1. Introduction

Head and neck squamous cell cancer (HNSCC) involves cancer of the oral cavity, oropharynx, hypopharynx and larynx. It constitutes the 7th most common malignancy in the world accounting for over 600,000 new cases per year. Dysphagia and treatment-related problems, such as mucositis and nausea, are common among patients with HNSCC. Due to these problems, food intake is often diminished, leading to unintentional weight loss, and malnutrition. Malnutrition in HNSCC may be caused by swallowing or chewing problems as a result of the location of the tumor, metabolic effects of the tumor itself (i.e. cancer cachexia), a history of heavy smoking and excessive alcohol consumption, and by the toxicity of the multimodal cancer treatment.

Before the start of radiotherapy (RT) or chemoradiotherapy (CRT), 3–52% of the patients are malnourished. During RT and CRT this percentage of malnourished patients rises to 44–88%.

Abbreviations: QoL, quality of life; HNSCC, head and neck squamous cell cancer; RT, randomized controlled trial; ONS, oral nutritional supplements; PEG, percutaneous endoscopic gastrostomy; RT, radiotherapy; CRT, chemoradiotherapy; NG, nasogastric.

Parts of the results were presented at the 34th congress of the European Society for Clinical Nutrition and Metabolism (ESPEN).
Prevalences of malnutrition vary considerably between the studies due to the location of the tumor, the intensity of the therapy and the different definitions for identification of malnutrition.

It is recognized that malnutrition causes a wide range of physiological and clinically relevant side effects. It is associated with lower physical functioning, lower immune status, more severe grade III/IV late RT-induced toxicities, treatment interruption of chemo(radio)therapy, lower chemotherapy response rates, hospital readmission, impaired quality of life (QoL), and increased mortality. Therefore, it is important to prevent, recognize and treat malnutrition in an early phase of HNSCC treatment. An overview of different types of nutritional interventions and their impact is missing. We therefore performed a systematic review of randomized controlled trials, examining the effect of nutritional interventions on nutritional status, QoL and mortality in RT or CRT-treated patients with HNSCC.

2. Materials and methods

This systematic review was performed by a predefined protocol according to the Cochrane Handbook for systematic reviews, and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

2.1. Data sources and searches

We conducted systematic searches for randomized controlled trials (RCTs). Trials were identified by searching Pubmed (MEDLINE), EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally, we examined reference lists of included studies for additional trials, and contacted authors if necessary. Our overall search strategy included terms for HNSCC (e.g., “head and neck neoplasms”, “head and neck squamous cell carcinoma”), RT or CRT (e.g., “radiotherapy”, “chemotherapy, adjuvant”), nutritional interventions (e.g., “nutrition therapy”, “dietary services”, “dietary supplements”), and randomized controlled trials (e.g., “controlled clinical trials”, “random allocation”). The full search strategy of each database is shown in Appendix 1. The electronic databases were searched for articles published through 3rd January 2012. There was no restriction regarding publication year, but we restricted our search to English and Dutch articles. An experienced information specialist supported the whole literature search process.

2.2. Eligibility criteria

We included randomized controlled trials examining adult HNSCC patients (≥18 years of age) with RT or CRT as primary therapy or as post-operative therapy. We also included trials with other types of cancer if more than two-thirds of the participants were HNSCC patients. Furthermore, interventions that aimed at maintenance and/or improvement of patients’ nutritional status before, during and/or after RT or CRT were included in the review. A broad range of nutritional support was considered: individualized dietary counseling, oral nutritional supplements (ONS), enteral feeding, parenteral nutrition, immunonutrition or a combination of these interventions. Any type of comparator intervention was included, for example maintenance of usual diet, usual care, placebo nutritional supplement, or optimal oral nutrition. Finally, we included trials that studied primary outcomes of this review: patients’ nutritional status, QoL and mortality. Secondary outcomes were nutritional intake, complication rate, treatment delay or interruption, unplanned hospital admissions, and clinical functioning. Any follow-up period was included. Unpublished studies and ongoing studies were excluded.

