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Review

Toward a holistic understanding of cancer cachexia: Application of the human response to illness model

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ABSTRACT

Cachexia is a commonly presenting multidimensional syndrome in individuals living with advanced cancer. Given its prevalence of between 50% and 80%, nurses are going to encounter individuals manifesting ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can be partially but not entirely reversed by conventional nutritional support. Thus nurses require a comprehensive understanding of this complex clinical problem. Research suggests, however, that nurses receive minimal education about cachexia or its management. Limited understanding undermines the ability to confidently care for patients with cachexia and their families, thereby hampering effective practice. The human response to illness model provides nurses with an organizing framework to guide and make sense of their assessments in clinical practice when caring for patients with cancer cachexia and provides direction for appropriate intervention. This article illustrates the integration of the human response to illness model to clinical practice, thereby assisting nurses to develop a comprehensive understanding of the physiological, pathophysiological, behavioral, and experiential facets of cachexia in advanced cancer patients. Contemporary areas of further interest and research will be presented.

Introduction

Cancer cachexia is a prevalent and complex metabolic syndrome associated with an underlying malignancy.[1] Features of cancer cachexia include anorexia, loss of weight and skeletal muscle, fatigue, poor quality of life (QOL), and reduced survival.[1,2] Though not necessarily experienced by all patients, the clinical stages of cancer cachexia include pre-cachexia, cachexia, and refractory cachexia.[2] Pre-cachexia is associated with less than 5% of total body weight loss, anorexia, and the onset of metabolic changes. Criteria for the cachexia phase includes weight loss greater than 5% or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (body mass index [BMI] < 20 kg/m^2) or skeletal muscle mass. Reduced food intake and inflammation is present. In refractory cachexia, significant weight loss and loss of lean muscle mass is present, functional status is poor, and expected survival is that of less than three months.[2,3]

Given its ubiquitous nature in advanced cancer populations, nurses need to be conversant with the causes of cachexia, its physical and psychosocial consequences for patients and families, and evidenced-based approaches to care. The three phases of cachexia previously identified provide guidance about the care nurses can provide. For example, in pre-cachexia, monitoring for the risk of malnutrition is important. In the cachexia and refractory cachexia phases, management of nutrition impact symptoms and attending to the psychosocial needs of patients and families become focal areas of care. The literature suggests, however, that nurses' knowledge about cachexia and its management is limited.[4] This finding is troublesome, given that the International Council of Nurses states that a unique function of nurses is to assess patient responses to their health status.[5]

The ability to meet this function requires the use of a multidimensional framework to guide practice that transcends the reductionism of a biomedical model of illness that allows nurses to see illness as what Rocca and Anjum[6] have described as a "matter of the whole person". Though criticized by some authors as having minimal clinical relevance,[7–9] Alligood[10] notes that use of models can provide nurses with direction and guidance in nursing practice because they assist in organizing and making sense of assessment data, identifying appropriate nursing interventions, and evaluate nursing care. Human Response to Health and Illness (HRTI) provides such a framework, encompassing physiologic, pathophysiologic, behavioral, and experiential perspectives that occur and are influenced by personal and environmental factors.[11] Accordingly, the model provides a comprehensive approach to examine

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the response of cachexia in the setting of advanced cancer from a nursing perspective and provides the foundation for holistic patient care.

Application of Theory to Practice: This article integrates literature related to these four perspectives: normal physiology (i.e., the normal mechanisms of metabolism and energy expenditure), pathophysiology (i.e., the complex neurometabolic alternations and multiorgan involvement that occur in cancer cachexia), behavioral (i.e., how the manifestations of involuntary weight loss that occurs in cachexia is objectively assessed), and experiential (i.e., the lived experience of cachexia for advanced cancer patients). Personal and environmental factors will also be discussed, and directions for practice arising from the model will be presented. Contemporary areas of further interest and research related to the components of the HRTI model will be suggested.

