

# BMJ Open The assessment and impact of sarcopenia in lung cancer: a systematic literature review

Jemima Collins,<sup>1</sup> Simon Noble,<sup>2</sup> John Chester,<sup>3</sup> Bernadette Coles,<sup>4</sup> Anthony Byrne<sup>5</sup>

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<sup>1</sup>Cardiff University, Cardiff, UK

<sup>2</sup>Department of Palliative Medicine, Cardiff University, Cardiff, South Wales, UK

<sup>3</sup>Department of Medical Oncology, Cardiff University, Cardiff, South Wales, UK

<sup>4</sup>Cancer Research Wales Library, Velindre NHS Trust, Cardiff, South Wales, UK

<sup>5</sup>Marie Curie Palliative Care Research Centre, Cardiff University, Cardiff, South Wales, UK

## Correspondence to

Dr Jemima Collins;  
[jemimacollins@doctors.net.uk](mailto:jemimacollins@doctors.net.uk)

## ABSTRACT

**Objectives:** There is growing awareness of the relationship between sarcopenia (loss of muscle mass and function), and outcomes in cancer, making it a potential target for future therapies. In order to inform future research and practice, we undertook a systematic review of factors associated with loss of muscle mass, and the relationship between muscle function and muscle mass in lung cancer, a common condition associated with poor outcomes.

**Design:** We conducted a computerised systematic literature search on five databases. Studies were included if they explored muscle mass as an outcome measure in patients with lung cancer, and were published in English.

**Setting:** Secondary care.

**Participants:** Patients with lung cancer.

**Primary outcome:** Factors associated with loss of muscle mass and muscle function, or sarcopenia, and the clinical impact thereof in patients with lung cancer.

**Results:** We reviewed 5726 citations, and 35 articles were selected for analysis. Sarcopenia, as defined by reduced muscle mass alone, was found to be very prevalent in patients with lung cancer, regardless of body mass index, and where present was associated with poorer functional status and overall survival. There were diverse studies exploring molecular and metabolic factors in the development of loss of muscle mass; however, the precise mechanisms that contribute to sarcopenia and cachexia remain uncertain. The effect of nutritional supplements and ATP infusions on muscle mass showed conflicting results. There are very limited data on the correlation between degree of sarcopenia and muscle function, which has a non-linear relationship in older non-cancer populations.

**Conclusions:** Loss of muscle mass is a significant contributor to morbidity in patients with lung cancer. Loss of muscle mass and function may predate clinically overt cachexia, underlining the importance of evaluating sarcopenia, rather than weight loss alone. Understanding this relationship and its associated factors will provide opportunities for focused intervention to improve clinical outcomes.

## INTRODUCTION

Over the last decade, there has been increasing recognition of the clinical importance of

## Strengths and limitations of this study

- Timely systematic review considering the increasingly recognised phenomenon of sarcopenia as it relates to cachexia.
- Evaluation of sarcopenia in lung cancer, as an example of a common cancer associated with poor outcomes and a significant prognostic impact.
- Limited to publications in English only.

sarcopenia as part of the cancer cachexia syndrome, and its impact has been evaluated in a wide range of malignancies including lung, breast, upper gastrointestinal, hepatocellular and colorectal cancers.<sup>1–5</sup> The term sarcopenia is derived from the Greek meaning ‘poverty of flesh’ and is characterised by a triad of progressive loss of skeletal muscle mass, muscle strength and physical performance.<sup>6</sup> It was originally described in the elderly non-cancer population, and is often now defined as a geriatric syndrome associated with functional impairment, increased risk of falls, fractures and reduced survival.<sup>7–9</sup> Sarcopenia becomes more prevalent with increase in age—of 1421 healthy adults aged 45 years or over, the overall prevalence was 15%, rising to 64% over the age of 85.<sup>10</sup> This loss of muscle mass is usually gradual and not necessarily associated with significant or sudden weight loss.

The detrimental effects of sarcopenia can also be seen in younger patients in association with muscle disuse, malnutrition or inflammatory conditions, particularly cancer. Interest in sarcopenia as a poor prognostic indicator in cancer is rising; in various populations with cancer sarcopenia is associated with poorer performance status (PS),<sup>1</sup> reduced overall survival<sup>11 12</sup> and increased risk of chemotherapy toxicities.<sup>2 4</sup> This interest is reflected in a recent international consensus on the definition of cancer cachexia, which established sarcopenia as a key diagnostic criterion.<sup>13</sup>

The hallmark of sarcopenia is low muscle mass, more specifically an appendicular skeletal muscle mass index of more than 2 SDs below the sex-specific mean of healthy adults (ie, 5.45 kg/m<sup>2</sup> for women and 7.26 kg/m<sup>2</sup> for men).<sup>8</sup> However, central to the concept of sarcopenia is the recognition that overall neuromuscular function, rather than muscle mass alone, is essential for maintenance of independence. Therefore, when defining sarcopenia, it is vital to assess muscle strength, or physical performance, in addition to muscle mass, as the relationship between muscle mass and strength is non-linear.<sup>14 15</sup>

While many different techniques have been used to measure muscle mass and strength, few have been incorporated into routine assessment of the cancer population. The current gold standards are CT, MRI and dual-energy X-ray absorptiometry (DEXA) scans. CT and MRI allow precise differentiation between fat and other soft tissue including muscle and are therefore investigations of choice. CT focuses on a specific area of the body—for example, muscle cross-sectional area at the third lumbar vertebra—which can be related to whole body muscle mass. It is the current gold standard in body composition research and has the advantage that many patients will have CT scans as part of their diagnostic and treatment assessments. However, DEXA involves less radiation exposure compared with CT and accurately and precisely differentiates between lean and fat body compartments.<sup>16</sup> More indirect techniques for measuring muscle mass include bioelectrical impedance analysis which is non-invasive but less accurate compared with DEXA. It includes a measure of organ mass other than skeletal muscle, but is easily performed in clinical settings.<sup>17</sup> Measurements of mid-upper arm circumference and arm muscle area using skinfold thickness methods have also been used,<sup>18</sup> although these assessments are less accurate and there exists considerable interobserver variability. Measurements of muscle strength in the literature have mainly centred around handgrip strength (HGS) and quadriceps strength, although in non-cancer elderly patients, functional assessments such as the Short Physical Performance Battery and sit-to-stand tests<sup>19 20</sup> have been shown to correlate with adverse outcomes.

