

## short commentary

### Should Nutrition and Exercise be Mandatory Supportive Care Services for Older Frail Patients during Chemotherapy? - A Lesson Learned from the GERICO Study

Cecilia Margareta Lund<sup>1,2,3\*</sup>, Anne Wilkens Knudsen<sup>4</sup>, Pernille Bardal<sup>4</sup> and Tina Munk<sup>4</sup>

<sup>1</sup>Department of Medicine, Copenhagen University Hospital, Herlev and Gentofte, Denmark

<sup>2</sup>CopenAge, Copenhagen Center for Clinical Age Research, University of Copenhagen, Denmark

<sup>3</sup>Department of Clinical Medicine, Faculty of Health and Medical Sciences, Copenhagen University, Denmark

<sup>4</sup>The Dietitians and Nutritional Research Unit, EATEN, Copenhagen University Hospital, Herlev and Gentofte, Denmark

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Supportive care, encompassing the prevention and management of cancer-related adverse events, including nutritional interventions, aims to enhance Quality of Life (QoL) and optimize the effectiveness of cancer treatment [1]. However, despite these efforts, many patients continue to face unmet supportive care needs [2]. Malnutrition and unintentional weight loss are known to negatively affect the trajectory of cancer treatment [3,4]. Poor nutritional status is associated with early dose reduction, increased toxicity, or discontinuation of chemotherapy [5,6]. Moreover, a further weight loss of only > 2.4% predicts poorer survival, regardless of disease, stage and performance status [7].

Reasons for malnutrition and unintentional weight loss in patients with cancer are multifactorial. In many types of cancers, the disease triggers a complex metabolic pathway which induces systemic

**\*Corresponding author:** Cecilia Margareta Lund, Department of Medicine, Copenhagen University Hospital, Herlev and Gentofte, Borgmester Ib Juuls Vej 1, DK-2730 Herlev, Denmark, Tel: +0045 60141841; E-mail: Cecilia.margareta.lund.01@regionh.dk

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inflammation. The increased inflammation reduces appetite due to increased levels of cytokines such as TNF- $\alpha$  and interleukin 6 (IL-6). Additionally, elevated levels of prostaglandins induce muscle wasting [8], a phenomenon known as cancer cachexia.

Chemotherapy side effects also play a role, with impaired food intake due to Nutrition Impact Symptoms as nausea, and taste changes but also fatigue induced reduction in physical activity, exacerbating muscle wasting [9,10]. Moreover, certain chemotherapy agents like irinotecan and platinum compounds directly induces muscle loss through proteolysis [11]. Cancer has significant consequences, particularly for many older patients, as it exacerbates the muscle wasting, that naturally occurs with aging, known as primary sarcopenia [12]. This age-related sarcopenia leaves older patients at an even more disadvantaged starting point for undergoing successful cancer treatment compared to their younger counterparts. Additionally, factors such as cognitive impairments or depression and pre- or post-operative complications, like nausea, vomiting, diarrhea, or malabsorption all contribute to a suboptimal nutritional status prior to chemotherapy. Therefore, nonpharmacological strategies to mitigate sarcopenia during chemotherapy must include both resistance training and dietary counselling [11].

It is widely acknowledged, that nutritional interventions in malnourished patients with cancer has several beneficial effects. In a RCT, Baldwin et al. found evidence for improved nutritional intake, maintain body weight, and improved Quality of Life (QoL) [13]. Xie et al., found higher chemotherapy completion rates [14]. A meta-analysis of 1414 patients across 13 RCTs with malnourished patients with cancer, revealed that nutritional intervention effectively increased nutritional intake and improved certain aspects of QoL, but had no impact on mortality [13]. However, a substantial randomized study conducted by Shuetz et al., (N = 2084) including older medically hospitalized patients at nutritional risk (with 20% of patients having various types of cancer in both groups), not only demonstrated significant effects on physical performance and QoL, but also on survival [15]. The Number Needed to Treat (NNT) was only 37. The subgroup analysis comprising only the patients with cancer (n=506) showed significant improvements in functional outcomes, QoL, and even mortality with an odds ratio of 0.57 (95% CI 0.35-0.94; P= 0.027) [16]. Consequently, nutritional support is now recommended for malnourished patients with gastrointestinal cancers, although unfortunately, it remains underutilized in clinical practice [17].

In addition to the positive effects of nutritional intervention in cancer treatment, there is growing evidence highlighting the importance of exercise to counteract the negative impact of the increased inflammation, muscle wasting, and physical decline [18]. Therefore, physical activity and early rehabilitation in the trajectory of cancer are now recommended to restore or maintain physical function and enhance tolerance to cancer treatment [19]. For older patients with cancer, exercise becomes even more crucial due to age-related sarcopenia, which, as previously mentioned, is further accelerated by both the cancer and the treatment related side effects [20]. However, it is worth noting that research on exercise in patients undergoing chemotherapy

for colorectal cancer is sparse, although positive effects in self-reported physical function, QoL, and reduced fatigue has been reported [21].

