Combining optimal nutrition and exercise in a multimodal approach for patients with active cancer with risk of losing weight – rationale and practical approach

Tora Skeidsvoll Solheim[1,2], Ola Magne Vagnildhaug[1,2], Barry J Laird[3,4], Trude Rakel Balstad[1,2]

[1]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU – Norwegian University of Science and Technology, Trondheim, Norway

[2]Cancer Clinic, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway

[3]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

[4]St Columba's Hospice, Boswall Road, Edinburgh, UK

Corresponding author: Tora Skeidsvoll Solheim, Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU – Norwegian University of Science and Technology, Trondheim, Norway

Telephone: +47 72826136, E-mail: tora.l.skeidsvoll@ntnu.no

Abstract

Background: Weight loss and functional decline is common and detrimental consequence of cancer. The interventions that are offered to patients suffering from this often seem haphazard and varying from center to center. The lack of stringent management is probably based both on lack of knowledge of existing treatment guidelines and the current weak level of evidence of clinical effects of different nutritional and exercise interventions. The aim of this review is to examine the evidence for combined treatments targeting weight loss in cancer patients.

Results: There are some studies evaluating multimodal interventions with various treatment combinations including nutrition and exercise that report clinical significant effects on cachexia outcomes. There are as of today, however, a paucity of large randomized controlled trials that incorporate both a fully structured exercise program and a well described nutritional intervention.

Conclusion: Studies investigating combinations of several interventions in patients with active cancer and risk of losing weight are too few and too heterogeneous to enable firm conclusions about effect, optimal dose or timing if interventions. However, data presented in this review suggest an overall benefit, especially if interventions are started before weight loss and loss of function become too severe.

Keywords: Cancer cachexia; Weight loss; Dietary counseling; Oral nutritional supplement; Resistance exercise; Aerobic exercise; Pharmaconutrients; N-3 polyunsaturated fatty acids

Introduction

Up to 50% of patients with cancer experience loss of weight with a resulting dramatic decline in physical function (1, 2). The reasons behind this loss are complex; for some the main cause is reduced food intake or malabsorption, for others inactivity causing muscle atrophy, while for others again cancer cachexia is the main cause (3). Commonly several factors contribute to what the patient experience as a wasting condition. Cancer cachexia has been defined as loss of muscle mass (and fat mass) that cannot be fully reversed by nutritional support (3). However, this definition does not imply that optimal nutrition is unimportant in patients with cancer cachexia. The intention of the definition is merely to differentiate cachexia from starvation-related malnutrition and acknowledge its complex pathophysiology and the variety of contributing factors that worsen patients' weight/muscle mass, appetite, food intake and physical function. The logical consequence of the complexity behind weight loss in patients with cancer is to take a multimodal approach to cachexia treatment, of which sufficient nutrition as well as physical exercise should form the basis in order to maintain muscle mass, strength and function (4) (Figure 1). The lack of progress in cachexia management might thus partly be caused by intervention studies mainly focusing on unimodal interventions, most commonly pharmacological interventions.

