

# Current Insights in Nutrition Assessment and Intervention for Malnutrition or Muscle Loss in People with Lung Cancer: A Narrative Review

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## ABSTRACT

Up to 70% of people with lung cancer may be affected by cancer-related malnutrition or muscle loss, depending on treatment modality and disease stage. This narrative review explores recent studies on malnutrition and muscle loss as well as nutritional and multimodal interventions to treat these conditions in the context of the changing treatment landscape in lung cancer. Various types of interventions, including individualized counseling, protein and other specific nutrient supplementation, as well as multimodal interventions to treat malnutrition and muscle loss, have been investigated. Overall, individualized dietary counseling, increasing protein intake, and supplementation with omega-3 (n-3) fatty acids appear to be beneficial for some, albeit varying, patient outcomes. Multimodal interventions, generally including a nutrition and exercise component, show promising results; however, the impact on patient outcomes is mixed. A key finding of this review is a lack of large, randomized trials to guide nutrition intervention specifically in people with lung cancer. Despite the high prevalence of malnutrition and muscle loss in people with lung cancer and the known adverse outcomes, current evidence for nutrition intervention is limited. A targeted effort is required to improve the quality of evidence for nutrition intervention in this population to provide support for clinicians to deliver effective nutrition care. *Adv Nutr* 2022;13:2420–2432.

**Statement of Significance:** Malnutrition and muscle loss affect as many as 70% of people receiving treatment for lung cancer and are associated with serious adverse outcomes for patients and high cost to the health system. Early nutrition intervention to prevent or treat malnutrition and muscle loss is vital to reduce the risk of mortality and treatment complications. This review presents the current evidence for the efficacy of nutrition interventions in people with lung cancer.

**Keywords:** malnutrition, muscle loss, nutrition, lung cancer, multimodal

## Introduction

Lung cancer was the second most commonly diagnosed cancer and the leading cause of cancer-related deaths globally in 2020, representing 11.4% of all new cancer diagnoses and 18% of all cancer-related deaths (1). People with lung cancer are at high risk of nutritional decline prior to, during, and following treatment secondary to the impact of the tumor

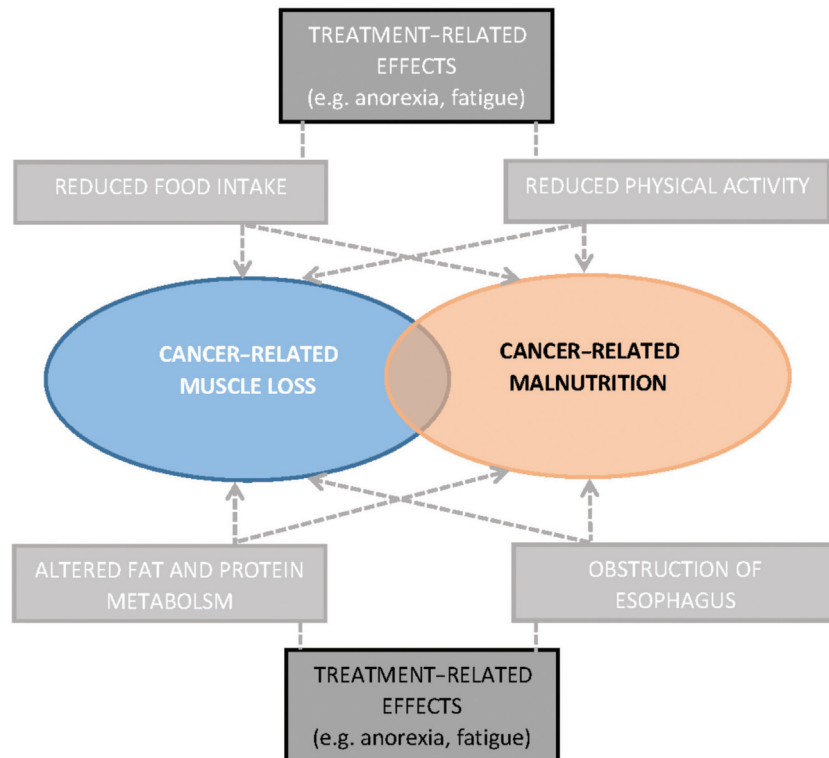
itself or the toxicities related to cancer treatment (2). People with lung cancer are known to experience a higher symptom burden than people with other cancer types due to the physical impact of the tumor and treatment, as well as the existential issues arising from the diagnosis (3). Symptoms that affect the ability to achieve an adequate nutritional intake are described as nutrition impact symptoms, such as loss of appetite, nausea, or vomiting, and increase the risk of developing malnutrition (4), which is associated with adverse outcomes including higher mortality (5). The Dietetic Assessment and Intervention in Lung Cancer (DAIL) trial, an observational study of 96 people with non-small cell lung cancer (NSCLC), found that 78% of participants required specialized nutrition advice and 52% had a critical requirement for dietetic intervention, predominantly due

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Abbreviations used: CT, computed tomography; GLIM, Global Leadership Initiative on Malnutrition; HMB,  $\beta$ -hydroxy  $\beta$ -methylbutyrate; MNA, Mini Nutrition Assessment; NSCLC, non-small cell lung cancer; PG-SGA, Patient-Generated Subjective Global Assessment; PNI, Prognostic Nutrition Index; SMI, skeletal muscle index.



