Cancerworld

SPCC task force raises awareness of malnutrition and cachexia in cancer patients

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Key points

- The presence of cachexia is being recognised to have a negative impact on surgery and immune therapy.
- In the absence of pharmacological therapies multimodal treatments, such as nutrition and exercise, should be used in cachexia patients.
- Surveys reveal majority of health care professionals are unaware of cachexia guidelines.
- Cross sectional CT scans and inflammatory biomarkers offer new approaches for detecting cachexia.
- All patients with cancer should be screened for nutritional risk early in the course of their care regardless of body mass index and weight history.

The urgent need for better recognition of malnutrition and cachexia in cancer patients was highlighted by the Sharing Progress in Cancer Care (SPCC) task force on Nutrition and Cachexia in Cancer Patients. The task force, held as a virtual meeting on June 22, 2020, with 13 stakeholders from organisations across Europe (see table 1), resulted in a call to action for early diagnosis of cancer patients with malnutrition/cachexia, the introduction of practical tools to identify patients, and multimodal supportive care to become an integral part of treatment.

The task force supported by an unrestricted grant from Fresenius Kabi and Helsinn, looked, among other actions, to disseminate findings from the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients (*Clin Nutr* 2017; 36: 11-48) and the related ESPEN expert group recommendations for action against cancer-related malnutrition (*Clin Nutr* 2017, 36: 1187-96). The ESPEN expert group meeting, held in Berlin in October 2016, had recommended three key steps:

- Screening all patients with cancer for nutritional risk early in the course of care, regardless of body mass index and weight history, and then regularly rescreening nutritional status.
- Expanding nutrition related assessment practices to include measures of anorexia, body composition, and inflammatory biomarkers.
- Using multimodal nutritional interventions, with individualised plans including care focused on increasing nutritional intake, decreasing inflammation and hypermetabolic stress, and increasing physical activity.

“In clinical practice, cachexia and malnutrition all too frequently go unrecognised and untreated with negative impact on the patient’s quality of life and their outcome,” said Matti Aapro, the SPCC President, who initiated the idea for the task force. “With this SPCC task force we want to bring the issue of cachexia to a wider audience and help health care professionals understand the importance of considering weight loss. Cachexia and malnutrition should be detected at cancer diagnosis, treated as early as possible and monitored through the patient journey.”

The intended outcomes for the task force, Aapro explained, include the development of educational webinars around prevention and early interventions for cachexia for dissemination at the end of 2020, an open meeting in the spring of 2021, and publication of a position paper focusing on unresolved issues in cancer cachexia.

One of the first issues identified by the task force was the need to align definitions of cachexia, since different scientific societies have produced varying definitions for the different stages of the disease. The latest definition from the Global Leadership Initiative on Malnutrition (GLIM) , explained Jann Arends, from the University Medical Centre, Freiburg, is of cachexia as a subtype of malnutrition, involving either weight loss, low BMI, or low muscle mass (sarcopenia) combined with systemic inflammation (*Clin Nutr* 2019; 38:1-9).

The GLIM definition builds on the 2011 international consensus definition of cachexia, produced by a task force led by the late Kenneth Fearon, which defined cachexia as weight loss greater than 5% or weight loss greater than 2% in individuals already showing depletion according to body mass index (BMI [BMI less than 20 kg/m2]]) or skeletal muscle mass (*Lancet Oncol* 2011; 12: 489-95). Fearon and colleagues also defined three distinct stages: precachexia (where the weight loss is less than 5% with anorexia and metabolic change), cachexia (see main definition), and refractory cachexia (where patients have a low performance scores and less than three months expected survival).

Health care professionals lack basic knowledge of cachexia

The widespread confusion around cachexia definitions and the need for education was underlined by

a survey of 742 health care professionals from 14 countries. The survey, undertaken by Maurizio Muscaritoli, from the University Sapienza, Rome, indicated that the majority of respondents were unaware of guidelines. When asked about the percentage of weight loss (from baseline) considered indicative of cancer cachexia, 46% indicated a weight loss of 10%, 35% said they would wait until weight loss was 15 to 20%, and over 10% of respondents would wait until weight loss was > 25% (*Annals of Oncology* 2016, 27: 2230-2236).

