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Review article

A systematic review of home-based dietary interventions during radiation therapy for cancer



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ABSTRACT

Purpose: Our objectives are to assess (1) the acceptability and feasibility of dietary interventions for patients undergoing radiation therapy (RT), and (2) the impact of dietary interventions on patient reported outcomes, toxicities, and survival.
Methods: A PICOS/PRISMA/MOOSE selection protocol was used to include articles that evaluate adding dietary interventions to patients receiving RT. Acceptability was defined as (# accepting/# approached); feasibility was (# completing/# approached). Patient-reported outcomes were reported based on questionnaires used in each study and survival was measured from the date of diagnosis until death in each study. Level of evidence was assessed with Center for Evidence-Based Medicine (CEBM) criteria.
Results: Sixteen articles were included; among these, 2027 patients were approached regarding the intervention, and 1661 accepted (81.9%); of these, 1543 (92.9%) completed the prescribed diet + RT course. The most common cancers included were gynecological, head and neck, and gastrointestinal. For patients with pelvic cancers, a high fiber diet may improve diarrhea (CEBM level 1b). Enteral nutrition formula, including formulas with proteins such as L-arginine, lipids such as eicosapentaenoic acids, glucids, and ribonucleotides, may help prevent of malnutrition in head and neck cancer patients undergoing RT (level 2b). Vitamin C and β-carotene may reduce of xerostomia in head and neck cancer patients; however, the studies evaluating these vitamins included vitamin E; which increases all-cause mortality (level 2b). No dietary intervention for cancer patients receiving RT has been shown to improve survival.
Conclusion: There are limited data to support safe and efficacious use of dietary interventions during RT.
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Introduction

In 2019, an estimated 1,762,450 new cases of cancer will be diagnosed in the United States [1]. Radiation therapy (RT) is used in 60% of cancer patients, and is associated with acutely pro-inflammatory toxicities known to negatively impact patient quality of life (QOL), including dermatitis, esophagitis, gastritis, diarrhea, and cystitis. Increased fatigue and poor QOL are surrogates of survival [2,3]; further, RT may increase fatigue and worsen QOL. For patients receiving RT, if QOL can be improved, then overall survival may increase as well.

Since the early 2000s, there has been an increased focus on the use of dietary interventions to decrease toxicities and improve outcomes of cancer patients [4]. For patients receiving RT, certain dietary interventions are hypothesized to minimize toxicity, while increasing cancer cell death, thereby widening the therapeutic window, potentially improving survival [5,6]. As of 2019, there are no recommendations from the National Comprehensive Cancer Network (NCCN), the American Society for Radiation Oncology (ASTRO), or the European Society for Radiation Oncology (ESTRO) regarding the integration of dietary changes in the treatment regimen for cancer patients undergoing RT [7]. There are, however, recommendations for clinical practice made by the Academy of Nutrition and Dietetics.

The purpose of this paper is to synthesize the evidence regarding dietary interventions for cancer patients receiving RT. Specifically, we focus on interventions on the level of macromolecules (i.e. changes in dietary fat/carbohydrate/protein/fiber levels) and micromolecules, such as vitamins. Our objectives are to assess (1) the acceptability, feasibility, and safety of dietary interventions for patients undergoing RT, and (2) the impact of dietary interventions on patient reported outcomes and toxicities related to RT. We provide summary recommendations of all dietary interventions. The results of this work may be used to supplement the guidelines of the NCCN, ASTRO, ESTRO, and the Academy of Nutrition and Dietetics [8].

Methods

Literature selection

The Population, Intervention, Control, Outcome, Study (PICOS) design approach was used to define the inclusion criteria (Supplementary Table 1). Additionally, a systematic search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process was conducted (Supplementary Fig. 1).

We searched for full-text medical literature (excluding abstracts) with human subjects from 1960 to 2018 in PubMed for the terms [(“cancer” and (“radiation therapy” or “radiotherapy”) and (“diet” or “nutrition” or “food” or “supplement” or “vitamin”)). The terms were in titles or in MeSH headings. After identifying 389 articles initially, three authors (TA, MC, KM)

screened each study and excluded any with the following features: (1) full manuscripts that could not be obtained or were not available online, (2) duplicate or updated studies (in which case the most recent version was used), (3) not written in English, (4) lacking patient reported outcomes, (5) systematic reviews and meta-analyses (though these were searched to find eligible articles), (6) abstract alone, (7) non-randomized studies, and (8) no use of RT. Additionally, some relevant articles were included from the reference lists of selected PubMed papers. The studies were then reviewed by a senior author (NZ) and discussed among the group. Of the 389 articles, 373 studies were not eligible, resulting in 16 total studies that met the inclusion criteria [9–24].