2.3. Study selection

Two review authors (J.L. and M.Z.), independently, first selected studies based on titles, keywords and abstracts. The same two reviewers independently performed the second selection, based on full-text trial reports. Any discrepancies were discussed and resolved in a consensus meeting.

2.4. Data extraction and quality assessment

Data from the included studies were collected on standardized data extraction forms. Furthermore, the risk of bias of the included studies was assessed using the Cochrane Collaboration’s tool. We categorized studies as “low risk” of bias, “high risk” of bias or “unclear risk” of bias. Two authors (J.L. and M.Z.) independently extracted data, and assessed the risk of bias of the original study reports. Disagreement was resolved by contacting a third author (S.E. or M.T.).

2.5. Data synthesis and analyses

A mean difference in the outcome between the intervention and control group was directly extracted from study reports or estimated indirectly from other reported data. These treatment effects were summarized descriptively in the systematic review. Although planned, we refrained from performing a meta-analysis due to substantial clinical heterogeneity with regard to intervention characteristics or reported outcome variables.

3. Results

3.1. Literature search

We identified 24 study reports after our first selection (see Fig. 1). After full-text assessment of those articles, we included 12 study reports in our review. These 12 articles reported on 10 different studies, since 2 studies have been presented in 2 publications each. One study reported the results of 2 different interventions. Therefore, we finally included 10 randomized controlled trials on 11 interventions with in total 536 participants.

3.2. Risk of bias assessment

All included studies had a high risk of bias (Appendix 2). None of the studies described a blinding procedure of patients and personnel and were rated as high risk on performance bias (Fig. 2). Five RCTs performed an appropriate randomization procedure. Two RCTs performed an inappropriate randomization procedure, and one trial used an inadequate randomization (postal code) and had a high risk of selection bias. Four studies did not report results on pre-stratified outcomes or reported outcomes differently than described in the method section. Therefore, these studies have a high risk on reporting bias. Furthermore, the most important source of other biases were an imbalance in prognostic factors between the groups at baseline, low compliance, and no intention-to-treat analysis.

3.3. Study description

The characteristics of the 10 included studies are summarized in Appendix 3. Publication year of the studies ranged from 1984 to 2012. The majority of the studies had small sample sizes, ranging from 23 to 134 participants. All study populations included more males (58% to 92%) than females. Participants were on
average 60 years of age, but one study had younger patients (mean age close to 50 years). The majority of the participants had cancer of the pharynx or larynx. The most common treatment-modality was primary RT or CRT, with a mean RT dose of approximately 65 Gy.

Four RCTs (5 publications) examined the effect of individualized dietary counseling by a dietitian versus no counseling or general nutritional advice by a nurse. Three trials examined the effect of oral nutritional supplements versus no supplements. The impact of tube feeding compared to oral nutrition was examined in one study with 2 reports. One study examined the impact of percutaneous endoscopic gastrostomy (PEG) feeding compared to nasogastric (NG) feeding. Two studies compared prophylactic PEG feeding with no prophylactic tube feeding.

3.4. Individualized dietary counseling versus no counseling or standard nutritional advice (4 studies)

All four studies examining the effect of individual dietary counseling reported positive effects on nutritional status in patients receiving counseling versus no counseling or standard nutritional advice by a nurse. Three of these studies reported on body weight changes during and after RT, and all found positive effects on body weight in patients receiving individualized dietary counseling. They reported less loss of body weight post-RT and maintenance of body weight within the individualized counseling group versus a decrease of body weight within the no or standard nutritional advice group during RT. Three studies reported on malnutrition, and showed less malnourished patients in the group receiving individualized dietary counseling compared to the no or standard nutritional advice group.
advice. However, two of these three studies reported this positive effect only at eight weeks after the start of RT and not at all points in time.