**FIGURE 1** An overview of the tumor-related and treatment-related factors contributing to the development of muscle loss and malnutrition in people with lung cancer.

to a high burden of nutrition impact symptoms (6). The high symptom burden, and subsequent risk of malnutrition, experienced by people with lung cancer mean that early identification and treatment of nutritional issues is vital. A narrative review, published in 2016, described the status of the literature at that time regarding the prevalence of malnutrition and other nutritional concerns, as well as current evidence for nutritional management of people undergoing or recovering from lung cancer treatment (7). However, over the last 5 y the treatment landscape for lung cancer has changed significantly, with subsequent implications for nutritional management. Immunotherapy agents, such as pembrolizumab, nivolumab, and atezolizumab, are widely used to treat locally advanced and metastatic NSCLC (8). In small cell lung cancer, trials are demonstrating efficacy of using immunotherapy to complement current chemotherapy regimens (8). We aimed to provide a narrative review of studies published in the past 5 y that report on the prevalence of malnutrition and muscle loss as well as nutritional and multimodal interventions to treat these conditions in the context of the changing treatment landscape.

### Current Status of Knowledge

#### Nutritional conditions affecting people with lung cancer *Malnutrition.*

Weight loss at the time of diagnosis and over the course of treatment is well established as an independent prognostic

indicator in people with lung cancer (9). However, the rising prevalence of overweight and obesity may complicate the identification of underlying weight or muscle loss (10). Nutrition assessment has moved beyond the simplistic measure of weight loss alone to encompass broader parameters to determine nutritional status and identify the presence or absence of malnutrition (11–13). The development of malnutrition is influenced by a number of factors related to the tumor itself, including proinflammatory mediators and tumor-derived catabolic factors, as well as the potential for the tumor to obstruct or partially obstruct the esophagus and consequently affect food intake (12, 14). In addition, the treatment itself induces side effects, such as esophagitis, anorexia, and nausea, which may further affect food intake as well as physical activity level, leading to loss of muscle mass and malnutrition (12, 14) (Figure 1). Malnutrition, assessed using various methods in people with lung cancer, is reported to have a prevalence of 35–70%, depending on treatment type, stage of disease, and assessment method (15). The adverse outcomes associated with cancer-related malnutrition in people with lung cancer, including reduced survival, poorer quality of life, and impaired physical function, have been well documented (16–19). However, this review was unable to identify studies investigating the prevalence or impact of malnutrition in people receiving immunotherapy for lung cancer. A systematic review and meta-analysis of 52 randomized controlled trials in NSCLC found a significantly higher incidence of colitis in patients

receiving immunotherapy compared with those receiving chemotherapy, potentially increasing nutritional risk (20). This remains a crucial area to be explored in view of the increased use of these therapies. In 2018, the Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis of malnutrition in clinical populations were published (12). The GLIM criteria were developed by representatives from global clinical nutrition societies and are proposed as the global consensus criteria to support standardization of malnutrition diagnosis in both clinical and research settings. The GLIM criteria contain 3 phenotypic criteria (weight loss, low BMI, reduced muscle mass) and 2 etiologic criteria (reduced food intake or assimilation, inflammation) (12). At least 1 phenotypic and 1 etiologic criteria must be met to diagnose malnutrition. In an observational cohort study of 1219 people with lung cancer treated with surgery or chemotherapy, Yin et al. (21) applied the GLIM criteria using multiple anthropometric measures to assess reduced muscle mass and found a malnutrition prevalence of 18–29%. In the same study, GLIM-defined malnutrition was associated with a 1.4 times higher risk of mortality (HR: 1.36; 95% CI: 1.12, 1.63;  $P = 0.001$ ), while in a secondary analysis of the same cohort the authors demonstrated that weight loss over 6 mo was the most important variable contributing to the malnutrition diagnosis using machine-learning algorithms (22). The Patient Generated Subjective Global Assessment (PG-SGA) is a nutrition assessment tool that effectively applies the GLIM phenotypic and etiologic criteria in practice (23). The PG-SGA generates a score as well as categorizes patients as well nourished, or having mild–moderate or severe malnutrition. A higher PG-SGA score has also been associated with worse overall survival in people with newly diagnosed stage IIIB and IV lung cancer (24). A systematic review and meta-analysis of 12 observational studies demonstrated higher mortality and lower quality of life in people with lung cancer diagnosed with malnutrition using the PG-SGA as well as other assessment tools such as the Mini Nutrition Assessment (MNA) or Prognostic Nutrition Index (PNI) (15). The MNA includes most of the GLIM phenotypic and etiologic criteria, with the exception of inflammation. However, although the PNI is considered a nutrition assessment tool, it only assesses serum albumin and blood lymphocyte count, predominantly reflecting systemic inflammation. A comparison of multiple definitions of malnutrition in a mixed population of 2794 people with cancer demonstrated that the GLIM criteria were superior at identifying malnourished patients and more strongly associated with poorer survival and hospital admission (25). Nutrition assessment tools that reflect the parameters within the GLIM criteria are likely to be the optimal tools for use in practice with people with lung cancer.

### **Muscle loss.**

Low muscle mass is a key feature of malnutrition and is one of the phenotypic criteria within the GLIM criteria (12). Low muscle mass is often referred to as sarcopenia in studies in people with cancer. However, the term “sarcopenia”

is more commonly used to refer to the age-related loss of muscle mass, muscle strength, and function (10). For the purpose of this review, the term “low muscle mass” will be used to more accurately reflect the condition under discussion. Low muscle mass is usually assessed using an objective measure such as DXA, computed tomography (CT) imaging, or bioelectrical impedance analysis (BIA), all of which have their own strengths and limitations (26). However, the equipment to support measurement of low muscle mass may not be readily available at many health services. In the absence of objective measurement techniques, anthropometric measures such as calf circumference or a subjective assessment of muscle stores may be utilized, such as the PG-SGA or SGA, although this will not provide a quantifiable measure of muscle mass (12). Over the past 10 y a large number of studies have been published that focus on the clinical impact of muscle loss in cancer; this has largely been driven by the opportunistic utilization of CT images taken as part of routine cancer treatment. Indeed, our literature search identified in excess of 40 studies on low muscle mass within the past 5 y. As such, we focus on a review of recent systematic reviews and meta-analyses in this area as well as some notable individual studies during this time period.

