW and $\uparrow$ QoL
Moses et al. (2004) [47]	24/pancreas	620 kcal, 29 g protein $\pm$ 2.2 g EPA $\times$ 2 months	$\uparrow$ total energy expenditure and level of physical activity only in EPA group
Bauer et al. (2005) [48]	200/pancreas	620 kcal, 29 g protein $\pm$ 2.2 g EPA $\times$ 1 month	BW gain in compliant pts. vs decrease in non-compliant
Shirai et al. (2017) [49]	57/GI, HPB	355–710 kcal, 16–28 g protein + 1.1–2.2 g EPA $\times$ 6 months vs non-supplemented diet during chemotherapy	$\uparrow$ LBM and survival in mGPS 1–2 patients

BW, body weight; LBM, lean body mass; EPA, eicosapentaenoic acid; QoL, quality of life; mGPS, modified Glasgow Prognostic Score;  $\uparrow$  means increase,  $\downarrow$  means decrease

continuous long-term intravenous nutritional support can achieve some beneficial effects in incurable cancer patients.

## Conclusion

This review shows that malnutrition and/or sarcopenia are associated, as expected from the literature regarding an unselected cancer population [4, 53], with an increased chemotherapy toxicity and poor compliance with oncologic therapies and this finally translates in a worse outcome.

What deserves a major attention by the oncologists is that about 20 to 30% of  $\geq$  65-year-old GI cancer patients suffer from major malnutrition and hence, the percentage of patients potentially requiring a nutritional intervention is relevant. The initial approach should be through the use of specific ONS, provided that the gut is normally working and accessible, because the simple administration of non-specific dietary counseling proved to be unsuccessful in a large RCT. It should also be considered that, in view of the high number of patients requiring a nutritional intervention, the simple prescription of  $\omega$ -3 fatty acids-enriched ONS could be directly made by the oncologist in the bunch including also oncologic drugs, pain killers, and antiemetic agents. There is a growing evidence that early interventions of a multimodal palliative/supportive care, including some kind of nutritional support, may be beneficial to the patients [54–56].

On the other hand, it should be reasonably considered that there are barriers to potentiate the oral intake of nutrients, the so-called nutrition impact symptoms [57] which depend on several factors: the GI involvement by the primary tumor, the level of the systemic inflammation and the consequent anorexia and taste alterations, the adverse effects of the oncologic treatments, and finally the presence of presbyphagia which is common in the elderly population. These barriers

are difficult to overcome in the everyday practical routine and make the intravenous route an attractive alternative. The results of the few studies in the elderly GI cancer patients parallel the benefits observed with sHPN on body composition and in quality of life in the unselected cancer population [58–60].

Even if studies comparing the effect of acute administration of nutrients in cancer patients through the enteral or the parenteral route have shown similar results [61–65], the practice of the long-term nutritional support may lead to different clinical conclusions.

While the internationally acknowledged recommendations always privilege the enteral route, whenever possible, the intravenous supplementation can represent, in some patients, an easy approach to integrate a deficient oral/enteral nutrition because it allows long periods of nutritional support in a way which is totally passive and well tolerated [66, 67].

On the contrary, the administration of special diets or supplements through the oral route may be penalized by a poor compliance, especially in the long-term treatments [42–44] and sometimes is felt as forced by the patients [68–70] and by the relatives [66].

## Compliance with ethical standards

**Conflict of interest statement** The authors declare that they have no conflict of interest.

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