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Muscle derangement and alteration of the nutritional machinery in NSCLC

Ilaria Trestini[a], Anastasios Gkountakos[b], Luisa Carbognin[a,c], Alice Avancini[d], Massimo Lanza[e], Alessio Molfino[f], Simonetta Friso[g], Vincenzo Corbo[b,h], Giampaolo Tortora[i,j], Aldo Scarpa[b,h], Michele Milella[a], Emilio Bria[i,j,1,*], Sara Pilotto[a,1]

[a] Medical Oncology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[b] Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy
[c] Division of Gynecologic Oncology, Department of Woman and Child Health, Fondazione Policlinico Universitario A. Gemelli, I.R.C.C.S., Università Cattolica del Sacro Cuore, Roma, Italy
[d] Biomedical Sciences, Department of Medicine, University of Verona, Italy
[e] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Italy
[f] Department of Clinical Medicine, Sapienza University of Rome, Italy
[g] Department of Medicine, School of Medicine, University of Verona, Verona, Italy
[h] ARC-NET, Applied Research on Cancer Center, University and Hospital Trust of Verona, Verona, Italy
[i] Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[j] Università Cattolica Del Sacro Cuore, Rome, Italy

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ABSTRACT

Weight loss and depletion of nutritional status are frequent presentation hallmarks in non-small cell lung cancer (NSCLC). Decline in muscle mass is a major component in weight loss and may have both a prognostic and predictive value for survival and treatment-related toxicities. Recent findings suggest that weight and skeletal muscle mass gain during treatment may represent surrogate markers for outcome in advanced NSCLC patients. Herein we present an in-depth view of the impact of nutritional status derangements on NSCLC patients' outcome, focusing on lean body mass variations during disease course. We explored the impact of malnutrition with a major attention on novel treatment options. We reviewed molecular, metabolic and immunological mechanisms underlying muscle-wasting condition, which may exhibit a meaningful targeting potential. Incorporating a specialized and accurate body composition assessment into a comprehensive, patient-centered and tailored intervention will facilitate the achievement of nutritional goals and optimal care for lung cancer patients.

1. Introduction

Lung cancer represents the second common cancer and the leading cause of cancer-related death in developed countries (Siegel et al., 2018). Non-small-cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases and usually presents as locally advanced or metastatic disease. The significant improvements in diagnostic tools and treatment options, with crucial advancements in surgery, radiotherapy and chemotherapy, as well as the emergence of innovative therapeutic strategies as targeted therapy and immunotherapy, represent an advantage over the previous care (Planchard et al., 2018). Nevertheless, these patients continue to face relevant nutritional and metabolic consequences, related both to illness process and to treatment-induced adverse events.

Reports from the literature show that patients with NSCLC present a high incidence of malnutrition at diagnosis, with weight loss happening in 54% of them at disease presentation (Tan and Fearon, 2008; Kovarik et al., 2014). Moreover, the nutritional status depletion is not a problem experienced only upon diagnosis, but is also commonly reported during chemotherapy, radiotherapy and, mainly, concurrent chemo-radiotherapy. In detail, NSCLC patients under treatment may experience several symptoms as loss of appetite, taste and smell alterations, nausea, vomiting, dysphagia and esophagitis, potentially affecting treatment schedule and adherence (Belqaid et al., 2014; Kiss, 2016). In

* Corresponding author at: Medical Oncology, Fondazione Policlinico Universitario A. Gemelli, I.R.C.C.S., Università Cattolica del Sacro Cuore, Rome, Italy.
E-mail addresses: ilariatrestini@alice.it (I. Trestini), anastasios.gkountakos@univr.it (A. Gkountakos), luisa.carbognin@univr.it (L. Carbognin), alice.avancini@univr.it (A. Avancini), massimo.lanza@univr.it (M. Lanza), alessio.molfino@uniroma1.it (A. Molfino), simonetta.friso@univr.it (S. Friso), vincenzo.corbo@univr.it (V. Corbo), giampaolo.tortora@unicatt.it (G. Tortora), aldo.scarpa@univr.it (A. Scarpa), michele.milella@univr.it (M. Milella), emilio.bria@unicatt.it (E. Bria), sara.pilotto@univr.it (S. Pilotto).

[1] Equally contributors (S.P and E.B. share the last co-authorship).

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this regard, a cross-sectional study by *Iyer et al.* including 450 patients with advanced NSCLC receiving pharmacological treatment reported that 97% experienced loss of appetite (Iyer et al., 2014). These symptoms adversely affect the ability to achieve adequate nutritional intake, placing these patients at increased risk of malnutrition, especially in advanced or metastatic setting or among the elderly (Gioulbasanis et al., 2011; Zhang et al., 2013).

During recent years, research has particularly focused on the role of the nutritional status as a novel prognostic and predictive factor for NSCLC patients (Kawaguchi et al., 2010). In this regard, data are concordant in suggesting that nutritional deficiency may adversely influence the prognosis of lung cancer patients (Jagoe et al., 2001; Attaran et al., 2012). First of all, as widely known, the loss of appetite and weight loss at disease diagnosis seem to predict unfavorable outcomes for survival in advanced NSCLC (Stanley, 1980). Secondly, weight loss may increase the risk of impaired response to chemo- or radiotherapy, the susceptibility to chemotherapy-induced toxicity, the incidence of post-operative complications and the treatment delays (Dewys et al., 1980; Buccheri and Ferrigno, 2001; Santarpia et al., 2011). Furthermore, patients with a normal nutritional status showed lower levels of perceived pain, anxiety and depression than patients with nutritional disorders (Khalid et al., 2007; Sanchez-Lara et al., 2012; Chabowski et al., 2018).

Nevertheless, variations in weight and body mass index (BMI), a ratio of weight relative to height measured in kilograms per square meters, may have low diagnostic accuracy in identifying patients with malnutrition. In fact, body weight is influenced by several physiological and pathological conditions and, for example, weight loss may be underestimated in patients with a large tumor mass or fluid retention, such as body edema or pleural effusion (Collins et al., 2014). Furthermore, body weight loss does not precisely reflect body composition derangements within the course of the disease (Nattenmuller et al., 2017). In this context, recent evidence utilizing computed tomography (CT) images to assess skeletal muscle mass has recognized that skeletal muscle loss is a prominent feature in cancer patients, even with normal or high BMI (Baracos et al., 2010; Martin et al., 2013). Notably, in NSCLC patients, several recent studies have identified loss of lean body mass, mainly skeletal muscle, both following lung resection of early-stage disease and during cytotoxic chemotherapy in patients with advanced cancer (Takamori et al., 2018; Stene et al., 2015).

