Evaluation of nutritional status in non-small-cell lung cancer: screening, assessment and correlation with treatment outcome

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ABSTRACT

Background
Nutritional derangements are common hallmarks of non-small-cell lung cancer (NSCLC). Nevertheless, their early detection is overlooked in clinical routine. This study aimed to evaluate nutritional status and its correlation with outcome in NSCLC patients.

Methods
Data regarding NSCLC patients undergoing nutritional evaluation were prospectively collected (May 2016–October 2018). Nutritional risk was assessed by Nutritional Risk Screening 2002 (NRS-2002). Bilateral psoas major muscles were measured at L3 vertebrae level with routine staging-computed tomography and changes were evaluated using Wilcoxon signed-rank test. Clinico-pathological and nutritional data were correlated to progression-free/overall survival (PFS/OS) and response rate (ORR) using a Cox and logistic regression model. Kaplan–Meier curves were compared with log-rank test.

Results
Thirty-eight patients were included. The majority (65.8%) of them were at nutritional risk (NRS-2002 ≥3). At multivariate analysis for patients with advanced disease, age (HR 2.44, p=0.05), performance status (HR 2.48, p=0.043) and NRS-2002 (HR 1.74, p=0.001) were significant independent predictors for PFS and weight loss (HR 1.07, p=0.008) for OS. Patients with baseline NRS-2002 <3 had significantly longer 1-year PFS (85.7% vs 19.4%, p=0.02) and higher ORR (66.7% *vs* 21.4%) than those with NRS-2002 ≥3. An explorative evaluation demonstrated that NRS-2002 score significantly decreased after nutritional intervention (p=0.001) for 3 months.

Conclusion
Baseline nutritional risk represents a prognostic factor in NSCLC. Nutritional counselling should be applied as a fundamental tool to improve nutritional risk in a short period, ameliorating patients' outcome.

INTRODUCTION

Despite advances in early detection, multidisciplinary management and systemic treatment, non-small-cell lung cancer (NSCLC) is diagnosed at a loco-regionally advanced or metastatic stage in the vast majority (>70%)

Summary box

What is already known about this subject?
► Nutritional status has recently emerged as a novel prognostic indicator in cancer patients.
► Loss of muscle mass is a prevalent body composition phenotype in cancer patients, associated with shorter survival, reduced quality of life and treatment tolerance.
► Malnutrition is usually under-recognised and undertreated in routine clinical practice.

What does this study add?
► Baseline nutritional depletion detrimentally impacts on response rate and survival outcomes.
► Nutritional counselling represents a tool to improve nutritional status in a short time frame and, consequently, to potentially improve the disease outcome.
► In patients treated with immunotherapy, muscle mass wasting seems to impact on efficacy.

How might this impact on clinical practice?
► Our study suggested that early identification and treatment of malnourished patients or those at increased risk of malnutrition should be performed in clinical routine for NSCLC, despite normal or heavy body weight. In this light, nutritional management, ideally integrated into a multidisciplinary approach, is strongly recommended to become part of a comprehensive approach to patients' well-being and it is able to ameliorate patients' outcome beyond quality of life.

of cases and long-term outcomes remain relatively poor, with an overall 5-year survival rate below 20%.[1]

Beyond the objective disease extension, the concomitant presence of multiple comorbidities and a clinically relevant symptomatic burden are often present in NSCLC patients (particularly in the advanced setting), profoundly impacting on both length and quality of residual life. Moreover,

treatment-related adverse events may also impact on patients' performance and quality of life.[2] Early multidisciplinary supportive care has been shown to significantly prolong overall survival and improve both quality of life and mood in metastatic NSCLC patients.[3]

In this regard, nutritional status has recently emerged as a potential novel prognostic indicator for survival and a predictive marker for treatment-related toxicities among NSCLC patients.[4] In particular, the detection of body composition is crucial for nutritional status assessment. Among available tools, CT scan represents an easy modality to provide a reliable estimation of body composition, through quantitative evaluation of the cross-sectional area of the psoas muscle at the level of the third lumbar vertebra (L3).[5] Besides body mass index (BMI) and history of weight loss, loss of muscle mass has emerged as a prevalent body composition phenotype in lung cancer patients, linked, in turn, to shorter survival,[6–9] reduced tolerance to treatment[10] and decreased quality of life and functional ability,[11 12] particularly in patients treated with chemotherapy and molecularly targeted therapy. Focusing on immune-checkpoint inhibitors, to date only few reports have tried to investigate the relationship between nutritional status and outcomes in lung cancer, suggesting that baseline low skeletal muscle mass has a considerable negative prognostic effect.[13–15] Although interesting, these analyses included a limited number of patients, had a retrospective design and performed only a partial evaluation of patients' nutritional profile. Nevertheless, these preliminary findings contributed to enrich the available background to speculate about the potential impact of nutritional status on immune response and clinical outcome during immunotherapy, which represents a fascinating and still unexplored research area.

Despite available evidence and increasing interest in this field, several studies suggested that physicians tend to neglect nutritional issues, presumably due to lack of time and limited specialised knowledge. Therefore, baseline nutritional risk is usually under-recognised and the potential nutritional and metabolic consequences of both the disease process itself and the treatment-related effects[16] are grossly undertreated in NSCLC patients in routine clinical practice.[17]

We therefore set out to prospectively evaluate baseline nutritional status, to explore its correlation with treatment outcome and to implement nutritional counselling measures in NSCLC patients.

