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Review

Clinically relevant determinants of body composition, function and nutritional status as mortality predictors in lung cancer patients

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ABSTRACT

Lung cancer belongs to the type of tumors with a relatively high frequency of malnutrition, sarcopenia and cachexia, severe metabolic syndromes related to impairment of physical function and quality of life, resistance to therapy and short survival. Inexpensive and accessible methods of evaluating changes in body composition, physical function and nutrition status are for this reason of great importance for clinical practice to enable the early identification, monitoring, preventing and treatment of these nutritional deficiencies. This could lead to improved outcomes in the quality of life, physical performance and survival of patients with lung cancer. The aim of this article is to summarize the recent knowledge for the use of such methods, their predictability for patient outcomes and an association with other clinically relevant parameters, specifically with lung cancer patients, because such an article collectively describing their practical application in clinical practice is lacking. The interest of this article is in the use of anthropometry, handgrip dynamometry, bioelectrical impedance analysis derived phase angle and nutritional screening questionnaires in lung cancer patients.

1. Introduction

Many serious illnesses (e.g. cancer, sepsis or AIDS) are associated with a severe metabolic syndrome called cachexia. The important clinical symptoms include involuntary weight loss accompanied by sarcopenia (skeletal muscle wasting and weakness), fatigue, anorexia, metabolic imbalance and signs of systemic inflammation. Cachexia cannot be fully reversed by conventional nutrition support [1].

In recent years, the staging of cachexia has occurred. An international panel of experts have created a three-stage classification specific for cancer cachexia: precachexia, cachexia and refractory cachexia. Precachexia is a state characterized by early clinical signs and metabolic disturbances preceding substantial weight loss. The criteria for cachexia are considerable body weight loss (more than 5% over the past 6 months) or a body mass index (BMI) of less than 20 in combination with weight loss (more than 2% over the past 6 months) or sarcopenia (appendicular skeletal muscle index determined by dual energy X-ray absorptiometry of lower than 7.26 and 5.45 $kg\,m^{-2}$ in men and women, respectively) in combination with body weight loss (more than 2% over the past 6 months), but have not entered the refractory stage. Refractory cachexia is a stage characterized by low performance status and low life expectancy (less than 3 months) due to very advanced or rapidly progressive cancer that is unresponsive to therapy [2,3].

Lung cancer belongs to the type of tumors with a relatively high frequency of malnutrition, sarcopenia and cachexia, as demonstrated by the result of recent works. According to the Mini Nutrition Assessment (MNA), 26% of patients with advanced non-small cell lung carcinoma (NSCLC) were malnourished and another 46% of patients were at risk of malnutrition [4]; according to Subjective Global Assessment (SGA), 60% of patients were malnourished [5]. Prado et al. demonstrated that the majority of overweight NSCLC patients (more than 53%) were sarcopenic [6]. According to cancer-specific cachexia classifications (as mentioned above), 18% of NSCLC patients were diagnosed as cachectic, 23% of patients were diagnosed as in a state of precachexia [7].

Cachexia and muscle wasting are related to the impairment of physical function [8], quality of life [5], resistance to therapy [9]

Abbreviations: ALI, Advanced lung cancer inflammation index; BIA, Bioelectrical impedance analysis; BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky performance status; LSMI, Lumbar skeletal muscle index; MAMC, Mid-arm muscle circumference; MNA, Mini Nutrition Assessment; NSCLC, Non-small cell lung carcinoma; PG-SGA, Patient generated Subjective Global Assessment; SGA, Subjective Global Assessment; TST, Triceps skinfold thickness.

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and shorter survival rate [10]. Early identification, monitoring, prevention and treatment of these nutritional deficiencies could lead to improved outcomes in the quality of life, physical performance and survival of patients with NSCLC. There are several inexpensive and accessible methods of evaluating changes in body composition, physical function and nutritional status including anthropometry, handgrip dynamometry, bioelectrical impedance analysis derived phase angle and nutritional screening questionnaires. The aim of this article is to summarize the recent knowledge of the use of these methods, their predictability of patient outcomes and the association of other clinically relevant parameters, specifically with lung cancer patients. Such an article collectively describing their practical application in clinical practice is lacking.