Changes in skeletal muscle volume have been reported to have a great impact on clinical outcomes in cancer patients. Low muscle mass may affect muscle function and lead to loss of strength, reduced pulmonary function, increased disability and, thereby, poorer quality of life (Kilgour et al., 2010, 2013). In addition, muscle wasting and low muscle mass have been related to a shorter survival and increased risk of developing dose-limiting toxicity in various cancer types, including NSCLC (Arrieta et al., 2015; Kazemi-Bajestani et al., 2016; Anandavadivelan et al., 2016; Tan et al., 2015; Jung et al., 2015; Sjoblom et al., 2015). Of interest, with the introduction of targeted therapies, recent studies investigated the predictive and prognostic role of low lean body mass in patients with advanced NSCLC treated with epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI), suggesting that the nutritional status should be considered as an important factor also in these patients subgroups (Arrieta et al., 2015; Park et al., 2016; Rossi et al., 2018). To date, although the depletion of muscle mass has emerged as a novel potential prognostic factor that may precede an overt cancer cachexia syndrome (Fearon et al., 2011), few attention has been paid to clarify the pathophysiological mechanisms underlying this complex phenomenon (Blum et al., 2011).

Given these perspectives, we carried out an in-depth review exploring the impact of malnutrition on NSCLC patients' outcomes, across the available therapies and in light of novel treatment options. We mainly focus the discussion on the lean body mass that has already been suggested as a potential target for tailored therapies. Based on the available published data, we explored molecular and metabolic factors leading to muscle tissue wasting, emphasizing the importance of incorporating into treatment programs a careful and accurate body composition's assessment, rather than weight measurement alone. The identification of those factors playing a crucial role in promoting nutritional derangements may allow the design of tailored interventions focused on reaching precise nutritional goals, in order to improve quality of life and clinical outcomes in NSCLC patients.

2. Prevalence and implications of malnutrition in NSCLC

Patients affected by NSCLC report a high prevalence of co-occurring symptoms that may contribute to a reduction in nutrients availability and increase the risk of malnutrition, often diagnosed before the treatment start. As reported in a study involving 220 lung cancer patients, fatigue, nausea, weakness, appetite loss and vomiting form a cluster of common symptoms already described at disease presentation (Gift et al., 2004). A retrospective study by *Ross et al.*, analysing 418 NSCLC patients, found that 58% had already experienced weight loss at diagnosis (Ross et al., 2004). These results are consistent with those observed from an earlier study, which reported that 61% of NSCLC patients initially presented weight loss (Dewys et al., 1980). In a prospective longitudinal study about the prevalence of malnutrition in patients who had not received any previous treatment, 69% of lung cancer patients were malnourished according to the patient-generated subjective global assessment (PG-SGA) (Read et al., 2006).

Beyond the diagnosis, malnutrition in NSCLC remains a crucial concern during the course of treatments, potentially worsening up to their completion. In particular, chemotherapy, which still represents a main treatment for advanced NSCLC patients, has been identified as a predictor of weight loss. Indeed, chemotherapy side effects, such as anorexia, nausea, vomiting, early satiety and mucositis, may adversely affect nutritional status. Furthermore, the alterations in taste and smell well known during chemotherapy, contribute to development of food aversion and reduce hedonic response (Cohen et al., 2016; Cranganu and Camporeale, 2009). Radiotherapy to the thoracic area was also associated with significant acute toxicities depending on the dose and volume delivered, including oesophagitis, anorexia, dysphagia and fatigue, which may significantly impact on the ability to achieve adequate nutritional intake and subsequently lead to nutritional depletion (Belderbos et al., 2005). More recent studies in radiotherapy-treated lung cancer patients found that 22%–31% had a significant weight loss (≥ 5%) within 90 days from the start of radiotherapy, with a median weight loss around 8%–9% (Kiss et al., 2014a, b). Of interest, the degree of weight loss increased during the post-treatment period, highlighting the importance of a long-term nutritional status monitoring. As suggested by a prospective study, malnutrition among lung cancer patients increased from 33% to 50% prior and at the end of radiotherapy, respectively (Unsal et al., 2006). Concurrent chemo-radiotherapy (CT-RT) is associated to a higher incidence of severe esophagitis (Jain et al., 2009) and dysphagia, which persist after treatment, leading to a decreased dietary intake. In a study conducted by *De Ruysscher et al.*, among 328 lung cancer patients, severe (grade 3 or more) dysphagia was reported in about 25% of patients treated with concurrent CT-RT and over 80% experienced difficulties in swallowing. In particular, patients receiving concurrent CT-RT experienced a significantly severe dysphagia than those without chemotherapy or treated with sequential chemotherapy and radiotherapy (12.8% *versus* 1.7% *versus* 4.7%; $p < 0.001$) (De Ruysscher et al., 2007). These results were confirmed in a subsequent study, which also suggested that further weight was lost in the next weeks of treatment and that body weight was only partially recovered 4 weeks after the end of concurrent CT-RT (Op den Kamp et al., 2014). Similarly, among lung cancer patients treated with high dose palliative or radical radiotherapy for a primary tumor, those receiving concurrent chemotherapy were more likely to have a clinically significant weight loss (≥ 5% between the start and up to 90 days from radiotherapy) (40% *versus* 0%; $p < 0.001$). Of interest, the risk of experiencing ≥ 5% weight loss for a patient with late-stage disease was 15 times greater than for a patient with earlier stage (Kiss et al., 2014a). As expected, a higher incidence of malnutrition can be found in late-stage disease (Segura et al., 2005; Hebuterne et al., 2014). Among metastatic lung cancer patients potentially eligible for a systemic treatment, only 27.8% had an adequate nutritional status according to the Malnutrition Nutritional Assessment, while 46.2% were at risk of malnutrition and 26.0% were already malnourished (Gioulbasanis et al., 2011). Similarly, an observational study of 148 patients with advanced chemotherapy-treated NSCLC reported that the mean energy and protein intake was significantly lower than the recommended and 64.9% reported a high risk of malnutrition (Mohan et al., 2017).

3. The influence of nutritional status and body weight on NSCLC patients' outcomes

In term of disease prevention, high BMI has been related to a reduced risk of lung cancer, especially among smokers. Conversely, waist circumference and waist-hip ratio (WHR) were associated with increased lung cancer risk, regardless of sex, smoking status, follow-up time and tumor histology (Yu et al., 2018).

At disease diagnosis, poor nutritional status is an independent negative prognostic variable in NSCLC. Considering patients who underwent major surgical resection for early-stage NSCLC, malnutrition assessed by the nutritional risk index (NRI), appeared to be a predictive factor for postoperative complications (odds ratio (OR) = 0.965; $p = 0.015$), mainly pneumonia (Ramos et al., 2018), in agreement with other studies (Jagoe et al., 2001; Bagan et al., 2013). Of interest, underweight patients had significantly shorter disease-free survival (DFS) compared with overweight and obese patients (BMI of 25–30.0 kg/m^2 and a BMI ≥ 30.0 kg/m^2, respectively) (hazard ratio (HR) = 6.181; $p < 0.001$) (Ramos et al., 2018). These results were consistent with those reported by other recent retrospective studies exploring the effect of BMI on the survival of surgically-resected NSCLC patients. *Xie et al.* found that overall survival (OS) was significantly longer in overweight patients compared with underweight (HR = 2.24; $p = 0.013$), normal weight (HR = 1.58; $p = 0.022$) and obese groups (HR = 2.87; $p = 0.002$). In addition, overweight patients presented a significant lower rate of postoperative complications, such as respiratory failure, myocardial infarction and perioperative death (Xie et al., 2017). Similarly, a large retrospective analysis of surgically-resected NSCLC patients, demonstrated that the increase in BMI as a continuous variable represented a significant predictor for survival (HR = 0.977; $p = 0.03$) and was related to a significantly longer OS (OR = 0.98; $p < 0.01$) (Sepesi et al., 2017).

