Sarcopenia has recently emerged as a new condition that, independently from malnutrition, may adversely affect the prognosis of cancer patients. Purpose of this narrative review is to define the prevalence of sarcopenia in different primaries, its role in leading to chemotherapy toxicity and decreased compliance with the oncological therapy and the effect of some drugs on the onset of sarcopenia. Finally, the review aims to describe the current approaches to restore the muscle mass through nutrition, exercise and anti-inflammatory agents or multimodal programmes with a special emphasis on the results of randomized controlled trials. The examination of the computed tomography scan at the level of the third lumbar vertebra—a common procedure for staging many tumours—has allowed the oncologist to evaluate the muscle mass and to collect many retrospective data on the prevalence of sarcopenia and its clinical consequences. Sarcopenia is a condition affecting a high percentage of patients with a range depending on type of primary tumour and stage of disease. It is noteworthy that patients may be sarcopenic even if their nutritional status is apparently maintained or they are obese. Sarcopenic patients exhibited higher chemotherapy toxicity and poorer compliance with oncological treatments. Furthermore, several antineoplastic drugs appeared to worsen the sarcopenic status. Therapeutic approaches are several and this review will focus on those validated by randomized controlled trials. They include the use of α-3-enriched oral nutritional supplements and orexigenic agents, the administration of adequate high-protein regimens delivered enterally or parenterally, and programmes of physical exercise. Better results are expected combining different procedures in a multimodal approach. In conclusion, there are several premises to prevent/treat sarcopenia. The oncologist should coordinate this multimodal approach by selecting priorities and sequences of treatments and then involving a nutrition health care professional or a physical therapist depending on the condition of the single patient.

**Key words:** sarcopenia, cancer and sarcopenia, sarcopenia and prognosis, sarcopenia and toxicity, sarcopenia and chemotherapy, sarcopenia therapy

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**Introduction**

The awareness that malnutrition is associated with a poor tolerance to chemotherapy dates back to late 1990s [1–8] and more recently research has focused on elderly cancer patients who appear to be especially exposed to this risk [9–14]. Malnutrition, regardless of the way of its evaluation—ranging from simple percentage of weight loss in a determinate span of time to more complex multiparametric scores—finally translates into a poorer response to chemotherapy. Several authors documented this effect in patients with tumours of the GI tract [1, 15], of the lung [16, 17] of the breast [18], of the ovary [19], in lymphoma [6] and other [20–22].

The issue appears quite worrying because recent prospective European surveys of the nutritional status on several hundreds of cancer outpatients and inpatients have shown that malnutrition roughly affects between 30% and 40% of cancer population [23–26] and even more in the Asian surveys [27].

The situation is furtherly magnified for a couple of reasons: (i) sarcopenia appears to be a major contributor to poor tolerance to chemotherapy and (ii) some patients who are defined...
well-nourished according to the international standard [28] may be sarcopenic. In fact, the simple measure of the body weight loss cannot capture changes in body composition and in muscle mass and a recent study [29] showed that 41% of patients with a weight loss < 5% actually had a depletion of muscle mass > 5% of the standard value.

This narrative review focuses on epidemiological literature investigating the prevalence of sarcopenia in patients with different primaries and different stages of disease and on observational researches concerning the relationship between sarcopenia and tolerance of chemotherapy. Furthermore, the review will report the recent data on the potential causal involvement of some oncological drugs on the onset of sarcopenia. Finally, it will deal with current clinical treatments of sarcopenia to restore the muscle mass through the use of anti-inflammatory nutrients, orexigenic agents, nutritional support and exercise, paying a special attention to the results of randomized controlled trials (RCTs).

