

Review

Optimising Outcomes in Non Small Cell Lung Cancer: Targeting Cancer Cachexia

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Abstract

Lung cancer is the commonest malignancy worldwide and the leading cause of cancer death. Half of patients with lung cancer present with advanced disease. The number of systemic therapies including immunotherapy and targeted treatment are rapidly increasing. Despite this, the outcomes for many patients with locally advanced and advanced lung cancer are poor, as many patients are too unwell for treatment. One of the reasons patients with Non-Small Cell Lung Cancer are not fit for treatment is cancer cachexia, which is common (upto 75% of patients) in this group. This metabolic syndrome presents clinically as weight loss (muscle +/- fat), decreased physical function (patients less active) and anorexia on a background of systemic inflammation. Currently there is not an optimal management pathway for these patients, however, there is emerging data that multi-modal intervention including nutritional support, physical training and pharmacological therapy may have a role in treating cachexia. This review discusses assessment and intervention in cancer cachexia.

Keywords: lung cancer; cachexia; weight loss; inflammation

1. The Evolving Treatment of Lung Cancer

Lung cancer is the commonest malignancy in the UK and Worldwide [1]. It is the leading cause of cancer death worldwide [2]. Treatment options for Non-Small Cell Lung Cancer (NSCLC) are increasing quickly in both the curative and incurable setting. Traditional chemotherapy has a small survival benefit in NSCLC [3,4]; however, new targeted therapies and immune stimulating therapies have been shown to have significant benefit in specific groups of patients. For example, nearly a third (31.5%) of patients with >50% of tumour cells exhibiting PD-L1 (Programmed Death-Ligand 1) in advanced NSCLC are now long-term survivors, with a median survival of 26.3 months [5].

Anti cancer drug treatment for locally advanced and advanced NSCLC now includes a range of drugs, including Tyrosine Kinase Inhibitors (TKIs), chemotherapy and immunotherapy. TKIs are routine 1st line treatment for patients with advanced, mutation driven tumours, including EGFR (Epidermal Growth Factor Receptor), ROS-1 and ALK (Anaplastic Lymphoma Kinase) [6–8]. Targeted therapies are now available for KRAS, MET, RET and NTRK mutation driven NSCLC [9–12]. There is also evidence to show that immunotherapy can benefit patients with locally advanced NSCLC when used as an adjuvant therapy after chemo-radiotherapy and surgery [13,14]. The use of adjuvant osimertinib for patients with EGFR positive resected tumours showed a hazard ratio for death or disease

recurrence of 0.17 and at 24 months the number of patients alive and disease free was double in those receiving osimertinib vs standard follow up (90%, 95% CI 84–93% vs 44%, 95% CI 37–51%) [15]. The plethora of therapies now available provide grounds for optimism that survival rates for NSCLC have the potential to change for the better. However, despite recent progress, locally advanced and advanced NSCLC still have a poor prognosis with many patients not fit for treatment. To illustrate this, recent UK data suggests that even with a fit cohort of patients (ECOG Performance Status (PS) 0–2), a third of patients with locally advanced lung cancer receive no active treatment, with only 11% receiving chemotherapy and radiotherapy [16]. Further, the UK National Lung Cancer Audit suggests that only 2/3 of fit patients with metastatic NSCLC receive anti cancer drug treatment [17].

As described above, treatment rates are low in fit patients. Outcome is poorer in those who are not fit. The 2022 National Lung Cancer Audit for England showed that in 2019 and 2020 43% and 44% of over 31,000 cases of lung cancer present with advanced disease [1]. Approximately half of patients with advanced disease are PS 0–1 (52% in 2019 and 47% in 2020), and just over half of them receive anti cancer drug treatment. The median survival of the whole cohort was poor at 100 days. This suggests that half of patients are PS 2 or worse and many will not receive drug therapy.



One of the main reasons that survival and treatment rates are so low in these settings is that patients are not sufficiently fit for treatment [18,19]. Although the causes of this are multifactorial, one of the fundamental barriers to treatment (particularly when there is a dynamic change in fitness over a relatively short period of time) is the presence of cancer cachexia, which is prevalent in as many as 75–80% of patients with lung cancer [1 USA, and Japan: facts and numbers update 2016] [2]. This metabolic syndrome presents clinically as weight loss (muscle \pm fat), decreased physical function (patients less active) and anorexia on a background of systemic inflammation [20]. It has been shown that cancer cachexia adversely affects outcomes in NSCLC including survival, treatment related side-effects, treatment delays and overall quality of life [21,22].

