MEETING REPORT

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Addressing unmet needs for people with cancer cachexia: recommendations from a multistakeholder workshop

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Meeting overview

In October 2020, LUNGevity Foundation hosted 75 participants for a comprehensive Unmet Needs Workshop focused on addressing the needs of patients with cancer cachexia and their caregivers. A unique aspect of this workshop was that it centred on the patient perspective and yielded active involvement of patients, caregivers, patient advocates, clinicians, scientists, investigators, industry representatives, and regulators. Participants met virtually to discuss the state of the science, identify clinical and research gaps, and develop concrete action plans. Three needs emerged: (i) need to expand education about cancer cachexia among patients, caregivers, and clinicians; (ii) need to increase evidence, resources, and insurance coverage for medical nutritional and physical therapy for patients with cancer cachexia; and (iii) need to refine preclinical research, definition, diagnostic criteria, biomarkers, clinical trial inclusion criteria, and clinically meaningful endpoints to develop and implement effective therapies. This paper summarizes the diverse perspectives presented during the workshop, describes the key themes, and outlines recommendations made by this multistakeholder group to effectively meet the needs of people with cancer cachexia and their caregivers.

The problem of cancer cachexia

Patients with cancer often experience progressive weight loss.[1] Indeed, unintentional weight loss often precipitates the first visit and subsequent diagnosis of cancer. Such weight loss, or cachexia, is particularly common in patients with cancers of the head and neck, lung, and gastrointestinal tract and contributes greatly to cancer morbidity and mortality, more so among the elderly.[2,3] Cachexia reduces appetite, social–emotional interactions, functional capacity, and quality of life, and up to a third of cancer deaths have been attributed to cachexia.[4–6] Despite its impact on cancer, there are no widely approved, effective therapies for cancer cachexia, and perhaps consequentially, there is typically minimal discussion of cachexia symptoms or interventions between patients and clinicians, including physicians, physician assistants, nurse practitioners, nurses, dieticians, and physical and behavioural therapists. Furthermore, available supportive care varies greatly by clinician, institution, and payer, leading to disparate outcomes for patients. Filling these gaps in cachexia care would reduce patient and caregiver distress and improve cancer outcomes.

Diagnostic criteria for cachexia vary somewhat, but a widely accepted consensus defines cachexia as >5% unintentional

weight loss over 6 months with muscle mass loss, with or without fat loss, that leads to progressive functional impairment.[1] Staging of cachexia is intended to represent its severity, understand who might benefit from targeted interventions, and guide treatment decisions for those at the end of life. While there are various approaches to the classification of patients, often cachexia is classified into three stages: pre-cachexia (weight loss of $<$5% with anorexia and metabolic changes), cachexia [weight loss of $>$5% or body mass index (BMI) $<$ 20 kg/m^2 with 2% weight loss, or sarcopenia with $>$2% weight loss, including poor oral intake and is often associated with systematic inflammation], and refractory cachexia (low performance status and life expectancy of $<$3 months). The latter is characterized by end-stage cancer and poor performance status and is typically thought of as unresponsive to cachexia-directed treatment.[1,5,7] Weight loss and reduction in BMI are associated with shorter median survival times in patients with cancer, which is further exaggerated with more severe weight loss and lower BMI.[8] Patients with cancer and combined weight and muscle loss experience the poorest survival outcomes irrespective of BMI,[9] in part due to the necessity of dose reductions and modifications. Conversely, weight stabilization has been tied to improved outcomes in several studies.[10,11]

