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The assessment and impact of sarcopenia in lung cancer: a systematic literature review, highlighting implications for research and clinical practice.

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Abstract

Objectives

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

Design

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

Setting

Secondary care

Participants

Patients with lung cancer.

Primary outcome

Muscle mass values associated with or without muscle strength or physical performance. We recorded the units and methods of measuring muscle mass, and the comparison or correlation that was assessed.

Results

We reviewed 5226 citations, and from these 29 papers were selected for analysis. Sarcopenia, as defined by reduced muscle mass alone, was found to be very prevalent in lung cancer patients, 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 adenosine triphosphate infusions on muscle mass showed conflicting results. There is very limited data on the correlation between degree of sarcopenia and muscle function, which has a non-linear relationship in older non-cancer populations.

Conclusion

Loss of muscle mass is a significant contributor to morbidity in lung cancer patients. Loss of muscle mass and function may pre-date 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.

Keywords

Sarcopenia; cachexia; muscle mass; physical performance; lung cancer

Article Summary

Article Focus

- Sarcopenia, the loss of muscle mass and muscle function, is a significant contributor to morbidity in lung cancer patients.
- Sarcopenia is a key component of a new definition of cancer cachexia, however its relationship to cachexia in the lung cancer literature is poorly defined.

Key messages

- Sarcopenia is prevalent in lung cancer patients regardless of body mass index and body weight, and where present is associated with poorer functional status and overall survival.
- There is very limited data on the correlation between the degree of loss of muscle mass and muscle function, which has a non-linear relationship in older non-cancer populations.
- The heterogeneity of cut-off values for cancer-related sarcopenia necessitates a standardised definition which can be used clinically and in the research setting, to harmonise reporting and allow for direct comparison of results as well as meta-analysis of data

Strengths and limitations of this study

- Timely systematic review considering the increasingly recognised phenomenon of sarcopenia, as it relates to cachexia, which affects not only patients with lung cancer, but also the wider cancer population
- Limited to publications in English only

Introduction

There are 42,000 cases of lung cancer diagnosed in the United Kingdom each year and approximately three quarters are over the age of 65 at diagnosis. Despite advances in anticancer therapies, survival benefits in lung cancer patients over the past thirty years have been relatively small compared to those seen in breast, colorectal and prostate cancers [1]. Whilst reasons for this are complex, many lung cancer patients are ineligible for radical treatment at presentation due to poor performance status or co-morbidity, while others fail to receive their intended treatment plan because of functional decline [2, 3].

Sarcopenia is a widely recognised phenomenon that has important clinical implications in the management of lung cancer. It is characterised by a triad of progressive loss of skeletal muscle mass, muscle strength and physical performance [4]. 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 [4-7]. However, sarcopenia may also be seen in younger patients in association with muscle disuse, malnutrition or inflammatory diseases, including cancer [4].

Central to the concept of sarcopenia is the recognition that overall neuromuscular function, rather than muscle mass alone, is essential for maintenance of independence. Although originally defined as an appendicular skeletal muscle mass index of more than two standard deviations below the sex-specific mean of healthy adults (i.e. 5.45kg/m^2 for women and 7.26 kg/m^2 for men) [6] the current consensus on defining sarcopenia requires assessment of muscle strength, or performance, as well as mass [8]. Loss of muscle mass is usually gradual and not necessarily associated with significant or sudden weight loss, and the relationship between muscle mass and strength is non-linear [9, 10].

Loss of muscle mass, with or without loss of fat mass, is also a predominant component of weight loss seen in cancer cachexia, a complex metabolic syndrome with inflammation recognised as a key feature [11]. The pathophysiological mechanisms responsible for loss of muscle mass in cancer cachexia differ, at least in part, from those in sarcopenia of ageing. Therefore, in established cachexia, most patients will have sarcopenia, whereas sarcopenic patients are often not cachectic.

Over the last decade, there has been increasing recognition of the importance of sarcopenia as part of the cancer cachexia syndrome and its impact has been evaluated in patients with lung, breast, upper gastrointestinal, hepatocellular and colorectal malignancies [12-16]. 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, 46.7% were defined as sarcopenic, based on muscle mass measurements [17]. As with the elderly non-cancer patient, sarcopenia in cancer has important clinical

implications. Most notably it is associated with poor performance status and reduced survival [12]. It also appears to be associated with an increase in chemotherapy-related toxicities [13, 15].

In the context of lung cancer, cachexia and sarcopenia frequently coexist and may be clinically indistinguishable. However, having clear working definitions may allow earlier recognition of the conditions and provide a framework for research to identify early markers and focused interventions, offering complementary therapeutic approaches. It is also important to consider that, although lung cancer cachexia may lead to sarcopenia, sarcopenia may itself pre-date cachexia. Failure to recognise this may lead to lost opportunities to limit and treat sarcopenia in the NSCLC patient, and thereby better preserve performance status. This could impact on survival for patients, through reduced eligibility for active treatments and reduced ability to tolerate chemotherapy toxicities [2, 12]. In the previously-mentioned cohort, where 46.7% of NSCLC patients were found to be sarcopenic, only 7.3% were underweight. Furthermore, of those classified as overweight in terms of body mass index, 59% were sarcopenic [17]. It may, therefore, be more useful to assess sarcopenia, rather than weight loss or BMI, when evaluating the suitability of NSCLC patients for future treatments.

Much of the discussion of sarcopenia, as it relates to cancer cachexia, has relied on the narrower definition of loss of muscle mass. Whilst loss of function is a recognised later consequence of cancer cachexia, muscle strength or performance have not been routinely measured as part of the initial assessment of cachexia severity, despite being central to the current, broader definition of sarcopenia. As clear consensus emerges on the definitions of

cachexia [18-20], a better understanding of the inter-dependence between cachexia and sarcopenia suggests that early recognition of sarcopenia as part of, or prior to, cachexia in NSCLC may yield improvements in patient outcomes.

To understand this further, we aimed to systematically review all relevant literature pertaining to factors associated with loss of muscle mass in lung cancer, and the relationship between muscle performance and muscle mass, in order to critically evaluate its implications for research and clinical practice.

Methods

Search strings and data sources

We 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 2012. 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.

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)

Paper retrieval

Citations were independently screened by two researchers (JC 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 citations without abstracts, case reports, review articles and opinion pieces were excluded. All studies that had a cohort of lung cancer patients were included, even if there were other cancer patient groups analysed. Retrieved papers were searched for additional relevant references.

Inclusion criteria and data extraction

The selected papers were reviewed in full by two independent researchers (JC and SN) for consideration of inclusion in the review. Where discordance in selection was observed, the paper in question was discussed until consensus was reached. As there were many papers describing muscle mass as part of routine anthropometry or body composition assessments, without directly exploring it, we only included papers in which muscle mass was explored as an outcome measure. Data including patient characteristics and numbers, histological subtype, and TNM stage, were collated and tabulated (Tables 3-4). We also noted units of muscle mass measurements, and techniques used to measure these.

Results

Using our broad search terms in 5 databases, we found an initial 5226 citations, from which we identified 57 potentially relevant papers. Three further potential papers [21-23] were identified from the references of these papers. From these, we excluded 11 abstracts with no published papers, a further abstract that did not mention muscle mass or body composition [24], and a systematic review of cancer cachexia [25]. Out of the 47 final papers, we excluded a further 13 papers which mentioned muscle mass in baseline anthropometry details but did not use it as an outcome measure [26-38], four papers which described weight loss rather than loss of muscle mass [39-42], and one paper describing the same results obtained from the same patient population as another paper [43], with slightly different secondary endpoints [44]. 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.

Figure 1 shows a breakdown of the results of our search using the search terms used, and the derivation of papers for final analysis.

Insert Figure 1 here

For the final analysis, 4 randomised controlled studies, 16 cross-sectional studies and 9 longitudinal studies met the established criteria: 29 papers in total. Muscle mass data were reported variously as fat free mass, body cell mass, lean body mass, appendicular skeletal muscle mass, smooth muscle area at L3,

mid upper arm circumference and arm muscle area. Notably, most studies described muscle mass in more than one way. Muscle function was described as hand-grip and/or quadriceps strength [21, 45-48], intensity of physical activity [49], patient-reported physical functioning [22], and both muscle strength and physical performance [50].

Table 2 shows an overview of the studies, whereas tables 3-4 show the studies' results in greater detail.

Table 2: Overview of studies exploring loss of muscle mass and/or sarcopenia in patients with lung cancer

Headings, *Authors*	**Muscle Mass Measurements**	**Results**	**p**
Factors associated with loss of muscle mass			
McMillan 2001[51]	BCM derived from TBK	Albumin concentrations correlate positively with BCM and inversely with C-reactive protein	p<0.001, r=0.686; r= -0.545, p<0.001
Crown 2002[52]	FFM, MUAC	No significant difference in IGF	p=NR

		system concentrations	
Jagoe 2002[53]	FFMi	Inverse relationship between cathepsin-B expression and FFMi	p=0.003, r=-0.57
Op den Kamp 2012[49]	FFMi	No significant difference in ubiquitin proteasome system concentration	p=NS
Vigano 2012[45]	LBM, ALM	Trend towards lower LBM in ACE gene polymorphism, ID compared to II groups	p=0.07
Harvie 2003[23]	FFM	Decreasing trend in FFM post-chemotherapy compared to baseline in men, not women	p=0.063
Harvie 2005 [54]	FFM	No significant change in FFM post-chemotherapy compared to baseline	p=NS
Bovio 2008 [55]	AMA	More men had AMA <5th percentile than women	p<0.01
Baracos 2010[17]	SMA at L3	Sarcopenia in 61% men, 31% women	p<0.001
Hansell 1985[56]	LBM, MUAC	Less LBM in weight-losing vs weight-stable cancer patients; No difference	p<0.005 p=NS

		in REE adjusted for LBM	
Fredrix 1990[57]	FFM	No significant difference in FFM; but REE/FFM significantly raised in LC	p=NS p<0.01
Staal van den Brekel 1997 [58]	FFM	REE/FFM decreased post-chemotherapy compared to baseline	p<0.005
Simons 1997[59]	FFM, FFMi	Detectable leptin vs non-detectable leptin groups, non-significant difference in FFM, nor in REE/FFM	p=NS
Simons 1999[60]	BCM, BCMi	High REE/BCM associated with low BCMi	r=-0.54 p=0.03
Scott 2001[61]	BCM derived from TBK	REE/BCM higher in LC compared to controls and correlates with inflammatory response	p<0.01 r=0.753
Jatoi 2001[62]	FFM, BCM, LBM	REE adjusted for BCM REE adjusted for LBM	p=0.032 p=0.001
Jagoe 2001[21]	FFM, FFMi, BFMAMA	No difference in muscle mass parameters pre-operative LC patients	p=NS

		vs controls	
Sarhill 2003[63]	AMA, LBM	Cachectic versus non-cachectic AMA 84% versus 69%	p=0.037
Prado 2008[12]	SMA at L3	SMA in sarcopenic obese significantly less than in non sarcopenic obese	p<0.0001
Kilgour 2010[47]	SMMI	Sarcopenic patients have higher levels of fatigue	p<0.01
Peddle-McIntyre 2012[50]	ALM, whole body SM (skeletal muscle)	No change in ALM or SM post resistance exercise training	p=NS
Bauer 2005[64]	LBM	No change in LBM post nutrition counselling and EPA	p=NS
Fearon 2006 [22]	LBM	No significant change in LBM in groups treated with 2g or 4g EPA	p=NS
Tozer 2008 [48]	BCM	BCM increased in group given cysteine-rich protein supplements	p=0.01
Murphy 2010[65]	SMA at L3	Sarcopenic patients had lower levels of EPA, DHA and n-3 fatty acids	All p<0.05