Data abstraction and analysis

From the 16 studies, characteristics of patients (e.g. age, gender), cancer (e.g. disease site, stage), treatment (e.g. RT doses, chemotherapy), dietary intervention (e.g. vitamins, supplements), patient-reported outcomes (PROs), toxicity, and other outcomes were coded. Dietary interventions in a clinical setting sit within a comprehensive, individualized nutritional consultation which encompasses nutritional screening, anthropometry and review of the clinical picture and medical history. The key dietary interventions used are: dietary counselling (diet modification/fortification techniques/eating strategies), oral nutritional supplementation, and reactive nutritional support in the form of nasogastric feeding, gastrostomy or jejunostomy tube feeding or total parenteral nutrition for cases where oral intake is not possible. Dietary interventions that involved a single supplement, such as amino acids or antioxidants, were coded as “micronutrient” interventions, while interventions changing the content of an entire meal, such as low fiber or fat, were coded as “macronutrient” interventions.

For objective 1, acceptability was defined as: (the number of patients agreeing to perform the dietary intervention + RT)/(the number of eligible participants). Feasibility was defined as: (number of patients who completed the dietary intervention + RT)/(number agreeing to perform the dietary intervention + RT). There were four papers that did not report adherence [9,10,21,24]. Four papers reported a feasibility rate for those who completed the study, with compliance ranging from 9% to 93% [12,18,20,22]. The remaining studies only included data for participants who maintained a particular level of compliance, ranging from 33% to 100% [11,19,16,17]. For reference, all values are listed in Table 1.

For objective 2, we assessed patient reported outcomes, toxicities, and survival per the primary endpoint listed in each study (listed in Table 1). Toxicities were recorded using the Common Terminology Criteria for Adverse Events (CTCAE) scale, attributable to the addition of the dietary modification, per the assessment of the authors of the primary study. QOL was most commonly measured pre- and post-treatment by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire- C30 (QLQ-C30) and QLQ-PR25. Adverse effects of RT were reported with Radiation Therapy Oncology Group (RTOG)

Table 1
Summary of studies evaluating RT +/- dietary interventions.