The pathophysiology of cancer cachexia, although not fully understood, is due to a variable combination of reduced food intake and altered metabolism (e.g. inflammation, decreased anabolism, and excess catabolism), arising from complex interactions among the tumour, host neuroendocrine and immune systems, and cancer treatments.[1,2,12,13] It is further characterized by dysregulation of host metabolic processes at the cellular and molecular level, including mitochondrial dysfunction, glucose dysmetabolism, and unbalanced lipolysis and proteolysis.[14,15] While it is unlikely that a single agent will treat all aspects of this syndrome, recent cachexia research has identified specific biological, endocrine, and immune mechanisms that precipitate loss of body weight, skeletal muscle, appetite, and physical function.[16] For example, factors produced by the tumour and by the host, including inflammatory cytokines, exosomes, small molecules, and microRNAs, signal on distant tissues to suppress food intake and induce catabolism of fat and muscle. Furthermore, comorbidities including depression, anxiety, frailty, hypogonadism, uncontrolled pain, and altered gastrointestinal function may exacerbate the weight loss and functional decline seen in these patients. Such complex pathophysiology involving multiple organ systems and diverse mechanisms across tumour types leads to heterogeneity in clinical presentation, course, and outcomes from this condition. This heterogeneity also impedes diagnosis, staging, clinical management, and the development of new cancer cachexia therapeutic strategies.[17]

Although cachexia is not reversible through improving nutritional status alone, early nutrition intervention to counter anorexia may slow cancer cachexia. However, to date, shortcomings in nutrition research in this patient population have stymied development of standardized, effective nutritional interventions.[18,19] Because there are currently no widely approved, targeted drug treatments, multiple professional societies have issued guidelines for best supportive care for cancer cachexia. These vary considerably by geographical region and society discipline, reflecting the insufficient evidence for specific interventions, low research activity, and paucity of clinical trials devoted to cachexia versus cancer overall. Indeed, few investigational drugs have been evaluated in clinical trials and with limited success.[20–22] However, a recent uptick in cachexia-specific research has begun to yield a better understanding of its underlying pathophysiology, and clinical trials of targeted therapies have begun to increase rapidly.

Stakeholder perspectives

As research and development efforts advance in this space, there is an opportunity for the multistakeholder community —scientists, investigators, clinicians, patients, caregivers, patient advocates, industry partners, and regulators—to work collaboratively in addressing cancer cachexia. Recognizing this opportunity, in October 2020, LUNGevity Foundation hosted a comprehensive workshop focused on addressing the unmet needs of patients and caregivers dealing with cancer cachexia (Unmet Needs Workshop) (*Figure* 1). Seventy-five participants met virtually over 2 days to discuss the state of the science, identify clinical and research gaps, and develop concrete action plans to meet critical areas of need in cancer cachexia. A unique aspect of this workshop was that it centred around the patient perspective and yielded active involvement of every stakeholder, ensuring input from all.

Workshop participants drew a clear picture of unmet needs, including lack of awareness among patients, caregivers, and clinicians, limited treatment options, and limited availability of supportive care, leading to a significant negative impact of cachexia on patients and their families. Participants focused on recommendations for action in three key areas: (i) expanding educational resources and awareness about cancer cachexia among key stakeholders; (ii) enhancing supportive care services including nutritional and physical therapy interventions for patients with cancer; and (iii) developing the evidence for pivotal clinical trials to support the development of effective therapies, including alignment on endpoints that meet patients' needs (*Figure* 2). This paper focuses on the context and content of these recommendations informed by each group's perspectives.