Therefore, if we aspire to optimally treat patients with NSCLC, we must address cancer cachexia as a central tenet impeding optimal therapy. This narrative review aims to summarise potential biomarkers and therapies for cancer cachexia, with the specific aim of improving treatment rates.

2. Clinicopathological Markers of Cachexia in NSCLC

2.1 Body Composition

The relationship between weight loss and poor outcomes in cancer has long been established. However, absolute weight loss alone does not sufficiently reflect wide inter-individual variability of body composition. The simplest, most conventional measure of body composition is the calculation of body mass index (BMI) (kg/m^2). Patients with advanced NSCLC and BMI <20 have an odds ratio of death within 90 days of 5.97 (95% confidence interval 2.20, 16.19) [23].

Interestingly, obesity may offer a survival advantage in patients with lung cancer treated with surgery or anti cancer drug treatment [24–26]. This paradoxical finding remains poorly understood and the reliability of BMI as a prognostic indicator, particularly in the context of an increased number of patients presenting in an overweight or obese state, has been questioned and increasingly replaced by other measures of body composition [26,27]. In a retrospective combined analysis of more than 2000 patients, increasing weight on chemotherapy in advanced NSCLC appears to be an early indicator of clinical benefit. [3 non-squamous, non-small-cell lung cancer patients], whereas weight loss is a poor prognostic sign [4].

Routine computed tomography (CT) scans for clinical assessment may be used to measure skeletal muscle mass. Skeletal muscle index (SMI) and/or skeletal muscle density (SMD) measures have been developed to quantify lean mass in terms of quantity and quality of muscle, respectively. Patients with locally advanced lung cancer and low muscle attenuation on CT had significantly reduced overall survival (median survival 15.2 months vs 23.0 months; $p =$

0.004) [23]. Skeletal muscle mass loss may underpin the association of weight loss and poor outcomes in patients with cancer [28,29].

2.2 Inflammatory Biomarkers

Both the ESPEN (European Society for Clinical Nutrition and Metabolism) and the ESMO (European Society for Medical Oncology) guidelines highlight that, in the assessment of cancer cachexia, the inflammatory status should be ascertained [30]. There are many ways to assess systemic inflammation; however, the most validated in cancer is the modified Glasgow Prognostic Score (mGPS), combining C-reactive Protein (CRP) and albumin, and is endorsed by the aforementioned guidelines [31]. It has been suggested that the mGPS and PS are the most important host-related biomarkers in lung cancer [22,32].

In lung cancer the mGPS has been assessed in over 70 studies demonstrating unequivocally the value of this score in predicting outcomes. For example, patients with high mGPS have shorter OS and PFS following stereotactic radiotherapy for early-stage inoperable NSCLC than those with low mGPS (33.3 vs 64.5 months ($p = 0.003$ and 23.8 vs 39.0 months ($p = 0.008$) respectively) [33].

A range of other scores have been developed, but are less well substantiated. The Prognostic Nutritional Index (PNI) combines albumin and total lymphocyte count to assess inflammation. In patients with operable NSCLC, PNI independently predicts survival (<50 vs >49 , HR 1.63, 95% CI 1.04–2.57 ($p = 0.031$)). Our local experience is that many patients do not have a CRP as part of their initial investigation for lung cancer. SIPS (Scottish Inflammatory Prognostic Score) predicts overall survival in patients with advanced NSCLC treated with first-line anti-PD1 monotherapy (HR 2.86, 95% CI 2.14–3.83 ($p < 0.001$)) using albumin and neutrophils [34]. Other scores exist including using Neutrophil/lymphocyte ratio, neutrophil count and the lung immune prognostic score (derived neutrophil count (neutrophil –lymphocytes) and LDH) [35–40]. Interestingly neutrophil/lymphocyte ratio does appear to predict outcome independent of treatment modality in advanced NSCLC [5] body weight changes, and overall survival in patients with non-small cell lung cancer [6].