Low muscle mass at the time of diagnosis is reported to affect from 47–71% of people with lung cancer (27, 28). Furthermore, additional loss of muscle mass may occur throughout the treatment and recovery period. A 2020 systematic review and meta-analysis of 15 prospective and retrospective observational studies examined changes in skeletal muscle index (SMI) during chemotherapy (29). Of the 15 studies, 60% were published in 2018–2019 and the predominant cancer type was advanced NSCLC. The SMI is calculated similarly to BMI, whereby skeletal muscle cross-sectional area ( $\text{cm}^2$ ) at the third lumbar vertebrae is divided by height ( $\text{m}^2$ ) to obtain the SMI ( $\text{cm}^2/\text{m}^2$ ). The meta-analysis revealed a mean reduction in SMI of  $2.72 \text{ cm}^2/\text{m}^2$  (95% CI: 1.77,  $3.67 \text{ cm}^2/\text{m}^2$ ;  $P < 0.001$ ), while the degree of muscle loss in males was 1.6 times higher than in females (males:  $4.52 \text{ cm}^2/\text{m}^2$ ; 95% CI: 3.34,  $5.71 \text{ cm}^2/\text{m}^2$ ;  $P < 0.001$ ; females:  $2.86 \text{ cm}^2/\text{m}^2$ ; 95% CI: 0.81,  $4.92 \text{ cm}^2/\text{m}^2$ ;  $P = 0.01$ ).

This indicates a high risk of ongoing muscle loss during chemotherapy treatment, particularly among males. Less is understood about the extent of muscle loss that occurs during curative intent (chemo)radiotherapy for lung cancer. Only 1 study has investigated muscle loss in a secondary analysis of 41 people with NSCLC treated with chemoradiation, and found that significant loss of muscle cross-sectional area ( $-6.6 \text{ cm}^2$ ; 95% CI:  $-9.7, -3.1 \text{ cm}^2$ ;  $P < 0.001$ ) occurs within the initial 4 wk of treatment (30). However, the same study found that minimal loss occurred after week 4 and up to 3 mo after treatment completion ( $-0.2 \text{ cm}^2$ ; 95% CI:  $-3.6, 3.1 \text{ cm}^2$ ;  $P = 0.91$ ). This suggests that muscle loss occurs rapidly and early during chemoradiation, which may be the optimal time for preventative intervention; however, further studies are required to confirm these findings.

Low muscle mass at the time of lung cancer diagnosis is associated with worse outcomes. A 2021 systematic review

**TABLE 1** Description of the types of nutrition interventions utilized in studies of people with lung cancer

Type of nutrition intervention	Description of the intervention
Dietary counseling	Individualized counseling that takes into consideration nutritional status, nutritional requirements, symptoms, treatment plan, comorbidities, and social situation to improve nutritional intake
Protein and amino acids	Consumption of foods and oral nutrition supplements rich in protein and amino acids and their derivatives to meet the increased nutritional needs of people with lung cancer
n-3 Fatty acids	Consumption of foods, oral nutrition supplements, and fish-oil supplements rich in n-3 fatty acids to induce anti-inflammatory benefits
Dietary patterns	Holistic dietary interventions that reflect the quantity, variety, and groupings of foods and beverages in the diet, better reflecting “real world” dietary intake. Assessed using a priori or a posteriori methods
Multimodal prehabilitation	Multimodal approaches including nutritional, physical activity, psychological, and/or pharmacological interventions in combination, commenced prior to cancer treatment to enhance treatment tolerability and outcomes in cancer
Multimodal rehabilitation	Multimodal and multidisciplinary approaches including nutritional, physical activity, psychological, and/or pharmacological interventions in combination, commenced after cancer treatment to improve cancer-related outcomes

and meta-analysis of 10 studies in people following resection for NSCLC reported low muscle mass was associated with significantly worse survival (OR: 3.07; 95% CI: 2.45, 3.85;  $P < 0.001$ ) and worse postoperative complications (OR: 1.86; 95% CI: 1.42, 2.44;  $P < 0.001$ ) (31). Similarly, a 2020 systematic review and meta-analysis investigated survival outcomes from 15 studies of people with lung cancer receiving surgery, chemotherapy, radiotherapy, targeted therapies, or combinations of these treatments (28). The meta-analysis found a 3.13-fold higher risk of mortality (95% CI: 2.06-, 4.76-fold;  $P < 0.001$ ) in lung cancer patients with low muscle mass. The greater risk of adverse outcomes in lung cancer patients with low muscle mass highlights the importance of early identification of its presence. Several screening tools have been developed and validated for detecting the risk of age-related sarcopenia; however, valid and reliable tools to screen for low muscle mass in cancer are just emerging (10). Currently, using the SARC-F in combination with calf circumference is recommended (10), although the sensitivity to detect low muscle mass is relatively low at 67% (32). In the interim, understanding who is at higher risk of low muscle mass may be beneficial in identifying people requiring further assessment and potentially intervention. Factors that have been associated with a higher risk of low muscle mass include male gender, poor performance status, advanced disease stage, smoking, and low handgrip strength (29, 33).

Cachexia is an additional condition affecting people with lung cancer with a complex and multifactorial pathophysiology (34). Although cachexia is commonly understood to feature muscle loss, anorexia, weight loss, and inflammation, similar to malnutrition, the diagnosis of cachexia is not currently well defined. Furthermore, it is generally understood that cachexia is unable to be reversed by nutrition therapy and may require concurrent pharmaceutical and medical intervention (35). Therefore, a comprehensive assessment of the recent evidence regarding the complex metabolic and

physical changes that occur with cachexia and potential therapeutical intervention is beyond the scope of this review.

