Dietary treatment of weight loss in patients with advanced cancer and cachexia: A systematic literature review

Trude R. Balstad[1], Tora S. Solheim[1,2], Florian Strasser[3], Stein Kaasa[1,2], Asta Bye[4, 5]

[1]European Palliative Care Research Centre (PRC), Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Oncology, St. Olavs University Hospital, Trondheim, Norway

[3]Oncological Palliative Medicine, Division of Oncology, Department of Internal Medicine and Palliative Care Center, Cantonal Hospital, St. Gallen, Switzerland

[4] Regional Centre for Excellence in Palliative Care, Department of Oncology, Oslo University Hospital, Oslo, Norway

[5] Department of Health, Nutrition and Management, Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Oslo, Norway

Contents

Correspondence: Asta Bye, Department of Health, Nutrition and Management, Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, PO Box 4 St. Olavs plass, 0130 Oslo, Norway
Telephone: +47 64849172, Fax: +47 64 849002, E-mail: asta.bye@hioa.no

Abstract

Purpose

A systematical literature review evaluating the effect of dietary counselling in treating weight loss and improving energy intake in patients with advanced cancer with different stages of cachexia.

Principal results

Five publications were retrieved, of which three were randomized. Two out of five studies showed less weight loss with dietary counselling (+1% weight gain vs. -1.5% weight loss, p=0.03, 1.4 kg vs. -2 kg, p<0.05), two presented positive effect on energy intake (92% of total caloric need vs. 73%, p<0.01, 1865±317 kcal vs. 1556±497 kcal, ns).

Conclusion

Dietary counseling can effect energy intake and body weight, however, apperent heterogeneity between studies is present. Based on these results there is not enough proof of evidence that dietary counselling given to patients with cancer is beneficial for improving weight or energy balance in the different cachexia stages. Nutrition is an essential part of cachexia treatment as it is not considered possible to increase or stabilize weight if nutritional needs are not met.

Keywords: Cancer; Cachexia; Dietary counselling; Weight loss; Nutritional status; Energy intake

1. Introduction

Weight loss is common in patients with progressive cancer and has major impact on both morbidity and mortality. The aetiology of cancer related weight loss is not fully understood, even though cancer cachexia usually is considered the main contributor [1, 2]. Cachexia is by definition associated with underlying illness and characterised by loss of lean tissue with or without loss of fat mass [2]. The definition also states that weight loss in advanced cancer is a consequence of a combination of metabolic abnormalities and reduced food intake leading to negative energy balance [2]. Reduced food intake may be a result of a wide variety of symptoms directly or indirectly limiting oral intake e.g. loss of appetite, taste change, dysphagia and pain [3]. The impact of impaired food intake on weight loss in cachexia has not yet been elucidated and remains undefined, and the clinical benefits of dietary intervention in the treatment of cachexia are not clarified.

The development of cachexia in cancer should be seen as a continuum moving through three different phases, namely pre-cachexia, cachexia and refractory cachexia [2]. During this cachexia trajectory, nutritional and dietary practices that promote energy balance may be of varying importance [2, 4], however, the scientific foundation to supports these assumptions are ambiguous. In pre-cachectic patients, the focus is on prevention of weight loss and the response to dietary treatment is expected to be fair [5, 6]. In patients with cachexia, dietary treatment is most likely insufficient to reverse cachexia since other factors such as metabolic and inflammatory changes are involved [2, 5]. If the patient has entered a stage of refractory cachexia, the response to dietary treatment is no longer anticipated due to very advanced or rapidly progressive cancer unresponsive to anti-cancer therapy [2]. Even if nutritional or dietary treatment do not influence weight loss or survival it may be highly significant when it comes to eating- and weight loss-related distress, relief of certain symptoms, quality of life and social meaningfulness for the patients [6, 7].

There are basically only three techniques/methods that are used to increase energy intake in patients; parenteral nutrition (PN), enteral nutrition (EN) or dietary counselling with advices aiming to increase oral intake. In dietary counselling the focus is commonly to increase intake of energy dense foods, increase meal frequency and/or to use oral liquid nutritional supplements (ONS) [8, 9]. Former reviews and guidelines have concluded that the benefits from PN or EN in advanced cancer are limited [10, 11]. The overall aim of this systematic review was therefore to evaluate the evidence of the effect of dietary counselling in treating weight loss and improving energy intake in patients with advanced cancer and different stages of cachexia. Secondary research questions were if dietary counselling is effective in improving physical function or quality of life.