From the literature it is clear that there is marked diversity in current clinical practice in assessing the degree of muscle loss in patients with cancer and in quantifying its functional implications. If the loss of muscle mass and strength have significant clinical implications for patients with cancer, then standardised, validated diagnostic thresholds are clearly needed. Furthermore, while the effects of sarcopenia have been extensively studied in the elderly patients, factors associated with loss of muscle mass and strength in cancer remain unclear. As the pathophysiological mechanisms responsible for loss of muscle mass in cancer differ, at least in part, from those in sarcopenia of ageing, it is necessary to evaluate cancer-specific causative factors and clinical implications.

We therefore undertook a systematic literature review to further understand the relationship between muscle function and muscle mass and its implications for research and clinical practice within the context of cancer. We limited the review to focus on lung cancer as an example of a common cancer, associated with poor outcomes, in which sarcopenia has been shown to have a significant prognostic impact. Lung cancer has a worldwide incidence rate of 1.61 million cases per year,<sup>21</sup> and frequently presents in the advanced stages. Despite advances in anticancer therapies, survival benefits in patients with lung cancer over the past 30 years have been relatively small compared with those seen in breast, colorectal and prostate cancers.<sup>22</sup> While reasons for this are complex, many patients with lung cancer are ineligible for radical treatment at presentation due to poor PS or comorbidity, while others fail to receive their intended treatment plan because of functional decline.<sup>23 24</sup> Non-small cell lung cancer (NSCLC) has a particularly strong association with loss of muscle mass—of 441 patients consecutively referred to a regional oncology service, 47% were found to be sarcopenic.<sup>25</sup> This prevalence can be compared with 16% of a cohort of 471 survivors with breast cancer<sup>26</sup> and 39% in a cohort of 234 patients with preoperative colorectal cancer.<sup>5</sup> We conducted this systematic review with this in mind.

## METHODS

### Search strings and data sources

We not only executed a broad literature search, including various terminologies used to describe loss of muscle mass, but also specifically used ‘sarcopenia’ as a multi-purpose field search term. Recognising that changes in muscle mass may impact on muscle strength and physical function, we included these terms in our search. We united two search strings: loss of muscle mass (and its implications) and lung cancer (see [table 1](#)). The search was limited to English language and humans, with a publication date from 1946 to October 2013. We used the same search strings to develop strategies in the following five databases in order to ensure maximal coverage: MEDLINE, MEDLINE In-Process, EMBASE, AMED and the Cochrane library.

### Article retrieval

Citations were independently screened by two researchers (JCo and SN) and included for initial analysis if they described muscle mass measurements or body composition in patients with lung cancer. Both prospective and retrospective original articles were included, but conference abstracts, citations without abstracts, case reports, review articles and opinion pieces were excluded. All studies that had a cohort of patients with lung cancer were included, even if there were patient groups with other cancer types analysed. Retrieved articles were searched for additional relevant references.

**Table 1** Search strings and terms

Search strings	Search terms
Loss of muscle mass	Sarcopenia OR
	Muscle atrophy OR
	Muscle weakness OR
	Muscle mass OR
	Muscle wasting OR
	Muscle loss OR
	Weight loss OR
	Muscle strength OR
	Physical fitness OR
	Physical exertion OR
	Activities of daily living OR
	Cachexia
	AND
Lung cancer	Lung (neoplasm OR malignancy OR tumour)
	Pleural (neoplasm OR malignancy OR tumour)

### Inclusion criteria and data extraction

The selected articles were reviewed in full by two independent researchers (JCo and SN) for consideration of inclusion in the review. Where discordance in selection was observed, the article in question was discussed until consensus was reached. As there were many articles describing muscle mass as part of routine anthropometry or body composition assessments, without directly exploring it, we only included articles in which muscle mass was explored as an outcome measure. Data including patient characteristics and numbers, histological subtype and TNM (tumour, node, metastasis) stage were collated and tabulated (tables 2 and 3). We also noted units of muscle mass measurements, and techniques used to measure these.

### RESULTS

Using our broad search terms in five databases, we found an initial 5726 citations, from which we identified 64 potentially relevant articles. Three further potential articles<sup>27–29</sup> were identified from the references of these articles. From these, we excluded 11 abstracts with no published articles, 2 further abstracts that did not mention muscle mass,<sup>30 31</sup> and a systematic review of cancer cachexia.<sup>32</sup> Of the 53 final articles, we excluded a further 13 articles which mentioned muscle mass in baseline anthropometry details but did not use it as an outcome measure,<sup>33–45</sup> 4 articles which described weight loss rather than loss of muscle mass,<sup>46–49</sup> and 1 article describing the same results obtained from the same patient population as another article,<sup>50</sup> with slightly different secondary endpoints.<sup>51</sup> During the process of data extraction, a number of recurring themes became apparent. We have presented these under two main headings—factors associated with loss of muscle mass, and degree of loss of muscle mass and physical functioning.

A number of studies explored multiple variables associated with loss of muscle mass, and are therefore mentioned under more than one heading.

For the final analysis, 4 randomised controlled studies, 17 cross-sectional studies and 14 longitudinal studies met the established criteria: 35 articles in total. Muscle mass data were reported variously as fat-free mass (FFM), body cell mass, lean body mass, appendicular skeletal muscle mass, smooth muscle area at the levels of lumbar vertebra L3 and thoracic vertebra T4, mid-upper arm circumference and arm muscle area. Notably, most studies described muscle mass in more than one way. Muscle function was described as HGS and/or quadriceps strength,<sup>17 27 52–54</sup> intensity of physical activity,<sup>55</sup> patient-reported physical functioning<sup>28</sup> and muscle strength and physical performance.<sup>56</sup>

As the studies in our review expressed muscle mass in different ways, we have used the term FFM or loss of muscle mass in the body of our article in order to allow direct comparison. In addition, where the studies in this review defined a patient group as having sarcopenia, they did so based on loss of muscle mass alone, without evaluation of muscle strength or performance. This needs to be borne in mind wherever the term sarcopenia is used throughout this review.