Murphy 2011[66]	SMA at L3	Rate of muscle loss in standard care group greater than in fish oil group	p<0.05
Agteresch 2002[43]	FFM, MUAC, BCM	All measures of muscle mass in ATP-treated group increased compared to controls	p=0.02, p=0.02, p=0.054
Beijer 2009[67]	MUAC	Effect of ATP no difference on MUAC, but confers survival benefit	p=NS p=0.025
Degree of loss of muscle mass and physical functioning			
Jagoe 2001[21]	FFM, FFMi, BFMAMA	HGS and FFM both not significantly different comparing pre-operative patients to controls	p=NS
Fearon 2006[22]	LBM	Physical functioning improved by 7% in group treated with 2g EPA vs placebo	p=0.04
Tozer 2008 [48]	BCM	HGS increased after treatment with cysteine-rich protein	p=0.044

Trutschnigg 2008 [46]	FFM	HGS and FFM both greater in men compared to women	p<0.05
Kilgour 2010[47]	SMMI	Fatigue related to poorer hand grip strength and quadriceps strength	Both p<0.05
Vigano 2012[45]	LBM, ALM	ACE gene DD group higher handgrip force compared to II group	p<0.05
Peddle-McIntyre 2012[50]	ALM, whole body skeletal muscle	Chest press and leg press increased post resistance training; as did functional performance	All p<0.05
Op den Kamp 2012[49]	FFMi	Higher intensity of physical activity	p=0.049

Keys: TBK – total body potassium, FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, SMMI – skeletal muscle mass index, SMA – skeletal muscle area, LC – lung cancer, NR – not recorded, NS – non significant, ILGF – insulin like growth factor, HGS – hand grip strength, QS – quadriceps strength, DL – detectable leptin, NDL – non detectable leptin, ACE – angiotensin converting enzyme, ID – insertion/deletion, II – insertion/insertion, DD – deletion/deletion, ATP – adenosine triphosphate, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid, REE – resting energy expenditure

Factors associated with loss of muscle mass

Table 3: Factors associated with loss of muscle mass

Authors	Patients				Study		Comparison	Result
	No, (M/F)	Tumour, Stage	Muscle Mass Measurement(s)	Method of Measurement	Design	Controls		
McMillan 2001	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	30 (NR/NR)	NSCLC in all Inoperable, stage NR	FFM, MUAC	BIA, upper arm measurements	Case-control, Longitudinal over 2 years	n=30 healthy volunteers (HV)	Insulin-like growth factor (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 sig longitudinal trend observed in IGFBP-3 and IL-6 and nutritional status, p=NS.
Jagoe 2002	36 (27/9)	Mix of NSCLC and	FFMi	BIA, Four skinfold	Cross-	n=10	Ubiquitin-proteasome and	Cathepsin B expression in LC inversely related to

		SCLC Stage 1 – 21 Stage 2 – 6 Stage 3 – 6 Stage 4 – 2		method, %BFMAMA	sectional	patients referred for thoracotomy for non-malignant conditions	lysosomal proteolytic pathway gene expression in LC and association with LMM	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
Op den Kamp 2012	16 (15/1)	NSCLC in all Stage I-II – 11 Stage IIIA – 2 Stage IIIB – 3	FFMi	DEXA	Cross-sectional	n=10 healthy volunteers	Skeletal muscle NF-kB and ubiquitin proteasome system activity in pre-cachexia	FFMi no significant difference in pre-cachectic cancer vs controls, p=NS; NF-kB, UPS E3-ligase and 26S proteasome activity not raised in pre-cachectic cancer patients, all p=NS
Vigano 2012	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^2- II , insertion/deletion- ID, deletion^2 -DD) on nutritional status	Trend (p=0.07) towards lower LBM in ID compared to II groups
Harvie 2003	50 (32/18)	NSCLC In all, Stage III and IV	FFM	Four skinfold method	Longitudinal	Nil	Exploration of gender-specific differences in body	Trend for FFM to decrease (p=0.063) and FFM decreased (p<0.05)

							composition and REE pre- and post-chemotherapy	in men after chemotherapy. No significant difference in FFM or REE in women.
Harvie 2005	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	Relationship between energy intake, REE and acute phase response vs changes in body composition over course of chemotherapy	No significant change in FFM over the course of chemotherapy, and no significant relationship with energy intake, REE or c-reactive protein (CRP) (all p=NS)
Bovio 2008	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 percentile (p<0.01)
Baracos 2010	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
Hansell 1985	98 (63/35)	Colorectal cancer n=55, Gastric	LBM, MUAC	Tritiated saline, upper arm	Cross-sectional	n=38 non-	REE in weight-losing cancer	WLC compared to WSC had lower LBM

		cancer n=24, LC n=12, Other cancer n=7 Stage NR		measurements		malignant illnesses	patients WLC = weight-losing cancer patients, WSC = weight-stable cancer patients, WSCon = weight-stable controls	(p<0.005); WLC compared to WSC and WSCon lower MAMC (p<0.0005); WLC had increased REE/kgBodyweight compared with both WS groups (p<0.005); No significant difference when REE is expressed in terms of kgLBM; WLC had positive relationship with REE, r=0.83, p<0.001
Fredrix 1990	39 (GCR 13/9, LC 16/1)	LC n=17 GCR – Gastric and colorectal cancer 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	12 (10/2)	All SCLC	FFM	BIA	Longitudinal	Nil	Assess REE and systemic inflammation pre- and post-chemotherapy	No change in FFM post-chemo (p=NS). Absolute REE and REE adjusted for FFM decreased post-chemotherapy (p<0.005)

Simons 1997	21 (21/0)	NSCLC n=19 Stage I – 3 Stage III – 5 Stage IV – 11 SCLC n=2 Limited stage – 2	FFM, FFMi	DEXA	Cross-sectional	Nil	Relationship between detectable leptin (DL) expression, body composition and REE	DL vs NonDL no significant difference between groups with regards FFM, FFMi, and REE/FFM, all p=NS
Simons 1999	20 (20/0)	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	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	12 (12/0)	NSCLC in all, locally advanced	BCM	Total body potassium	Longitudinal	n=7, healthy subjects	Inter-relationship between systemic inflammation and REE pre- and post-onset 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	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, healthy volunteers	REE in nonmetastatic NSCLC	REE in cancer vs controls significantly raised when adjusted for LBM, $p=0.001$; and also when adjusted for BCM, $p=0.032$
Jagoe 2001	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 lung cancer operations	No difference in FFMi and BFMAMA comparing LC and controls, all p=NS
Sarhill 2003	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	N=250, with	TNM for	SMA and SMAi at	CT of L3	Cross-	Nil	Prevalence of	SMA in OS 128.1±29.1,

	LC 60 (24%) of cohort (136/114)	cohort Stage I – 24 Stage II – 56 Stage III – 74 Stage IV – 96	L3		sectional		sarcopenic obesity and chemotherapy toxicity in this cohort OS = obese sarcopenic ONonS = obese non-sarcopenic	ONonS 160±38.1, p<0.0001 SMAi in OS 43.3±6.3, ONonS 56.4±9.9; Median survival assoc with sarcopenia log rank, p<0.0001, OS 11.3months and ONonS 21.6 months, p<0.0001
Kilgour 2010	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	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 lung cancer survivors	LBM and ALM no change from baseline to post training, all p=NS

Bauer 2004	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	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 2g and 4g doses of EPA diester vs placebo in the process of cachexia	Group given 2g EPA gained mean 0.9kg LBM and group given 4g EPA lost mean 0.1kg LBM compared to placebo (p=NS)
Tozer 2008	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	41 (19/22)	NSCLC in all Stage I – 2	SMA at L3	CT of L3	Longitudinal, cohort study over 2.5	Nil	Relationship between muscle mass, rate of muscle mass	Sarcopenia at baseline in 63% men and 59% women;

		Stage II – 2 Stage III – 13 Stage IV – 24			months		change, and plasma fatty acids	Sarcopenic patients 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	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 fish oil (FO) n=17 and standard care (SC) n=24	Effect of fish oil (FO) on body composition	Sarcopenic at baseline FO 46%, SC 46%; Muscle loss rate per 100d, 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^2=0.55, p=0.01.
Agteresch 2002	N=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 -0.5kg in controls, but +0.1kg in ATP group, between group difference p=0.02 MUAC -1.8% in controls, but +1.1% in ATP group, between group difference p=0.02

								BCM -0.6% per 4weeks in controls, but -0.1% in ATP group, between group diff p=0.054
Beijer 2009	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, Standard care (SC) n=49; Completed study: ATP n=29, SC n=28	Effect of ATP on nutritional status and survival	Post ATP loss of MUAC -2.24mm, SC group -1.52mm, p=NS Short term 0-8wks survival benefit with ATP (HR 0.17, p=0.023), and long term 0-6mths survival benefit (HR 0.35, p=0.025)

Keys: FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, SMMI – skeletal muscle mass index, SMA – skeletal muscle area, LC – lung cancer, NR – not recorded, NS – non significant, ILGF – insulin like growth factor, HGS = hand grip strength, QS = quadriceps strength, DL – detectable leptin, NDL – non detectable leptin. LC – lung cancer, SCLC – small cell lung cancer, NSCLC – non-small cell lung cancer, BIA – bioelectrical impedance analysis, RCT – randomised controlled trial, CT of L3 – computed tomography of the 3rd lumbar space, DEXA – dual energy xray absorptiometry, ATP – adenosine triphosphate, REE – resting energy expenditure

The studies in our review expressed muscle mass in different ways; we have used the term fat-free mass (FFM) or loss of muscle mass 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 taken into consideration wherever the term sarcopenia is used throughout this review.

In this review, many studies found that those with cachexia and/or weight loss also had coexistent loss of muscle mass [17, 22, 52, 56, 57, 60, 63]. Despite this, none prospectively evaluated the impact this had 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 sarcopenic [17] [55], and that they exhibited a decreasing trend in FFM after chemotherapy compared with baseline, whereas women did not [23]. Reflecting the process of loss of muscle mass in the different stages of cancer, a study of sixty pre-operative NSCLC patients with stage I and II disease showed no difference in FFM compared to controls [21], whereas in a cohort of 352 advanced cancer patients, 84% of those with cachexia had a reduced FFM [63].