2. Methods

2.1. Search strategy and selection criteria

Studies with adult patients with advanced cancer that evaluated the effect of oral dietary interventions were included. Studies were excluded if the main aim was to evaluate the effect of either PN or EN or if the intervention was selected nutritional compounds such as certain vitamins, fatty acids, proteins or amino acids. Studies were also excluded if they at baseline did not report data necessary to classify cachexia or if only treatment with curative intent was given. The recent consensus criteria for diagnosis of cancer cachexia were used to classify cachexia [2]. Patients with weight loss ≤5% at inclusion were classified as pre-cachectic. Patients with weight loss >5% or body mass index (BMI) <20 and weight loss >2% or weight loss >2% and sarcopenia were classified as cachectic. Simple starvation should be ruled out as a reason for weight loss. Patients were considered having refractory cachexia if the criterions for cachexia were fulfilled and expected survival was ≤ 3 months, WHO performance status was ≥3 or they did not respond to anti-cancer therapy. The classification into cachexia stages

was based on the information provided in the articles; no attempts were made to obtain further information from the study authors.

Primary outcomes of interest in this review were weight (measured in kg, pound or percent change in lean body mass, total body mass or fat mass) and energy intake (measured as kcal, kJ or MJ, absolute intake and/or energy balance). *Secondary outcomes* were physical functioning and quality of life (QoL).

This review considered quantitative study designs including randomised controlled trials (RCT's), quasi-RCT, cohort studies, pre-post study design and case control studies.

Case series with 10 or less participants were not included, neither were qualitative studies. Only studies published in full-text in peer-reviewed journals were included. Language was limited to English, German and Scandinavian languages.

The literature search was conducted in PubMed (includes MEDLINE), Embase (through OvidSP), and The Cochrane Central Register of Controlled Trials (CENTRAL), last search date April 2013. Searches were performed together with a trained research advisor in literature searches. The search strategy for all databases is reported in supplementary material. Appropriate strategies were developed for each database. A hand search of the references list of the selected papers was also performed.

2.2. Study selection and data extraction

All records identified by the database searches were collated into a computer based reference management system (EndNote x5) and checked for duplicates. After deduplication titles and abstracts were reviewed and assessed for inclusion independently by two authors (AB and TRB). Disagreements were resolved by discussion with third author (TSS) and reasons for excluding trials were reported. If abstracts were missing the full text papers were screened. The Prisma statement for reporting systematic reviews was used [12].

2.3. Description of study quality and content

The content of each included study was analysed following reading full text articles using methodological indications from the Cochrane Handbook for Systematic Reviews of Interventions [13], and summarized according to a standardized form. The authors of the Cochrane handbook state that there is no single recommended instrument for assessing the quality of trials when the systematic review also includes non-randomized trials. Therefore, a pragmatic quality assessment model based on the Cochrane guidelines was applied for the non-randomized trials were used.

3. Results

3.1. Search results and selection of studies

The literature review retrieved 634 papers (Fig. 1). Three studies were added after a hand search of the reference lists of full-text articles assessed for eligibility. After excluding duplicate studies, and studies that did not meet the inclusion criteria based on reading title and abstract, 23 papers were selected for full-text examination. Eighteen papers were excluded; nine in which the target population was not clearly defined as patients with advanced cancer and/or treatment with curative intent was given [9, 14-19], four in which there was not given enough information to classify cachexia [20-23] and five in which the effect of other interventions than dietary counselling were evaluated [24-28]. The present review is thus based on two non-randomized studies and three RCT's. Three studies included only cachectic patient [29-31] (Table 1), one study reported inclusion of both pre-cachectic and cachectic patients [32] and one reported inclusion of patients with all stages of cachexia [33] (Table 2).

3.2. Dietary counselling in studies including patients with cachexia

Three studies had included patients that could be classified as cachectic, two RCT's [29, 30] and one non-randomized study [31]. The available data could not exclude starvation as the reason for weight loss. The studies represents in total 419 patients with a variety of type and stage of cancer. The studies are summarized in the next paragraph.

Baldwin (2011) [29]. 358 patients with gastrointestinal (GI) cancers (n=277) and non-small cell lung cancer (NSCLC) (n=81), were randomized to four groups, 1) dietary counselling aiming to increased energy intake by 600 kcal using regular food, 2) oral liquid nutritional supplements (ONS) (240 ml providing 588 kcal/day), 3) a combination of dietary advice, ONS and vitamins or 4) ad lib intake. The intervention period lasted for six weeks during chemotherapy. After this the patients were allowed to continue with their intervention if desired. They were followed for one year. The overall compliance with prescribed ONS was low. In the first week, 31% of the patients reported taking all of their prescribed drink. This decreased to 19% at week six. Analyses of data on dietary intake were not performed due to low compliance with food diaries (25%- 17%). Mean weight change after six weeks of intervention was small (0.0 kg to – 0.7 kg), and no statistically significant differences between the four groups were found. After one year 68 (19%) patients were alive, of whom 31 had received dietary counselling (group 1 and 3). These patients reported a weight gain of 4.8 kg compared to 1.4 kg ($p<0.05$) among patients not receiving counselling. However, the most important predictor of weight gain was survival and not nutritional intervention. The authors suggest that weight gain might be a surrogate marker of tumor response to chemotherapy. Physical performance and QoL was evaluated, but no differences between the groups were found.