METHODS
Study design and patients' population
This prospective observational analysis included patients with histologically confirmed diagnosis of NSCLC (both squamous and non-squamous). Inclusion criteria included all consecutive NSCLC patients with a histologically confirmed diagnosis who received a baseline nutritional status evaluation carried out by a trained dietitian, with documented skills for an evidence-based dietetic practice in cancer patients' care, at the Oncology Unit of the University Hospital of Verona, between May 2016 and October 2018. In that time frame, patients were addressed to nutritional evaluation on patient's demand according to oncologist's prescription. NSCLC patients were excluded from our analysis if they did not receive the nutritional evaluation in the specified 2-year period (exclusion criteria).

For every patient, the study staff reviewed medical records. Information on patient's demographics, clinical variables, smoking history, family history, performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) score, histology, tumour stage according to TNM classification, molecular profile, type of treatments (surgery, chemotherapy, radiotherapy, immunotherapy, target therapy) and response (both clinical and radiological) to treatments were collected.

Evaluation of nutritional status and nutritional intervention
The nutritional risk was detected using the Nutritional Risk Screening 2002 (NRS-2002), a screening tool recommended by a European Society for Clinical Nutrition and Metabolism (ESPEN) working group for nutritional screening in hospitals.[18] NRS-2002 consists of two parts. The first part includes the assessment of patient's nutritional status and food intake issues, while the second part contains information associated with the influence of disease severity on nutritional status. Each part is scored from 0 to 3 points, and patients receive an extra point for age ≥70 years. The total NRS-2002 score ranges from 0 to 7. The total score exceeding 3 suggested nutritional risk, whereas the total score below 3 denotes no nutritional risk is present, at least temporarily. NRS-2002 was evaluated by the trained dietitian at the initial baseline visit.

According to standard protocols, height and weight were measured using a calibrated scale with a stadiometer. BMI was calculated as (weight in kg)/(height in m)^2 and categorised based on the WHO criteria. History of unintentional weight loss (WL) in the previous 6 months was retrospectively obtained. It was determined as {[usual body weight (UBW) − actual body weight]/UBW}*100.

Muscle mass was estimated by measuring the cross-sectional area of the psoas muscle at the level of L3 vertebra with routine staging CT images by a trained radiologist. The measured total psoas area (TPA) was then normalised for height,[2] as per convention for body composition measurements, and reported as TPA index (TPAI mm^2/m^2).

Patients were stratified by quartiles according to TPAI and sarcopenia was defined in the categorical analyses as the lowest quartile for men and women separately.

Symptoms with potential nutritional impact were routinely assessed by the dietitian. Oral intake of calories and proteins was assessed using 24 hours dietary recall. The energy requirement of the patients was calculated by multiplying the resting energy expenditure, determined using the Harris & Benedict equation, by a correction factor of 1.5 (in patients with BMI >30 kg/m^2, ideal

body weight (ie, with BMI=23 kg/m^2) was used in the equation). Patients' daily protein needs were estimated at 1.5 g/kg of actual body weight (in patients with BMI >30 kg/m^2: 1.2 g/kg of ideal body weight). Dietary intakes were considered satisfied when total energy and protein requirements were ≥90% and ≥1.5 g/kg/day, respectively.

All patients received individualised nutrition intervention, including intensive dietary counselling every 2 weeks at the first step, to maintain or improve energy and/or protein intake and to manage the nutritional impact of disease-related and treatment-related symptoms. Based on the actual calories intake and requirements, the dietitian provided tailored sample meal plans, recipe suggestions adjusted on personalised eating patterns and preferences and recommendations to minimise the side effects of both the disease and the ongoing therapies. The dietitian clearly informed all patients about the potential treatment-related gastrointestinal toxicities and the importance of maintaining and improving the nutritional status. Nutritional consultations were performed face-to-face.

End points
The primary end point of the present study was to evaluate the nutritional risk and the nutritional status of NSCLC patients. The secondary end point was to explore the correlation between baseline nutritional profile and outcome, in terms of overall response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Response and survival analysis
Objective response to treatment was evaluated using CT images and classified according to Response Evaluation Criteria in Solid Tumors V.1.1[19] as follows: complete response (CR), partial response (PR), stable disease (SD) or progression disease (PD). Patients with either CR or PR were classified as responders and those with SD or PD as non-responders.

The PFS was defined as the interval between the diagnosis of NSCLC and disease progression or death from any cause, and the OS as the time between the diagnosis of NSCLC and death from any cause or last follow-up.

Statistical analysis
Descriptive statistics were used to summarise pertinent study information. Follow-up was reported according to Shuster et al. The HR and the 95% CI were estimated for each variable using the Cox model. Changes in psoas muscles observed in subsequent scans were evaluated using Wilcoxon signed-rank test. The included variables in the univariate analysis for ORR, PFS and OS were age at diagnosis, PS, stage at the moment of nutritional evaluation, presence of driver gene alterations, BMI, NRS-2002 and changes in psoas muscle mass. A multivariate Cox proportional hazard model with clinical, pathological and nutritional factors was developed using the stepwise regression (forward selection, enter limit and remove limit, p=0.10 and 0.15, respectively) to identify

independent predictors of PFS. The Harrell's guidelines for the identification of the correct number of covariates were taken into account for the power analysis. Outcomes were estimated by the Kaplan–Meier product limit method. The log-rank test was used to assess differences between subgroups. Associations between variables and groups according to nutritional variables were analysed (χ^2 test). Significance was defined at p<0.05. The SPSS (V.18.0), R (V.2.6.1) and MedCalc (V.14.2.1) licensed statistical programs were adopted for all analyses.