**Sarcopenia**

**Definition, prevalence and pathophysiology**

Baumgartner et al. [30] first used the term ‘sarcopenia’ to describe the age-related loss of muscle mass of older adults. Through the use of DEXA, Baumgartner et al. [30] calculated the appendicular skeletal muscle mass divided by the square of height (m²), defining the so-called index of relative muscle mass. Sarcopenia was then defined as muscle mass two standard deviations below the mean muscle mass of healthy younger adults. However the most common way to estimate the muscle mass in the clinical practice is through a computed tomography (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 ($r^2 = 0.86$) [31]. 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 [32]. The updated L3 skeletal muscle index cut-points classify sarcopenia based on both sex and body mass index (BMI) [33]. A recent review [34] has shown that the advantages of CT imaging are the high resolution and the three-dimensional reconstruction of muscle mass as well as the measure of the muscle density. DEXA cannot specifically discern muscle mass and quality as CT. In addition, there are weight and size restriction with DEXA scanning making difficult to accurately measure people taller or wider than the scan area. Finally, bioimpedance analysis is useful for longitudinal studies but sensitive to hydration and recent activity of the patient, and instrument predictions may be population specific.

Recent research [35] has shown reductions (~20%) in single muscle fibre cross-sectional areas in both slow-twitch (red), myosin heavy chain I and fast-twitch, myosin heavy chain IIA (white) fibres in both weight-stable cancer patients and those with a history of weight loss. Fibre-type distribution showed a shift from red, myoglobin- and mitochondries-rich fibres (relying on oxidative phosphorylation of lipids and glucose), towards fast-twitch (white) phenotype (relying on anaerobic alactacid glycolytic metabolism) which may preserve muscle function in cancer patients despite atrophy.

Skeletal muscle protein degradation is promoted by ubiquitin–proteasome and autophagy–lysosomal pathways, as well as the calcium-dependent enzymes (calpains), which can be activated by the proteolysis-inducing factor, myostatin, activin A and cytokines. Proteolysis-inducing factor not only promotes protein degradation by increasing mRNA levels of ubiquitin–carrier protein and proteasome subunits, but also inhibits protein synthesis through activation of the RNA-dependent protein kinase.

Myostatin and activins are members of the transforming growth factor B family and trigger skeletal muscle protein breakdown by upregulating MuRF1 and MAFbx/Atrogin1, as well as decreasing protein synthesis via inhibition of the Akt/mTOR pathway.

Cytokines (TNF, IL-1, IL-6) play a pivotal role in promoting skeletal muscle atrophy. TNF-induced atrophy is mediated by the induction of MAFbx/Atrogin1 in muscle by the attenuation of FoxO activation as well as by increasing MuRF1. TNF also suppresses the PI3K/Akt pathway.

Moreover, cytokines induce anorexia by activating neuronal cells expressing pro-opiomelanocortin neuropeptides in the arcuate nucleus of the hypothalamus, which increases the central melanocortin system timbre and hence they contribute to the energy-protein deprivation of the patient.

Some of these aetiological factors are also observed as consequent to oncological therapies such as surgery, chemotherapy and radiotherapy, which may cause anorexia, early satiation, nausea, vomiting, loss of taste and smell, fatigue and pain. Moreover, sarcopenia per se is a factor of further muscle mass depletion because reduced activity deprives the body of physiological anabolic drivers.

It should be pointed out that general muscularity varies according to several factors including ethnicity, age, gender and prevalence of obesity and there are no well-established worldwide thresholds to define a normally low muscle mass. Muscle mass starts to decline around the age of 40 years with a mean loss of ~8% per decade until the age of 70 [36] and then declines more quickly at a rate of 25%–40% muscle loss every 10 years [37, 38]. Since most cancers appear in the adult-elderly age, sarcopenia too is expected to have a high prevalence in this population.

Prevalence of sarcopenia in patients with different primary tumours, determined in most cases through CT imaging, is reported in Table 1. It is noteworthy that most of the studies reported a percentage of sarcopenia exceeding 40% of the observed patients. Primaries which showed the highest average percentage of sarcopenia were cancer of pancreas, lung and bladder and in some tumours (pancreas and breast) sarcopenia appeared to be more frequent in advanced stages than in earlier stages.

Sarcopenia reduces compliance to chemotherapy

There is a wide literature showing that sarcopenic patients have an excess of toxicity from oncological therapies and consequently are forced to reduce dosage or to delay the cycles of administration. The excess of toxicity ranges from 1.6 to a 13 factor, mainly depending on the drug investigated in the different studies (Table 2).