Breitkreuz (2005) [30]. Twenty-three patients with advanced colorectal or gastric cancer receiving chemotherapy were randomised to 1) fat-enriched ONS (237 ml providing 355 kcal) in combination with usual care (nutritional advice before treatment and thereafter every 2nd weeks) or 2) control group, usual care only. Energy intake was higher in the intervention group than the control group (1865 kcal vs. 1556 kcal, not statistically significant). After 56 days the intervention patients had gained in average 1.4 kg while the control group lost 2 kg ($p<0.05$). Fat free mass increased 1 kg in the intervention group and decreased 1 kg in the control group ($p<0.05$). The intervention group had stable albumin values during the study while a fall (-4.57 ± 1.86 g/l, $p<0.05$) was seen in the control group. In the intervention group ratings of quality of life leisure activity increased (4.9 ± 0.9 vs 6.7 ± 0.7 out of 10 units, $p<0.01$) compared to a detoriation in control group (exact figures were not available, $p<0.01$).

van den Berg (2010) [31]. Thirty-eight head and neck (HN) cancer patients (stages II-IV) receiving radiotherapy were included and assigned to treatment based on postal code. The intervention group received systematic dietary counselling (1-2 times a week) during radiotherapy and follow up (20 weeks) aiming to meet total caloric need and protein requirements. High energetic ONS (type not stated) and EN was used when energy intake was too low. The control group received standard care (dietary counselling twice before start of RT and advice by a nurse during treatment, patients losing >10% of weight received EN). Two weeks after RT both groups had lost 3% of their initial weight. Two months after treatment the intervention group increased weight (1%) while the control group continued to lose weight (-1.5%), $p=0.03$.

3.3. Dietary counselling in studies including patients with pre-cachexia, cachexia, and refractory cachexia

Evans (1987) [32] reported inclusion of both pre-cachectic and cachectic patients and evaluated the effect of dietary counselling. The RCT included 180 patients with metastatic NSCLC (n=102) and Duke's D colorectal carcinoma (CRC) (n=90), all receiving 12 weeks chemotherapy. At randomization patients were stratified by weight loss (≤5% or >5%) and then randomized to one of three groups, 1) standard nutrition (dietary counselling to meet total caloric need), 2) augmented nutrition (protein, zinc and magnesium supplementation in addition to dietary counselling) or 3) control (ad libitum intake). Fifty one patients received standard nutrition and of these 22 (43%) were cachectic. Sixty patients received the augmented nutrition (28 (47%) cachectic) and 69 were allocated to the control group (33 (48%) cachectic). Patients receiving nutritional intervention (group 1 and 2) had higher caloric intake compared to patients in the control group, covering respectively 91-92% and 62-73% of total caloric need ($p<0.01$). In spite of this, the overall weight change between treatment groups during chemotherapy did not differ. The patients with NSCLC lost weight, median -1.2% in the two intervention groups and -3.1% in the control group (ns). The patients with CRC gained weight, 0.8 % in the intervention groups and 2.1% in the control group (ns). For both tumor types a positive association between caloric intake and weight change was found. The association was strongest among patients with NSCLC. No analyses were performed to differentiate the effect between patients being cachectic or pre-cachectic. The intervention had no effect on survival, response to chemotherapy or treatment toxicity.

Percival (2013) [33]. Two hundred and forty-three patients with thoracic cancer (NSCLC (77%), small cell lung cancer (SCLC) (13%), mesothelioma (4%), no histology available (6%)) underwent nutritional assessment (height, weight, weight loss, body composition,

nutritional intake, and nutritional impact symptoms) before cancer treatment. Eighty-four (35%) were identified as malnourished and reported weight loss or BMI consistent with cachexia or refractory cachexia. Information from the nutritional assessment together with patient's likely prognosis was used to develop an individualized intervention plan (high protein and energy foods, dietary fortification, ONS). There was no control group. After one month 61 (73%) of the malnourished patients could be re-evaluated. Fourteen (23%) had received dietary counselling and 47 (77%) had received dietary counselling in combination with ONS. Twenty two (37%) patients had gained weight (median 2.0 kg), 20 (33%) had stable weight and 19 (32%) lost weight (median –3.0 kg). The type of nutritional intervention was not essential for weight development, but it seemed that patients who gained weight were younger (mean age 68 vs 71 years, p=0.04) than patients that stabilized or lost weight.

3.4. Summary of findings

Most studies included patients with a variety of cancer diagnosis, even if NSCLC and HN were most common. Three out of five studies included only patients with cachexia, one both pre-cachectic and cachectic patients and one with all stages. On the basis of available data it was not possible to exclude that weight loss was due to starvation. The effect of dietary counselling on energy intake (absolute intake and/or energy balance) was evaluated in two RCTs. The results indicated that it was possible to increase energy intake by various combinations of high energy foods, fortifications and ONS. All five studies evaluated the effect of dietary counselling on weight. Two studies reported statistical significant differences in weight loss among patients receiving dietary counselling compared to patients not receiving counselling. The secondary outcome QoL was evaluated in one study but no effect was found. Physical functioning was evaluated in two studies where one found increased leisure activities and psychological functions in favour of dietary counselling. No analyses

were performed to differentiate effects between pre-cachectic and cachectic patients in any of the studies.