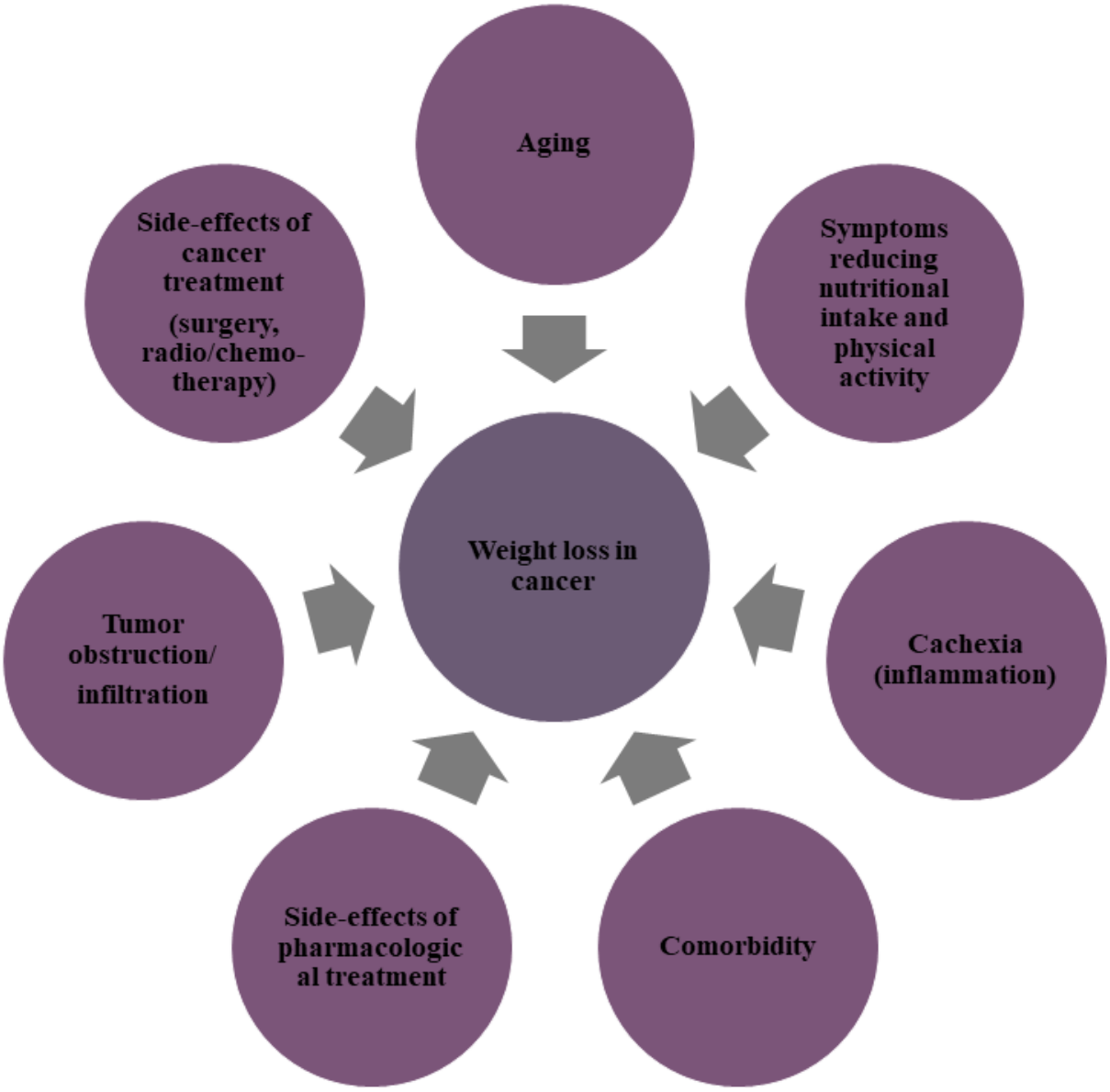

Figure 1. Factors that can contribute to weight loss in patients with cancer

The relatively few cancer cachexia trials investigating combination treatments have generally explored the combinations of various drugs (5, 6), or drugs in combination with nutrients in pharmacological doses (pharmaconutrients) (7, 8). Few larger studies investigate more complex interventions where drugs or pharmaconutrients are combined with nutritional intervention and exercise programmes (9-12). The purpose of this review is to give an overview of clinical findings from multimodal interventions targeting weight loss in patients

with active cancer and suggestions for practical approach to exercise and nutritional interventions.

Nutrition and pharmaconutrients

Disease related malnutrition can be complex as it can arise from inadequate intake, increased demands, increased nutrient loss or malabsorption, together or as isolated factors (13, 14). Nutritional support has been advocated to be the cornerstone in any cachexia treatment (3, 15-17), but attempts to increase food intake alone will result in variable weight responses if hypermetabolism is apparent (18, 19). Whether individual patients are likely to respond to nutritional treatment depends on additional factors such as compliance, symptom burden, response to anti-neoplastic treatment and proximity to death (18, 20, 21). Inconsistent effects on body weight, energy intake, quality of life (QoL) and physical function has consequently been reported (22-24). Positive effects on body weight have in a recent meta-analysis been attributed to a subset of patients given energy-dense high-protein oral nutritional supplements (ONS) enriched with n-3 Poly Unsaturated Fatty Acids (PUFA) (20). N-3 PUFAs are to date the most promising and well-studied pharmaconutrients in cancer cachexia often given incorporated in ONS (15, 20). Even though results have been inconclusive, and the level of evidence is weak, guidelines on nutrition in cancer support the use of fatty acids as a supplement to improve appetite and body weight (15). Other pharmaconutrients have been investigated in cachexia, however, insufficient data exist for recommending medical use of e.g. branched-chain or other amino acids, amino acid metabolites or L-carnitine (15). Pharmaconutrients should never substitute conventional nutritional support, and patients' basic needs should be adequately met.