Historically, serum albumin was widely utilised as a biomarker of malnutrition and weight loss [41–43]. However, it is now more accurately recognised as a negative biomarker of systemic inflammation, which influences albumin synthesis, catabolism and its ability to escape into tissues [43,44]. As such, albumin may also be considered a biomarker of cachexia, which itself is an inflammatory condition [20]. Hypoalbuminaemia is a recognised poor prognostic feature in patients with lung cancer [44]. Our group has recently demonstrated that serum albumin independently predicts survival in patients with metastatic NSCLC treated with either first-line targeted or immunotherapy-based treatments [45].

A key question is whether intervention that moves patients from poor prognostic to favourable prognostic groups defined by these biomarkers can improve outcomes. If so, these biomarkers may be useful for identifying patients for such interventions. Significantly, serial measurements of albumin in patients with metastatic NSCLC being treated with anti cancer drug treatment suggest it may be useful as a tool for monitoring treatment response [45]. Improved, or maintained normal, serum albumin levels on treatment may represent better cancer control, either by directly reducing cancer activity or indirectly by reducing systemic inflammation.

Inflammatory biomarkers such as a rise in CRP and fall in albumin, are likely to occur as part of a pro-inflammatory milieu, with increased levels of pro inflammatory cytokines including $\text{TNF}\alpha$, IL-6 and IL1 [7].

Significantly, body composition measures such as SMI or SMD have been reported to be inversely associated with biomarkers of systemic inflammation, such as the mGPS and increased levels of proinflammatory cytokines. The exact relationship underlying this is poorly understood, but it confirms that inflammation and sarcopenia are closely related. This interplay has important implications for clinical practice and supports the use of multifactorial assessment and intervention.

2.3 Cachexia and Nutritional Screening

Nutritional screening has been recommended in Europe by ESPEN for all patients with cancer [46]. Need for formalised dietetic input is high. In a previous study, we identified that 78% of NSCLC patients needed to see a dietitian and 52% met criteria for a critical need to see a dietitian [47]. Other studies have confirmed this result [48].

One of the current challenges is how to achieve mass screening. Few nutritional screening tools are validated in the cancer setting and there is no single validated screening tool that can be implemented for the simultaneous assessment of cachexia, sarcopenia, and malnutrition [49]. Screening tools require time and expertise for completion and analysis. Few Cancer Centres in the UK routinely screen patients for malnutrition and rely more on a subjective assessment by the multidisciplinary team. Access to a dietitian is also not always available to lung cancer patients and the COVID pandemic has meant that many appointments are carried out remotely, further reducing the opportunities for screening. To achieve successful screening, novel techniques may be required. We recently published an initial analysis of using machine learning to differentiate between those who did and didn't need to see a dietitian. Using 5 or 10 data points, rather than hundreds, still gave a low misclassification rate [50]. These techniques could potentially be used early in the referral pathway, meaning screening would not require trained staff to do it, or the patient to be present.

3. Treatment Strategies

Given that we know that many patients with advanced NSCLC are co-morbid, have multiple symptoms, and are malnourished, it raises the question as to whether aggressive early intervention can improve patient fitness. Could this lead to improved treatment rates and potentially improved overall survival?

Several strategies could be employed to achieve this, which are described below.

3.1 Early Intervention by a Health Professional

A single study by Temel *et al.* [8] has shown that patients with advanced NSCLC referred for early palliative care assessment and intervention (within 10 weeks of diagnosis) led to improved survival (11.6 months vs 8.9 months, $p = 0.02$) when compared to referral to palliative care when it was felt appropriate [51]. This suggests that earlier symptom control may affect outcome in advanced NSCLC.

Prehabilitation has been defined by Macmillan, a leading UK cancer charity, as having 3 domains including psychological support, nutrition and activity/patient fitness [52].