3.5. Quality of evidence

The quality of the included studies is summarized in Table 3. Two studies were carried out on a small number of patients (N<40) [30, 31], three studies were RCTs and two of these studies performed sample size estimations [29, 32]. Four out of five studies had a comparative control group. Two studies [29, 32] described control patients to receive respectively "ad libitum diet" and "no nutritional support" while one study [31] described that patients in the control group getting "standard care" received dietary advice by a dietitian twice before starting radiotherapy continuing with weekly body weight measurements by a nurse.. One of five studies reported allocation concealment, intention-to-treat analysis and presented data on compliance to dietary counselling [29]. Studies could not be directly compared with each other due to different intervention periods, outcomes, registrations and follow-up. All included studies described body weight as one of their outcomes, but only two [29, 32] showed data on energy intake and only one study had data on physical function and QoL parameters [29].

4. Discussion

This systematic literature review identified five studies evaluating the effectiveness of dietary counselling in treating weight loss and improving energy intake in patients with advanced cancer and cachexia. Counselling included increased intake of energy dense foods, increased meal frequency and/or use of oral liquid nutritional supplements (ONS). Most studies showed some effect on body weight, stabilization or increase, during the intervention either in subgroups or at some given time point. There is not enough evidence to conclude

whether patients with advanced cancer and different cachexia stages benefit from dietary counselling.

Only two included studies [30, 32] used energy intake and energy balance as outcome variables. Both studies showed that it was possible to improve energy intake with dietary counselling but one of of the studies did not reach statistical significance. Nevertheless, the effect of increased intake was not followed by increased body weight. These findings are consistent with the findings of a recent Cochrane review and meta-analysis that did not find a consistent effect of oral nutritional interventions on energy intake and weight gain in malnourished cancer patients [34]. The explanation for such findings may be that weight loss in cancer patients in general, and particularly in advanced cancer, is not always a result of low energy intake and malnutrition but rather occurs as a result various combination of low intake, increased tumor activity and metabolic changes [35, 36]. This assumption is in accordance with the international cachexia definition [2], declaring that cachexia cannot be treated with nutrition alone. Today this is perceived as an indication for the use of multimodal treatment in cancer cachexia [37], suggesting that cancer cachexia needs to be treated with a combination of physical exercise to counteract inactivity atrophy and catabolism, pharmacological agents affecting metabolism, and nutritional intervention to secure sufficient energy intake [6]. Nevertheless, for clinical practice and the design of future studies it is important to determine if response to nutritional interventions can be expected in cachexia and thus clearify the role of nutritional interventions.

Most studies in this review have grouped together patients with different diagnosis receiving different treatments. This leads to a heterogeneity that may have interfered with the results of the interventions. It is obvious that patients experiencing starvation and mainly lose weight due to readily reversible factors such as untreated candida stomatitis, will have more effect from dietary counselling than patients with any stage of cachexia [2, 4, 5]. For

classification of cachexia it is important to rule out simple starvation as the reason for weight loss [2]. The main difference between starvation and cachexia is that refeeding reverses starvation but is less effective for cachexia. However, the studies included in this review did not provide data making such an exclusion possible e.g information about nutritional impact symptoms lacked in all of them and thus the possibility to assess if this was contributing to patient weight loss. It is very challenging to exclude starvation and untangle the relative contribution of symptoms, low food intake and metabolic changes to weight loss in cancer patients, as this varies both between patients and in the individual patient with time [3]. Normally is assessment of nutritional status used to decide if a patient is starved or not. However, the assessment instruments normally used overlap the cachexia classification and is therefor not suitable for excluding starvation [38]. A separation between starvation and cachexia could be achieved if information about nutritional impact symptoms causing reduced food intake were available, such as mechanical intestinal obstructions,constipation, stomatitis and untreated pain.

In dietary intervention trials both non-compliance as well as an risk of adoption of the intervention program in the control group (cross over) may be a problem and tend to equalise outcomes between the groups, minimising the chance of seeing an effect even if there is one. Unfortunately it is not possible to administer an intervention trial based on counselling as a double-blind experiment in order to conclude that any difference that develops between the groups is directly caused by the factor under investigation [39]. It is therefore of great importance to evaluate the compliance when evaluating the effect of dietary counselling. However, most studies in this review lack such an evaluation. In the study of Baldwin et al. [29] the compliance to ONS was evaluated. They found that only 31% of the patients reported taking all of their prescribed drink. This may have had an devastating effect on the result, as it is demonstrated that maximum weight gain is dependent on full compliance [24]. ONS are

often used in dietary intervention trials since they usually are nutritional complete and easy to use, nevertheless, compliance can be challenging. Lack of compliance may be related to taste and smell problems aggravated by chemotherapy side effects. In addition, most supplements are sweet-flavored which may not appeal to all patients.