### Advances in Nutritional Knowledge in Lung Cancer

There are a number of factors that are under consideration for the treatment of malnutrition and low muscle mass in lung cancer. The following sections of this review highlight advances in nutritional and multimodal practices and consider potential recommendations for practice. **Table 1** describes the types of interventions considered in this review. **Table 2** provides an overview of the studies examining nutrition interventions without a multimodal component.

#### Dietary counseling and nutrition support

Individualized dietary counseling, considering factors such as treatment type, symptom burden, and social context, is the first-line treatment to maintain and improve nutritional status in patients with cancer (36). In a clinical prospective study of 48 patients receiving chemotherapy for nonresectable lung cancer, an early intensive nutritional intervention including dietitian-led dietary counseling and ad libitum intake of a protein- and antioxidant-rich oral nutrition supplement, effectively counteracted weight loss compared with retrospective controls (37) (**Table 2**). BMI, SMI, handgrip strength, and quality of life were not significantly improved after 9 d of intervention. However, the duration of intervention was most likely too short to observe an effect on these outcomes (37). Notably, the limited sample and use of retrospective controls are further limitations, with potential implications for the study findings. In a larger secondary data analysis of 506 hospitalized patients with various cancer types, including 113 patients with lung cancer, those who received individualized nutritional support from a dietitian consumed significantly higher average daily protein (52.7 g/d vs. 44.2 g/d;  $P < 0.001$ ) and caloric intake (1411 kcal/d

**TABLE 2** Clinical studies and systematic and scoping reviews assessing the effect of nutrition interventions in people undergoing treatment for lung cancer<sup>1</sup>

Study (ref), year, setting	Study design	Population	Intervention	Results
Tanaka et al. (37) 2018, Japan	Prospective cohort (n = 10) with historical controls (n = 38)	Inoperable or recurrent NSCLC treated with first-line chemotherapy	Individualized nutrition counseling monthly by a registered dietitian, plus whey peptide oral nutrition supplement for 90 d	Intake of energy (kcal/d) and all macronutrients remained stable over the 90 d. Body weight, BMI, and SMI remained stable over the 90 d. Participants receiving individualized counseling had significantly higher odds of gaining weight after 90 d than historical controls (OR: 8.4; 95% CI: 1.6, 42; P = 0.01)
Bargetzi et al. (38) 2021, Switzerland	Secondary analysis of randomized controlled trial: n = 506; n = 113 (lung cancer)	Hospital inpatients with a cancer diagnosis, NRS 2002 score $\geq 3$ and expected hospital length of stay $>4$ d	Individualized nutrition support (oral nutrition, escalating to enteral or parental nutrition according to a predefined protocol) delivered by a dietitian; control group received usual hospital food	Individualized nutrition support decreased 30-d mortality (OR: 0.57; 95% CI: 0.35, 0.94; P = 0.027) and reduced risk of functional decline (OR: 0.59; 95% CI: 0.38, 0.93; P = 0.021). No significant difference in hospital stay or nonelective hospital readmission
Kaya et al. (43) 2016, Turkey	Randomized controlled trial (n = 58)	NSCLC undergoing anatomic resection	Preoperative nutrition program of immune-modulating formula (enriched with arginine, n-3 fatty acids, nucleotides) for 10 d; control group continued usual diet	Fewer postoperative complications were observed in the group receiving preoperative immune-modulating formula compared with controls (6/11 vs. 12/27, P = 0.049)
Pascoe et al. (46) 2021, United Kingdom	Randomized controlled trial (n = 38)	Newly diagnosed NSCLC or SCLC, performance status of 0-2, life expectancy of $>4$ mo; patients suitable for curative intent treatment were excluded	Daily oral supplement containing HMB, arginine, and glutamine for 12 wk; control arm received no supplement; all participants received structured nutrition, exercise, and symptom control advice	Trial ceased early due to nonadherence to the intervention due to the unpalatable supplement. Of the participants enrolled, no significant change from baseline to 12 wk in lean body mass or grip strength between groups. Odds of being alive without significant loss of lean body mass were reduced in the intervention arm (OR: 0.21; 95% CI: 0.045, 0.96; P not reported)
Wang et al. (47) 2021, China	Systematic review and meta-analysis (n = 22 studies)	All cancer types (including lung cancer) receiving chemo(radiotherapy)	Supplementation with n-3-enriched oral nutrition supplements during chemo(radiotherapy)	Meta-analysis found body weight increased significantly (MD = 0.59 kg; 95% CI: 0.06, 1.13; P = 0.03) and BMI (MD = 0.43 kg/m <sup>2</sup> ; 95% CI: 0.07, 0.79; P = 0.02) increased significantly with oral nutrition supplementation

(Continued)