The pathophysiology of loss of muscle mass in lung cancer patients is complex, as illustrated in the diversity of papers exploring this. Low FFM was associated with low albumin and high acute phase protein concentrations [51, 52, 60], reflecting the inflammatory pathways involved. Abnormal protein metabolism is implicated in the development of sarcopenia, however in this review neither anabolic [52] nor proteolytic pathways [53] [49] 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 [53]. The pathophysiology may also differ depending on disease stage and cachexia phase. There is some evidence ,for example, that in pre-cachectic NSCLC patients, despite weight loss, the ubiquitin-proteasome proteolytic pathway may not be activated [49, 68]. Different ACE-gene polymorphism allelic combinations [45] and leptin expression [59] had no significant effects on muscle mass.

Fat free 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 [69]. In lung cancer cachexia, this relationship seems to be distorted [58, 60] but results have been conflicting as to whether REE contributes to the development of lung cancer cachexia [56, 57, 61, 62].

Seven interventional studies explored the effect of either nutritional supplements or adenosine triphosphate (ATP) infusions on muscle mass and function. A randomised controlled study with 518 participants, examining the effect of eicosapentaenoic acid (EPA, found in fish oil) supplements revealed increased patient-rated physical functioning, but no significant change in FFM, at the end of the study period [22]. A similar, smaller study of 8 participants concurred [64]. By contrast, one study of fish oil supplementation demonstrated a reduction in the rate of loss of muscle mass; however study numbers were 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 NSCLC patients [65, 66]. An interventional randomised controlled study with 66 participants found that cysteine-rich protein supplements increased

FFM, as well as hand-grip strength (HGS), compared to conventional protein supplements [48]. 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 [43] while the other (N=100) did not [67]. Only the study by Fearon et al was described power calculations to detect a statistically significant difference.

Degree of sarcopenia or loss of muscle mass and physical functioning

Table 4: Degree of loss of muscle mass and physical functioning

Authors	**Patients**				**Study**		**Comparison**	**Result**
	No, (M/F)	Tumour, Stage	Muscle Function and Muscle Mass Measurements	Method of Measurement	Design	Controls		
Jagoe 2001	60 (43/17)	LC in all	Grip strength Z-score	HDA dynamometer	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
			FFM, MAMC, BFMAMA	BIA, four skinfold-thickness, upper arm measurements				No difference in FFMi and BFMAMA comparing LC and controls, all p=NS

Fearon 2006	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 2g and 4g doses of EPA diester vs placebo in the process of cachexia	Patient-reported physical functioning increased by 7% in group receiving 2g EPA compared with controls (p=0.04)
Tozer 2008	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	81 (NR/NR) 74 completed muscle function tests (48/26)	Advanced NSCLC and Gastro-intestinal cancer patients, breakdown NR Stage NR	Handgrip strength In Newton metre for Biodex, and pounds for Jamar	Jamar and Biodex dynamometer (n=74 completed) DEXA, BIA (n=70	Cross-sectional	Nil	Relationship between DEXA and BIA, and Jamar and Biodex dynamometry and their precision in advanced cancer patients	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,

			FFM	completed)				DEXA vs BIA, p=NS, but low %CV for FFM DEXA (0.79) and BIA (0.42)
Kilgour 2010	N=84, with LC 16 (19%) of cohort (48/36)	Metastatic 57%, locally advanced 43%, stage NR	Handgrip strength (HGS) in kg, Quadriceps strength (QS) in Newton metre SMMI, ALM	Jamar (HGS) and Biodex (QS) DEXA	Cross-sectional	Nil	Relationship of fatigue to muscle mass and strength	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 2012	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[2]- II , insertion/deletion-ID, deletion[2] -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	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 – six minute walk distance, Get-up-and-go (GUAG), chair stands and arm curls in 30s] LBM, ALM	1 Repetition-maximum (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 12.3-17.5, Leg press 23.5-39.8, 6MWD 48-124, GUAG -0.4 to -1.2, chair stands 2.3-6.1, arm curls 2.1-5.1, all p<0.05 LBM and ALM no change from baseline to post training, all p=NS
Op den Kamp 2012	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 pre-cachexia	High intensity physical activity in LC vs controls p=0.049; FFMi no significant difference in pre-cachectic cancer vs controls, p=NS

Keys: **:** FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, SMMI – skeletal muscle mass index, SMA – skeletal muscle area, LC – lung cancer, NR – not recorded, NS – non significant, HGS – handgrip strength, QS – quadriceps strength, LC – lung cancer, NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer, EPA – eicosapentaenoic acid, DEXA – dual energy xray absorptiometry, BIA – bioelectrical impedance analysis, ACE – angiotensin converting enzyme.

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 pre-cachectic patients, exercise capacity was significantly reduced, despite maintenance of muscle mass [49], and resistance exercise training increased all parameters of muscle strength and physical performance, with no difference to muscle mass [50].

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 pre-date clinically overt cachexia, as part of aging or secondary to inflammation/disuse. This implies that consideration of both muscle mass and performance, 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. Whilst 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 lung cancer patients demonstrates inconsistency of findings as to the factors implicated in the development of cachexia,

compared to 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 pharmaceutical intervention [70]. This review highlights inherent challenges of such an approach, with nutritional interventions in particular failing to demonstrate efficacy [71], although the role of exercise is emerging [50, 72]. It also suggests the need to represent NSCLC patients 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 in cut-off values for defining sarcopenia. These values were derived from a large elderly cohort and the cut-off values based on healthy young adult reference values. These values have been used to define sarcopenia in cancer [20, 73], including one in this review [47]. The relevance of this definition to cancer patients is debatable, for a number of reasons. Firstly, sarcopenia manifests in

cancer patients of all ages and is not isolated to the elderly alone. Secondly, the pathophysiology of sarcopenia in cancer patients may differ at least in part to that of the non-cancer elderly population [74]. Finally, the recognition of muscle strength and performance as a defining component of sarcopenia in the elderly needs consideration, within the context of secondary causes – including cancer.

The argument for the objective evaluation of physical performance is pertinent, particularly as part of the definitive assessment of sarcopenia along with measurements of muscle mass. Currently, physical fitness for treatment is determined largely by the performance status (PS) score. This score is imperfect as it is subjective, with reports of inter-observer variability [75], and there is only a modest correlation between PS and observed physical performance [76]. Inter-clinician performance status discordance has led to a lower percentage of PS 0 and 1 patients appearing to get chemotherapy [77], and has led to a call for objective evaluation of physical functioning [78]. 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 performance status as a predictor of fitness for systemic treatment, and more successful completion thereof.

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 types of studies from large randomised controlled trials to small observational studies. The inclusion of a wide range of studies was necessary as this is the first systematic review of sarcopenia in lung cancer, to the best of our knowledge. 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 paper by Temel et al, 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 [79]. As such, focusing research on the identification and management of sarcopenia in lung cancer patients may prove to be a tolerable and cost effective adjunct to current lung cancer care.

Whilst 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 NSCLC coherently and to link them with changes in tumour phenotype which impact on morbidity and survival.

Conflict of interest statement

None declared.

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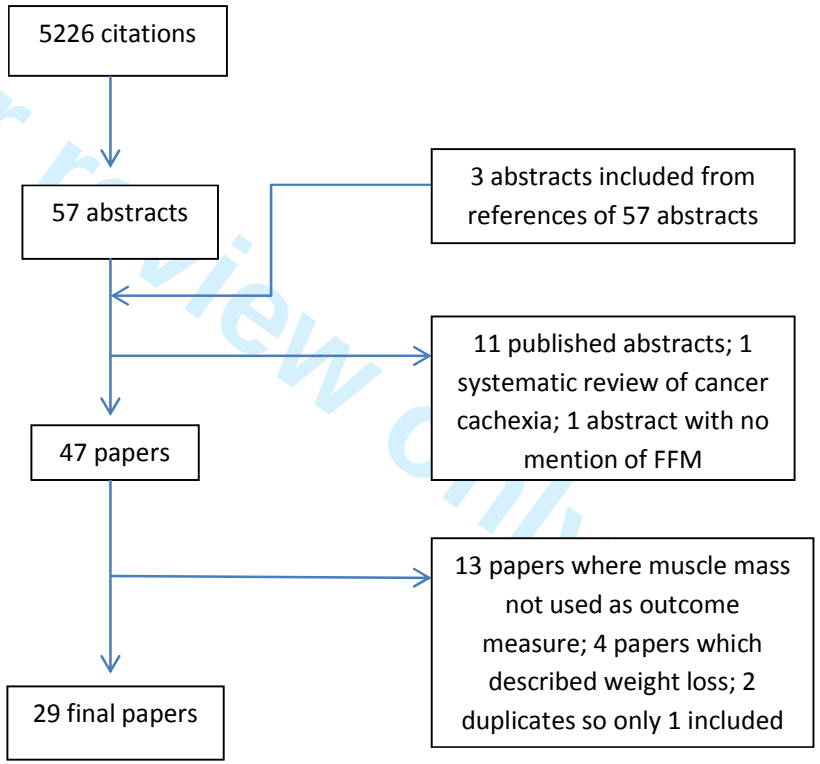
Systematic Review – Sarcopenia in Lung Cancer

FIGURE 1

Figure 1: Systematic review search methods



Research Checklist for Systematic Review manuscript for BMJ Open

PRISMA statement

From Moher D et al. *BMJ 2009; 339:b2535*

Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	1-3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	8
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	N/A
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	8,9
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	9
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	10, Figure 1
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from	10

Section/topic	Item No	Checklist item	Reported on page No
		investigators	
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	12; Table 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	See notes below
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	See notes below
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	See notes below
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	See notes below
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	See notes below
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	See notes below ref item 12
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Tables 3 and 4; pages 18-34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	N/A
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	N/A
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	34-37
Limitations	25	Discuss limitations at study and outcome level (such as risk	36-37

Section/topic	Item No	Checklist item	Reported on page No
		of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	37
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	N/A

NOTES

- With reference to item 12, we have tried to account for individual study bias by reporting study sample size and power calculations where reported.
- With reference to items 13, 14 and 16, as this is a systematic review rather than a meta-analysis, this was not performed.
- With reference to item 15, we have not accounted for publication bias. With regards to selective reporting within studies, this was not possible to be performed in great detail but we paid particular attention to the individual reporting of participant numbers, and whether the authors accounted for the number of those not completing the study.
- With reference to item 27, we received no external funding for this systematic review.

BMJ open

The assessment and impact of sarcopenia in lung cancer: a systematic literature review.

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The assessment and impact of sarcopenia in lung cancer: a systematic literature review.

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Keywords

Sarcopenia; cachexia; muscle mass; physical performance; lung cancer

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 lung cancer patients, 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 lung cancer patients.

Results

We reviewed 5726 citations, and 35 papers were selected for analysis. Sarcopenia, as defined by reduced muscle mass alone, was found to be very prevalent in lung cancer patients, 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 adenosine triphosphate infusions on muscle mass showed conflicting results. There is very limited data on the correlation between degree of sarcopenia and muscle function, which has a non-linear relationship in older non-cancer populations.

Conclusion

Loss of muscle mass is a significant contributor to morbidity in lung cancer patients. Loss of muscle mass and function may pre-date 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.

Article Summary

Article Focus

- Sarcopenia, the loss of muscle mass and muscle function, is a significant contributor to morbidity in lung cancer patients.
- Sarcopenia is a key component of a new definition of cancer cachexia, however its relationship to cachexia in the lung cancer literature is poorly defined.

