TREATING CACHEXIA-ANOREXIA IN LUNG CANCER PATIENTS: WHAT DO PATIENTS WANT?

A white paper by LUNGevity Foundation
ACKNOWLEDGMENTS

LUNGevity is deeply indebted to the lung cancer patient/survivor community for taking the time to share their perspectives and make this study possible.

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ABOUT LUNGevity

LUNGevity, one of the nation's largest lung cancer non-profits, is dedicated to changing outcomes for people with lung cancer through research, education, and support.

We focus on research because the link between research spending and improved survival is clear. Survival rates have dramatically improved for colorectal, breast, and prostate cancers over the last several decades in step with the exponential growth in their research spending. Our goal is to accelerate progress for lung cancer in the same way in order to dramatically improve on the current 18% five-year survival rate.

LUNGevity research investments focus on early detection because survival rates rise when lung cancer is detected while still localized. We also focus on more effective treatment approaches—getting the right treatment to the right patient at the right time to help people with lung cancer live longer and better.

LUNGevity also provides a community of empowerment, support, and hope for everyone affected by lung cancer through our extensive educational resources, online peer-to-peer support, and in-person survivorship programs, as well as through more than 70 grassroots awareness and fundraising events held from coast to coast each year.

For more information visit us at www.LUNGevity.org

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EXECUTIVE SUMMARY

Cachexia-anorexia is a weight-loss/appetite loss syndrome that commonly affects cancer patients. Different from other types of wasting syndromes, cancer-associated cachexia-anorexia is characterized by progressive sarcopenia (loss of muscle mass) accompanied by weight and appetite loss. Cachexia-anorexia is common in lung cancer patients, especially in patients with advanced-stage disease. These physiological changes lead to decreased ability to perform daily activities and a reduction in the quality of life of the patient. It also impairs the efficacy of chemotherapy and other types of treatment.

Typically, oncologists focus on palliation of the symptoms of cachexia-anorexia and the reduction of distress of patients and families rather than on cure. Standard methods of treatment, such as increase in nutritional uptake do not reverse loss of appetite and weight loss. Recently, newer treatment approaches that target the ghrelin axis – the primary hormone-controlled food intake mechanism – have been shown to be successful in clinical trials. However, the willingness of lung cancer patients to adopt such treatment strategies is unclear.

In line with our patient-centric approach to improve services for lung cancer patients, LUNGevity conducted an online survey of lung cancer patients. The primary aim of the survey was to understand from the patient perspective:

- Prevalence of cachexia-anorexia among lung cancer patients
- Extent of impairment of quality of life of lung cancer patients
- How patients are managing the symptoms of cachexia-anorexia

Of the 335 lung cancer patients surveyed,

- Cachexia-anorexia is occurring; 6-in-10 report experiencing one or more of the physical changes asked about (unintended weight loss, loss of appetite, loss of muscle mass, and malnutrition)
- Patients currently undergoing lung cancer treatment and those who are Stage IV are more likely to experience these changes and be concerned than those who are not currently undergoing treatment or have less advanced lung cancer
- Unintended weight loss and other physical changes are most likely to lead to a decline in patients’ strength, energy level, and ability to engage in physical activities. Among patients who have experienced a decrease in quality of life, the most important aspects they would like to improve or maintain are their energy level and their ability to remain independent.
- Among those who have suffered potentially harmful effects of weight loss, about half are willing to take a pill to reduce harmful levels of weight loss.

In summary, cachexia-anorexia is common in lung cancer patients and results in a decrease in the quality of life, and lack of approved effective treatment for these symptoms is an unmet need for the majority of advanced lung cancer patients.
Cachexia is a complex metabolic syndrome characterized by the loss of muscle with or without loss of fat mass (Fearon et al., 2011; Tisdale, 2009). It is associated with underlying medical conditions, such as cancer, acquired immunodeficiency syndrome (AIDS), chronic obstructive pulmonary disease, multiple sclerosis, chronic heart failure, tuberculosis, familial amyloid polyneuropathy, mercury poisoning (acrodynia), and hormonal deficiency (Fearon, Arends, & Baracos, 2013). Typically, cachexia co-exists with anorexia (loss of appetite and decreased food intake), and the syndrome is referred to as cachexia-anorexia. It is extremely common in cancer patients where an estimated half of all late-stage patients will eventually develop it, with a progressive loss of adipose tissue and skeletal muscle mass (Diffee, Kalfas, Al-Majid, & McCarthy, 2002). The prevalence rises to as high as 86% in the last 1-2 weeks of life, and 45% of patients lose more than 10% of their original body weight over the course of their disease progression (Argiles, 2005; Teunissen et al., 2007). The highest incidence of cachexia-anorexia is reported in lung and colon cancer patients (Temel et al., 2016).

