Faculty of Health Sciences UiT the Arctic University of Norway

Individualized dietary counseling on nutritional status in head and neck cancer patients undergoing radiotherapy: A systematic review

Ida Karen Lyhne Rasmussen

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Supervisor:

Professor Rigmor Berg

Department of Community Medicine. UiT-The Arctic University of Norway

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ABSTRACT

Individualized dietary counseling given with or without oral nutritional supplements, on the outcome of nutritional status, in head and neck cancer patients undergoing radiotherapy, compared to standard routine clinical care, with or without other nutritional interventions: A systematic review.

Background: Malnutrition and unintentional weight loss is common in patients with head and neck cancer. Malnutrition is a serious risk factor for morbidities, mortality, and heavily increased health care costs.

Nutritional interventions available today include individualized dietary counseling by a registered dietitian (RD), use of oral nutritional supplements, and the application of nutritional support by enteral tube feeding, and parenteral intravenous nutrition. Emerging research suggests that nutritional interventions may be helpful in decreasing unintended weight loss and malnutrition, reversing malnutrition and reducing its devastating consequences, but groups of experts recommend more research to draw firm conclusions about these effects.

Individualized regular dietary counseling by an RD throughout radiotherapy cancer treatment is not a standard treatment provided for head and neck cancer patients today. Rather, doctors may refer patients to an RD once malnutrition is already determined. Studies have shown effect of dietary counseling by an RD as one important nutritional intervention for patients at risk of malnutrition. More research is needed in order to ascertain the harms and benefits of making the intervention available to patients at risk of malnutrition and to patients with head and neck cancer undergoing radiotherapy, on a regular basis.

Objectives: To determine the effects of individualized dietary counseling by an RD, given with or without the use of oral nutritional supplements, on nutritional status, in adult patients with a diagnosis of head and neck cancer, who are, or will be undergoing radiotherapy treatment.

Methodology: This is a systematic review of randomized controlled trials (RCTs). It was conducted in accordance with the steps in The Cochrane Handbook of Systematic Reviews for Interventions 5th Edition.

The population was both genders ≥19 years with a medical diagnosis of cancer of the head and neck who underwent radiotherapy cancer treatment with the intervention of one or more individualized dietary counseling sessions performed by an RD, given with or without the use of oral nutritional supplements. The comparator was standard routine clinical care with no individualized dietary counseling, with or without other nutritional interventions. The primary outcome was nutritional status measured by changes in weight and/or measured by changes in caloric intake. Secondary outcomes were quality of life, physical fitness, hospital readmissions, and mortality. Searches were technically performed by a skilled librarian in the following databases: MEDLINE (OVID), EMBASE (OVID), Cochrane Library (CENTRAL) (Wiley), CINAHL (EBSCO), Web of Science Core Collection (SCI-EXPANDED & SSCI) (Clarivate). Relevant data was extracted onto an excel sheet, and a narrative summary was constructed in a word document. Studies' risk of bias (RoB) was performed for every included RCT in accordance with criteria of Cochrane. The Review Manager 5.4.1 (Revman 2020) tool, was used to generate forest plots for displaying results of two of the outcome measures, though not pooling results in meta-analysis, and tables displaying results for two outcome measures. A narrative summary grading of recommendations assessment, development, and evaluation (GRADE) assessment was performed to assess the certainty of the evidence.

Results: The database searches resulted in 969 studies after deletion of duplicates, the screening-process, full-text reading, and selection of studies that met inclusion criteria finally resulted in 3 studies presented in 4 articles. Three RCTs presented in four articles met the inclusion criteria for this systematic review, (n = 146 participants). The three RCTs were conducted in high income countries. The nutritional intervention for all three RCTs was dietary counseling by an RD where two of the studies included the use of oral nutritional supplements if this was deemed appropriate for participants, while one study only gave dietary counseling of ordinary foods without the use of oral nutritional supplements. Follow-up time for all included RCTs was 12 weeks, two studies gave nine dietary counseling sessions and one study gave seven sessions. Only two participants from the control group of one of the studies were given tube feeding due to rapid deterioration in nutritional status during the study period. All the three RCTs were assessed as having high risk of bias. All three studies measured outcomes on changes in weight, two studies measured outcomes on changes in energy intake, quality of life and physical function. None of the included studies measured mortality and hospital

readmission. Results were not statistically pooled for any of the outcome measures due to insufficient data reporting. Further, meta-analyses were deemed inappropriate due to the studies' high risk of bias which could further produce erroneous pooled results. All results favored dietary counseling given with or without oral nutritional supplements, although the effect estimates greatly differed. Results of the included studies suggest, with low and very low quality of evidence, that dietary counseling given with or without the use of oral nutritional supplements, may improve nutritional status in patients with head and neck cancer undergoing radiotherapy compared to standard clinical care with or without other nutritional interventions.

Author's conclusions: From this systematic review, evidence of low and very low quality suggests that dietary counseling during radiotherapy for head and neck cancer patients, given with or without oral nutritional supplements may improve weight, energy intake, quality of life and physical function. Adequately powered RCTs, performed with pristine methodology ensuring appropriate blinding, and even multi-center studies are required to evaluate these effects in the future.

Key words: Registered dietitian, individualized dietary counseling, head and neck cancer, radiotherapy, nutritional status, oral nutritional supplements, disease-related malnutrition.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DRM	Disease Related Malnutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
GLIM	Global Leadership Initiative on Malnutrition
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HNC	Head and Neck Cancer
ICD-10	International Classification of Disease
MD	Mean Difference
NIPH	Norwegian Institute of Public Health
Non-RCTs	Non-Randomized Controlled Trials
PICO	Population, Intervention, Comparator, Outcome
PG-SGA	Patient generated – Subjective Global Assessment
RCT	Randomized Clinical Trial
RD	Registered Dietitian
RoB	Risk of Bias
RR	Risk Ratio
SoF	Summary of Findings

CHAPTER 1: INTRODUCTION

1.1 Background

In March of 2015, the title of an online newspaper article published in Norway reported: "73-year old lost 21 kilos while in hospital, and died shortly after" (1). His son had contacted the local newspaper to tell his story of what he thought to be a failure on the part of hospital staff to identify serious medical issues that may have led to his father's death. After undergoing hip-surgery on March 8th of 2013, the man consumed a regular hospital-dinner that resulted in severe pneumonia, an inflammation of the lungs. How could this have happened and why?

The patient's medical history is confidential so one can only speculate as to what happened in this situation, but, according to the article, the patient had a swallowing impairment that went undetected by hospital staff. The difficulties swallowing led to an aspiration to the lungs whereby bits of food end up in the lungs causing an inflammatory response named *aspiration pneumonia* (2). Swallowing impairment, also named *dysphagia* is a medical diagnosis; a neurological impairment of the muscles of the throat responsible for coordinating the swallowing process (3). Various degrees of dysphagia is a common clinical and elusive condition invisible to the eye where the muscles of the throat are weakened and in more progressed states cannot coordinate properly to ensure the protection of the airways during the swallowing process. In this case, dysphagia was likely a permanent consequence of a stroke the 73-year old man had endured (4). Some degree of dysphagia in the elderly is normal and a result of natural aging. Degenerative neurological diseases and cerebral strokes may affect the brain, and can result in more severe swallowing difficulties due to individual degrees of permanent destruction of the neurological pathways that control the muscles of the swallowing process (4). A consequence of severe dysphagia can lead to foods and fluids ending up in the lungs, causing either aspiration pneumonia or even death due to asphyxiation (5). A person with severe dysphagia is commonly afraid and cautious when eating and drinking. Choking, gaging, and coughing are common during eating and drinking in dysphasic patients and coughing is a reflex that serves to regurgitate foods that are entering the airways (6). The core of the allegation made by the patient's son, was the failure of hospital staff to identify the patient's inability to eat safely and sufficiently, leading to aspiration pneumonia and severe unintended weight loss. According to the article, the failure of hospital staff to identify these issues during the patient's 5-week hospital stay led to a fatal state of *disease-related malnutrition* (DRM) (7, 8). DRM is

the medical issue of this thesis and will be described in the next section 1.2 of the introduction of this thesis.

The pneumonia was diagnosed and treated, but there is no mention of any intervention of the patient's swallowing and nutritional difficulties. The necessary medical intervention for dysphagia would be a multidisciplinary approach and texture modification of foods and drinks (9-13). Texture modification makes it to a degree safer and easier for the patient to swallow foods and fluids, as soft foods and thickened fluids glide easier and slower into the esophagus thereby helping protect the airways. An important member of the multidisciplinary team in hospitals is a *registered dietitian* (RD). On referral by a doctor, an RD provides medical treatment in the form of a thorough nutritional assessment for the identification of the patient's individual nutritional needs and problem areas, and in the form of evidence based *dietary counseling* helping the patient aiming at meeting nutritional needs in the light of dysphagia and unintended weight loss (14-16). Though posing ethical issues, if a patient's swallowing ability is of such a degree that texture modified foods and fluids are no longer safe due to danger of asphyxiation and aspiration, a feeding tube may be inserted for tube-feeding to ensure nutritional needs are met (17-20).

According to the article, the patient died in June of 2013 due to DRM weighing 49 kg, after allegedly rapidly losing 21 kg. Cause of death will only be known by medical records, but the article suggests the cause of death was in fact due to DRM. This is, unfortunately not an unusual medical case in affluent western countries.

1.2 Description of the condition

Essential nutrients ensure the maintenance and functioning of organs such as the brain, skeleton, heart, kidneys, liver, muscles, and the skin, as well as optimal healthy development in infants and children. In a state of malnutrition, it is the breakdown of fat-free mass that poses a threat to a person's health (21). Nordic countries have nutritional guidelines for the general population giving specific recommendations of daily intake of all nutrients according to age (22).

Malnutrition may happen due to poverty and social issues where there is a lack of access to foods also referred to as starvation-related malnutrition (23, 24). The medical issue of this systematic review is malnutrition due to acute and chronic disease, referred to as disease-

related-malnutrition. Medical issues almost always affect a patient's ability to either shop, cook, and/or eat, leading to unintentional weight loss and disease-related malnutrition (DRM) (8, 25-29). In affluent western countries, DRM is a very common complication of chronic and acute illness and studies have shown that between 10 – 60% of patients admitted to hospitals in Norway are malnourished on admission depending on patient population (26). DRM commonly worsens unless identified and interventions implemented in order to aim for its prevention and minimization (25, 30, 31).

Clinical research has many times disclosed the devastating consequences of DRM (25, 31-37). Fat-free body mass, also known as lean body mass refers to skeletal muscle mass and vital organs (38). It is the breakdown of these functional tissues that affect normal bodily functions and increases the risk of other illnesses, complications, and premature death. Some diseases can potentially markedly increase the body's need for nutrients and calories due to metabolic changes further complicating this issue by increasing inflammatory responses created by the primary disease (25, 39-41). DRM leads to increased medical issues, complication rates, infection rates, reduced effects of medical treatments and surgeries, increased lengths of hospital stay, increased and frequent readmissions to hospital, increased amount of in-hospital deaths, and generally an increased rate of complications, morbidity, mortality, reduced quality of life, and huge economic costs for society and for the healthcare systems (42, 43).

DRM is categorized in the ICD-10 code system as a medical diagnosis (7, 26). The most commonly used ICD-10 diagnosis codes for malnutrition used in Norwegian hospitals are: E46 (risk of malnutrition), E44 (mild to moderate malnutrition), and E43 (severe malnutrition) (26, 44). The diagnosis E46 is given to patients who are screened to be at risk of DRM where intervention is required as a preventative measure to minimize DRM.

Validated malnutrition screening tools are medical tools for diagnosing DRM and risk of DRM (45-49). All patients must be screened on admission to hospital and regularly every week thereafter while an in-patient (26). DRM is not obvious to the naked eye unless severe, and overweight patients and patients at risk may go undetected if not screened (50). Screening for malnutrition and a thorough nutritional assessment is one way to aim to identify patients. Another way is the use of anthropometric measurements such as mid-arm muscle circumference measurement in the assessment of nutritional status (51, 52). A report published in 2019 by The

Global Leadership Initiative on Malnutrition (GLIM) (8), focuses on the consensus that the global nutrition community has reached of core diagnostic criteria that may be relevant: three of which are physical consequences; *low BMI*, *unintentional weight-loss*, *loss of skeletal muscle mass*, and two of which are causal; *reduced absorption of nutrients*, *reduced nutritional intake*, and *metabolic- and other consequences of disease*. One distinguishes between malnutrition with the presence of inflammatory responses caused by metabolic changes and malnutrition without the presence of inflammation. One causal and one consequential criteria is proposed to be sufficient for the diagnosis of DRM, according to the GLIM community (8).