Key messages

- Sarcopenia is prevalent in lung cancer patients regardless of body mass index and body weight, and where present is associated with poorer functional status and overall survival.

- There is very limited data on the correlation between the degree of loss of muscle mass and muscle function, which has a non-linear relationship in older non-cancer populations.
- The heterogeneity of cut-off values for cancer-related sarcopenia necessitates a standardised definition which can be used clinically and in the research setting, to harmonise reporting and allow for direct comparison of results as well as meta-analysis of data.

Strengths and limitations of this study

- Timely systematic review considering the increasingly recognised phenomenon of sarcopenia, as it relates to cachexia, which affects not only patients with lung cancer, but also the wider cancer population.
- Limited to publications in English only.

Introduction

Over the last decade, there has been increasing recognition of the clinical importance of 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 (1-5). 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 (6). 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 (7-9). Sarcopenia becomes more prevalent as we age - of 1,421 healthy adults aged 45 years or over, the overall prevalence was 15%, rising to 64% over the age of 85 (10). 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 cancer populations sarcopenia is associated with poorer performance status (1), reduced overall survival (11, 12), and increased risk of chemotherapy toxicities (2, 4). This interest is reflected in a recent international consensus on the definition of cancer cachexia, which established sarcopenia as a key diagnostic criterion (13).

The hallmark of sarcopenia is low muscle mass, more specifically an appendicular skeletal muscle mass index of more than two standard deviations below the sex-specific mean of healthy adults (i.e. 5.45kg/m^2 for women and 7.26 kg/m^2 for men) (8). 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 (14, 15).

Whilst 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 computed tomography (CT), magnetic resonance imaging (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 – e.g. 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 to CT and accurately and precisely differentiates between lean and fat body compartments (16). More indirect techniques for measuring muscle mass include bioelectrical impedance analysis which is non-invasive but less accurate compared to DEXA. It includes a measure of organ mass other than skeletal muscle, but is easily performed in clinical settings (17). Measurements of mid upper arm circumference and arm muscle area using skinfold thickness methods have also been used (18), although these assessments are less accurate and there exists considerable inter-observer variability. Measurements of muscle strength in the literature have mainly centred around handgrip and quadriceps strength, although in non-cancer elderly patients, functional assessments such as the Short Physical Performance Battery and sit-to-stand tests (19, 20) 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 cancer patients and in quantifying its functional implications. If the loss of muscle mass and strength have significant clinical implications for cancer patients, then standardised, validated diagnostic thresholds are clearly needed. Furthermore, while the effects of sarcopenia have been extensively studied in the elderly, 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 (21), and frequently presents in the advanced stages. Despite advances in anticancer therapies, survival benefits in lung cancer patients over the past thirty years have been relatively small compared to those seen in breast, colorectal and prostate cancers (22). Whilst reasons for this are complex, many lung cancer patients are ineligible for radical treatment at presentation due to poor performance status or co-morbidity, while others fail to receive their intended treatment plan because of functional decline (23, 24). 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 (25). This prevalence can be compared with 16% of a cohort of 471 breast cancer survivors (26) and 39% in a cohort of 234 pre-operative colorectal cancer patients (5). We conducted this systematic review with this in mind.

Methods

Search strings and data sources

We 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.

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)

Paper retrieval

Citations were independently screened by two researchers (JC 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 lung cancer patients were included, even if there were other cancer patient groups analysed. Retrieved papers were searched for additional relevant references.

Inclusion criteria and data extraction

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

Results

Using our broad search terms in 5 databases, we found an initial 5726 citations, from which we identified 64 potentially relevant papers. Three further potential papers (27-29) were identified from the references of these papers. From these, we excluded 11 abstracts with no published papers, two further abstracts that did not mention muscle mass (30, 31), and a systematic review of cancer cachexia (32). Out of the 53 final papers, we excluded a further 13 papers which mentioned muscle mass in baseline anthropometry details but did not use it as an outcome measure (33-45), four papers which described weight loss rather than loss of muscle mass (46-49), and one paper describing the same results obtained from the same patient population as another paper (50), with slightly different secondary endpoints (51). 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.

Figure 1 shows a breakdown of the results of our search using the search terms used, and the derivation of papers for final analysis.

Insert Figure 1 here

For the final analysis, 4 randomised controlled studies, 17 cross-sectional studies and 14 longitudinal studies met the established criteria: 35 papers in total. Muscle mass data were reported variously as fat free mass, 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 hand-grip and/or quadriceps strength (17, 27, 52-54), intensity of physical activity (55), patient-reported physical functioning (28), and both muscle strength and physical performance (56).

As the studies in our review expressed muscle mass in different ways, we have used the term fat-free mass (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

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

First author, year	Patients				Study		Comparison
	No, (M/F)	Tumour, Stage	Muscle Mass Measurement(s)	Method of Measurement	Design	Controls	
McMillan 2001(57)	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 alb body cell ma the systemic inflammator response
Crown 2002 (58)	30 (NR/NR)	NSCLC in all Inoperable, stage NR	FFM, MUAC	BIA, upper arm measurements	Case-control, Longitudinal over 2 years	n=30 healthy volunteers (HV)	Insulin-like g factor (ILGF) and cancer cachexia

Jagoe 2002 (59)	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 lysosomal proteolytic pathway ger expression i and associat with LMM
Wieland 2007 (60)	286 (NR/NR)	NSCLC n=181, stage IIIB or IV	SMA at T4	CT at T4	Longitudinal	n=7 healthy volunteers	Establish prevalence o proteolysis-inducing fact (PIF) in canc patients, and association v muscle loss
Martinez-Hernandez 2012 (61)	21 (19/2)	Lung cancer n=13, GI cancer n=6, Other cancer n=2 Stage according to tumour group NR	FFM	BIA	Longitudinal	n=8 healthy volunteers	The role of interleukin-1 15) in cache cancer patie
Op den Kamp 2012 (55)	16 (15/1)	NSCLC in all Stage I-II – 11 Stage IIIA – 2 Stage IIIB – 3	FFMi	DEXA	Cross-sectional	n=10 healthy volunteers	Skeletal mus kB and ubiqu proteasome activity in pr cachexia

Vigano 2009 (52)	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 polymorphis (insertion^2- I insertion/de ID, deletion^2 on nutritiona status
Op den Kamp 2013 (62)	26 (17/9)	NSCLC Stage IIIB – 10 Stage IV – 16	FFMi, AMMi	DEXA	Cross-sectional	n = 10 healthy volunteers	Expression o signalling mo in protein metabolism cancer cache
Harvie 2003 (29)	50 (32/18)	NSCLC In all, Stage III and IV	FFM	Four skinfold method	Longitudinal	Nil	Exploration gender-spec differences i composition REE pre- and chemothera
Harvie 2005 (63)	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	Relationship between ene intake, REE a acute phase response vs changes in b composition course of chemothera
Bovio 2008 (64)	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 o nutritional s patients with advanced ca
Baracos 2010 (25)	441 (229/212)	NSCLC in all Stage III – 206	SMA at L3	CT of L3	Cross-sectional	Nil	The use of C images in evaluating b composition

		Stage IV – 235					NSCLC
Martin 2013 (65)	1473 (828/645)	Colorectal cancer n=773, Lung cancer n=440, Other GI cancer n=260 Stage according to cancer NR	SMA at L3, SMAi	CT of L3	Longitudinal	Nil	Prognostic significance weight loss, mass index a muscle atter
Prado 2013 (66)	368 (216/152)	NSCLC n=242 GI tract cancer n=126	SMA at L3	CT of L3	Longitudinal	Nil	Clinical cours skeletal mus wasting in advanced ca
Hansell 1986 (67)	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 weigh losing cance patients WLC = weigh losing cance patients, WS weight-stabl cancer patie WSCon = we stable contr
Fredrix 1990	39 (GCR 13/9, LC	LC n=17	FFM	BIA	Cross-	n=40	REE and wei

(68)	16/1)	GCR – Gastric and colorectal cancer n=22 Stage NR			sectional	healthy	
Staal-van den Brekel 1997 (69)	12 (10/2)	All SCLC	FFM	BIA	Longitudinal	Nil	Assess REE a systemic inflammatio and post-chemothera
Simons 1997 (70)	21 (21/0)	NSCLC n=19 Stage I – 3 Stage III – 5 Stage IV – 11 SCLC n=2 Limited stage – 2	FFM, FFMi	DEXA	Cross-sectional	Nil	Relationship between detectable le (DL) express body compo and REE
Simons 1999 (71)	20 (20/0)	NSCLC n=18 I-II – 2 III – 5 IV – 11 SCLC n=2	BCM, BCMi	DEXA	Cross-sectional	Nil	Relationship between we loss, low BCI systemic inflammatio
Scott 2001 (72)	12 (12/0)	NSCLC in all, locally advanced	BCM	Total body potassium	Longitudinal	n=7, healthy subjects	Inter-relatio between sys inflammatio REE pre- and onset of wei

Jatoi 2001 (73)	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, healthy volunteers	REE in nonmetastat NSCLC
Jagoe 2001 (27)	60 (43/17)	LC in all	FFM, MAMC, BFMAMA	BIA, four skinfold-thickness, upper arm measurements	Cross-sectional	n=22, mild COPD	Nutritional s of patients undergoing l cancer opera
Sarhill 2003 (74)	N=352 but LC only 18% of cohort ()	NR	MUAC, AMA	BIA (n=329)	Cross-sectional	Nil	Prospective evaluation o nutritional s advanced ca
Prado 2008 (1)	N=250, with LC 60 (24%) of cohort (136/114)	TNM for cohort Stage I – 24 Stage II – 56 Stage III – 74 Stage IV – 96	SMA and SMAi at L3	CT of L3	Cross-sectional	Nil	Prevalence o sarcopenic o and chemoth toxicity in th cohort OS = obese sarcopenic ONonS = obe non-sarcope
Kilgour 2010 (53)	N=84, with LC 16 (19%) of cohort (48/36)	Metastatic 57%, locally advanced 43%, stage NR	SMMI, ALM	DEXA	Cross-sectional	Nil	Relationship fatigue to m mass and str
Peddle-McIntyre 2012	17 (7,10)	NSCLC n=16	LBM, ALM	DEXA	Longitudinal, duration 10	Nil	Resistance e training effic

(56)		Stage I-II –11 Stage III – 5 Limited stage SCLC n=1			weeks		and feasibilit lung cancer survivors
Bauer 2004 (75)	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 nut counselling a EPA supplem on body composition
Fearon 2006 (28)	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 2g a doses of EPA diester vs pla in the proces cachexia
Tozer 2008 (54)	66 (49/17); only 35 completed study	All LC Stage NR	BCM	NR	RCT (Double blind, placebo controlled, randomised)	Nil	Effect of cys rich protein supplement body weight body cell ma
Murphy 2010 (76)	41 (19/22)	NSCLC in all Stage I – 2 Stage II – 2 Stage III – 13 Stage IV – 24	SMA at L3	CT of L3	Longitudinal, cohort study over 2.5 months	Nil	Relationship between mu mass, rate o muscle mass change, and fatty acids
Murphy 2011 (77)	40 (21/19)	NSCLC in all	SMA at L3	CT of L3	Longitudinal, duration 6	Nil controls; cohort divided into	Effect of fish (FO) on body