In summary, despite the various and limited effects reported, and also uncertainties on the optimal timing and duration of nutritional intervention (in any form), meta-analysis of RCTs report benefits of pharmaconutrients n-3 PUFAs supporting energy and protein intakes on body weight during radiochemotherapy (20).

Resistance and aerobic exercise

The effect of physical exercise on patients with cancer has been the subject of many clinical studies and systematic reviews (12, 25-29), and physical exercise is shown to be safe, feasible and effective also in patients with advanced cancer (30, 31). Although studies often are small and the risk of bias high (26), there seems to be an overall positive and clinically relevant effect of exercise on several outcomes, especially on aerobic capacity, muscle strength, cancer-related fatigue and QoL (25). However, effect on fatigue is not more than moderate (32), and effect on QoL seems to be small (33).

Weight loss and loss of function is most common in patients with advanced cancer, but few studies have evaluated the effect of exercise on patients in this patient group (34). A randomised controlled trial (RCT) testing resistance and cardiovascular training in 269 patients with mixed cancer types, of whom >50% had advanced cancer, found a small to moderate improvement of fatigue, and a 10.7% improvement in VO2max and 29.6% improvement in muscular strength (35). Adherence to the intervention was 70.8%. In an RCT with 231 patients with incurable cancer, improvements in hand grip strength and shuttle walk test were observed after eight weeks of supervised circuit resistance, balance and endurance training twice weekly although no effects on fatigue was observed (31). A eight –week resistance, endurance and balance training (2x week for 60 minutes) RCT in 30 patients with colorectal cancer during palliative chemotherapy, found stabilization of neuropathic symptoms, improved strength and balance function in favour of intervention arm (36). A recent six months supervised resistance training study including 65 patients with pancreatic cancer reported strength improvements in some muscle groups compared to either home based resistance training or usual care (30).

In summary, a growing number of RCTs now show positive effects of resistance training on muscle strength and body composition, also in patients with advanced cancer, even though most studies are conducted in breast cancer and cancer survivors (12, 37, 38). As of today, it is difficult to conclude what is the optimal exercise strategy in terms of frequency, intensity and duration.

Pharmacological agents and pharmaconutrients

Megestrol acetate (MA) has been the pharmacological agent showing the most consistent effects on anorexia and is one of the drugs most commonly used in trials investigating combinations of pharmacological interventions.

In a double-blinded three-armed study,421 patients losing weight were randomised to 1) n-3 PUFA enriched ONS + placebo 2) ONS without n-3 PUFAs + MA 2) or 3) n-3 PUFA enriched ONS in combination with MA This study could not conclude that combination treatment was superior in improving weight or appetite than MA alone (39). Equally, another study by the same research group could not find an improved effect when dronabinol was combined with MA compared to MA alone. (40). Conversely did a combination of MA with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) preform superior in improving body weight and appetite than either of the two drugs given separately in another study (6). Likewise did a phase III study show improved effect of a combination treatment when randomising between five different arms: 1) MA; 2) n-3 PUFA enriched ONS; 3) L-carnitine; 4) thalidomide or 5) a combination of all the above (41). After 4 months' intervention, the combination arm showed a better effect on both muscle mass and secondary endpoints (appetite, systemic inflammation and Eastern Cooperative Oncology Group [ECOG] performance status). Another phase III study including 104 patients found that the combination treatment of MA, L-carnitine, celecoxib and antioxidants (alpha lipoic acid and carboxycysteine) was superior to MA alone and improved muscle mass, resting energy expenditure (REE), fatigue and QoL at endpoint after four months (8). However, a later phase III study, did not find added benefit on muscle mass or physical function when adding MA to an intervention including L-carnitine and celecoxib (42). In the two previous mentioned studies all patients received polyphenols, alpha lipoic acid, carbocysteine and vitamins A, C and E (42, 43).

A multimodal pilot study in 22 patients with advanced cancer aiming to determine maximum tolerable dose of fish oil, combined fish oil capsules (total of 6 gram) with celecoxib or fish oil plus placebo (7). All included patients received oral food supplementation. Both groups had improved appetite, fatigue and C-reactive protein (CRP) levels six weeks from baseline, but the combination treatment provided

greater effects on CRP, muscle strength and body weight (7). Another combination regimen randomised 108 patient with cancer that were losing weight and reported increased body weight, REE and exercise capacity (maximal power on a treadmill) when patients were treated with erythropoietin (EPO) in addition to indomethacin (44).

In summary, when examining studies investigating combinations of pharmacological intervention, it is obvious that the data is very heterogeneous considering design, interventions and results, and rarely high quality RCTs have been performed to validate the conclusions from studies with promising results. Therefore, it is not possible to draw conclusions about optimal combinations of pharmacological interventions to improve body weight and physical performance.