RESULTS
Patients' characteristics
A total of 38 patients (20 men (52.6%) and 18 women (47.4%)) met the inclusion criteria and were enrolled in the study. Baseline patients' characteristics are summarised in table 1. Biomolecular characterisation of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS-1) and programmed death ligand 1 (PD-L1) was performed according to stage at diagnosis and tumour histotype. EGFR status was available in 23 patients and the presence of an activating mutation was found in 5 of them (13.2%). ALK translocation was reported in 1 case (out of 23 evaluated), whereas ROS-1 translocation was not detected in any of the evaluated patients. PD-L1 status was analysed in 16 patients, 12 had a score between 1% and 49% and 2 had a score ≥50%. Fifteen patients underwent thoracic surgery (39.5%), followed by adjuvant chemotherapy in eight cases. Twenty-one patients received radiotherapy at any time of their oncological history (on primary or metastatic sites). Thirty-two patients received first-line treatment for advanced disease, which in most cases (23 out of 32) consisted in platinum-based chemotherapy. Immunotherapy was administered in 15 patients (39.5%), considering any treatment line.

Nutritional screening and assessment
Baseline nutritional evaluation was performed at the start of first-line treatment in patients with advanced disease (84.2%) and during treatments in patients who underwent surgery and adjuvant chemotherapy (15.8%). Baseline nutritional measures are reported in table 2.

Mean BMI in the entire population was 26.8±5.9 kg/m^2, with a proportion of underweight, normal weight, overweight and obese patients of 15.8%, 18.4%, 34.2% and 31.6%, respectively. According to NRS-2002, most patients (65.8%) were at risk of malnutrition. Several patients reported multiple symptoms with a potential nutritional impact, in particular loss of appetite (47.4%), xerostomia (47.4%), dysgeusia (42.1%), early satiety (39.5%) and oral mucositis (34.2%).

Regarding the correlation between specific symptoms and NRS-2002, patients at nutritional risk (NRS-2002 ≥3) were significantly more likely to report loss of appetite (r=0.684, p<0.001), dysgeusia (r=0.503, p=0.001), early satiety (r=0.469, p=0.003), mucositis (r=0.403, p=0.012)

Table 1 Baseline patients' characteristics

Variable	Patients number (%)
Gender	
Male	20 (52.6%)
Female	18 (47.4%)
Median age in years (range)	59 (42–82%)
Median follow-up in months (range)	9.6 (1–32%)
ECOG performance status	
0	26 (68.4%)
1	10 (26.3%)
2	2 (5.3%)
Smoker	
Current	10 (26.3%)
Former	7 (18.4%)
Never	6 (15.8%)
Not evaluable	15 (39.5%)
Histology	
Adenocarcinoma	24 (65.8%)
Squamous cell carcinoma	11 (28.9%)
Not specified	2 (5.3%)
Stage at diagnosis	
I	4 (10.5%)
II	6 (15.8%)
III	11 (28.9%)
IV	17 (44.7%)
Number of metastatic sites at diagnosis	
1	6 (15.8%)
2 or more	11 (28.9%)
Localisation of metastases at diagnosis	
Lung	10 (26.3%)
Liver	4 (10.5%)
Bone	8 (21.1%)
Brain	3 (7.9%)
Other	4 (10.5%)
Surgery	
Yes	15 (39.5%)
No	23 (60.5%)
Radiotherapy	
Yes	21 (55.3%)
No	17 (44.7%)
First-line treatment for advanced disease	32 (82.2%)
Chemotherapy	23 (60.5%)
Target therapy	5 (13.2%)
Immunotherapy	4 (10.5%)
Best response to first-line treatment	

Continued

Table 1 Continued

Variable	Patients number (%)
Partial response	15 (46.9%)
Stable disease	10 (31.3%)
Progressive disease	5 (15.6%)
Not available	2 (6.3%)
Immunotherapy as second or further lines	11 (28.9%)

ECOG, Eastern Cooperative Oncology Group.

Table 2 Baseline nutritional features of the study population

Variable	
Body weight (kg), mean (SD)	75.5 (21.5)
Usual BMI (kg/m^2), mean (SD)	26.7 (5.1)
BMI (kg/m^2), mean (SD)	26.8 (5.9)
<18.5 kg/m^2, N (%)	6 (15.8)
18.5–24.9 kg/m^2, N (%)	7 (18.4)
25.0–29.9 kg/m^2, N (%)	13 (34.2)
≥30 kg/m^2, N (%)	12 (31.6)
6 months weight loss (%), mean (SD)	−0.4 (12.6)
NRS-2002 score, N (%)	
0	9 (23.7)
1	1 (2.6)
2	3 (7.9)
3	10 (26.3)
4	15 (39.5)
TPA (cm^2), mean (SD)	153 (51.9)
TPAI (cm^2/m^2), mean (SD)	90 (27.9)
Estimated energy requirements (kcal/day), mean (SD)	1836 (380)
Estimated protein requirements (g/kg/day), mean	1.5
Baseline energy intake (kcal/day), mean (SD)	1460 (596)
Baseline protein intake (g/kg/day), mean (SD)	0.7 (0.2)
Early satiety, N (%)	15 (39.5)
Dysphagia, N (%)	7 (18.4)
Loss of appetite, N (%)	18 (47.4)
Dysgeusia, N (%)	16 (42.1)
Oral mucositis, N (%)	13 (34.2)
Dyspepsia, N (%)	14 (36.8)
Nausea or vomiting, N (%)	8 (21.1)
Xerostomia, N (%)	18 (47.4)
Diarrhoea or constipation, N (%)	11 (28.9)

BMI, body mass index; NRS-2002, Nutritional Risk Screening 2002; TPA, total psoas area; TPAI, total psoas area index.

and nausea or vomiting (r=0.372, p=0.021) than patients with NRS-2002 <3. No associations were found between other recorded symptoms reported in table 2 and NRS-2002 score.

