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ORIGINAL ARTICLE

Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review

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Abstract
Purpose Squamous cell carcinoma of the head and neck (HNSCC) is associated with weight loss before, during, and after treatment with radiotherapy (RT). This systematic review addressed the question "Which interventions aimed at optimizing nutrition are of benefit to HNSCC patients receiving RT?"
Methods Randomized controlled trials (RCTs) studying interventions directed at nutritional support of adult patients with HNSCC receiving RT with or without chemotherapy were eligible. RCTs studying prophylaxis of acute mucositis, perioperative nutrition, or palliative and non-HNSCC populations were excluded. A comprehensive literature search was done and meta-analyses planned.
Results Ten unique RCTs were identified (n=585). All randomized less than 50 patients per trial arm. Five trials studied dietary counseling and/or nutritional supplements, four studied drug interventions, and one studied prophylactic enteral tube feeding. Nutritional status appeared to be maintained or improved with dietary counseling, megestrol acetate, and prophylactic enteral tube feeding.
Conclusions Data from RCTs supporting the use of interventions to optimize nutrition in HNSCC patients receiving RT are limited in both quantity and quality. Potentially effective interventions have not been tested comparatively or in combination, and few patients receiving chemoradiotherapy were studied. Further research in this area is a priority.

Keywords Nutrition · Radiotherapy · Head and neck neoplasms · Megestrol acetate · Enteral feeding

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Introduction

Although squamous cell carcinomas of the head and neck cancers (HNSCC) account for only 4% of all malignancies in the USA, more than 900,000 cases are diagnosed annually worldwide [1]. Head and neck cancer and its treatment may have serious functional consequences for patients. The majority of HNSCC patients present with locally advanced disease, and over half are nutritionally compromised at the time of diagnosis due to dysphagia or odynophagia from the primary tumor [2]. Treatment typically includes radical external beam radiotherapy (RT), which may further exacerbate nutritional compromise as a result of acute mucositis and loss of taste sensation. One third of patients experience severe weight loss during RT. Acute toxicities are exacerbated by the use of concurrent chemotherapy (CRT), which may additionally cause anorexia, nausea, and vomiting [3]. Futhermore, nutritional compromise may continue after treatment due to chronic xerostomia, dysphagia, and fibrosis [4].

Nutritional compromise is associated with increase in morbidity and mortality in HNSCC patients. Nutritionally compromised patients have higher susceptibility to infection, less resistance to treatment toxicity, and a worse response to treatment [5]. Despite the recognized importance of nutrition, the optimal approach to maintaining nutrition in HNSCC patients is unclear. Treatment of acute RT-related oropharyngeal mucositis is symptomatic, so attention has been directed toward prophylaxis, and this topic has been recently reviewed [6]. Only amifostine was found to have a significant prophylactic effect. Palifermin (recombinant keratinocyte-growth factor) reduces the frequency and severity of acute mucositis from CRT by facilitating regeneration of the oropharyngeal mucosal lining and is currently under study.

Currently, most HNSCC patients receiving RT or CRT are offered dietary counseling and nutritional supplements plus enteral tube feeding if significant weight loss is present prior to treatment. Prophylactic enteral feeding tubes may also be offered. The use of nasogastric vs percutaneously placed tubes in this setting is controversial [7]. This systematic review attempted to answer the question "Which interventions aimed at optimizing nutrition are of most benefit to HNSCC patients receiving RT or CRT?" by identifying randomized controlled clinical trials (RCTs), studying these interventions and synthesizing and analyzing their results.

Methods

Data sources and searches

Electronic databases were searched for relevant citations including MEDLINE (1966 to December 2007), the Cochrane clinical trials database (CCTR), EMBASE, and the American Society of Clinical Oncology and European Society of Medical Oncology abstract databases. A comprehensive hierarchical literature search of the electronic databases was conducted using the following terms: "nutrition in head and neck cancer," "head and neck neoplasms," "radiation," "radiotherapy," "chemoradiotherapy," "feeding or gastrostomy tube," "anabolics," "megestrol," "nutrition," and "weight loss." These terms were combined (with truncations as necessary) into search phrases like the following: (1) "Nutrition in head and neck cancer," (2) "(head and neck) and (radiat* or radio*) and (feeding or gastrostomy) tube," (3) "(head and neck) and (radiat* or radio*) and (megestrol)," (4) "(head and neck) and (radiat* or radio*) and (nutrition)," (5) "(head and neck) and (radiat* or radio*) and (weight loss)." Additional terms ("supplements," "counseling," and "protein intake") were also used and truncated where necessary. Those terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. The bibliographies of eligible RCTs and relevant review articles were also searched for additional trials.

