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EDITORIAL

Pitfalls in defining and quantifying cachexia

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Abstract Cancer-related symptoms such cachexia and pain are subjects of a proliferation of assessment tools, diagnostic criteria, and systems for staging, which are notably disparate, and lack agreement on the variables to be measured. Teams of experts have worked diligently to develop consensus definitions of the terms cachexia and cancer cachexia, and these efforts provide the basis to develop agreement upon the measurements and tools that are applicable to the diagnosis and staging of cancer cachexia.

Cachexia has lacked a universally accepted definition. Descriptions of cachexia in much of the early literature invariably presented it as *a multidimensional condition* or syndrome, encompassing a constellation of contributing factors (i.e., weight loss, anorexia, chemosensory distortion, early satiety, inflammation, hypermetabolism) and outcomes (i.e., asthenia, dyspnea, anemia, psychosocial distress, dependency upon others, treatment toxicity, death). These descriptive terms captured the context and conveyed a sense of the suffering, but did not constitute a definition.

The teams of experts have worked diligently to develop consensus definitions of the terms cachexia and cancer cachexia [1–3]. A series of core concepts are consistently included in these definitions: (a) Cachexia is characterized by progressive depletion of body reserves (loss of weight, lean tissue, and fat mass). (b) Cachexia is associated with reduced food intake and altered metabolism, in varying proportions. (c) Reduced food intake is due to anorexia as well as a series of disease- and treatment-related symptoms which impact intake. (d) Changes in metabolism are also a defining feature of cachexia, and include tumor metabolism, inflammation, increased proteolysis and lipolysis, and the presence of comorbid conditions further exacerbate these changes. (e) Cancer cachexia develops over time, starting with early and subtle manifestations, progressing eventually to an advanced stage. (f) Loss of physical function, quality of life, enhanced treatment toxicity, and shortened survival are regarded as key consequences of cachexia.

With the advent of a definition for cancer cachexia, it is possible to proceed to the next step—diagnostic criteria and staging. Both of these tasks imply the assessment and the quantification of the multiple features mentioned above. Crucial to this enterprise is a definition of the variables that should be measured, the appropriate tools to measure them with, and appropriate statistical methods to evaluate the data.

These quantified variables are necessarily stratified in the levels of screening, full clinical assessment, and research (investigational assessment). The first level (screening) encompasses a brief overall assessment that has widespread clinical utility and can be used in places not necessarily equipped with all facilities and expertise for the full clinical and investigational assessments. The elements of the screening assessment will have utility as part of a *minimum essential data set* which can be combined across sites to develop demographic profiles of the problem. It will be possible to develop high quality international data sets demonstrating the key demographics of cachexia features, on a worldwide basis, including all types of settings where cancer patients are to be found.

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There already exist multiple clinical tools intended for the assessment of cancer cachexia (i.e., [4–7]), and the new ones are being proposed (i.e., Busquets et al., in this issue). There is also a long list of potential in depth and investigational assessments to be considered. However, the efforts to build assessment tools, unless coordinated and based on consensus processes, risk producing a disparate set of instruments, forming data sets that are incoherent, and most importantly, will not be amenable to meta-analysis owing to a lack of agreement on even the most basic of parameters to be evaluated.

An example illustrating this point is the lack of a standardized method for recording weight history. Cancer cachexia is defined by the presence of involuntary weight loss, and while that may seem simply quantified, there is great disparity in the way that this is done. Weight loss (a continuous variable) is graded with varying cut points of 2%, 5%, 10%, 12%, 15%, and 20%. Time frame of the weight loss, 1, 3, or 6 months or since premorbid state (not usually clearly defined), is variously reported. While the intensity of the loss (rate of loss per unit time) is viewed as crucial by experts in clinical nutrition, the time frame of weight loss is frequently not specified. The current crop of mismatched information with arbitrarily chosen cut points need to be replaced with well-powered representative samples, with an agreed set of measures related to body weight taken over a known time frame, coupled with rigorous statistical approaches (receiver operating curves, optimal stratification) to detect the cut points that are relevant to cancer-specific outcomes.

Beyond the simple assessment of body weight is the daunting issue of defining the crucial measures related to all of the other dimensions of cachexia, including erosion of the lean body mass, food intake, the symptoms impairing dietary intake metabolic alterations as well as physical functioning and other outcomes. Measures in each of these domains will require validation. The cost, availability, and invasiveness of each measure will define whether they can be used in screening, full assessment, or investigational (research) studies only. Availability is not a trivial issue, and Fearon et al. [1] suggest that any of anthropometry, computed tomography, dual energy X-ray, or bioelectrical impedance could be used to define lean tissue/muscle depletion ($\leq$5th percentile compared to healthy adults). This approach sets a standard, but allows for the assessment to be done with the tools at hand, in any setting. The metabolic abnormalities associated with cancer cachexia will be the most difficult domain in which to resolve the key measures, as essentially none are validated and many are costly, invasive, or of limited availability. The first and most widely agreed biomarker of metabolic abnormality is C reactive protein, and there is a need for investigation and validation of the additional assessments. It seems premature [8] to propose that plasma levels of interleukins-6 and 2, blood triglyceride analyses, glucose tolerance, and skin hypersensitivity test are ready to be incorporated in the first-line assessments of cancer cachexia.

We certainly need validated tools, and this may be best accomplished from working off the platform of a robust conceptual framework and by collaborating closely to build the diagnostic criteria and develop staging. These issues are not unique to cancer cachexia. I would point to the ~50 different tools for assessment of cancer pain in the literature [9]. This proliferation of cancer pain assessments is not useful, and now efforts are ongoing by consensus groups to reduce this to a parsimonious number of more widely accepted tools [9, 10]. My hope is that the cachexia community will work together to limit the duration of its own transit through the stage in which, like the parable of the *Tower of Babel*, our efforts are diminished by the lack of a common language.

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