Further data about the potential protective effect of overweight/obesity on outcomes of NSCLC patients come from studies including chemotherapy. A retrospective analysis combining data from three consecutive first-line trials in advanced NSCLC, reported that obese patients had superior outcomes earlier on study compared with normal or overweight patients (HR = 0.86; $p = 0.04$) (Dahlberg et al., 2013). Among patients undergoing chemotherapy, the unintentional weight loss was an independent predictor of shorter OS in stage III and IV NSCLC (relative risk (RR) = 1.33; $p = 0.009$). The investigators also found that weight loss was associated with fewer symptomatic responses (44% *versus* 60%; $p = 0.004$), the delivery of fewer chemotherapy cycles (64% *versus* 78%; $p = 0.003$) and more treatment delays (9% *versus* 4%, $p = 0.04$) (Ross et al., 2004). These results are further supported by another retrospective study conducted in stage III NSCLC patients undergoing concurrent CT-RT, suggesting that weight loss was related to a shorter progression-free survival (PFS) ($p = 0.005$) and could impact on OS (HR = 1.869; $p = 0.008$) (Wei and Xie, 2017).

Focusing on chemotherapy-induced toxicity, the prospective analysis performed by *Arrieta et al.* found that NSCLC patients who were well-nourished experienced less toxicity after two cycles of cisplatin and paclitaxel, in comparison with malnourished patients (22% *versus* 31%, $p = 0.02$), mainly in terms of anemia, neuropathy and nausea (Arrieta et al., 2010). Another retrospective study in 425 stage IIIB NSCLC receiving concurrent CT-RT, detected significantly more grade 3 hematological and non-hematological toxicities, mainly acute radiation-induced esophagitis, and a higher rate of hospitalization (11.3% *versus* 6.4%, $p = 0.01$) in patients who lost weight during treatment than in patients who maintained or gained weight (Topkan et al., 2013).

4. The particular prognostic significance of weight preservation or gain

Although most of the attention in literature was focused on weight loss, small retrospective studies proposed also the weight gain as a potential prognostic factor in advanced NSCLC. In this regard, the largest analysis retrospectively examined data from three phase III clinical trials, including 2,301 stage IIIb or IV NSCLC patients. A significant association between superior median OS and > 5% weight gain during treatment (16.7 *versus* 10.7 months, $p < 0.001$) was reported. Likewise, patients who experienced > 5% weight gain reported statistically longer median PFS (6.9 *versus* 4.8 months, $p < 0.001$), superior overall response rate (50.8% *versus* 25.4%, $p < 0.001$) and disease control rate (91.5% *versus* 63.6%, $p < 0.001$), independently of their baseline weight (Patel et al., 2016). During split-course CT-RT in patients with locally advanced NSCLC, weight gain was significantly associated to a longer survival (3-year OS, 55% *versus* 31%, $p = 0.04$) and a prolonged distant-metastasis-free survival (24.6 *versus* 14.3 months, $p = 0.02$). Moreover, weight gain was the strongest prognostic factor for survival (HR = 0.5; $p = 0.04$) (Sher et al., 2013). Similar associations have been identified in a previous analysis (Gielda et al., 2011). However, additional prospective studies are needed to confirm weight gain as a prognostic marker for survival (Bonomi et al., 2017).

5. The detection of body composition derangements in patients with NSCLC

Overall, these recent data suggested that poor nutritional status is related to a shortened survival and may predict chemotherapy-induced toxicities. Interestingly, a higher BMI seems to carry a paradoxical relationship with better outcomes in surgically resected lung cancer, as well as in advanced NSCLC, introducing the intriguing clinical phenomenon of the *obesity paradox*. Additionally, small studies proposed that NSCLC patients who maintained or gained weight during treatment survived significantly longer. Therefore, the assessment of nutritional status may represent an early indicator of clinical benefit associated with tumor control and treatment tolerability.

Besides weight loss, body composition derangements, particularly the condition of sarcopenia (a wasting of lean mass and a loss of muscle strength (Muscaritoli et al., 2010)), were the prominent feature of NSCLC patients, despite normal BMI (Baracos et al., 2010). Computed tomography scanning is considered accurate and appropriate for skeletal muscle mass assessment in cancer patients (Mourtzakis et al., 2008), usually analysing the third lumbar vertebral level (L3), which was strongly correlated to whole body skeletal muscle mass (Martin et al., 2013). In this regard, *Baracos et al.* evaluated the loss of skeletal muscle applying this technique in a prospective cohort of 441 NSCLC patients. At disease diagnosis, the vast majority (92%) of NSCLC patients were within BMI ranges considered normal weight, overweight and obese. Nevertheless, analysis of body composition described a high prevalence of skeletal muscle wasting, with an overall prevalence of severe muscle depletion in 46.8%, regardless of the BMI category (Baracos et al., 2010). However, the L3 level is not always included in routine follow-up CT scans. A recent small study investigated the accuracy of including L1 level, rather than L3, to estimate the skeletal muscle mass for NSCLC patients (Recio-Boiles et al., 2018). They

Table 1
Correlation between skeletal muscle mass loss and outcome of medical treatments (chemotherapy, targeted therapy, immunotherapy) in advanced NSCLC.