Normal physiological perspective

In order to be able to appreciate the perturbations that give rise to cancer cachexia, nurses must first understand normal metabolism. Metabolism refers to the biochemical reactions that occur in cells involved in the production and release of energy.[12] The ingestion of the macronutrients protein, carbohydrate, and fat provides the cells of the body with energy, growth, maintenance, and the repair of body tissues.[13,14] The amount of potential energy in these macronutrients is measured in kilocalories (kcal).[15] The amount of energy in kilocalories used to perform basic bodily functions such as digestion and respiration is known as the basal metabolic rate and accounts for between 60%–75% of a person's daily calorie expenditure. The energy a person expends in an awake resting state engaging in low effort daily activities is referred to as resting energy expenditure (REE). Body weight is maintained when the amount of kilocalorie-containing sources of carbohydrate, protein, and fat ingested is equivalent to energy expended.[16,17] Under normal circumstances, weight loss occurs when more kilocalories are expended relative to those ingested, whereas weight gain represents kilocaloric intake in excess of energy expended.[17]

The physiological control of energy intake involves integration of peripheral afferent signals from adipose tissue and the gastrointestinal tract in the hypothalamus.[18] Orexigenic neuronal pathways (those that stimulate appetite) in the hypothalamus promote food intake and reduce energy loss, while anorexigenic pathways (those that cause loss of appetite) inhibit food intake and increase the use of energy.[18]

Pathophysiological perspective

The pathophysiology of cancer cachexia is exceedingly complex.[19] While early explanations for the weight loss seen in patients with cancer was attributed to inadequate caloric intake, research has revealed that cachexia is in fact a complex systemic disease, characterized by tumor–host interactions, metabolic aberrations that result in negative energy balance, increased lean muscle proteolysis and adipose lipolysis, and neurohormonal dysregulation.[20,21]

Proinflammatory cytokines, altered metabolism, and cachexia

Cytokines are regulatory proteins released by cells of the immune system and act asintercellular mediators in the generation of an immune response.[21] Upregulation of proinflammatory cytokines are implicated in altered metabolism and increased energy expenditure. Studies have demonstrated disturbances in REE in cancer patients such that even at rest, compared to healthy controls, cancer patients have increased rates of REE.[22,23] This increase in overall metabolic rate explains why unintentional weight loss continues unabated in cachectic patients when adequate caloric intake is provided through both enteral feeding and the administration of total parenteral nutrition. Accordingly, guidelines published by the American Society of Clinical Oncology recommend that neither enteral tube feeding nor total parenteral nutrition be implemented to manage cachexia in those with advanced cancer.[24] Notable exceptions include short time-limited trials of parenteral nutrition to patients who are reasonably fit but are experiencing malabsorption issues such as a reversible bowel obstruction or short bowel syndrome.[25]

Research indicates that the inflammatory response associated with cachexia may result from tumor necrosis[26] and the release of pro-inflammatory factors secreted by tumors[27] such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), IL-1β, IL-6, and interferon gamma,[23] which can induce tissue catabolism by altering adipose tissue and muscle cell gene expression.[26,27] Interleukin 1, in particular, has been implicated in contributing to cancer cachexia through several mechanisms including increased tryptophan secretion resulting in satiety and suppression of appetite.[28,29] IL-1 also suppresses the orexigenic effect of the brain neuropeptide, neuropeptide Y.[30] IL-1β exerts an influence on the hypothalamic-pituitary-adrenal axis in the central nervous system, where it releases multiple inflammatory factors that contribute to increased lean muscle proteolysis and adipose lipolysis. TNF-α interferes with the ubiquitin-dependent proteolysis system (UPS).[31] This system controls the crucial functions of cell growth, apoptosis, and immune responses. UPS is also responsible for maintaining protein stability and turnover that when disrupted, leads to excess protein degradation and catabolism of skeletal muscle.[31,32] Interestingly, UPS disruption of proteostasis also appears to be implicated in neurodegenerative disorders such as Huntington's and Parkinson's disease.[33]