Median energy intake of the whole population was 1509 (range 1078–2821) kcal/day and only 12 patients (31.6%) satisfied the estimated caloric requirements. The frequency of nutritional impact symptoms reported by patients was also inversely correlated with the energy intake. In particular, there was a significant inverse correlation between reduced energy intake and loss of appetite (r=−0.639, p<0.001), dysgeusia (r=−0.387, p=0.016), early satiety (r=−0.538, p<0.001), mucositis (r=−0.339, p=0.0376) and nausea or vomiting (r=−0.327, p=0.045).

The median protein intake per kilogram of body weight was 0.7 (range 0.4–0.9) g/kg/day, less than 50% of the recommended daily protein intake (1.5 g/kg), and no patients satisfied the estimated protein needs. A significant inverse correlation between oral protein intake and oral mucositis (r=−0.336, p=0.039) was found (online supplementary table 1).

With regard to body composition, median TPA was 1529±519.3 mm^2 and median TPAI was 904±279.8 mm^2/m^2. The lowest quartile TPAI threshold for men was 946 mm^2/m^2 vs 562 mm^2/m^2 for women. According to these cut-off values, seven patients (18.4%) were found to be sarcopenic at baseline.

After 3 months of treatment, complete radiological images were available for 21 patients. Median TPA was 1435±562.1 mm^2 and median TPAI was 881±309.1 mm^2/m^2. The lowest quartile TPAI threshold for men was 893 mm^2/m^2 vs 552.5 mm^2/m^2 for women and, using these cut-off values, 6 patients (18.4%) presented sarcopenia after 3 months. Moreover, a significant loss in TPAI during treatment, regardless of the type of treatment, was observed (p=0.01 and 0.002 in patients treated with immunotherapy (n=15) or other therapies (n=23), respectively) (online supplementary table 2).

Impact of NRS-2002 score on treatment outcome
At a median follow-up of 9.6 months (range 1–32 months), median PFS was 10 months (95% CI 7 to 13 months) with a 1year PFS rate of 43.7%.

In patients who underwent first-line treatment for advanced stage disease, age, ECOG PS and NRS-2002 score were significant independent predictors for PFS at multivariate analysis (online supplementary table 3). Figure 1 shows the Kaplan–Meier curves for PFS at 12 months according to age, PS and NRS-2002.

Among 35 patients affected by locally advanced or advanced NSCLC, median OS was 22 months (95% CI 6 to 38). Overall, the 1-year and 2-year OS rates were 67.8% and 47.7%, respectively. At multivariate analysis, WL was the only significant predictor for OS (HR 1.07, 95% CI 1.02 to 1.13, p=0.008) (figure 2 shows the Kaplan–Meier curves for OS according to WL) and was significantly associated with the NRS-2002 (p=0.001). Patients with baseline WL <5% experienced significantly longer 2-year OS (64.4% vs 13.3%, p=0.0001).

Overall, ORR to first-line treatment was significantly different in patients at risk of malnutrition (baseline NRS-2002 ≥3) as compared with those with a baseline NRS-2002 <3 (21.4% vs 66.7%, p=0.016). Conversely, BMI did not affect ORR, PFS and OS.

In the subset of 15 patients (46.9%) treated with immunotherapy in any treatment line, there was not a significant trend suggesting a correlation between loss in TPAI during treatment and lack of objective response (p=0.186), which was not observed for patients treated with other therapies.