		Stage III – 13 Stage IV – 27			weeks Open label study	those receiving fish oil (FO) n=17 and standard care (SC) n=24	composition
Winter 2012 (78)	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 pro anabolism in response to hyperamino mia, in cache insulin resist patients
Agteresch 2002 (50)	N=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 body compo
Beijer 2009 (79)	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, Standard care (SC) n=49; Completed study: ATP n=29, SC n=28	Effect of ATP nutritional s and survival

Keys: FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, AMMi – appendicular muscle mass index, SMMI – skeletal muscle mass index, 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, LC – lung cancer, NR – not recorded, NS – non significant, ILGF – insulin like growth factor, HGS = hand grip strength, QS = quadriceps strength, DL – detectable leptin, NDL – non detectable leptin. LC – lung cancer, SCLC – small cell lung cancer, NSCLC – non-small cell lung cancer, BIA – bioelectrical impedance analysis, RCT – randomised controlled trial, CT of L3 – computed tomography of the 3rd lumbar space, DEXA – dual energy xray absorptiometry, ATP – adenosine triphosphate, REE – resting energy expenditure

In this review, many studies found that those with cachexia and/or weight loss also had coexistent loss of muscle mass (25, 28, 58, 67, 68, 71, 74). Despite this, none prospectively evaluated the impact this had 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 (25) (64), and that they exhibited a decreasing trend in FFM after chemotherapy compared with baseline, whereas women did not (29). Reflecting the process of loss of muscle mass in the different stages of cancer, a study of sixty pre-operative NSCLC patients with stage I and II disease showed no difference in FFM compared to controls (27), whereas in a cohort of 352 advanced cancer patients, 84% of those with cachexia had a reduced FFM (74).

The pathophysiology of loss of muscle mass in lung cancer patients is complex, as illustrated in the diversity of papers exploring this. Low FFM has been associated with low albumin and high acute phase protein concentrations (57, 58, 71), reflecting the inflammatory pathways involved. Abnormal protein metabolism is implicated in the development of sarcopenia, however in this review neither anabolic (58) nor proteolytic pathways (59) (55) 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 (59). The pathophysiology may also differ depending on disease

stage and cachexia phase. There is some evidence, for example, that in pre-cachectic NSCLC patients, despite weight loss, the ubiquitin-proteasome proteolytic pathway may not be activated (55, 80). Different ACE-gene polymorphism allelic combinations (52) and leptin expression (70) have not been shown to have significant effects on muscle mass. Fat free 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 (81). In lung cancer cachexia, this relationship seems to be distorted (69, 71) but results have been conflicting as to whether REE contributes to the development of lung cancer cachexia (67, 68, 72, 73).

The use of CT images for diagnosis of muscle mass depletion alone showed a high prevalence of this phenomenon in NSCLC patients (25), regardless of BMI and even amongst the obese (1). 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 (65, 66). 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 adenosine triphosphate (ATP) infusions on muscle mass and function. A randomised controlled study with 518 participants, examining the effect of eicosapentaenoic acid (EPA, found in fish oil) supplements revealed increased patient-rated physical functioning, but no significant change in FFM, at the end of the study period (28). A similar, smaller study of 8 participants concurred (75). By contrast, one study of fish oil supplementation demonstrated a reduction in the rate of loss of muscle mass; however study numbers were 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 NSCLC patients (76, 77). An interventional randomised controlled study with 66 participants found that cysteine-rich protein supplements increased FFM, as well as hand-grip strength (HGS), compared to conventional protein supplements (54), 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 (78). 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 (50) while the other (N=100) did not (79).Only the study by Fearon et al (28) described power calculations to detect a statistically significant difference.

Degree of sarcopenia or loss of muscle mass and physical functioning

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

Authors	**Patients**				**Study**		**Comparison**
	No, (M/F)	Tumour, Stage	Muscle Function and Muscle Mass Measurements	Method of Measurement	Design	Controls	
Jagoe 2001 (27)	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 s of patients undergoing l cancer opera
Fearon 2006 (28)	518 (355/163)	LC n=231 Upper GI cancer n=198 Other GI	LBM	BIA	RCT (Double blind, placebo controlled, randomised)	Nil	Effect of 2g a doses of EPA diester vs pla in the proces cachexia

		cancer n=89 Stage NR					
Tozer 2008 (54)	66 (49/17); only 35 completed study	All LC Stage NR	BCM	NR	RCT (Double blind, placebo controlled, randomised)	Nil	Effect of cys rich protein supplement body weight body cell ma
Trutschnigg 2008 (17)	81 (NR/NR) 74 completed muscle function tests (48/26)	Advanced NSCLC and Gastro-intestinal cancer patients, 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 DE BIA, and Jam Biodex dynamomet their precisio advanced ca patients
Kilgour 2010 (53)	N=84, with LC 16 (19%) of cohort (48/36)	Metastatic 57%, locally advanced 43%, stage NR	Handgrip strength (HGS) in kg, Quadriceps strength (QS) in Newton metre SMMI, ALM	Jamar (HGS) and Biodex (QS) DEXA	Cross-sectional	Nil	Relationship fatigue to m mass and str
Vigano 2009 (52)	N=172 (101/71)	NSCLC n=64, Stage III and IV, breakdown NR	Handgrip force and percentile	Jamar dynamometer	Cross-sectional	Nil	ACE gene polymorphis (insertion^2- I insertion/de ID, deletion^2 on nutritiona

		Metastatic GI cancer n=108	LBM, ALM	DEXA (n=64)			status
Peddle-McIntyre 2012 (56)	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 – six minute walk distance, Get-up-and-go (GUAG), chair stands and arm curls in 30s] LBM, ALM	1 Repetition-maximum (1RM) in kg DEXA	Longitudinal, duration 10 weeks	Nil	Resistance e training effic and feasibilit lung cancer survivors
Martinez-Hernandez 2012 (61)	21 (19/2)	Lung cancer n=13, GI cancer n=6, Other cancer n=2 Stage according to tumour group NR	Handgrip strength (HGS) and treadmill 6 minute walk test (6MWT) FFM	BIA	Longitudinal	n=8 healthy volunteers	The role of interleukin-1 15) in cache cancer patie
Op den Kamp 2012 (55)	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 mus ubiquitin proteasome activity in pr cachexia
Op den Kamp 2013 (62)	26 (17/9)	NSCLC Stage IIIB – 10	Quadriceps strength (QS)	DEXA	Cross-sectional	n = 10 healthy volunteers	Expression o signalling mo in protein metabolism

Stage IV – 16	FFMi, AMMi	cancer cache

Keys: **:** FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, SMMI – skeletal muscle mass index, SMA – skeletal muscle area, LC – lung cancer, NR – not recorded, NS – non significant, HGS – handgrip strength, QS – quadriceps strength, LC – lung cancer, NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer, EPA – eicosapentaenoic acid, DEXA – dual energy xray absorptiometry, BIA – bioelectrical impedance analysis, ACE – angiotensin converting enzyme.

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 pre-cachectic patients, exercise capacity was significantly reduced, despite maintenance of muscle mass (55), and resistance exercise training increased all parameters of muscle strength and physical performance, with no difference to muscle mass (56). In this review, cachectic patients showed reduced strength in terms of walking distance (61) and quadriceps strength (62) compared to 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 pre-date clinically overt cachexia, as part of aging 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. Whilst 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 lung cancer patients demonstrates inconsistency of findings as to the factors implicated in the development of cachexia, compared to 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 (82). This review highlights inherent challenges of such an approach, with nutritional interventions in particular failing to demonstrate efficacy altho(83),ugh the role of exercise is emerging (56, 84). It also suggests the need to represent NSCLC patients 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 in cut-off values for defining sarcopenia. Current standardised values were derived from a large elderly cohort and the cut-off values based on healthy young adult reference values. These values have been used to define

sarcopenia in cancer (13, 85), including one in this review (53). The relevance of this definition to cancer patients is debatable, for a number of reasons. Firstly, sarcopenia manifests in cancer patients of all ages and is not isolated to the elderly alone. Secondly, the pathophysiology of sarcopenia in cancer patients may differ at least in part to that of the non-cancer elderly population (86). With this in mind, the more recent international consensus document recommending a reference value of absolute muscularity below the 5th centile is to be welcomed (13). Finally, the recognition of muscle strength and performance as a defining component of sarcopenia in the elderly 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 performance status (PS) score. This score is imperfect as it is subjective, with reports of inter-observer variability (87), and there is only a modest correlation between PS and observed physical performance (88). Inter-clinician performance status discordance has led to a lower percentage of PS 0 and 1 patients appearing to get chemotherapy (89), and has led to a call for objective evaluation of physical functioning (90). 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 performance status 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 papers included in this review, whilst 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 paper by Temel et al, 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 (91). As such, focusing research on the identification and management of sarcopenia in lung cancer patients may prove to be a tolerable and cost effective adjunct to current lung cancer care.

Whilst 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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Contributorship Statement

JC and SN were responsible for the conception and design of this review.

JC and BC conducted the searches.

JC and SN independently reviewed the citations, and were responsible for analysing and interpreting the data.

SN, JDC and AB and JC drafted the article and revised its content to its final version.

Data Sharing Statement

No additional data

Conflict of interest statement

None declared.

Figure legend

shows a breakdown of the results of our search using the search terms used, and the derivation of papers for final analysis.

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The assessment and impact of sarcopenia in lung cancer: a systematic literature review~~, highlighting implications for research and clinical practice~~.

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Abstract

Objectives

There is growing awareness of the relationship between sarcopenia (loss of muscle mass and function), and outcomes in ~~lung~~ cancer, making it a potential target for future therapies. In order to inform future ~~lung cancer~~ 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 lung cancer patients, and were published in English.

Setting

Secondary care

Participants

Patients with lung cancer~~.~~

Primary outcome

~~Muscle mass values associated with or without muscle strength or physical performance.~~ Factors associated with loss of muscle mass and muscle function, or sarcopenia, and the clinical impact thereof in lung cancer patients. ~~We recorded the units and methods of measuring muscle mass, and the comparison or correlation that was assessed.~~

Results

We reviewed ~~5226~~5726 citations, and 35 papers were selected for analysis. Sarcopenia, as defined by reduced muscle mass alone, was found to be very prevalent in lung cancer patients, 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 adenosine triphosphate infusions on muscle mass showed conflicting results. There is very limited data on the correlation between degree of sarcopenia and muscle function, which has a non-linear relationship in older non-cancer populations.

Conclusion

Loss of muscle mass is a significant contributor to morbidity in lung cancer patients. Loss of muscle mass and function may pre-date 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.

Keywords

Sarcopenia; cachexia; muscle mass; physical performance; lung cancer

Article Summary

Article Focus

- Sarcopenia, the loss of muscle mass and muscle function, is a significant contributor to morbidity in lung cancer patients.
- Sarcopenia is a key component of a new definition of cancer cachexia, however its relationship to cachexia in the lung cancer literature is poorly defined.