Study	Number of pts		Body composition evaluation	Main results	Details
Sjoblom et al., 2017*Sjøblom et al.* (2017) Retrospective	424	Carboplatin-doublet (gemcitabine, pemetrexed, vinorelbine)	Total cross-sectional SMM area estimated from L3 CT scan	Significant correlation with toxicity	Dose/kg LBM of the non-platinum drug was significantly associated with hematological toxicity (p = *0.004*).
Sjøblom et al. (2015) Retrospective	153	Gemcitabine + vinorelbine	Total cross-sectional SMM area estimated from L3 CT scan	Significant correlation with toxicity	Higher dose/kg LBM of gemcitabine and vinorelbine were associated with grade 3-4 hematological toxicity (OR = 1.15, 1.01-1.29; *p = 0.018*; OR = 10.42, 1.36-80.0, *p = 0.024*).
Stene et al. (2015) Retrospective	35	Carboplatin-doublet (gemcitabine, vinorelbine)	SMM was evaluated by SMCA, estimated from L3 CT scan	Significant correlation with OS	● Maintaining or gaining SMM was a significant prognostic factors for OS (HR = 3.6, 1.1-12.5; *p = 0.040*). ● No association between low SMM and grade 3-4 toxicity. ● No association between maintaining or gaining SMM and grade 3-4 toxicity.
Sjøblom et al. (2016) Prospective	734	Carboplatin-doublet (gemcitabine, pemetrexed, vinorelbine) or gemcitabine + vinorelbine	SMM was evaluated by SMD and SMI, estimated from L3 CT scan	Significant correlation with OS	SMD was independently prognostic for OS (HR = 0.98, 0.97-0.99, *p* = 0.001), while SMI was not.
Cortellini et al. (2018) Retrospective	81	Carboplatin-doublet (pemetrexed, gemcitabine, paclitaxel/ bevacizumab, paclitaxel, etoposide, vinorelbine) or single agent (carboplatin, docetaxel, vinorelbine)	SMM was evaluated by SMD and SMI, estimated from L3 CT scan	Significant correlation with PFS and toxicity	● Low SMI was a predictor of shorter PFS (HR = 0.54, 0.31-0.93; *p* = 0.0278), while low SMD was not. ● A difference in hematological toxicity between pts with baseline low and non-low SMM was observed (*p = 0.0358*).
Arrieta et al. (2015) Prospective	84	Afatinib	SMM was evaluated by SMI, estimated from L3 CT scan	Significant correlation with toxicity	● A trend to poorer PFS and OS was observed in pts with low SMM compared with pts with no low SMM (6.1 ms *vs* 9.2 ms and 27.8 ms *vs* 39.5 ms). ● More dose-limiting toxicity in pts with low SMM and BMI < 25 kg/m^2 (71.4 *vs* 18.8%; *p = 0.0017*).
Rossi et al. (2018) Retrospective	33	Gefitinib	SMM was evaluated by SMI, estimated from L3 CT scan	Correlation with OS	● No association between SMM and treatment-response. ● Low SMM was a predictor of OS (*p = 0.035*).
Cortellini et al., 2019*Cortellini et al.* (2019) Retrospective	23	Nivolumab	SMM was evaluated by SMD and SMI, estimated from L3 CT scan	No significant correlation with survival/toxicity	● A trend of longer median PFS and median OS among pts with non-low SMM than those with low SMM. ● Higher incidence of immune-related adverse events of any grade in pts with non-low SMM.

Legend- Table 1: Pts, patients; CT, computerized tomography; HR, hazard ratio; LBM, lean body mass; ms, months; OR, odds ratio; SMM, skeletal muscle mass; SMCA, skeletal muscle cross sectional area; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; NS, not significant.

demonstrated that skeletal mass assessment at L1 was achievable and accurate with routine chest CT, and, as similarly reported for L3 (Baracos et al., 2010), BMI was not adequate for estimation of muscle mass with only a weak correlation (*r = 0.329*) (Recio-Boiles et al., 2018). Moreover, capturing serial images of the thorax is even more feasible in patients undergoing thoracic procedures and it has been described that muscle mass at the level of thoracic spine 12 (T12) and in the region of L3 is comparable (Nemec et al., 2017). Future studies focusing on the identification of the optimal level and cut-off for sarcopenia definition are necessary to improve the estimation of skeletal muscle loss in cancer.

6. The preeminent role of skeletal muscle mass loss in NSCLC

The loss of skeletal muscle mass represents an independent predictor of poor prognosis in several malignancies with ample supportive evidence (Villasenor et al., 2012; Levolger et al., 2015; Shachar et al., 2016). Among NSCLC patients, those with muscle mass depletion, even having a high BMI as sarcopenic obese patients, had a significantly worse outcome (HR = 4.2; $p < 0.0001$) (Prado et al., 2008). Focusing on patients with early-stage lung cancer, the available studies suggested that skeletal muscle loss is related to postoperative poor outcomes. The analysis of a retrospective cohort of 137 surgically-resected NSCLC patients described that 16/52 male (30.8%) and 22/38 female (57.9%) were sarcopenic, according to the pre-defined cut-off values. Patients with sarcopenia had a significantly worse outcome than those without sarcopenia (5-year-OS 72.8% *versus* 85.8%, $p = 0.028$). In addition, sarcopenia was a significant independent prognostic factor for poor survival (HR = 7.09; $p = 0.0008$) (Suzuki et al., 2016). In another study performed in 299 patients undergoing lobectomy, the volume of skeletal muscle area at T12 level normalized for height has been found to be inversely correlated with the 30-day mortality risk (OR = 0.77; $p = 0.036$) and with the length of hospital stay ($p = 0.019$) (Miller et al., 2018). Similarly, a retrospective study among 101 surgically-resected stage I NSCLC patients found that poor performance status was significantly associated with decreased in skeletal muscle mass ($p = 0.048$), using measurements at T12 level. Decreased skeletal muscle mass represented an independent prognostic factor for DFS (HR = 2.88; $p = 0.010$) and OS (HR = 3.82; $p = 0.0072$) (Takamori et al., 2018).

Among 734 advanced NSCLC patients, there was a significant correlation between increased skeletal muscle radiodensity, obtained by CT scan at L3 level, and longer OS (HR = 0.98; $p = 0.001$) (Sjoblom et al., 2016). Regarding correlation with medical treatment outcome, a cohort of 35 advanced NSCLC patients receiving three cycles of first-line platinum-based chemotherapy, were analysed for potential changes in muscle mass before and after treatment. Both the muscle mass maintenance and gain resulted in longer median OS (loss 5.8 months *versus* stable/gain 10.7 months, $p = 0.073$) and they were significant prognostic factors at the multivariate survival analyses (HR = 3.6; $p = 0.040$) (Stene et al., 2015). Besides the impact in terms of prognosis, emerging evidence suggest a significant association between lean body mass and toxicity from chemotherapeutic agents. In this regard, a retrospective analysis of 81 advanced NSCLC patients treated with first-line chemotherapy (platinum-based doublets or single-agent chemotherapy) reported that baseline low skeletal muscle mass was an independent predictor of PFS (HR = 0.54; $p = 0.0278$) and was associated with a significant increase of any grade hematological toxicities ($p = 0.0358$) (Cortellini et al., 2018). A pooled analysis including two randomized controlled trials comparing first-line carboplatin-based chemotherapy, suggested that the dose of non-platinum agents normalized per lean body mass (estimated from diagnostic CT scans at L3) was a significant independent predictor of severe (grade 3–4) hematologic toxicity (Sjoblom et al., 2017). These findings are consistent with a previous analysis, which observed that higher drug doses per kilogram of lean body mass were related to increased risk of hematologic toxicity in NSCLC patients treated with gemcitabine (OR = 1.15; $p = 0.018$) and vinorelbine (OR = 10.42; $p = 0.024$) (Sjoblom et al., 2015). A possible explanation is that lean body mass, containing several metabolic tissues, is associated with the volume of distribution for non-lipophilic drugs and, therefore, it may impact on chemotherapy clearance and toxicity (Morgan and Bray, 1994). The correlation between skeletal muscle mass loss and chemotherapy outcome in advanced NSCLC is reported in Table 1. Collectively, these data highlight the importance of baseline body composition evaluation and serial monitoring of muscle mass changes in daily clinical practice to improve the prognostic estimation and the individualization of chemotherapy dose. The decrease in toxicity frequency and severity is of considerable importance, particularly in advanced settings and among patients with severe comorbidities.