Nutritional changes after intensive dietary counselling
Effect on dietary intake
Nutritional intervention led to a significantly higher daily energy and protein intake (p=0.005 and <0.0001, respectively). On average, after nutritional counselling, energy intake increased from 1509 kcal (range 1078–2821) to 1747 kcal (range 1103–2700) and protein intake from 0.7 g/kg/die (range 0.4–0.9) to 1.2 g/kg/die (range 0.8–1.5).
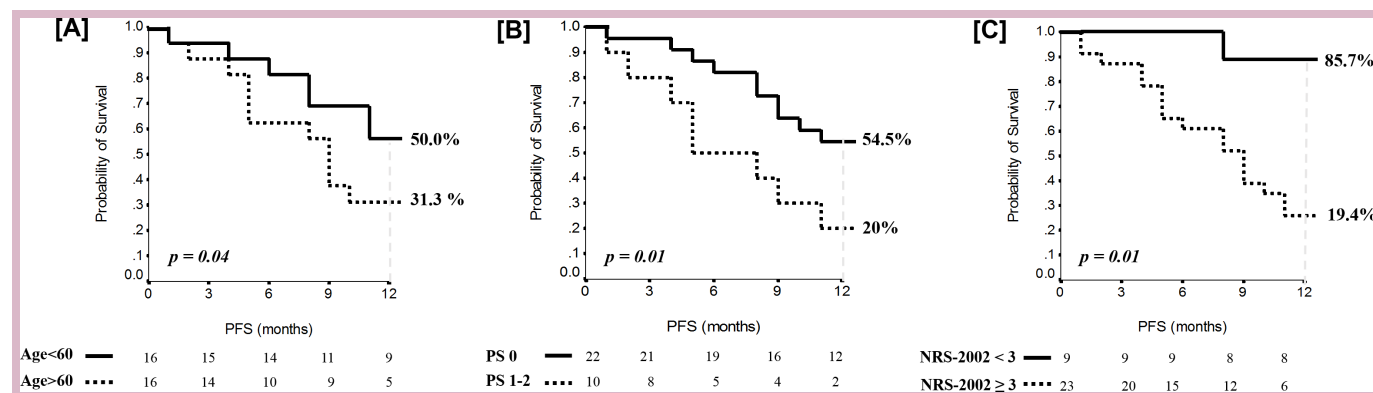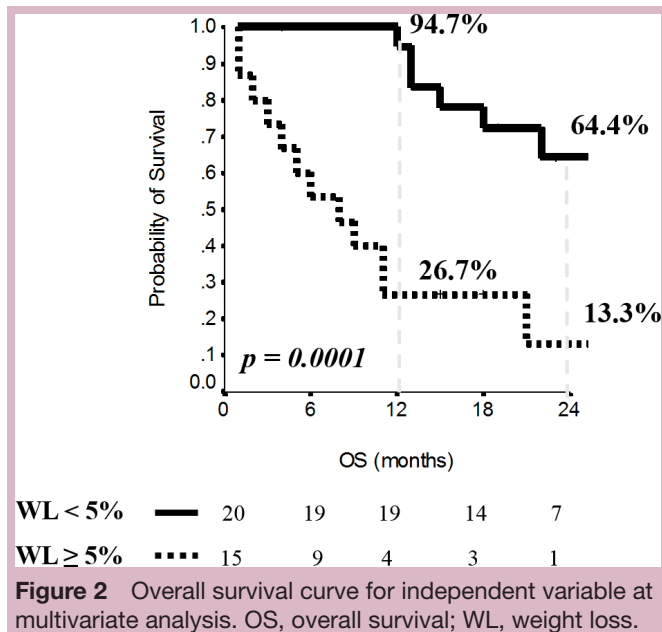

Figure 1 PFS curves for independent variables at multivariate analysis. NRS-2002, Nutritional Risk Screening 2002; PFS, progression-free survival; PS, performance status.

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Figure 2 Overall survival curve for independent variable at multivariate analysis. OS, overall survival; WL, weight loss.
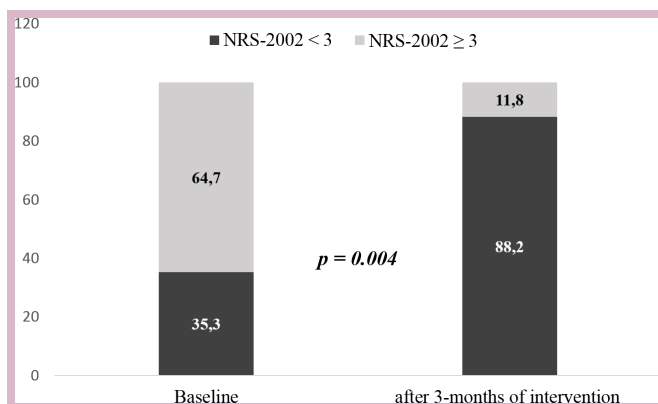
Nutritional risk

An explorative evaluation of the NRS-2002 changes after an intensive 3-month nutritional intervention was also performed. NRS-2002 at baseline and after 3 months was available for 19 patients. NRS-2002 score significantly decreased from a median of 3 (range 0–4) at baseline to a median of 1 (range 0–3) after 3 months of intervention (p=0.001) (figure 3).

DISCUSSION

Our preliminary results suggest that patients with NSCLC reported a prevalence of notably high risk of malnutrition and symptoms that were associated with the reduction of nutrient intake and the nutritional risk. Moreover, baseline risk of malnutrition has been found to detrimentally impact on ORR and PFS, while baseline WL on OS.

Nutritional status has traditionally been evaluated using BMI. However, this parameter is not accurate to detect nutritional risk and nutritional status in the oncological setting.[20 21] Several nutritional screening and assessment

Figure 3 Changes in nutritional risk after intensive dietary counselling. NRS-2002, NutritionalRisk Screening 2002.

scores have been created to effectively detect the risk of developing malnutrition and its magnitude. In this regard, an observational study by Bauer et al, evaluated the presence of malnutrition using the Subjective Global Assessment (SGA), which assess nutritional status based on the features of medical history and physical examination, and the BMI in 71 cancer patients. They showed that if the value of BMI was considered alone, no malnutrition was reflected in this index according to the WHO definition. Nevertheless, the majority of patients were malnourished as estimated by other parameters such as SGA.[22] The features of our patient population also suggested some limitations in the conventional notions of nutritional risk focusing on BMI. Indeed, only 15.8% overall were underweight as conventionally considered (BMI $<18.5 \, kg/m^2$). According to NRS-2002, an appropriate and validated malnutrition screening tool recommended by the ESPEN,[23] most of our patients were at high risk of malnutrition. Thus, a nutritional screening tool that encompasses several parameters may be more sensitive and careful compared with a single nutritional variable. Notably, we found that the NRS-2002 score was a significant independent predictor for PFS. Moreover, patients with NRS-2002 <3 had a better ORR than those with NRS-2002 ≥3, suggesting that nutritional risk screening affects not only survival outcomes but also tumour response in NSCLC patients. These results are consistent with those of a retrospective study by Illa et al. They found that nearly half of newly diagnosed patients with lung cancer, across all stages, were at nutritional risk before treatment start. The authors also showed that the objective response was significantly worse in patients categorised at nutritional risk. Patients with NRS-2002 <3 achieved significantly better ORR (higher proportion of complete and partial response), irrespective of treatment modality, than those with NRS-2002 ≥3.[24] In our study, baseline WL was a significant predictor for OS at multivariate analysis. Although we did not observe the same correlation with NRS-2002, WL is one of the variables included in this score and, therefore, the two parameters were significantly associated.