A plausible explanation for the excess of toxicity of sarcopenic patients is the usual practice of dosing chemotherapy as function
Table 1. Prevalence of sarcopenia by different primary tumours

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Primary tumour</th>
<th>Median % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prado [93] (2009)</td>
<td>Penis</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 2. Increased toxicity due to sarcopenia

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Primary</th>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prado [105] (2007)</td>
<td>Colon</td>
<td>5-FU</td>
<td>1.7† toxicity if &gt; 20 mg/kg LMB</td>
</tr>
<tr>
<td>Barret [48] (2014)</td>
<td></td>
<td>Fluropirimidines±oxaliplatin, irinotecan</td>
<td>13.5† grade 3–4 toxicity at oxaliplatin 3 mg/Kg LBM</td>
</tr>
<tr>
<td>Ali [106] (2016)</td>
<td>Oesophago-Gastric J</td>
<td>FOLFOX</td>
<td>44% versus 0 in nonsarcopenic</td>
</tr>
<tr>
<td>Jung [41] (2015)</td>
<td></td>
<td>FOLFOX</td>
<td>1.5† grade 3–4 toxicity/1PI*SD&lt;ref. value</td>
</tr>
<tr>
<td>Anandavadelan [74] (2015)</td>
<td></td>
<td>Cisplatinum + 5-FU</td>
<td>5.5† DLT in obese sarcopenic patients</td>
</tr>
<tr>
<td>Tan [107] (2015)</td>
<td>Breast</td>
<td>Capecitabine</td>
<td>2.9† DLT in sarcopenic patients</td>
</tr>
<tr>
<td>Prado [93] (2009)</td>
<td></td>
<td>Epirubicine</td>
<td>2.5† toxicity</td>
</tr>
<tr>
<td>Shachar [109] (2016)</td>
<td>Renal cell</td>
<td>Sorafenib</td>
<td>3.1† grade 3–4 toxicity</td>
</tr>
<tr>
<td>Antoun [82] (2010)</td>
<td>Carcinoma</td>
<td>Sunitinib</td>
<td>6.4† toxicity</td>
</tr>
<tr>
<td>Houillard [85] (2013)</td>
<td></td>
<td>Sunitinib</td>
<td>4.1† toxicity</td>
</tr>
<tr>
<td>Cushen [86] (2014)</td>
<td></td>
<td></td>
<td>1.6† dose-limiting toxicity</td>
</tr>
<tr>
<td>Mir [50, 51] (2012)</td>
<td></td>
<td>Safeni, vandetanib, Phase 1 drugs</td>
<td>2.6† DLT, 5.2† DLT</td>
</tr>
<tr>
<td>Massicotte [110] (2013)</td>
<td></td>
<td>carboplatinum,pemetrexed/ gemcitabine/vinorelbine</td>
<td>6† toxicity</td>
</tr>
<tr>
<td>Sjoblom [111] (2016)</td>
<td></td>
<td>rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone</td>
<td>2† toxicity</td>
</tr>
<tr>
<td>Choi [70] (2016)</td>
<td></td>
<td>R-CHOP</td>
<td>2.4† early discontinuation</td>
</tr>
<tr>
<td>Go [112] (2016)</td>
<td></td>
<td></td>
<td>1.3† discontinuation</td>
</tr>
</tbody>
</table>

LMB: lean body mass; PI: psoas index; DLT:dose lethal toxicity; R-CHOP: radiotherapy-cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone
of each patient’s height and weight (hence the body surface area) without considering that fat mass accounts for a large and unpredictable part of body weight. It should be noted that body surface area was originally calculated by Du Bois and Du Bois [113], one century ago, in only nine subjects after considering the body composed by eight segments, in which the surface was extrapolated through the measure of the length and the volume of the single segments and then cumulated. It is clear that, regardless the concept that some physiological constants may be more related to the body surface area than to other anthropometric parameters, the methodology per se was poorly validated. In addition Prado et al. [32] have shown that fat-free mass, which represents the volume of distribution of many cytotoxic chemotherapy drugs [114] has a poor association with body-surface area ($r^2=0.37$) in obese cancer patients and its individual variation can account for up to three-times variation in effective volume of distribution for chemotherapy administered per unit body-surface area. In a subsequent study Prado et al. [108] also reported that lean soft tissue (LST) and aspartate transaminase explained 33% of the variation in epirubicin clearance providing proof of principle of LST relationship with epirubicin pharmacokinetics. Hence there is a risk of an overestimation of posology when relying on body-surface area which appears to be more likely as the BMI increases. These data provide a rationale for dosing platinum-based chemotherapy on patient’s body composition [115].

