Editorial

Sarcopenia in resected non-small cell lung cancer: let's move to patient-directed strategies

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Sarcopenia is a loss of skeletal muscle mass, quality and function associated with poor nutrition, ageing, sedentarity, and chronic diseases, in particular chronic obstructive pulmonary disease (COPD) and malignancies (1). In cancer, the association of sarcopenia with poor nutrition, lipolysis, inflammatory status and vicious metabolic cycles promote the occurrence of cachexia, a nutritional and psychological condition considered as the direct cause of death in at least 20% of patients with advanced cancers (2-4).

Cachexia is a wasting syndrome occurring even in the presence of an adequate caloric intake, which affects more than 80% of patients with gastric and pancreatic cancer, approximately 50% of those with lung, prostate and colon malignancies, and around 40% of patients with breast cancers and leukemias (2-4). Thus, it is fundamental to detect early markers of tissue wasting to develop strategies aiming to reverse or, at least, counteract metabolic alterations supporting cancer progression or recurrence, and to improve quality of life. For this purpose, as we will briefly explain, understanding the metabolism of tumor cells, their micro-environment, and the induced distant metabolic effects, is fundamental to develop new strategies that may improve results of current therapies (4-7).

The prognostic significance of sarcopenia in patients with resectable non-small cell lung cancer (NSCLC) is a new subject of interest, since the recent works of Suzuki *et al.* (8) on a population of 90 patients undergoing sublobar or lobar resection, and ours reporting on 240 patients who had undergone pneumonectomy for NSCLC (9). In that study, we found that body mass index (BMI) ≤25 kg/m^2 and sarcopenia affected short and long term outcome in an independent manner; we defined sarcopenia as total psoas cross-sectional area at third lumbar vertebra (L3) level ≤33rd percentile of the studied population, on a sex-based distribution (9). The impact on survival of sarcopenia in patients treated by lobectomy for NSCLC has been confirmed in the recent series of by Nakamura *et al.* which has been published in a recent issue of the *Journal of Thoracic Oncology* (10). These authors reported, in a series of 328 lobectomies for NSCLC, that sarcopenia (observed in as much as 55.8% of cases) was an independent negative prognostic factor of post-operative morbidity and mortality as well as of long-term survival.

Globally, the prevalence of sarcopenia appears higher in men, increases with age, and is more frequently associated with lower BMI (3). As it has been reported in other cancers (11), sarcopenia is associated in resected lung cancers with longer hospital stay, occurrence of postoperative complications and mortality (9,12). This impact of sarcopenia—as an expression of pre-cachexia—on postoperative outcome is in agreement with previous works reporting the influence of lower BMI on post-

resection complications. In a recent large French cohort from the EPITHOR project dealing with 19,635 patients treated by lobectomy, underweight patients (BMI <18.5 kg/m^2, n=857) experienced more pulmonary, surgical (air leaks and bronchial dehiscence) and infectious complications than normal and overweight patients (13). In contrast, obesity (BMI ≥30 kg/m^2) was not associated with increased incidence of postoperative complications, except for arythmia, deep venous thrombosis and pulmonary embolism (13). Very recently, we also found that lower BMI is also associated with occurrence of post-pneumonectomy respiratory failure (14).

It is noteworthy that sarcopenic obesity (SO), which is strongly associated with chronic inflammation, is also associated with an increase in the risk of postoperative complications in colorectal, gastric and pancreatic cancers (15). According to these authors, around one in four cancer patients with BMI ≥30 kg/m^2 would be sarcopenic. However the prevalence of SO is variable in different series and it is likely to depend on ethnicity, sex, age, stage of disease, associated comorbidities, and, probably more importantly, cancer type. Prevalence in resectable lung cancer has been poorly investigated so far, but we speculate that "paradigms" differ from a type of cancer to another, due to different risk factors and tumor-promoting factors.

Sarcopenia appears also as a strong and independent predictor of poor long-term survival in resected NSCLC: in our series, the 5-year survival rate after pneumonectomy was 19.6% in sarcopenic patients and 34.8% in non-sarcopenic patients (P=0.029) (9). Similarly, in the series of Nakamura *et al.* (10), 5-year survival rate after lobectomy was 61% in patients with sarcopenia and 91% in those without (P<0.001). Importantly, sarcopenia appears also as an independent prognostic factor for resected stage I: in the series of Suzuki on 90 operated patients, the 5-year survival rates were 72.8% and 85.8% in sarcopenic and non-sarcopenic subjects, respectively (P=0.028; with an hazard ratio as high as 7.09 and a P value of 0.0008 on multivariate analysis) (8).