It is well known that radiotherapy-induced toxicity leads to oral morbidities as part of the side effects of radiotherapy treatment such as dry mouth (xerostomia), distortion of the sense of taste (dysgeusia), painful swallowing (odynopgagia), and swallowing difficulties (dysphagia), as well as the tumor and potential surgeries (53) (54). All patients with a diagnosis of head and neck cancer who undergo radiotherapy qualify for an ICD-10 diagnosis of E46 (at risk of malnutrition). It is therefore reasonable to aim for medical treatment in the form of nutritional interventions to prevent consequences of potential DRM and ensure maximization of radiotherapy treatment.

The clinical guidelines provided by the European Society for Clinical Nutrition and Metabolism (ESPEN), are used by clinicians who specialize in medical nutrition therapy, although not all clinicians are aware of these guidelines. A survey conducted in Scandinavia in 2004 by Fjeldstad et al., (55) disclosed the lack of competence, nutritional care, and nutritional practice among doctors and nurses, especially in Norway. A new survey by the same authors 10 years later, revealed that routines in nutritional practice had significantly improved, much due to the evolvement of the Norwegian national clinical guidelines that are paramount for the success of this work (26, 55).

The ESPEN guidelines are disease-specific, and the ESPEN expert group recommendations for action against cancer-related- malnutrition of 2017 (56, 57), report that DRM in patients with a cancer diagnosis range from 20% to more than 70% from globally conducted studies according to type and stage of cancer. According to ESPEN, patients with abdominal cancer and cancer of the head and neck, are at even higher risk of DRM, and with higher age and more advanced stage of cancer, the risk increases even further (56). ESPEN points out that studies remain

inconclusive in proving the true effects of oral nutrition interventions for patients with a cancer diagnosis, which may likely be because cancer is a disease with individual complexities in its pathophysiological pathways, proving the need for individualized nutritional treatment strategies for each individual patient (58).

1.3 Description of the intervention

DRM has its own ICD-10 medical diagnosis codes (59). Medical nutritional interventions implemented with the aim to reduce and treat DRM are categorized as *medical treatment* and are usually provided by a clinical multidisciplinary team and the medical doctor in charge, and is individualized according to the patient's needs (60, 61). Every decision made in Medicine, will always be based on risk versus benefit, and the benefits must outweigh the risks for it to be ethically sound. Making decisions as to which nutritional intervention is the one that will benefit the patient, must be evaluated in each case, although research should always support these decisions in order to avoid harms as far as possible.

Medical nutrition therapy is an independent empirical science characterized as an applied science with a multidisciplinary approach (60). It is a young and new science with an epistemological basis of its own, and has proved some of its efficacy and cost effectiveness already (43, 62-66). Medical nutrition therapy has multiple disease-specific guidelines worldwide (67) (68), its own clinical terminology (69), and its own ethical code of professional conduct (69), in addition to frameworks such as The Nutrition Care Process for its clinical application (70). Nutritional assessments and interventions must be legally documented in the patient's medical records as interdisciplinary communication and documentation with the aim to help secure the treatment process in both primary and secondary care (71).

Medical nutrition therapy consists of different possible treatment regimens with regard to DRM (72). This includes the use of ready to drink formulas, some of them nutritionally complete, named *oral nutrition supplements* (73, 74), and *tube-feeding* often referred to as Enteral Nutrition which involves a feeding tube inserted into the patient's gastrointestinal tract to supply the patient with nutritionally complete formulas (75, 76). Another treatment regimen is *intravenous nutrition,* often referred to as Parenteral Nutrition, which means that nutrition is supplied intravenously and thereby bypassing the digestive system (77). Last but not least, *dietary counseling* by an RD aims to counsel the patient on individualized meal plans with the

aim of meeting the patient's daily nutritional needs. This entails advising the patients on good eating habits with high-protein and high-energy foods, which means meals that are smaller but have a higher energy and protein density. Dietary counseling is an intervention which is considered medical treatment (78-82). An RD is a clinical professional who, on referral from a doctor, is trained and certified to patient-centered assess, diet counsel, and legally document the entire range of medical nutrition therapies to patients who have received a diagnosis of one or more medical disorders that require nutritional interventions (83, 84). Dietary counseling for cancer-related DRM should focus on the degree of decreased appetite (anorexia), nausea, swallowing difficulties (dysphagia), abdominal issues such as diarrhea, constipation, bloating according to ESPEN. And in patients with head and neck cancer, dietary counseling also focuses on the radiotherapy-oral-induced-morbidities (53).

1.4 How the intervention might work

Dietary counseling is a frequently used treatment as primary management of many diseases where changes in eating habits can reduce negative clinical outcomes (85, 86). An RD has the scientific knowledge of the nutritional needs in health and illness according to age and diagnosis of the patient, based on individualized assessments and clinical evidence based guidelines (95). Studies have already provided some evidence of treatment-success and cost-effectiveness of dietary counseling by an RD (87, 88). Dietary counseling by an RD is considered an important and appropriate form of nutritional treatment for patients with a diagnosis of head and neck cancer from point of diagnosis until they reach the rehabilitation stage of their cancer disease (89, 90). Nutritional management is considered a potentially life-saving part of the multidisciplinary treatment in head and neck cancer patients, and a few studies have shown improvement in clinical outcomes and survival in these patients (91, 92).

The use of oral nutritional supplements, is fairly widespread among patients who are at risk of DRM, or who are already malnourished. Oral nutritional supplements are energy and protein dense ready-to-drink industrial formulas with various flavors. They provide a lot of kilocalories, protein, and micronutrients as well as fluid in a small volume. In many ways, they are similar to the concept of formulas given in tube feedings, and produced by the same companies, but are drinks instead of formulas given in feeding tubes.

Since DRM is prevalent in head and neck cancer patients and the consequences of DRM are potentially severe both for patients and society as a whole, this non-invasive form of nutritional intervention consisting of dietary counseling by an RD to head and neck cancer patients could potentially save lives and increase survival time and quality of life, reduce hospital re-admissions and healthcare costs, and reduce complications associated with cancer and its treatments (25, 35, 63, 78, 93, 94).

If the effect of dietary counseling by an RD is proved effective in reducing loss of fat-free mass, reversing and preventing DRM to the degree possible in head and neck cancer patients throughout radiotherapy treatment, then individualized regular dietary counseling by an RD should be made available to head and neck cancer patients as routine clinical care. The pain, cost and unnecessary suffering could with this non-invasive patient-centered intervention easily be markedly reduced.

1.5 Why it is important to do this review

As a new and young applied science, medical nutrition therapy is a medical field that will continuously need to adapt, change and develop in accordance with best-practice and new changes in healthcare in the future (95). As an applied scientist in clinical settings, the RD has an ethical and professional responsibility to continuously abide by the latest evidence based knowledge in order to give patients the highest quality treatments available. Dietetics and medical nutrition therapy are emerging medical professions that require RDs and other nutritional workers to look ahead and be willing to make flexible changes, adapt to new technology, and finally yet importantly produce up-to date research to ensure delivery of the best evidence based practice to all patients. Clinical-work is hectic, and the need for evidence based knowledge is as crucial for the clinical RD as it is for other health professionals. A systematic review is considered the best way of synthesizing and summarizing available knowledge, and develop guidelines which help clinicians make better every day clinical decisions for patient care, treatment and prevention of disease and complications (96).

While a few systematic reviews have been published on the effectiveness of individualized dietary counseling by an RD (97-100), these all have different populations and control groups than the systematic review presented in this thesis. For example, one systematic review by

Baldwin et al. (79) included 26 studies with a total of 2123 participants on the outcome of the management of malnourished patients in a variety of disease populations.

The current review focuses only on patients with a diagnosis of head and neck cancer. This population may frequently endure obstructions by tumors, surgeries, effects of radiation, pain, and discomfort in the mouth and throat area contributing to a reduced capacity for eating and drinking (27, 101-105). It follows that head and neck cancer patients have an array of nutritional issues due to the disease and its treatment rendering them at high risk of DRM and negative outcomes (106-109). A prospective longitudinal observational study by Citak et al., (54), of 54 patients with head and neck cancer who underwent radiotherapy, showed that 90% of the patients were well nourished at baseline, but 74% of the patients were malnourished at the end of radiotherapy treatment ($p < 0.001$) with an unintended weight loss of 5% due to reduction in food intake. This study also showed an association between reduced nutritional status with reduced quality of life.

In order for policy makers to help ensure that the best treatment options are available for head and neck cancer patients who are undergoing radiotherapy, continuous research and development of up to date guidelines is crucial to help reduce morbidity, mortality, hospital readmissions, and costs as much as is at all possible.

To the best of our knowledge, no systematic review exists per date, on the effect of individualized dietary counseling by an RD given with or without the use of oral nutritional supplements, on nutritional status, in head and neck cancer patients undergoing radiotherapy, compared to usual clinical care with or without other nutritional interventions.

1.6 Review question

What is the effect on nutritional status, of regular individualized dietary counseling by an RD, given with or without the use of oral nutritional supplements, in patients with a diagnosis of head and neck cancer, who will, or are undergoing radiotherapy, compared with standard routine clinical care with or without other nutritional interventions?

1.7 Objective of this review

The objective of this review is to assess the effect of regular individualized dietary counseling by an RD, given with or without the use of oral nutritional supplements, on nutritional status in patients with head and neck cancer, undergoing radiotherapy.

CHAPTER 2: METHODOLOGY

We conducted a systematic review of individualized dietary counseling on nutritional status in patients with head and neck cancer undergoing radiotherapy. The main reviewer prepared a protocol for this study which was registered in PROSPERO (International Prospective Register of Systematic Reviews) 06.08.20 (Reference number: CRD42020203020). Unfortunately, the protocol is as of yet not published. According to information received from PROSPERO administrators 12.01.21, this is due to prioritization of Covid-19 registrations and internal delays due to the global pandemic (110).

The Cochrane handbook recommends that in order to reduce risk of bias, systematic reviews are conducted by two or more reviewers together (111). For the current review, two people collaborated with respect to the screening and selection of studies, data extraction, risk of bias assessment, and the assessment of the certainty of results. Although the pronoun ‘we’ is used in this thesis, it is important to stress that the master’s student is the main reviewer and the principal researcher who undertook the overwhelming majority of the work, made the final decisions, and wrote the protocol as well as this thesis.

2.1 Eligibility criteria

2.1.1 Study design

Randomized controlled trials (RCTs).

2.1.2 Population

Both genders, age ≥ 19 years with a diagnosis of head and neck cancer, diagnosed with either of these ICD-10 diagnosis codes by a certified oncologist: C00-C14, C30-32. Assessed to be nutritionally at risk by either criteria by European Society for Clinical Nutrition and Metabolism

(ESPEN) (112) or by a validated malnutrition risk screening tool (48, 113-115). The study population either underwent or would undergo radiotherapy as part of medical treatment for head and neck cancer. All ethnic and racial groups were eligible. In the event that a study sample had a mix of eligible and non-eligible patients, the studies were included if at least 50% of the patients met the inclusion criteria, or results were reported separately.

2.1.3 Intervention

A minimum of 30 minutes of individualized dietary counseling by a registered dietitian (RD), given with or without the use of oral nutritional supplements, with or without follow-up sessions. Only studies where the dietary counseling was carried out by an RD were included. In the event that too few studies met this criteria, studies where dietary counseling was carried out by other healthcare professionals would have been considered. Initially, studies where dietary counseling was carried out one-to-one were included, but in the event that too few studies met this criteria the inclusion of studies with group-counseling would have been considered.

2.1.4 Control group

Standard routine clinical care or nutrition talk by a nurse, no individualized dietary counseling by an RD, with or without other nutritional interventions.

2.1.5 Primary outcome

The primary outcome measure was nutritional status. Nutritional status measured as either:

- Body weight. Measured in kilograms (kg) or pounds (lb)
- Energy intake. Measured in kilocalories (kcal) or kilojoules (kj)

2.1.6 Secondary outcomes

- Quality of life
- Physical fitness
- Hospital readmissions
- Mortality

Quality of Life and physical function had to be analyzed using a validated and reliability tested instrument such as The Quality of Life Scale (QOLS) (116) and the mini physical performance test (117), or other validated tests.