Increased rates of tumor glycolysis and gluconeogenesis are reflective of the altered carbohydrate metabolism that is present in cancer cachexia.[34,35] Research with drosophilia (i.e., fruit flies) also suggests that tumor secreted insulin growth factor binding protein reduces insulin activity in tumor-bearing hosts which in turn drives systematic wasting because of insulin resistance.[36,37]

The role of adipose tissue in cachexia

Evidence also implicates adipose tissue as a contributor to the metabolic dysfunction seen in patients with cachexia.[38] White adipose tissue located subcutaneously and intraabdominally in humans contains fat droplets called adipocytes that can be mobilized for energy through lipolysis.[30,38] White adipocytes secrete proteins called adipokines that contribute to derangements in lipid metabolism.[39] One such adipokine is the hormone leptin, which controls when the body stores fat.[40] In healthy individuals, increased levels of leptin promote fat release, decrease feelings of hunger, and increase energy expenditure. Conversely, low levels of leptin result in the promotion of fat storage, increased hunger, and decreased energy expenditure.[41] Despite the fact that cachectic cancer patients have decreased leptin levels compared to healthy individuals, this feedback mechanism does not result in decreased energy expenditure, increased fat storage, or feelings of hunger.[41] Leptin dysregulation is believed to be impacted by proinflammatory cytokines such as TNF-α and IL-1 and IL-6.[42]

Brown in white, or beige adipose tissue has been detected within white adipose tissue and is found to expend energy through the process of white adipose tissue browning.[43] This browning activity is believed to contribute to increased REE in individuals with cancer and is implicated in the progression of hypercatabolism.[43] The adipokine zinc-α2-glycoprotein is also implicated in contributing to adipose tissue atrophy. Research indicates that elevated levels of lipid mobilizing factors such as zinc-α2-glycoprotein correlate positively with weight loss and are elevated in cachectic cancer patients.[31]

Personal and environmental factors

Intentional weight loss may occur through caloric restriction such as dieting or fasting. Loss of appetite and decreased intake can also be caused by infections,[44] stress,[45] anxiety,[46] and depression.[47] Weight loss may also occur as a part of normal aging.[48] Poverty, food insecurity, impaired cognition, and social isolation are risk factors that contribute to decreased food intake in the elderly.[49,50]

Individuals with cancer cachexia typically experience a myriad of symptoms that also negatively impact food intake. These nutritional impact symptoms include unrelieved pain, early satiety, chronic nausea, vomiting, and asthenia.[51] Patients receiving chemotherapy[52] and radiotherapy[53] commonly report abnormalities in taste and smell, and such alterations affect appetite and energy intake. However, there is evidence in the literature that such chemosensory distortions also occur in palliative cancer patients not receiving those treatments. Hutton et al.'s[54] study of 66 patients with advanced cancer receiving palliative care (median survival 7.4 months) found that individuals experiencing severe chemosensory alterations had lower intakes of between 900 and 1100 kcal/day, contributing to higher rates of weight loss and lower QOL scores than those with moderate alterations.

Behavioral perspective

The behavioral component of the HRTI model includes directly observable and/or measurable behavioral responses.[11] These data can be obtained through anthropometric tests such as body weight, mid-arm circumference, calculation of body mass index, and bioelectrical impedance.[55] And, though counterintuitive, when collecting data about body weight, nurses must be mindful that research has shown that wasting of skeletal muscle can occur in individuals who are normal weight, overweight, or obese.[56] Thus weight in and of itself does not capture the changes in body composition that occur with cachexia. Computed tomography and magnetic resonance imaging modalities provide more detailed information about the specifics of body composition.[57] Measurement of skinfold thickness is also a helpful measure. Ye et al.'s retrospective analysis of a seven-year multicentre prospective study examining malnutrition in Chinese cancer patients and factors associated with negative outcomes identified that the triceps skin fold was an anthropometric measurement useful for predicting 1-year survival in cachectic cancer patients.[58]