Key messages

- Sarcopenia is prevalent in lung cancer patients regardless of body mass index and body weight, and where present is associated with poorer functional status and overall survival.
- There is very limited data on the correlation between the degree of loss of muscle mass and muscle function, which has a non-linear relationship in older non-cancer populations.
- The heterogeneity of cut-off values for cancer-related sarcopenia necessitates a standardised definition which can be used clinically and in the research setting, to harmonise reporting and allow for direct comparison of results as well as meta-analysis of data.

Strengths and limitations of this study

- Timely systematic review considering the increasingly recognised phenomenon of sarcopenia, as it relates to cachexia, which affects not only patients with lung cancer, but also the wider cancer population.
- Limited to publications in English only.

Introduction

Over the last decade, there has been increasing recognition of the clinical importance of 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 (1-5). 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 (6). 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 (7-9). Sarcopenia becomes more prevalent as we age - of 1,421 healthy adults aged 45 years or over, the overall prevalence was 15%, rising to 64% over the age of 85 (10). 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 cancer populations sarcopenia is associated

with poorer performance status (1), reduced overall survival (11, 12), and increased risk of chemotherapy toxicities (2, 4). This interest is reflected in a recent international consensus on the definition of cancer cachexia, which established sarcopenia as a key diagnostic criterion (13).

The hallmark of sarcopenia is low muscle mass, more specifically an appendicular skeletal muscle mass index of more than two standard deviations below the sex-specific mean of healthy adults (i.e. 5.45kg/m^2 for women and 7.26 kg/m^2 for men) (8). 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 (14, 15).

Whilst 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 computed tomography (CT), magnetic resonance imaging (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 – e.g. 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 to CT and accurately and precisely differentiates

between lean and fat body compartments (16). More indirect techniques for measuring muscle mass include bioelectrical impedance analysis which is non-invasive but less accurate compared to DEXA. It includes a measure of organ mass other than skeletal muscle, but is easily performed in clinical settings (17). Measurements of mid upper arm circumference and arm muscle area using skinfold thickness methods have also been used (18), although these assessments are less accurate and there exists considerable inter-observer variability. Measurements of muscle strength in the literature have mainly centred around handgrip and quadriceps strength, although in non-cancer elderly patients, functional assessments such as the Short Physical Performance Battery and sit-to-stand tests (19, 20) 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 cancer patients and in quantifying its functional implications. If the loss of muscle mass and strength have significant clinical implications for cancer patients, then standardised, validated diagnostic thresholds are clearly needed. Furthermore, while the effects of sarcopenia have been extensively studied in the elderly, 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 (21), and frequently presents in the advanced stages. Despite advances in anticancer therapies, survival benefits in lung cancer patients over the past thirty years have been relatively small compared to those seen in breast, colorectal and prostate cancers (22). Whilst reasons for this are complex, many lung cancer patients are ineligible for radical treatment at presentation due to poor performance status or co-morbidity, while others fail to receive their intended treatment plan because of functional decline (23, 24). 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 (25). This prevalence can be compared with 16% of a cohort of 471 breast cancer survivors (26) and 39% in a cohort of 234 pre-operative colorectal cancer patients (5). We conducted this systematic review with this in mind.

~~There are 42,000 cases of lung cancer diagnosed in the United Kingdom each year and approximately three quarters are over the age of 65 at diagnosis. Despite advances in anticancer therapies, survival benefits in lung cancer patients over the past thirty years have been relatively small compared to those seen in breast, colorectal and prostate cancers [1]. Whilst reasons for this are complex, many lung cancer patients are ineligible for radical treatment at presentation due to poor performance status or co-morbidity, while others fail to receive their intended treatment plan because of functional decline [2, 3].~~

~~Sarcopenia is a widely recognised phenomenon that has important clinical implications in the management of lung cancer. It is characterised by a triad of progressive loss of skeletal muscle mass, muscle strength and physical performance [4]. 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 [4-7]. However, sarcopenia may also be seen in younger patients in association with muscle disuse, malnutrition or inflammatory diseases, including cancer [4].~~

~~Central to the concept of sarcopenia is the recognition that overall neuromuscular function, rather than muscle mass alone, is essential for maintenance of independence. Although originally defined as an appendicular skeletal muscle mass index of more than two standard deviations below the sex-specific mean of healthy adults (i.e. 5.45kg/m^2 for women and 7.26 kg/m^2 for men) [6] the current consensus on defining sarcopenia requires assessment of muscle strength, or performance, as well as mass [8]. Loss of muscle mass is usually gradual and not necessarily associated with significant or sudden weight loss, and the relationship between muscle mass and strength is non-linear [9, 10].~~

~~Loss of muscle mass, with or without loss of fat mass, is also a predominant component of weight loss seen in cancer cachexia, a complex metabolic syndrome with inflammation recognised as a key feature [11]. The pathophysiological mechanisms responsible for loss of muscle mass in cancer cachexia differ, at least in part, from those in sarcopenia of ageing. Therefore, in established cachexia, most patients will have sarcopenia, whereas sarcopenic patients are often not cachectic.~~

~~Over the last decade, there has been increasing recognition of the importance of sarcopenia as part of the cancer cachexia syndrome and its impact has been evaluated in patients with lung, breast, upper gastrointestinal, hepatocellular and colorectal malignancies [12-16]. 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, 46.7% were defined as sarcopenic, based on muscle mass measurements [17]. As with the elderly non-cancer patient, sarcopenia in cancer has important clinical implications. Most notably it is associated with poor performance status and reduced survival [12]. It also appears to be associated with an increase in chemotherapy-related toxicities [13, 15].~~

~~In the context of lung cancer, cachexia and sarcopenia frequently coexist and may be clinically indistinguishable. However, having clear working definitions may allow earlier recognition of the conditions and provide a framework for research to identify early markers and focused interventions, offering complementary therapeutic approaches. It is also important to consider that, although lung cancer cachexia may lead to sarcopenia, sarcopenia may itself pre-date cachexia. Failure to recognise this may lead to lost opportunities to limit and treat sarcopenia in the NSCLC patient, and thereby better preserve performance status. This could impact on survival for patients, through reduced eligibility for active treatments and reduced ability to tolerate chemotherapy toxicities [2, 12]. In the previously-mentioned cohort, where 46.7% of NSCLC patients were found to be sarcopenic, only 7.3% were underweight. Furthermore, of those classified as overweight in terms of body mass index, 59% were sarcopenic [17]. It may, therefore, be more useful to assess sarcopenia, rather than weight loss or BMI, when evaluating the suitability of NSCLC patients for future treatments.~~

~~Much of the discussion of sarcopenia, as it relates to cancer cachexia, has relied on the narrower definition of loss of muscle mass. Whilst loss of function is a recognised later consequence of cancer cachexia, muscle strength or performance have not been routinely measured as part of the initial assessment of cachexia severity, despite being central to the current, broader definition of sarcopenia. As clear consensus emerges on the definitions of cachexia [18-20], a better understanding of the inter-dependence between cachexia and sarcopenia suggests that early recognition of sarcopenia as part of, or prior to, cachexia in NSCLC may yield improvements in patient outcomes.~~

~~To understand this further, we aimed to systematically review all relevant literature pertaining to factors associated with loss of muscle mass in lung cancer, and the relationship between muscle performance and muscle mass, in order to critically evaluate its implications for research and clinical practice.~~

Methods

Search strings and data sources

We 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~~2012~~. 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.

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)

Paper retrieval

Citations were independently screened by two researchers (JC 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 lung cancer patients were included, even if there were other cancer patient groups analysed. Retrieved papers were searched for additional relevant references.

Inclusion criteria and data extraction

The selected papers were reviewed in full by two independent researchers (JC and SN) for consideration of inclusion in the review. Where discordance in selection was observed, the paper in question was discussed until consensus was reached. As there were many papers describing muscle mass as part of routine anthropometry or body composition assessments, without directly exploring it, we only included papers in which muscle mass was explored as an outcome measure. Data including patient characteristics and numbers, histological subtype, and TNM stage, were collated and tabulated (Tables 2~~3~~-3~~4~~). We also noted units of muscle mass measurements, and techniques used to measure these.

Results

Using our broad search terms in 5 databases, we found an initial 5726~~5226~~ citations, from which we identified 64~~57~~ potentially relevant papers. Three further potential papers (27-29) were identified from the references of these papers. From these, we excluded 11 abstracts with no published papers, two~~a~~ further abstracts that did not mention muscle mass ~~or body composition~~ (30, 31), and a systematic review of cancer cachexia (32). Out of the 53~~47~~ final papers, we excluded a further 13 papers which mentioned muscle mass in baseline anthropometry details but did not use it as an outcome measure (33-45), four papers which described weight loss rather than loss of muscle mass (46-49), and one paper describing the same results obtained from the same patient population as another paper (50), with slightly different secondary endpoints (51). 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.

Figure 1 shows a breakdown of the results of our search using the search terms used, and the derivation of papers for final analysis.

Insert Figure 1 here

For the final analysis, 4 randomised controlled studies, 17~~16~~ cross-sectional studies and 14~~9~~ longitudinal studies met the established criteria: 35~~29~~ papers in total. Muscle mass data were reported variously as fat free mass, body cell mass, lean body mass, appendicular skeletal muscle mass, smooth muscle area at the levels of lumbar vertebra L3 and thoracic vertebra T4~~L3~~, mid upper arm circumference and arm muscle area. Notably, most studies described muscle mass in more than one way. Muscle function was described as hand-grip and/or quadriceps strength (17, 27, 52-54), intensity of physical activity (55), patient-reported physical functioning (28), and both muscle strength and physical performance (56).