Sarcopenia poses a multitude of questions about definition, methods of calculation and measure (3), as well as about possible mechanisms. Criteria should consider sex, age, height and ethnicities. Based on consensus definition of the European Working Group on Sarcopenia in Older People (EWGSOP) (1), the definition is: a low muscle mass, (e.g., >2 standard deviations below that mean measured in young adults of the same sex and ethnic background); and either: a low gait speed (e.g., a walking speed below 0.8 m/s in the 4-m walking test), or a low muscular strength (e.g., grip strength: <30 kg in males, <20 kg in females). Definition of severe sarcopenia would require the presence of all these three conditions. Of note, other methods of calculation have been proposed and even the concept of a cut-off determination is discussed: for example, Miller *et al.* did not consider cutoff nor separated patients into quartiles, considering that muscle mass is a continuous variable (12), allowing speculation that on an individual-based analysis, even slight variations could have an impact on outcome.

Sarcopenia is often assessed by measure of as the total psoas area recorded at L3 level on computed tomography (CT) scan, but other methods have been proposed, including the measure of skeletal muscle area at T12, L1 or L3 level with normalization by square of height, the so-known skeletal muscle index (SMI, cm^2/m^2). This method of calculation has been employed by Prado *et al.* to study SO (16). The cut-offs proposed were: ≤52.4 cm^2/m^2 in men, and ≤38.5 cm^2/m^2 in women, because of the frequent different distribution of muscular tissue, bone and fat between sexes. Five years ago, Martin *et al.* (17), extended Prado's data set to include non-obese patients, and indicated SMI thresholds for sarcopenia according to sex and BMI categories: <41 and <43 cm^2/m^2 in normal weight (BMI <25 kg/m^2) women and men, respectively, and <53 in overweight women and men. In the recent report of Nakamura *et al.* (10), cut-offs of height-normalized total psoas area at L3 level were 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women: these cut-off were adapted to Asian population.

Although CT measurement are more and more employed in assessment of sarcopenia, as outlined by Nakamura *et al.* (10), other methods exist, including dual x-ray absorptiometry (DEXA) and bioimpedance analysis (BIA) which allow determination of body composition, and assessment of fat and lean mass. Although DEXA has been longtime considered as the gold standard, it has been shown that the determination of total-body skeletal muscle mass can be easily and accurately assessed also by simple anthropometric measurements (18). Mid-arm circumference and tricipital fold allow determination of mid-arm muscular area (MAMA), and sex-corrected MAMA (scMAMA); height-indexed total muscular mass (hiTMM) may be derived by a simple equation: hiTMM = height (cm) × (0.0264 + 0.0029 × scMAMA) (19).

A serious problem for the interpretation of sarcopenia results from the lack of knowledge about its occurrence, and the evolution of muscle (and fat) loss in the months or weeks

preceding or following surgery. First, it is fundamental to distinguish patients who are naturally lean (and sometimes sarcopenic, especially in the elderly) from those who lost weight because of cancer development or recurrence. Secondly, ideally not only pre-surgery sarcopenia but also pre-disease sarcopenia should be taken into account; thirdly, post-treatment occurrence of sarcopenia should be also recorded. Takamori *et al.* (20) identified 31 patients (30.7%) among 101 individuals who underwent lobectomy for stage I NSCLC as having decreased SMI in the year following surgery. These patients had a significantly shorter disease-free survival (DFS) (P<0.001) and overall survival (OS) (P<0.001) than non-sarcopenic patients. At multivariate analysis, decreased SMI was found to be an independent prognostic factor for DFS (P=0.010) and OS (P=0.0072) and independent risk factors for skeletal muscle loss included poor PS ≥1 and obstructive ventilatory impairment (20). Obviously, it is not clear if post-surgery undetectable residual disease was at the origin of muscle waste or if the occurrence of sarcopenia (because of poor nutrition and low physical exercise) favored disease relapse. However, the two mechanisms could co-exist in some patients, although mechanisms of cancer-associated sarcopenia remain currently largely speculative.

It would seems intuitive that wasting of fat and muscle is a consequence of the action of primary tumor acting as a "metabolic parasite", because of its great avidity for glucose (provided by daily food intake and glycogen storage) and glutamine (the more abundant amino acid in bloodstream). Cancer cells increase their aerobic glycolysis, secrete lactate, even in the presence of oxygen, and down regulate mitochondria. This so-called "Warburg effect" promotes accelerated glycolysis, lactate secretion, down regulation and loss of mitochondria, aggressiveness and drug resistance (4,7). Importantly, high glucose consumption by cancer cells inhibits functioning of tumor-infiltrating lymphocytes (TILs), which rely also on glycolysis to be activated (21). Lactate derived from tumor cells sustains liver neoglucogenesis, which is also fed by glycerol derived from lipolysis and by alanine derived from proteolysis. Neoglucogenesis is stimulated by glucagon and corticosteroids. The recycling of lactate (named as Cory cycle) conspires with other vicious cycles to waste energy: neoglucogenesis consumes ATP to produce glucose in abundance, which serves as nutrient for cancer cells. Note that tumor cells have often a plastic metabolism and may sometimes consume lipids (in particular in tissues rich in lipids) and/or proteins (22).