No validated instrument was identified in the literature to capture nutrition impact symptoms in heterogenous cancer populations. However, nurses can still collect important assessment information using tools widely used in clinical research and practice. For example, the Patient-Generated Subjective Global Assessment[59] incorporates information from patients about weight, food intake, activity and function, and symptoms that have prevented them from eating enough in the past two weeks. Information is also collected about the presence of fever, use of corticosteroid medications, and existing comorbid conditions. A limitation of the tool is that only the presence of the patient's symptom is captured by the tool and not its level of severity, thereby requiring nurses to further probe to quantify this dimension of symptom experience. The Edmonton Symptom Assessment System-revised[60] does make provision to assess the symptom severity but does not consider symptoms that might impact oral intake such as diarrhea and early satiety. Information should also be collected about the patient's height and their weight-loss history. Self-reports from patients and families on these measures are deemed in the literature to be valid.[61,62] Thus, such information can be confidently collected from patients or family caregivers.

Despite the importance of collecting the aforementioned assessment data, a scoping review conducted by Sato et al.[63] identified barriers to the assessment of cancer cachexia including inconsistent use of tools, tool complexity, failure to use standardized instruments, reluctance of physicians to use assessment tools, and nurses lacking authority to make dietician referrals.

Experiential perspective

Holistic or whole-person nursing care requires healthcare providers to attend both to the biomedical and social impacts of cancer cachexia.[64] The human response to illness model's experiential perspective refers to patients' verbalizations of the experience of involuntary weight loss and wasting and its impact on their lives.[11] This requires that nurses seek to understand the patient's lived experience of their illness by listening carefully to the patient's verbal accounts and self-report. The experience of unwanted changes such as the marked weight loss and muscle wasting that occurs in patients with cachexia affects body image[65] and can result in social isolation, anxiety, depression, and decreased self-esteem and QOL.[66,67]

Over the past several decades, research has been conducted contributing to the body of evidence examining the lived experience of progressive weight loss in cancer cachexia. Hopkinson, Wright, and Corner's[68] study exploring weight loss in a sample of 33 patients with heterogenous cancer diagnoses identified that patients were aware of their weight loss and its heralding of death. However, palliative nurse specialists did not routinely address weight loss with patients, believing that nothing could be done to abate it.[68] Hughes and Hinsley's[69] conversational interviews with 12 palliative cancer patients with heterogenous cancer diagnoses living in the community identified that the weight loss they experienced and the reactions of other people to it engendered feelings of self-consciousness. In response, patients limited their interactions with others and experienced increased social isolation.

Schragge et al.'s[70] qualitative interviews with seven men and nine women experiencing cancer anorexia identified use of the strategy coined, 'shifting to conscious control.' In 'shifting to conscious control,' patients make concerted efforts to overeat, despite a lack of appetite and presence of symptoms that made it challenging to do so. Patients deployed this strategy to try and redress decreased oral intake and manage its accompanying social and emotional consequences.

Grounded theory conducted my McClement et al.,[65] examining the experience of involuntary weight loss and muscle wasting through interviews with 15 palliative cancer patients attending an outpatient pain and symptom management clinic identified the overarching theme of patient experience as that of, 'dealing with a body in shambles.' "Participants evoked graphic images to convey the physical changes that were happening to their bodies. Statements such as "I look like a concentration camp survivor starving in Dakau" and "This bony thing shows up in the mirror every morning, and my eyes fall on this creature on the other side of the mirror," speak to the experience of emaciation, excessive depletion, and carnage of the physical body that rendered it foreign and almost unrecognizable to its owner" (p. 503).[65]

There is consensus in the literature that the psychosocial consequences of cancer cachexia for both patients and their families need to be recognized and addressed by healthcare providers.[71] Work aimed at developing a tool to assess psychosocial consequences indexing the psychosocial consequences of cancer cachexia has been conducted. Strasser et al. explored eating-related distress with 18 male patients with advanced cancer and their partners using a combination of focus groups and questionnaires.[72] Their findings suggest that patients experience distress due to challenges with eating and loss of weight. Patient partners experience distress resulting from changes in their own eating and cooking habits. Couple distress arises from the dominance of issues related to food and eating in the relationship. These issues were echoed in Reid et al.'s[73] phenomenological study of cancer patients ($n = 15$) and family members ($n = 12$).