Sarcopenia decreases response to chemotherapy and survival

If patients are sarcopenic, the response to chemotherapy may be lower. Sarcopenic patients with breast cancer showed a poorer response to capcitabine [116] and to paclitaxel, docetaxel or nab-paclitaxel [117]. Data regarding the relationship between sarcopenia and final outcome are reported in Table 3 where cut-off for defining sarcopenia in females ranged from 41 cm$^2$/m$^2$ and in men from 36 to 55.4 cm$^2$/m$^2$. Table 3 shows that approximately in two-thirds of the published papers encompassing a large variety of tumours treated with several different chemotherapy drugs and schedules, sarcopenia was an unfavourable prognostic factor for survival. A recent meta-analysis [109] reported that sarcopenia was an unfavourable prognostic factor for both cancer-specific survival and cumulative cancer survival and patients with a tumour of colon rectum, of liver, of kidney and of oesophagus and stomach had an excess of risk of mortality (hazard ratio 2.2, 2.1, 1.7, 1.5, respectively) if patients were sarcopenic. This study is very comprehensive despite some limitations including the heterogeneity of tumours considered in the analysis, their stages and treatments as well as the different cut-off points for defining sarcopenia. Finally most of the studies were retrospective thus limiting definite conclusions. Poor outcomes may be related to higher toxicity rates that, in turn, may lead to dose reduction and delivering lower doses of effective oncological treatment [93].

Chemotherapy as a cause of sarcopenia

While sarcopenia is a distinct feature of incipient or full-blown cancer cachexia, there is some evidence that a short-term chemotherapy per se can lead to a muscle mass depletion. It is known since 2004 that adjuvant chemotherapy in women with breast cancer is associated with an increase of the percentage of body fat assessed and a decrease of the fat-free mass [120]. The literature regarding some oncological drugs that, administered for some time, were recognized as responsible for sarcopenia, is summarized in Table 4. It is noteworthy that the rate of muscle loss observed in the recent study of Blauwhoff-Buskermolen et al. [122] compared with muscle loss that occurs in normal aging (1%/year), was 24-fold more rapid. It is also noteworthy that in the study of Prado et al. [121] patients receiving selumetinib showed an increase of the muscle mass.