### Factors associated with loss of muscle mass

In this review, many studies found that those with cachexia and/or weight loss also had coexistent loss of muscle mass.<sup>25 28 58 67 68 71 74</sup> Despite this, none of the studies prospectively evaluated the impact of loss of muscle mass on cancer outcomes, specifically relating to treatment. Three studies explored the loss of muscle mass comparing men and women, finding that a significantly greater percentage of men were affected,<sup>25 64</sup> and that they exhibited a decreasing trend in FFM after chemotherapy compared with baseline, whereas women did not.<sup>29</sup> Reflecting the process of loss of muscle mass in the different stages of cancer, a study of 60 patients with preoperative NSCLC with stage I and II disease showed no difference in FFM compared with controls,<sup>27</sup> whereas in a cohort of 352 patients with advanced cancer, 84% of those with cachexia had a reduced FFM.<sup>74</sup>

The pathophysiology of loss of muscle mass in patients with lung cancer is complex, as illustrated in the diversity of articles exploring this. Low FFM has been associated with low albumin and high acute phase protein concentrations,<sup>57 58 71</sup> reflecting the inflammatory pathways involved. Abnormal protein metabolism is implicated in the development of sarcopenia; however, in this review, neither anabolic<sup>58</sup> nor proteolytic pathways<sup>59 55</sup> had any consistent effect on loss of muscle mass. The exception to this was the lysosomal protease cathepsin-B, which was significantly increased in depleted FFM patients.<sup>59</sup> The pathophysiology may also differ depending on disease stage and cachexia phase. There is some evidence, for example, that in patients with precachectic NSCLC, despite weight loss, the ubiquitin–proteasome

**Table 2** Loss of muscle mass as outcome measures and factors associated with it

First author (year)	Patients		Muscle mass measurement(s)	Method of measurement	Study			Result
	n (M/F)	Tumour, stage			Design	Controls	Comparison	
McMillan (2001) <sup>57</sup>	40 (40/0)	NSCLC n=11, upper GI n=22, colon n=7 All locally advanced or metastatic	BCM	Total body potassium	Cross sectional	Nil	The inter-relationship between albumin, body cell mass and the systemic inflammatory response	Albumin concentrations correlated with BCM ( $r=0.686$ , $p<0.001$ ) and negatively correlated with CRP ( $r=-0.545$ , $p<0.001$ )
Crown (2002) <sup>58</sup>	30 (NR/NR)	NSCLC in all Inoperable, stage NR	FFM, MUAC	BIA, upper arm measurements	Case-control, longitudinal over 2 years	n=30 HV	ILGF system and cancer cachexia	More LC than HV had MAMC in the lowest quartile ( $p<0.05$ ) at baseline, Male LC patients had lower FFM than male HV ( $p<0.05$ ) at baseline, No significant longitudinal trend observed in IGFBP-3 and IL-6 and nutritional status, $p=NS$
Jago (2002) <sup>59</sup>	36 (27/9)	Mix of NSCLC and SCLC Stage 1–21 Stage 2–6 Stage 3–6 Stage 4–2	FFMi	BIA, Four skinfold method, %BFMAMA	Cross sectional	n=10 patients referred for thoracotomy for non-malignant conditions	Ubiquitin-proteasome and lysosomal proteolytic pathway gene expression in LC and association with LMM	Cathepsin B expression in LC inversely related to FFMi, $p=0.003$ ; Cathepsin-B expression increased in 'depleted FFMi cancer patients' vs controls $p=0.003$ ; No relationship between cathepsin B expression and %BFMAMA, $p=NS$
Wieland (2007) <sup>60</sup>	286 (NR/NR)	NSCLC n=181, stage IIIB or IV	SMA at T4	CT at T4	Longitudinal	n=7 HV	Establish prevalence of PIF in patients with cancer, and its association with muscle loss	In patients with NSCLC: PIF unrelated to survival and muscle loss, $p=NS$ ; PIF positive patients rate of loss of muscle mass per 100 days

Continued

**Table 2** Continued

First author (year)	Patients			Study				
	n (M/F)	Tumour, stage	Muscle mass measurement(s)	Method of measurement	Design	Controls	Comparison	Result
Martinez-Hernandez (2012) <sup>61</sup>	21 (19/2)	LC n=13, GI cancer n=6, Other cancer n=2 Stage according to tumour group NR	FFM	BIA	Longitudinal	n=8 HV	The role of IL-15) in patients with cachectic cancer	-3.4±2.1% vs PIF negative patients -2.4±1.7%, p=NS At weeks 4 and 8, patients with cancer lost FFM in tandem with decreasing IL-15 levels, r=0.514 and r=0.535, both p<0.05
Op den Kamp (2012) <sup>55</sup>	16 (15/1)	NSCLC in all Stage I–II—11 Stage IIIA—2 Stage IIIB—3	FFMi	DEXA	Cross sectional	n=10 HV	Skeletal muscle NF-κB and ubiquitin proteasome system activity in precachexia	FFMi no significant difference in precachectic cancer vs controls, p=NS; NF-κB, UPS E3-ligase and 26S proteasome activity not raised in patients with precachectic cancer, all p=NS
Vigano (2009) <sup>52</sup>	N=172 (101/71)	NSCLC n=64, All stage III and IV. Metastatic GI cancer n=108	LBM, ALM	DEXA (n=64)	Cross sectional	Nil	ACE gene polymorphism (insertion <sup>2</sup> -II, insertion/deletion-ID, deletion <sup>2</sup> -DD) on nutritional status	Trend (p=0.07) towards lower LBM in ID compared to II groups
Op den Kamp (2013) <sup>62</sup>	26 (17/9)	NSCLC Stage IIIB—10 Stage IV—16	FFMi, AMMi	DEXA	Cross sectional	n=10 HV	Expression of signalling molecules in protein metabolism in LC cachexia	AMMi 20% lower in cachectic group compared with controls, p<0.05; Akt concentration increased in cachectic group (p<0.05), but no downstream signal phosphorylation, that is, impaired anabolic activity
Harvie (2003) <sup>29</sup>	50 (32/18)	NSCLC in all, stage III and IV	FFM	Four skinfold method	Longitudinal	Nil	Exploration of gender-specific differences in body composition and REE	Trend for FFM to decrease (p=0.063) and FFM decreased (p<0.05) in men after