**TABLE 2** (Continued)

Study (ref), year, setting	Study design	Population	Intervention	Results
de van der Schueren et al. (48) 2018, Netherlands	Systematic review and meta-analysis ( <i>n</i> = 11 studies)	All cancer types (including lung cancer)	Dietary counseling, oral nutrition supplements (with or without protein or n-3 fatty acid enrichment)	Meta-analysis found a benefit overall for these interventions on body weight (+1.31 kg; 95% CI: 0.24, 2.38; <i>P</i> = 0.02) during chemo(radio)therapy. Individually, only high-protein, n-3-enriched supplements improved body weight (+1.89; 95% CI 0.51, 3.27 kg; <i>P</i> = 0.02)
Lam et al. (49) 2021, Australia	Systematic review and meta-analysis ( <i>n</i> = 31 studies)	All cancer types (including lung cancer)	Supplementation with n-3 capsules, pure fish oil or oral nutrition supplements compared with a control	Meta-analysis found no significant between-group benefit from supplementation on muscle mass (MD: -1.58 kg; 95% CI: 3.25, 0.09; <i>P</i> = 0.06) or body weight (MD: -4.02 kg; 95% CI: -0.11, -8.15; <i>P</i> = 0.06)
Cheng et al. (50) 2021, China	Randomized controlled trial ( <i>n</i> = 60)	Diagnosis of lung cancer and NRS 2002 score $\geq 4$	n-3 fatty acid capsules (1.6 g EPA, 0.8 g DHA) for 12 wk; participants in both arms received nutrition counseling	Higher weight was observed in the intervention arm after 12 wk (66.71 $\pm$ 9.17 vs. 61.33 $\pm$ 8.03 kg; <i>P</i> = 0.021). No differences in BMI or upper arm circumference between study arms
Curtis et al. (55) 2022, Australia	Scoping review ( <i>n</i> = 7 included studies)	All cancer types (including lung cancer)	Various dietary patterns investigated in the included studies (Mediterranean diet, ketogenic diet, adherence to Healthy Eating Index, and PCA-derived dietary patterns)	Adherence to a diet high in "fat and fish," derived using PCA, was associated with reduced odds of low muscle mass (OR: 0.30; 95% CI: 0.10, 0.83; <i>P</i> = 0.02). Other dietary patterns demonstrated inconsistent findings
Torricelli et al. (63) 2019, Italy	Prospective cohort ( <i>n</i> = 30) with historical controls ( <i>n</i> = 30)	Advanced NSCLC receiving chemotherapy	Texidrofólico® (Citozeatec) dietary supplement twice daily for 90 d plus individual nutrition counseling	After 90 d, the mean weight in the intervention arm had increased (baseline: 55.2 $\pm$ 12.49 kg; 90 d: 63.0 $\pm$ 10.14 kg) and decreased in the historical controls (baseline: 54.3 $\pm$ 12.88 kg; 90 d: 48.0 $\pm$ 11.66 kg); <i>P</i> < 0.05
Laviano et al. (64) 2020, Croatia, Italy, Slovakia, Sweden	Randomized controlled trial ( <i>n</i> = 55)	NSCLC commencing first-line chemotherapy	Whey-based oral nutrition supplement with DHA, EPA, vitamin D for 12 wk; control group received isocaloric supplement	No between-group difference at 12 wk for changes in weight (0.8 kg vs 0.6 kg; <i>P</i> = 0.66), waist circumference (not reported), calf circumference (not reported), or lean body mass (437.6 g vs. 1888 g; <i>P</i> value not reported)

<sup>1</sup>HMB,  $\beta$ -hydroxy  $\beta$ -methylbutyrate; MD, mean difference; NRS 2002, Nutrition Risk Score 2002; NSCLC, non-small cell lung cancer; PCA, principal components analysis; ref, reference; SCLC, small cell lung cancer; SMI, skeletal muscle index.

vs. 1154 kcal/d;  $P < 0.001$ ) during hospital admission (38) (Table 2). Participants who received individualized nutrition support reported increased quality of life and had reduced odds of death within 30 d and 6 mo of intervention. Overall, few studies have investigated the efficacy of dietary counseling in patients with lung cancer. Those that have demonstrate the potential benefits of individualized dietary counseling and/or nutritional interventions led by a qualified dietitian, which commenced early and continued throughout treatment and into recovery. However, scope remains for further high-quality and larger studies in this patient group to confirm these benefits and inform the optimal management pathway.

### Protein and amino acids

Adequate protein intake is the foundation for the retention or gain of muscle mass (39, 40). Current evidence-based nutritional guidelines recommend protein intake between 1.0 g/(kg · d) to 1.5 g/(kg · d) for people undergoing cancer treatment (36). However, recent literature supports intakes of up to 2 g/(kg · d) to attenuate muscle loss, especially in severe illness (41). In an observational study of 52 patients receiving first-line treatments for inoperable NSCLC, Tobberup et al. (42) demonstrated that relative protein intakes tended to increase during treatment [1.14 g/(kg · d) to 1.32 g/(kg · d)] and were higher in those who maintained muscle mass [1.4 g/(kg · d)] compared with those who lost muscle mass [1.0 g/(kg · d)]. A higher protein and energy intake and stable body weight were associated with maintenance of muscle mass (42). Considering the timing of protein intake, dinner meals were, on average, the biggest contributor to protein consumption (>30 g protein), while breakfast and lunch meals were lower in protein (on average, <20 g protein) (42).

Protein-rich nutrition supplementation may be important for postoperative recovery in lung cancer patients. A single-center prospective trial of 58 patients undergoing anatomic resection for NSCLC found that a 10-d preoperative nutrition program, including a protein-rich supplement [containing arginine, omega-3 (n-3) fatty acids, and nucleotides], decreased the risk of postoperative complications (6/11 vs. 12/27 developed complications;  $P = 0.049$ ), time to chest tube removal [4 (2–15) d vs. 6 (1–42) d;  $P = 0.019$ ], and smaller reduction in albumin concentrations (14.69% vs. 25.71%;  $P < 0.001$ ) compared with patients who consumed a usual diet (43) (Table 2). However, it must be noted that energy and protein intakes of the patients were not assessed, and it remains unclear which nutritional components of the supplement may have most greatly influenced these early postoperative benefits.