Study selection

Articles were eligible for inclusion if they were RCTs studying interventions directed at nutritional support of adult patients with a diagnosis of HNSCC receiving either RT or CRT as a component of definitive treatment. Previous systematic reviews or evidence-based guidelines that addressed this topic were also potentially eligible. Retrospective studies, narrative reviews, and nonrandomized trials were excluded. RCTs studying interventions aimed at prophylaxis of acute mucositis, perioperative nutritional interventions, or nutritional interventions in a palliative setting or in non-HNSCC populations were also excluded.

Data extraction and quality assessment

Citations identified by the literature search strategy were screened for eligibility by two of the authors (SG, EW) and discrepancies resolved by consensus. Data pertaining to trial design, participants, interventions, and outcomes were extracted from each eligible trial by one reviewer (SG) and audited by a second reviewer (EW) independently. Outcomes of interest included: weight loss, measures of nutritional status, measures of nutritional intake, adverse effects of nutritional interventions, health-related quality of life (HRQoL) measures, cancer treatment toxicity, tumor response to cancer treatment, and overall mortality. Where multiple publications of the same RCT were available, the report referenced was that from which data were extracted for analyses. Information indicative of trial quality, including methods of randomization, absence or degree of blinding, completeness of patient follow-up, and whether statistical analyses were performed by intent-to-treat were also extracted from each trial report. In cases where there were questions regarding trials results, the corresponding author was contacted for clarification.

Statistical analysis

This review is based on data provided by published reports. Statistical pooling (meta-analysis) of data from RCTs was done if similar control arms and outcomes measures were reported. Where pooling was not possible, an interpretive summary of the data was generated. Meta-analysis used a random effects model, and forest plots were computed using Review manager 5.

Results

Literature search results

The literature search identified ten unique RCTs published between 1984 and 2005 studying interventions aimed at optimizing nutritional status in HNSCC patients receiving RT or CRT (Table 1) [8–17]. Five trials studied dietary counseling and/or nutritional supplements, four studied drug interventions, and one studied prophylactic enteral tube feeding. Eight were published as full reports in English; one was published as full report in the Norwegian language with only an abstract available in English; and one was available only as a meeting abstract. No published systematic reviews or evidence-based guidelines specific to this topic were identified.

A total of 585 patients were randomized, ranging from 23 to 129 per RCT. All trials randomized less than 50 patients per arm. Three trials included other cancer types in their reports (59 lung cancer patients in two reports; 14 esophageal, abdominal, and rectal in one report); thus, the trials randomized a total of 512 head and neck cancer patients. There were eight two-arm and two three-arm trials, providing 22 comparisons. Only the four drug trials were placebo-controlled, and three of these were the only double-blinded trials. Two trials described the methods used to randomize patients [12, 15], and three reported that treatment arms were balanced for important baseline prognostic factors [12, 14, 15]. Four performed statistical analyses according to intent to treat [9, 11, 12, 15]. Two trials excluded patients receiving enteral or parenteral feeding [11, 15], and three trials reported the number of these patients [8, 13, 17]. Over 95% of the evaluable HNSCC patients received RT alone, or after neoadjuvant chemotherapy in one trial [12].

Dietary counseling and nutritional supplements

Five trials studying dietary counseling with or without nutritional supplements were identified [8–12]. A total of 257 patients (240 HNSCC) were randomized. Counseling consisted of intensive nutrition advice from trained dieticians. Supplements used in studies included protein-rich liquids (Ensure™ and Sustacal™). Four of the studies showed reduced weight loss for the counseling and/or nutritional supplement groups compared to the control (Table 2). Meta-analysis was not performed due to differences in reported outcome measures.