Continued

Table 2 Continued

First author (year)	Patients		Muscle mass measurement(s)	Method of measurement	Study			Result
	n (M/F)	Tumour, stage			Design	Controls	Comparison	
Harvie (2005) <sup>63</sup>	43 (28/15)	NSCLC in all, stage III and IV. Alongside this metastatic breast and melanoma patients evaluated separately	FFM	Four skinfold method	Longitudinal	Nil	prechemotherapy and postchemotherapy Relationship between energy intake, REE and acute phase response vs changes in body composition over course of chemotherapy	chemotherapy. No significant difference in FFM or REE in women No significant change in FFM over the course of chemotherapy, and no significant relationship with energy intake, REE or CRP (all p=NS)
Bovio (2008) <sup>64</sup>	144 (92/52)	LC n=46, colon n=22, HCC n=11, other n=65 Stage NR	AMA	Upper arm measurements	Cross sectional	Nil	Evaluation of nutritional status in patients with advanced cancer	63% men vs 19% women had AMA<5th centile (p<0.01)
Baracos (2010) <sup>25</sup>	441 (229/212)	NSCLC in all Stage III—206 Stage IV—235	SMA at L3	CT of L3	Cross sectional	Nil	The use of CT images in evaluating body composition in NSCLC	61.1% men in cohort were sarcopenic, 31.3% of women sarcopenic, p<0.001
Martin (2013) <sup>65</sup>	1473 (828/645)	Colorectal cancer n=773, LC n=440, other GI cancer n=260 Stage according to cancer NR	SMA at L3, SMAi	CT of L3	Longitudinal	Nil	Prognostic significance of weight loss, muscle mass index and muscle attenuation	Concordance model using variables of BMI, weight loss, MI and MA found a concordance statistic (predictive accuracy of survival) of 0.92 Regardless of BMI, pts with weight loss, low MI and MA reduced survival (8.4 months), compared to those with none of these features (28.4 months), p<0.001
Prado (2013) <sup>66</sup>	368 (216/152)	NSCLC n=242 GI tract cancer n=126	SMA at L3	CT of L3	Longitudinal	Nil	Clinical course of skeletal muscle wasting in advanced cancer	Being <90 days from death increases risk of muscle loss, OR 2.67, p=0.002; and decreases chance of

Continued

Table 2 Continued

First author (year)	Patients		Muscle mass measurement(s)	Method of measurement	Study			Result
	n (M/F)	Tumour, stage			Design	Controls	Comparison	
Hansell (1986) <sup>67</sup>	98 (63/35)	Colorectal cancer n=55, gastric cancer n=24, LC n=12, other cancer n=7 Stage NR	LBM, MUAC	Tritiated saline, upper arm measurements	Cross sectional	n=38 non-malignant illnesses	REE in weight-losing patients with cancer WLC=weight-losing patients with cancer, WSC=weight-stable patients with cancer, WSC on=weight-stable controls	muscle gain, OR=0.37, p=0.002 WLC compared to WSC had lower LBM (p<0.005); WLC compared to WSC and WSC on lower MAMC (p<0.0005); WLC had increased REE/kg bodyweight compared with both WS groups (p<0.005); No significant difference when REE is expressed in terms of kg LBM; WLC had positive relationship with REE, r=0.83, p<0.001
Fredrix (1990) <sup>68</sup>	39 (GCR 13/9, LC 16/1)	LC n=17 GCR—n=22 Stage NR	FFM	BIA	Cross sectional	n=40 healthy	REE and weight loss	FFM: LC 50.4±8.9, Controls 51.1±9.6, p=NS; REE/FFM: LC 33.5±5.4, Controls 29.6±2.9, p<0.01
Staal-van den Brekel (1997) <sup>69</sup>	12 (10/2)	All SCLC	FFM	BIA	Longitudinal	Nil	Assess REE and systemic inflammation prechemotherapy and postchemotherapy	No change in FFM postchemotherapy (p=NS). Absolute REE and REE adjusted for FFM decreased postchemotherapy (p<0.005)
Simons (1997) <sup>70</sup>	21 (21/0)	NSCLC n=19 Stage I—3 Stage III—5 Stage IV—11	FFM, FFMi	DEXA	Cross sectional	Nil	Relationship between DL expression, body composition and REE	DL vs non-DL no significant difference between groups with regards FFM, FFMi,

Continued

Table 2 Continued

First author (year)	Patients			Study				Result
	n (M/F)	Tumour, stage	Muscle mass measurement(s)	Method of measurement	Design	Controls	Comparison	
Simons (1999) <sup>71</sup>	20 (20/0)	SCLC n=2 Limited stage—2 NSCLC n=18 I—II—2 III—5 IV—11 SCLC n=2	BCM, BCMi	DEXA	Cross sectional	Nil	Relationship between weight loss, low BCM and systemic inflammation	and REE/FFM, all p=NS BCM lower in group with weight loss ≥10% compared to group with weight loss <10%, p=NS; Low BCMi associated with high REE/BCM, r=-0.54, p=0.03; BCMi positively correlated with Karnofsky PS, p=0.02
Scott (2001) <sup>72</sup>	12 (12/0)	NSCLC in all, locally advanced	BCM	Total body potassium	Longitudinal	n=7, healthy participants	Inter-relationship between systemic inflammation and REE preonset and postonset of weight loss	Cancer group had lower REE (p<0.05) and BCM (p<0.001). Cancer group REE adjusted for BCM correlated with CRP concentrations (r=0.753, p<0.01)
Jatoi (2001) <sup>73</sup>	18 (10/8)	NSCLC in all Stage IA—6 Stage IB—3 Stage IIB—3 Stage IIIA—4 Stage IIIB—2	FFM, BCM, LBM	DEXA, Potassium-40, tritium dilution	Cross sectional	n=18, HV	REE in non-metastatic NSCLC	REE in cancer vs controls significantly raised when adjusted for LBM, p=0.001; and also when adjusted for BCM, p=0.032
Jago (2001) <sup>27</sup>	60 (43/17)	LC in all	FFM, MAMC, BFMAMA	BIA, four skinfold thickness, upper arm measurements	Cross sectional	n=22, mild COPD	Nutritional status of patients undergoing LC operations	No difference in FFMi and BFMAMA comparing LC and controls, all p=NS
Sarhill (2003) <sup>74</sup>	n=352 but LC only 18% of cohort ( )	NR	MUAC, AMA	BIA (n=329)	Cross sectional	Nil	Prospective evaluation of nutritional status in advanced cancer	Cachexia group vs non-cachexia group, reduced AMA in 84% vs 69%, p=0.037
Prado (2008) <sup>1</sup>	n=250, with LC 60 (24%) of	TNM for cohort Stage I—24 Stage II—56	SMA and SMAi at L3	CT of L3	Cross sectional	Nil	Prevalence of sarcopaenic obesity and chemotherapy	SMA in OS 128.1±29.1, ONonS 160±38.1, p<0.0001