All outcomes measured as a mean difference between the control group and the intervention group.

2.1.7 Other

Studies had to be published in 1987 or more recent. In the event a large number of studies were eligible for inclusion, the narrowing down of publications from 2010 up to date would be considered, as well as including only the most prevalent diagnosis of head and neck cancer as opposed to all diagnosis of head and neck cancer.

2.2 Search methods for identification of studies

The main search method was systematic searches in electronic literature databases. The search strategy was planned by the main author in collaboration with the supervisor and a skilled librarian. The searches in literature databases consisted of a combination of medical subject headings and text words related to the population and the intervention and were tailored for each database search.

The following databases were searched:

- MEDLINE (OVID)
- EMBASE (OVID)
- Cochrane Library (CENTRAL) (Wiley)
- CINAHL (EBSCO)
- Web of Science Core Collection (SCI-EXPANDED & SSCI) (Clarivate)

We searched the years 1987 to August 2020 and used neither filters for study design nor language. The year 1987 was selected because it was around this time that the international clinical nutrition community commenced more serious work on the development of criteria for diagnosis of DRM in clinical settings (118). The search strategies are included in Appendix 1.

After database searches, the main author manually checked Google Scholar, relevant websites, reference lists of related systematic reviews, and literature reviews to identify potential publications not available in databases. The main author also checked clinicaltrials.gov for potential ongoing studies.

2.3 Selection process

All records from the main search were imported into Endnote version X9, where duplicates were removed, and then into Rayyan (119). Endnote version X9 is a bibliography and reference manager to aid in the citations and archiving of all references for this thesis (120). Rayyan is a web-based tool that helps reviewers work more efficiently when screening abstracts and titles.

Two reviewers independently read and screened all titles and abstracts from the main searches based on the inclusion criteria. Thereafter, they read all relevant studies in full-text. The two reviewers discussed any uncertainties about the exclusion or inclusion of studies during the screening process, and resolved to either exclude or include the study. The flow diagram for studies selection is included in Appendix 2.

2.4 Assessment of methodological quality (Risk of bias assessment)

The revised tool for the assessment of risk of bias in randomized trials, RoB 2, was used by two reviewers in accordance with the Cochrane Handbook, independently and then jointly, reaching an overall risk of bias in the included studies (121).

Five domains were assessed for bias:

- Domain 1: Risk of bias arising from the randomization process
- Domain 2: Risk of bias due to deviations from the intended interventions
- Domain 3: Risk of bias due to missing outcome data
- Domain 4: Risk of bias due to measurement of the outcome
- Domain 5: Risk of bias in selection of the reported result

Results of each domain assessed for each study were categorized as either ‘Low Risk’, ‘Unclear Risk’, or ‘High Risk’ using Review Manager Software version 5.4.1 (RevMan 2020). According to the study protocol, risk of bias in included non-RCT studies would be assessed

using the Cochrane Effective Practice and Organization of Care (EPOC group) tool (122), but only RCT studies were included in this systematic review.

2.5 Extraction of data

The following data sections were collected from each of the included studies onto an excel sheet, then written and summarized narratively in a word document. The main author extracted the data, and a second person checked extracted data thoroughly. Lastly, discussion of any differences was done and agreement was reached as to its accuracy.

The following core data was extracted from the included studies:

- Title, authors, year of publication and other publication details
- Setting, hospital, department, country
- Study design and aim of the study
- Patient characteristics of treatment group
- Patient characteristics of comparator group
- Type of validated screening tool used to assess nutritional status
- Medical diagnosis of head and neck cancer
- Medical treatment (Radiotherapy)
- Intervention characteristics (individualized dietary counseling, by who, duration, no. of interventions, minutes, follow-ups, place and method of interventions, use of oral nutritional supplements or not)
- Comparator characteristics
- Outcome measures/results
- Primary outcome (Nutritional status, energy intake)
- Secondary outcomes (Quality of life, physical fitness, hospital readmissions, mortality)

2.6 Dealing with missing data

Authors in two of the included studies Ravasco et al., (123) and Isenring et al., (124) analyzed data on an intention-to-treat basis irrespective of reasons for loss to follow-up. The study by Isenring et al., (125), did not state any information about this. The study by Ravasco et al., (123), had no loss to follow-up. In the study by Isenring et al., (125) there was a percentage of loss to follow-up in the dietary counseled group of 7%, and 14% in the group that received

usual care and this study only reported results for the participants who completed the study. In the study by Isenring et al., (124), there was a 14% loss to follow-up in the dietary counseled group, and 6.5% loss to follow-up in the usual care control group. Where missing data were not stated in the published articles, the main author of this systematic review contacted the main researchers of the included studies but did not receive sufficient data, only some parts of the relevant missing data. Data of standard deviations for some of the results were missing.

2.7 Data Analysis

From each included study, data for each outcome measure was summarized and presented narratively in text and tables for comparison. According to the study protocol, calculations of effect sizes for continuous data would be calculated by using the group post-test means and standard deviations. When possible, these effect sizes would be expressed as mean differences (MD) and 95% confidence intervals (CI). The calculation of the standard estimation of the risk ratio (RR) and its 95% CI would be performed for the binary outcomes reported in the included studies.

The Review Manager Software version 5.4.1 (RevMan 2020) was used to produce forest plots to display the results of two of the outcome measures, and tables displayed the remaining two outcome measures. There were no deaths or hospital readmissions reported in any of the included articles, therefore there was no data for evaluating if calculations of dichotomous data was appropriate, or for the display of results. If different scales were used to measure the same outcome, standardized mean differences (SMD) with corresponding 95% CI would have been calculated. Due to missing data, and to results being of low quality, meta-analysis were not performed of measure outcomes in this systematic review. Instead, results were synthesized narratively where subjective measures were used rather than statistical measures. This encompasses the direction of the effect measure, the size of the effect measure, the consistency across studies, and the strength and certainty of the evidence for the effect measure.

The certainty of the evidence for the primary outcome and secondary outcomes were assessed and summarized narratively by using the GRADE approach since meta-analysis were not available. GRADE is a method for assessing the quality of the evidence of the studies in systematic reviews. Evidence from observational studies start with low certainty and may be

upgraded according to criteria. Evidence from RCTs start with high certainty evidence and may be downgraded depending on the following five GRADE approach criteria (126, 127):

- Methodological study quality as assessed by review authors
- Degree of inconsistency
- Indirectness
- Imprecision
- Publication bias

GRADE has four levels of certainty, described as the following levels:

- **High quality:** We are very confident that the estimate of the effect lies close to the true effect. This means that further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** We are moderately confident in the estimate of effect. Although the true effect is likely to be close to the effect estimate, there might be a possibility that it is substantially different. This means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** We have limited confidence in the estimate of effect because the true effect may be substantially different from the effect estimate. This means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We have very little confidence in the estimate of effect because the true effect is likely to be substantially different from the effect estimate. This means that we are very uncertain about the estimate.

GRADE assessment was performed for the primary outcome and two of the secondary outcomes, based on evidence coming from the individual studies.

Changes made to the protocol

According to the study protocol the risk of bias assessment would be conducted by one reviewer then checked by another reviewer and in the event of any disagreements in the reviewers' assessments, these would be resolved by discussion until consensus and if necessary by a third reviewer. This was changed to the two reviewers first assessing RoB independently and then jointly, reaching a consensus. The protocol of this systematic review states that the databases that were initially planned for searches were MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO), Cochrane Library (CENTRAL) (Wiley), and EPISTEMONIKOS. After discussion

with the librarian we decided to exclude one database, add one database, and keep four of the planned databases for searches.

CHAPTER 3: RESULTS

3.1 Results of the search

There were 1781 hits from the database searches in MEDLINE (OVID), EMBASE (OVID), Cochrane Library (CENTRAL) (Wiley), CINAHL (EBSCO), Web of Science Core Collection (SCI-EXPANDED & SSCI) (Clarivate).

After the removal of duplicates from the main search, 969 records remained for screening of titles and abstracts. Of these 969 records, 21 remained for full-text assessment based on the inclusion criteria. Most of the studies identified from the database searches were excluded due to not matching the inclusion criteria concerning study designs and outcomes, and a few of the records were conference abstract presentations. After full-text reading, three studies presented in four articles, fulfilled the pre-specified inclusion criteria for this systematic review (124, 125, 128, 129).

No studies were identified that met inclusion criteria from Google Scholar, clinicaltrials.gov, relevant websites, reference lists of other systematic reviews, or literature reviews.

A detailed record of the reasons for exclusion of 17 articles from full-text reading, is available in Appendix 3.

3.2 Description of included studies and their context

Three RCTs presented in four articles were included in this systematic review totaling 146 randomized participants of both genders, aged ≥ 19 years (Table 1 and Appendix 4). The number of participants ranged from 36 to 60 with a diagnosis of head and neck cancer and in radiotherapy treatment. The patients were about 61 years on average and the studies were conducted in Australia (two studies) and Portugal (one study) in 2003, 2004, and 2005. According to the protocol, studies where at least 50% of the patients met our inclusion criteria or the results were reported separately, would be included in this review. One of the studies by Isenring et al., (124) included seven patients with cancer of the abdomen (12%), and 57 patients with head and neck cancer (88%). The other two included studies had only head and neck cancer

patients. With regard to the intervention, all three included studies had individualized dietary counseling by an RD given with our without oral nutritional supplements as the intervention. The two studies by Isenring et al., (124, 130) planned to include oral nutritional supplements if deemed appropriate for the intervention groups, which a few patients did add to their diet during the study period, while the study by Ravasco et al., (123) only based dietary counseling on normal foods without oral nutritional supplements. Similarly, with respect to the control groups, these consisted of patients who received standard clinical care mostly without any other nutritional interventions given. Only two participants in one of the control groups received tube feeding as a nutritional intervention due to rapid deterioration of nutritional status. In the study by Isenring et al., (124), participants in the control group were given the option of requesting a referral to an RD for dietary counseling of maximum two sessions during the study period which five out of 31 participants did request. All three studies included changes in body weight as one outcome measure, although Ravasco et al., (131) only reported results of changes in body weight in eight patients in the intervention group who had been screened to be malnourished at baseline, while the two studies by Isenring reported results for the entire study population. Changes in energy intake as measured by changes in daily calorie intake were reported by Isenring et al., (128), and Ravasco et al., (123) . Physical function and quality of life were secondary outcome measures of interest reported in Isenring et al., (124) and Ravasco et al., (123) .

Table 1: Characteristics of included studies (N=3)

Study	Population	Intervention	Comparison	Outcome	Measure of nutritional status	Duration
Isenring et al, 2003 (125)	n = 36 at baseline Age: 63 ± 15 years Gender: male, female Head and neck cancer outpatients for radiotherapy, implicitly at risk of malnutrition	n = 15 6 dietetic sessions until week 6, then 3 dietetic sessions after radiotherapy, 9 sessions from baseline of individualized dietary counseling by a dietitian. Oral nutrition supplements prescribed if appropriate	n = 21 Usual care	Body composition Measured as: - Body weight (kg) - Fat-free mass - Fat mass	Foot-to-foot bioelectrical Impedance analysis scale (Foot-to-foot BIA) This scale measures body composition by weight, fat-free mass, and fat-mass	12 weeks Nutritional status measured at baseline and at 12 weeks after baseline
Isenring et al, 2004 (124) **Isenring et al, 2007** (128)	n = 60 at baseline Age: 61.9 ± 14 years Gender: male, female 53 head and neck cancer and 7 abdomen cancer outpatients for radiotherapy, implicitly at risk of malnutrition	n = 29 6 dietetic sessions until week 6, then 3 dietetic sessions after radiotherapy, in total 9 sessions from baseline of individualized dietary counseling by a dietitian. Oral nutrition supplements prescribed if deemed appropriate	n = 31 Usual care Could request dietitian of a maximum of 2 sessions during study period. 5 patients requested this	Body weight (kg) Physical function Quality of Life Energy intake	Patient generated – Subjective Global Assessment screening tool (PG-SGA): 21 patients screened to be malnourished at baseline (35% of total study population)	12 weeks Nutritional status measured at baseline, at week 4, 8, and 12
Ravasco et al, 2005 (129)	n = 50 at baseline Age: 60 ± 11 years Gender: male, female Head and neck cancer outpatients for radiotherapy, implicitly at risk of malnutrition	n = 25 7 dietetic sessions during radiotherapy of individualized dietary counseling by a dietitian using regular foods (no oral nutritional supplements prescribed)	n = 25 Usual care 2 patients received tube feeding due to rapid deterioration of nutritional status	Body weight (kg) Physical function Quality of Life Energy intake	Patient generated – Subjective Global Assessment screening tool (PG-SGA): <u>Intervention group:</u> 16 patients screened as malnourished at baseline <u>Control group:</u> 15 patients screened as malnourished at baseline	12 weeks Nutritional status measured at baseline and weekly for 7 weeks, and at 12 weeks

3.3 Assessment of risk of bias in included studies

RCTs have a consistent methodological approach and systematic errors can be made during the research process that could affect the study outcomes resulting in either underestimating or overestimating the true effect of the intervention thus giving false results of its true effect. Biases are on a continuum and may affect the results of an intervention in either a small or in a more substantial way depending on the study methodology. In a systematic review, it is important to assess each included study for systematic errors by analyzing the methodological quality by performing a risk of bias (RoB) assessment. This helps us assess the certainty of the results of each included study and whether or not to trust the results.