A second survey involving 907 cancer patients from 10 countries, again by Muscaritoli and his team, revealed how few physicians actually assess nutritional issues in cancer patients. The results showed although feeding problems during illness/ therapy were experienced by 72.5% of all respondents, and 69.6% reported weight loss after their cancer diagnosis, only 35% reported having their weight measured regularly during treatment and that 45.7% believed their physicians considered cancer-related weight loss unimportant (.J Cachexia Sarcopenia Muscle 2019; 10: 517-525). “Our surveys reveal most physicians have no clear idea of the levels of significant weight loss,” Muscaritoli told the SPCC meeting.

New approaches for assessing cachexia

For accurate diagnosis of cachexia health care professionals need clinically applicable tools. With the growing epidemic of obesity, Jacqueline Bowman, from the European Association for the Study of Obesity (EASO) told the meeting, the proportion of cachexia patients presenting with severe weight loss and BMI < 20 is in decline. To overcome patients with obesity experiencing ‘hidden cancer cachexia syndrome’, she said, it was important to consider changes in muscle mass as opposed to just measuring weight or BMI.

The diagnostic approach advocated by Riccardo Audisio, from Sahlgrenska University Hospital, Gothenburg Sweden, was cross-sectional analysis of single CT images, typically landmarked at the 3rd lumbar vertebra (L3) which has been shown to correlate with whole body mass muscle. This method was felt feasible in oncology where CT scans are already standard-of-care for diagnosis and surveillance, making secondary analysis highly feasible. “CT data should be mandatory for prospective data collection,” Audisio told the meeting. Since body composition represents an important determinant of the likelihood of response to treatment as well as toxicity greater knowledge was felt to be of immense value.

The drawback is that analysis of CT images currently involves using trained raters with anatomical knowledge to assess muscle areas in the L3 cross section, a process that takes around half an hour. However, the development of automated analysis of body composition as promised by Vickie Baracos from the University of Alberta, Canada, offers the potential to reduce this work load and make the approach routine. “My dream is to routinely receive information on muscle mass and density derived from diagnostic CT scans obtained for follow-up during anti-cancer treatment,” said Arends. Other proxy methods for exploring muscle mass and function include bioelectrical impedance analysis, measuring the patient’s upper arm circumference, hand grip strength, or other functional tests, e.g. six-minute walk tests or the chair-rise test.

A method that is already widely available for early detection of the inflammatory component of cachexia, Arends added, is identifying the presence of alterations in inflammatory biomarkers. The modified version of the Glasgow Prognostic Score (mGPS) developed by Donald McMillan, from the University of Glasgow, reflecting both the acute (serum concentration of C-reactive protein) and chronic (albumin) contributions to systemic inflammation, is highly prognostic in many different categories of cancer patients (*Cancer Treat Rev* 2013; 39: 534-40). Patients with a raised CRP > 10 mg/L and decreased albumin levels < 35g/L are given the worst score of 2, while patients with a normal CRP receive a score of zero. An intermediate score of 1 is assigned if CRP is raised but

albumin levels are normal.

With all these new methods, said Aapro, it should not be forgotten that health care professionals do not have to over complicate the situation. “Assessments can be as simple as asking the patient their weight now, and what it was a few months back. For men it’s the patient telling you they’ve had to tighten their belt by two more holes,” he said.

Where cachexia affects cancer treatment

Two clinical situations where it is recognised to be especially valuable to diagnose cachexia are when cancer patients are scheduled for surgery or receiving immunotherapy treatment.