The cachexia-anorexia syndrome is characterized by systemic inflammation, negative protein and energy balance, and an involuntary loss of lean body with or without wasting of adipose tissue (Del Ferraro, Grant, Koczywas, & Dorr-Uyemura, 2012). While the most obvious musculoskeletal change is the depletion of skeletal muscle, sometimes cardiac muscle atrophy is also seen in cancer patients suffering from cachexia-anorexia (Giordano et al., 2003). Current therapies focus on palliation of symptoms and the reduction of distress of patients and families rather than on cure. In many cases, cachexia-anorexia remains a largely underestimated and untreated condition.

The European Palliative Care Research Collaboration (EPCRC) has developed a classification system for cachexia in patients with advanced cancer (EPCRC, 2011). The cachexia guideline expert group identified cancer cachexia as a continuum of three stages of clinical relevance: pre-cachexia, cachexia, and refractory cachexia. The stages of cachexia are defined on the basis of the patient's characteristics and circumstances.

![Figure 1: Different stages of cachexia](image-url)
Quality of life (QOL) is influenced by cachexia-anorexia that leaves patients weak and unable to perform their daily activities (NCI, 2016). Furthermore, patients are emaciated and may have issues with body image. They may feel isolated from family and friends and disinclined to participate in social activities (Hopkinson, 2014).

QOL encompasses four dimensions of well-being: physical, psychological, social, and spiritual (City-of-Hope, 2015; Del Ferraro et al., 2012). In some ways, the dimensions are distinct; however, there is tremendous overlap. The impact of cachexia-anorexia on QOL, seen in late stage lung cancer, is illustrated in the following figure, adapted from the City of Hope Quality of Life model. Whether physical, psychological, social, or spiritual, a deficit that is identified in one domain impacts all other domains of QOL.

**Figure 2:** Quality of Life Model to understand impact of cachexia-anorexia

According to the Surveillance, Epidemiology, and End Results Program, approximately 224,390 new cases of lung cancer will be diagnosed in 2016, and more than 50% of these new cases will be diagnosed with advanced-stage disease (SEER, 2016). These statistics suggest that more than 50,000 of these new cases will have an increased risk of lung cancer-associated cachexia-anorexia. There are reports of weight gain during treatment of stage III (Topkan, 2016), and stage IV lung cancer patients (Patel et al., 2016) which suggest that effective cancer treatment can reverse the anorexia-cachexia syndrome. Lung cancer patients who gained weight lived significantly longer. For patients with progressive advanced-stage lung cancer who are losing weight, a treatment option would be to increase nutritional intake by dietary counseling and education and oral nutritional supplements (Temel et al., 2010). Increase in nutritional uptake addresses some of the issues associated with anorexia but does not address the cachexia-anorexia syndrome as a whole. Multimodal management that helps stabilize body weight,
improves comfort, and increases strength and energy, with the overall goal of improving the QOL of the patient, is critical.

In recent years, ghrelin, often called the hunger hormone, has been shown to increase appetite and to increase growth hormone release. An oral ghrelin agonist is being evaluated in clinical trials as possible treatment for cachexia-anorexia (Aoyagi, Terracina, Raza, Matsubara, & Takabe, 2015). This agent works by activating the hunger response leading to increased food intake. Ghrelin can also correct metabolic imbalances associated with cachexia-anorexia. Some of the newer ghrelin agonists are available as oral formulations that are easier to take (Temel et al., 2016) and also lead to increased patient adherence.

While these new treatments offer a potential management strategy for lung cancer-associated cachexia-anorexia, it is important to understand the patient perspective and what their needs are. Patient-derived information is critical for developing treatment plans that are most beneficial to patients because individual needs and priorities may vary. Furthermore, such information is useful to drive policy and treatment for cachexia-anorexia in other cancers as well.

In line with LUNGevity’s mission to make an immediate impact on increasing quality of life and survivorship of people with lung cancer, we asked the patient community how they are impacted by cachexia-anorexia and what their most important priorities in terms of symptom management are. The study included the following broad research questions:

**Study Questions:**

- What are some of the major issues associated with weight and appetite loss? (quality-of-life issues, social issues)
- What are some of the quality-of-life issues associated with weight and appetite loss? (inability to work, inability to climb stairs, inability to function independently)
- What are some of the social issues associated with weight and appetite loss? (body image, stigma of attending social occasions)
- How are lung cancer patients managing their symptoms? What types of treatment options for weight and appetite loss would patients consider?