Author, Year	Cancer	Dietary Intervention vs Control Group	Concurrent Treatment (n)	Diet type (-molecule)	n control	n diet	n screened	n accepted (%)	n completed (%)	Primary endpoint(s)	Results of intervention vs control
Rubio, 2013 [9]	Breast	Glutamine supplementation vs placebo	Tamoxifen (12) and/or chemotherapy (6)	Micro-	8	9	20	17 (85)	17 (100)	Skin radiation injury	Unclear improvement in cosmesis, patients receiving oral Gln scored an average of 0.9 ± 0.2 vs 1.4 ± 0.2 in the placebo group ($P < .05$).
Fuchs-Tarkovsky, 2013 [10]	Cervical	Antioxidants (β -carotene, vitamin C/E, selenium) vs placebo	Cisplatin (103)	Micro-	54	49	103	103 (100)	103 (100)	Oxidative stress, hematological toxicity, and QOL	Antioxidants improve QOL, but not other endpoints.
Ishikawa, 2016	Esophageal	Amino acid-rich elemental diet vs oral rinse	Chemotherapy (17) + RT (16)	Micro-	16	17	NR	36 (NR)	33 (92)	Oral mucositis	Amino acid-rich elemental diet does not improve mucositis, sarcopenia.
Bairati, 2005 [12], 2006 [13] Meyer, 2007 [14]	Head & neck	Vitamin E (α -tocopherol), β -carotene vs placebo	Pre-RT surgery (32)	Micro-	263	272	NR	540 (NR)	535 (99)	Occurrence and severity of acute effects of radiation therapy Xerostomia	α -tocopherol increases all-cause mortality β -carotene reduces mucositis and local recurrence Vitamin C + E reduce xerostomia acutely
Chung, 2016 [15]	Head & neck	Vitamin E (α -tocopherol) + C vs placebo	Chemotherapy (30)	Micro-	20	25	76	52 (68)	45 (87)	Grade 3 dermatitis	HMB/Arg/Gln did not prevent grade 3 dermatitis
Imai, 2014 [16]	Head & neck	HMB/Arg/Gln vs none	Cisplatin (34)	Micro-	18	16	40	40 (100)	34 (85)	Nutritional status, and functional capacity.	Arginine/omega-3/nucleotides improve weight loss, but do not improve mucositis, other outcomes.
Vasson, 2014 [17]	Head & neck, esophagus	Arginine, omega-3 fatty acid, nucleotides- vs placebo	Surgery (unknown)	Micro-	13	15	47	37 (79)	28 (76)	Diarrhea	Probiotics may reduce diarrhea.
Demers, 2013 [18]	Mixed pelvic	Bacterial probiotics vs placebo	Surgery (81), chemotherapy (120)	Micro-	89	150	410	246 (60)	239 (97)	Diarrhea/stool consistency	Fiber improves stool consistency and diarrhea.
Garcia-Peris, 2016 [19]	Mixed GYN	Fiber (prebiotic) vs placebo	Surgery (38)	Macro-	18	20	47	46 (98)	38 (83)	Acute GI toxicity	Amino acid-based formula does not improve GI toxicity.
McGough, 2008 [20]	Mixed pelvic	Amino acid-based formula vs normal diet	Chemotherapy (18)	Micro-	25	25	77	50 (65)	50 (100)	Survival	Selenium does not impact survival.
Muecke, 2010 [21]	Mixed GYN	Selenium supplementation vs no supplementation	Surgery (81)	Micro-	42	39	108	81 (75)	81 (100)	Acute GI toxicity (IBDQ)	Low or modified fat diet does improve GI toxicity
Wedlake, 2012 [22]	Mixed pelvic	Low fat diet vs modified fat diet vs normal fat diet	Chemotherapy (59)	Macro-	25	50	374	117 (31)	75 (64)	Acute and chronic GI toxicity (IBDQ)	High-fiber diet reduces acute* and chronic† GI toxicity
Wedlake, 2017 [23]	Mixed pelvic	High-fiber diet vs habitual-fiber diet vs low-fiber diet	Chemotherapy (121)	Macro-	53	106	583	166 (28)	159 (96)	GI toxicity (diarrhea, constipation, bloating, blood in stools), QOL	Dietary intervention does not change GI toxicity or QOL.
Petterson, 2014 [24]	Prostate	Reduced insoluble dietary fiber, lactose, soluble fiber vs normal diet	Pre-RT endocrine therapy (69)	Macro-	55	51	142	130 (92)	106 (86)		

* Baseline to 5–7 weeks.

† 1 year after completion of RT.

Table 2
Assessment of risk of bias of included studies.

	Selection bias (randomization)	Performance bias (blinding of subjects)	Detection bias (blinding of assessors)	Attrition bias (outcomes obtained)	Other biases (similar at baseline)
Rubio [9]	⊕	⊕	⊕	⊕	NR
Petterson [24]	⊕	⊖	⊖	⊕	⊕
Petterson [30]	⊕	⊕	⊖	⊕	⊕
Bairati [12]	⊕	⊕	⊕	⊕	⊕
Bairati [13]	⊕	⊕	⊕	⊕	⊕
Chung [15]	⊕	⊕	⊕	⊕	⊕
Imai [16]	⊕	⊖	⊖	⊕	⊕
Meyer [14]	⊕	⊕	⊕	⊕	⊖
Fuchs-Tarlovsky [10]	⊕	⊕	⊖	⊕	NR
Garcia-Peris [31]	⊕	⊕	⊕	⊕	⊕
Garcia-Peris [19]	⊕	⊕	⊕	⊕	⊕
Muecke [21]	⊕	⊖	⊖	⊕	⊕
Demers [18]	⊕	⊕	⊕	⊕	⊕
Mcgough [20]	⊕	⊖	⊕	⊕	⊖
Vasson [17]	⊕	⊕	⊕	⊖	⊕
Wedlake [22]	⊕	⊖	⊖	⊕	⊕
Wedlake [23]	⊕	⊖	⊖	⊕	⊕
Ishikawa [11]	⊕	⊖	⊖	⊕	⊕

⊕ = Low risk of bias.
⊖ = High risk of bias.

Acute Radiation Morbidity Scale and CTCAE questionnaires. Gastrointestinal (GI) adverse events were reported most commonly using the GI Side Effects Questionnaire [24], Inflammatory Bowel Disease-Questionnaire (IBD-Q) [25], and Vaizey Incontinence Questionnaire [26].