Audisio considered the importance of improving nutritional status of cancer patients prior to surgery. The PreOp study, involving 345 patients over the age of 70 undergoing surgery for solid tumours, found major post-operative complications were more likely to occur in patients with moderately and severely impaired nutritional status than those who were normal or who had mild impairments (Oncologist 2005; 10: 262-8). These findings, he added, were reinforced by a study in rectal cancer showing that malnutrition related factors doubled the risk of anastomotic leaks (*BioMed Research International*. 2020. doi.org/10.1155/2020/5059670). “Most patients have three to four weeks between diagnosis and undergoing surgery which offers the plenty of opportunity to prehabituate the patient,” said Paolo Bossi, from the University of Brescia, Italy.

The presence of cachexia, explained Florian Strasser, from the Integrated Cancer Rehabilitation and Cancer Fatigue Clinic, Gais, Switzerland, represents a negative predictor of efficacy for immune therapy with check-point inhibitors. It is known that catabolic drivers accompanying skeletal muscle loss in cachexia promote elimination pathways for pembrolizumab and other biologics. The resulting high drug clearance is detrimental for treatment since a study of pembrolizumab in melanoma and non-small cell lung cancer (NSCLC) found patients with slower drug clearance achieved double the life expectancy (*Clin Cancer Res* 2018; 24: 5841-9).

The view that cachexia leads to reduced immune check-point inhibitor responses is supported by a recent study showing NSCLC patients with sarcopenia and cachexia treated with anti-PD-1 ICPI therapy have shorter progression free survival and overall survival than patients without sarcopenia and cachexia (*Lung Cancer* 2020; 143: 19-26).

Taken together, such research suggests that patients treated with check point inhibitors might benefit from additional treatment of their cachexia. Indeed, a murine model of pancreatic cancer found that blockage of the pro-inflammatory cytokine IL-6, a marker of cachexia, in combination with anti PD-L1 checkpoint inhibitor therapy resulted in improved T-cell activation and anti-tumour responses (Gut 2018; 67: 320-32). The time has come, Strasser concluded, to conduct clinical studies combining immunotherapy with anti-cachexia treatments.

Lack of available treatments

Undoubtedly the challenge here is that no pharmacological therapies have been specifically approved for the treatment of cancer cachexia, although a number of multimodal approaches can be offered including nutritional support, physical exercise (which has been shown to enhance muscle protein synthesis), and psychological support (which may help cachectic patients to be more compliant with therapy).

But trials of multimodal therapies suffer from poor study design, with few double blinded, and a lack of consensus regarding both clinically relevant endpoints and definitions for the different stages of

disease. “The problem is that companies can’t patent basic nutritional support or muscle training since they are not drugs, with the result that there are few financial incentives for companies to fund good-quality trials,” explained Arends.

The dearth of phase 3 trials for nutritional treatments resulted in the recent ASCO guidelines concluding that enteral and parental nutrition should not be used routinely, and that instead patients should be offered dietary counselling (*Journal of Clinical Oncology*, 2020; 38: 2438-53). “But in clinical practice when there are so few treatments to offer patients, therapies supported by only lower levels of evidence can also be extremely valuable,” argued Arends. The ESPEN and upcoming European Society of Medical Oncology (ESM0) guidelines, he added, allowed for assessment also of data based on lower levels of evidence and include more specific recommendations for nutrition and exercise.

Perhaps the greatest challenge for the cancer nutrition field that is obstructing the development of pharmaceutical treatments is that cancer cachexia represents a true ‘Catch 22’ paradoxical situation. The lack of agreed clinically relevant definition has been a hindrance to the demonstration of clinical efficacy of drugs. Yet, as Fearon himself argued, we are unlikely to achieve a definitive definition until we have a drug available to treat the condition. “While we may not have phase 3 data, we do have lots of observational studies that patients feel better when their nutritional status is taken into consideration. It needs to be remembered that these interventions are simple, not expensive and above all improve the patient’s quality of life”, said Aapro.

The meeting resulted in the following Call-To-Action for:

- Early diagnosis of cancer patients with malnutrition/cachexia.
- Introduction of practical guidance tools to routinely identify cancer patients at risk.
- A multimodal supportive care approach becoming an integral part of treatment for malnutrition/cachexia.

“In short we strive for better implementation of clinical nutrition guidelines in daily practice”, concluded Aapro.

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