**APPROACH**

We constructed an online structured survey with questions about a patient’s perspective on weight and appetite loss and self-reported issues with QOL. Information related to histology of lung cancer at diagnosis and stage at diagnosis was also collected.

Participation in the survey was open to anyone who was living with a diagnosis of lung cancer, even if they showed no evidence of disease. Excluded from the survey were anyone who was
less than 21 years of age and/or was a caregiver or healthcare professional. We did not screen for cachexia-anorexia using the FAACT questionnaire (FACIT, 2007). The words “cachexia” and “anorexia” were not used in the survey. Instead, surrogate terminology, such as “weight loss,” “appetite loss,” and “loss of muscle mass” were used to determine a patient’s perceived diagnosis. In addition, questions on QOL based on the City of Hope model, as well as cachexia-anorexia management plans, were included in the survey. The survey did not require reporting of anthropometric parameters such as weight, height, and body mass index (BMI). The study protocol was evaluated by Schulman IRB and found to be human subjects research-exempt (IRB # 20160060). A copy of the survey is available upon request.

Survey respondents were recruited:

- Through email invitation to survivors who had requested to receive electronic communication from LUNGevity
- By posting a link of the electronic version of the survey on the Support and Survivorship Resources section of the LUNGevity website (http://www.LUNGevity.org/support-survivorship)
- By posting a link of the electronic version of the survey on LUNGevity’s social media pages (Facebook, Twitter, Lung Cancer Survivor Community (LCSC))
- Through email invitations to an independent research panel recruited by Edge Research.

Data were collected between February 12, 2016, and March 1, 2016. All data from the survey were tabulated in Microsoft Excel. In the Major Findings section, we have used the words “weight loss,” “appetite loss,” and “muscle wasting/loss of muscle mass” to accurately convey patient perceptions.

**MAJOR FINDINGS**

We surveyed 335 lung cancer patients/survivors (223 from the LUNGevity community and 112 from the research panel). Detailed demographics of the survey patients are provided in Appendix A.

**Patients’ experience with weight loss and other physical changes following a lung cancer diagnosis**

Survey respondents were asked whether they had experienced any of the following physical changes following their lung cancer diagnosis: weight loss, decrease in appetite, loss of muscle mass/muscle wasting, and malnutrition. Sixty percent had experienced at least one of these physical changes, and 41% had experienced more than one of these changes (Figure 3).
Figure 3: Prevalence of weight loss/other physical changes in survey respondents

Stage IV lung cancer patients were more likely to report loss of appetite and muscle wasting/loss of muscle mass than were non-Stage IV patients. Also, 59% of respondents who were undergoing some form of treatment at the time of the survey reported loss of appetite; only 34% of the respondents who were not undergoing any treatment at the time of this survey reported this.

Among the respondents who experienced unintended weight loss following their diagnosis, 53% of them did so within 6 months of their diagnosis. Forty-eight percent reported that they lost between 5% and 14% of their body weight following their lung cancer diagnosis.

Respondents were also asked whether they perceived these physical changes as harmful or detrimental to their health. Among the different types of physical changes observed, most patients found loss of muscle mass/muscle wasting to be of the greatest concern. We then stratified the data from the respondents into three groups:

- Group A – Those who report one of the physical changes described in Figure 3 (n = 203)
- Subgroup A – Those who report one of the physical changes described in Figure 3 AND whose lifestyle has been impacted negatively by this/these change(s) (n = 158, which is a subset of the 203 respondents in Group A)
- Group B – Those who have not experienced any physical changes (n = 132)

Respondents from both Groups A and Subgroup A were concerned about weight loss and other physical changes they had undergone following their diagnosis. They were most concerned
about muscle wasting/loss of muscle mass, followed by unexpected/unintended weight loss, and appetite loss (Figure 4).

**Figure 4:** Concern about weight loss and other physical changes

Based on the City of Hope Quality of Life Model, respondents from Group A were then asked how weight loss and other physical changes had impacted different dimensions of their quality of life (Figure 5). Most felt that the physical changes they had experienced impacted their energy levels, with a decline in strength and their ability to perform day-to-day activities such as climbing stairs.

**Figure 5:** Self-reported negative impact on lifestyle
Among the respondents who experienced unintended weight loss, not all perceived it to be harmful. In fact, of the 133 respondents who lost weight, 41% of them actually felt that weight loss was “very beneficial” or “somewhat beneficial” to their overall health. This most likely can be attributed to the respondent’s perception that they are overweight, and the high prevalence of obesity (69% of the adult US population is considered overweight). (CDC, 2015)

Respondents in Groups A were then asked whether their doctor (oncologist/primary care physician) had addressed the physical changes related to weight and/or appetite loss (Figure 6). Most of these respondents felt that their doctors were treating them for weight and/or appetite loss and other physical changes that they had undergone following their lung cancer diagnosis.