Given the risk of primary sarcopenia nutritional and physical interventions are corner stones of a Comprehensive Geriatric Assessment (CGA), which serves as the golden standard for evaluating the overall health status of older individuals. Interventions are undertaken on all identified health issues including medical capability, mental state, functional ability, nutritional status and physical performance [22] also in older patients with cancer [23]. In the GERICO study [24], CGA followed by targeted interventions was found to improve chemotherapy completion rates among frail patients  $\geq 70$  years receiving adjuvant or first line palliative chemotherapy for colorectal cancer. Frail patients (scoring  $\leq 14/17$  points according to the geriatric oncology screening tool G8 [25]) were eligible for inclusion in the trial. Patients were randomized to undergo geriatric assessment with targeted interventions or standard care. As part of the geriatric intervention nutritional status were assessed for all patients. Those experiencing more than a 5% weight loss in the last 3 months were offered referral to a hospital dietitian for nutritional guidance. Patients in the intervention group were also screened for physical weakness with handgrip strength and 10 m gait speed. Those falling below the cutoff were offered referral to a 12-week supervised exercise program at the hospital. Out of the 71 patients in the intervention group, 52 (73%) had a weight loss of  $\geq 5\%$  and were offered referral to the dietitian. However, only 37 out of these 52 patients (71%) accepted the referral for nutritional guidance and intervention. Reasons for declining included lack of resources and additional hospital visits. Some patients felt capable of managing their nutritional risk independently, while others were content with their weight loss and had no desire to regain weight. Regarding physical performance, 47 patients (66%) were considered physical frail and in need of exercise. In the end, only 26 of the 71 frail older patients engaged in exercise during their chemotherapy, with 7 undergoing municipal rehabilitation and 19 participating in the hospital's exercise program [26].

The GERICO study was designed for frail older patients, with high flexibility including paid transportation for hospital consultations, and option of receiving geriatric assessment in the patient's home. Nonetheless, many patients declined several interventions including nutritional assessment by a dietitian and physical exercise. Participants could decline the offer of interventions, as these interventions were voluntary rather than mandatory.

Even in clinical practice, many patients who experience physical or functional decline or weight loss during treatment, do not receive supportive interventions, possibly due to lack of knowledge of referral options. Additionally, Wood et al. found health care professionals assess patients' performance status higher than the patients themselves in 20% of cases [27]. Thus, functional decline during chemotherapy is probably often overlooked.

The absence of focus may be due to that many patients do not consider nutritional interventions as a part of hospital treatment. A qualitative study among older patients following lower limb amputation revealed that patients often consider themselves as responsible for their nutritional care, not expecting health care professionals to engage in this aspect of care [28]. Successful nutritional interventions face challenges such as lack of knowledge among health care professionals and insufficient interdisciplinary collaboration between nurse staff, physicians, and clinical dietitians [29].

Adherence to the nutritional interventions may also be challenged by the lack of understanding among both patients and health care professionals regarding the importance of sufficient nutritional intake for successfully completion of cancer treatment. Nutritional intake and adherence to a nutritional treatment plan, is crucial for the effect of nutritional interventions. Thus, low adherence in clinical trials could potentially underestimate the beneficial effects of nutritional therapy.

Despite the evidence of positive effect of exercise on physical function and QoL, as well as the effect of nutritional therapy on maintaining body weight, QoL, continuing active chemotherapy and decrease mortality [13,14,16], these fundamental yet crucial cost-effective interventions have not yet been fully implemented as an obligate part of the cancer treatment plans.

While new and expensive anticancer drugs enter the market, it is concerning that essential and cost-effective supportive interventions, that enable patients to receive and continue active cancer treatment remain underutilized.

Therefore, we pose this question: should exercise and nutritional therapy continue to be optional offerings during cancer treatment, or should they become mandatory components? With the aging population and the number of older patients with cancer increasing, maintaining independence throughout the cancer care trajectory is crucial for both the individual patients and the health care system. In our opinion it is time for health care professionals to fully recognize the importance of the supportive interventions, and actively convince patients to accept these beneficial interventions as integral parts of the cancer treatment. It is time to make these supportive interventions mandatory elements of cancer treatment.

## Disclosure Statement

The authors report there are no competing interests to declare.

## Ethics approval

The study was approved by the local ethics committee (reference number: H-7-2014-015) and the Danish Data Protection Agency, reference number: 03339, HEH-2014-112).

## Data Availability Statement

For data supporting the results of this study contact the corresponding author.

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