The Cochrane RoB2 tool for assessing risk of bias of RCTs in a systematic review was used for assessing methodological quality in the three studies (111). Assessment, judgement and explanations supporting the judgements for each of the domains are summarized below, and are described in more detail in the 'Characteristics of included studies' (See Appendix 4). The figures (adapted using Review Manager 5.4.1 software-RevMan 2020) below provide graphical summaries of the review authors' judgements about each RoB across the studies presented as percentages (Figure 1), as well as judgement of RoB for each included study (Figure 2).

Figure 1: RoB graph. Review authors' judgements about each RoB item presented as percentages across included studies

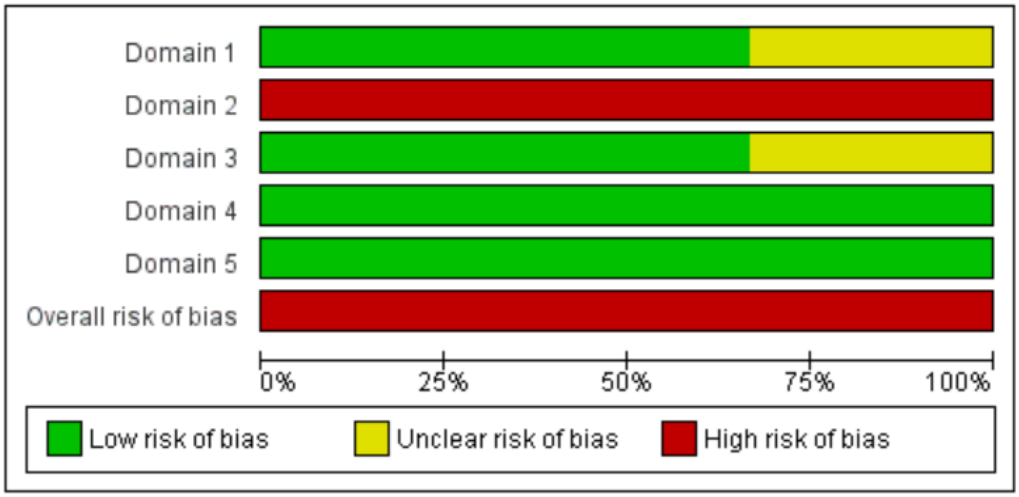
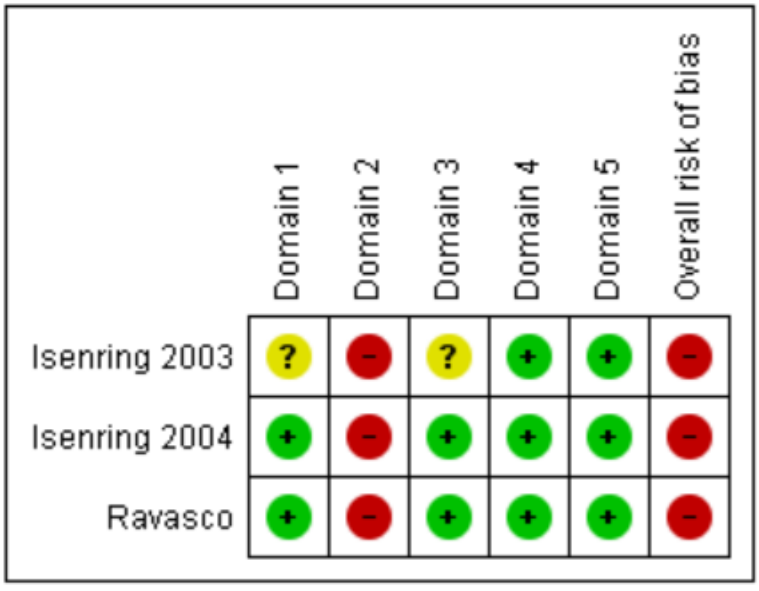


Figure 2: RoB summary. Review authors' judgements about each RoB item for each included study



Domain 1: Risk of bias arising from the randomization process

There were low risk of bias found in two of the three studies related to selection bias. One study did not state any information and was assessed as unclear risk of bias in this domain.

Domain 2: Risk of bias due to deviations from the intended interventions

All studies in this domain were assessed as having high risk of bias due to inadequate blinding of participants and dietitians.

Domain 3: Risk of bias due to missing outcome data

Two studies in this domain were assessed as having low risk of bias. These studies reported that all analysis were performed on an intention-to-treat basis. Two studies had a low/moderate loss to follow-up, one had none. One study did not state information on intention-to-treat analysis and only stated results for participants who completed the study and therefore judged as unclear risk of bias.

Domain 4: Risk of bias due in measurement of the outcome

All studies were assessed as low risk of bias in this domain.

Domain 5: Risk of bias in selection of the reported result

All studies in this domain was assessed as low risk of bias.

3.4 Loss to follow-up

Table 2: Loss to follow-up in the dietary counseling group and in the standard clinical care group

	Dietary counseling group			Standard clinical care group		
Study	Baseline number (n)	No. lost to follow-up	Percentage % lost to follow-up	Baseline number (n)	No. lost to follow-up	Percentage % lost to follow-up
Isenring et al. 2003	15	1	6.7%	21	3	14.3%
Isenring et al. 2004	29	4	13.8%	31	2	6.5%
Ravasco et al. 2005	25	0	0%	25	0	0%

The table above shows the percentage loss to follow-up in the dietary counseling group and in the standard clinical care group for all three included studies in this systematic review. The study by Isenring et al., (130) had a higher percentage loss to follow-up in the standard clinical care group (14.3%) than in the dietary counseling group (6.7%) (125). The study by Isenring et al., (132) was opposite, with the largest percentage loss to follow-up in the dietary counseling group (13.8%) and a lower loss to follow-up in the standard clinical care group (6.5%). The study by Ravasco et al., (123) had no loss to follow-up (129).

3.5 Effects of the intervention

In this systematic review, the intervention was dietary counseling by an RD, given with or without oral nutritional supplements, on nutritional status, in patients with head and neck cancer undergoing radiotherapy, compared to standard clinical care, with or without other nutritional interventions.

The primary outcome was nutritional status measured as mean differences between the two groups in *weight* and *energy intake*, while secondary outcomes were measured as mean differences between the two groups in *quality of life*, *physical function*, *readmissions to hospital*, and *mortality*. None of the included studies measured the secondary outcomes for *readmission to hospital* and *mortality*.

Results are presented in forest plots for differences in mean weight and energy intake, though without pooling the results in meta-analysis due to high risk of bias, which could lead to increased erroneous results. Results for the outcome measures for mean differences in quality of life and physical function are presented in tables due to missing standard deviations, but pooling results in meta-analysis would not be justifiable due to high risk of bias nonetheless.
The PICO of the included studies differed slightly in some aspects, and the results of the individual studies differed greatly for most of the outcomes.

After synthesizing results for each outcome measure, the assessments of the certainty of evidence was assessed by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (127). The overall certainty of evidence for each outcome is presented below the presentation of results for each outcome. The GRADE assessment is

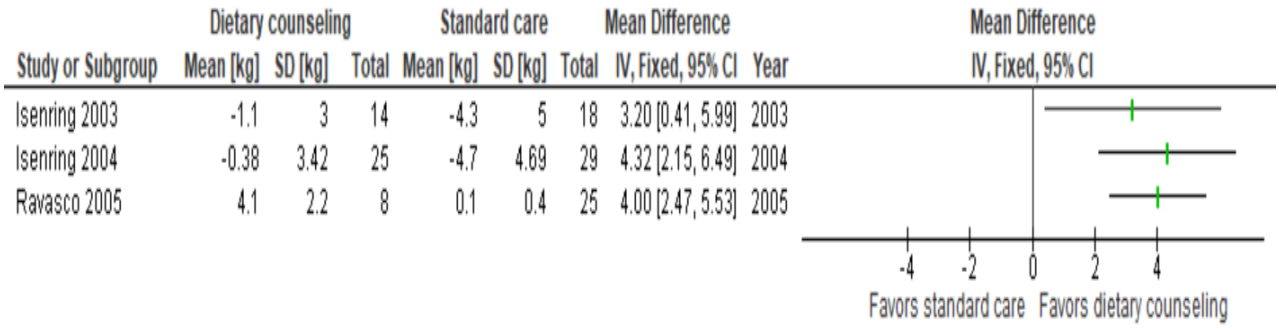
presented as a narrative summary due to outcome measures not being pooled in meta-analysis. See Appendix 5 for detailed GRADE assessments for the narratively summarized body of evidence for each outcome measure for methodological limitations of the studies, indirectness, imprecision, inconsistency, and publication bias.

Study results for two of the primary outcome measures are illustrated graphically in the forest plots below without pooled results, and results for two of the secondary outcome measures are illustrated in tables. The graded quality of evidence for each outcome measure is stated below each forest plot and each table.

3.5.1 Weight (kg)

All the three included studies in this systematic review measured weight in kilos (kg) in the dietary counseling group and the standard clinical care group. The three included studies with their individual mean results for this outcome measure are graphically illustrated in the forest plot below (Figure 3). The GRADE assessment for the certainty of results for this outcome is shown in the table below (Table 3).

Figure 3: Forest plot. Comparison between dietary counseling versus standard clinical care for the outcome of mean weight (kg)



Two of the studies showed a lower loss in weight (kg) and one study showed a greater gain in kg, compared to people in the control group. All three studies favor dietary counseling in comparison to standard clinical care. All three confidence intervals are overlapping, though

confidence intervals for the study by Ravasco et al. are narrower than the two studies by Isenring et al., (124, 130).

Table 3: Quality of the body of evidence for weight for dietary counseling versus standard clinical care, assessed by GRADE

Outcome	Effect	No of participants (studies)	Certainty of evidence
Weight.in kilograms (kg)	Three studies showed increase in weight favoring dietary counseling	146 participants (results stated for 119 participants) (3 studies)	⨁⨁◯◯ LOW

The outcome of interest is weight (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided).Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⨁⨁⨁⨁, moderate certainty ⨁⨁⨁O, low certainty ⨁⨁OO and very low certainty ⨁OOO.

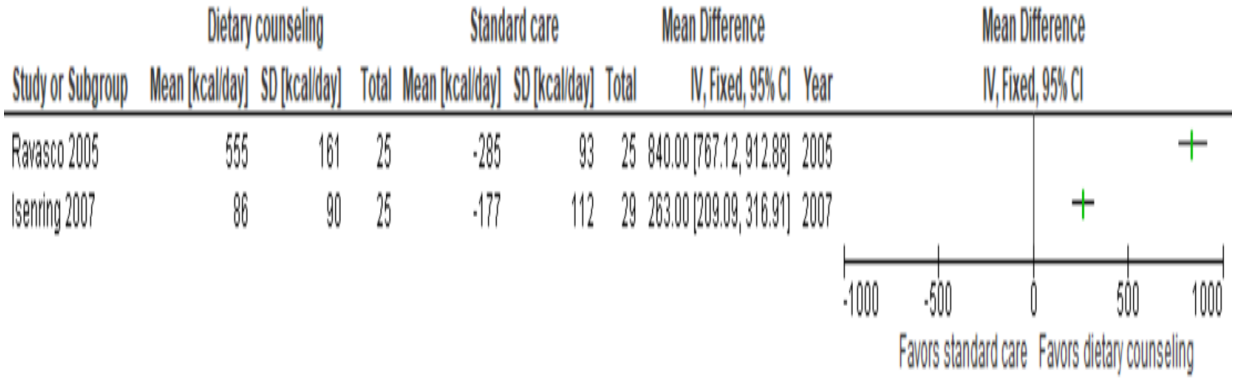
Low quality: We have limited confidence in the estimate of effect because the true effect may be substantially different from the effect estimate. This means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

This is the summary table only of the GRADE assessment. The remaining information is in table in appendix 5.