Recognizing that the alleviation of psychosocial consequences is predicated on their identification, Häne et al.[74] systematically developed an item bank of 117 questions related to the domains of patient, partner, couple, family, social, existential, physical, and emotional distress. Despite its small sample size ($n = 20$) and overrepresentation of male and inpatients, the findings of this study provides clinicians with direction about salient questions to ask when assessing the psychosocial impact of cancer cachexia on the patient and family.

Finally, given extant research regarding cancer patients' widespread use of complimentary and alternative medicine (CAM),[75,76] an important part of learning about the lived experience of cachexia should explore past or present use of CAM and its perceived results. Fear of healthcare provider disapproval may result in nondisclosure of CAM use; thus, nurses need to approach this issue in a nonjudgmental manner. The

literature suggests that cancer patients use CAM to manage pain, fatigue, loss of appetite, and psychological distress—symptoms frequently experienced by patients with cachexia. CAM usage in this context may be driven in part by ineffective symptom management, thereby prompting a review of the efficacy of more standardized approaches to care.[77]

Implications for practice

The following implications for practice arise from the application of the human response to illness framework (Fig. 1).

First, it is important for nurses to use validated tools to conduct baseline and ongoing assessments of patients to obtain information about their nutritional status, remembering that obesity does not preclude the presence of cachexia. In the absence of a comprehensive validated nutrition impact symptom tool for use in patients with a wide variety of cancer diagnoses, some assessment data can be gleaned from components of tools such as the Patient-Generated Subjective Global Assessment and Edmonton Symptom Assessment System-revised. Nurses must also explore the extent to which personal and environmental factors previously described might be contributing to nutritional challenges for patients.

Second, given the myriad of symptoms that those with cancer cachexia experience, nurses must ensure impeccable management of symptoms that can impact nutritional intake.

Third, it is critical to understand that the involuntary weight loss and muscle wasting that occurs in patients with cachexia is not a simple matter of caloric deficit but that it reflects a complicated morass of metabolic derangements that render the body unable to utilize protein, carbohydrate, and fat in the way healthy individuals can. This understanding is foundational to conversations with patients and families explaining why interventions such as total parenteral nutrition or enteral feedings are not part of the plan of care.

Fourth, the changes in body image that occur when weight loss is highly visible can be distressing to patients. Research underscores the importance of healthcare providers' acknowledgment of the psychosocial impact of cancer cachexia.[78,79] Creating a therapeutic space in which discussion of this impact can be shared is important in affirming the patient's lived experience of significant bodily changes and more clearly understanding its consequences and the strategies patients use to mitigate them. Such conversations are critically important, given the limited pharmacological and nutritional interventions available to manage cancer cachexia.[24]

Finally, nurses must remember that cancer is an illness that affects both patient and family. Opportunities to listen to family concerns and provide psychosocial support and factual information about the patient's condition are an essential part of multimodal interventions for cancer cacheixa.[80] Work by Hopkinson[80] has reported that "psychosocial components of multimodal interventions with the holistic focus can enable adherence, alleviate cachexia-related stress and distress in patients and their family members, and/or treat comorbid mental health problems". Evidence suggests, however, that this does not happen consistently in practice. A recent nation-wide survey of healthcare providers in Japan (n = 1188) indicated that only 20% of the sample regularly provided education or psychosocial support to cachectic cancer patients or their