Patients in our study experienced a variety of symptoms potentially affecting the enjoyment of eating. The mean energy and protein intake was significantly lower than that recommended according to the ESPEN guidelines on nutrition in cancer patients. Of interest, the frequency of symptoms reported by the patients was related to the poor dietary intake and nutritional risk, underlining the importance to monitor symptom burden during treatment in these patients to ensure an optimal nutrient intake.

Wasting of muscle mass in particular is a prominent feature in NSCLC patients, despite normal or heavy body weight. In view of an increase of overweight and obesity prevalence, high BMI in cancer patients could lead clinicians to underestimate the nutritional risk.[25] In this context, a study by Baracos et al, analysing data from a prospective cohort of NSCLC patients, reported that at

presentation nearly half of the patients were overweight or obese, and among those classified as overweight more than half met the criteria for muscle depletion.[6] Diagnostic images collected for staging and evaluation of tumour response are suitable for body composition analyses. Nevertheless, these images are not usually applied for body-composition assessment despite their wide availability and the potential role of lean tissue to individualise chemotherapy dosing and to predict toxicity and efficacy. Moreover, a careful evaluation of muscle cross-sectional area can be alternatively performed using image-analysis software that is usually costly, time-consuming and does not integrate into routine radiological reporting. Its broad clinical application requires a more efficient and cost-effective method of assessing lean muscle mass. In this context, the cross-sectional area of the psoas muscle evaluated by CT scan provides an estimation of overall muscle mass and has been used as a 'convenient and easy-to-measure' surrogate marker in several studies to predict lean muscle mass.[26 27] Given these findings, in the current study, we used the TPAI to evaluate muscle mass and its changes during treatments. In examining our NSCLC cohort, at baseline 18.4% of patients had sarcopenia. Additionally, all patients reported a significant loss in TPAI during treatments, probably due to a combination of reduced food intake and metabolic derangements which may be either host-derived or tumour-derived.[4]

Of interest, despite the absence of statistical significance, likely related to the limited sample, in patients treated with immunotherapy, muscle mass wasting seems to impact on efficacy outcome in line with recent literature.[13–15] In online supplementary figure 1, the case of an immunotherapy-treated patient experiencing disease response concurrently with an increase in the TPA is reported. There are several possible explanations for the association between muscle wasting and worse outcome with immunotherapy, involving in particular the modulation of immune response mediated by the skeletal muscle cells[28 29] and the immunological consequences of cancer-induced chronic inflammation.[30–32]

Regarding nutritional intervention, according to NRS-2002, our explorative evaluation on 19 patients suggested that, in a short period of 3 months an intensive dietary counselling may improve energy and protein intakes, as well as nutritional risk. The pathogenesis of cancer-related malnutrition is complex and multifactorial, but reduced energy and protein intakes contributes to progressive wasting. Closing the gap between recommended and current nutrient intake, which is the first aim of a nutritional intervention, remains a key step in the prevention and treatment of malnutrition.

Only few studies have investigated this intervention in NSCLC patients. A prospective study by Tanaka et al in a small cohort of patients with lung cancer did not find any significant improvement in weight and BMI during chemotherapy after 90 days of nutritional intervention with dietary counselling and oral nutritional supplement. However, the number of patients who gained body weight after 90 days in the study cohort was significantly higher compared with patients who received standard care.[33] A pilot randomised trial by Kiss et al showed clinically important differences favouring the intensive, individualised dietary counselling in terms of weight, fat-free mass, physical well-being and functional well-being in lung cancer patients receiving radiotherapy.[34] In light of our and the above-mentioned data, randomised trials examining nutritional intervention impact on treatment outcome in patients affected by lung cancer are required, given that nutritional status seems to impact on therapy response and survival.

Beyond the nutritional intervention alone, recent evidence proposed the early implementation of a multimodal treatment, given the multifactorial and complex pathogenesis of nutritional depletion in cancer patients. This treatment should be based on current evidence and consists in pharmacological agents, targeted nutritional support, personalised exercise programmes and psychosocial interventions.[35 36] With regards to pharmacological intervention, ongoing research allowed the identification of some potential therapeutic targets and promising new agents, such as anamorelin, MABp1 and enobosarm.[37] Unfortunately, the impact of these combined intervention has not been evaluated in this analysis. However, in our Unit, nutritional management is part of an integrated multidisciplinary care that combines a comprehensive approach to patients' well-being with a rigorous scientific method, composed by oncology-trained dietitians, kinesiologists and psychologists (figure 4).

This study has several limitations. In particular, the single centre study design and the small sample size precluded definite conclusions. Only 15 patients in our series received immunotherapy, thus further research on patients suffering from NSCLC receiving immunotherapy are required. Furthermore, data on other measures of muscle strength and function, such as handgrip strength, walking speed and subjective measures of tiredness and exhaustion were missing. Notably, only NSCLC patients receiving nutritional status evaluation were included, which may lead to an intrinsic selection bias. The high OS rate observed in our population may reflect the selection of a prognostically favourable subgroup of patients.