Branched-chain amino acids and their metabolites, such as  $\beta$ -hydroxy  $\beta$ -methylbutyrate (HMB), a metabolite of the branched-chain amino acid leucine, have been shown to be promising nutrition components able to promote muscle protein synthesis and suppress protein degradation (44). A recent systematic review and meta-analysis of 15 randomized controlled trials of various clinical conditions, including 2 studies of cancer cachexia, found evidence to

support HMB supplementation (alone or in combination with other nutritive supplements) to increase muscle mass and strong evidence to support improvements in muscle strength compared with the controls (45). However, no effects were observed for body weight or other clinical outcomes. The authors also noted issues relating to bias—in particular, regarding lack of blinding and poor intervention compliance across several studies. Very few studies have investigated the effects of HMB supplementation in lung cancer. A 2021 randomized controlled phase II trial was commenced, recruiting 38 patients with newly diagnosed advanced small cell or NSCLC who received 1.2 g HMB, 7 g arginine, and 7 g glutamine twice per day or no supplement for 12 wk (46) (Table 2). Initial findings demonstrated detrimental effects on survival without significant loss of muscle mass for the intervention and no effect on lean body mass or handgrip strength (46). However, the investigation was halted early due to poor adherence and early discontinuation from treatment, which begins to highlight the challenges associated with adherence to nutritional interventions in this vulnerable cohort; yet, these findings must be interpreted with the strongest of caution (46). Current evidence in lung cancer supports protein intake levels in line with current nutrition guidelines for cancer. However, the optimal timing, quality, and type remain elusive. Future studies should aim to uncover novel strategies to overcome issues such as poor intervention compliance.

### n-3 Fatty acids

Systemic inflammation has been posited as a major component driving the progression of malnutrition and muscle loss (14). n-3 Fatty acids are anti-inflammatory substances that have been shown to improve appetite, food intake, body weight, and body composition in patients with various cancers (36). In the past 5 y, several reviews and meta-analyses of randomized controlled trials have examined the effect of n-3 fatty acids in various cancer types, including lung cancer, with mixed findings. Wang et al. (47) demonstrated that intake of n-3 fatty acid-enriched oral nutrition supplements resulted in increased body weight and BMI and reduced inflammatory markers, including plasma C-reactive protein, TNF- $\alpha$ , and IL-6, and incidence of adverse events during chemotherapy (Table 2). de van der Schueren et al. (48) demonstrated similar effects on body weight compared with isocaloric controls, an effect not observed with dietary counseling or high-energy oral nutritional supplements alone, during chemotherapy (Table 2). Attenuation of lean body mass loss and improvement in several quality-of-life domains were also observed during this systematic review (48). However, these findings are not entirely consistent with another meta-analysis of 26 randomized controlled trials in various cancers, including lung cancer, which found that n-3 supplementation significantly reduced the likelihood of developing treatment-related toxicities, such as peripheral neuropathy (Table 2). No differences in muscle mass, quality of life, or body weight were observed compared with the controls (49). Few recent studies have examined the efficacy

of n-3 fatty acids in lung cancer specifically. In a 2021 randomized, double-blind, parallel clinical trial of 60 nutritionally at-risk patients with lung cancer, supplementation with 1.6 g/d EPA and 0.8 g/d DHA resulted in significantly higher body weight, albumin, and triglycerides and reduced inflammatory markers compared with the placebo group (50) (Table 2). However, no differences were observed between groups for BMI, upper arm circumference, or skinfold thickness (50). Notably, the authors acknowledged the limited sample size, which included participants at risk of nutritional issues. Data relating to overall dietary intake and level of physical activity were also not reported and may have precluded nutrition- and muscle-related findings. In line with current nutrition guidelines for cancer (36), n-3 fatty acids, alone or as a component of oral nutrition supplements, are a beneficial addition to nutrition interventions in lung cancer given their strong biological rationale and potential to improve risk of treatment toxicities, quality of life, and anthropometric factors. However, larger studies that focus on patients with lung cancer are required to confirm the current limited evidence.

### Dietary pattern approaches

Dietary pattern approaches are emerging as a complementary method to traditional nutrient-specific studies of diet-disease relations. Conceptually, dietary patterns represent “real world” intake and reflect the quantity, variety, and groupings of foods and nutrients in the diet, where nutrients are not commonly consumed in isolation (51). Adherence to certain dietary patterns, such as a Mediterranean-style diet and “healthy” or “prudent” dietary patterns, has been shown to be beneficial in reducing risk of mortality and cancer recurrence in various cancer types (52–54). However, few studies have investigated the efficacy of dietary patterns on intermediate cancer-related outcomes, such as malnutrition or low muscle mass. A recent scoping review of 7 studies summarized the state of current literature, demonstrating that adherence to a dietary pattern high in dietary fat and fish may be associated with lower odds of having low muscle mass in patients with gastrointestinal cancer (55) (Table 2). However, the small body of literature and heterogeneity between studies in terms of cancer type and dietary pattern approaches used meant that no definitive conclusions could be drawn (55). In a substudy of 62 weight-stable and weight-losing patients receiving first-line systemic therapy for NSCLC, weight-losing patients were more likely to consume a diet characterized by fewer grain and animal products and more oral nutrition supplements, based on mean energy intake from each food group (56). During treatment, weight losers tended to further increase consumption of oral nutrition supplements and decrease intake of sweets and alcohol, while relative protein intake appeared to increase (56). However, of note, the potential reasons why dietary changes occurred during treatment were not considered—for example, whether participants received dietary counseling—which may have impacted findings. Novel dietary pattern approaches for the treatment of

malnutrition in cancer are promising and build upon current nutrient-specific recommendations. However, the optimal dietary pattern requires further investigation, especially in lung cancer.

### Vitamin D

Vitamin D is a nutrient of concern for patients with cancer as malnutrition and change in diet and lifestyle habits may result in vitamin D deficiency or insufficiency (57). To negate this risk and the risk of other vitamin and mineral deficiencies, the American Cancer Society and European Society for Clinical Nutrition and Metabolism (ESPEN) nutritional guidelines recommend that vitamins and minerals are consumed in amounts adequate to achieve recommended daily allowances while avoiding high-dose supplementation in the absence of an existing deficiency (36, 58). Previous meta-analyses have indicated that adequate vitamin D intake and status may be associated with reduced risk of lung cancer mortality (59, 60). However, there remains controversy as to the role of vitamin D for body composition and function in head and neck and colorectal cancers (61, 62).