3.5.2 Energy intake

Two of the included studies, Isenring et al., (124) and Ravasco et al., (123) measured daily energy intake in the dietary counseling group and the standard clinical care group, measured by daily intake of kilocalories (kcal/day). The publication of Isenring et al., (2007) is a publication reporting the outcome measure of energy intake from the study of Isenring et al., (2004). The two included studies with their individual mean results of this outcome measure are graphically illustrated in the forest plot below (Figure 4). The GRADE assessment for the certainty of results for this outcome is shown in the table below (Table 4).

Figure 4: Forest plot. Comparison of dietary counseling versus standard clinical care for the outcome of daily energy intake (kcal/day)



Both studies showed an increase in daily energy intake (kcal/day) for the dietary counseling group, compared to the standard clinical care group who both had a decrease in daily energy intake (kcal/day) compared to baseline. Results for the two studies varied greatly, one study had a larger increase in daily energy intake in the intervention group than the other study, and the same study had a larger decrease in daily energy intake in the control group than the other study did.

Table 4: Quality of the body of evidence for daily energy intake for dietary counseling versus standard clinical care, assessed by GRADE

Outcome	Effect	No of participants (studies)	Certainty of evidence
Energy intake. Assessed by kilo caloric intake per day	Two studies showed increase in energy intake favoring dietary counseling	104 participants (2 studies)	⊕◯◯◯ VERY LOW

The outcome of interest is daily energy intake (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided).Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

Very low quality: We have very little confidence in the estimate of effect because the true effect is likely to be substantially different from the effect estimate. This means that we are very uncertain about the estimate.

This is the summary table only of the GRADE assessment. The remaining information is in table in appendix 5.

3.5.3 Quality of life

Two of the included studies, Isenring et al., (124) and Ravasco et al., (123) measured quality of life in the dietary counseling group and the standard clinical care group, measured by the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 (Version 3) questionnaire. The EORTC is a 30-item validated cancer-specific questionnaire tool that includes functional scales (*physical, emotional, cognitive, social, role, and emotional*), symptom scales (*fatigue, pain, nausea, vomiting*), and a *global quality of life scale*. Test results from the EORTC questionnaire show scores in continuous data out of 100 possible, where 100 shows the highest quality of life (133). The two studies both assessed the effect of dietary counseling given with or without oral nutritional supplements, on quality of life by the EORTC questionnaire at baseline and at end of study at 12 weeks, compared to standard clinical care. The two included studies with their individual mean results of this outcome measure are shown in the table below (Table 5). The GRADE assessment for the certainty of results for this outcome is shown in the table below (Table 6).

Table 5: Comparison of dietary counseling versus standard clinical care for the outcome of quality of life (points)

Study	**Dietary counseling** (mean points)	No of participants	**Standard clinical care** (mean points)	No of participants
Isenring et al. 2004	5	25	-12.7	29
Ravasco et al. 2005	34	25	-17	25

Both studies showed an increase in score of points for the dietary counseling group, compared to the standard clinical care group who both had a decrease in score of points, compared to baseline. Results for the two studies varied greatly. Both studies showed a decrease in score of points for the standard clinical care group.

Table 6: Quality of the body of evidence for quality of life for dietary counseling versus standard clinical care, assessed by GRADE

Outcome	Effect	No of participants (studies)	Certainty of evidence
Quality of life Assessed by EORTC scores in points, the higher the points the higher the quality of life	Two studies showed increase in quality of life favoring dietary counseling	104 participants (2 studies)	⨁◯◯◯ VERY LOW
The outcome of interest is quality of life (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided).Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⨁⨁⨁⨁, moderate certainty ⨁⨁⨁O, low certainty ⨁⨁OO and very low certainty ⨁OOO.			

Very low quality: We have very little confidence in the estimate of effect because the true effect is likely to be substantially different from the effect estimate. This means that we are very uncertain about the estimate.

This is the summary table only of the GRADE assessment. The remaining information is in table in appendix 5.

3.5.4 Physical function

Two of the included studies, Isenring et al., (124) and Ravasco et al., (123) measured physical function in the dietary counseling group and the standard clinical care group, measured by the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 (Version 3) questionnaire. The EORTC is a 30-item validated cancer-specific questionnaire tool that includes functional scales (physical, emotional, cognitive, social, role, and emotional), symptom scales (fatigue, pain, nausea, vomiting), and a global quality of life scale. Test results from the EORTC questionnaire show scores in continuous data out of 100 possible, where 100 shows the highest quality of life (130). The two studies both assessed the effect of dietary counseling given with or without oral nutritional supplements, on physical function by the EORTC questionnaire at baseline and at end of study at 12 weeks, compared to standard clinical care. The two included studies with their individual mean results of this outcome measure are shown in the table below (Table 7). The GRADE assessment for the certainty of results for this outcome is in the table below (Table 8).

Table 7: Comparison of dietary counseling versus standard clinical care for the outcome of physical function (points)

Study	**Dietary counseling** (mean points)	No of participants	**Standard clinical care** (mean points)	No of participants
Isenring et al. 2004	-0.30	25	-12.7	29
Ravasco et al. 2005	30	25	-23	25

One study showed an increase, and one study showed a small decrease score of points for the dietary counseling group, compared to the standard clinical care group for the measure of physical function, compared to baseline. Both studies showed a very similar decrease in score of points for the measure of physical function in the standard clinical care group, compared to baseline.

Table 8: Quality of body of evidence for physical function in dietary counseling versus standard clinical care, assessed by GRADE

Outcome	Effect	No of participants (studies)	Certainty of evidence
Physical function Assessed by EORTC scores in points, the higher the points the higher the physical function	One study showed increase in physical function favoring dietary counseling. One study showed a slight decrease in physical function in the dietary counseling group	104 participants (2 studies)	⨁◯◯◯ VERY LOW

The outcome of interest is physical function (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided). Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⨁⨁⨁⨁, moderate certainty ⨁⨁⨁O, low certainty ⨁⨁OO and very low certainty ⨁OOO.

Very low quality: We have very little confidence in the estimate of effect because the true effect is likely to be substantially different from the effect estimate. This means that we are very uncertain about the estimate.

This is the summary table only of the GRADE assessment. The remaining information is in table in appendix 5.

3.5.5 Hospital readmissions

None of the included studies reported on hospital readmission.

Table 9: Quality of body of evidence for hospital readmission in dietary counseling versus standard clinical care

Outcome	Effect	No of participants (studies)	Certainty of evidence
Hospital readmission	We have no evidence on the effect of dietary counseling versus standard clinical care on hospital readmission	N/A	N/A

The outcome of interest is hospital readmissions.

Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

3.5.6 Mortality

None of the included studies reported on mortality.

Table 10: Quality of body of evidence for mortality in dietary counseling versus standard clinical care

Outcome	Effect	No of participants (studies)	Certainty of evidence
Mortality	We have no evidence on the effect of dietary counseling versus standard clinical care on mortality	N/A	N/A

The outcome of interest is mortality.

Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

CHAPTER 4: DISCUSSION

4.1 Summary of main results

The aim of this systematic review was to investigate the effect of dietary counseling by an RD, given with or without oral nutritional supplements, to head and neck cancer patients undergoing radiotherapy on the outcomes of nutritional status, quality of life, physical function, readmission to hospital and mortality. This systematic review identified three randomized controlled studies (n = 146), presented in four articles which met the pre-specified inclusion criteria. All included studies measured weight, energy intake, quality of life, and physical function, but none measured readmission to hospital and mortality. All the included studies were assessed as having high risk of bias in their methodological processes mostly due to inadequate blinding. Due to high risk of bias, meta-analysis of results were not performed and results in this systematic review have therefore been presented as a narrative synthesis for each individual study. With regards to the certainty of evidence of the results, one outcome measure was assessed as having low quality of body of evidence, and three outcome measures were assessed as having very low quality of body of evidence. The overall very low and low quality of the body of evidence from these RCTs suggests that dietary counseling given with or without the use of oral nutritional supplements can increase weight, daily energy intake, quality of life, and physical function, compared to standard clinical care. For the future, adequately blinded and adequately powered studies are required to evaluate the true effect of dietary counseling given with or without oral nutritional supplements in patients with head and neck cancer undergoing radiotherapy, on nutritional status and other clinical outcomes.

4.2 Overall completeness and applicability of evidence

The population of the studies in this systematic review had the same clinical diagnosis of head and neck cancer, although head and neck cancer is a cluster of various types of cancer of the mouth and throat area, it is also likely that participants had different stages and severities of their cancer diagnosis. This would inevitably result in an extent of incomparable challenges with regards to food intake for the study populations across the included studies. With regards to the interventions, two of the included studies had dietary counseling by an RD given with or without the use of oral nutritional supplements, although it was not stated how many participants were prescribed oral nutritional supplements. Oral nutritional supplements are

highly calorie-dense and could potentially make a big difference in overall caloric intake (65). These two studies had in total nine dietary counseling sessions by an RD during the study period. The intervention of one of the studies had dietary counseling by an RD based on regular foods only given without oral nutritional supplements. This study had in total seven dietary counseling sessions by an RD during the study period. The same study had also offered the patients in the control group two dietary counseling sessions during the study period of which five out of thirty-one participants had requested. The results from the studies generally differed greatly for the same outcome measures. Overall, there was clinical as well as statistical heterogeneity across the groups of the studies in this systematic review.

This systematic review set out to investigate the effect of dietary counseling by an RD on weight, energy intake, quality of life, physical function, readmission to hospital, and mortality. All outcomes except readmission to hospital and mortality were investigated.

The amount of studies in this systematic review were few, the study samples were small and the body of evidence for the results were of a very low and low quality.

4.3 Certainty of the evidence

Study design is of great importance with regards to the quality of the evidence. This systematic review only included RCTs which are considered a high quality study design.

The included RCTs in this systematic review did not manage to answer the question it set out so answer sufficiently. However, all the included studies have suggested that the tendency of its effect lies in favor of dietary counseling for all the outcomes of interest, compared to standard clinical care.

The body of evidence for the outcome of weight was assessed as low certainty of evidence by the GRADE approach, and the body of evidence for energy intake, quality of life, and physical function was assessed as very low certainty of evidence by the GRADE approach.

A thorough database search was performed to identify all relevant studies by pre-specified inclusion criteria. In addition hand searching was performed as well as searching for studies in clinicaltrials.gov. We are quite certain that we did not miss any relevant studies. The screening and selection of studies was performed by two reviewers who did this work systematically and

thoroughly and it is not suspected that relevant studies were unselected in this process for any of the inclusion criteria.

All relevant data was not obtained from all the included publications with regards to standard deviations for results. One study did not report results for outcome measures at 12-weeks, but the author did reply and report this particular requested data.

The risk of bias assessment showed that all the studies had an overall high risk of bias especially due to the lack of blinding of personnel in the included studies.

4.4 Agreements and disagreements with other reviews

We are not aware of any other systematic reviews that have investigated the effects of dietary counseling by an RD, given with or without oral nutritional supplements, exclusively in patients with head and neck cancer undergoing radiotherapy. Although, in a systematic review by Lee et al., (134), all the three studies presented in four publications that were included in this systematic review that investigated the effect of dietary counseling by an RD, given with or without oral nutritional supplements, in patients with head and neck cancer undergoing radiotherapy (123-125, 128), were among the thirteen included studies in the review by Lee et al., (134). The systematic review compared different nutritional interventions to reduce malnutrition in patients with different diagnosis of cancer. Results suggested that dietary counseling, with or without oral nutritional supplements was associated with consistent improvements in several nutrition status outcomes. The systematic review by Lee et al., (134) recommends that all patients with a diagnosis of cancer should be referred for dietary counseling due to strong evidence of beneficial effects in preventing and reducing disease-related-malnutrition found in the review. The review concluded that dietary counseling given with or without the use of oral nutritional supplements was associated with a lot more consistent and significant bettering of nutritional status compared to the other nutritional interventions such as tube-feeding or oral supplements alone without dietary counseling. The authors suggest that the explanation may be that patients easier adhere to the dietary advice given due to regular appointments for dietary counseling as well as the motivational aspects and individualized dietary advice given by the dietitians.