Assessment of the risk of bias

The risk of bias for each study included was assessed using the Cochrane's "Risk of Bias" Assessment Tool, which uses 6 domains to rank bias as low, medium, or high risk. These domains include: selection bias (i.e. use of randomization), performance bias (i.e. blinding of participants and study personnel), detection bias (i.e. blinding of outcome assessors), attrition bias (i.e. incomplete outcome data collection), reporting bias (i.e. selective reporting of some outcomes but not others, depending on the nature and direction of the results) and other additional sources of bias (i.e. dissimilarities in groups at baseline).

All 16/16 studies avoided biasing the selection process by randomizing the participants. 9/16 studies blinded participants, while 8/16 studies blinded the assessors. 15/16 studies avoided attrition bias by obtaining outcomes from more than 85% of their participants. Finally, 15/16 studies reported on similarity between groups at baseline. These findings are summarized in Table 2. A heterogeneity assessment was not performed because the measurement of endpoints varied among the included studies.

Results

Studies and patients

The 16 studies included in the analysis were published from 2005 to 2017 across 10 countries, including USA [9], Sweden [27], Canada [13,14], Korea [15], Japan [11,16], Mexico [10], Spain [19], Germany [21], France [17], and the UK [20,22,23]. In total, the 16 studies included 1567 patients, with 857 in the intervention groups and 710 in the control groups. The mean age of all participants was 61.7 years. Cancer types included were breast [9], prostate [27], head/neck [12–17], gynecological [10,19,21], mixed pelvic [18,20,22,23], and esophageal [11], with the largest percentage of papers focusing on head and neck cancers (6/16). Dietary

interventions were grouped into two categories, macronutrient (4/16 studies) and micronutrient (12/16).

Objective 1: Acceptability and feasibility of dietary interventions for patients receiving RT

All studies included the number of patients initially approached, except for four [9,10,14,16]. Among those that reported the number of patients approached, there were 2027 patients approached, of which 1661 accepted (81.9%); of these, 1543 (92.9%) completed the prescribed diet + RT course. From a cancer perspective, the studies looking at head/neck and gynecological cancers had the highest acceptability (100%), while studies examining prostate cancers had an acceptability of 91.5%. As a function of both cancer type and intervention type, the overall feasibility for all studies was >75%, with the exception of the 2012 study published by Wedlake et al., which reported an overall feasibility rate of 64%. In this study, compliance was >75% for the low- and moderate-fat intake group arms; however, the compliance for the normal fat diet was 21% and 0% for women and men, respectively. Participants in this group consumed less than the targeted fat intake. These results may be due to underreporting of fat intake. These results are summarized in Table 1.

Objective 2: Patient reported outcomes, toxicity, and survival of patients receiving dietary interventions during RT

Outcomes of interest

The most commonly reported patient reported outcomes were GI toxicity, diarrhea alone, and QOL. GI toxicity, as measured by standardized questionnaires such as IBD-Q, IBDQ-B, and RTOG, was improved in 1/4 studies [23], and unchanged in 3/4 studies [20,22,27]. In a mixed pelvic cancer population, neither an amino-acid supplementation nor a low-fat diet appeared to have any effect on GI toxicity [20,22]; however a high fiber diet appeared to improve GI toxicity in this population [23]. In the 2017 study published by Wedlake et al., the authors found that a high-fiber diet, in comparison to a low-fiber or habitual fiber diet, resulted in a significantly smaller change in IBDQ-B scores in patients receiving pelvic RT from before to after RT completion, indicating an improvement in GI toxicity scores. Diarrhea, as

measured separately from other GI symptoms, was improved in 3/3 studies [18,19,21]. Muecke et al. found that supplementation with selenium improved diarrhea severity as measured by the NCI's Common Toxicity Criteria, though this was not the primary outcome of their study. Demer et al. and Garcia-Peres et al. found that probiotic and prebiotic supplements improve stool consistency as measured by the Bristol Stool Chart. QOL improved in 1/3 studies [10], and remained unchanged in 2/3 studies [17,27]. Fuchs-Tarlovsky et al. found that antioxidant supplementation improved QOL as measured by the EORTC QLQ-C30 in women with cervical cancer [10].