In lung cancer, there are very limited data regarding the benefits of vitamin D. In a retrospectively controlled study of 60 patients with NSCLC receiving chemotherapy, individualized nutrition counseling and oral supplementation with Texidrofólico (Citozeatec), containing bioactive components such as vitamin D, vitamin C, pantothenic acid, and folate, for 90 d resulted in improved quality of life and greater likelihood of maintaining or increasing body weight during treatment (63) (Table 2). Then, in a pilot, double-blinded comparator-controlled trial of 55 patients receiving first-line chemotherapy for NSCLC, consumption of a juice-based oral nutrition supplement twice daily for 12 wk, containing 200 kcal, 10 g whey protein, 2.0 g EPA/DHA in fish oil, and 10  $\mu$ g 25-hydroxycholecalciferol, resulted in few adverse events from treatment but no differences between groups for appendicular lean mass (+173.5 g vs. +87.9 g;  $P > 0.05$ ), fat mass (+437.6 g vs. +1188.8 g;  $P > 0.05$ ), or waist and calf circumference compared with an isocaloric milk-based comparator (64) (Table 2). Handgrip strength and daily walking distance appeared improved in the intervention group; however, no significant differences were observed (64). Notable limitations include moderate compliance to the intervention (59% compared to 74% for the comparator) and a lack of quantitative dietary intake assessment, which may have implications for the observed findings. Outside of cancer, there is stronger evidence from systematic reviews to support the role of vitamin D supplementation to improve muscle strength and function in healthy and older adults (65, 66). Although such evidence in lung cancer is limited, the risk of deficiency is considered high and, as such, it is recommended that patients consume vitamins at levels adequate to meet their nutritional needs. Future larger studies should consider the individual role of vitamin D in adults with lung cancer and determine whether



supplementation is an effective tool in the management of nutrition and muscular decline.

### Early intervention to improve success

Nutritional interventions in cancer are most effective when commenced early, focusing on the prevention or management of nutrition impact symptoms and treatment of mild to moderate malnutrition or muscle loss (34). In fact, all patients with cancer should be screened for malnutrition as soon as possible after diagnosis and nutrition assessment and interventions should continue alongside treatment and recovery to counteract potentially detrimental effects of nutritional status and muscle mass (36, 67). Currently, there are no lung cancer-specific guidelines regarding when to commence nutritional interventions and the optimal type of intervention to use. However, when commenced early, prior to chemotherapy or radiotherapy treatments, intensive nutrition interventions including individualized dietary counseling with or without the use of oral nutrition supplements demonstrate positive effects for body composition and physical function in patients with lung cancer (37, 68). To achieve early intervention, the importance of nutritional screening and assessment must be recognized and prioritized by a range of clinicians and initiated upon diagnosis of lung cancer.

### Multimodal Treatment Approaches

Cancer-related malnutrition is a multifaceted condition that requires a multimodal treatment approach to improve nutritional intake and status, muscle mass and physical function, quality of life, and treatment outcomes (69). Models of care involving nutritional, physical activity, psychological, and pharmaceutical interventions have demonstrated beneficial effects in various cancers, with international expert organizations recognizing their importance to provide comprehensive high-quality cancer care (10, 69).

### Multimodal prehabilitation

Prehabilitation is the process of enhancing an individual's functional capacity prior to surgery in order to optimize physiological reserves and improve tolerance for forthcoming surgery-related stressors (70). A 2021 systematic review of 5 studies, 1 nutrition-only and 4 multimodal prehabilitation studies, examined the effect of preoperative prehabilitation on clinical and functional outcomes in patients with lung cancer, with mixed findings (71). The review demonstrated multimodal prehabilitation to be effective in improving preoperative functional capacity, including walking capacity (i.e., 6-min walk test time) and pulmonary function. However, no effects were observed on postoperative outcomes or complications (71). Several additional studies have investigated multimodal prehabilitation in patients with lung cancer. Two studies, including a secondary analysis of randomized controlled trials and 1 cohort study involving 162 patients with lung cancer, have examined the effects of prehabilitation on physical function prior to lung cancer

resection. These studies demonstrated prehabilitation involving personalized home-based exercise and nutritional and psychological support for 4 wk prior to surgery resulted in improved physical function (6-min walk test), particularly in patients who were considered at high nutritional risk (72). Completion of a similar home-based intervention, with the addition of smoking cessation support and physiotherapy, was also associated with fewer postoperative complications (73). In older adults (>70 y) with low body weight scheduled to undergo lobectomy for lung cancer, participation in a comprehensive preoperative pulmonary rehabilitation program involving physical therapy and exercise, nutrition support, and Japanese herbal medicine supplementation resulted in a lower rate of postoperative complications (74). A similar multimodal prehabilitation program, including twice-daily protein supplementation (10 or 20 g whey protein isolate with 3 g added leucine) and once-daily nutrient supplementation (1500 mg/d EPA, 1000 mg/d DHA, and 200 IU/d 25-hydroxycholecalciferol), a personalized exercise regime, and psychological support, was tested in a randomized controlled feasibility study of 35 patients with NSCLC (75). Improved nutritional intake was observed, although there were no significant effects on muscle cross-sectional area, potentially limited by the small sample size. The pretreatment period provides an excellent opportunity to initiate early multimodal interventions with the aim to improve patient outcomes. However, given the often short duration between diagnosis and treatment, early recognition of nutrition and muscular decline is essential and requires input from the multidisciplinary team. Larger high-quality studies are required to confirm the benefits of multimodal prehabilitation in lung cancer and may support the development of practical recommendations for implementation into practice.