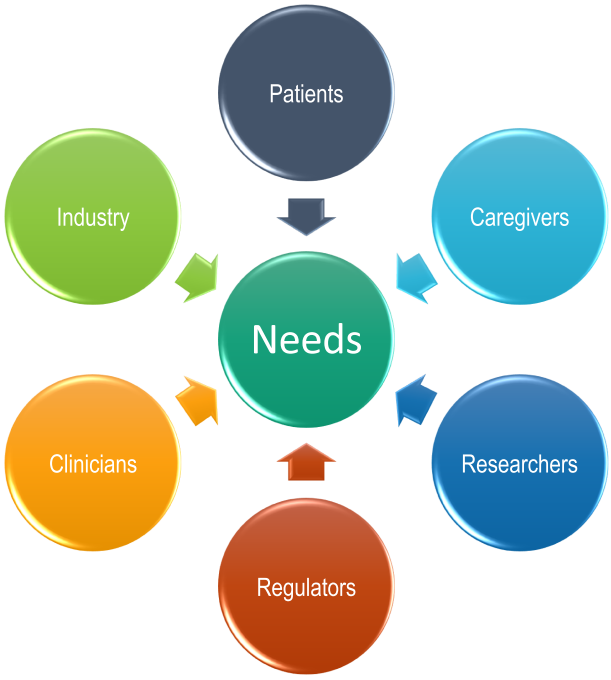

Figure 1 The LUNGevity Foundation's Unmet Needs Workshop engaged the multistakeholder community in prepared talks and guided discussion over 2 days to identify key needs and recommendations for addressing the burden of cachexia across all types of cancers.

Patients

During the workshop, patients with cancer described being aware of their early symptoms, including loss of smell and taste, loss of appetite, nausea and food aversion, and the subsequent weight loss, weakness, and unwelcome and unpleasant changes to their body's appearance. Even those with medical training often did not realize that this cluster of symptoms had a 'label' or diagnosis independent of their specific cancer diagnosis and believed the symptoms were attributable to their anti-cancer treatment alone rather than their underlying cancer. Workshop participants spoke of having no information about how cachexia would affect their bodies, self-image, or ability to engage in daily activities. They reported receiving no specific information on cachexia, rarely hearing the word. Patient participants indicated that, ideally, patients would be taught to recognize and report cachexia early and view it as an integral part of their underlying cancer occurring concomitantly with cancer treatments. Patient awareness of what to expect from cachexia could help set expectations for potential outcomes and mitigate some negative impacts, even providing some emotional relief for people when they understand what is happening. Patients also expressed a strong desire to participate in anti-cachexia trials.

NEEDS in CANCER CACHEXIA

- Comprehensive education for patients, caregivers and clinicians
- Evidence, resources, insurance coverage for medical nutritional and physical therapy
- Refined pre-clinical research, definition, diagnostic criteria, biomarkers, clinical trial inclusion criteria and endpoints

Figure 2 Guided discussion over the 2 days of the workshop identified three areas of unmet needs that must be addressed to substantively impact patient experience, discovery, and clinical care in cancer cachexia.

Caregivers

Caregivers described being aware of their loved one's anorexia, reduced strength and mobility, and progressive weight loss, recognizing these as signs of cancer mortality. Without understanding that these symptoms are related to the tumour, they would urge their loved one to eat, often to the point of conflict. Once a source of joy and social comfort, shared meals became a source of stress, guilt, and anxiety instead. Surviving family members described dismay and anger upon learning that this syndrome has a name and well-characterized biology that was never explained during cancer care. They expressed concern that the oncologist was potentially avoiding the conversation due to lack of available interventions or a lack of knowledge. Workshop participants who have cared for cancer patients emphasized the need to enhance education for clinicians to help them prepare their patients and families for the onset and impact of cachexia and provide appropriate palliative care. Additionally, they stressed the impact that cachexia can have on caregivers regarding stress and emotional distress. The consensus was that providing proper knowledge and guidance to caregivers could reduce familial strife, facilitate acceptance, and enable partnering for best supportive care and participation in research and trials. Caregivers expressed willingness to facilitate or participate in anti-cachexia clinical trials with their loved one.