Combination of nutrition and exercise

A few studies combining exercise and nutrition have been conducted. One feasibility study randomised 41 patients with head and neck cancer undergoing radiochemotherapy to either standard oncological treatment or a program consisting of 12 supervised sessions of 30 minutes resistance training in combination with a minimum of one milk-based nutritional drink daily (45). Both arms lost both weight and muscle mass, but statistically significant loss on within-group level was reported only in the control arm (45). It is worth mentioning that 50% of the patients received nasogastric tube feeding in both arms during radiotherapy, which might influence the lack of significant effect on muscle mass in favour of the treatment arm (45). Another feasibility study included 30 patients with head and neck cancer and prescribed identical progressive resistance exercises (30 session during 12 weeks) to both arms. Patients in the experimental arm received 5 g carnitine and 30 g protein before each training session in addition to seven days' pre-training supplementation (46). There were no statistically significant differences between the arms on any outcomes. Patients in both arms increased in body weight, muscle mass, muscle strength, sit-to-stand and stair climb performance testing and compliance were high in both arms (>90%) (46).

In palliative cancer populations, one study included 58 patients with advanced gastrointestinal or lung cancer and randomized patients to either individual nutritional counselling (e.g. use enrichments of

foods, energy and protein-rich snacks or ONS) plus supervised resistance exercise twice a week or usual care. There were no differences in QoL, body weight or performance testing between the arms (47). Patients in both arms increased in body weight and improved on all performance tests with a greater improvement in the intervention arm without reaching the level of statistical significance. Energy and protein intake was assessed by three-day food diaries and had at 12 weeks increased in the intervention arm and decreased in the control arm. A statistically significant difference was observed only for protein intake in favour of the intervention arm, but the clinical relevance of this difference (about 8 grams) is questionable as the intake at baseline was already quite high (81 grams) in the whole population (47). This study was closed prematurely due to slow accrual. A high number (63%) of eligible patients refused to participate, but patients included were considered to have good adherence to the programme (47). A single–arm feasibility and safety study in 30 elderly cancer patients consisted of an 8 week low-intensity resistance training programme,counselling to promote increased physical activity, dietary counselling and a daily nutritional supplement (139 kcal/125 gram/2500mg branched-chain amino acids/L-carnitine 50 mg) (48). A maintenance of muscle mass, caloric intake and physical function were observed (48).

In summary, studies investigating combination of nutrition and exercise are very small, and several aimed at investigating feasibility and not effect on clinical outcomes. This might be a reason for the lack of reaching statistically significant results, even though several studies show a trend towards improved effect when the interventions are combined. The studies also demonstrate the importance of control groups in clinical trials, as some studies show improvement in both arms indicating that also other factors than the studied intervention can have impact on weight and physical function. Compliance with nutrition and exercise interventions was acceptable in all studies with few dropouts.

Combination of nutrition and pharmacological agents

Two RCTs by the same research group have been conducted exploring effects of interventions combining individual nutrition support with pharmacological agents given on a patient-by-patient basis (49, 50). In one study with 309 patients with progressive cachexia, all patients in both arms were given 50 mg indomethacin daily and EPO only when haemoglobin levels were low. The intervention

arm received in addition individual nutrition support when needed by counselling, ONS when food intake decreased <90% of needs or, if intake decreased to 70-80% of expected needs, parenteral nutrition (PN) (49). Patients were followed until death and about 50% of patients in the intervention arm received PN. Intention-to-treat analysis revealed statistically significant differences only in food intake and energy balance over time in favour of the nutritionally supported arm. No effects on body weight, muscle mass, fat mas, performance tests or survival were observed (49). Twenty-six control patients received nutritional support during follow-up and were thus excluded from the per-protocol analysis, which demonstrated improved survival, fat mass and maximum exercise capacity, but no effects on lean body mass (49). A later RCT in 138 patients with advanced gastrointestinal malignancy presented that adding insulin to a standard treatment of 1) indomethacin (if they had increased inflammation markers), 2) EPO (if haemoglobin were low) and 3) nutritional support (counseling, ONS or PN) (49), significantly stimulated carbohydrate intake and increased body fat and improved survival (median 181 days versus 128 days), but did not result in a difference over time in physical activity, energy and protein intake, body weight, QoL or fat-free mass (50).