Arnold et al. [8] compared nutritional supplements (Sustacal™) to a control group. All patients received intensive nutritional counseling. The control group was slightly older and had more male patients. No difference in weight loss between groups at any stage of treatment was reported. This study also reported no difference in tumor response to cancer treatment or patient survival based on whether or not patients received nutritional supplements. Nayel et al. [9] also studied nutritional supplements (Ensure™). It was unclear whether patients also received dietary counseling. More control group patients (58%) lost weight compared to the supplemented group (0%). Control patients lost a median of 2% body weight, and supplemented patients gained a median 5%. Fewer treatment interruptions were reported in the supplemented group due to a reduction in the frequency and severity of acute mucositis and/or maintenance of performance status. Oral nutritional supplements did not affect patient rated scores of dry mouth, changes in taste, or changes in appetite.

Lovik et al. [10] compared nutritional counseling from a trained dietician to general nutritional advice from a nurse. Nutrition was evaluated using anthropometry and blood tests. Outpatients lost more weight than inpatients. A lower incidence of malnutrition was reported in the group receiving nutritional counseling. Isenring et al. [11] compared individualized nutritional counseling from dieticians to regular dietary advice from nurses. Nutritional status ranged from malnourished to obese with 35% of the patients malnourished. There was less weight loss in the counseled group (0.4 kg) at 12 weeks compared to usual care (4.7 kg). Results also indicated less deterioration in Patient-Generated Subjective Global Assessment (PG-SGA) scores for patients receiving counseling [18]. More rapid recovery in overall HRQoL for patients receiving dietary counseling was reported using the European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC QLQ-C30). Greater mean total energy and protein intake, mean intake per kilogram body weight, mean protein intake, and a trend to fiber intake were reported in the counseling group [19].

Ravasco et al. [12] compared dietary counseling including a therapeutic diet, nutritional supplements alone, and ad lib diet in a three-arm trial. Patients receiving counseling had identical contact time with the dietician. Counseled patients gained an average of 4 kg, and 50% of malnourished patients in this group improved their weight. Nutritional status measured by PG-SGA was improved in patients receiving counseling. In contrast, none of the patients receiving supplements alone or ad lib diet improved their nutritional status. Higher functional scores were also reported for patients receiving counseling or supplements compared to ad lib intake group.

Drugs

Four RCTs studying drugs to optimize nutrition on HNSCC patients treated with RT or CRT were identified [13–16]

Table 1 Randomized trials of nutritional support for head and neck cancer

Trial	Patients randomized	Patient characteristics	Intervention(s) (evaluable patients)	Study duration
Arnold 1989 [8]	50	58% male Median age 66.2 yrs 50% stage III–IV Mean RT dose 65.8 Gy (no CRT) 36% pretreatment swallowing difficulty	Nutritional supplements (Sustacal™ 960 or 1,080 kcal/day) (23) Diet ad libitum + usual nutritional counseling (27)	10 weeks
Nayel 1992 [9]	23	76% male Mean age 49 yrs Nasopharyngeal primary 22% 26% >5% weight loss/6 months RT dose 66–75 Gy, pre-op 40 Gy (1 pt), post-op 50 Gy (13 pts)	Nutritional supplements (Ensure™, dose by calculated need=1,500–2,000 kcal/day) (11) RT alone (12)	10–15 days before RT for malnourished, otherwise day 17–18 to day 24-25 of RT
Lovik 1996 [10] (abstract)	49	Not available	Tailored dietary information and instruction from clinical nutritionist Regular dietary information from a nurse	6 weeks
Isenring 2004 [11]	60	85% male Mean age 61.9 yrs H&N 72%; esophageal, abdominal or rectal cancer 12% 35% malnourished No enteral/parenteral nutrition	Dietary counseling (ADA medical nutrition therapy protocol) ± nutritional supplements (29) Usual practice (general advice and nutrition booklet) (31)	12 weeks
Ravasco 2005 [12]	75	80% male Mean age 60 yrs 60% stage III–IV All had neoadjuvant chemotherapy RT dose 70 Gy 60% malnourished	Dietary counseling (25) Supplements 2 cans/day (25) Ad lib diet (25)	12 weeks
Fietkau 1997 [13]	64 (61 analyzed) 2 excluded due to AEs and 1 WD	80% male Median age 50 yrs T3/T4 69%, N2/N3 51%; RT 77% Median RT dose 60 Gy (23% CRT) PEG 56%	MA 160 mg (31) Placebo (30)	12 weeks