Outcomes as a function of dietary intervention type

The most common interventions were supplementation with antioxidants (5/16) [10,12–15], amino acids [11,16,17,20] and fiber [19,23,27]. Of the 5 studies that assessed antioxidant supplementation, only 2 found significant improvements in any outcomes [10,15]. Fuchs-Tarlovsky et al. found that QOL in patients with cervical cancer was significantly higher in the group receiving antioxidant supplementation compared to the control group, as measured by the EORTC QLQ-C30. Chung et al. found that vitamin C and E supplementation significantly reduced xerostomia in patients with head and neck cancer 6 months post-radiation as measured by a patient reported xerostomia questionnaire (mean reduction in score of 2.7) and an observer-rated xerostomia score (mean reduction in score of 1.3). Bairati et al. did not find any significant improvements; however, they did find a significant increase in all-cause mortality (HR = 1.38, 95% CI 1.03–1.85) in patients with head and neck cancers who took α -tocopherol, a type of vitamin E, with or without β -carotene supplements [13]. This data suggests that α -tocopherol increases all-cause mortality; no significant increase in mortality was seen, however, with the addition of β -carotene.

Of the 5 studies that used amino acid supplementation, 3 found significant improvements in any outcome [9,16,17]. Imai et al. found that amino acid supplementation significantly decreased the severity of dermatitis as measured by the CTCAE-4, whereas Vasson et al. found that amino acid supplementation significantly improved weight-loss when combined with omega-3 fatty acids [16,17]. Rubio et al. found that glutamine alone helped decrease skin toxicity as measured by the Radiation Therapy Oncology Group in patients with breast cancer [9]. Amino acid supplementation did not have any effect on mucositis, sarcopenia, or GI toxicity across all studies [11,20].

Three studies evaluated fiber intake [19,23,27]. One study found that reduced fiber intake combined with a reduced lactose intake had no effect on GI toxicity as measured by the EORTC QLQ-30 and QLQ-PR25 at 12- or 24-months post radiation [27]. A second study found that a high fiber diet significantly improves GI toxicity as measured by the IBD-Q at the end of RT [22]. Taken together, these two studies suggest that a diet high in fiber may help decrease GI toxicity experienced by patients with mixed pelvic cancers immediately after RT, whereas a low-fiber intake will have no long-term impact on GI toxicity. The third study found that prebiotic supplementation resulted in decreased diarrhea as measured by the EORTC QLQ-C30 in patients with mixed gynecological cancers [19].

Outcomes as a function of disease site

Of the 16 studies, the most common cancers studied were gynecological [10,18–23], head and neck [12–17], GI [18,20,22–23], and prostate [18,20,27]. Five of the papers included patients with metastatic cancer [11,16,17]. Of the 7 studies looking at gynecological cancer patients, improvements were seen in diarrhea (3/7), GI

toxicity (2/7) and QOL (1/7) [10,18,19,21–23]. Diarrhea and GI toxicity were improved by high-fiber diets, low-fat diets, probiotics, and selenium supplementation; however, most of these studies evaluated diarrhea as a secondary endpoint, and the strongest prospective evidence currently only exists for fiber [19,21–23]. Of the 5 studies looking at patients with head and neck cancer, improvements were seen in xerostomia (1/5), dermatitis (1/5), and weight-loss (1/5) [15–17]. Of the 4 studies looking at GI cancer patients, improvements were seen in GI toxicity (2/4) and diarrhea (1/4) through protective effects of dietary interventions [18,22,23]. GI toxicity was reduced in the population consuming high-fiber and low-fat diets [22,23]. These studies suggest a protective effect of high-fiber, low-fat diets and probiotics against GI toxicity and diarrhea in patients receiving RT for a cancer diagnosis. Of the 3 studies analyzing the effects of diet + RT on participants with prostate cancer, improvements were only seen in diarrhea (1/3) [18]. This was in patients taking probiotic supplements.

Survival

Adverse events due to dietary interventions were uncommon among the studies included in this review. Of those included, two studies assessed survival as an outcome. Bairati et al. reported an overall 38% increase in all-cause mortality (HR 1.38, 95% CI 1.03–1.85) for individuals who consumed α -tocopherol or β -carotene alone, or in conjunction with other supplements [13]. Participants who reported use of α -tocopherol alone had the greatest increase in overall all-cause mortality (HR = 1.43, 95% CI 0.98–2.07). Second, Muecke et al. [21] found no difference in survival with the addition of selenium for gynecological cancer patients receiving RT.