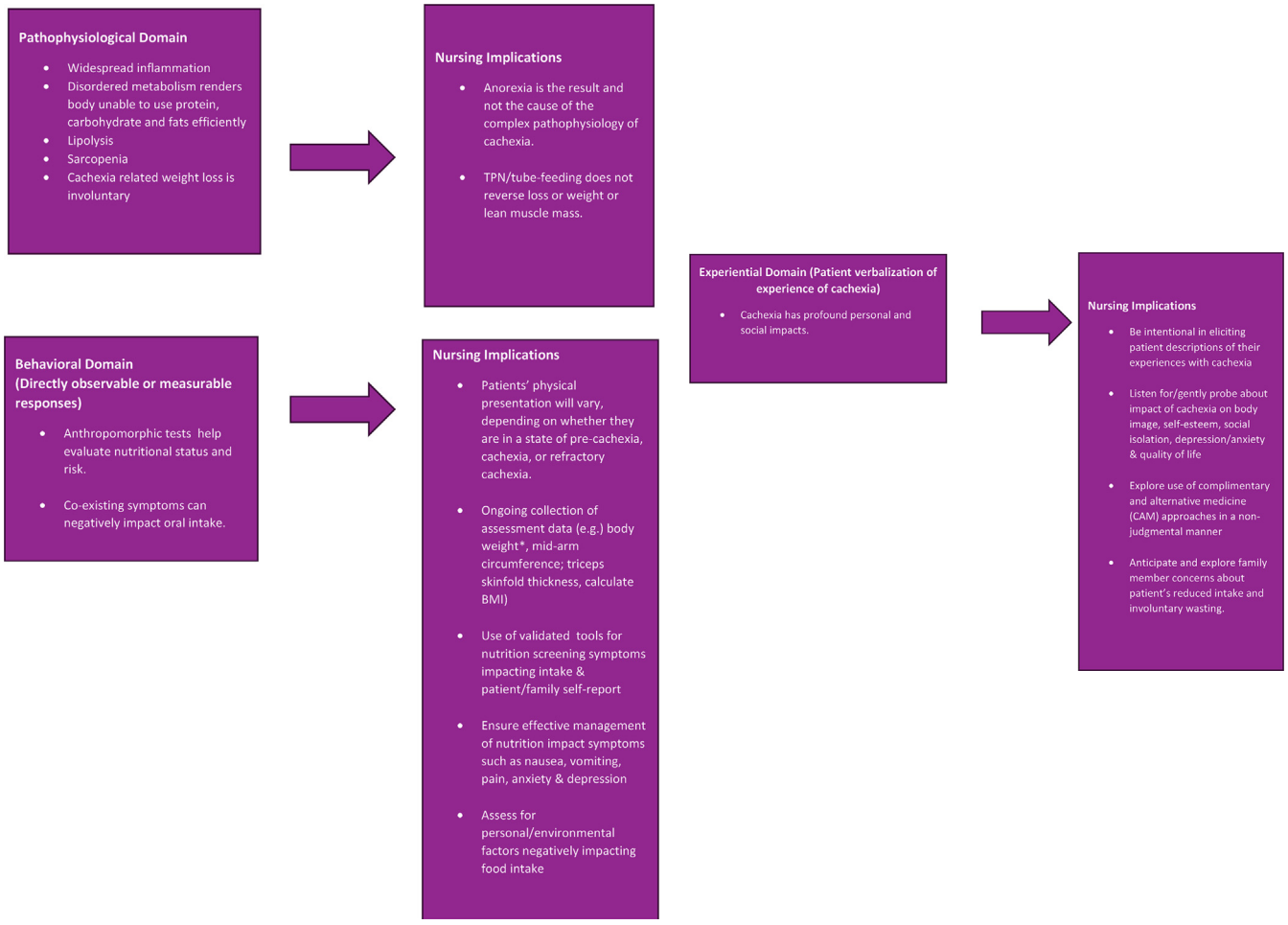

Fig. 1. Application of the human response to illness model to clinical practice.

families.[80] This finding, while troublesome, underscores the opportunities for nurses to take a leadership role in ensuring that the education and support needs of patients and families are met.