		All had weight loss of 5%/6 wks or 10%/6 months pretreatment		
Chen1997 [14]	129 (128 analyzed) 1 excluded cisapride	74% male Median age 51 yrs 90% stage III–IV 68% nasopharynx primary Mean RT dose 68.2 Gy 18% underweight	MA 40 mg qid (48) Cisapride 5 mg tid (41) Placebo (40)	7–10 weeks (duration of RT)
McQuellon 2002 [15]	57 (56 analyzed) 1 ineligible	64% male Mean age 63 yrs 23 H&N (RT 74%, CRT 26%) 34 lung cancer (RT 27%, CRT 73%), planned H&N RT dose 70 Gy No enteral/parenteral feeding	MA 800 mg (28) Placebo (28)	12 weeks
Farmer 2005 [16] (abstract)	38	84% male Mean age 61 yrs 13 H&N, 25 lung cancer Proportion CRT not reported RT dose ≥50 Gy over 5-7 weeks	MA 800 mg (20) Placebo (18)	RT +12 weeks
Daly 1984 [17]	40 (35 analyzed) 1 ineligible 3 WD 1 died 2 each arm converted to other arm and analyzed with this arm	80% Male Mean age 55 yrs Able to ingest food orally 45% abnormal swallowing 78% stage III–IV Nasopharynx primary >38% Median RT dose to primary site: nasopharynx 70 Gy other 61–68.5 Gy [38% CRT) Higher RT dose in non-nasopharynx oral group to primary and lower dose to neck: 68.5 vs 61 Gy and 42 vs 50 Gy, respectively	Nasogastric tube feeding (22) Optimal oral nutrition (18) (40 kcal/kg/d and 1–1.5 g protein $kg^{-1} day^{-1}$ initially for both)	8 weeks

ADA American Dietetic Association, *RT* radiotherapy, *CRT* chemoradiotherapy, *Gy* Gray, *H&N* head and neck cancer, *yrs* years, *wks* weeks, *pts* patients, *PEG* percutaneous endoscopically guided gastrostomy tube, *MA* megestrol acetate, *WD* withdrawal

Table 2 Results of randomized trials studying dietary counseling and nutritional supplements

Trial	Outcomes	Weight	Nutritional status	Quality of life	Other outcomes	Treatment effects
Arnold 1989 [8]	Weight	No significant difference in weight loss between nutrition and control groups at any stage of treatment	Not studied	Not studied	Albumin dropped in no supplements group (p= NR)	No significant difference in mucositis, pharyngitis, esophagitis or other side effects
	Serum albumin				Mean total protein improved with supplements (p=0.01)	Treatment interruptions similar in both groups
	Total protein intake Total calorie intake				Total energy intake greater with supplements (p=0.07)	No difference in response/death
	Tumor status					
Nayel 1992 [9]	Weight	Weight loss in 58% of control (median −2%) vs 0% (median +5%)	NS dry mouth, changes in taste, loss of appetite	Not studied	Mid-arm circumference and triceps skin-fold thickness decreased in 33% (median −1%) vs 0 (median +4%) (all p=0.001)	Grade 3 mucositis: 0% vs 25% functional impairment: 0% vs 33% Duration mucositis >2 weeks: 9% vs 25% (p= NS)
	Nutritional status Subjective nutritional assessment	More effect in malnourished patients				Treatment interrupted in 5 pts vs 0 for supplements
Lovik 1996 [10]	Anthropometrics Blood tests	Not reported	Not reported	Not studied	Intensive dietary advice beneficial	Not reported
	Weight loss					
Isenring 2004 [11, 19]	Weight FFM (BIA)	Reduced weight loss in counseling group (0.4 kg) vs usual care (4.7 kg) (p<0.001)	Less deterioration in PG-SGA in counseling group (p=0.02)	Smaller decrease and faster recovery in global HRQoL (p=0.009) and physical function (p=0.012)	Reduced loss FFM NS Counseling superior for staff interpersonal skills (p<0.001), perceived health benefits (p=0.008)], staff presentation skills (p=0.044)] and overall patient satisfaction with nutrition services (p=0.002)	Not reported