Need for a dietitian is common, with more than 2/3 of fit patients meeting criteria to see a dietitian [53]. There is minimal data on the effect of nutritional intervention in patients with lung cancer. A previous study showed that nutritional supplements alone did not improve nutritional status; however, only 30% of patients in the interventional arm took the supplements [54]. A small study of 40 patients by Leedo *et al.* [55] using 3 \times a week high energy and protein meals showed improved QoL, functional score and performance score. Differences between the 2 groups were seen as early as 6 weeks into the intervention suggesting that dynamic changes can occur early [55]. A meta analysis of dietetic intervention in patients receiving chemo-radiotherapy identified 11 studies, which were heterogeneous in terms of; intervention, outcome and tumour type. For many of these studies the clinical outcomes were secondary endpoints. These studies suggest that nutritional intervention may affect outcome, but there is insufficient data to understand its effect on treatment toxicity and overall survival [9]. A secondary analysis of the EFFORT trial suggested that in hospital in patients with cancer, a more aggressive nutritional intervention may have reduced mortality [10].

However, this shows that larger randomised controlled trials are required, as confirmed by a recent review of nutrition support in patients receiving chemotherapy in a variety of cancer types [56].

3.2 Physical Activity

Physical interventions need to be mindful of the co-existence of co-morbidities, principally COPD in patients with lung cancer. As a result, prehabilitation protocols for advanced NSCLC should specifically include pulmonary

training. Pulmonary rehabilitation has a proven role in improving quality of life in patients with recent acute exacerbations of COPD, but whether there is sufficient effect to reduce hospital admissions or mortality is not clear [57].

Exercise training within 12 months of surgery for NSCLC has been shown to reduce dyspnoea, increase exercise capacity and improved the physical component of quality of life scores [58]. A Cochrane review of exercise training identified 6 randomised trials, but only included a total of 221 patients and a wide range of training, including aerobic, resistance, inspiratory muscle training and balance training [59]. These studies are heterogeneous, so although they improved exercise capacity, the findings should be viewed with caution. Exercise training in these studies did not appear to improve dyspnoea, fatigue, mood or lung function.

3.3 Pharmacological Therapies

Pharmacological treatments should be considered as part of the holistic management of cancer cachexia. Symptoms contributing to reduced appetite or function should be treated, for example pain, nausea and constipation. In addition, several drugs have been investigated to specifically target loss of appetite, body weight and muscle mass, and we will consider some of these in further detail.

Corticosteroids are commonly used to treat cancer-related weight loss. They improve appetite with short term use. A 2005 systematic review found evidence to support their use in the treatment of cancer-associated anorexia, with multiple RCTs showing improvements in appetite and well-being with short duration of use [60]. However, most of the included trials did not record weight as an outcome measure, and those that did showed no significant effect of steroids on patient weight. Toxicities are an obvious concern with longer term use, notably risk of myopathy and osteopenia. The ESMO guidelines for management of cancer cachexia recommend that corticosteroids “may be used to increase appetite for a short period of up to 2–3 weeks”, but precise guidelines for when to consider their use do not exist [61]. In practice, their use for cachexia is usually reserved for patients with limited life expectancy.

The gut hormone ghrelin is an important regulator of appetite, adiposity and glucose homeostasis [62]. This pathway is of interest in translational cachexia research, and a ghrelin receptor antagonist, anamorelin, has recently been approved for use in Japan for cachexia associated with lung, gastric, pancreatic, and colorectal cancer [63]. Japanese Phase 2 trials have shown an increase in lean body mass, measured by dual energy X-ray absorptiometry (DEXA) in patients with NSCLC and unresectable gastrointestinal cancer, with mean increases in lean body mass of 1.38 kg \pm 0.18 and 1.89 kg \pm 0.36, respectively [64,65]. Two international phase 3 studies of anamorelin in advanced NSCLC (ROMANA 1 and ROMANA 2) also demonstrated increases in lean body mass with treatment [66]. How-

ever, the increases were more modest than those seen in the Japanese studies, with a median increase of 0.99 kg [95% CI 0.61–1.36] in ROMANA 1, and 0.65 kg [95% CI 0.38–0.91] in ROMANA 2. Despite the effect on body mass, both trials failed to show any difference in handgrip strength between the treatment and placebo groups, raising questions about the clinical significance of these changes. A safety extension showed that anamorelin was well tolerated in this population with advanced cancer throughout the 24-week study period and that improvements in body weight persisted throughout this time [67]. However, due to small effect on body mass, lack of proven effect on functional outcomes or quality of life and inadequate recording of safety data, anamorelin has not been approved for use in Europe. However, there are further ongoing clinical trials to assess clinically meaningful benefit in weight [68].