Clinicians

The complexity of cancer cachexia, lack of diagnostic criteria, and paucity of evidence to inform clinical practice guidelines continue to impede consistent diagnosis and management even among the expert cancer cachexia community. Despite significant progress in developing the discipline of palliative care in recent years, these services are not readily available. Clinicians noted gaps in training about cachexia and its clinical management, leading many medical oncologists to miss

the diagnosis, recognizing cachexia only when people have become profoundly emaciated and weak. Furthermore, with no validated cachexia screening tool readily available for clinicians in oncology care and a lack of consistent malnutrition screening, there are significant gaps in detection and management of the syndrome for many patients.[16]

Among the cachexia academic community, there is significant enthusiasm for expanding awareness about cancer cachexia. Extending knowledge to primary care, community oncologists, patients, caregivers, and advocates is key to supporting the development of novel therapies, integration of supportive care, and implementation of care pathways that can successfully address the aspects of cancer cachexia most meaningful to the patient experience. To detect nutritional disturbances at an early stage, clinicians should regularly evaluate nutritional intake, weight change, and BMI, beginning with a cancer diagnosis and repeated depending on the stability of the clinical situation.

Researchers and industry experts

Experts summarized the outcomes of anti-cachexia trials to date and outlined challenges that have beset previous trials and those that hinder planned studies. These include a lack of biomarkers to prognosticate, diagnose, stage, and monitor cachexia, heterogeneity in patient selection, bias against anti-cachexia trials in favour of anti-tumour trials, lack of appropriate infrastructure, and absence of clarity regarding meaningful clinical endpoints from the regulatory agencies. The relatively low research activity in cachexia relative to cancer overall was also cited as a potential barrier to identifying novel targets for therapy.[16] Recommendations emerging from this discussion included the refinement of diagnostic criteria, development of biomarkers, organization of a cachexia-specific clinical trials consortium, engagement of regulators to facilitate robust trial designs, and continued prioritization of cachexia research by funding agencies.

Regulators

Regulatory officials pointed to challenges in selecting appropriate clinical assessments and outcomes for clinical studies, also noting that there are currently no validated surrogate endpoints approved for use in cancer cachexia clinical trials, and that there remains a lack of alignment among patients, researchers, and clinicians on what endpoints would be most meaningful in this setting. The discussion identified a need to improve the mechanistic understanding of cachexia in different cancer types and the development of clear diagnostic criteria. It was suggested that drug effectiveness measures could target specific cancer types and cachexia phenotypes. Moreover, regulators stressed the importance of defining issues that matter most to patients and their caregivers, including what constitutes a meaningful clinical benefit. Understanding clinical benefits ultimately will guide clinical trial endpoint selection and the development of clinical outcomes assessments to advance clinical trials.

Recommendation 1: There is a need to expand education and awareness about cancer cachexia among patients, caregivers, and clinicians

As discussed above, cachexia can have profound negative impacts on a patients' autonomy, daily function, and quality of life.[1] Cachexia is underdiagnosed in patients with advanced cancer due to inconsistent or ineffective screening practices,[23] limiting opportunities for intervention.

Despite the clear ties between cachexia, adverse outcomes, and mortality among patients with cancer, many patients, caregivers, and clinicians lack awareness about this debilitating syndrome. Patients may be overwhelmed at receiving information about cachexia at their initial oncology appointments. However, workshop participants agreed that cachexia-specific education throughout the cancer journey is important to help patients and caregivers understand their experience. This was thought particularly important for patients suffering cancers with high cachexia prevalence, including most advanced and metastatic diseases. Educational materials should define the condition, highlight the key signs and symptoms of cancer cachexia, including involuntary weight loss and changes in food intake, and urge patients to seek nutritional counselling and supportive care from reliable sources vetted by qualified and regulated practitioners. To create awareness, educational materials must include consistent messaging and be made widely available at cancer centres, cancer care websites, including advocacy groups, major medical reference repositories, and National Cancer Institute (NCI) information sites. The content of such materials should be developed in collaboration with patients and caregivers, should include culturally appropriate, in-depth, evidence-based recommendations, and should be communicated per health literacy standards.[24] Such information would provide a measure of autonomy and purpose in addressing nutrition and exercise, and may help educate caregivers about cachexia, providing more realistic expectations for both patients and family members/carers.