As the studies in our review expressed muscle mass in different ways, we have used the term fat-free mass (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

Table 2~~3~~: Loss of muscle mass as outcome measures and factors associated with it~~Factors associated with loss of muscle mass~~

~~Authors~~First author, year	Patients				Study		Comparison	Result
	No, (M/F)	Tumour, Stage	Muscle Mass Measurement(s)	Method of Measurement	Design	Controls		
McMillan 2001(57)	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 (58)	30 (NR/NR)	NSCLC in all Inoperable, stage NR	FFM, MUAC	BIA, upper arm measurements	Case-control, Longitudinal over 2 years	n=30 healthy volunteers (HV)	Insulin-like growth factor (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 sig longitudinal trend observed in IGFBP-3 and IL-6 and nutritional status, p=NS.
Jagoe 2002 (59)	36 (27/9)	Mix of NSCLC and SCLC	FFMi	BIA, Four skinfold method,	Cross-sectional	n=10 patients referred for	Ubiquitin-proteasome and lysosomal	Cathepsin B expression in LC inversely related to FFMi, p=0.003;

		Stage 1 – 21 Stage 2 – 6 Stage 3 – 6 Stage 4 – 2		%BFMAMA		thoracotomy for non-malignant conditions	proteolytic pathway gene expression in LC and association with LMM	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 (60)	286 (NR/NR)	NSCLC n=181, stage IIIB or IV	SMA at T4	CT at T4	Longitudinal	n=7 healthy volunteers	Establish prevalence of proteolysis-inducing factor (PIF) in cancer patients, and its association with muscle loss	In NSCLC patients: PIF unrelated to survival and muscle loss, p=NS; PIF positive patients rate of loss of muscle mass per 100days -3.4±2.1% vs PIF negative patients -2.4 ±1.7%, p=NS
Martinez-Hernandez 2012 (61)	21 (19/2)	Lung cancer n=13, GI cancer n=6, Other cancer n=2 Stage according to tumour group NR	FFM	BIA	Longitudinal	n=8 healthy volunteers	The role of interleukin-15 (IL-15) in cachectic cancer patients	At weeks 4 and 8, cancer patients lost FFM in tandem with decreasing IL-15 levels, r=0.514 and r=0.535, both p<0.05
Op den Kamp 2012 (55)	16 (15/1)	NSCLC in all Stage I-II –	FFMi	DEXA	Cross-sectional	n=10 healthy	Skeletal muscle NF-kB and ubiquitin proteasome system	FFMi no significant difference in pre-cachectic cancer vs

		11 Stage IIIA – 2 Stage IIIB – 3				volunteers	activity in pre-cachexia	controls, p=NS; NF-kB, UPS E3-ligase and 26S proteasome activity not raised in pre-cachectic cancer patients, all p=NS
Vigano 2009 (52)	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^2- II , insertion/deletion- ID, deletion^2 -DD) on nutritional status	Trend (p=0.07) towards lower LBM in ID compared to II groups
Op den Kamp 2013 (62)	26 (17/9)	NSCLC Stage IIIB – 10 Stage IV – 16	FFMi, AMMi	DEXA	Cross-sectional	n = 10 healthy volunteers	Expression of signalling molecules in protein metabolism in lung cancer 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 i.e. impaired anabolic activity
Harvie 2003 (29)	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	Trend for FFM to decrease (p=0.063) and FFM decreased (p<0.05) in men after

							REE pre- and post-chemotherapy	chemotherapy. No significant difference in FFM or REE in women.
Harvie 2005 (63)	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	Relationship between energy intake, REE and acute phase response vs changes in body composition over course of chemotherapy	No significant change in FFM over the course of chemotherapy, and no significant relationship with energy intake, REE or c-reactive protein (CRP) (all p=NS)
Bovio 2008 (64)	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 percentile (p<0.01)
Baracos 2010 (25)	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 (65)	1473 (828/645)	Colorectal cancer n=773,	SMA at L3, SMAi	CT of L3	Longitudinal	Nil	Prognostic significance of weight loss, muscle mass index and	Concordance model using variables of BMI, weight loss, muscle index (MI) and muscle

		Lung cancer n=440, Other GI cancer n=260 Stage according to cancer NR					muscle attenuation	attenuation (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 (8.4mo), compared to those with none of these features (28.4mo), p<0.001
Prado 2013 (66)	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 <90days from death increases risk of muscle loss, OR 2.67, p=0.002; and decreases chance of muscle gain, OR=0.37, p=0.002
Hansell 1986 (67)	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 cancer patients WLC = weight-losing cancer patients, WSC = weight-stable cancer patients,	WLC compared to WSC had lower LBM (p<0.005); WLC compared to WSC and WSCon lower MAMC (p<0.0005); WLC had increased REE/kgBodyweight compared with both WS

							WSCon = weight-stable controls	groups (p<0.005); No significant difference when REE is expressed in terms of kgLBM; WLC had positive relationship with REE, r=0.83, p<0.001
Fredrix 1990 (68)	39 (GCR 13/9, LC 16/1)	LC n=17 GCR – Gastric and colorectal cancer 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 (69)	12 (10/2)	All SCLC	FFM	BIA	Longitudinal	Nil	Assess REE and systemic inflammation pre- and post-chemotherapy	No change in FFM post-chemo (p=NS). Absolute REE and REE adjusted for FFM decreased post-chemotherapy (p<0.005)
Simons 1997 (70)	21 (21/0)	NSCLC n=19 Stage I – 3 Stage III – 5 Stage IV – 11	FFM, FFMi	DEXA	Cross-sectional	Nil	Relationship between detectable leptin (DL) expression, body composition and REE	DL vs NonDL no significant difference between groups with regards FFM, FFMi, and REE/FFM, all p=NS

		SCLC n=2 Limited stage – 2						
Simons 1999 (71)	20 (20/0)	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	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 (72)	12 (12/0)	NSCLC in all, locally advanced	BCM	Total body potassium	Longitudinal	n=7, healthy subjects	Inter-relationship between systemic inflammation and REE pre- and post-onset 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 (73)	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, healthy volunteers	REE in nonmetastatic NSCLC	REE in cancer vs controls significantly raised when adjusted for LBM, p=0.001; and also when adjusted for BCM, p=0.032
Jagoe 2001 (27)	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 lung cancer operations	No difference in FFMi and BFMAMA comparing LC and controls, all p=NS
Sarhill 2003 (74)	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 (1)	N=250, with LC 60 (24%) of cohort (136/114)	TNM for cohort Stage I – 24 Stage II – 56 Stage III – 74 Stage IV – 96	SMA and SMAi at L3	CT of L3	Cross-sectional	Nil	Prevalence of sarcopenic obesity and chemotherapy toxicity in this cohort OS = obese sarcopenic ONonS = obese	SMA in OS 128.1±29.1, ONonS 160±38.1, p<0.0001 SMAi in OS 43.3±6.3, ONonS 56.4±9.9; Median survival assoc

							non-sarcopenic	with sarcopenia log rank, p<0.0001, OS 11.3months and ONonS 21.6 months, p<0.0001
Kilgour 2010 (53)	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 (56)	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 lung cancer survivors	LBM and ALM no change from baseline to post training, all p=NS
Bauer 2004 (75)	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	518	LC n=231	LBM	BIA	RCT (Double	Nil	Effect of 2g and 4g	Group given 2g EPA

(28)	(355/163)	Upper GI cancer n=198 Other GI cancer n=89 Stage NR			blind, placebo controlled, randomised)		doses of EPA diester vs placebo in the process of cachexia	gained mean 0.9kg LBM and group given 4g EPA lost mean 0.1kg LBM compared to placebo (p=NS)
Tozer 2008 (54)	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 (76)	41 (19/22)	NSCLC in all Stage I – 2 Stage II – 2 Stage III – 13 Stage IV – 24	SMA at L3	CT of L3	Longitudinal, cohort study over 2.5 months	Nil	Relationship between muscle mass, rate of muscle mass change, and plasma fatty acids	Sarcopenia at baseline in 63% men and 59% women; Sarcopenic patients 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 (77)	40 (21/19)	NSCLC in all	SMA at L3	CT of L3	Longitudinal, duration 6 weeks	Nil controls; cohort divided into those	Effect of fish oil (FO) on body composition	Sarcopenic at baseline FO 46%, SC 46%; Muscle loss rate per

		Stage III – 13 Stage IV – 27			Open label study	receiving fish oil (FO) n=17 and standard care (SC) n=24		100d, 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^2=0.55, p=0.01.
Winter 2012 (78)	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 (50)	N=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 -0.5kg in controls, but +0.1kg in ATP group, between group difference p=0.02 MUAC -1.8% in controls, but +1.1% in ATP group, between group difference p=0.02 BCM -0.6% per 4weeks in

								controls, but -0.1% in ATP group, between group diff p=0.054
Beijer 2009 (79)	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, Standard care (SC) n=49; Completed study: ATP n=29, SC n=28	Effect of ATP on nutritional status and survival	Post ATP loss of MUAC -2.24mm, SC group -1.52mm, p=NS Short term 0-8wks survival benefit with ATP (HR 0.17, p=0.023), and long term 0-6mths survival benefit (HR 0.35, p=0.025)

Keys: FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, AMMi – appendicular muscle mass index, SMMI – skeletal muscle mass index, 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, LC – lung cancer, NR – not recorded, NS – non significant, ILGF – insulin like growth factor, HGS = hand grip strength, QS = quadriceps strength, DL – detectable leptin, NDL – non detectable leptin. LC – lung cancer, SCLC – small cell lung cancer, NSCLC – non-small cell lung cancer, BIA – bioelectrical impedance analysis, RCT – randomised controlled trial, CT of L3 – computed tomography of the 3rd lumbar space, DEXA – dual energy xray absorptiometry, ATP – adenosine triphosphate, REE – resting energy expenditure

~~The studies in our review expressed muscle mass in different ways; we have used the term fat-free mass (FFM) or loss of muscle mass 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 taken into consideration wherever the term sarcopenia is used throughout this review.~~

In this review, many studies found that those with cachexia and/or weight loss also had coexistent loss of muscle mass (25, 28, 58, 67, 68, 71, 74). Despite this, none prospectively evaluated the impact this had 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 ~~sarcopenic~~ affected (25) (64), and that they exhibited a decreasing trend in FFM after chemotherapy compared with baseline, whereas women did not (29). Reflecting the process of loss of muscle mass in the different stages of cancer, a study of sixty pre-operative NSCLC patients with stage I and II disease showed no difference in FFM compared to controls (27), whereas in a cohort of 352 advanced cancer patients, 84% of those with cachexia had a reduced FFM (74).

The pathophysiology of loss of muscle mass in lung cancer patients is complex, as illustrated in the diversity of papers exploring this. Low FFM has been~~was~~ associated with low albumin and high acute phase protein concentrations (57, 58, 71), reflecting the inflammatory pathways involved. Abnormal protein metabolism is implicated in the development of sarcopenia, however in this review neither anabolic (58) nor proteolytic pathways (59) (55) 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 (59). The pathophysiology may also differ depending on disease stage and cachexia phase. There is some evidence, for example, that in pre-

cachectic NSCLC patients, despite weight loss, the ubiquitin-proteasome proteolytic pathway may not be activated (55, 80). Different ACE-gene polymorphism allelic combinations (52) and leptin expression (70) have not been shown to have~~ad no~~ significant effects on muscle mass. Fat free 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 (81). In lung cancer cachexia, this relationship seems to be distorted (69, 71) but results have been conflicting as to whether REE contributes to the development of lung cancer cachexia (67, 68, 72, 73).

The use of CT images for diagnosis of muscle mass depletion alone showed a high prevalence of this phenomenon in NSCLC patients (25), regardless of BMI and even amongst the obese (1). 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 (65, 66). The presence of muscle mass attenuation was associated with poorer functional status and overall survival.

~~Seven~~Nine interventional studies explored the effect of either nutritional supplements or adenosine triphosphate (ATP) infusions on muscle mass and function. A randomised controlled study with 518 participants, examining the effect of eicosapentaenoic acid (EPA, found in fish oil) supplements revealed increased patient-rated physical functioning, but no significant change in FFM, at the end of the study period (28). A similar, smaller study of 8 participants concurred (75). By contrast, one study of fish oil supplementation demonstrated a reduction in the rate of loss of muscle mass; however study

numbers were 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 NSCLC patients (76, 77). An interventional randomised controlled study with 66 participants found that cysteine-rich protein supplements increased FFM, as well as hand-grip strength (HGS), compared to conventional protein supplements (54), 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 (78). 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 (50) while the other (N=100) did not (79). Only the study by Fearon et al (28) described power calculations to detect a statistically significant difference.