However, tumor burden would be often less than 1% when there is already profound cachexia, suggesting that tumor metabolic requirement is lower than distant metabolic effects on the host (23). Lipolysis seems to anticipate in most instances loss of skeletal muscle, with the possible exception of SO. It has been suggested that some signaling factors promoting lipolysis also activate proteolysis (2,4). A complex mixture of factors and cytokines secreted by cancer cells and tumor microenvironment (TNFα, IL-6, myostatin, PTHrp, …) would induce increase in mitochondrial fatty acid β-oxidation in myofibers, which in turn would enhance the production reactive oxygen species and other toxic molecules responsible for destruction of myofibers, while uptake of glucose for mitochondrial oxidation is suppressed (4,6,24).

Of note, IL-6 secreted by tumors induces liver CRP synthesis, a key mediator of inflammation, which is an independent marker of lower survival in resected NSCL (25). Inflammatory status (which can be preexistent or concomitant with lung cancer) is associated with increased energy consumption, contributes to malnutrition and, in turn, facilitates catabolic processes. Inflammation is likely to participate to mitochondrial loss and/or energy inefficiency, which enhances destruction of mitochondria and/or their host cells (mitophagy and autophagy), resulting in massive lipolysis and/or sarcopenia (4,6,24). Finally, inflammatory leanness or inflammatory obesity promotes sarcopenia, probably depending on the specific cancer type. Of note, systemic inflammation induces a reduction in liver albumin synthesis, whose levels can further lower because it can be directly used as nutrient by cancer cells, especially those harboring RAS mutations (22).

The complex interactions between host and tumor via the tumor microenvironment are corroborated by our previous studies showing that patient fitness (Karnofsky index and American Society of Anesthesiologists class), systemic inflammation parameters and tumoral immune contexture ($CD8^+$ lymphocytes and mature dendritic cells) are each-other correlated and are all strong prognostic determinants of outcome (5). Indeed, among a population of 303 consecutive lung cancer patients undergoing resection, those with undetectable CRP, high prealbumin levels and high $CD8^+$ cell count had a 5-year survival rate of 80% as compared to 18% in patients with an opposite pattern of values. When stages I–II were considered alone, the prognostic significance of these factors was even more pronounced (5).

Hormonal changes (e.g., insulin and IGF-1 resistance, increased plasma levels of glucagon and glucocorticoids)

promote reprogramming of host metabolism. In particular, liver neoglucogenesis would play a central role as it is sustained by fat and muscle wasting and leads to glucose production which facilitates tumor growth. Transformation of white fat in brown fat increases the energy expenditure and heat generation, even at rest, possibly because this process induces mitochondrial uncoupling (4).

Finally, sarcopenia should be replaced in a larger and comprehensive vision including assessment of patient phenotype (morphomic) and not only the sole measure of muscle mass. Thus, physical performance (in particular assessed by respiratory tests and low or high technology exercise test), inflammatory and nutritional status (assessed by CRP, albumin, pre-albumin, transferrin levels and measure of BMI) should be systematically recorded and studied to provide additional discriminatory information for predicting outcome after surgery. This understanding should help to imagine new strategies aiming at counteracting cancer growth and systemic inflammation, improving nutritional status, promoting physical exercise, in the idea of restoring patient fitness. This patient-directed strategy would be an important therapeutic tool to be added to tumor directed strategies, (surgery, chemotherapy, targeted therapies and radiotherapy).

Thus, morphomic (BMI, muscle mass assessment), nutritional and inflammation parameters are fundamental in the pre-therapeutical work-up of lung cancer patients. Knowledge of the strong and independent prognostic values of these parameters should help in the shift of mentality from a clinical and scientific reasoning mainly based on tumor characteristics (histology, grading, stage, emboli, mutations) to a reasoning taking into account together with tumor characteristics, the host's ones (nutrition, inflammation, fitness) and their continuous interactions which are represented on one side by tumor immune microenvironment, and on the other by tumoral and, probably more importantly, global metabolism. Hopefully, this shift in mentality could promote clinical trials to assess the impact on outcome of tumor and host- tailored therapeutical intervention.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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