Though empowering patients is an attractive strategy to address cachexia, the onus should not fall on the patient and caregiver. Workshop participants agreed that cachexia education plays a vital role for all clinicians. Unfortunately, many clinicians lack sufficient knowledge regarding cachexia and thus, may underestimate its prevalence and fail to recog-

nize it in its early stages.[25] In addition to poor recognition, the clinician's knowledge gaps and time pressures can lead to cachexia being overlooked during the oncology visit.[26] Because some patients may initially welcome weight loss without understanding the urgency of early intervention, clinicians must recognize cachexia's early signs and seek to intervene.

While palliative care physicians have long been concerned with cachexia and cancer nutrition, particularly in Europe,[27,28] awareness among oncologists has lagged, particularly in the United States. Workshop participants expressed optimism that awareness among cancer-focused clinicians is improving with the emergence of academic conferences and societies, journals, and new funding opportunities dedicated to advancing cachexia research. For example, the publication of the inaugural American Society of Clinical Oncology (ASCO) cachexia guidelines was a crucial step in raising awareness about cachexia among oncology clinicians in the United States.[7] These guidelines highlight limitations within the current state of cachexia clinical care, as there remain few effective, evidence-based treatments.

Educational material on recognizing, diagnosing, and treating cachexia should be created and widely disseminated to clinicians starting in medical school and throughout training for physicians, as well as for registered dietitians, physical therapists, nurses, and behavioural health therapists. For both patient-directed and clinician-directed materials, eventual consensus on definitions and best practice would be ideal, given that the 2020 ASCO[7] and 2021 ESMO guidelines[24] on the management of cancer cachexia used different definitions and endorse different recommendations. A revision of the 2011 definition of cachexia[1] is underway and is expected to influence the vision that all stakeholders have of cachexia. Nevertheless, educational efforts should not be postponed. As medical options and sophistication in cachexia care grow, these same educational outlets should be updated to reflect new knowledge.

Recommendation 2: There is a need to increase evidence and insurance coverage for medical nutritional and physical therapy for oncology

In the absence of proven drug therapies and despite limited high-quality evidence on the potential clinical benefit of nutrition interventions, nutritional and behavioural interventions—including exercise and individualized nutritional counselling—remain essential. As the field progresses towards developing more sophisticated therapeutic interventions, near-term goals for optimizing general nutrition, promoting movement, and reducing patient and caregiver anxiety could be achieved through enhanced nutritional, behavioural, and physical therapy for patients and specific policy changes to increase access to appropriate care.

Data indicate that patients with cancer frequently receive and often follow nutritional advice from friends and caregivers rather than qualified clinicians, despite the inconsistent, vague, and lack of evidence of such advice.[29] Workshop participants agreed that high-quality, consistent nutrition information should be available to patients, caregivers, and clinicians. While cachexia is not solely a result of reduced food intake, nutrition risk screening identifies patients who require intervention immediately and creates an opportunity for early intervention to slow cachexia's progression.[30] While all patients diagnosed with cancer should be screened with a validated nutrition risk screening tool and referred to a registered dietitian if appropriate, most cancer centres in the United States currently have limited nutrition resources, averaging one qualified registered dietitian for 2308 patients. This ratio compares to a perceived need for one registered dietician to serve 120 patients.[31]

Additionally, there is currently no reimbursement by the US Centers for Medicare Service (CMS) for most nutrition services, including specific interventions and counselling or oral nutrition supplements. As additional evidence supporting the potential beneficial impact of these interventions is developed, insurance and medical payment plans should move to cover them. Additionally, patients may need referrals to physical therapy to develop tailored strategies to address cancer-related fatigue and promote movement. Patients and caregivers may also need behavioural therapy for evaluation and treatment recommendations to reduce anxiety and depression while increasing well-being.

