

## **It's time to rethink weight loss in cancer**

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Nihilism is all too common at the intersection of nutrition and cancer care. It is far too easy to see a person in clinic with cancer and weight loss, and to reflect silently on the apparent inevitability of this scenario. In the busy clinical environment, our focus moves quickly to other seemingly more pressing (or tangible) issues in the consultation. Because we are so used to seeing people lose weight, there is a risk that other causes of weight loss may be overlooked, including poor nutritional status (whether recent or long term), cachexia, or both.

We tend to lump together anorexia and cachexia in textbooks and scholarly articles, but these discrete concepts must be separated, just as we separate vomiting from nausea, so that we may more fully understand their underlying mechanisms, and the contribution of each to the other. By “splitting” rather than “lumping,” we develop more sophistication and nuance in our approach to such problems, and identify new targets for intervention. As the paradigms of nutrition, anorexia and cachexia evolve, so must our clinical history taking, investigations and treatments.

Nutrition in cancer care must take a proverbial page from the cancer pain management book, in shifting our approach and calibrating expectations. Thirty years ago, pain was an expected and accepted reality for people living with cancer. Today, however, people rightfully expect that their pain will be assessed and managed. In 2018, no clinician would accept the notion that a person must be expected to live with pain simply because they have cancer. So too should we expect that nutritional issues be assessed and addressed in cancer care. In the years ahead, we will no longer be able to accept that weight loss is an inevitable aspect of the patient experience of illness for those with advanced cancer. As therapies directed at cachexia become available, each of us must approach the patient with cancer and weight loss through new eyes – eyes that were not necessarily part of our training.

### ***Nutritional status***

In high income countries, people with poorer long-term nutritional status include those where the social determinants of health are prominent: the socio-economically disadvantaged; the elderly; people living in rural or remote communities; and people from first nations / indigenous communities. Those with cancers of the aerodigestive tract may simply not be able to eat, even if a good appetite is maintained. In low- and middle-income countries there is growing concern about the impact of nutritional status on cancer-related outcomes, given the growing burden of cancer in these nations. As other more traditional health issues are successfully addressed, poor nutritional status at the time of diagnosis will limit the benefit of available cancer-directed therapies in these locales.

We propose that every person who comes to an oncology clinic should receive a nutritional assessment, irrespective of weight loss. If weight loss has occurred, a more detailed assessment should be seen as a mandatory, standard-of-care practice. Without such an assessment, we will only see what we expect to see, continuing the historical pattern of therapeutic nihilism regarding weight loss in cancer care.

The findings of a comprehensive nutritional assessment may reflect several important possibilities, each of which calls for different approaches, including: (a) long-standing nutritional problems that have never been explored by a clinician; (b) disease-related nutritional deficits that could be addressed; or (c) both. Importantly, were any of these scenarios to be a possibility, there is a high likelihood that there would be reversible components that could help improve outcomes for the

patient. Opportunities for intervention may be missed amid the usual nihilistic approach, wherein weight loss is just an expected part of patients' experiences.

### **Cachexia**

The impacts of cachexia are well documented: poorer function; [1] impaired quality of life, [2,3] and worse survival. [4] Its prevalence increases as death approaches, and is a direct cause of death for up to 25% of people with advanced cancer. [5,6]

There is now an international consensus classification schema for the systematic syndrome that is cachexia, which includes three putative groupings: pre-cachexia; cachexia; and refractory cachexia. [7] However, unanswered questions remain regarding including the prognostic implications of each stage of cachexia, and where current and future interventions are best aimed in order to make the most difference in modifying this disabling syndrome. Unfortunately, most of what clinicians think of as "cancer cachexia" is the late-stage, refractory type. Making the diagnosis this late offers little opportunity to potentially improve patient outcomes.

Until recently, the clinical paradigm surrounding the management of cachexia has been focused on treatment of its underlying cause; whether due to uncontrolled cancer, heart failure or late stage chronic obstructive pulmonary disease. A paradigm shift is on the horizon, however, with novel therapies that directly address the underlying causes and mechanisms of cachexia. As new classes of interventions become available, we must change clinicians' attitudes, knowledge and practices. The days of cachectic nihilism must be relegated to the rear view mirror.

This issue of *Annals of Oncology* features a timely systematic review and meta-analysis on nutrition in cancer care. We wish to highlight two of its salient results. [8] Firstly, there are only a relatively small number of high-quality studies on the topic. This is especially concerning given the number of people whose lives are affected by anorexia and cachexia. Work to progress the science of nutrition, anorexia and cachexia is gaining momentum, but more progress is sorely needed. Secondly, clinical signals are not sought often enough in existing studies, so clinical responses may be lacking or underestimated.

In studies done to date, there is marked heterogeneity, with a striking lack of agreement on the ideal outcomes to measure in such trials. Not only does this limit meta-analyses, it leaves future studies without clear guidance for design. With no medication yet registered for the treatment of cachexia, guidance as to acceptable outcomes by regulatory agencies is still ill-defined. This has led to significant complications in the pursuit of regulatory approvals of novel treatments for cachexia, despite positive randomized trials for several agents. [9-11] The combination of gains in lean body mass and appetite must eventually be matched with increases in the ability to tolerate disease-directed therapies, better maintain function, or improve survival. Without such end-points, the clinical world and regulatory agencies will continue to struggle with defining new clinical indications.

The quest for new and effective therapies for cancer cachexia requires the development of a fuller understanding of the underlying mechanisms that contribute to this syndrome. The role of ghrelin agonists and selective androgen receptor modulators is being established. [9-11] Perhaps even more exciting is recent work in upstream signalling, including targets such as FN14, which appears to be an essential component in the cascade of neurohormonal and inflammatory changes leading to cachexia.

Ultimately, there is need for every oncology clinician to ensure that: (a) malnutrition is not mislabelled as cancer cachexia, especially in populations who are at high risk of malnutrition; (b) even when cachexia is diagnosed, that nutritional support relevant to the stage of cachexia is

considered; and (c) as new therapies become available, our histories, investigations and clinical interventions must quickly reflect the changing treatment paradigms. Nutritional assessment must become a more universal practice, to position us to shed the therapeutic nihilism of the past, and look ahead to the future of novel therapies for cachexia.

### **Conflict of Interest**

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