Continued



**Table 2** Continued

First author (year)	Patients			Study				
	n (M/F)	Tumour, stage	Muscle mass measurement(s)	Method of measurement	Design	Controls	Comparison	Result
	cohort (136/114)	Stage III—74 Stage IV—96					toxicity in this cohort OS=obese sarcopaenic ONonS=obese non-sarcopaenic	SMAi in OS 43.3±6.3, ONonS 56.4±9.9; Median survival assoc with sarcopenia log rank, p<0.0001, OS 11.3 months and ONonS 21.6 months, p<0.0001
Kilgour (2010) <sup>53</sup>	n=84, with LC 16 (19%) of cohort (48/ 36)	Metastatic 57%, locally advanced 43%, stage NR	SMMI, ALM	DEXA	Cross sectional	Nil	Relationship of fatigue to muscle mass and strength	Brief fatigue index associated with SMMI (95% CI -8.4 to -1.3) p<0.01, and sarcopenia, p<0.01
Peddle-McIntyre (2012) <sup>56</sup>	17 (7,10)	NSCLC n=16 Stage I-II—11 Stage III—5 Limited stage SCLC n=1	LBM, ALM	DEXA	Longitudinal, duration 10 weeks	Nil	Resistance exercise training efficacy and feasibility in LC survivors	LBM and ALM no change from baseline to post training, all p=NS
Bauer (2005) <sup>75</sup>	n=7, with NSCLC 2 (28.6%) of cohort	Adenocarcinoma pancreas n=5, NSCLC n=2 Stage NR	LBM	Deuterium dilution	Longitudinal, duration 10 weeks	Nil	Effect of nutrition counselling and EPA supplements on body composition	Change in LBM post intervention, p=NS
Fearon (2006) <sup>28</sup>	518 (355/ 163)	LC n=231 Upper GI cancer n=198 Other GI cancer n=89 Stage NR	LBM	BIA	RCT (double blind, placebo controlled, randomised)	Nil	Effect of 2 g and 4 g doses of EPA diester vs placebo in the process of cachexia	Group given 2 g EPA gained mean 0.9 kg LBM and group given 4 g EPA lost mean 0.1 kg LBM compared to placebo (p=NS)
Tozer (2008) <sup>54</sup>	66 (49/17); only 35 completed study	All LC Stage NR	BCM	NR	RCT (double blind, placebo controlled, randomised)	Nil	Effect of cysteine-rich protein supplement on body weight and body cell mass	Cysteine group +11.55 ±18.05% vs control group -5.47±34.63% after treatment (p=0.01), and compared to baseline (p=0.02)
Murphy (2010) <sup>76</sup>	41 (19/22)	NSCLC in all Stage I—2 Stage II—2	SMA at L3	CT of L3	Longitudinal, cohort study	Nil	Relationship between muscle mass, rate of	Sarcopenia at baseline in 63% men and 59% women;

Continued

Table 2 Continued

First author (year)	Patients			Study				Result
	n (M/F)	Tumour, stage	Muscle mass measurement(s)	Method of measurement	Design	Controls	Comparison	
		Stage III—13 Stage IV—24			over 2.5 months		muscle mass change, and plasma fatty acids	Patients with sarcopenia had lower plasma EPA (p=0.001), lower plasma DHA (p=0.003), and lower n-3 fatty acids (p=0.002) compared to non-sarcopenic patients
Murphy (2011) <sup>77</sup>	40 (21/19)	NSCLC in all Stage III—13 Stage IV—27	SMA at L3	CT of L3	Longitudinal, duration 6 weeks Open label study	Nil controls; cohort divided into those receiving FO n=17 and SC n=24	Effect of FO on body composition	Sarcopenic at baseline FO 46%, SC 46%; Muscle loss rate per 100 days, FO 0.1 ±1.6%, SC -6.8±2.6%, p<0.05; Positive relationship between plasma EPA concentration and rate of muscle gain, r <sup>2</sup> =0.55, p=0.01
Winter (2012) <sup>78</sup>	10 (10/0)	NSCLC in all Stage IIIA—2 Stage IIIB—3 Stage IV—5	LBM, AMMi	DEXA	Longitudinal	n=10 healthy men	Effect on protein anabolism in response to hyperaminoacidaemia, in cachexic insulin-resistant patients	Mean AMMi cancer group defined as sarcopenic, p=NS; Hyperaminoacidaemia stimulates a normal anabolic protein response, p<0.05
Agteresch (2002) <sup>50</sup>	58 (38/20)	NSCLC in all including controls (RCT) All Stage IIIB or IV, breakdown NR	FFM, MUAC, BCM	Four skinfold thickness, deuterium dilution	Longitudinal, duration 28 weeks RCT	Randomised to ATP group n=28, to control group n=30, all NSCLC	Effect of ATP on body composition	FFM -0.5 kg in controls, but +0.1 kg in ATP group, between group difference p=0.02 MUAC -1.8% in controls, but +1.1% in ATP group, between