To further complicate the estimation of effectiveness of dietary interventions in this review, both the length of interventions and the interventions themselves varied considerably and not all studies were randomized. Other intervention studies in cachexia have demonstrated that positive single arm interventions studies often are followed by RCTs where there are no difference between active arm and placebo [40]. Even if most of the included studies were randomized it is still a challenge to conclude if a true control group existed since the patients received "usual care". "Usual care" was also some kind of nutritional intervention, although less intensive and poorly described, and the consequence may be reduced effect size.

In intervention trials it is of course essential that the primary outcome is of relevance. When the intervention is dietary increased energy intake and stabilized body weight might be objective measurements of the intended effect. However, one challenge in using weight as an outcome is that it does not take into account that changes in weight may be caused by other factors (edema, ascites and increased tumor load) and not only changes in muscle and fat mass. More objective measures such as CT scans may thus be more reliable when muscle and fat mass is of interest [41]. Another discussion is whether improved or stabilized body weight is transferable to other, more patient centered outcomes such as quality of life parameters and physical function. This was the reason for choosing these as the secondary outcomes in this review. The evidence from the retrieved studies was however very limited as one of the retrieved studies used this outcome. It could also be discussed if more traditional oncological outcomes such as survival, tumor response or toxicity should have been used as outcomes in

this review, since there is an abundance of evidence that malnourished patients have reduced survival [42]. Only one of the reviewed studies evaluated survival, treatment response and toxicity [32] but did not find any improvements with nutritional intervention. However, for future studies it may be relevant to have a more oncologic focus on outcomes especially since it is not proven that reversal of nutritional deficits improves survival [43].

Several studies were excluded from this review due to missing or insufficient information on cancer staging, treatment intent and weight loss before inclusion and/or BMI because it was impossible to classify the patients according to the international consensus classification system for cachexia [2]. Studies were also excluded if patients receiving curative treatment were included. Because of this two of the most promising studies regarding dietary counselling from the analysis unfortunately had to be excluded [20, 21]. These two studies demonstrate that early individualized dietary counselling is effective in preventing weight loss in cancer but the results cannot be transferred directly to patients with advanced cancer and cachexia. However, it is worth to mention the most striking finding from these two studies, that individualized dietary counselling based on regular foods was the most effective intervention to prevent weight loss in cancer patients, far more effective than e.g. ONS [20, 21].

This is the first review attempting to resolve a question clinicians often struggle with in their daily practice. Which patients should receive what kind of dietary counselling? It is of great significance that this difficult question is untangled. It is important both when deciding how to treat patients, and when considering how and what information to give to patients and their loved ones. Several get caught in the general nihilism surrounding this issue, while others become too proactive resulting in frustration for cancer patients and families feeling that counting of calories wrongfully occupies the last time of their life. Future studies investigating the effect of dietary counselling are therefore needed. However, it is important

to describe the population well, and interventions should be randomized and easily replicated. There is a need for higher focus on compliance as well as attrition. Eligibility criteria should probably be narrower to ensure that treatment effect is not diluted due to inclusion of patients in whom treatment effect is not anticipated. It is furthermore necessary to ensure that all patients receive good symptomatic treatment in order to have the possibility to reasonably valuate the effect of the dietary interventions. It is not to be expected that patients will be able to comply with dietary interventions if nutritional impact symptoms such as constipation, stomatitis and pain is left untreated. In cachexia nutrition probably needs to be combined with treatment trying to modify inflammation/catabolism.

5. Conclusion

Based on the limited number of conducted studies, the inconsistent results, as well as the moderate quality of the included studies, it is not possible to conclude firmly on the effectiveness of dietary interventions in advanced cancer and cachexia. This review shows that dietary counselling can have some effect on body weight and energy intake although heterogeneity between studies is present. Few studies measured energy intake in this review, but itseems that dietary interventions can improve energy intake. Still, the increase in energy intake seems not transferable to improvement in patients' weight. This observation emphasizes the correctness of the international cachexia definition stating that cachexia cannot be treated with nutrition alone. It was not possible to give information on whether there were differences in the effectiveness of dietary treatment between patients having pre-cachexia, cachexia or refractory cachexia.

This review highlights that dietary intervention trials generally report poorly both when characterising patient populations and when describing the nutritional intervention. In order to advance the evidence for dietary interventions, it is mandatory that future studies take this into

account. However, nutrition is a crucial part of a multimodal cachexia intervention, and it is not plausible to increase or stabilise weight if nutritional needs are not met.

Conflict of interest

The authors have no conflict of interest associated with this manuscript.

Acknowledgements

The authors thanks Ingrid Riphagen, trained research advisor, Unit for Applied Clinical Research, Faculty of Medicine NTNU, for help with the systematic searches and valuable input on the process.