In summary, two RCTs investigating slightly different interventions targeting cachexia with the mainly use of 'as needed' nutrition and pharmacological interventions (targeting inflammation, low haemoglobin and glucose metabolism) has been undertaken by the same research group. In one study, nutrition was added and in the other insulin, the studies demonstrated no effect on weight and physical activity, but both showed increased survival and fat mass (by as-treated analysis in one study) in favor of the intervention arm. Unfortunately, these results have not been confirmed by other studies, and some of the drugs (indomethacin) are no longer available.

Combination of nutrition, exercise and pharmacological agents

To our knowledge, only one RCT is so far published where a combination of nutrition (including pharmaconutrients), exercise and a pharmacological agent is tested. This was a phase II feasibility study testing a six week multimodal intervention combining celecoxib, nutritional advice, two cans of n-3 PUFA enriched ONS daily, aerobic exercise 30 minutes twice per week and resistance exercise targeting major muscle groups three times weekly (51). Forty-six patients with lung and pancreatic

cancer commencing chemotherapy was randomised to either multimodal treatment or standard care. Compliance to the individual components of the intervention was 76% for celecoxib, 60% for exercise, and 48% for ONS. The multimodal intervention resulted in a stabilization of body weight, whilst patients who did receive standard care lost weight (51). A phase III study following this trial is ongoing (52).

One non-randomized study included 15 patients with lung cancer and explored the effect of combining medroxyprogesterone, celecoxib, ONS, initiation and/or maintenance of a regular exercise program (type not specified) and provision of psychological/psychiatric assistance (53). No cancer treatment was given for four weeks before or during the six-week intervention. Thirteen of 15 patients were weight stable or gained weight, and improvements in caloric intake, nausea, fatigue, performance status and appetite were reported (53). However, only 20% of the patients followed the advice of daily exercise in this very small single arm study (53).

In summary, as of today more evidence for optimal multimodal treatment including nutrition, exercise and pharmacological interventions is needed. However, such complicated study interventions are feasible, even in patients with advanced cancer.

Experiences from programmes combining nutrition, exercise and pharmacological interventions

Grounded in the reasonable clinical rationale, several centres have established multimodal nutrition and exercise cachexia treatment programs as part of standard cancer care (54-57), even though major RCTs demonstrating reliable clinical effects are lacking. Some effects on improvement of symptoms such as appetite and body weight have been observed (57), and patients improving weight or physical function have also been described more likely to improve QoL (55, 56). Unfortunately, the nutrition and exercise interventions given in these programs are often not thoroughly described, and the attrition rate at follow-up visits introduces bias and concern considering which patients that choose to come back to clinical appointments/evaluations. This is exemplified by a prospective study that evaluated a 10-12-week interdisciplinary outpatient programme for patients with advanced cancer. This

programme aimed to teach and empower patients into physical self-care and symptom management with the assistance of various specialists (physician, nurse specialist, clinical dietitian, physical therapist, occupational therapist, and if needed, a psychologist and a social worker) (54). Out of 181 included patients, 131 completed the programme. Only a quarter of the patients included had poor nutritional status at inclusion and poor nutritional status and/or CRP >20 mg/L increased the risk of not completing the programme. For patients completing, 77% maintained or increased body weight, physical performance and improved alterations in smell and taste (54).

Taken together, programmes including multimodal treatment show a potential benefit that needs to be evaluated in RCTs. Challenges of adherence to a complex intervention if the patients had more advanced cachexia, emphasize the importance of early intervention.

Practical approach when combining exercise and nutrition in patients with risk of losing weight

Fundamental to any approach in patients with cancer is to have a thorough understanding of the patient's cancer disease, his/hers expected survival and duration and consequences of tumour directed treatment. Further, it is imperative that all patients receive optimal symptom assessment and treatment, so that symptoms such as pain, nausea or depression does not influence patients' physical activity or nutritional intake. To improve or stabilise nutritional status and physical function, it is important to detect the decline before the losses have become too severe, as it probably is more feasible to counteract decline early in the disease trajectory (3, 15). In patients with longer expected survival, as well as for patients where cure is expected, both nutritional and exercise interventions are expected to have greater impact on patients QoL and physical function, and more comprehensive interventions should be prescribed.