Continued

Table 2 Continued

First author (year)	Patients		Muscle mass measurement(s)	Method of measurement	Study			Result
	n (M/F)	Tumour, stage			Design	Controls	Comparison	
Beijer (2009) <sup>79</sup>	n=100, with LC n=44 n=57 completed 8-week study period	LC in 44% (most frequent), colon cancer 13%, various other cancers 43% Stage NR 'preterminal'	MUAC	Upper arm measurements	Longitudinal, duration 8 weeks RCT	Baseline: ATP n=51, SC n=49; Completed study: ATP n=29, SC n=28	Effect of ATP on nutritional status and survival	group difference p=0.02 BCM -0.6% per 4 weeks in controls, but -0.1% in ATP group, between group diff p=0.054 Post ATP loss of MUAC -2.24 mm, SC group -1.52 mm, p=NS Short term 0-8 weeks survival benefit with ATP (HR 0.17, p=0.023), and long term 0-6 months survival benefit (HR 0.35, p=0.025)

ALM, appendicular lean mass; AMA, arm muscle area; AMMi, appendicular muscle mass index; BCM, body cell mass; BCMi, BCM index; BFMAMA, bone free mid arm muscle area; BIA, bioelectrical impedance analysis; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CT of L3, CT of the third lumbar space; DEXA, dual-energy X-ray absorptiometry; DL, detectable leptin; EPA, eicosapentaenoic acid; F, female; FFM, fat-free mass; FFMi, FFM index; FO, fish oil; GCR, gastric and colorectal cancer; GI, gastrointestinal; HV, healthy volunteers; IL-15, interleukin 15; ILGF, insulin-like growth factor; LBM, lean body mass; LC, lung cancer; M, male; MI, muscle index; MUAC, mid-upper arm circumference; MA, muscle area; NR, not recorded; NS, non-significant; NSCLC, non-small cell lung cancer; PS, performance status; RCT, randomised controlled trial; REE, resting energy expenditure; SCLC, small cell lung cancer; SMA at L3 or T4, skeletal muscle area at the level of the lumbar vertebra L3 or thoracic vertebra T4; SMAi, skeletal muscle area index; SMMI, skeletal muscle mass index; TNM, tumour, node, metastasis; HCC, hepatocellular carcinoma; MAMC, mid-arm circumference; PIF, proteolysis inducing factor.

**Table 3** Degree of loss of muscle mass and physical functioning

First author (year)	Patients			Study				
	N (M/F)	Tumour, stage	Muscle function and muscle mass measurements	Method of measurement	Design	Controls	Comparison	Result
Jagoe (2001) <sup>27</sup>	60 (43/17)	LC in all	Grip strength Z-score FFM, MAMC, BFMAMA	HDA dynamometer BIA, four skinfold-thickness, upper arm measurements	Cross sectional	n=22, mild COPD	Nutritional status of patients undergoing lung cancer operations	Grip strength in absolute terms or Z-score no difference LC vs controls, p=NS No difference in FFMi and BFMAMA comparing LC and controls, all p=NS
Fearon (2006) <sup>28</sup>	518 (355/163)	LC n=231 Upper GI cancer n=198 Other GI cancer n=89 Stage NR	LBM	BIA	RCT (double blind, placebo controlled, randomised)	Nil	Effect of 2 g and 4 g doses of EPA diester vs placebo in the process of cachexia	Patient-reported physical functioning increased by 7% in group receiving 2 g EPA compared with controls (p=0.04)
Tozer (2008) <sup>54</sup>	66 (49/17); only 35 completed study	All LC Stage NR	BCM	NR	RCT (double blind, placebo controlled, randomised)	Nil	Effect of cysteine-rich protein supplement on body weight and body cell mass	Handgrip force improved by +12.41 ±16.52% in cysteine group compared to baseline (p=0.019)
Trutschnigg (2008) <sup>17</sup>	81 (NR/ NR) 74 completed muscle function tests (48/26)	Patients with advanced NSCLC and gastrointestinal cancer, breakdown NR Stage NR	Handgrip strength In Newton metre for Biodex, and pounds for Jamar FFM	Jamar and Biodex dynamometer (n=74 completed) DEXA, BIA (n=70 completed)	Cross sectional	Nil	Relationship between DEXA and BIA, and Jamar and Biodex dynamometry and their precision in patients with advanced cancer	Biodex HGS mean ±SD: men 47.8 ±13.6 vs women 32.7±9.3, p<0.05 Jamar HGS mean ±SD: men 78.5±21.6 vs women 49.7±13.5, p<0.001; %CV biodex 16.7%, Jamar 6.3% Wide limits of agreement in determining FFM, DEXA vs BIA, p=NS, but low %CV for FFM DEXA