References

1. Evans WJ, Morley JE, Argiles J et al. Cachexia: a new definition. Clin Nutr 2008; 27: 793-799.
2. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology 2011; 12: 489-495.
3. Blum D, Omlin A, Baracos VE et al. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol 2011; 80: 114-144.
4. Blum D, Omlin A, Fearon K et al. Evolving classification systems for cancer cachexia: ready for clinical practice? Support Care Cancer 2010.
5. Blum D, Strasser F. Cachexia assessment tools. Current Opinion in Supportive & Palliative Care 2011; 5: 350-355.
6. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol 2013; 10: 90-99.
7. Oberholzer R, Hopkinson JB, Baumann K et al. Psychosocial Effects of Cancer Cachexia: A Systematic Literature Search and Qualitative Analysis. Journal of pain and symptom management 2013; 46: 77-95.
8. Wallengren O, Lundholm K, Bosaeus I. Diet energy density and energy intake in palliative care cancer patients. Clinical Nutrition 2005; 24: 266-273.
9. Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. In Journal of the American Dietetic Association. 2007; 404-412.
10. Radbruch L, Elsner F, Trottenberg P et al. Clinical practice guidelines on cancer cachexia in advanced cancer patients. In. Aachen: Department of Palliative Medicin/European Palliative Care Research Collaborative 2010.
11. Koretz RL. Should patients with cancer be offered nutritional support: does the benefit outweigh the burden? Eur J Gastroenterol Hepatol 2007; 19: 379-382.
12. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339.
13. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. . In Version 5.1.0 Edition. The Cochrane Collaboration 2011.
14. Ovesen L, Allingstrup L, Hannibal J et al. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. In Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1993; 2043-2049.
15. Lovik A, Almendingen K, Dotterud M et al. [Dietary information after radiotherapy of head and neck cancer]. Tidsskr Nor Laegeforen 1996; 116: 2303-2306.
16. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. In British journal of cancer. 2004; 447-452.
17. Casas F, Leon C, Jovell E et al. Adapted ice cream as a nutritional supplement in cancer patients: Impact on quality of life and nutritional status. Clinical and Translational Oncology 2012; 14 (1): 66-72.
18. Valentini V, Marazzi F, Bossola M et al. Nutritional counselling and oral nutritional supplements in head and neck cancer patients undergoing chemoradiotherapy. J Hum Nutr Diet 2012; 25: 201-208.

19. Persson CR, Johansson BBK, Sjoden P-O, Glimelius BLG. A randomized study of nutritional support in patients with colorectal and gastric cancer. Nutrition & Cancer 42: 48-58.
20. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. In Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005; 1431-1438.
21. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. In Head & neck. 2005; 659-668.
22. Dixon J. Effect of nursing interventions on nutritional and performance status in cancer patients. In Nursing research. 1984; 330-335.
23. Paccagnella A, Morello M, Da Mosto MC et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. Support Care Cancer 2010; 18: 837-845.
24. Bauer J, Capra S, Battistutta D et al. Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer. In Clinical nutrition (Edinburgh, Scotland). 2005; 998-1004.
25. Daly JM, Weintraub FN, Shou J et al. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. In Annals of surgery. 1995; 327-338.
26. Mercuri A, Joon DL, Wada M et al. The effect of an intensive nutritional program on daily set-up variations and radiotherapy planning margins of head and neck cancer patients. Journal of Medical Imaging and Radiation Oncology 2009; 53 (5): 500-505.
27. Wallengren O, Bosaeus I, Lundholm K. Dietary energy density, inflammation and energy balance in palliative care cancer patients. Clin Nutr 2013; 32: 88-92.
28. Wang CH, Wang HM, Pang YP, Yeh KY. Early nutritional support in non-metastatic stage IV oral cavity cancer patients undergoing adjuvant concurrent chemoradiotherapy: analysis of treatment tolerance and outcome in an area endemic for betel quid chewing. Support Care Cancer 2012; 20: 1169-1174.
29. Baldwin C, Spiro A, McGough C et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. J Hum Nutr Diet 2011; 24: 431-440.
30. Breitkreutz R, Tesdal K, Jentschura D et al. Effects of a high-fat diet on body composition in cancer patients receiving chemotherapy: a randomized controlled study. In Wiener klinische Wochenschrift. 2005; 685-692.
31. van den Berg MG, Rasmussen-Conrad EL, Wei KH et al. Comparison of the effect of individual dietary counselling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. Br J Nutr 2010; 104: 872-877.
32. Evans WK, Nixon DW, Daly JM et al. A randomized study of oral nutritional support versus ad lib nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. J Clin Oncol 1987; 5: 113-124.
33. Percival C, Hussain A, Zadora-Chrzastowska S et al. Providing nutritional support to patients with thoracic cancer: Findings of a dedicated rehabilitation service. Respiratory Medicine 2013; 107: 753-761.
34. Baldwin C, Spiro A, Ahern R, Emery PW. Oral Nutritional Interventions in Malnourished Patients With Cancer: A Systematic Review and Meta-Analysis. Journal of the National Cancer Institute 2012; 104: 371-385.
35. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev 2009; 89: 381-410.