On the other hand, we performed a prospective and comprehensive nutritional profile assessment in NSCLC population. Moreover, this analysis may be propaedeutic to future trials aimed to explore the impact of nutritional status derangements on declining immunity.

In conclusions, our study revealed the importance of baseline nutritional risk as a prognostic factor in NSCLC and suggested that nutritional counselling represents a tool to improve this parameter in a short time frame and, consequently, to potentially improve the disease outcome. In this light, early identification and treatment of already malnourished patients or those at increased risk of malnutrition is highly recommended in clinical routine for NSCLC patients, particularly in those who are scheduled to receive immune checkpoint inhibitors, despite normal
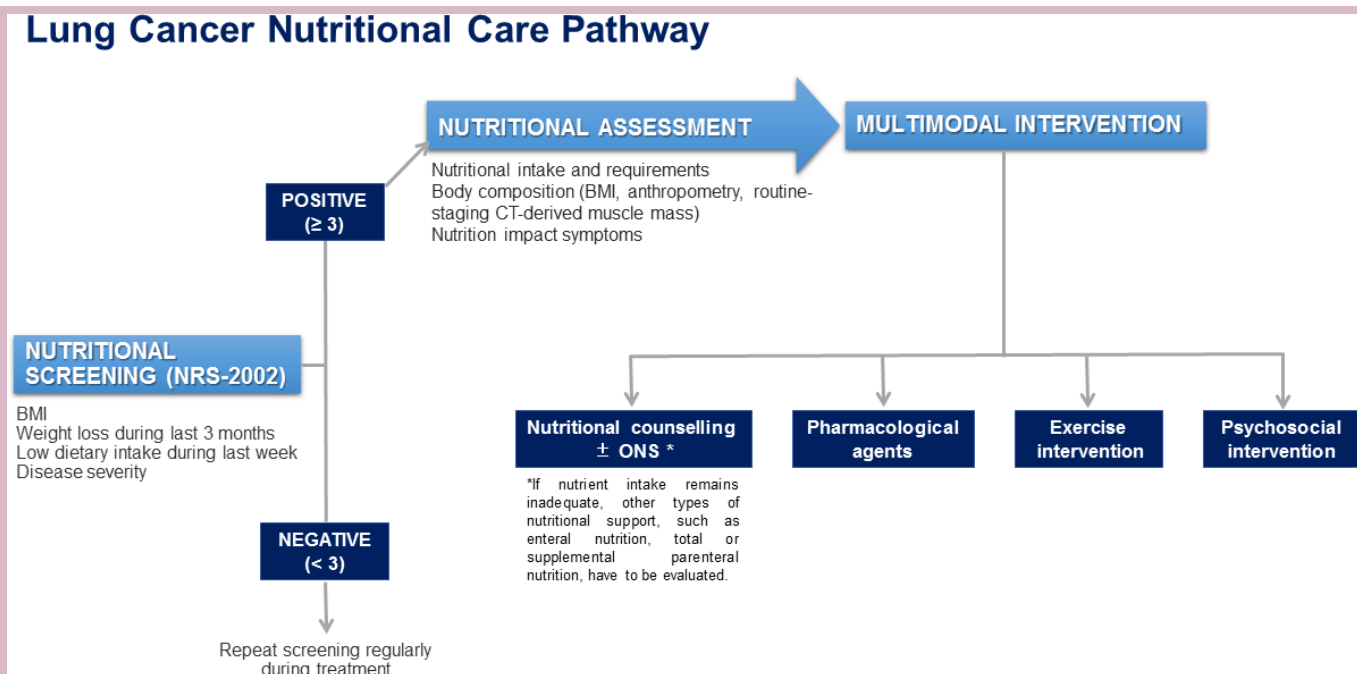
Figure 4 Lung cancer nutritional care pathway. A proposed model of multidisciplinary care management for lung cancer patients. BMI, body mass index; NRS-2002, Nutritional Risk Screening 2002; ONS, oral nutritional supplement.

or heavy body weight. Indeed, the prevention of nutritional derangements and the development of predictive biomarkers will be crucial to gain the greatest benefit from immunotherapy. Further prospective researches on this emerging topic are required.

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REFERENCES
1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7–34.
2 Polanski J, Jankowska-Polanska B, Rosinczuk J, *et al*. Quality of life of patients with lung cancer. *Onco Targets Ther* 2016;9:1023–8.
3 Temel JS, Greer JA, Muzikansky A, *et al*. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733–42.
4 Trestini I, Gkountakos A, Carbognin L, *et al*. Muscle derangement and alteration of the nutritional machinery in NSCLC. *Crit Rev Oncol Hematol* 2019;141:43–53.
5 Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* 2017;28:2107–18.
6 Baracos VE, Reiman T, Mourtzakis M, *et al*. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* 2010;91:1133S–7.
7 Cortellini A, Palumbo P, Porzio G, *et al*. Single-Institution study of correlations between skeletal muscle mass, its density, and clinical outcomes in non-small cell lung cancer patients treated with first-line chemotherapy. *Thorac Cancer* 2018;9:1623–30.

8 Kim EY, Kim YS, Park I, *et al*. Prognostic significance of CT-Determined sarcopenia in patients with small-cell lung cancer. *J Thorac Oncol* 2015;10:1795–9.