The systematic review by Baldwin et al., (79), compared dietary counseling by an RD, given with or without the use of oral supplements in the management of malnourished patients. This review included a diversity of patient populations, but also a diversity of intervention and comparisons in addition to dietary counseling. The review concluded that dietary counseling given with or without oral supplements is effective at increasing nutritional intake and weight in different patient populations, but authors recommend that adequately powered studies in similar patient populations are required.

A systematic review by Langius et al., (135), compared a variety of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving chemo/radiotherapy. They found effects of nutrition counseling on nutritional status and quality of life. This review did not find that oral nutritional supplements or tube feeding alone without dietary counseling had any benefits.

A more recent systematic review by Mello et al., (136), included fifteen trials and compared the effect of oral nutritional supplements, given with or without nutritional counseling on mortality, treatment tolerance, and quality of life in head and neck cancer patients receiving chemo/radiotherapy. They found that dietary counseling with oral nutritional supplements increased patient's body weight slightly, but they found adverse effects of the use of oral nutritional supplements like feeling nauseas, feeling full and vomiting. The authors of the review suggest that the negative effects of oral nutritional supplements should be further investigated and that the slight increase in body weight also be further investigated.

The ESPEN guidelines on Nutrition in Cancer Patients (56), recommend that patients with a diagnosis of cancer of the abdominal area, or cancer of the head and neck area should undergo thorough nutritional assessments and dietary counseling in addition to other nutritional interventions if deemed appropriate. Under section C2 – Radiotherapy: *Ensuring adequate nutritional intake,* ESPEN guidelines give a strength of recommendation: Strong:

> "We recommend that during radiotherapy with special attention to radiotherapy of the head and neck, thorax and gastrointestinal tract an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of oral

nutritional supplements, in order to avoid nutritional deterioration, maintain intake and avoid radiotherapy interruptions".

ESPEN has a strong consensus that patients with a cancer diagnosis, who have problems eating, digesting or absorbing foods due to either surgery or treatment-induced morbidities, should be considered for artificial nutritional support in the form of either tube-feeding or intravenous nutrition as a measure of delivering nutrients and fluids. The consensus is also similarly strong for the patients who have tumors that obstruct the intake of foods and fluids. ESPEN specifies that there must be paid particular attention to two subgroups of patients with a cancer diagnosis: those undergoing surgery and those patients that are close to their end of life. These situations may be especially challenging and need very individualized approaches to nutritional treatment interventions in order to ensure delivery of both nutrition and fluids without posing any harm, and pose ethical questions as to the best aims of treatment (57).

4.5 Implications for practice/policy and for future research

Two of the included studies in this systematic review were conducted in Australia, and one was conducted in Portugal. These are both high-income countries, and it is difficult to assess if the indications from this systematic review are transferable to countries of very different food-cultures or availability of foods and oral nutritional supplements in low- to middle-income countries. It is also unclear if patients in low- to middle-income countries are granted the access to an RD, or to oral nutritional supplements depending on how healthcare is financed in different countries around the world.

Dietitians in hospitals today frequently receive referrals from oncologists and other medical doctors for dietary counseling for patients with a diagnosis of head and neck cancer, although most patients with this diagnosis never see an RD. Doctors, as previously mentioned often do refer patients to an RD once DRM is already present. The external validity of this systematic review puts focus on the obvious nutritional challenges at hand, experienced by this population (137-140). Especially during radiotherapy treatment, doctors could consider offering all patients with head and neck cancer a referral to an RD since to this day, no harm has been proven of this non-invasive intervention that also encompasses important motivational- and care aspects for the patient.

The included studies in this systematic review were conducted between 2003 and 2005. Today, certified video consultations have become an efficient and frequently used method of patient-consultations, both for RDs and for other healthcare professionals. This can give all patients access to this service, and saves costs. Future research should conduct studies on the effect of dietary counseling by an RD given with or without the use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy, using certified video consultations as well as face-to-face consultations, compared to standard clinical care.

More adequately powered studies are needed to bring about a confirmation of the effect of dietary counseling given with or without the use of oral nutritional supplements, on nutritional status in head and neck cancer patients undergoing radiotherapy compared to standard clinical care with or without other nutritional interventions. Multi center studies involving hospitals around the world could be one way to power these studies and reach a conclusion, and hopefully confirm this effect.

4.6 Strength and weaknesses of the review process

This systematic review was conducted according to the steps in the Cochrane Handbook for Systematic Reviews of Interventions (111). Two reviewers performed screening of studies, assessment of risk of bias, and the GRADE assessment of this review. The technical search of databases was conducted by a professional librarian who executed the searches in relevant databases which were carefully planned when designing the search. Publication bias was not assessed due to the low number of included studies, but we believe it is unlikely that studies have been missed due to a thorough search conducted in relevant databases.

Meta-analyses were not performed due to low quality evidence and missing data. The assessment scales used by the researchers for the outcome measurements in the included studies were all the same in this systematic review.

This review was mainly conducted by the master's student, which in itself may be a weakness of the review process. This is the first major research project by the master's student, a great learning process rendering the risk that small parts could be missing, overlooked or erroneous.

4.7 Author's conclusion

Despite all studies and all efforts from healthcare professionals and of studies performed by researchers in the field of medical nutrition, cancer-related-malnutrition still remains a huge challenge that too often goes unresolved for patients with a cancer diagnosis. The challenge remains in the implementation of high quality guidelines, into applied clinical practice in order to reach the patients. The ESPEN guidelines for nutrition in cancer very clearly state their recommendations for combating cancer-related-malnutrition (56, 57), as well as ESPEN guidelines for screening all patients for malnutrition (141). As long as our research does not show evidence that dietary counseling has negative effects in reducing the impact of and treating disease-related-malnutrition and specifically cancer-related-malnutrition, we should consider continuing dietary counseling by an RD, given with the use of oral nutritional supplements whenever deemed appropriate.

The ESPEN expert-study-group has stated clear recommendations for the individualized assessment and treatment with regards to fighting cancer-related-malnutrition as the following:

- Screen all patients with cancer for nutritional risk early in their course of care, regardless of body mass index and weight history; regularly rescreen nutritional status.
- Increase nutrition assessment to include measures of anorexia, body composition, inflammatory biomarkers (e.g., Glasgow prognostic score), resting energy expenditure, and physical function.
- Use nutritional intervention with individualized plans, including care focused on increasing nutritional intake, decreasing inflammation and hyper-metabolic stress, and increasing physical activity.

The combination of the recommendations from the ESPEN expert study group on nutrition in cancer (56) with The Norwegian Guidelines for the Prevention and Treatment of Malnutrition (26), are strong recommendations and ought to be sufficient in order to justify their implementation in all oncological clinical settings in order to combat cancer-related-malnutrition. More research is needed in order to ascertain the harms and benefits of making the intervention of dietary counseling by a registered dietitian available to all head and neck cancer patients during radiotherapy as a preventative measure, on a regular basis. But in the

meantime, doctors should consider referring patients with head and neck cancer to an RD at start of radiotherapy, instead of referring the patients once malnutrition is already prevalent.

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APPENDICES

Appendix 1: Search strategy in electronic databases

Total hits: 1781

Duplicates: 812

Total hits after deduplication: 969

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to August 11, 2020

Date: 11.08.2020

Hits: 434

1	"Head and Neck Neoplasms"/	54641
2	"Squamous Cell Carcinoma of Head and Neck"/	5452
3	("head and neck" adj10 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*)).ti,ab,kf.	55258
4	or/1-3	78716
5	Radiotherapy/	42461
6	(radiotherap* or radio-therap* or (radiation* adj4 (treat* or therap*))).ti,ab,kf.	260631
7	5 or 6	274285
8	Nutritional Support/	6299
9	Enteral Nutrition/	19703
10	Diet Therapy/	10559
11	Dietetics/	7776
12	Nutritionists/	1222
13	Dietary Supplements/	57352
14	(((nutrition* or diet*) adj5 (advice* or advis* or care plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or meal* or mentor* or program* or recommend* or referral* or regimen* or supplement* or support* or teach* or therap* or treat*)) or (eating adj5 (advice* or advis*)) or (meal adj5 replacement*) or (sip* adj5 feed*)).ti,ab,kf.	201199

15 or/8-14265233

16 4 and 7 and 15439

17 exp animals/ not humans.sh. 4724690

18 (news or editorial or comment).pt. 1420838

19 16 not (17 or 18) 435

20 remove duplicates from 19 434

Database: Embase 1974 to 2020 August 11 [Ovid]

Date: 12.08.2020

Hits: 560

1 "head and neck tumor"/ 14981

2 "head and neck cancer"/ 44735

3 "head and neck squamous cell carcinoma"/ 13352

4 "head and neck carcinoma"/ 8539

5 ("head and neck" adj10 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*)).ti,ab,kw. 79929

6 or/1-5 104606

7 radiotherapy/ 142792

8 cancer radiotherapy/ 199837

9 (radiotherap* or radio-therap* or (radiation* adj4 (treat* or therap*))).ti,ab,kw. 383263

10 or/7-9 495485

11 nutritional support/ 19264

12 diet therapy/ 53103

13 diet supplementation/ 87160

14 enteric feeding/ 32209

15 dietetics/ 5454

16 dietitian/ 12004

17 (((nutrition* or diet*) adj5 (advice* or advis* or care plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or meal* or mentor* or program* or recommend* or referral* or regimen* or

supplement* or support* or teach* or therap* or treat*)) or (eating adj5 (advice* or advis*)) or (meal adj5 replacement*) or (sip* adj5 feed*)).ti,ab,kw. 265907

18 or/11-17 380434

19 6 and 10 and 18 1003

20 (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/) 6500798

21 (news or editorial or comment).pt. 661357

22 19 not (20 or 21) 997

23 remove duplicates from 22 983

24 limit 23 to embase 560

Database: Cochrane Library (CENTRAL) [Wiley]

Date: 11.08.2020

Hits: 176

#1 [mh ^"Head and Neck Neoplasms"] 2105

#2 [mh ^"Squamous Cell Carcinoma of Head and Neck"] 179

#3 ("head and neck" near/10 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*)):ti,ab,kw6759

#4 {or #1-#3} 7107

#5 [mh ^Radiotherapy] 1175

#6 (radiotherap* or radio-therap* or (radiation* near/4 (treat* or therap*))):ti,ab,kw 36380

#7 #5 or #6 36380

#8 [mh ^"Nutritional Support"] 237

#9 [mh ^"Enteral Nutrition"] 1811

#10 [mh ^"Diet Therapy"]369

#11 [mh ^Dietetics] 96

#12 [mh ^Nutritionists] 42

#13 [mh ^"Dietary Supplements"] 10159

#14 (((nutrition* or diet*) near/5 (advice* or advis* or care-plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or meal* or mentor* or program* or recommend* or referral* or regimen* or supplement* or support* or teach* or therap* or treat*)) or (eating near/5 (advice* or advis*)) or (meal near/5 replacement*) or (sip* near/5 feed*)):ti,ab,kw 61277

#15 {or #8-#14} 62324

#16 #4 and #7 and #15 in Trials 176

Database: CINAHL [EBSCO]

Date: 11.08.2020

Hits: 74

S1 (MH "Head and Neck Neoplasms") 13,459

S2 (MH "Squamous Cell Carcinoma of Head and Neck") 173

S3 TI (("head and neck" N9 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*))) OR AB (("head and neck" N9 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*))) OR SU (("head and neck" N9 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*))) 13,661

S4 S1 OR S2 OR S3 18,635

S5 (MH "Radiotherapy") 18,188

S6 TI ((radiotherap* or radio-therap* or (radiation* N3 (treat* or therap*)))) OR AB ((radiotherap* or radio-therap* or (radiation* N3 (treat* or therap*)))) OR SU ((radiotherap* or radio-therap* or (radiation* N3 (treat* or therap*)))) 73,358