As cancer cachexia is a multifactorial/multidimensional syndrome, it will likely require multimodal interventions to be successfully addressed. The extent to which standard-of-care measures such as nutritional support and exercise can be optimized or routinely integrated interventions in pharmacological trials remains unknown and should be the subject of future studies. Once pharmacotherapies become available, implementation research will be needed to assess the uptake and impact of different guidelines and these therapies on clinical practice.

Recommendation 3: It is crucial to refine knowledge around cancer cachexia clinical trials, particularly appropriate endpoints, to enable demonstration of effective therapies

Several gaps in scientific and clinical knowledge were discussed at the workshop, including limitations around

preclinical research, lack of consensus on the definition of cachexia, absence of validated biomarkers, diversity of opinion on appropriate eligibility criteria, and confusion around clinically meaningful endpoints. The last was viewed as the most significant in impeding the advancement of anti-cachexia therapies currently in development, while addressing the others were considered essential for developing future effective interventions.

Gaps in basic and translational research include developing and validating appropriate preclinical models to provide evidence of potential translational value to humans. More efforts are needed to ensure scientific rigour, validation of reagents, and reproducibility of results for these models across laboratories.

Gaps in clinical research must be addressed to enable pivotal clinical trials. Currently, validated cancer cachexia-defining criteria are not available, and the commonly used definition of cachexia published in 2011 lacks specificity in this regard.1 While efforts are ongoing to update this definition, its shortcomings create challenges for clinical trial design and eligibility criteria in the interim. Biomarkers may be useful to diagnose cachexia, identify patients at risk of cachexia, stage cachexia, and determine treatment response. These could include laboratory assays, radiological images, physical signs, in-clinic functional studies, home actigraphy assessments, or even patient-reported outcome measures (PROs). For robust trials, cancer cachexia trial eligibility should account for tumour-specific characteristics (e.g. tumour type and stage), host-specific factors (e.g. age, sex, BMI, nutritional status, and degree of weight loss or functional impairment), and treatment-specific characteristics (e.g. type of systemic therapy and radiotherapy) factors.

Finally, to empower investigators to test potential interventions, there must be some consensus regarding what potential clinical trial endpoints would be clinically meaningful. Currently, multiple primary and secondary endpoints are included in cachexia studies to assess the efficacy and safety of interventions. Such endpoints include muscle mass, body composition, strength or physical functioning, anorexia and nausea, fatigue, quality of life, cancer treatment tolerability, hospitalizations, and survival. To date, regulatory agencies have indicated that measures of skeletal muscle mass are not acceptable as primary endpoints beyond proof-of-concept studies as they provide no measurement of clinical benefit. Isolated function measures, including hand grip strength, have unclear relevance to clinical outcomes in this condition. Other tools to assess physical functioning (functional performance measures) or PROs have not been sufficiently validated in this population.[32] We require more clinical studies in patients with cancer cachexia to prospectively validate potential endpoints, determine their minimal clinically important differences (MCIDs), and inform optimal clinical trial design. From the patients' perspective, more work is required to define what is meaningful to them, including finding measurements to capture how an intervention might change how they feel, function, and survive. Moreover, testing must not place an undue burden on these patients already undergoing complicated and often invasive therapies and thus should be limited to those tests essential for determining safety and effectiveness of the tested therapies.

Conclusions

Cachexia remains a significant challenge for many patients with cancer and their caregivers. The persistent lack of awareness and understanding of cachexia among patients and their clinicians is an ongoing challenge that can and should be addressed with multistakeholder collaboration and education. Additionally, ensuring that all patients who need nutritional and support services receive them should be an achievable near-term objective, given the potential for benefit and low risk of harm.[10] The field remains focused on the longer-term objective of developing effective, novel treatments for cachexia to improve clinically meaningful endpoints.

Based on the workshop's outcomes, the authors see a clear call to action for the community to advance progress in these areas. By working together to define and measure what matters most to patients with cachexia and their caregivers, leaders from the scientific, clinical, patient advocacy, industry, and regulatory sectors can significantly improve the lives of people living with cancer.

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Conflict of interests

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