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**Table 3. Risk of mortality due to sarcopenia**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Primary tumour</th>
<th>Hazard ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorensen [46] (2013)</td>
<td></td>
<td>1.74 (0.99–3.04)</td>
</tr>
<tr>
<td>Yamamoto [44] (2015)</td>
<td></td>
<td>2.27 (1.15–4.49)</td>
</tr>
<tr>
<td>Dhooge [52] (2012)</td>
<td>Hepatocellular carcinoma</td>
<td>2.87 (0.41–20.27)</td>
</tr>
<tr>
<td>Mir [50] (2012)</td>
<td></td>
<td>1.66 (0.64–4.27)</td>
</tr>
<tr>
<td>Mir [51] (2012)</td>
<td></td>
<td>4.84 (1.20–19.44)</td>
</tr>
<tr>
<td>Fujwara [56] (2013)</td>
<td></td>
<td>1.52 (1.18–1.96)</td>
</tr>
<tr>
<td>Harimoto [53] (2013)</td>
<td></td>
<td>1.11 (1.04–1.19)</td>
</tr>
<tr>
<td>Moza-Junco [54] (2013)</td>
<td></td>
<td>2.53 (1.35–4.74)</td>
</tr>
<tr>
<td>Itoh [117] (2014)</td>
<td></td>
<td>1.96 (1.04–3.68)</td>
</tr>
<tr>
<td>Intani [58] (2015)</td>
<td></td>
<td>3.18 (1.68–6.03)</td>
</tr>
<tr>
<td>Levolger [59] (2015)</td>
<td></td>
<td>3.76 (1.78–7.93)</td>
</tr>
<tr>
<td>Kaido [118] (2017)</td>
<td></td>
<td>95% versus 57% 3-year survival</td>
</tr>
<tr>
<td>Tan [68] (2009)</td>
<td>Pancreas/biliary tract</td>
<td>1.28 (0.86–1.91)</td>
</tr>
<tr>
<td>Dalal [62] (2012)</td>
<td></td>
<td>1.48 (0.76–2.87)</td>
</tr>
<tr>
<td>Mir [50] (2012)</td>
<td></td>
<td>3.27 (0.80–13.44)</td>
</tr>
<tr>
<td>Choi [70] (2015)</td>
<td></td>
<td>1.72 (1.39–2.28)</td>
</tr>
<tr>
<td>Cooper [60] (2015)</td>
<td></td>
<td>0.99 (0.96–1.02)</td>
</tr>
<tr>
<td>Rollins [71] (2015)</td>
<td></td>
<td>1.10 (0.77–1.58)</td>
</tr>
<tr>
<td>Yip [73] (2013)</td>
<td>Oesophagus/gastric</td>
<td>2.38 (0.48–11.69)</td>
</tr>
<tr>
<td>Harada [76] (2015)</td>
<td></td>
<td>1.07 (0.69–1.67)</td>
</tr>
<tr>
<td>Tamandl [77] (2015)</td>
<td></td>
<td>1.87 (1.15–3.03)</td>
</tr>
<tr>
<td>Tan [107] (2015)</td>
<td></td>
<td>1.80 (0.95–3.42)</td>
</tr>
<tr>
<td>Sharma [88] (2015)</td>
<td></td>
<td>2.13 (1.15–3.93)</td>
</tr>
<tr>
<td>Smith [89] (2014)</td>
<td></td>
<td>1.11 (1.07–1.15)</td>
</tr>
<tr>
<td>Fukushima [87, 90] (2015, 2015)</td>
<td></td>
<td>2.58 (1.16–5.74), 1.11 (1.07–1.15)</td>
</tr>
<tr>
<td>Psutka [91, 84] (2015, 2015)</td>
<td></td>
<td>1.93 (1.24–3.01), 1.71 (1.14–2.57)</td>
</tr>
<tr>
<td>Martin [33] (2013)</td>
<td></td>
<td>1.20 (1.05–1.38)</td>
</tr>
<tr>
<td>Sharma [99] (2015)</td>
<td></td>
<td>1.95 (0.68–5.64)</td>
</tr>
<tr>
<td>Lanic [119] (2014)</td>
<td></td>
<td>3.22 (1.73–5.98)</td>
</tr>
</tbody>
</table>
Does quantity or quality of muscle mass matter?

In the assessment of muscle mass through the CT imaging, the skeletal mass densitometry is expressed as the mean Hounsfield Units of a measured cross-sectional muscle area. Low values usually mean increased fat deposits and have been reported in obese and diabetic patients and are associated with a poor functional performance. Since there is not, to date, a general agreement of cutoff points to define sarcopenia, there was recently a growing interest to investigate whether there was some relationship between skeletal mass density and oncological outcome. A growing number of studies have also reported a negative prognostic impact of reduced skeletal mass density in patients with different solid tumours [33], non-small cell lung carcinoma [111], malignant melanoma [123], adrenocortical carcinoma [124], metastatic renal cell carcinoma [82] and pancreatic cancer or distal cholangiocarcinomas [71] and in follicular lymphoma [125, 126]. A large study on non-small cell lung carcinoma [111] showed that skeletal mass radiodensity was a significant independent prognostic factor for overall survival. It also showed that muscle mass measured by the cross-sectional muscle area at the lumbar level (expressed as skeletal muscle index that is total cross-sectional skeletal muscle area (cm²) normalized for stature by dividing by height squared (m²)) was not prognostic for survival. It is interesting that a recent study on elderly cancer patients [127] showed that skeletal muscle density was more associated with physical function than skeletal muscle mass obtained by routine CT imaging and hence may aid in identifying patients at risk for functional impairments.