7. The impact of nutritional status and body composition in the era of the new therapies in NSCLC

The introduction of targeted agents and immune-checkpoint inhibitors radically changed the therapeutical perspectives and the prognosis of a proportion of NSCLC patients. Considering their relatively recent availability in clinical practice, only limited data focusing on the assessment and impact of nutritional status on the outcome of NSCLC patients treated with these innovative therapies are present. A retrospective analysis, conducted in a small cohort of 65 advanced NSCLC patients, compared body composition measures through CT scans at L3 level between patients receiving molecular targeted therapy (EGFR and ALK TKI) and cytotoxic chemotherapy. The skeletal muscle loss was significantly lower in patients receiving molecular targeted therapy than in patients treated with chemotherapy ($p = 0.03$), highlighting potential differences in term of chemotherapy-related adverse events, such as fatigue, loss of appetite, nausea, vomiting, and diarrhea which may negatively affect food intake and physical activity, contributing to a more relevant loss of lean body mass (Kakinuma et al., 2018). Regarding the impact in terms of prognosis, a retrospective study conducted by *Park et al.* in a cohort of 630 EGFR-mutant NSCLC patients treated with EGFR TKI (gefitinib or erlotinib), identified the pre-treatment nutritional status as a prognostic marker. In detail, at multivariable analysis, a BMI $< 18.5\,kg/m^2$ and a prognostic nutritional index (PNI, calculated based on serum albumin concentration and total lymphocyte count in the peripheral blood) < 45 were independent predictors for a shorter PFS and OS (Park et al., 2016). Similarly, previous retrospective studies suggested that BMI and body surface area (BSA) correlated with PFS in EGFR-mutant NSCLC patients treated with gefitinib (Ichihara et al., 2013; Sun et al., 2016a), in contrast with another analysis which did not reported any difference in clinical outcome according to BSA and BMI (Imai et al., 2017).

Besides BMI and BSA, weight loss may represent a useful tool to assess and monitor the changes in nutritional status in cancer patients (Davies, 2005). In this regard, *Lin et al.* reported that weight loss at diagnosis had an adverse impact on survival in 75 EGFR-mutant NSCLC patients receiving first-line gefitinib or erlotinib. In particular, patients without weight loss had a significantly longer median PFS (12.4 *versus* 7.6 months, $p < 0.001$) and OS (28.5 *versus* 20.7 months, $p = 0.006$) than those with weight loss. Moreover, at multivariate analysis, weight loss at presentation was identified as a negative independent prognostic factor for both PFS (HR = 0.315; $p < 0.001$) and OS (HR = 0.384; $p = 0.011$) (Lin et al., 2018).

Focusing on body composition, *Arrieta et al.* emphasized the potential impact of a CT-detected low lean body mass in advanced NSCLC patients receiving afatinib after progressing to prior chemotherapy. Although the median BMI was $24\,kg/m^2$, a high prevalence of sarcopenia (68.8%) was detected in the 84 enrolled patients. Poor nutritional status was associated with a higher risk, although without a strong statistical significance, of developing severe afatinib-induced gastrointestinal toxicity (HR = 3.308; $p = 0.047$), as well as it represented an independent risk factor for the occurrence of dose-limiting toxicity (HR = 4.14; $p = 0.006$). In particular patients with both a low lean body mass and BMI developed more dose-limiting toxicity (71.4% *versus* 18.8%, $p = 0.0017$). Moreover, in sarcopenic patients was described a not-statistically significant trend towards poor PFS (6.1 *versus* 9.2 months) and OS (27.8 *versus* 39.5 months) compared with patients without sarcopenia (Arrieta et al., 2015). A small retrospective study, including 33 EGFR-mutant NSCLC patients treated with gefitinib, showed that sarcopenia (defined as low skeletal muscle index ≤ 39 cm^2/m^2 for women and ≤ 55 cm^2/m^2 for men) represents a negative prognostic indicator for OS ($p = 0.035$), introducing the idea of modulating TKI dose in sarcopenic patients (Rossi et al., 2018). Molecular targeted therapies, widely used in different types of malignancies, are administered in fixed dose, regardless of patient's anthropometrical variables such as weight and body surface. Moreover, if patients are malnourished and/or sarcopenic they could have alterations in drug metabolism due to a lower lean body mass and, therefore, a higher TKI exposure with an increase risk of developing severe toxicities (Arrieta et al., 2015). As a possible explanation, the involuntary weight loss may represent the most visible manifestation of cachexia, which is strongly related to increased levels of several proinflammatory cytokines, such as interleukin-6 (IL-6) (Diakos et al., 2014). Interestingly, through the interaction with their specific receptors, IL-6 and EGF share common downstream signaling pathways, as the transducers and activators of transcription 3 (STAT3), eventually mediating cell proliferation and survival. Considering this, IL-6 signaling may up-regulate STAT3 pathway, inducing tumor proliferation, immunosuppression and TKI resistance (Makino et al., 2017).

Regarding immunotherapy, only few preliminary studies evaluated the nutritional status in NSCLC patients.

In the context of a retrospective analysis including 20 not-oncogene addicted NSCLC treated with nivolumab, low pre-treatment PNI was significantly associated with early nivolumab termination both in the overall cohort ($p = 0.016$) and in the patients subgroup with performance scores of 0–1 ($p = 0.028$) (Nakao et al., 2017). Additionally, a more recent retrospective study performed in a cohort of 23 NSCLC patients treated with second-line nivolumab, suggested that there was a trend towards a longer median PFS and median OS among patients with non-low skeletal muscle mass than those with low skeletal muscle mass, despite the absence of statistical significance ($p = 0.0560$ and $p = 0.2866$, respectively) (Cortellini et al., 2019). In the light of these results, nutritional status may affect the immune response and clinical outcomes and thus should be included among the potential marker for selecting proper candidates for immunotherapy.

The correlation between skeletal muscle mass loss and outcome of targeted therapy and immunotherapy in advanced NSCLC is reported in Table 1. To summarize, the assessment of first-of-all pre-treatment nutritional status and body composition should be promoted in order to identify NSCLC patients with low lean body mass potentially candidate to innovative treatment options, as targeted therapy and immunotherapy. Moreover, additional studies need to explore dose adjustment according to body composition, especially in therapies that are administered at fixed dose.

8. Mechanisms underlying NSCLC muscle wasting

The malnutrition in NSCLC patients is driven by a combination of reduced food intake and metabolic derangements, which may be either host- or tumor-derived. However, the molecular mechanisms underlying NSCLC-related muscle wasting have not yet been fully elucidated. The candidate signaling networks involved in lung cancer-induced cachexia in three different cell types (muscle cells, adipocytes and adipose tissue-derived mesenchymal stem cells) and the proposed targeting approaches are presented in Fig. 1.