The two out of four included studies examining quality of life (QoL) reported positive effects of individualized dietary counseling versus no or standard nutritional advice. One of these studies found a greater deterioration in global QoL and physical functioning in the group with no or standard nutritional advice when compared to the individualized counseling group. The other QoL-study reported a major deterioration in global QoL and physical functioning after no or standard advice, and an improvement of global QoL and physical functioning scores in the individualized dietary counseling group.

None of the four included studies reported the impact of individualized dietary counseling on mortality. Intake of energy and protein was investigated in two out of four studies. Intake was significantly higher after individualized dietary counseling than after no or standard advice (Appendix 4). One individualized counseling study found a worsening of RT-induced symptoms in the group with no or standard nutritional advice, and no worsening after individualized counseling. Another study reported no major differences in RT-induced symptoms between both groups at the end of RT. Between the end of RT and 3 months after RT, the group receiving individual dietary counseling had greater reduction in symptom incidence than the control group.

One of the four included studies found a statistically significant deterioration in serum protein, albumin, and transferrin after no or standard nutritional advice, and maintenance of these parameters reported.

In summary, individualized dietary counseling showed beneficial effects in nutritional intake, nutritional status and QoL in HNSCC patients undergoing RT or CRT-treatment. Effects on complications seemed to be inconsistent; effects on mortality were not reported.
3.5. Oral nutritional supplements (3 studies)

Three studies examined the impact of ONS versus no supplements on nutritional status.21,22,25 Two of them showed positive effects in the group receiving ONS after RT,21,22,25 the third study did not.25 One of the positive studies21 reported a significant increase of body weight, triceps skin-fold and mid-arm circumference after ONS compared to the patients without oral supplements. The other positive study reported that less patients in the supplemented group experienced nutritional deterioration during RT, but no difference was found at three months post-RT.12

One out of three studies reported a major deterioration in global QoL and physical functioning in patients receiving no ONS, and an improvement of these QoL scores after ONS at the end of RT and post-RT.26 None of the three studies reported the impact on mortality.

Two of the three studies examined total energy intake.22,25 Both studies reported higher energy intake in the ONS group than in the no ONS group during RT, although one of them did not reach significance (p = 0.07).22 These two studies also showed higher intake of protein in the ONS group during RT.22,25 Three months post-RT, no difference was seen in energy and protein intake between groups.22

Furthermore, one study found no major differences in RT-induced symptoms between both groups at the end of RT and 3 months after RT.22

In summary, ONS showed beneficial effects on energy and protein intake during radiotherapy in patients with HNSCC. Beneficial effects were also found for QoL, but this was only based on one study. Effects on nutritional status were inconsistent.

3.6. NG tube feeding versus optimal oral nutrition (1 study)

One study (two reports) examined the effect of NG tube feeding compared to oral nutrition on nutritional status in locally advanced HNSCC of the oral cavity, larynx, oropharynx, hypopharynx, and nasopharynx (primary and recurrent tumors). This study showed positive effects on body weight, but only in the subgroup of NG tube fed patients with other HNSCC than primary nasopharyngeal cancer (Appendix 4).18,26

The study reported no significant differences in survival-rates between the NG tube feeding and control group.

Energy and protein intake were reported to be significantly higher than baseline in NG tube fed patients, not in patients receiving oral nutrition.18,26 The study showed negative effects on the incidence of severe (grade III) toxicity (dysphagia, xerostomia, mucositis, nausea, vomiting, constipation and diarrhea) in NG tube fed patients.26 These acute toxicities also had a significantly longer duration in NG tube fed patients.26

3.7. PEG versus nasogastric tube feeding (1 study)

One study examined the effect of PEG feeding compared to NG feeding on nutritional status, and reported positive short-term effects on body weight and triceps skin-fold thickness, but not on mid-arm circumference (see Appendix 4).17 Patients with PEG feeding had gained body weight at six weeks post-RT. At six months post-RT, body weight was not significantly different between groups. QoL and mortality were not examined in this study.

The study reported no feeding tube dislodgement in the PEG feeding group (n = 0/15) versus 12 patients with dislodgements in the NG group (n = 12/18).