Table 4. Chemotherapy-associated sarcopenia

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Primary tumour</th>
<th>Duration of the observation</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prado [121] (2012)</td>
<td>Cholangiocarcinoma</td>
<td>&gt;/&lt; 150 days</td>
<td>Platinum, paclitaxel, etoposide, gemcitabine, epirubicin</td>
</tr>
<tr>
<td>Barret [48] (2014)</td>
<td>mColorectum</td>
<td>2 months</td>
<td>Platinum, fluoropyrimidine, irinotecan</td>
</tr>
<tr>
<td>Stene [79] (2015)</td>
<td>Lung</td>
<td>3 months</td>
<td>Platinum</td>
</tr>
<tr>
<td>Blauwkoff-Buskermolen [122] (2016)</td>
<td>mColorectum</td>
<td>3 months</td>
<td>Platinum, irinotecan, bevacizum</td>
</tr>
</tbody>
</table>

Finally, while it is well-known that muscle exercise is essential to maintain/increase the muscular mass provided that nutrients are correctly administered, however, a programme combining nutrition and exercise can be realistically proposed only to patients who do not suffer of severe fatigue. The detailed analysis of all potential clinical approaches to intervene against the sarcopenia is beyond the aims of this review. This more simply follows, as regards the priority of presentation, first the historically more consolidated and nutrient-based interventions (ω-3FAs, nutritional support) which usually represent the most common first clinical approach, and then the more recent agents (Anamorelin) or complex procedures (the so-called multimodal therapies), with a special reference to the results from RCT.

Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) favours production of 3-series prostaglandins and 5-series leukotrienes (which are associated with improved immunocompetence and reduced inflammatory responses) while levels of the PGE2 and 4-series leukotrienes (immunosuppressive and proinflammatory) are reduced. In addition to the effects on prostaglandin synthesis and COX-2 inhibition, EPA is effective in reducing the proinflammatory cytokines and consequent catabolic mediators involved in sarcopenia. There is also growing evidence that 2.4–3.0 g EPA and docosahexaenoic acid (DHA), the so-called ω-3FAs, per day, stimulates gains in muscle mass in older adults by overcoming aging-induced anabolic resistance [128–130].

Most of RCTs have used ω-3FA-enriched supplements or ω-3FA capsules. RCTs before 2007 have been generally unsuccessful in demonstrating a benefit on the muscle mass [131–136] even if Fearon et al. [131] reported that increased plasma EPA levels in patients randomized to take ω-3FA-enriched supplements were associated with weight and LST gain. RCTs published in the last 10 years are reported in Table 5. This shows that out of 6 studies [137–143] investigating the effect of ω-3FA on LST, 4 reported statistically significant positive results [137, 138, 141], 1 a borderline result [141] and 1 [140] with only 11 patients, no effect. It is interesting to observe that this last study was on 11 patients only, ω-3FAs were administered as capsule at low dosage and without a concurrent nutritional intervention. It is also noteworthy that all these studies were carried out while patients were receiving an oncological therapy. A large study [143] combining EPA with medroxyprogesterone acetate/megestrol acetate, l-carnitine for 4 months also reported a benefit on LST but it is impossible to understand the role of the ω-3FA due to the variety of agents used in such, never repeated, investigation. A collateral remark is that a systematic review of 10 RCTs on ω-3-enriched supplements for

Strategies to reverse sarcopenia

The clinical approach to sarcopenia has to follow a strategy that takes into account on one side the use of treatments to fight the muscle loss whose efficacy was proved by RCTs, on the other side the general status of the patient and his/her compliance with the treatment. In fact, a prerequisite of any treatment to expect a benefit on the muscle mass is that the patient has a normal intake of nutrients. In such a case, the first approach considers the use of anti-inflammatory agents that have both anabolic and catabolic effects as ω-3 fatty acids (ω-3FAs), while, if nutrition is poor because of anorexia, there is a place for orexigenic agents as ghrelin.