### Multimodal rehabilitation

Few recent studies of multimodal rehabilitation have been completed in lung cancer. In a retrospective analysis of 37 patients with NSCLC who underwent lobectomy and 29 patients with chronic obstructive pulmonary disease, a 3-wk pulmonary rehabilitation program involving resistance exercise training and nutrition advice combined with breathing exercises, respiratory hygiene, and other lifestyle-related education resulted in improved 6-min walking distance and quality of life compared with baseline (76). However, the study cohort was small and details of the nutritional aspect of the intervention were not specified. Two further studies that combined lifestyle and pharmaceutical interventions in cancer also showed promising results. In 28 patients with cancer (majority lung cancer;  $n = 17$ ) who were experiencing fatigue, Yennurajalingam et al. (77) found that 100 mg/d of Anamorelin, a selective ghrelin receptor agonist, with standardized physical activity and nutritional counseling for 43 d, was associated with significant improvements in cancer-related fatigue, physical activity levels, body weight, and lean mass and insulin-like growth factor I (IGF-I) compared with baseline measures. It should be noted that the authors acknowledged the lack of a control or placebo arm as a

major limitation, meaning that contribution of the “placebo effect” to efficacy of the intervention could not be assessed. In 76 malnourished patients with lung cancer following completion of any type of anti-cancer treatment, Duan et al. (78) demonstrated that those who received 160 mg/d of megestrol acetate, a synthetic steroid and appetite stimulant, combined with oral nutrition supplements (~750 kcal/d) improved BMI, Eastern Cooperative Oncology Group (ECOG) score, midupper arm circumference, and serum albumin and pre-albumin compared with those who received megestrol acetate alone. However, treatment toxicity was comparable between groups (78).

Multimodal pre- and rehabilitation models have been shown to be generally well received by both patients and health care professionals alike. A qualitative investigation was conducted to determine the level of acceptance of tailored multimodal care before, during, and after treatment, including in people with lung cancer, their carers, and multi-disciplinary team members. In summary, patients welcomed clinicians proactively offering advice and information about well-being, preferred being informed of practical advice on what they “can do” (rather than “cannot do”), and expressed a need for social and peer support (79). However, factors such as multiple comorbidities, living alone, the psychosocial impact of diagnosis, and physical effects of treatment have also been presented as major barriers to patients completing rehabilitation programs (73, 79).

### Multimodal approaches for palliative care

There are currently limited data for multimodal interventions in patients with advanced and incurable lung cancers. However, multimodal approaches may be beneficial during palliative care, with improvements in depression scores, physical endurance, quality of life, and fatigue, with lower-level evidence supporting overall function and nutritional status in various cancers (80). A small feasibility study of 10 patients with advanced NSCLC showed that an individually tailored, 12-wk multimodal intervention including physical exercise, behavior-change education, nutritional counseling, and palliative care consultations was associated with maintenance of physical activity levels, symptom burden, and quality of life, and a significant decrease in tiredness (81).

Investigations into multimodal pre- and rehabilitation in patients with advanced lung cancer are few; however, preliminary studies indicate that these approaches may be feasible. In an 8-wk single-arm prospective study of 30 older adults ( $\geq 70$  y) scheduled to receive first-line chemotherapy for advanced pancreatic cancer ( $n = 6$ ) or NSCLC ( $n = 24$ ), a multimodal intervention involving home-based resistance exercise and nutritional counseling plus a daily branched-chain amino acid-rich oral nutrition supplement (139 kcal; branched-chain amino acids, 2500 mg/d; coenzyme Q10, 30 mg/d; and L-carnitine, 50 mg/d) was well tolerated. Notably, 96.7% of participants demonstrated excellent attendance ( $\geq 4$  of 6 planned sessions) and the median proportions of days of compliance with supplement consumption and exercise interventions were 99% and 91%, respectively (82).

Muscle mass, nutritional status, caloric intake, and physical function were shown to be maintained, while muscle strength and exercise capacity (i.e., daily steps and time spent in moderate-vigorous physical activity) were improved (82). However, given the small sample size, the efficacy of the interventions should be interpreted with caution. In all, there has been a recent expansion of evidence for multimodal models of care in lung cancer pre- and rehabilitation with largely beneficial findings. Larger high-quality studies, considering the acknowledged patient barriers, are needed to confirm these findings and investigate whether nutrition and physical exercise, with or without pharmaceutical input, can improve lung cancer-related outcomes. Future trials should particularly focus on people with lung cancer receiving chemotherapy, given that it is one of the main treatment options.

### Conclusions

Malnutrition and muscle loss are common in people with lung cancer and occur across treatment modalities, albeit with a lack of investigation in immune and targeted therapies, and are associated with poor patient and treatment outcomes. Validated screening and assessment tools should be integrated into current care and utilized to identify these conditions as early as possible to initiate treatment. Interventions involving dietary counseling, high dietary protein, and n-3 fatty acids in people with lung cancer show some benefits in a variety of patient outcomes. Interventions using specific amino acids or derivatives, dietary patterns, or vitamin D supplementation have been the subject of very limited studies in people with lung cancer and require further investigation. Multimodal interventions, delivered before, during, or after treatment (prehabilitation or rehabilitation), are promising, albeit with mixed findings. However, as we have noted, current evidence for all of these interventions is limited by small sample sizes and lack of large randomized trials specific to lung cancer. Furthermore, this review identified no studies investigating nutrition or multimodal interventions in people with lung cancer receiving immunotherapies or targeted therapies, despite the increasing use of these treatments in the clinical setting. There is an urgent need for investment in large nutrition and multimodal trials to determine effective treatment for malnutrition and muscle loss in people with lung cancer, including newer treatment modalities, particularly in view of the strong evidence for adverse outcomes related to these conditions.

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