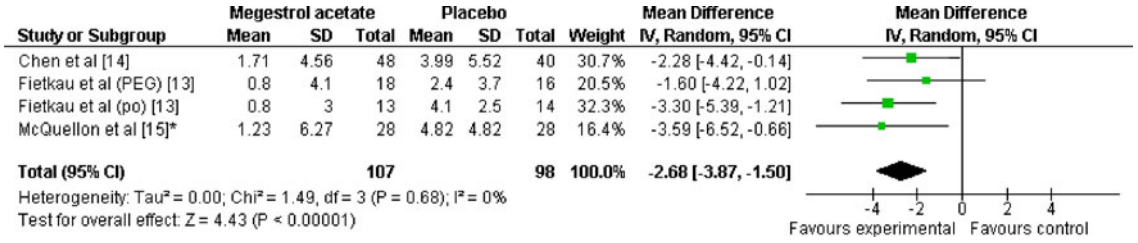
	Nutritional status (PG-SGA) Quality of life (EORTC QLQ-C30) Patient satisfaction (subset n=54)				Counseling superior for mean total energy (p=0.029) and protein intake (p<0.001) Counseling superior for mean intake/kg body weight (p=0.022], mean protein intake (p=0.001), and trend to higher fiber intake (p=0.083)	
Ravasco 2005 [12]	Nutritional intake (Burke's diet history and 24-h recall)	Not reported	Nutritional status maintained/improved at end of RT and 3 months in diet counseling (p< 0.001). 8/16 malnourished patients at baseline improved by average of 4 kg for counsel vs none for other groups	Function scales better for counseling and supplements only, worse for ad lib intake; symptom scales better for nutrition and ad lib intake	Net energy intake increased for diet counseling (+521 kcal/day, p=0.002) and supplements only (322 kcal/day, p=0.05) vs ad lib intake (-400 kcal/day, p<0.01)	Improved grade 1–2 anorexia, N&V, xerostomia, dysguesia at 3 months: 90% vs 67% vs 51% (p<0.0001)
	Nutritional status (PG-SGA) Morbidity Quality of Life (EORTC QLQ-C30]		Dietary intake correlated with nutritional status (p≤0.002)		Net protein intake increased for diet counseling (26 g/day, p=0.006) and supplements only (35 g/day, p=0.001) vs ad lib intake (−15 g/day, p<0.01). At 3 months, diet counseling maintained energy and protein intake, other 2 groups dropped to baseline or below	

NR not reported, *NS* not significant, *RT* radiotherapy, *FFM* fat-free mass, *BIA* bioelectrical impedence analysis, *PG-SGA* Patient Generated Subjective Global Assessment, *HRQoL* health-related quality of life, *pts* patients

Table 3 Results of randomized trials studying drugs for nutritional support

Trial	Intervention(s)	Outcomes	Weight	Anthropometrics	Quality of life	Anorexia	Biochemical	Side effects
Fietkau 1997 [13]	MA 160 mg	Weight at 12 weeks	Reduced weight loss for MA (0.6 kg) vs placebo (3.2 kg) (p=0.0095).	Triceps stable in MA and decreased in control (p=0.001); no change in upper arm circumference	NS stable MA vs decrease control		Overall NS	MA arm—impotence in one case
	Placebo	Anthropometrics (upper arm circumference and triceps skinfold thickness	Weight increased 45% vs 20% (p=0.034)					Placebo—unexplained diarrhea in one case
		Biochemical Quality of life (Padilla Index)	More benefit if no PEG					
Chen 1997 [14]	MA 40 mg qid Cisapride 5 mg tid	Weight Appetite	Reduced weight loss for MA (1.71 kg) vs cisapride (5.41 kg) vs control (3.99 kg) at 8 weeks (p=0.003)			Less appetite deterioration with MA (p=0.0001)	Albumin NS	MA arm—mild peripheral edema in one case, pruritis and erythematous papules in one case
	Placebo	PS Albumin						
McQuellon 2002 [15]	MA 800 mg	Weight	Overall reduced weight loss in MA (2.7 lb) compared to placebo (10.6 lb) (p=0.02). H&N lost more weight than lung (7.5 lb) at 12 wks. MVA model confirmed and most weight loss most after 6 wks		Overall NS. Domains favoring MA: eating (p=0.02), appetite trend, HRQoL; worst in H&N CRT pts			Dyspnea, cough grade 1–2 more common in MA arm (5 vs 1, 7 vs 2)
	Placebo	Quality of life (FACT-G) ECOG PS						Nausea more common in placebo arm
Farmer 2005 [16] (abstract)	MA 800 mg Placebo	Weight Quality of Life (FACT-G)	Over 17–19 wks, MA no change wt (p=0.98), placebo mean weekly wt loss of 0.56 lb (p=0.001)		Overall NS	Overall NS, mean score anorexia subscale favored MA (p=0.008)		1 DVT placebo
		Anorexia (FAACT)						