S7 S5 OR S6 73,358

S8 (MH "Enteral Nutrition") 9,521

S9 (MH "Diet Therapy") 3,651

S10 (MH "Dietetics") 2,309

S11 (MH "Nutrition Services") 1,012

S12 (MH "Dietary Supplements") 24,352

S13 (MH "Nutritional Support") 5,099

S14 TI ((((nutrition* or diet*) N4 (advice* or advis* or care plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or

meal* or mentor* or program* or recommend* or referral* or regimen* or supplement* or support* or teach* or therap* or treat*)) or (eating N4 (advice* or advis*)) or (meal N4 replacement*) or (sip* N4 feed*))) OR AB ((((nutrition* or diet*) N4 (advice* or advis* or care plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or meal* or mentor* or program* or recommend* or referral* or regimen* or supplement* or support* or teach* or therap* or treat*)) or (eating N4 (advice* or advis*)) or (meal N4 replacement*) or (sip* N4 feed*))) OR SU ((((nutrition* or diet*) N4 (advice* or advis* or care plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or meal* or mentor* or program* or recommend* or referral* or regimen* or supplement* or support* or teach* or therap* or treat*)) or (eating N4 (advice* or advis*)) or (meal N4 replacement*) or (sip* N4 feed*))) 123,979

S15 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 131,888

S16 S4 AND S7 AND S15 248

S17 S4 AND S7 AND S15 [Limiters - Exclude MEDLINE records] 74

Database: Web of Science Core Collection (SCI-EXPANDED, SSCI) [Clarivate]

Date: 12.08.2020

Hits: 363

1 TOPIC: (("head and neck" NEAR/9 (cancer* or malign* or tumor* or tumour* or sarcoma* or carcinoma*))) 55,415

2 TOPIC: ((radiotherap* or radio-therap* or (radiation* NEAR/3 (treat* or therap*)))) 285,439

3 TOPIC: ((((nutrition* or diet*) NEAR/4 (advice* or advis* or care-plan* or coach* or consult* or councel* or counsel* or educat* or guid* or inform* or intervention* or manag* or meal* or mentor* or program* or recommend* or referral* or regimen* or supplement* or support* or teach* or therap* or treat*)) or (eating NEAR/4 (advice* or advis*)) or (meal NEAR/4 replacement*) or (sip* NEAR/4 feed*))) 214,182

4 #3 AND #2 AND #1 363

Appendix 2: Flow diagram for studies selection

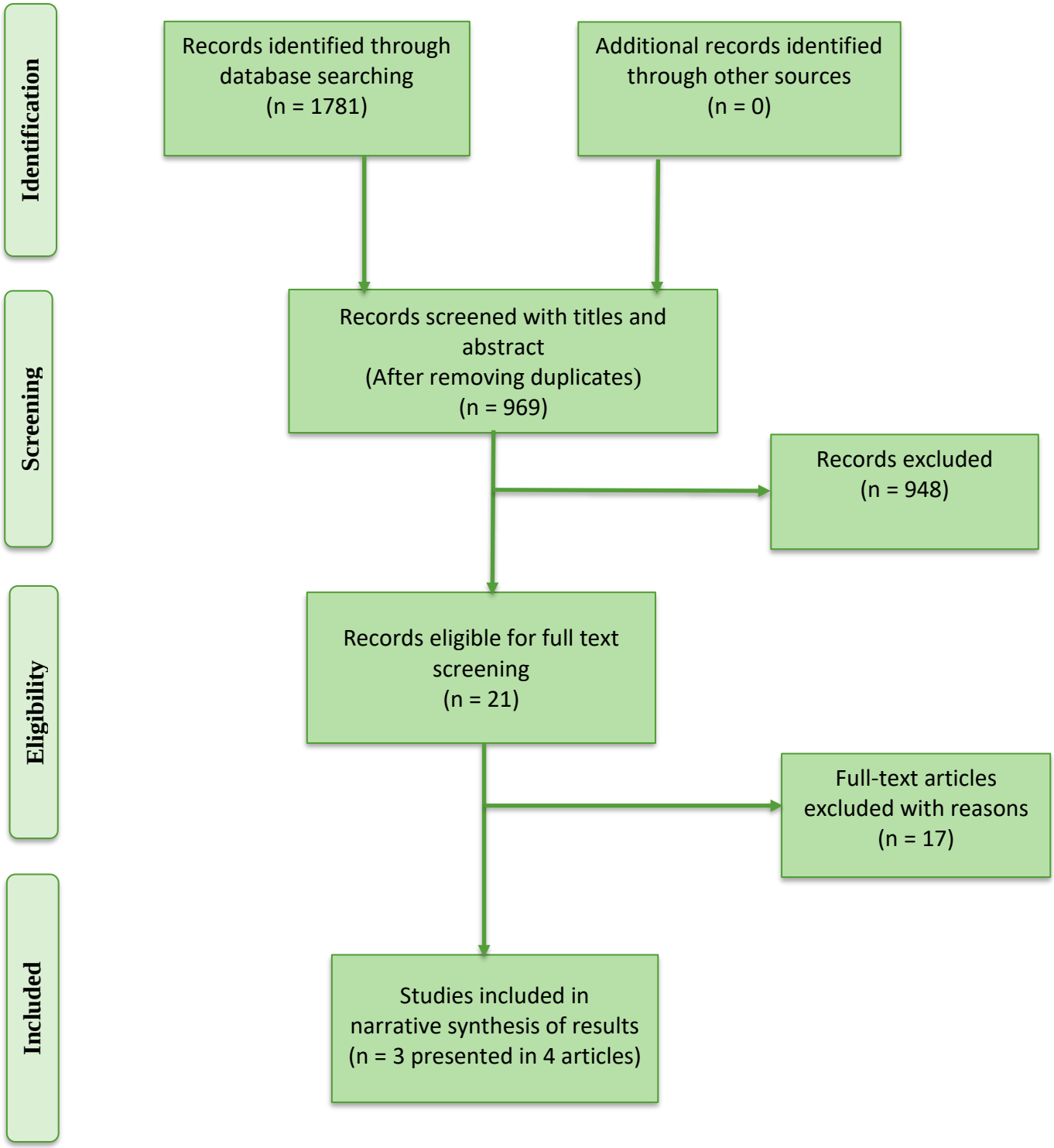

Figure: Flow diagram for selection of studies for systematic review

Appendix 3: Excluded studies read in full text

Author	Year	Title	Exclusion expl
Daly, John M	1984	Nutritional rehabilitation in patients with advanced head and neck cancer receiving radiotherapy	Year of publication is too old for inclusion
Hopanchi Bicakli, D	2017	The effects of compliance with nutritional counselling on body composition parameters in head and neck cancer patients under radiotherapy	All participants received dietary counseling
Kristensen, M, B	2020	Rationale and design of a randomized controlled trial investigating the effect of multidisciplinary nutritional rehabilitation for patients treated for head and neck cancer	Trial registration/protocol
Soria, A	2013	Nutritional support in patients with head and neck cancer during radiotherapy alone or combined chemotherapy	Incorrect intervention for inclusion
Rabinovitch, R	2006	Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive radiotherapy: A secondary analysis of RTOG trial 90-03	Incorrect intervention for inclusion
Cereda, E	2017	Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy	Duplicate article already excluded in initial screening
Bayard, I.G.	2019	Nutritional intervention in head and neck cancer patients undergoing radiotherapy	Incorrect intervention for inclusion
Kang, W. X.	2016	Effects of nutritional intervention in head and neck cancer patients undergoing radiotherapy: A prospective randomized clinical trial	All participants received dietary counseling
Kristensen, M. B.	2020	Rationale and design of a randomized controlled trial investigating the effect of multidisciplinary nutritional rehabilitation for patients treated for head and neck cancer	Trial registration/protocol
Roussel, M. L.	2016	Intensive nutritional care for patients treated with radiotherapy in head and neck cancer: a randomized study and meta-analysis	All participants received dietary counseling
Ravasco, P.	2007	Cancer wasting and quality of life react to early individualized nutritional counselling	Narrative/summary of studies
Ravasco, P.	2011	Nutritional support in head and neck cancer: how and why?	Narrative/summary of studies
Ravasco, P.	2003	Does nutrition influence quality of life in cancer patients undergoing radiotherapy?	Incorrect study design for inclusion
Gilliard, L. M.	2008	Impact of interventions by a registered dietitian on nutritional outcomes in head and neck cancer patients undergoing radiotherapy	Incorrect intervention for inclusion
Leistra, E.	2015	Effect of early individualized dietary counseling on weight loss, complications, and length of hospital stay in patients with head and neck cancer: A comparative study	Incorrect study design for inclusion
Van den Berg, M. G. A.	2010	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	Incorrect intervention for inclusion
Peyronnet, D.	2016	Limits of intensive nutritional care for patients treated by radiotherapy in head and neck cancer	Insufficient data about intervention

Appendix 4: Characteristics of the included studies

4.1 Isenring et al. 2003 (125)

Characteristics of included study (Isenring et al., 2003)		
Methods	Randomized controlled trial Parallel design with 2 treatment arms Duration: 12 weeks. Location: RT outpatient clinic on the Gold Coast, Queensland, Australia	
Participants	Adult patients > 18 years with a diagnoses of head and neck cancer, referred for RT N = 36 (intervention group n = 15; control group 21) Mean age = 63 ± 15 years Both genders No significant difference in patient characteristics at baseline Attrition: 4 loss to follow-up (1 NI / 3 UC)	
Interventions	Individualized dietary counseling by an RD + Oral nutrition supplements if deemed appropriate 12 weeks. Weekly sessions for the first 6 weeks thereafter each fortnight for the remaining 6 weeks, in total 9 sessions with and RD	
Comparison	Standard routine clinical care (UC). No other interventions	
Outcomes	**Body composition** measured as: Body weight (kg) Fat-free-mass Fat-mas	
Risk of Bias (RoB) assessment		
Risk of Bias	***Authors judgement***	***Support for judgement***
Domain 1 ***Arising from the randomization process***	High risk of bias	Quote: "Subjects were randomized to receive either NI (n=15) or UC (n=21). Randomization occurred after consent to participate was obtained" Comment: Described as randomized but method not stated. Allocation concealment, method not stated. Blinding of personnel, participants and assessors not stated
Domain 2 ***Due to deviations from the intended interventions***	High risk of bias	Hard to blind participants, dietitians and assessors adequately, therefore assessed at high risk of bias.
Domain 3 ***Due to missing outcome data***	Unclear risk of bias	4 participants lost to follow-up 7% loss from intervention group, and 14% loss from the control group. Did not state information on intention-to-treat analysis and only stated results for participants who completed the study
Domain 4 ***In measurement of the outcome***	Low risk of bias	Methods of assessment were standard scales or BIA body composition scales, and validated questionnaires for physical function and quality of life.
Domain 5 ***In selection of the reported result***	Unclear risk of bias	Not stated information about missing data
Overall risk of bias	**High risk of bias**	

4.2 **Isenring et al. 2004** (124) **Isenring et al. 2007** (128)

Characteristics of included study (Isenring et al., 2004) (Isenring et al., 2007)		
Methods	Randomized controlled trial Parallel design with 2 treatment arms. Duration: 12 weeks. Dates of study period not stated Location: Private radiotherapy clinic in Australia	
Participants N = 60 Population: 88% (53) HNC 12% (7) abdomen cancer	Adult patients > 18 years with a diagnoses of 53 participants with head and neck cancer and 7 participants with abdomen cancer, referred for RT N = 60 (intervention group n = 29; control group 31) 51 males and 9 females Mean age = 61.9 ± 14 years Both genders No other significant difference in patient characteristics at baseline Inclusion criteria: adults receiving radiotherapy for cancers of head and neck (88%) or abdomen (12%). Attrition: 6 participants lost to follow-up (4 from the intervention group) 4 deaths and 1 participant deteriorated, and 1 participant did not wish to complete RT treatment At baseline 65% of participants were well-nourished and 35 % malnourished (PG-SGA)	
Interventions	Individualized dietary counseling by an RD and oral nutritional supplements if appropriate. 12 weeks. Weekly sessions with an RD the first 6 weeks and fortnightly for the remaining 6 weeks. In total 9 sessions	
Comparison	Standard nutrition booklet and participants could request a referral to a dietitian of a maximum of 2 dietetic sessions during the study period. 5 participants from the control group requested referral to a dietitian. No other interventions. 2 participants in the comparison group received tube-feeding due to deterioration in oral intake	
Outcomes **Isenring et al. 2004**	Body weight (kg) Physical function Quality of Life	
Outcome **Isenring et al. 2007**	Energy intake	
Risk of Bias (RoB) assessment		
Risk of Bias	**Authors judgement**	**Support for judgement**
Domain 1 **Arising from the randomization process**	Low risk of bias	Quote: "60 patients were randomised to receive either NI (29) or UC (31)" Comment: Author of this SR received information from study author about allocation concealment method. Concealed opaq envelopes and randomized.
Domain 2	High risk of bias	Hard to blind participants, dietitians and assessors adequately, therefore assessed at high risk of bias.