Degree of sarcopenia or loss of muscle mass and physical functioning

Table 3~~4~~: Degree of loss of muscle mass and physical functioning

Authors	**Patients**				**Study**		**Comparison**	**Result**
	No, (M/F)	Tumour, Stage	Muscle Function and Muscle Mass Measurements	Method of Measurement	Design	Controls		
Jagoe 2001 (27)	60 (43/17)	LC in all	Grip strength Z-score	HDA dynamometer	Cross-sectional	n=22, mild COPD	Nutritional status of patients undergoing lung	Grip strength in absolute terms or Z-score no difference LC vs controls,

							cancer operations	p=NS
			FFM, MAMC, BFMAMA	BIA, four skinfold-thickness, upper arm measurements				No difference in FFMi and BFMAMA comparing LC and controls, all p=NS
Fearon 2006 (28)	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 2g and 4g doses of EPA diester vs placebo in the process of cachexia	Patient-reported physical functioning increased by 7% in group receiving 2g EPA compared with controls (p=0.04)
Tozer 2008 (54)	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 (17)	81 (NR/NR) 74 completed muscle function tests	Advanced NSCLC and Gastro-intestinal cancer patients, breakdown	Handgrip strength In Newton metre for Biodex, and pounds for Jamar	Jamar and Biodex dynamometer (n=74 completed)	Cross-sectional	Nil	Relationship between DEXA and BIA, and Jamar and Biodex dynamometry and their precision in 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,

	(48/26)	NR Stage NR	FFM	DEXA, BIA (n=70 completed)			patients	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 (0.79) and BIA (0.42)
Kilgour 2010 (53)	N=84, with LC 16 (19%) of cohort (48/36)	Metastatic 57%, locally advanced 43%, stage NR	Handgrip strength (HGS) in kg, Quadriceps strength (QS) in Newton metre SMMI, ALM	Jamar (HGS) and Biodex (QS) DEXA	Cross-sectional	Nil	Relationship of fatigue to muscle mass and strength	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 (52)	N=172 (101/71)	NSCLC n=64, Stage III and IV, breakdown	Handgrip force and percentile	Jamar dynamometer	Cross-sectional	Nil	ACE gene polymorphism (insertion[2]- II , insertion/deletion- ID, deletion[2] -DD)	DD allele group showed greater handgrip force and grip percentile than II group, p<0.05; but no difference in LBM or ALM

		NR Metastatic GI cancer n=108	LBM, ALM	DEXA (n=64)			on nutritional status	p=NS Trend (p=0.07) towards lower LBM in ID compared to II groups
Peddle-McIntyre 2012 (56)	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 – six minute walk distance, Get-up-and-go (GUAG), chair stands and arm curls in 30s] LBM, ALM	1 Repetition-maximum (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 12.3-17.5, Leg press 23.5-39.8, 6MWD 48-124, GUAG -0.4 to -1.2, chair stands 2.3-6.1, arm curls 2.1-5.1, all p<0.05 LBM and ALM no change from baseline to post training, all p=NS
Martinez-Hernandez 2012 (61)	21 (19/2)	Lung cancer n=13, GI cancer n=6, Other cancer n=2	Handgrip strength (HGS) and treadmill 6 minute walk test (6MWT)	BIA	Longitudinal	n=8 healthy volunteers	The role of interleukin-15 (IL-15) in cachectic cancer patients	HGS no difference comparing cachectic group to controls, p=NS;

		Stage according to tumour group NR	FFM					6MWT in cachectic group 369±73m vs 474±57m, p<0.05
Op den Kamp 2012 (55)	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 pre-cachexia	High intensity physical activity in LC vs controls p=0.049; FFMi no significant difference in pre-cachectic cancer vs controls, p=NS
Op den Kamp 2013 (62)	26 (17/9)	NSCLC Stage IIIB – 10 Stage IV – 16	Quadriceps strength (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

Keys: **:** FFM – fat free mass, FFMi – fat free mass index, MUAC – mid upper arm circumference, TSFT – triceps skinfold thickness, AMA – Arm muscle area, BFMAMA – bone free mid arm muscle area, BCM – body cell mass, LBM – lean body mass, ALM – appendicular lean mass, SMMI – skeletal muscle mass index, SMA – skeletal muscle area, LC – lung cancer, NR – not recorded, NS – non significant, HGS – handgrip strength, QS – quadriceps strength, LC – lung cancer, NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer, EPA – eicosapentaenoic acid, DEXA – dual energy xray absorptiometry, BIA – bioelectrical impedance analysis, ACE – angiotensin converting enzyme.

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 pre-

cachectic patients, exercise capacity was significantly reduced, despite maintenance of muscle mass (55), and resistance exercise training increased all parameters of muscle strength and physical performance, with no difference to muscle mass (56). In this review, cachectic patients showed reduced strength in terms of walking distance (61) and quadriceps strength (62) compared to 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 pre-date clinically overt cachexia, as part of aging 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. Whilst 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 lung cancer patients demonstrates inconsistency of findings as to the factors implicated in the development of cachexia,

compared to 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 ~~ceutical~~ intervention (82). This review highlights inherent challenges of such an approach, with nutritional interventions in particular failing to demonstrate efficacy (83), although the role of exercise is emerging (56, 84). It also suggests the need to represent NSCLC patients 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 in cut-off values for defining sarcopenia. ~~These~~Current standardised values were derived from a large elderly cohort and the cut-off values based on healthy young adult reference values. These values have been used to define sarcopenia in cancer (13, 85), including one in this review (53). The relevance of this definition to cancer patients is debatable, for a number of reasons.

Firstly, sarcopenia manifests in cancer patients of all ages and is not isolated to the elderly alone. Secondly, the pathophysiology of sarcopenia in cancer patients may differ at least in part to that of the non-cancer elderly population (86). With this in mind, the more recent international consensus document recommending a reference value of absolute muscularity below the 5th centile is to be welcomed (13). Finally, the recognition of muscle strength and performance as a defining component of sarcopenia in the elderly needs consideration, within the context of cancer cachexia ~~secondary causes – including cancer~~.

The argument for the objective evaluation of physical performance is pertinent, particularly as part of the definitive assessment of sarcopenia alongside ~~with~~ measurements of muscle mass. Currently, physical fitness for treatment is determined largely by the performance status (PS) score. This score is imperfect as it is subjective, with reports of inter-observer variability (87), and there is only a modest correlation between PS and observed physical performance (88). Inter-clinician performance status discordance has led to a lower percentage of PS 0 and 1 patients appearing to get chemotherapy (89), and has led to a call for objective evaluation of physical functioning (90). 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 performance status as a predictor of fitness for systemic treatment, provided that they can be readily performed in routine clinical settings. ~~and more successful completion thereof~~.

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 types~~ of studies from large randomised controlled trials to small observational studies. This limitation also means that some papers included in this review, whilst being relevant to sarcopenia, were more broadly related to muscle mass outcomes in cancer cachexia, rather than assessing sarcopenia directly. ~~The inclusion of a wide range of studies was necessary as this is the first systematic review of sarcopenia in lung cancer, to the best of our knowledge.~~ 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 paper by Temel et al, 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 (91). As such, focusing research on the identification and management of sarcopenia in lung cancer patients may prove to be a tolerable and cost effective adjunct to current lung cancer care.

Whilst 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 ~~NSCLC~~ coherently and to link them with changes in tumour phenotype which impact on morbidity and survival.

Conflict of interest statement

None declared.

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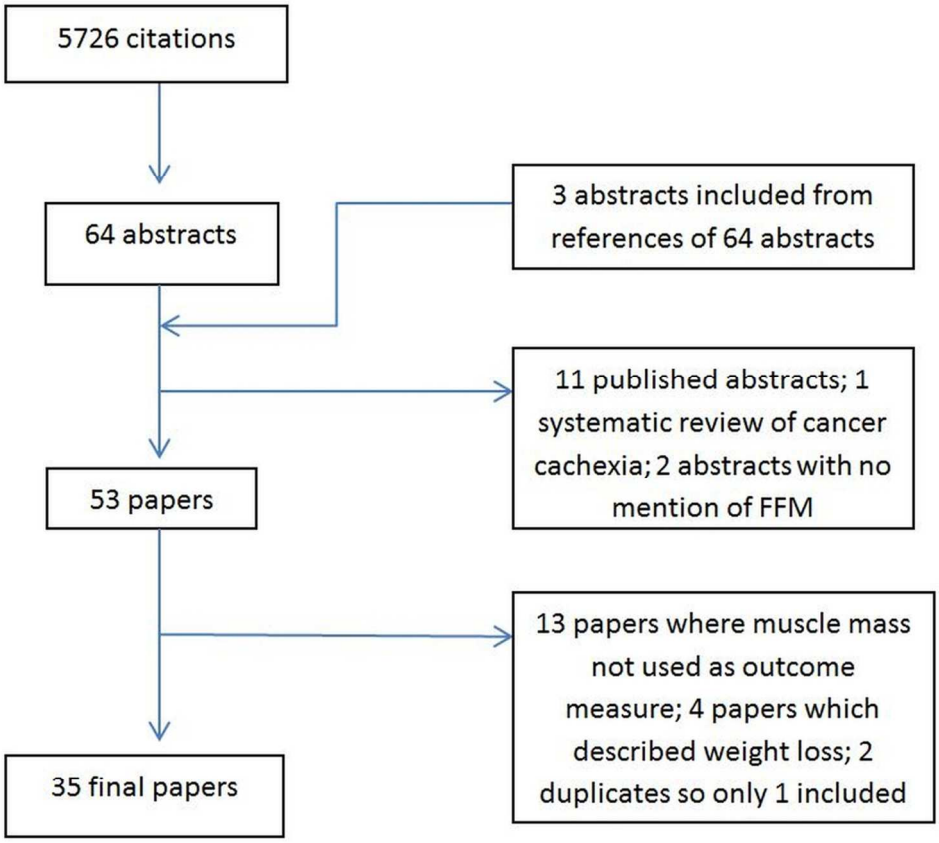

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Research Checklist for Systematic Review manuscript for BMJ Open

PRISMA statement

From Moher D et al. *BMJ 2009; 339:b2535*

Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	1-3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	8
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	N/A
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	11-13
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	11-12
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	12
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	13, Figure 1
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from	13

Section/topic	Item No	Checklist item	Reported on page No
		investigators	
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	13
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	See notes below
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	See notes below
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	See notes below
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	See notes below
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	See notes below
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Table 2-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	See notes below ref item 12
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Tables 2 and 3; pages 16-34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	N/A
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	N/A
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	35-39
Limitations	25	Discuss limitations at study and outcome level (such as risk	38

Section/topic	Item No	Checklist item	Reported on page No
		of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	38-39
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	N/A

NOTES

- With reference to item 12, we have tried to account for individual study bias by reporting study sample size and power calculations where reported.
- With reference to items 13, 14 and 16, as this is a systematic review rather than a meta-analysis, this was not performed.
- With reference to item 15, we have not accounted for publication bias. With regards to selective reporting within studies, this was not possible to be performed in great detail but we paid particular attention to the individual reporting of participant numbers, and whether the authors accounted for the number of those not completing the study.
- With reference to item 27, we received no external funding for this systematic review.