Furthermore, if these approaches fail, the use of enteral or parenteral feeding not only can ensure an adequate nutrition but it is possible to modulate these artificial regimens providing with nutrients that are able to optimise the muscular protein synthesis.

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patients in chemotherapy and/or radiotherapy showed that they can improve quality of life of patients [144] and a recent RCT reported that fish oil supplementation during chemotherapy increases time to tumour progression in colorectal cancer [145].

**Enteral and parenteral nutrition**

The provision of an adequate nutritional support is a *conditio sine qua non* to achieve a benefit on the nutritional status. A consistent preclinical experience has shown that the acute oral administration of an optimized mixture of amino acids (usually enriched in leucine or in branched-chain amino acids) is capable of increasing protein synthesis [146–148] or decreasing breakdown [149], also in losing-weight cancer patients [149] and those under chemotherapy [149]. A literature review [150] has reported that ~2 g amino acid/kg/day may be necessary to stimulate synthesis and to decrease breakdown of muscle protein in cancer patients.

The clinical experience is much more limited, however, two RCTs are worth to be mentioned. Lundholm et al. [151, 152] studied the potential of a ‘supplemental’ home parenteral nutrition (HPN) in 309 weight-losing patients with solid tumours (primarily gastrointestinal lesions) using a multimodal palliation which included COX inhibitors, erythropoietin and insulin. On an intention-to-treat basis, patients randomized to receive supplemental nocturnal HPN (20–25 kcal/kg/day and 0.10–0.15 g nitrogen/kg/day) had a significant improvement in energy balance only, but the as-treated analysis demonstrated a prolonged survival, improved energy balance increased body fat and a greater maximum exercise capacity in those patients receiving HPN (total dose of amino acid about 1.6 g/kg/day). Although the authors did not measure the muscle mass, it is difficult to explain the finding of an improved physical exercise capacity without accepting an anabolic response of the muscular tissue due to HPN. Breiikrutz et al. [153] following the rationale widely reported elsewhere [154] that tumour cell utilizes glucose as preferential fuel whereas the cancer patient better utilizes fat, randomized 23 moderately malnourished patients with gastrointestinal carcinomas to receive either a conventional diet supplying 35 non-protein kcal and 1.1 g of protein/kg/day or a fat-enriched artificial liquid diet, where fat accounted for 66.6% of non-protein energy. Body cell mass was maintained throughout the study in the experimental group, but declined significantly in the control one after 1 and 2 months of follow-up.

**Anamorelin**

Anamorelin is an orally administered low molecular weight ghrelin-like agonist with the chemical structure 3-([2R]-3-[(3R)-3-benzyl-3-[(trimethylhydrazino) carbonyl] piperidin-1-yl]-2-[(2-methylalanyl) amino]-3-oxopropyl}-1H-indole. Preclinical studies have demonstrated that anamorelin is able to increase food intake and body weight in rats without promoting tumour growth. Two large multicentre RCTs (ROMANA 1 and ROMANA 2) [155] randomized 484 patients with inoperable stage III or IV non-small cell lung cancer and cachexia (defined as ≥5% weight loss within 6 months or BMI <20 kg/m²) to anamorelin 100 mg orally once daily or placebo. Over 12 weeks, LST, measured by DEXA, increased in patients assigned to anamorelin compared with those assigned to placebo. More recently, Takayama et al. [156] randomized 181 patients with non-small cell lung cancer and >5% weight loss within the previous 6 months, to receive 50 or 100 mg anamorelin, or placebo, orally, every day for 12 weeks, and found a significant increase in LST, measured by DEXA, at the higher dosage. It is noteworthy that in both studies there was no improvement of the hand grip strength. These findings were confirmed in a recent meta-analysis [157].