3.8. Prophylactic PEG versus no prophylactic PEG (2 studies)

Two studies examined the effect of prophylactic PEG feeding compared to no prophylactic PEG feeding on nutritional status (Appendix 3). One of these two studies reported no significant changes in BMI between the groups at the end of RT and 6 months after RT.23 The other study reported no significant differences in body weight at six months, one year and two years after the start of the anti-cancer treatment (Appendix 4).28 However, when only patients who lost weight were taken into account, body weight loss was lower in prophylactic PEG fed patients compared to control patients. They also found a positive trend for less malnourished patients in the prophylactic PEG group 2 months after start of treatment (p = 0.059), but did not find differences at other time-points during and after RT.28

Both studies examined the effect of prophylactic PEG feeding on QoL. One study found significantly less deterioration of QoL in the prophylactic PEG feeding group in one dimension scale (in mental functioning), and at only one point in time (at the end of RT), but no difference on other dimensions of QoL or other time-points.23 The other study reported higher global QoL and physical functioning scores in the prophylactic PEG group than in the no prophylactic PEG group at 6 months after the start of the anti-cancer treatment, but not at 1 year and 2 year follow-up.28

Both studies did not find significant differences in mortality between groups.

One study28 reported less prophylactic PEG fed patients suffering from dysphagia than the control group at one year after start of anti-cancer treatment.

In summary, two studies examining prophylactic PEG feeding in HNSCC patients showed no beneficial effects on nutritional status compared to tube feeding if required. No differences were found for mortality. Effects on QoL were inconsistent.

4. Discussion

Weight loss during RT or CRT is a substantial problem in HNSCC patients and it is accompanied by loss of fat free mass, i.e. muscle and organ mass, deterioration in QoL, more severe treatment-induced toxicity, and a shorter survival.12

In this systematic review we studied the effects of different types of nutritional interventions in patients with HNSCC receiving RT or CRT. Individualized dietary counseling versus no or standard nutritional advice showed consistent beneficial effects on energy and protein intake, nutritional status and QoL, but inconsistent effects on complications. Oral supplementation versus no oral supplementation showed short-term effects on energy and protein intake and inconsistent effects on nutritional status. It also showed beneficial effects on QoL, although this is based on only one study. NG tube feeding versus oral nutritional supplements showed no beneficial effects on mortality, negative effects on treatment toxicities, and beneficial effects on nutritional status in a subgroup of patients with other HNSCC than primary nasopharyngeal cancer. PEG feeding versus NG feeding showed beneficial short-term, but no long-term effects, on nutritional status. Also, comparison of prophylactic PEG feeding versus no prophylactic PEG feeding showed no effects on nutritional status and mortality and inconsistent effects on QoL. However, effects of the different kinds of tube feeding were based on three comparisons with only one or two studies each.