ESPEN guidelines strongly recommend screening all cancer patients for risk of malnutrition, this also applies to patients with advanced cancer (15). Validated nutritional screening tools identify domains of starvation-related malnutrition (weight loss, BMI and dietary intake), but have shortcomings regarding important cachexia domains such as muscle mass, quantification of weight loss, inflammation, fatigue

and anorexia (14, 58). Further nutritional assessment is important to quantify nutritional intake and identify nutrition-related problems. Nutritional interventions should include advice to increase oral intake if patients are able to eat, a diet enriched with energy and protein is recommended to maintain or improve nutritional status (15). Additional use of ONS is advised when diet alone is not sufficient to reach nutritional goals, enriched with n-3 PUFAs could be preferred if available (15). Tube feeding or PN is indicated when intake is lower than 60% of requirements for more than 1-2 weeks or if enteral feeding is not feasible (e.g. compromised gastrointestinal function) (15). Artificial nutrition in patients with advanced cancer and loss of appetite should be carefully considered with regards to prognosis and expected benefit on QoL and potentially survival.

Guidelines recommend resistance exercise in addition to aerobic exercise to maintain muscle mass and strength (15). Considering the beneficial effects of physical activity, it is equally important to monitor physical activity as nutritional status. Physical activity is well tolerated and safe at different stages of cancer. Cancer patients should avoid a sedentary lifestyle and be recommended to follow the guidelines for the general population which include supervised or home-based moderate-intensity aerobic training three sessions per week in addition to resistance exercise (15).

In addition to ensure adequate energy and protein intake and physical activity, multimodal treatment should ideally include pharmacological and pharmaconutritional treatment targeted at reversing the pathophysiologic mechanisms of cachexia development (Figure 2). However, as of yet there are no specific pharmacological interventions that can be recommended. Corticosteroids and MA are the drugs that most consistently have shown effect on appetite, but they convey a risk of side effects and have no or only little effect on weight and physical function (59, 60).

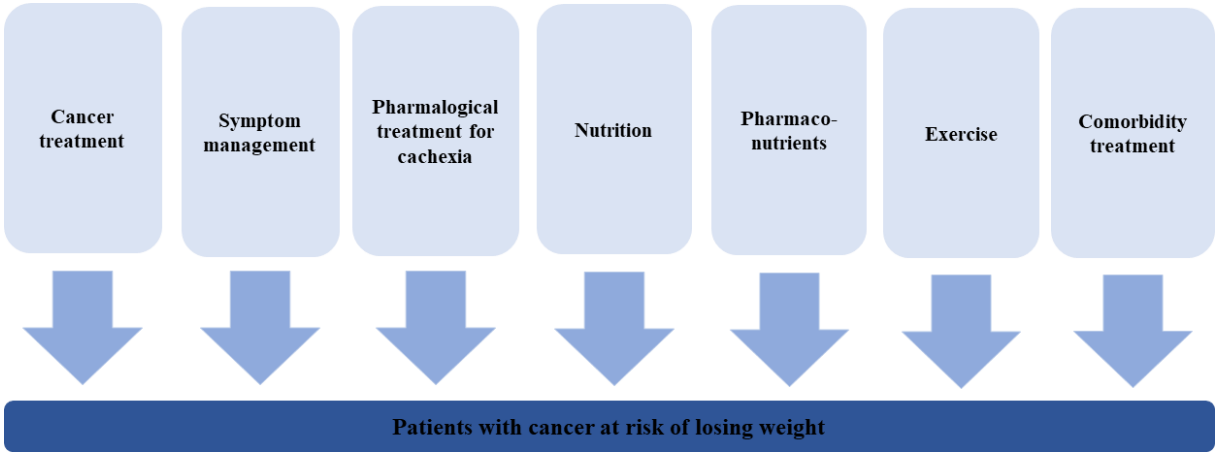

Figure 2. Multimodal interventions in patients with cancer at risk of losing weight

If the patient has short expected survival and has entered a refractory cachexia stage, interventions need to be focused on immediate symptom relief (3). In this phase of the disease, exercise and nutritional interventions will probably not be of major importance in improving performance status or QoL. Still, for many patients it is, even in this phase, important to keep up with daily routines as long as possible, and some find comfort in being helped to maintain a certain level of physical activity and to be served small quantities of food. However, it is important that the patient does not feel pressured to do so.

In this narrative review, we have focused on nutrition and exercise interventions as part of multimodal approaches in patients with cancer at risk of losing weight. We have selectively not included and discussed studies on weight reduction in cancer, post treatment rehabilitation programmes or post/pre surgery interventions (pre-nutrition, mobilization, "enhanced recovery after surgery" (ERAS) programmes). Discussing the effects of invasive artificial nutrition (tube feeding and PN) in advanced cancer we consider beyond the scope of this review.

Conclusion

As of today, studies investigating combinations of several interventions in patients with active cancer and risk of losing weight are too few and too heterogeneous to enable firm conclusions about effect, or even the optimal dose or timing. However, data presented in this review may indicate an overall

benefit, especially if interventions are started before weight loss and loss of function become too severe.