Cachexia-anorexia is a multi-factorial condition and requires a combination of treatment approaches. Currently, management includes use of nutritional or dietary supplements, exercise regimens, and nutritional counseling for patients with early-stage cachexia (pre-cachexia). As the condition progresses, pharmacological interventions such as megestrol acetate, melanocortin antagonists, or anti-inflammatory agents (NSAIDS/thalidomide/etanercept) are prescribed (Fearon et al., 2013). Currently, ghrelin agonists are being tested in clinical trials.

**Figure 6: Management of weight loss/physical change symptoms by physicians**

We asked respondents in Group A how their physicians were managing their symptoms. Patients in both groups reported that vitamins or other dietary supplements were commonly prescribed by their doctors. The likelihood of seeking out treatment was higher in respondents in Subgroup A, who were experiencing weight loss or other physical changes as well as experiencing a decline in their quality of life (Figure 7). About a fifth of the respondents (21%) from Group A did not take any steps to alleviate the symptoms of weight/appetite loss.
Figure 7: Treatment approach employed for symptom alleviation

Patients’ interest in a treatment that potentially reverses harmful effects of weight/appetite loss – use of an oral formulation with daily dosing

We then asked respondents about their interest in a daily medication (in a pill formulation) that can potentially reverse the harmful effects of weight/appetite loss.

Forty-seven percent of respondents from Group A and 45% respondents from Subgroup A were willing to take a pill that their doctor prescribed if it would reverse the potentially harmful effects of weight loss. About a third of the respondents in both Groups A and Subgroup A were unsure about taking such an oral medication. As expected, respondents in Group B were less inclined to take a pill. Almost 50% of the respondents from Group B were unsure of taking an oral formulation to reverse the effects of cachexia even if their doctors prescribed it.
Figure 8: Patient preference for an oral formulation that potentially reverses harmful effects of cachexia-anorexia

We also asked respondents reasons for their unwillingness to take an oral formulation. This was an open-ended question. Respondent responses are classified into three main themes, which are presented in Figure 9.

- Respondent perception that weight loss is not a problem
- Possible side effects of the formulation
- Respondents are already taking too many medications

Figure 9: Respondent-cited reasons for not willing to take an oral formulation

How does impact of weight loss intersect with patient priorities for treatment of cachexia-anorexia?

In the final section of the survey, we asked respondents what their major priorities and expectations were from a weight loss/appetite loss treatment regimen.

In the first set of questions, respondents were asked to rate how important it was for a treatment to restore/maintain different quality-of-life parameters (based on the City of Hope model). Again, we stratified the responses into Groups A, Subgroup A, and B.

For respondents who had experienced weight loss or any physical change after their lung cancer diagnosis that has not negatively impacted their life (Group A), ability to be independent and care for oneself, as well as performing activities such as walking, were rated high in the quality-of-life parameter list. Respondents from this group also felt that a treatment for weight loss/appetite loss should help their adherence to cancer medication (Figure 10).
Figure 10: Priorities of Group A patients about quality-of-life parameters and weight loss treatment.
Figure 11: Priorities of Subgroup A patients about quality-of-life parameters and weight loss treatment.

For **Subgroup A** respondents (who had experienced weight/appetite loss and whose quality of life had been negatively impacted), maintaining levels of energy that allowed them to carry on with their daily activities, as well as retain the ability to be independent and care for oneself, were of paramount importance. Most of the other aspects were also very important, particularly maintaining their mood and walking ability (Figure 11). This group also reported that a treatment for weight loss/appetite loss should increase one’s ability to tolerate cancer therapy as well as increase patient adherence to cancer therapy.

Even though **Group B** did not report any weight/appetite loss and decline in quality-of-life parameters, they were asked to rate quality-of-life parameters. This information is important to understand the needs of patients who might develop cachexia-anorexia at some point in the future. This group of respondents also reported that ability to remain independent was important to them (Figure 12).
Figure 12: Priorities of Group B patients about quality-of-life parameters and weight loss treatment.

From this quantitative analysis, patient autonomy and ability to maintain a normal life emerged as the main reasons why respondents would consider taking a medication that would potentially reverse the harmful effects of weight loss/appetite loss. These themes were also reflected in the responses to an open-ended question in which we asked respondents what would be their primary reasons to take an oral medication (Figure 13).