36. Bosaeus I. Nutritional support in multimodal therapy for cancer cachexia. Supportive Care in Cancer 2008; 16: 447-451.
37. Solheim TS, Laird BJ. Evidence base for multimodal therapy in cachexia. Curr Opin Support Palliat Care 2012; 6: 424-431.
38. Thoresen L, Frykholm G, Lydersen S et al. Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. Clinical Nutrition 2013; 32: 65-72.
39. Welch RW, Antoine J-M, Berta J-L et al. Guidelines for the design, conduct and reporting of human intervention studies to evaluate the health benefits of foods. British Journal of Nutrition 2011; 106: S3-S15.
40. Baracos VE. Clinical trials of cancer cachexia therapy, now and hereafter. J Clin Oncol 2013; 31: 1257-1258.
41. Prado CM. Body composition in chemotherapy: the promising role of CT scans. Curr Opin Clin Nutr Metab Care 2013; 16: 525-533.
42. Dewys WD, Begg C, Lavin PT et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980; 69: 491-497.
43. Baracos VEa, Pichard Cb, Attaix Dc. Survival: the relevant primary outcome for nutrition therapy in cancer patients. Current Opinion in Clinical Nutrition & Metabolic Care 2012; 15: 211-212.

Bibliography

Asta Bye (Dietician, PhD) has a research position at the Regional Centre for Excellence in Palliative Care at Oslo University Hospital. She also holds a position as associate professor at the Department of Health, Nutrition and Management, Oslo and Akershus University College of Applied Sciences.

Table 1. Characteristics of studies investigating the effects of dietary counselling in patients with cancer cachexia.

	Patients				Results			Effects	
Author, year and study design	***Total no. of patients***	***Patient characteristics***	***Intervention***	***Duration of intervention***	***Outcomes[1]***	***Body weight***	***Other outcomes***	***Effect on weight and energy intake***	***Effect on QoL and physical function***
Baldwin, 2011 (28) RCT	N=358	GI, NSCLC or mesothelioma Metastatic or locally advanced disease Palliative chemotherapy	*Group 1*, Dietary advice to increase intake by 600 kcal per day. Booklet with commonly used foods and snacks in portion sizes each providing 150 kcal *Group 2*, One sachet of ONS each day providing 588 kcal. A daily multivitamin and mineral supplement *Group 3*, Dietary advice to increase food intake by 600 kcal per day, one sachet of ONS and vitamins. *Group 4*, Control; Ad lib intake	6 weeks After this the patients were allowed to continue with their intervention if desired	1=X 2=X 3=X 4=X	No differences between the groups after 6 weeks After 1 year, group 1 (N=31) had gained more than group 4 (N=37) (mean 4.8 kg vs. 1.4 kg, p<0.05)	Compliance with prescribed quantity of supplement fell during the whole study No differences in QoL (EORTC-C30 and FAACT) No differences in physical performance *(*hand grip strength) No differences in overall survival	Limited effect on weight Energy intake NA.	No effect on QoL or physical function
Breitkreutz, 2005 (29) RCT	N=23	CRC and gastric cancer, with metastases Not resectable or advanced cancer Chemotherapy	*Group 1*, Usual care (nutritional advice every 14 days) and commercial fat-enriched ONS. The drink should provide at least 20 non-protein kcal/kg per day. 100 ml of the drink contained 9.3g fat *Group 2*, Control: Usual care (nutritional advice every 14 days) Nutritional target for both groups was an intake of 35 non protein kcal/kg body weight per day and 1.1 g protein/kg per day	56 days	1=X 2=X 3=X 4=0	Group 1 gained weight and group 2 lost weight (mean + 1.4 kg vs. -2 kg, p<0.05)	Group 1 increased 1 kg fat free cell mass versus 1 kg loss in group 2 (p<0.05) Stable albumin in group 1, fall (-4.75 g/l) in group 2 Energy intake higher in group 1, 1865 kcal vs. 1556 kcal (NS) Consumption of energy from fat higher (66 %) in group 1 LASA scale: Improved rating of leisure activities (p<0.01) and psychological (p<0.05) conditions in group 1 versus deterioration in the group 2	Beneficial effect on weight NS effect on energy intake	Limited effect on QoL No data on physical function
van den Berg, 2010 (30) Prospective intervention study	N=38	HN (stage II-IV) Radiotherapy	*Group 1*, Systematically dietary advice by dietitian to meet TCN and protein requirement by regular food (1-2 times a week). High energetic ONS and EN were used if energy intake was too low *Group 2*, Dietary counselling twice by a dietitian before RT. Thereafter, weight at least once a week and nutritional advice by a nurse. Symptom management and ONS. EN used for patients losing>10% weight. Patients seen once a week during RT and at least once 3-4 months after treatment. Estimated TCN >30 - ≤ 40 kcal kg per day Estimated protein 1g – 1.5g/kg per day	20 weeks	1=X 2=0 3=0 4=0	Two weeks after RT 3% weight loss in both groups Two months after RT group 1 gained weight, group 2 continued to lose (+1% vs. -1.5%, p=0.03)	Two weeks after RT, lower prevalence of malnutrition in group 1 than in group 2 (0/20 vs. 5/18, p<0.05). Two months after RT (1/20 vs. 3/18, NS) Differences in malnutrition was not associated with disease stage	Limited effect on weight Energy intake NA	No data on QoL or physical function