References

1. Vagnildhaug OM, Balstad TR, Almberg SS, Brunelli C, Knudsen AK, Kaasa S, et al. A cross-sectional study examining the prevalence of cachexia and areas of unmet need in patients with cancer. Support Care Cancer. 2018;26(6):1871-80.
2. Sun L, Quan XQ, Yu S. An Epidemiological Survey of Cachexia in Advanced Cancer Patients and Analysis on Its Diagnostic and Treatment Status. Nutr Cancer. 2015;67(7):1056-62.
3. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. The lancet oncology. 2011;12(5):489-95.
4. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer. 2008;44(8):1124-32.
5. Greig CA, Johns N, Gray C, MacDonald A, Stephens NA, Skipworth RJ, et al. Phase I/II trial of formoterol fumarate combined with megestrol acetate in cachectic patients with advanced malignancy. Support Care Cancer. 2014;22(5):1269-75.
6. McMillan DC, Wigmore SJ, Fearon KC, O'Gorman P, Wright CE, McArdle CS. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. Br J Cancer. 1999;79(3-4):495-500.
7. Cerchietti LC, Navigante AH, Castro MA. Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. Nutr Cancer. 2007;59(1):14-20.
8. Maccio A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecol Oncol. 2012;124(3):417-25.
9. Solheim TS, Laird BJ. Evidence base for multimodal therapy in cachexia. Current opinion in supportive and palliative care. 2012;6(4):424-31.
10. Balstad TR, Kaasa S, Solheim TS. Multimodal nutrition/anabolic therapy for wasting conditions. Current opinion in clinical nutrition and metabolic care. 2014;17(3):226-35.
11. Thorne F, Baldwin C. Multimodal interventions including nutrition in the prevention and management of disease-related malnutrition in adults: a systematic review of randomised control trials. Clin Nutr. 2014;33(3):375-84.
12. Stene GB, Helbostad JL, Balstad TR, Riphagen, II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment--a systematic review. Critical reviews in oncology/hematology. 2013;88(3):573-93.
13. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49-64.
14. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9.
15. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11-48.
16. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr. 2017;36(5):1187-96.
17. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.
18. Nasrah R, Kanbalian M, Van Der Borch C, Swinton N, Wing S, Jagoe RT. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. Clin Nutr. 2018;37(1):235-41.

19. Vazeille C, Jouinot A, Durand JP, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr. 2017;105(5):1139-47.
20. de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. Ann Oncol. 2018;29(5):1141-53.
21. Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, 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(5):431-40.
22. Balstad TR, Solheim TS, Strasser F, Kaasa S, Bye A. Dietary treatment of weight loss in patients with advanced cancer and cachexia: a systematic literature review. Critical reviews in oncology/hematology. 2014;91(2):210-21.
23. van der Werf A, Blauwhoff-Buskermolen S, Langius JA, Berkhof J, Verheul HM, de van der Schueren MA. The effect of individualized nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy: a randomized controlled trial protocol. BMC Cancer. 2015;15:98.
24. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(5):371-85.
25. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A Systematic Review of Exercise Systematic Reviews in the Cancer Literature (2005-2017). PM R. 2017;9(9S2):S347-S84.
26. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. The Cochrane database of systematic reviews. 2018;9:CD010192.
27. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvao DA, Cavalheri V. Exercise training for advanced lung cancer. The Cochrane database of systematic reviews. 2019;2:CD012685.
28. Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. The Cochrane database of systematic reviews. 2017;6:CD012020.
29. Sommer MS, Staerkind MEB, Christensen J, Vibe-Petersen J, Larsen KR, Holst Pedersen J, et al. Effect of postsurgical rehabilitation programmes in patients operated for lung cancer: A systematic review and meta-analysis. J Rehabil Med. 2018;50(3):236-45.
30. Wiskemann J, Clauss D, Tjaden C, Hackert T, Schneider L, Ulrich CM, et al. Progressive Resistance Training to Impact Physical Fitness and Body Weight in Pancreatic Cancer Patients: A Randomized Controlled Trial. Pancreas. 2019;48(2):257-66.
31. Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, et al. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist. 2011;16(11):1649-57.
32. Oberoi S, Robinson PD, Cataudella D, Culos-Reed SN, Davis H, Duong N, et al. Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis of randomized trials. Critical reviews in oncology/hematology. 2018;122:52-9.
33. Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck-de Leeuw IM, Courneya KS, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2018;52(8):505-13.

34. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A systematic review. Prev Med. 2017;104:124-32.
35. Adamsen L, Quist M, Andersen C, Moller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. Bmj. 2009;339:b3410.
36. Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Support Care Cancer. 2018;26(2):615-24.
37. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. Med Sci Sports Exerc. 2013;45(11):2080-90.
38. Cheema BS, Kilbreath SL, Fahey PP, Delaney GP, Atlantis E. Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;148(2):249-68.
39. Jatoi A, Rowland K, Loprinzi CL, Sloan JA, Dakhil SR, MacDonald N, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. J Clin Oncol. 2004;22(12):2469-76.
40. Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol. 2002;20(2):567-73.
41. Mantovani G, Maccio A, Madeddu C, Serpe R, Massa E, Dessi M, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. Oncologist. 2010;15(2):200-11.
42. Madeddu C, Dessi M, Panzone F, Serpe R, Antoni G, Cau MC, et al. Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib +/- megestrol acetate for patients with cancer-related anorexia/cachexia syndrome. Clin Nutr. 2012;31(2):176-82.
43. Mantovani G. Randomised phase III clinical trial of 5 different arms of treatment on 332 patients with cancer cachexia. Eur Rev Med Pharmacol Sci. 2010;14(4):292-301.
44. Daneryd P, Svanberg E, Korner U, Lindholm E, Sandstrom R, Brevinge H, et al. Protection of metabolic and exercise capacity in unselected weight-losing cancer patients following treatment with recombinant erythropoietin: a randomized prospective study. Cancer Res. 1998;58(23):5374-9.
45. Sandmael JA, Bye A, Solheim TS, Stene GB, Thorsen L, Kaasa S, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: A pilot randomized trial. Cancer. 2017;123(22):4440-8.
46. Lonbro S, Dalgas U, Primdahl H, Overgaard J, Overgaard K. Feasibility and efficacy of progressive resistance training and dietary supplements in radiotherapy treated head and neck cancer patients--the DAHANCA 25A study. Acta oncologica (Stockholm, Sweden). 2013;52(2):310-8.
47. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, et al. Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial. Clin Nutr. 2018;37(4):1202-9.
48. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle. 2018.
49. Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with

malignant disease: Effects on survival, metabolism, and function. Cancer. 2004;100(9):1967-77.
50. Lundholm K, Korner U, Gunnebo L, Sixt-Ammilon P, Fouladiun M, Daneryd P, et al. Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. Clin Cancer Res. 2007;13(9):2699-706.
51. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(5):778-88.
52. Solheim TS, Laird BJA, Balstad TR, Bye A, Stene G, Baracos V, et al. Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. BMJ Support Palliat Care. 2018;8(3):258-65.
53. Cerchietti LC, Navigante AH, Peluffo GD, Diament MJ, Stillitani I, Klein SA, et al. Effects of celecoxib, medroxyprogesterone, and dietary intervention on systemic syndromes in patients with advanced lung adenocarcinoma: a pilot study. J Pain Symptom Manage. 2004;27(1):85-95.
54. Gagnon B, Murphy J, Eades M, Lemoignan J, Jelowicki M, Carney S, et al. A prospective evaluation of an interdisciplinary nutrition-rehabilitation program for patients with advanced cancer. Current oncology. 2013;20(6):310-8.
55. Parmar MP, Swanson T, Jagoe RT. Weight changes correlate with alterations in subjective physical function in advanced cancer patients referred to a specialized nutrition and rehabilitation team. Support Care Cancer. 2013;21(7):2049-57.
56. Parmar MP, Vanderbyl BL, Kanbalian M, Windholz TY, Tran AT, Jagoe RT. A multidisciplinary rehabilitation programme for cancer cachexia improves quality of life. BMJ Support Palliat Care. 2017;7(4):441-9.
57. Del Fabbro E, Hui D, Dalal S, Dev R, Nooruddin ZI, Bruera E. Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. J Palliat Med. 2011;14(9):1004-8.
58. Healy E, Yaxley A, Isenring E, Bannerman E, Miller M. Ability of existing Malnutrition Screening Tools to identify risk of starvation, sarcopenia and cachexia: A systematic review. e-SPEN Journal. 2014;9(3):e109-e22.
59. Ruiz-Garcia V, Lopez-Briz E, Carbonell-Sanchis R, Bort-Marti S, Gonzalvez-Perales JL. Megestrol acetate for cachexia-anorexia syndrome. A systematic review. J Cachexia Sarcopenia Muscle. 2018;9(3):444-52.
60. Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol. 2005;23(33):8500-11.