9 Nattenmüller J, Wochner R, Muley T, *et al*. Prognostic impact of CT-Quantified muscle and fat distribution before and after First-Line-Chemotherapy in lung cancer patients. *PLoS One* 2017;12:e0169136.

10 Sjøblom B, Benth Jūratė Šaltytė, Grønberg BH, *et al*. Drug dose per kilogram lean body mass predicts hematologic toxicity from Carboplatin-Doublet chemotherapy in advanced non-small-cell lung cancer. *Clin Lung Cancer* 2017;18:e129–36.

11 Bye A, Sjøblom B, Wentzel-Larsen T, *et al*. Muscle mass and association to quality of life in non-small cell lung cancer patients. *J Cachexia Sarcopenia Muscle* 2017;8:759–67.

12 Naito T, Okayama T, Aoyama T, *et al*. Unfavorable impact of cancer cachexia on activity of daily living and need for inpatient care in elderly patients with advanced non-small-cell lung cancer in Japan: a prospective longitudinal observational study. *BMC Cancer* 2017;17:800.

13 Cortellini A, Verna L, Porzio G, *et al*. Predictive value of skeletal muscle mass for immunotherapy with nivolumab in non-small cell lung cancer patients: A "hypothesis-generator" preliminary report. *Thorac Cancer* 2019;10:347–51.

14 Nishioka N, Uchino J, Hirai S, *et al*. Association of sarcopenia with and efficacy of anti-PD-1/PD-L1 therapy in non-small-cell lung cancer. *J Clin Med* 2019;8:450.

15 Shiroyama T, Nagatomo I, Koyama S, *et al*. Impact of sarcopenia in patients with advanced non-small cell lung cancer treated with PD-1 inhibitors: a preliminary retrospective study. *Sci Rep* 2019;9:2447.

16 Corbaux P, Fontaine-Delaruelle C, Souquet P-J, *et al*. Is nutritional screening of patients with lung cancer optimal? an expert opinion survey of French physicians and surgeons. *Nutr Cancer* 2019;71:971–80.

17 Rauh S, Antonuzzo A, Bossi P, *et al*. Nutrition in patients with cancer: a new area for medical oncologists? A practising oncologist's interdisciplinary position paper. *ESMO Open* 2018;3:e000345.

18 Kondrup J, Rasmussen HH, Hamberg O, *et al*. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 2003;22:321–36.

19 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.

20 Trestini I, Carbognin L, Bonaiuto C, *et al*. The obesity paradox in cancer: clinical insights and perspectives. *Eat Weight Disord* 2018;23:185–93.

21 Fearon K, Strasser F, Anker SD, *et al*. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489–95.

22 Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr* 2002;56:779–85.

23 Arends J, Bachmann P, Baracos V, *et al*. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36:11–48.

24 Illa P, Tomiskova M, Skrickova J. Nutritional risk screening predicts tumor response in lung cancer patients. *J Am Coll Nutr* 2015;34:425–9.

25 Rier HN, Jager A, Sleijfer S, *et al*. The prevalence and prognostic value of low muscle mass in cancer patients: a review of the literature. *Oncologist* 2016;21:1396–409.

26 Nakamura R, Inage Y, Tobita R, *et al*. Sarcopenia in resected NSCLC: effect on postoperative outcomes. *J Thorac Oncol* 2018;13:895–903.

27 Zakaria HM, Llaniguez JT, Telemi E, *et al*. Sarcopenia predicts overall survival in patients with lung, breast, prostate, or myeloma spine metastases undergoing stereotactic body radiation therapy (SBRT), independent of histology. *Neurosurgery* 2020;86:705–16.

28 Afzali AM, Müntefering T, Wiendl H, *et al*. Skeletal muscle cells actively shape (auto)immune responses. *Autoimmun Rev* 2018;17:518–29.

29 Quinn LS. Interleukin-15: a muscle-derived cytokine regulating fat-to-lean body composition. *J Anim Sci* 2008;86:E75–83.

30 Wherry EJ. T cell exhaustion. *Nat Immunol* 2011;12:492–9.

31 Mariathasan S, Turley SJ, Nickles D, *et al*. Tgfβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* 2018;554:544–8.

32 Tsukamoto H, Fujieda K, Miyashita A, *et al*. Combined blockade of IL6 and PD-1/PD-L1 signaling abrogates mutual regulation of their immunosuppressive effects in the tumor microenvironment. *Cancer Res* 2018;78:5011–22.

33 Tanaka N, Takeda K, Kawasaki Y, *et al*. Early intensive nutrition intervention with dietary counseling and oral nutrition supplement prevents weight loss in patients with advanced lung cancer receiving chemotherapy: a clinical prospective study. *Yonago Acta Med* 2018;61:204–12.

34 Kiss N, Isenring E, Gough K, *et al*. Early and Intensive Dietary Counseling in Lung Cancer Patients Receiving (Chemo) Radiotherapy-A Pilot Randomized Controlled Trial. *Nutr Cancer* 2016;68:958–67.

35 Avancini A, Sartori G, Gkountakos A, *et al*. Physical activity and exercise in lung cancer care: will promises be fulfilled? *Oncologist* 2019:theoncologist.2019-0463.

36 Solheim TS, Laird BJA, Balstad TR, *et al*. Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, nutrition and anti-inflammatory medication for cachexia) trial. *BMJ Support Palliat Care* 2018;8:258–65.

37 Naito T. Emerging treatment options for cancer-associated cachexia: a literature review. *Ther Clin Risk Manag* 2019;15:1253–66.