Individualized dietary counseling was found to be effective in maintaining weight and/or nutritional status, when compared to standard nutritional advice by a nurse20,24 or ad libitum intake.22,27 Individualized dietary counseling, as described in the included studies, consisted of regular counseling by a dietician to reach the
individual requirements through normal food products. If required, additional nutritional supplements were advised in two studies and NG or PEG tube feeding in one study. The effectiveness of dietary counseling may probably be attributed to the individual approach of an expert, by calculating individual nutritional requirements, choosing an appropriate regimen that meets these requirements and making a personalized plan. Also, the frequent evaluation of dietary intake allows for timely adjustments to be made in dietary advice. Arnold et al. did not show a benefit of ONS on nutritional status above intensive dietary counseling. However, ONS versus ad libitum intake might have short-term beneficial effects on nutritional status. NG tube feeding might be a solution in case of inadequate intake in patients receiving dietary counseling, but the benefit of NG tube feeding is only seen in a selection of patients. Daly et al. and Hearne et al. only found less weight loss in NG tube fed patients compared to controls in the subgroup of patients with other HNSCC than primary nasopharynx cancer. Reason for concern was the higher proportion of patients with severe RT-induced toxicity in the NG tube fed group. This adverse event might be due to the slightly larger RT field size in this group, but definitive conclusions cannot be drawn from this small study. From the thoracic CRT is one of the standard treatment modalities in HNSCC, but it is associated with more therapy-induced toxicity and weight loss. In CRT-patients the use of tube feeding by prophylactic PEG has become an accepted practice. A prophylactic PEG ensures optimal nutrition as soon as toxicity diminishes oral food intake and the possibility of continuing tube feeding for a prolonged period. Retrospective studies showed that patients with PEG feeding maintained their nutritional status better than patients with NG tube feeding or oral nutrition. Not all of the randomized controlled studies included in our systematic review support this finding. Corry et al. did find less weight loss at the end of CRT in favor of PEG feeding over NG tube feeding. Moreover, they and others also found less treatment interruptions in patients receiving PEG feeding. On the other hand, Salas et al. and Silander et al. did not find beneficial effects of prophylactic PEG feeding versus tube feeding on indication. One of the reasons for no differences between groups in these studies could be that the effect is underestimated, since approximately two-third of the control patients also required tube feeding. Moreover, Silander only measured long-term effects of PEG feeding on weight loss, while the effect of early prophylactic PEG feeding might be more apparent shortly after RT.

It has been suggested that patients with PEG feeding develop severe dysphagia more often. This phenomenon was also seen in the randomized controlled study of Corry et al., although not significantly different between groups. Grade 3 dysphagia was present at 6 months in 4 out of 15 patients with PEG feeding against 1 out of 18 patients with NG tube feeding. Moreover, duration of PEG feeding was over two times longer than the duration of NG feeding. PEG insertion and removal is not without risk. The prevalence of major complications related to the PEG procedure in HNSCC patients was calculated to be 7.4%, and could include gastrointestinal bleeding, gastrocutaneous fistula, peritonitis, perforation, aspiration, pneumonia, metastasis to the gastrostomy site and even procedure related mortality. Therefore, it is important to study which groups do benefit of prophylactic PEG feeding and to start nutritional support based on risk profiles. If prophylactic PEG feeding is indicated, it might be effective to encourage oral intake and to give swallowing exercises.

The strength of our review is a solid literature search, inclusion of RCTs only, assessment of the risk of bias, and the complete overview of nutritional interventions in patients with HNSCC. Unfortunately, we were not able to perform a meta-analysis due to clinical heterogeneity. Since the majority of the included studies had small sample sizes, a meta-analysis would have been useful to increase precision.

The included studies were all rated as high risk of bias. None of the studies reported on blinding the participants and personnel. We assumed that in some nutritional interventions it was not feasible to blind participants or personnel (tube feeding versus oral nutrition), but the consequence is that the results of these studies should be carefully interpreted.

Keeping these limitations in mind, we can still conclude that individualized dietary counseling by a dietician has some beneficial effects on both nutritional status and quality of life, compared to no counseling or standard nutritional advice by a nurse. Effects of ONS and tube feeding were inconsistent. However, there were only a few studies, with small sample sizes, control groups hardly distinguishable from intervention groups and a high risk of bias. Thus, strong conclusions are not warranted. Future studies should focus on defining risk factors for intensive nutritional support, and on evaluating decision trees for stepped care nutritional intervention programs.

**Author contribution**

The authors’ responsibilities were as follows: J.L. conceived the study in accordance with S.E. and R.L. J.L. and M.Z. designed the study, determined eligibility of trials, extracted data from the trials, assessed the methodological quality of the trials, interpreted results and drafted the manuscript. S.E. and M.T. contributed to the assessment of methodological quality of the trials. S.E., M.T., R.L., M.K. and P.W. critically revised the article for important intellectual content. All authors approved the final version.

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**Conflict of Interest**

J.L. has received part of her honorarium at the VU University Medical Center Amsterdam from payment by the funding source. M.Z., S.E., M.T., R.L. and P.W. indicated no potential conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clnu.2013.06.012.

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