[1]Outcomes: 1: Weight (kg, % weight change), 2: Energy intake (kcal, kJ; MJ) and/or energy balance, 3: QoL parameters 4: Physical function (Karnosfky, ECOG, grip strength)

Abbreviations: HN, head and neck cancers, TCN, total caloric need , ONS, oral nutritional supplement, EN, enteral nutrition, NS, not significant, NA, not assessed, QoL, quality of life, RCT, randomized controlled trial, GI, gastrointestinal cancers, NSCLC, non-small cell lung cancer, CRC, colorectal cancer.

Table 2. Characteristics of studies investigating the effects of dietary counselling in patients with all stages of cancer cachexia.

	Patients				**Results**			**Effect**	
Author, year and study design	***Total no. of patients***	***Patient characteristics***	***Intervention***	***Duration of intervention***	***Outcomes*** [1]	***Body weight***	***Other***	***Effect on weight and energy intake***	***Effect on QoL and physical function***
Evans, 1987 (31) RCT	N=180	Metastatic NSCLC and Duke's D CRC Chemotherapy	*Group 1*, Standard nutrition; dietary advice to meet TCN, EN if necessary *Group 2*, Augmented nutrition; Standard nutrition and in addition 25% of calories from protein, supplements of zinc and magnesium *Group 3*, Control; Ad lib intake 24-hour recalls used to assess energy intake Harris Benedict equation used to calculate resting energy expenditure and TCN	3 months	1=X 2=X 3=0 4=0	NSCLC: Less weight loss in group 1 and 2 than group 3 after 4 weeks (-0,6 kg vs. -2,1 kg, p=0.06) CRC: No differences	NSCLC: Energy intake 91% of TCN in group 1 and 2 vs 62% group 3 (p<0.01) CRC: Energy intake 92% of TCN in group 1 and 2 vs 73% in group 3 (p<0.01) Significant correlation between energy intake and weight change No effect on overall survival	Limited effect on weight for NSCLC No effect for CRC Beneficial effect on energy intake in both cancer types	No data on QoL or physical function
Percival, 2013 (32) Prospective cohort study	N=243	Thoraic cancer (NSCLC stage I-IV, SCLC mesothelioma (local and extensive) Surgery Radiotherapy CRT Palliative Care	Systematic screening of malnutrition after diagnosis. Nutritional assessments were used to develop an individualized nutritional plan and written information. Dietary counselling aimed to optimize intake with high protein and energy foods, use of fortification and snacks. ONS was offered to malnourished or at risk patients	4 weeks	1=X 2=0 3=0 4=0	After one month, weight gain in 23% and stable weight in 46% of not malnourished patients vs 36% and 33% in malnourished, respectively, NS	Malnutrition associated with a reduced survival (median 155 days, p<0.01) Patient who gained weight were younger (mean age 68 vs. 71 years, p=0.04)	Limited effect on weight Energy intake NA	No data on QoL or physical function

[1]Outcomes: 1: Weight (kg, % weight change), 2: Energy intake (kcal, kJ; MJ) and/or energy balance, 3: QoL parameters 4: Physical function (Karnosfky, ECOG, grip strength)
Abbreviations: NSCLC, non-small cell lung cancer, CRC, colorectal cancer, TCN, total caloric need, EN, enteral nutrition, QoL, quality of life, SCLC small cell lung cancer, CRT, chemoradiotherapy, ONS, oral nutritional supplement, NS, not significant, NA, not assessed.

Table 3. Quality of studies.

Author/year	*Design*	*Allocation concealment*	*Losses to follow-up*	*Intention to treat analysis*	*Blinding*	*Sample size calculation*
van den Berg 2010	Prospective intervention study		38 of 38 at week 20	Not described		
Percival 2013	Prospective cohort study		191 of 414 at 4 weeks			
Evans 1987	RCT	Not described	111 of 180 at 12 weeks	Not described		X
Breitkreutz 2005	RCT	Not described	23 of 23 at day 28 23 of 23 at day 56	Not described		
Baldwin 2011	RCT	X	323 of 358 at week 6 346 of 358 at week 26 153 of 358 at week 52	X		X

Fig. 1. Flow chart summarizing the stages of the systematic review and reasons for exclusion.