Current evidence focused the attention on the role of the muscle protein degradation, together with impaired muscle protein synthesis and defective myogenesis. Furthermore, alterations in energy metabolism involving mitochondrial dysfunctions have been implicated in the wasting process (Johns et al., 2013). Indeed, Lewis lung carcinoma (LLC) bearing mouse, a well-established and widely used model in lung cancer-induced cachexia, initially showed metabolic disorders in mitochondria function and only at week 4 (the last week of the experiment) first signs of cachexia. Accordingly, the transcriptomic analysis throughout this 4-week period reported that there was an increase in gene expression alteration of those genes belonging to inflammatory pathways, oxidative metabolism and protein ubiquitination, suggesting the possibility to screen the cachexia development process (Blackwell et al., 2018).

Toll-Like Receptor 4 (TLR4) is a critical transmembrane receptor for the initiation of immune response and represents a crucial initiator of cachexia phenotype [Fig. 1a]. LLC-bearing $TLR4^{-/-}$ mice suffered a less severe muscle waste, abrogating activation of downstream cascades like p38 MAPK, NF-κB and ubiquitin ligases UBR2 and atrogin1, C/EBPβ and autophagy. Furthermore, deletion of TLR4 inhibited the increase of the muscle waste-inducing circulating cytokines (TNF-α and IL-6). Similarly, *in vitro* culture of C2C12 myotubes with LLC conditioned medium (LCM)-containing cachexins triggered the TLR4 axis and downstream signaling in less than an hour in an immune response-independent manner (Zhang et al., 2017a). Extracellular vesicles (EV) have emerged as a new mean for intercommunication between cancer cells. EV-associated with heat shock protein 70 and heat shock protein 90 are produced by LLC-bearing mice and activate TLR4 and p38 MAPK, promoting muscle degradation and increase of circulating cytokines (Zhang et al., 2017b).

Interestingly, genetic ablation of TLR4 in LLC-bearing mice, but also pharmacological inhibition by atorvastatin, a HMG-CoA reductase inhibitor, downregulated adipose tissue atrophy and p38 MAPK activation, as well as other cachexia markers, eventually increasing survival (Henriques et al., 2018). IMO-8503 that is a TLR-7, 8 and 9 antagonist, protected LLC-bearing mice from lean muscle loss, while downregulating cachexia-inducing factors like Pax-7 and reversing the negative regulation on MyoD. Interestingly, IMO-8503 had no effect on tumor growth, but downregulated caspase-3 and PARP cleavage in myoblasts (Calore et al., 2018). Mechanisms counteracting cachexia development, include the activation of ghrelin receptor (mediated by anamorelin and macimorelin) and β receptor (mediated by espindolol), eventually inducing the anabolic process.

In a cachectic mouse model of NSCLC, a reduced peroxisome proliferator-activated receptor-α (PPARα)-mediated ketone production in liver was observed, which resulted in low production of ketones and elevated glucocorticoids and subsequently into muscle mass loss and gluconeogenesis [Fig. 1a]. However, treatment with fenofibrate, a PPARα agonist, re-promoted ketone generation ameliorating cachexia phenotype *in vivo* (Goncalves et al., 2018). Another cachexia mechanism involves poly (ADP-ribose) polymerases (PARP) 1/2 [Fig. 1a]. Their genetic ablation in lung cancer-induced cachexia murine models ameliorated several points of the cachectic phenotype decreasing tumor size and downregulating oxidative stress and protein degradation (Chacon-Cabrera et al., 2017). An epigenetic drug, valproic acid, a histone deacetylase (HDAC) inhibitor, decreased the loss of muscle mass, by inhibiting C/EBPβ binding to ubiquitin-ligase MAFbx/atrogin promoter, but also it favoured protein anabolism by inducing Akt phosphorylation (Sun et al., 2016b). Similarly, AR-42, another epigenetic HDAC inhibitor restrained muscle waste in LLC models (Tseng et al., 2015).

LLC-origin medium contains exosomes, which were able to initiate lipolysis in 3T3-L1 adipocytes [Fig. 1b]. Treatment of LLC-cultured 3T3-L1 adipocytes with the sphingomyelinase inhibitor GW4869, which is known to abrogate exosomes generation, showed that exosome release and exosome markers were significantly downregulated. Similar findings were observed *in vivo*, where GW4869 treatment inhibited the browning of adipose tissue (lipolysis) and the onset of cachexia

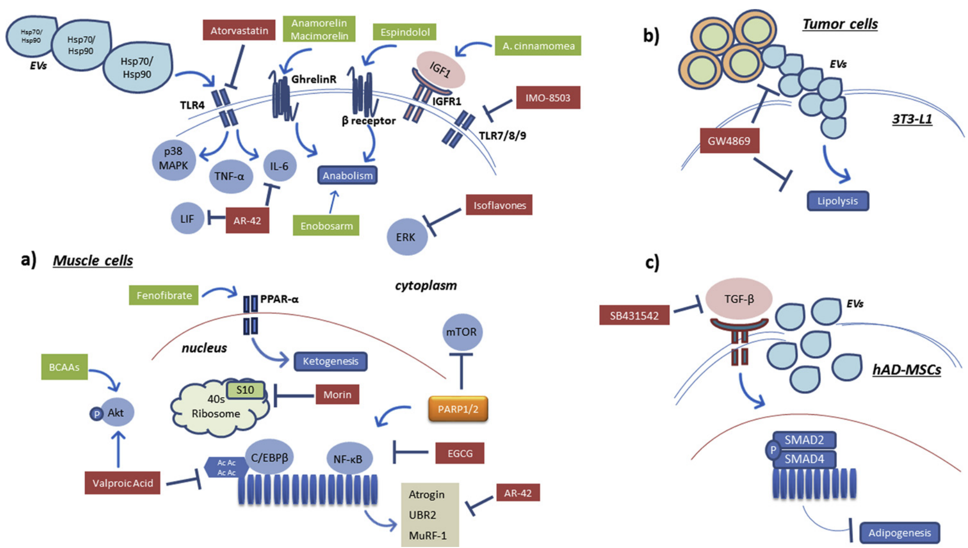

Fig. 1. Signaling network involved in lung cancer-induced cachexia syndrome.
Current understanding of the activated signaling cascades and downstream mediators in cachexia.
a) Activation of different transmembrane toll-like receptors (TLRs) on the surface of muscle cells induces catabolic events mainly protein degradation by activating muscle-specific ubiquitin ligases and promotes the generation of pro-inflammatory cytokines. Similarly, in the nucleus, poly(ADP-ribose) polymerase-1 (PARP-1), upregulates the expression of ubiquitin ligases as well. On the other hand, Ghrelin and β receptors in the presence of appropriate agonists could promote anabolism.
b) Extracellular vesicles derived from tumor cells intrude into the 3T3-L1 adipocytes and enhance lipolysis, while c) exosomes entering into human adipose tissue-derived mesenchymal stem cells (hAD-MSCs) activate TGF-β axis that leads to SMAD2/SMAD4 translocation to nucleus and eventually to adipogenesis inhibition. Different potential treatment approaches might utilize the following commercially available targeted agents and naturally produced compounds: Atorvastatin, IMO-8503: TLR4 inhibitor, TLR7/8/9 inhibitor, Valproic Acid, AR-42: histone deacetylase inhibitor, GW4869: sphingomyelinase inhibitor, SB431542: TGF-β inhibitor, Anamorelin, Macimorelin: Ghrelin receptor agonists, Espindolol: β-receptor agonist, Enobosarm: selective androgen receptor modulator, Fenofibrate: PARP-1 agonist, A.cinnamomea, BCAAs, Morin, EGCG, Isoflavones: natural anti-cachectic compounds.
Legend - Fig. 1: Hsp70/Hsp90, heat shock protein 70/heat shock protein 90; IGF-1, Insulin-like growth factor 1; p38 MAPK, p38 mitogen-activated protein kinases; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; LIF, leukemia inhibitory factor; ERK, extracellular signal-regulated kinases; mTOR, mechanistic target of rapamycin; PPAR-alpha, peroxisome proliferator-activated receptor alpha; C/EBP-β, CCAAT/enhancer-binding protein beta; NF-κB, nuclear factor-kappa beta; TGF-β, transforming growth factor-beta; MuRF1, muscle RING-finger protein-1; UBR-2, ubiquitin protein ligase E3 component N-recognin 2; EVs, extracellular vesicles; BCAAs, branched chain amino acids; EGCG, epigallocatechin-3-gallate.