MA megestrol acetate, *PEG* percutaneous endoscopically guided gastrostomy tube, *NS* not significant, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CRT* chemoradiotherapy, *DVT* deep vein thrombosis, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire, *FAACT* Functional Assessment of Anorexia/Cachexia Therapy, *FACT-G* Functional Assessment of Cancer Therapy: General, *H&N* head and neck cancer patients, *HRQoL* health-related quality of life, *RT* radiotherapy, *MVA* multivariable analysis



*59% of patients in this trial had lung cancer treated with chemoradiotherapy.

Abbreviations: SD, standard deviation; IV, inverse variance; CI, confidence interval; PEG, percutaneous endoscopically guided gastrostomy tube; po, per os

Fig. 1 Meta-analysis for weight loss (megestrol acetate vs placebo)

(Table 3). These trials randomized a total of 288 patients (229 HNSCC). All studied megestrol acetate (MA), and cisapride was also studied in one trial. Meta-analysis was limited to the outcome of mean weight loss reported in three RCTs studying MA (Fig. 1). This outcome was reported at 12 weeks in two RCTs and at 8 weeks in one RCT [14]. As the data necessary for statistical pooling were reported separately for patients with and without a percutaneous endoscopically guided gastrostomy tube (PEG) in one trial, these groups were included separately in meta-analysis [13]. All patients were included in meta-analysis, although 59% of patients in one trial had lung cancer treated with CRT, as separate data for HNSCC patients was not provided [15]. Results of meta-analysis were similar whether this RCT was included or not (data not shown). Overall meta-analysis showed that mean weight loss was reduced by 2.68 kg (95% confidence interval, 1.50–3.87 kg) in MA-treated patients ($p<$ 0.00001).

Fietkau et al. [13] compared MA to placebo. Patients at risk for MA adverse effects including those having a history of coronary artery disease, hypertension, or thrombosis were excluded. Slightly more patients in the control group had N2 or N3 disease. Weight loss was reduced for MA patients (average 0.6 kg) compared to placebo patients (average 3.2 kg) at 12 weeks (p=0.0095). There was less difference in weight loss between the two arms for patients receiving enteral feeding via gastrostomy tubes. No significant difference in upper arm muscle circumference was reported. Three patients with adverse effects were not included in the analyses, including a patient receiving MA who developed impotence. Chen et al. [14] randomized 128 patients to receive MA, cisapride, or placebo in a three-arm trial predominantly in nasopharynx cancer patients (68%). Patients with diabetes mellitus, congestive heart failure, edema, or ascites were excluded. Slightly higher baseline weight, appetite, and albumin were noted in the cisapride group. There was less weight loss with MA (average 1.71 kg) compared to both cisapride (average 5.41 kg) and control (average 3.99 kg) at 8 weeks (p=0.003). MA also improved appetite assessed by patient self reporting.

McQuellon et al. [15] compared MA to placebo in patients receiving RT for HNSCC or CRT for lung cancer. Patients requiring enteral or parenteral feeding were excluded. Overall mean weight loss was reduced with MA (2.7 lb) compared to placebo (10.6 lb) at 12 weeks (p= 0.02). HNSCC patients had a mean weight loss 7.5 lb greater than lung cancer patients in this study. Overall HRQoL scores measured using the Functional Assessment of Cancer Therapy: General (FACT-G) questionnaire were similar, but MA patients had greater mean scores for the item “I am able to eat as much food as I like” compared to placebo patients (p=0.02). Nausea was less common, and mild dyspnea and cough was more common among MA patients compared to controls. Farmer et al. [16] also compared MA to placebo patients receiving RT for HNSCC or CRT for lung cancer. Over a period of 17–19 weeks, MA patients had a mean weekly weight gain of 0.01 lb (95%CI, −0.39 to 0.4 lb, p=0.98). In contrast, placebo patients had a mean weekly weight loss of 0.56 lb (95% CI, −0.98 to −0.15 lb, p=0.001). The study also reported better anorexia scores for MA measured with the Functional Assessment of Anorexia/Cachexia Therapy compared to placebo patients. No significant differences in the HRQoL measured by FACT-G were reported. This trial was ended prematurely due to withdrawal of the pharmaceutical sponsor's support.