Contemporary areas of interest and future research directions

The complex nature of cancer cachexia requires ongoing research in each domain of the human response to illness model. While not meant to be an exhaustive list, suggestions for such work are provided here. For example, in the pathophysiological component of the model, research in animal models has identified the role gut microbiota plays in the metabolic derangements present in cachexia.[81] Future work in this area might include, but is not limited to, identifying an inventory of gut microbiota present in different types of cancers, their possible role in adipose tissue metabolism and the development of insulin resistance, and exploring the therapeutic potential of interventions designed to modulate their effects.[82]

Research has identified the interaction or "cross-talk" between factors released by bone (osteokines) and skeletal muscle (myokines) in the context of cachexia that contribute to musculoskeletal pathology.[83] Further work to better understand this biochemical signaling activity may provide the foundation for future research targeting myokine and osteokine activity to help preserve bone and muscle in cachectic cancer patients.[84]

Within the behavioral component of the model, because nurses play a key role in the assessment of patients with cachexia, consistent sequential use of validated user-friendly instruments to screen for risk of malnutrition should be incorporated into practice to generate data to inform the plan of care. The literature suggests that automated malnutrition-screen implementation in electronic patient charts appears to effectively identify oncology patients at risk.[85] The extent to which the identification of malnutrition result in improved patients outcomes needs to be evaluated in longitudinal studies.

Observational studies report the association between inflammation, pain, and cachexia.[86] Pain is a nutrition-impact symptom, thus assessment and effective management of pain in cachectic patients is an important nursing responsibility. Determination of the relationship between pain management and its impact on the clinical outcomes of anorexia, nutritional intake, functional status, and body weight and composition might be examined in prospective clinical studies.

Instrument development to classify cachexia stages based on the consensus definition articulated by Fearon et al.[2] has been undertaken.[87,88] For example, the Radiotherapy Cachexia Staging Score has been developed for use with patients undergoing radiotherapy.[87] While able to delineate phases of cachexia, future research is needed to address study limitations of heterogeneity of cancer types and treatments received and the lack of longitudinal data.

Within the experiential domain, ongoing research is needed regarding the psychosocial distress family caregivers experience when caring for relatives with cachexia. Research conducted to date identifies that the responses of family members to marked muscle wasting and weight loss are not uniform. While some families are resigned to the illness taking its course, others try to ameliorate diminished intake. Still, yet other families become entrenched in fighting back against decline through trying to bolster nutritional intake by any means possible.[89–91] Research has yet to be conducted to discern if the severity of cachexia correlates with family member distress or family functioning.

Previous research examining the impact of exercise for patients with cancer has typically not included individuals with cachexia. To address this limitation, Gale, Hopkinson, Wasley, and Byrne[92] conducted qualitative research grounded in theories of behavioral change that generated principles to guide healthcare professionals in promoting home-based physical activity in cachectic lung cancer patients. Given the important role that healthcare providers play in promoting patients' physical activity, such principles are invaluable to guiding practice. Future research in this area needs to examine the impact of such activity on outcomes related to patients' physical functioning and emotional well-being.[92]

Finally, the extent to which patients with cachexia specifically might use CAM to mitigate symptoms and their perceived burdens and benefits of such use has not been well documented and is a worthwhile area of inquiry.

Conclusions

Cancer cachexia is a prevalent and vexing clinical problem with significant physical and psychosocial impacts for patients and families. Nurses need an approach to praxis to guide them in the provision of care that considers physiological and psychosocial domains of illness. Application of the human response to illness model in practice can guide nurses in the provision of a systematic and holistic approach to care for advanced cancer patients with cachexia and their families.

Declaration of competing interest

The author has none to declare.

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Ethics statement

No required.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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