Continued

**Table 3** Continued

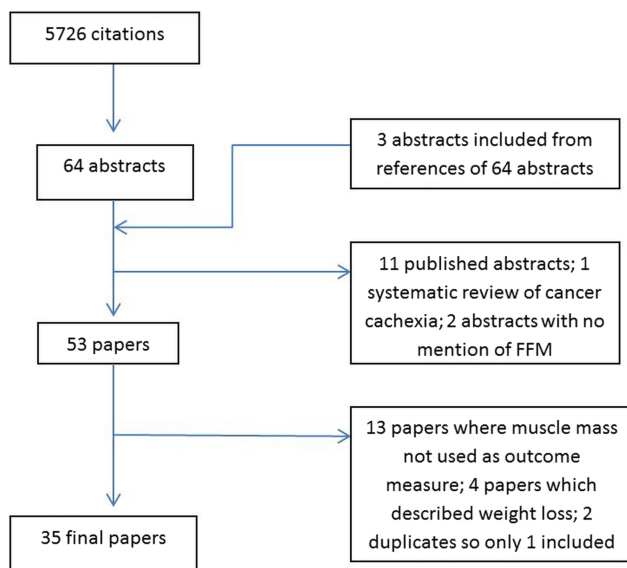
First author (year)	Patients			Study				
	N (M/F)	Tumour, stage	Muscle function and muscle mass measurements	Method of measurement	Design	Controls	Comparison	Result
Kilgour (2010) <sup>53</sup>	N=84, with LC 16 (19%) of cohort (48/36)	Metastatic 57%, locally advanced 43%, stage NR	HGS in kg, QS in Newton metre SMMI, ALM	Jamar (HGS) and Biodex (QS) DEXA	Cross sectional	Nil	Relationship of fatigue to muscle mass and strength	(0.79) and BIA (0.42) HGS on fatigue, 95% CI -1.1 to -0.15, p<0.05; QS on fatigue, 95% CI -0.2 to -0.01, p<0.05; Brief fatigue index associated with SMMI (95% CI -8.4 to -1.3) p<0.01, and sarcopenia, p<0.01
Vigano (2009) <sup>52</sup>	N=172 (101/71)	NSCLC n=64, Stage III and IV, breakdown NR Metastatic GI cancer n=108	Handgrip force and percentile LBM, ALM	Jamar dynamometer DEXA (n=64)	Cross sectional	Nil	ACE gene polymorphism (insertion <sup>2</sup> -II, insertion/deletion-ID, deletion <sup>2</sup> -DD) on nutritional status	DD allele group showed greater handgrip force and grip percentile than II group, p<0.05; but no difference in LBM or ALM p=NS Trend (p=0.07) towards lower LBM in ID compared to II groups
Peddle-McIntyre (2012) <sup>56</sup>	17 (7/10)	NSCLC n=16 Stage I-II—11 Stage III—5 Limited stage SCLC n=1	Chest press, Leg press, functional performance measure (6MWD—6-min walk distance, GUAG, chair stands and arm curls in 30 s) LBM, ALM	1RM in kg DEXA	Longitudinal, duration 10 weeks	Nil	Resistance exercise training efficacy and feasibility in lung cancer survivors	Mean change from baseline to end of training in 95% CI chest press 12.3 to 17.5, leg press 23.5 to 39.8, 6MWD 48 to 124, GUAG -0.4 to -1.2, chair stands 2.3 to 6.1, arm curls 2.1 to 5.1, all p<0.05 LBM and ALM no change from

Continued

Table 3 Continued

First author (year)	Patients		Muscle function and muscle mass measurements		Study			
	N (M/F)	Tumour, stage	Method of measurement	Design	Controls	Comparison	Result	
Martinez-Hernandez (2012) <sup>61</sup>	21 (19/2)	Lung cancer n=13, GI cancer n=6, Other cancer n=2 Stage according to tumour group NR	HGS and treadmill 6MWT FFM	BIA	Longitudinal	n=8 healthy volunteers	The role of IL-15 in patients with cachectic cancer	baseline to post training, all p=NS HGS no difference comparing cachectic group to controls, p=NS; 6MWT in cachectic group 369±73 m vs 474±57 m, p<0.05
Op den Kamp (2012) <sup>55</sup>	16 (15/1)	NSCLC in all Stage I–II—11 Stage IIIA—2 Stage IIIB—3	Intensity of physical activity FFMi	Triaxial accelerometer (Tracmor) in counts/min DEXA	Cross sectional	n=10 healthy volunteers	Skeletal muscle ubiquitin proteasome system activity in precachexia	High intensity physical activity in LC vs controls p=0.049; FFMi no significant difference in precachectic cancer vs controls, p=NS
Op den Kamp (2013) <sup>62</sup>	26 (17/9)	NSCLC Stage IIIB—10 Stage IV—16	QS) FFMi, AMMi	DEXA	Cross sectional	n=10 healthy volunteers	Expression of signalling molecules in protein metabolism in lung cancer cachexia	QS 31% lower in cachectic group compared to controls, p<0.05

1RM, 1 Repetition-maximum; 6MWT, 6 min walk test; ALM, appendicular lean mass; AMA, Arm muscle area; AMMi, appendicular muscle mass index; BCM, body cell mass; BFMAMA, bone free mid arm muscle area; BIA, bioelectrical impedance analysis; COPD, chronic obstructive pulmonary disease; DEXA, dual-energy X-ray absorptiometry; EPA, eicosapentaenoic acid; F, female; FFM, fat-free mass; FFMi, FFM index; GI, gastrointestinal; GUAP, get-up-and-go; HGS, handgrip strength; IL-15, interleukin 15; LBM, lean body mass; LC, lung cancer; M, male; MUAC, mid-upper arm circumference; NR, not recorded; NS, non-significant; NSCLC, non-small cell lung cancer; QS, quadriceps strength; RCT, randomised controlled trial; SCLC, small cell lung cancer; SMMI, skeletal muscle mass index; MAC, mid arm circumference.



**Figure 1** Flowchart showing a breakdown of the results of our search using the search terms used and the derivation of articles for final analysis. FFM, fat-free mass.

proteolytic pathway may not be activated.<sup>55–80</sup> Different ACE-gene polymorphism allelic combinations<sup>52</sup> and leptin expression<sup>70</sup> have not been shown to have significant effects on muscle mass. FFM is the major determinant of energy metabolism in humans, represented by resting energy expenditure (REE), and there exists a linear relationship between REE and FFM in healthy adults.<sup>81</sup> In lung cancer cachexia, this relationship seems to be distorted<sup>69–71</sup> but results have been conflicting as to whether REE contributes to the development of lung cancer cachexia.<sup>67–68, 72–73</sup>

The use of CT images for diagnosis of muscle mass depletion alone showed a high prevalence of this phenomenon in patients with NSCLC,<sup>25</sup> regardless of body mass index and even among the obese.<sup>1</sup> CT images were also used to chart progressive muscle loss over time, and to create a prognostic model for survival based on weight loss, muscle mass and muscle attenuation.<sup>65–66</sup> The presence of muscle mass attenuation was associated with poorer functional status and overall survival.

Nine interventional studies explored the effect of either nutritional supplements or ATP infusions on muscle mass and function. A randomised controlled study with 518 participants, examining the effect of eicosapentaenoic acid (found in fish oil) supplements, revealed increased patient-rated physical functioning, but no significant change in FFM, at the end of the study period.<sup>28</sup> A similar, smaller study of eight participants concurred.<sup>75</sup> By contrast, one study of fish oil supplementation demonstrated a reduction in the rate of loss of muscle mass; however, the number of studies was small—40 patients in total. In addition, those considered sarcopenic were found to have lower plasma fatty acids than those without, in a study with 41 patients with NSCLC.<sup>76–77</sup> An interventional randomised controlled

study with 66 participants found that cysteine-rich protein supplements increased FFM, as well as HGS, compared with conventional protein supplements,<sup>54</sup> and a small case-control study with 10 patients found that hyperaminoacidaemia stimulated a normal anabolic protein response even in the presence of insulin resistance, in patients with cancer cachexia.<sup>78</sup> Two randomised controlled studies investigating the effect of ATP infusions on body composition gave conflicting reports, one (N=58) finding that ATP slowed the rate of loss of muscle mass<sup>50</sup> while the other (N=100) did not.<sup>79</sup> Only the study by Fearon *et al*<sup>28</sup> described power calculations to detect a statistically significant difference.