Prophylactic tube feeding

Daly et al. [17] compared oral feeding to prophylactic enteral feeding using a nasogastric tube in HNSCC patients receiving RT or CRT. Patients unable to ingest food orally were excluded. Two patients initially randomized to tube feeding were converted to oral feeding due to noncompliance, and two patients randomized to oral feeding were converted to tube feeding due to nutritional issues. The analysis was carried out for patients as treated and therefore cannot be considered an intention-to-treat analysis. More

abnormal swallowing at baseline was present in the intervention group. Results indicated that loss of total body weight loss was reduced for tube-fed patients (0.6%) compared to oral nutrition (6.1%; $p<0.04$). It appeared that the subgroup of patients with primary nasopharyngeal carcinoma might have benefited less from tube feeding. No differences in tumor response to treatment or overall survival were detected.

Discussion

The RCTs identified were consistent in their observations that individualized dietary counseling by a professional dietician was associated with less weight loss and improved intake both of total calories and protein compared to other approaches. The data for nutritional supplements was conflicting and supported use of these as an adjunct to a therapeutic diet and counseling by a professional dietician rather than as a solitary intervention. As the trials identified had small sample sizes and were unblinded, further research to elucidate the impacts of dietary counseling and nutritional supplements is of interest. However, as this has become a standard of practice, it is unlikely that control arms without dietary counseling would be acceptable or feasible. Certainly, further research regarding optimal counseling techniques and methods and types of nutritional supplementation is warranted.

Megestrol acetate is a progestational agent initially used for the treatment of hormone-sensitive breast cancer and subsequently found to be of palliative benefit for patients with cancer anorexia–cachexia. Four placebo-controlled RCTs reported reductions in weight loss with MA compared to control. Specific items and subdomains of HRQoL showed better appetite scores and reduced anorexia. No major adverse effects were reported with MA, although edema has been associated with MA in a meta-analysis of cancer patients with anorexia–cachexia [20]. MA is available in a liquid formulation which could facilitate its use in patients with dysphagia, odynophagia, or enteral feeding tubes. Ideally, the benefits observed with MA should be confirmed in a large RCT, but a recent attempt to do this was unsuccessful [16]. With recognition of the limitations of the RCTs identified, the data are consistent in suggesting that MA in doses between 120 and 800 mg/day may be a useful adjunct to reduce weight loss and maintain nutritional status in HNSCC patients receiving RT who are not receiving enteral tube feeding.

Use of enteral feeding tubes is a standard of practice to support nutrition in HNSCC patients with significant dysphagia and/or weight loss prior to treatment. There is controversy regarding the optimal type of enteral feeding tube (nasogastric, percutaneous, or surgically placed); however, no RCTs addressing this question were identified. Benefit of prophylactic nasogastric enteral feeding was addressed by one RCT, but the size and validity of this trial were limited [17]. The prophylactic use of enteral feeding for all HNSCC patients receiving RT and type of tube should be topics of further research, particularly in HNSCC patients treated with CRT and preferably in RCTs.

Nutritional complications in HNSCC patients treated with radiotherapy are associated with significant costs both to patients and the healthcare system. This review identified limited data from RCTs studying interventions to support nutrition in HNSCC receiving curative radiation therapy. Small RCTs are intrinsically associated with greater variability, and although this may be overcome in part by statistical pooling, this remains the major limitation of this systematic review. Possible benefits with dietary counseling, megestrol acetate, and prophylactic enteral feeding were identified; however, these were not studied comparatively or in combination, so it can neither be assumed they are equivalent nor would have additive benefits. No RCTs studying other drugs of interest, such as anabolic steroids, were identified by this review. Chemoradiotherapy is the current standard of practice for HNSCC, and this approach is clearly associated with more frequent and severe acute and chronic toxicity. As nearly all patients in this review received radiation alone, the effectiveness of these interventions in HNSCC patients treated with chemoradiotherapy is less certain. Clearly, more prospective randomized trials aimed at improving nutritional outcomes and other short- and long-term consequences of radiotherapy treatment in HNSCC need to be done, especially if chemoradiotherapy remains a standard therapeutic approach.

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