Two progesterone analogues, megestrol acetate and medroxyprogesterone acetate, have been studied extensively, with multiple RCTs examining their effect on cancer associated anorexia and weight loss. A Cochrane review of the use of megestrol acetate in the anorexia-cachexia syndrome found that, in cancer patients, treatment was associated with a significant improvement in appetite (RR 2.57) and weight gain (RR 1.55) [69]. Quality of life measures were also examined, but no clear benefits were seen in this domain. Adverse effects including thromboembolic events and oedema were seen in patients treated with megestrol acetate (RR 1.36 and 1.91 respectively). Although the initial Cochrane review reported that deaths were more frequent in patients treated with megestrol acetate, an update to the review showed no differences in mortality between treatment and placebo groups [70].

The use of cannabis and synthetic cannabinoids in cancer cachexia is an area of popular interest and intense debate. While evidence for their use is limited, it is a topic often encountered in clinical practice. Several RCTs have examined the use of cannabinoids as appetite stimulants in cancer cachexia. One randomized, placebo controlled trial consisting of 243 patients with cancer-associated cachexia showed no effect of cannabis extract or tetrahydrocannabinol (THC) on appetite or quality of life [71]. A further small RCT with 21 participants found no difference in total caloric intake between patients receiving THC or placebo [72]. Another study of 469 patients compared dronabinol (a synthetic THC) with placebo or megestrol acetate and found megestrol acetate to be superior for both appetite and weight gain, with no additional benefit seen with combination therapy compared to megestrol acetate alone [73]. Although there is limited evidence for efficacy, a systematic review of the use of cannabinoids in palliative medicine found that, in the studies available, tolerability was generally similar to placebo, but evidence was of very low quality [74]. As such ESMO do not currently support the use of medical cannabis or cannabis derivatives in cancer cachexia.

In addition to drugs targeting loss of appetite, growing evidence for the role of inflammation in the aetiology of cachexia has led to interest in the role of anti-inflammatory drugs. A number of studies have examined the use of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer cachexia, with most showing some effect on weight stabilisation or weight gain [75].

3.4 Multi-Modal Intervention

It is likely that to overcome the effects of cachexia, multi-modal intervention is necessary. A recent systematic review suggests that there is limited data for patients with incurable cancer but that it can improve physical endurance and mood [76]. The MENAC trial is an international study currently recruiting patients with advanced NSCLC and pancreatic cancer [77]. Here, nutritional support, physical activity and an anti-inflammatory drug are combined with the aim to increase weight. This is built on a feasibility study showing that a multi-modal intervention study is feasible [78]. This also combines well with the publication of the ENERGY trial, a multi-modal intervention study in palliative cancer patients that has shown an adherence to a physical and nutrition intervention of greater than 80%. It also suggests that this intervention showed a lower mean incremental cost, suggesting it saved money compared to standard care [79].

4. Conclusions

Maximising outcome in NSCLC is complex. It requires accurate diagnosis and staging of the primary tumour, particularly as this can now lead to very different treatments. From the small studies available it seems that a multi-modal intervention including symptom control, nutritional support and exercise intervention has the potential to improve outcomes. What is not clear, is whether this intervention, carried out early in the diagnostic pathway, has the potential to improve treatment rates, leading to improved overall survival.

Abbreviations

NSCLC, Non-Small Cell Lung Cancer; PD-L1, Programmed Death-Ligand 1; TKIs, Tyrosine Kinase Inhibitors; PS, Performance Status; BMI, body mass index; SMI, Skeletal muscle index; SMD, skeletal muscle density; ESPEN, European Society for Clinical Nutrition and Metabolism; ESMO, European Society for Medical Oncology; mGPS, Glasgow Prognostic Score; CRP, combining C-reactive Protein; DEXA, dual energy X-ray absorptiometry; THC, tetrahydrocannabinol; NSAIDs, non-steroidal anti-inflammatory drugs.

Author Contributions

These should be presented as follows: IP, MS and BL designed the research study. All authors contributed to

the literature review. IP, JS and MS wrote the manuscript. IP, MS, JS, LA, RS and BL contributed to editing the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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