### Degree of sarcopenia or loss of muscle mass and physical functioning

There was very little direct evaluation of the relationship between muscle mass and muscle function. However, the studies that evaluated muscle mass alongside muscle function show that there is limited correlation. Muscle strength seemed to be affected, regardless of loss of muscle mass. In patients with precachexia, exercise capacity was significantly reduced, despite maintenance of muscle mass,<sup>55</sup> and resistance exercise training increased all parameters of muscle strength and physical performance, with no difference to muscle mass.<sup>56</sup> In this review, patients with cachexia showed reduced strength in terms of walking distance<sup>61</sup> and quadriceps strength<sup>62</sup> compared with controls.

### DISCUSSION

Loss of muscle mass, as part of a weight-losing syndrome, is a central feature of cancer cachexia. However, changes in muscle mass, and/or performance, may predate clinically overt cachexia, as part of ageing or secondary to inflammation/disuse. This implies that consideration of both muscle mass and function, rather than weight loss alone, is clinically important. Understanding this relationship, and the factors associated with each, will provide opportunities for focused intervention to improve clinical outcomes.

The findings of our review highlight several important issues. While studies exploring molecular and metabolic factors associated with loss of muscle mass have contributed to a better understanding of the pathophysiology of cancer cachexia, there remains considerable uncertainty in relation to mechanisms. Our review in patients with lung cancer demonstrates inconsistency of findings as to the factors implicated in the development of cachexia, compared with other cancer sites. It highlights the lack of clear therapeutic targets and emphasises the need for concerted, appropriately-sized exploration of predictive and prognostic factors in lung cancer cachexia.

This uncertainty with regard to precise pathophysiological mechanisms is reflected in the lack of consistent effect of interventions aimed at slowing the rate of loss

of muscle mass and improving muscle function in lung cancer. Studies reviewed which refer to cachexia management support a multimodal approach, including targeted exercise, nutritional counselling, social support and pharmacological intervention.<sup>82</sup> This review highlights inherent challenges of such an approach, with nutritional interventions in particular failing to demonstrate efficacy,<sup>83</sup> although the role of exercise is emerging.<sup>56–84</sup> It also suggests the need to represent patients with NSCLC adequately within trials of new interventions, such as myostatin antibody therapies, rather than assuming a class effect across tumour sites.

Strikingly, our review has demonstrated that, to date, there has not been due attention to the concept of sarcopenia as a distinct, if overlapping syndrome, in a condition affecting a largely elderly population. It also highlights the difficulty in making comparisons between studies, due to the heterogeneity of methods employed in measuring muscle mass and different cut-off values used for defining sarcopenia. Current standardised values were derived from a large elderly cohort and the cut-off values were based on healthy young adult reference values. These values have been used to define sarcopenia in cancer,<sup>13–85</sup> including one in this review.<sup>53</sup> The relevance of this definition to patients with cancer is debatable, for a number of reasons. First, sarcopenia manifests in patients with cancer of all ages and is not isolated to the elderly alone. Second, the pathophysiology of sarcopenia in patients with cancer may differ at least in part to that of the non-cancer elderly population.<sup>86</sup> With this in mind, the more recent international consensus document recommending a reference value of absolute muscularity below the fifth centile is to be welcomed.<sup>13</sup> Finally, the recognition of muscle strength and performance as a defining component of sarcopenia in the elderly patients needs consideration, within the context of cancer cachexia.

The argument for the objective evaluation of physical performance is pertinent, particularly as part of the definitive assessment of sarcopenia alongside measurements of muscle mass. Currently, physical fitness for treatment is determined largely by the PS score. This score is imperfect as it is subjective, with reports of inter-observer variability,<sup>87</sup> and there is only a modest correlation between PS and observed physical performance.<sup>88</sup> Interclinician PS discordance has led to a lower percentage of PS 0 and 1 patients appearing to get chemotherapy,<sup>89</sup> and has led to a call for objective evaluation of physical functioning.<sup>90</sup> Some proposed methods include tests of gait speed and muscle strength. It is postulated that objective measures of muscle mass and strength together may complement, or even outperform, PS as a predictor of fitness for systemic treatment, provided that they can be readily performed in routine clinical settings.

Our review has several limitations. The heterogeneity of the studies included in this review made it difficult to account for individual risk of bias, not least because we

included a broad range of studies from large randomised controlled trials to small observational studies. This limitation also means that some articles included in this review, while being relevant to sarcopenia, were more broadly related to muscle mass outcomes in cancer cachexia, rather than assessing sarcopenia directly. Our search also was limited to studies published in English, and although our review included some studies with negative or inconclusive findings, there may indeed exist some publication bias for which we are unable to account.

The article by Temel *et al.*,<sup>91</sup> which demonstrated that early palliative care involvement increased patient survival, as well as quality of life, has highlighted the importance of supportive measures in a poor-prognosis population receiving active oncological intervention. As such, focusing research on the identification and management of sarcopenia in patients with lung cancer may prove to be a tolerable and cost-effective adjunct to the current lung cancer care.

While development of a clearer definition of cancer cachexia provides an additional component of a robust, objective clinical framework for stratification of patients for focused interventions, the enhanced role of muscle strength/performance as a defining assessment of sarcopenia requires attention. A standardised definition of cancer-related sarcopenia which can be used clinically and in the research setting will harmonise reporting, allowing for direct comparison of results as well as meta-analysis of data. In the era of stratified medicine, this review identifies opportunities to examine cellular and genetic factors associated with sarcopenia in lung cancer coherently and to link them with changes in tumour phenotype which impact on morbidity and survival.

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