2. Anthropometry

2.1. Basic anthropometric parameters

For a relatively long time weight loss has been known as an important prognostic factor in lung cancer patients [11,12]. Perhaps the first work of trying to determine the prognostic value of basic anthropometric parameters like triceps skinfold thickness (TST), arm and wrist circumference and their association with clinical and biochemical parameters in NSCLC patients were the study of Ferrigno and Buccheri [13]. The statistical analysis proved an association of all three determined anthropometric parameters with body weight. In addition TST correlated with albumin; arm circumference correlated with albumin, haptoglobin and Eastern Cooperative Oncology Group Performance Status (ECOG) score; wrist circumference correlated with creatinine and ECOG score. Although the univariate survival analysis showed the significant impact of TST and arm circumference on prognosis, the results of multivariate analysis did not confirm these parameters as independent prediction factors. Later it was described in NSCLC patients with weight loss the negative correlation of TST and adiponectin ($r = -0.576$; $P = 0.010$) and the positive correlation of TST and free ($r = 0.888$; $P < 0.001$) and total leptin ($r = 0.892$; $P < 0.001$) [14]. The use of combined anthropometric scores could be superior to isolated anthropometric parameters as demonstrated by Tartari et al. [15]. They combined mid-arm circumference and TST and assessed the mid-arm muscle circumference (MAMC) as follows:

$$MAMC\,(cm) = mid - arm\,circumference\,(cm) - (3.1415 \cdot TST\,(mm))$$

After categorizing the patients according to the percentage of gender and age adjusted expected reference values they found that depleted patients (MAMC below 90% of expected values) had more than twice as short overall survival than patients with normal values of MAMC (90% of expected values and higher) (137 versus 306 days; $P = 0.001$). Also the results of the multivariate survival analysis confirmed the MAMC as an independent prognostic factor. Physiological ranges of the MAMC for men over 20 years are 27.5–41.2 cm and for women 24.5–42.1 cm [16].

2.2. Body mass index

In the past years there have appeared several works concerned with the effect of BMI value on survival in lung cancer patients. Leung et al. [17] described a relatively specific association of obesity (BMI higher than 30) and the reduction of lung cancer deaths (adjusted hazard ratio 0.55; $P < 0.001$), while obesity has no significant effect on other smoking-related and non-tobacco related malignancies. BMI was shown as an independent predictor of survival in this study. Longer median survival rates in obese lung cancer patients in comparison with non-obese patients were confirmed by Yang et al. [18] (13 months in obese versus 8.4 months in non-obese patients), this effect was independently significant on cancer stage or histological type. The opposite effect on survival time was found in cases of weight loss (6.4 and 9.2 months for patients with and without weight loss, respectively). These results were evaluated by multivariate survival analysis: absence of obesity was found to be an independent predictor of a worse survival rate (hazard ratio 1.12; $P < 0.001$) and absence of weight loss to be an independent predictor of a longer survival rate (hazard ratio 0.087; $P < 0.001$). The results of the association of BMI value with the survival of lung cancer patients (patients with the lowest BMI have the shortest survival) was also demonstrated by other studies [19–21].

2.3. Advanced lung cancer inflammation index (ALI)

An interesting approach enabling the enhanced prediction of survival of advanced lung cancer patients was brought about by Jafri et al. [22]. They combined the BMI value with markers of systemic inflammation, serum albumin level and neutrophil to lymphocyte ratio (calculated as the ratio of absolute neutrophil and lymphocyte count), and created the so called advanced lung cancer inflammation index (ALI):

$$ALI = \frac{BMI\,(kg\,m^{-2}) \cdot serum\,albu\min\,(g\,dl^{-1})}{neutrophil\,to\,lymphocyte\,ratio}$$

When choosing the cutoff value of ALI 18, the patients with low ALI values were found with a worse performance status, progression free (2.4 versus 5.1 months; $P < 0.001$) and overall survival rate (3.4 versus 8.3 months; $P < 0.001$). The multivariate analysis confirmed the ALI value as an independent predictor of the outcome (hazard ratio for progression free survival was 1.66, $P = 0.003$ and for overall survival 1.42, $P = 0.047$).

2.4. Lumbar skeletal muscle index (LSMI)

As cancer patients show large variability in body composition, muscle wasting is present, even in obese persons, estimation of skeletal muscle mass is of high importance. The higher predictive value of muscle mass determined by weight loss was shown in obese patients with lung and gastrointestinal cancer [10]. The presence of sarcopenia in these patients has proven to be an independent predictor of mortality according to both univariate and multivariate survival analysis (hazard ratio 4.2, $P < 0.001$), while weight loss was not significantly associated with mortality. Patients were classified as sarcopenic according to the value of lumbar skeletal muscle index (LSMI) (men below 52.4 cm m^{-2}, women below 38.5 cm m^{-2}) determined from the computed tomography scan as follows:

$$LSMI\,(cm\,m^{-2}) = \frac{msuscle\,cross - \sec tional\,area\,L3\,(cm^2)}{height\,(m^2)}$$

Martin et al. [21] described the prognostic value of LSMI as further enhanced when combined with other computed tomography scan derived parameter, muscle attenuation, and weight loss. They computed the BMI-dependent threshold values associated with a low survival for these parameters (see Table 1). Stratifying patients according to these threshold values were discovered to have a close association between the number of presented prognostic variables (sarcopenia, low muscle attenuation and body weight loss) and patient survival: median survival rate of patients with zero variables was more than 24 months, patients with one or two variables 16 months and patients with 3 variables with only about 8.5 months. The survival rate of patients with a low BMI was short regardless of the number of presented prognostic variables.