phenotype in LLC-bearing mice (Hu et al., 2018). Integration of NSCLC-derived exosomes by human adipose tissue-derived mesenchymal stem cells (hAD-MSCs) resulted in adipogenesis downregulation [Fig. 1c]. TGF-β signaling, which regulates the expression of numerous target genes, was activated by secreted NSCLC exosomes with concurrent translocation of SMAD4 in the nucleus of hAD-MSCs. Interestingly, TGF-β signaling inhibition by SB431542 abrogated the hAD-MSCs adipogenesis downregulation mediated by NSCLC exosomes (Wang et al., 2017).

Parental $KRAS^{G12D}$ models sufficiently preserved their body composition whereas $Gp130^{F/F}KRAS^{G12D}$ is a KRAS-induced lung cancer mouse model with a hyperactive IL6/STAT3 signaling and cachexia phenotype including muscle-adipose tissue waste and weight loss. The use of an anti-IL-6R agent reduced the cachexia phenotype suggesting a strong role of STAT3 (Miller et al., 2017).

Endoplasmic reticulum upon stress conditions triggers unfolding protein response pathways, preserving muscle mass and cachexia-free status in LLC-bearing mice. Its role in the homeostasis of body composition was demonstrated upon its inhibition by 4-phenylbutyrate, which reversed this safe state inducing muscle wasting, by activating protein ubiquitination and autophagy (Bohnert et al., 2016).

In conclusion, TLR signaling-mediated increase of different proinflammatory cytokines and transcription factors, as well as the upregulation of protein degradation mechanisms such as cleaved caspases and ubiquitin ligases, seem to contribute decisively to the development of cachexia. Further *in vitro* and *in vivo* studies exploring the anti-cachectic effect of TLR inhibitors (Atorvastatin, TAK-242, IMO-8503) might generate more solid insights, paving the way for introduction of these molecules into clinical studies.

9. New scenarios and opportunities for prevention and treatment of muscle loss

Given the multifactorial complex pathogenesis of muscle wasting in NSCLC, both preventive and therapeutical options should be part of an integrated support program, based on different and multidimensional approaches, including early, targeted and specialized nutritional supports, personalized exercise programs and pharmacological agents (Molfino et al., 2016). In particular, ongoing research exploring the molecular mechanisms underlying muscle loss in NSCLC allowed the identification of some potential therapeutic targets and promising agents. Although OS was not a primary endpoint in clinical studies testing these agents, important proofs of activity are already available for some of them. A summary of the main clinical trials exploring pharmacological management of muscle loss in NSCLC is reported in Table 2.

Anamorelin, an oral selective ghrelin-receptor agonist, has been proposed as a safe and effective treatment option for sarcopenia in cancer patients. Ghrelin is the natural ligand for the G-protein-coupled ghrelin receptor that, once activated, has anabolic and appetite-stimulating properties, partly due to a transient increase in growth hormone and insulin-like growth factor (IGF-1) (Garcia et al., 2015). Two randomized, double-blind, placebo-controlled, phase III trials (ROMANA 1 and 2) demonstrated that anamorelin significantly increased lean body mass in advanced NSCLC patients. In detail, over the 12 weeks study period, lean body mass increased in patients treated with anamorelin compared with placebo in ROMANA 1 (median increase 0.99 kg *versus* -0·47 kg, $p < 0.0001$) and ROMANA 2 (0.65 kg *versus* -0·98 kg, $p < 0.0001$). The most common treatment-related adverse events were hyperglycemia, diabetes and gastrointestinal disorders, mainly grade 1 or 2 nausea (Temel et al., 2016). These findings are consistent with the recent results of randomized, double-blind, placebo-controlled, multicenter study conducted by *Katakami et al.* among 174 unresectable stage III/IV NSCLC patients. Particularly, they found that patients in Anamorelin group presented a significant increase in lean body mass compared with the placebo group ($p < 0.001$) (Katakami et al., 2018). Other novel ghrelin agonists, such as macimorelin, are currently under investigation (Dingemans et al., 2014).

Another agent for the prevention and treatment of lean body mass loss is enobosarm, an orally nonsteroidal selective androgen receptor's modulator (SARM). SARM selectively activates the skeletal muscle androgen receptor, avoiding the androgenic steroid-related adverse side

Table 2
Summary of the main clinical trials exploring pharmacological management of muscle loss in NSCLC.

Study	Study type	Number of pts	Treatment	Main results
Temel et al. (2016) ROMANA 1 and ROMANA 2	Phase III, randomized, double-blind	ROMANA 1: 484 ROMANA 2: 495	Arm 1: Anamorelin (100 mg) Arm 2: Placebo x 12 weeks	Increase in LBM: ROMANA 1: +0.99 kg vs -0,47 kg ($p < 0.0001$) ROMANA 2: +0.65 kg vs -0.98 kg ($p < 0.0001$)
Katakami et al. (2018) ONO-7643-04	Phase III, randomized, double-blind	174	Arm 1: Anamorelin (100 mg) Arm 2: Placebo x 12 weeks	Increase in LBM: +1.06 kg vs -0.50 kg ($p < 0.001$)
Crawford et al. (2016) POWER 1 and POWER 2	Phase III, randomized, double-blind	300	Arm 1: Enobosarm (3 mg) Arm 2: Placebo x 21 weeks	Preliminary data: POWER 1: increase in LBM and stair-climb power POWER 2: increase in LBM
Stewart Coats et al. (2016) ACT-ONE	Phase II, randomized, double-blind	87	Arm 1: High dose Espindolol (10 mg bd) Arm 2: Placebo Arm 3: low dose Espindolol (2.5 mg bd) x 4 weeks	Increase in LBM: +1.76 kg vs +0.57 kg vs +0.25 kg ($p = 0.012$)

Legend – Table 2: LBM, Lean Body Mass LBM; BD, twice daily.

effects. Phase III studies of enobosarm in NSCLC patients initiating first-line chemotherapy are the POWER 1 (with platinum-taxane) and the POWER 2 (with platinum-non-taxane) trials. Preliminary data reported both an increase in muscle mass and stair-climb power in the POWER 1 trial, while in the POWER 2 trial only a significant increase in muscle mass (Crawford et al., 2016).