**Physical exercise**

It is well known from the experience of sport medicine as well as from the common practice of rehabilitation that physical exercise plays an essential role in restoring a depleted muscle mass. In the elderly people both resistance training and aerobic training
interventions or their combination are able to increase the muscle mass [158]. Exercise can significantly remodel glycolytic fibres to become more oxidative: that is, to produce more myoglobin, increase lipid metabolism, and enhance mitochondrial biogenesis and angiogenesis. From the practical point of view, however, it is extremely important to know that a net-positive protein balance following exercise only occurs when an adequate amount of protein (>20 g) is consumed during the post-exercise period, which results in greater muscle protein synthesis and protein balance compared with protein ingestion or exercise alone [159–161]. The stimulatory effect of acute hyperaminoacidemia on muscle protein synthesis has short duration (~90 min) [162, 163], after which the anabolic response returns to baseline even in the presence of sustained elevations in plasma amino acid concentration. Clinical results of physical exercise in patients with active cancer have been so far quite modest because many patients are suffering from chronic fatigue, mainly due to oxidative metabolism impairment [164] or because the exercise was not planned together with concurrent adequate nutritional support. A further limitation is the methodology to estimate the muscle mass: in fact Dual-energy X-ray absorptiometry (DEXA), air displacement plethysmography, or bioelectrical impedance analysis measure a total LST where muscle only contributes ~50% of the total [165].

Out 15 studies reviewed by Focht et al. [166] two only [167, 168] reported a positive result on the muscle mass with resistance exercise and, interestingly, both were in breast cancer patients. Stene et al [169] reviewed the effect on muscle mass of a combined resistance and aerobic approach and reported a benefit in two studies out of five they collected and, more precisely again in breast cancer [170] and, then, in myeloma [171] patients. In one study [172], the effect on muscle mass at post-treatment evaluation was better in the control group compared with group receiving resistance exercise and a low fat vegetable diet. This emphasises, once more, the tenet that an adequate intake of high quality protein should follow the physical exercise. However, while maximization of nutrient intake is imperative to attenuate/treat muscle loss, it should be considered that improvement in muscle mass does not necessarily reflects an increase of type I and II muscle fibre cross-sectional area [173] and this may explain the lack of benefit in muscular force even when muscle mass was increased [155, 156].

Multimodal treatment

The approach through a multicomponent therapy which includes nutritional support to promote energy balance and ensure optimal protein intake, aerobic and resistance exercise to stabilize muscle mass, strength and improve physical performance, celecoxib to target overproduction of inflammatory cytokines is still in its dawn [173]. The rationale is that nutrition is an essential part of cachexia treatment as it is not considered possible to increase or stabilize body composition if nutritional needs are not met. Furthermore, multimodal treatment aims to delete/blunt the role of some factors (as the excess of cytokines and sarcopenia) which have been identified as negative prognosticators and to increase compliance with chemotherapy. Similar approaches have been recently attempted [174–176] with promising results and are now recommended in the international literature [177].

Conclusive remarks

The onset of artificial nutrition dates back 50 years [178] and that of the modern chemotherapy about 70 [179]. During this period artificial nutrition has evolved from the simple provision of energy and blocks to maintain body weight to a concept that considers nutrients as capable of regulating gene expression, interfering in signal transduction pathways and activating specific immune responses and anabolic functions. On the other hand medical oncology made giant progresses, moving from a simple antiproliferative approach to the recent personalized targeted therapies. Despite the clinical success achieved in their respective areas, nutritional therapy and medical oncology have progressed in parallel pathways without talking each other.

The modern recognition of the deleterious impact of a deteriorated nutritional status and of depleted muscle mass in affecting both compliance and response to the oncological therapy, as well as the knowledge that the current nutritional interventions, especially if associated with physical exercise, can favourably interfere in this vicious circle, should open the way to a fruitful cooperation between these two branches of the medical science. In 1973, Dr Bonadonna [180] wrote that the oncologist should be a conductor who coordinates the priority and the sequence of the therapeutic approaches (that were, at that time, surgery, chemotherapy and radiation therapy) of the patient. Now, it is time [181] for the oncologist to look at his/her patient with a large comprehensive view and to be able to involve specialists of other areas (nutrition, supportive care, palliative care, physical therapy, occupational therapy etc.) when it is necessary, and often also in the early phases of therapy [174–176], to improve the outcome of the cancer patients.

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