Due to deviations from the intended interventions		
Domain 3 ***Due to missing outcome data***	Low risk of bias	6 participants lost to follow-up 14% loss from intervention group and 6.5% loss from control group. All analysis were performed on an intention-to-treat basis.
Domain 4 **In measurement of the outcome**	Low risk of bias	Methods of assessment were standard scales or BIA body composition scales, and validated screening tool
Domain 5 **In selection of the reported result**	Low risk of bias	Pre-specified outcome measurements Not eligible for multiple measurements
Overall risk of bias	**High risk of bias**	

4.3 Ravasco et al. 2005

Characteristics of included study (Ravasco et al., 2005)		
Methods	Randomized controlled trial Parallel design with 3 arms (2 intervention groups, 1 control group) Study period: 12 weeks University Hospital Lisbon Portugal	
Participants	Adult patients > 18 years with a diagnoses of HNC, referred for RT N = 75 (60 males and 15 females) (Intervention group 1 n = 25. Dietary counseling) (Intervention group 2 n = 25. The use of oral nutritional supplements) (Control group 3 n = 25) Mean age = 60 ± 11 years Attrition: 0 pts lost to follow-up No significant difference in patient characteristics at baseline Nutritional status: at baseline 45/75 participants were 'malnourished' (identified by nutritional screening tool PG-SGA); intervention group 1 n = 16 ; intervention group 2 n = 14; control group 15)	
Interventions	Group 1. Individualized dietary counselling to achieve calculated energy and protein requirements using real foods, no use of oral nutritional supplements, only real foods. (Group 2. 2x 200 mL cans of nutritional supplement) 7 dietary counseling sessions. Each session lasting about 40-60 minutes.	
Comparison	Standard routine clinical care (UC) Eat ad lib. No other intervention	
Outcomes	Survival, weight (kg), energy intake, nutritional status (PG-SGA), symptom-induced morbidity, QoL, physical function	
Risk of Bias (RoB) assessment		
Risk of Bias	***Authors judgement***	***Support for judgement***
Domain 1		Quote:

Arising from the randomization process	Low risk of bias	"Subjects were randomized to receive either NI (n=15) or UC (n=21). Randomization occurred after consent to participate was obtained" Comment: Author of this SR received information about randomization and concealment. Concealment by opaque sealed envelopes, and randomization by correct measures.
Domain 2 ***Due to deviations from the intended interventions***	High risk of bias	Hard to blind participants, dietitians and assessors adequately, therefore assessed at high risk of bias.
Domain 3 ***Due to missing outcome data***	Low risk of bias	No participants lost to follow up Intention-to-treat analysis stated
Domain 4 ***In measurement of the outcome***	Low risk of bias	Methods of assessment were standard scales or BIA body composition scales, and validated questionnaires for physical function and quality of life.
Domain 5 ***In selection of the reported result***	Low risk of bias	Pre-specified outcome measurements
Overall risk of bias	High risk of bias	

Appendix 5: Certainty of evidence

5.1 GRADE assessment for body of evidence for weight

GRADE domain	Outcome of interest: Weight (kg) Judgement		Concerns about certainty domains
Methodological limitations of the studies	The three studies that measured changes in weight all had high risk of bias in Domain 2, due to concerns of lack of blinding. In one of the studies, there was concern of research bias. The overall risk of bias for these three studies had serious methodological limitations. This lowers our confidence in any effect		Very serious
Indirectness	The patients, interventions, and comparisons in the three studies mostly gave direct evidence to the clinical question asked in the two studies. The interventions included dietary counseling by an RD, two studies included use of oral nutritional supplements if deemed appropriate. The third study offered 2 dietary counseling sessions to the standard clinical care group (5 out of 31 requested this service). All used same numeric weight scale (kg). We judged that there was not serious indirectness between these studies.		Not serious
Imprecision	Number of participants n = 146 although results only stated for 119 for this outcome measure. Small study samples and confidence intervals were moderately wide, although overlapping. The studies all reported changes in weight in favor of dietary counseling with or without oral nutritional supplements. Number of interventions were 7-9 sessions during 12-week study periods. Mean results were not very different, but we still judged the evidence to have some serious imprecision.		Serious
Inconsistency	Results showed smaller decrease in weight loss and increase in weight favoring dietary counseling with or without oral nutritional supplements. The size of the effect varied between the studies, though confidence intervals overlap. We judged the evidence to have no serious inconsistency in results across studies.		Not serious
Publication bias	Publication bias has not been detected comprehensive database searches were performed for this SR. Negative and positive studies published.		Not suspected
Outcome	Effect	No of participants (studies)	Certainty of evidence
Weight.in kilograms (kg)	Three studies showed increase in weight favoring dietary counseling	146 participants (results stated for 119 participants) (3 studies)	⊕⊕◯◯ LOW

The outcome of interest is weight (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided).Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

5.2 GRADE assessment for body of evidence energy intake

GRADE domain	Outcome of interest: Energy intake (kcal/day) Judgement		Concerns about certainty domains
Methodological limitations of the studies	Two studies that measured energy intake had low risk of bias in Domain 1, but high risk of bias in Domain 2, due to concerns of lack of blinding. In one of the two studies, there was concern of research bias. The overall risk of bias for these two studies had serious methodological limitations. This lowers our confidence in any effect		Very serious
Indirectness	The patients, interventions, and comparisons in the included studies mostly gave direct evidence to the clinical question asked in the two studies. The interventions included dietary counseling by an RD, one study included use of oral nutritional supplements if deemed appropriate. The other study offered 2 dietary counseling sessions to the standard clinical care group (5 out of 31 requested this service). The two studies used the same numeric kilo caloric scale for the outcome measure for energy intake. We judged that there was not serious indirectness between these studies.		Not serious
Imprecision	Number of participants n = 104. Small study samples and confidence intervals were moderately wide, and not overlapping. Number of interventions were 7-9 sessions during 12-week study periods. Both studies reported changes in energy intake in favor of dietary counseling with or without oral nutritional supplements. The mean results for this outcome measure were very different, and we judged the evidence to have very serious imprecision.		Very serious
Inconsistency	Results showed increase in energy intake favoring dietary counseling with or without oral nutritional supplements. The size of the effect varied largely between the two studies and confidence intervals did not overlap. We judged the evidence to have serious inconsistency in results across the two studies.		Serious
Publication bias	Publication bias has not been detected comprehensive database searches were performed for this SR. Negative and positive studies published.		Not suspected
Outcome	Effect	No of participants (studies)	Certainty of evidence
Energy intake. Assessed by kilo caloric intake per day	Two studies showed increase in energy intake favoring dietary counseling	104 participants (2 studies)	⊕◯◯◯ VERY LOW

The outcome of interest is daily energy intake (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided).Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

5.3 GRADE assessment for quality of life

GRADE domain	Outcome of interest: Quality of life (points) Judgement		Concerns about certainty domains
Methodological limitations of the studies	Two studies that measured quality of life had low risk of bias in Domain 1, but high risk of bias in Domain 2, due to concerns of lack of blinding. In one of the two studies, there was concern of research bias. The overall risk of bias for these two studies had serious methodological limitations. This lowers our confidence in any effect		Very serious
Indirectness	The patients, interventions, and comparisons in the two studies mostly gave direct evidence to the clinical question asked in the two studies. The interventions included dietary counseling by an RD, one study included use of oral nutritional supplements if deemed appropriate. The other study offered 2 dietary counseling sessions to the standard clinical care group (5 out of 31 requested this service) The two studies both used the same numeric EORTC points score scale to measure quality of life. We judged that there was not serious indirectness between these studies.		Not serious
Imprecision	Number of participants n = 104. Small study samples. No confidence intervals were available due to missing SDs. Number of interventions were 7-9 sessions during 12-week study periods. Both studies reported quality of life in favor of dietary counseling with or without oral nutritional supplements. The results for this outcome measure were very different, and we judged the evidence to have very serious imprecision.		Very serious
Inconsistency	Results showed increase in quality of life favoring dietary counseling with or without oral nutritional supplements. The size of the effect varied between the two studies. We judged the evidence to have serious inconsistency in results across the two studies.		Serious
Publication bias	Publication bias has not been detected comprehensive database searches were performed for this systematic review. Negative and positive studies published		Not suspected
Outcome	Effect	No of participants (studies)	Certainty of evidence
Quality of life Assessed by EORTC scores in points, the higher the points the higher the quality of life	Two studies showed increase in quality of life favoring dietary counseling	104 participants (2 studies)	⊕◯◯◯ VERY LOW

The outcome of interest is quality of life (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided).Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

5.4 GRADE assessment for physical function

GRADE domain	Outcome of interest: Physical function Judgement		Concerns about certainty domains
Methodological limitations of the studies	Two studies that measured physical function had low risk of bias in Domain 1, while both studies had high risk of bias in Domain 2, due to concerns of lack of blinding. In one of the two studies, there was concern of research bias.in one study. The overall risk of bias for these two studies had serious methodological limitations. This lowers our confidence in any effect		Very serious
Indirectness	The patients, interventions, and comparators in the included studies mostly gave direct evidence to the clinical question asked in the studies. The interventions included dietary counseling by an RD, only two studies included use of oral nutritional supplements if deemed appropriate. One study offered 2 dietary counseling sessions to the standard clinical care group (5 out of 31 requested this service). Both studies used the EORTC points score scale for physical function. We judged that there was not serious indirectness between these studies.		Not serious
Imprecision	The number of included participants in the studies that measured physical function was n = 104. Number of interventions were 7-9 sessions during 12-week study periods. Small study samples. No confidence intervals were available due to missing data of standard deviations. Both studies reported physical function in favor of dietary counseling with or without oral nutritional supplements. The results for these two studies for physical function were very different, and we judged the evidence to have very serious imprecision.		Very serious
Inconsistency	For physical function results showed increase in physical function favoring dietary counseling with or without oral nutritional supplements. The results varied between the two studies. We judged the evidence to have serious inconsistency in results across the two studies.		Serious
Publication bias	Publication bias has not been detected comprehensive database searches were performed for this SR. Negative and positive studies published.		Not suspected
Outcome	Effect	No of participants (studies)	Certainty of evidence
Physical function Assessed by EORTC scores in points, the higher the points the higher the physical function	One study showed increase in physical function favoring dietary counseling. One study showed a slight decrease in physical function in the dietary counseling group	104 participants (2 studies)	⊕◯◯◯ VERY LOW

The outcome of interest is physical function (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided). Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

5.5 GRADE assessment for readmissions to hospital

GRADE domain	Outcome of interest: Hospital readmission Judgement	Concerns about certainty domains
Methodological limitations of the studies	Not measured	
Indirectness	Not measured	
Imprecision	Not measured	
Inconsistency	Not measured	
Publication bias	Not measured	

Outcome	Effect	No of participants (studies)	Certainty of evidence
Hospital readmission	We have no evidence on the effect of dietary counseling versus standard clinical care on hospital readmission	N/A	N/A

The outcome of interest is hospital readmissions.

Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.

5.6 GRADE assessment for mortality

GRADE domain	Outcome of interest: Mortality Judgement		Concerns about certainty domains
Methodological limitations of the studies	Not measured		
Indirectness	Not measured		
Imprecision	Not measured		
Inconsistency	Not measured		
Publication bias	Not measured		
Outcome	Effect	No of participants (studies)	Certainty of evidence
Mortality	We have no evidence on the effect of dietary counseling versus standard clinical care on mortality	N/A	N/A

The outcome of interest is mortality.

Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ⊕⊕⊕⊕, moderate certainty ⊕⊕⊕O, low certainty ⊕⊕OO and very low certainty ⊕OOO.