In advanced NSCLC patients, the ACT-ONE, a multicentre, randomized, double-blind, placebo-controlled phase II trial, suggested that espindolol, a novel non-selective β receptor blocker with central serotonin antagonism and partial β2 receptor agonist effect, might antagonize cancer cachexia, reducing catabolism, fatigue and thermogenesis and increasing anabolism. An absolute median lean body mass gain of 1.76 kg was detected in the espindolol group compared with a gain of 0.57 kg in the placebo group ($p = 0.012$). Nevertheless, appropriate phase III clinical studies are necessary to confirm the efficacy of espindolol in treating muscle wasting in NSCLC patients (Stewart Coats et al., 2016).

Evaluating candidate markers able to help clinicians to identify those patients more likely to develop cachexia, the angiotensin-converting gene polymorphism has been independently associated with changes in body composition and muscle strength in advanced cancer patients, including NSCLC (Vigano et al., 2009).

Of interest, more recent data suggest anti-microRNAs as another potential therapeutic option to counteract muscle loss in cancer, but their real therapeutic role deserves further investigations (Molfino et al., 2016). Another hypothesis to prevent cancer-related muscle wasting, particularly in the immunotherapy era, is represented by the modulation of gut microbiota currently under study in a series of pre-clinical models (Varian et al., 2016).

Considering the complex scenario, a single therapy is likely to be insufficient alone to reverse muscle wasting typically affecting oncological patients. This underlies the need of integrating pharmacologic agents into an early multimodal approach able to manage the multi-faceted aspects of this concomitant disease (Aversa et al., 2017).

10. Nutritional interventions as an essential step for a multimodal approach against cancer-related muscle wasting

An early, adequate and comprehensive nutritional support, based on the tailored energy and proteins intake needed for a specific patient (according to the gender) is necessary to slow and ideally antagonize the NSCLC-related muscle wasting process (Frega et al., 2019). This implies that every single patient should be nutritionally assessed and monitored since cancer diagnosis (Kiss, 2016; Aversa et al., 2017). In detail, specific attention should be paid to the role of dietary protein intake to maintain muscle mass by stimulation of protein synthesis, according to the recommendations of the recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, which underline the increased protein needs (1–1.5 g/kg/day) in cancer patients (Arends et al., 2017). Considering that the protein synthesis is responsive to the dietary proteins, NSCLC patients present a normal whole-body anabolic protein response to hyperaminoacidemia, despite they had a considerable insulin resistance, a commonly proposed mechanism in attenuating protein anabolism to muscle wasting in cancer. These results suggested that an appropriate good quality protein intake at every meal is necessary to induce whole-body anabolism in NSCLC patients (Winter et al., 2012). In particular, branched chain amino acids (BCAAs) have been shown to mitigate the muscle loss in patients with NSCLC, potentially by stimulating protein synthesis signaling at the level of Akt (as part of the anabolic PI3K/Akt/mTOR pathway) and attenuating protein degradation (Op den Kamp et al., 2013).

Several studies have identified different natural substances that could be of benefit for NSCLC-related cachexia [Fig. 1]. Among them, the introduction of a flavonoid, morin, into the diet of LLC-bearing mice reversed muscle weight loss and myofiber size reduction, as well as reduced tumor weight. However, this anti-cachectic effect can be indirectly mediated by a suggested anti-oncogenic function *in vitro*, due to the binding to ribosomal protein S10 (Yoshimura et al., 2018). The potential utility of isoflavones was also proved in a similar study where diet with isoflavones protected LLC-bearing mice from muscle mass loss, while downregulating ERK phosphorylation that has been associated with muscle waste (Hirasaka et al., 2016). *Antrodia cinnamomea* is a medically used fungus and exerted anti-cachectic function in LLC bearing mice by activating IGF-1 and inhibiting cytokine production and muscle-wasting factors such as FoxO3, MuRF-1 and MAFbx/atrogin (Chen et al., 2018). Another natural compound, (-)-Epigallocatechin-3-O-gallate, a catechin of green tea not only demonstrated anti-oncogenic activity *in vitro* and *in vivo*, but also abrogated muscle waste restricting body weight loss while simultaneously negatively regulating the expression of NF-κB and its downstream muscle-specific ubiquitin ligases MuRF-1 and MAFbx/atrogin, eventually reducing inflammation (Wang et al., 2011).

Overall, an early and structured multimodal nutritional management, including targeted evidence-based nutritional intervention, physical activity (according to the exercise capacity of the patient) and pharmacological agents, is mandatory to successfully prevent and manage NSCLC-related muscle wasting. Future well-designed trials are needed to validate the role of nutritional support as part of a multimodal care approach, combining this intervention to the use of biological agents (Aversa et al., 2017; de van der Schueren et al., 2018).

11. Conclusion and suggestions for future research

Increasing evidence is available to support the role of nutritional status on patients' quality of life, morbidity and mortality. Particularly, muscle mass loss is related to reduced survival and an increased likelihood of dose-limiting anticancer-related drug toxicity. In this regard, its detection and monitoring may allow more accurate drug dose calculation than body surface area or flat-fixed dosing and could be helpful for evaluating the risk assessment of anticancer treatment, even in NSCLC patients receiving targeted therapy and immunotherapy. Our findings provide insight into the multifactorial nature of muscle mass wasting in NSCLC patients, suggesting the multidirectional approach, selectively tailored, rather than a single potential intervention, may be of vital importance on the way of success. In detail, it requires early and careful pre-treatment evaluation of the specific patient's nutritional status by imaging technologies for quantification of muscle mass. However, currently, individual nutritional status is overlooked, and patients are only screened for body weight. In addition, many patients are evaluated too late, when a high percentage of body weight and muscle has already been lost and the severe sarcopenia stage (like the refractory stage of cancer cachexia) has already occurred, which cannot be fully reversed by conventional nutritional support alone. Hence, there is a strong need of implementing early multi-modal treatment, as it happens in the MENAC trial (Solheim et al., 2018), to preserve or increase muscle mass, encompassing nutritional, exercise and pharmacological interventions, on a background of tailored oncology care, in order to prevent or minimize muscle loss and thus, improve anticancer treatment tolerance and efficacy in NSCLC patients.

Author contributions

Conception and design: All authors.

Manuscript writing: Ilaria Trestini, Anastasios Gkountakos, Sara Pilotto, Emilio Bria.

Drafting the article and revising it for important intellectual content: All authors.

Final approval of manuscript: All authors.

Declaration of Competing Interest

S.P. received honoraria or speakers' fee from Astra-Zeneca, Eli-Lilly, BMS, Boehringer Ingelheim, Roche, MSD and Istituto Gentili, outside the submitted work. E.B. received honoraria or speakers' fee from MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis, and Roche, outside the submitted work. A.S. received speaker fee from Astra-Zeneca and Ypsen, outside the submitted work. All remaining authors have declared no conflicts of interest.

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