Figure 13: Patient autonomy and ability to lead a normal life are major reasons why respondents would take medication that would potentially reverse the harmful effects of weight/appetite loss. These quotes come from respondents in Subgroup A.
CONCLUSIONS AND IMPLICATIONS

We found that cachexia-anorexia is prevalent in lung cancer patients, with 60% of the patients reporting at least one symptom of the syndrome. Patient attitudes towards cachexia-anorexia differ among those whose quality of life has been impaired due to weight loss and those who are able to continue living a normal life. However, when we asked about managing cachexia-anorexia, in all groups of patients we found that maintaining a sense of independence was of primary importance.

- **Patient Education**: We found that not every respondent who lost weight found it to be harmful, suggesting that a patient’s self-perception of being overweight might guide their responses. It is therefore important to educate patients that true cachexia-anorexia is often masked by adipose tissue loss that people find appealing. Patients should alert their physicians if they observe loss of appetite, weakness, fatigue, or weight loss.

- **Provider Education**: Oncologists and physicians should screen their patients for precachexia and cachexia-anorexia, even if they are early-stage cancer patients. Sometimes symptoms start manifesting in early-stage patients and such patients would be good candidates for preventive treatment so that they do not progress to refractory cachexia. Apart from using the FAACT questionnaire, if a provider suspects that their patient may be cachexic-anorexic, then measurement of muscle mass loss should be carried out (muscle mass measurement is available only as a research tool) because it often precedes adipose tissue loss (Martin et al., 2013).

We also noted the following limitations of the study:

- **Capturing the effects of race and ethnicity**: Our respondents were predominantly White/Caucasian. The voices of other races and ethnicities may not be adequately represented in the findings.

- **Variation of cachexia-anorexia prevalence within the US**: In our survey, we did not query about where respondent sought treatment: which state and whether in a community oncology clinic or in an academic medical center. Our data capture geographical variation in neither prevalence nor patient attitude and knowledge.

- **Global generalization**: The study surveyed respondents in the continental USA; therefore, the opinions captured in this study may not reflect that of lung cancer patients globally.

- **Effect of computer literacy**: Perspectives of only those survivors with access to social media as well as computers were captured in this survey, so most likely the results are skewed toward younger individuals.
• **Pre-selection of patients for cachexia**: We did not pre-select patients using the FAACT questionnaire. Our study included all lung cancer survivors, and their diagnosis of cachexia-anorexia is self-reported. We adopted this approach to remain as close to the patient perspective as possible.

Although data from our study does not adequately capture the quality of life issues that advanced-stage lung cancer patients with cachexia-anorexia face, our observations are consistent with previous reports showing a high frequency of anorexia-cachexia in lung cancer patients. Also our patient reported information indicates that what patients want most is to preserve their independence and maintain their energy levels. Anorexia and cachexia are major threats to these goals. Further studies are warranted to develop treatment strategies for the management of anorexia-cachexia.
REFERENCES


Almost all (98%) had some form of health insurance.

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<td>Stage III</td>
<td>34%</td>
<td>43%</td>
<td>16%</td>
</tr>
<tr>
<td>Stage III</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
<td></td>
<td>Stage IV</td>
<td>Limited stage</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td>Extensive stage</td>
<td>12%</td>
<td>8%</td>
<td>20%</td>
</tr>
<tr>
<td>Extensive stage</td>
<td>8%</td>
<td>3%</td>
<td>17%</td>
<td></td>
<td>Not sure of stage, but it was “localized”</td>
<td>8%</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>Not sure of stage, but it was “non-localized”</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have not discussed my current stage with my doctor</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not sure</td>
<td>8%</td>
<td>7%</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health Insurance Status</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of health insurance</th>
<th>Coverage through your current or former employer or spouse’s employer or union</th>
<th>Coverage purchased directly from health insurance company (you pay for it yourself)</th>
<th>Medicare – insurance program for seniors</th>
<th>Medicaid – insurance provided through your state</th>
<th>Coverage through your parents’ health insurance</th>
<th>Other, please describe:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59%</td>
<td>65%</td>
<td>49%</td>
<td>18%</td>
<td>17%</td>
<td>19%</td>
</tr>
</tbody>
</table>

| Race | White/Caucasian | 91% | 93%  | 89%  | Black/African American | 3%  | 1%  | 8%  | Asian/Pacific Islander | 3%  | 4%  | 3%  | American Indian | 0%  | 0%  | 0%  | Other | 1%  | 2%  | -    | Prefer not to answer | 1%  | 2%  | 1%  |