Discussion

There are currently no guidelines recommending the integration of dietary modifications for patients receiving RT. This is the first review that provides some consensus in support of dietary modifications in reducing adverse toxicities experienced as a consequence of RT. We found that patients receiving RT are accepting of dietary interventions and that dietary studies have an acceptability rate of 82% and a high feasibility rate of 93%. However, there are limited data showing that any of these interventions improve toxicity. Further, no home-based dietary intervention improves survival.

There is level 1b evidence (randomized controlled trial with narrow confidence interval) that a high fiber diet improves RT-related diarrhea. The amount of fiber considered a high fiber diet (>18 g/day), however, is lower than the recommended 25–30 g/day. The improvement in RT-related diarrhea is therefore more likely due to the nonstarch polysaccharides rather than the amount of fiber. There is level 2b evidence (individual cohort study) that a solution of proteins, lipids, and sugars may improve RT-related malnutrition and weight loss. This finding supports the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients which recommend a protein intake of 1.0–1.5 g/kg/day to maintain energy and substrate requirements [28]. There is also level 2b evidence that vitamin C and β -carotene may improve xerostomia, though studies using these interventions combined the drugs with vitamin E (tocopherol), which has been shown to increase the risk of cancer development, cancer recurrence, and all-cause mortality [29]. This suggests that vitamin E supplementation should be monitored in individuals at risk for cancer and undergoing treatment for cancer. Further testing should be done to determine the threshold above which vitamin E consumption increases risk for recurrence. No

Table 3
Recommendations regarding dietary intervention during RT.

Condition	Associated Cancer	Evidence-based strategies to reduce effects	Patient Sample Size	Oxford Center of Evidence Based Medicine (CEBM) level of evidence
Diarrhea	Pelvic, GYN	High fiber diet (≥ 18 g NSP*/d) [19,23]	197	1b [†]
Malnutrition	Head & neck, esophagus	Enteral nutrition formula, which includes proteins, (e.g. L-arginine), lipids (e.g. eicosapentaenoic, docosahexaenoic acids), glucids (e.g. mono, disaccharides) and ribonucleotides [17]	28	2b [‡]
Xerostomia	Head & neck	Possible improvement with Vitamin C (50 mg/d) [15] and β -carotene (6 mg/day) [14] though the studies using them combined them with Vitamin E. Notably, RT + vitamin E + β -carotene has been shown to increase all cause mortality over RT alone [12,13]	580	2b [‡]

* Non-starch polysaccharide.

[†] Therapy/Prevention, Etiology/Harm: individual RCT (with narrow confidence interval).

[‡] Therapy/Prevention, Etiology/Harm: individual cohort study (including low quality RCT; e.g., <80% follow-up).

dietary intervention for cancer patients receiving RT has been shown to improve survival (Table 3).

Quality of life affects patient treatment compliance and completion. Only one study in our review found a statistically significant increase in quality of life secondary to a dietary intervention. Donovan et al. found that prostate cancer patients who received RT initially had decreased quality of life measured by sexual function, bowel function, urinary voiding, and nocturia. Patients reported, however, recovery in these symptoms after six months of RT [30]. Similar improvements in quality of life after initial decreases with RT are seen in head and neck and breast cancer patients [31,32].

Weight loss in cancer patients is associated with an unfavorable prognosis, increased toxicity of anti-cancer treatments resulting in reductions or interruptions of scheduled treatment and reduced quality of life (ESPEN). Ishikawa et al. found a decrease in body mass index (BMI) and body fat mass (FM) after chemoradiation treatment. Lean body mass (LBM), however, increased in patients receiving Elental (amino-rich elemental diet) compared to patients receiving azulene oral rinse for oral mucositis. For head and neck cancer patients who received immunomodulating enteral nutrition (IEN), Vasson et al. reported statistically significant increases in weight, BMI, and LBM compared to patients receiving standard enteral nutrition (SEN). For malnourished patients, increases in weight, BMI, and LBM were seen with IEN and SEN. Wedlake et al. did not find a statistically significant difference in body weight or BMI at baseline or at the end of RT for patients receiving low- or habitual-fiber diets but the difference in the change in BMI between groups was significant. We recommend future studies follow the ESPEN guidelines in reporting weight status as a measured outcome due to the effect on treatment prognosis.

While there is one published paper evaluating the nutritional recommendations for adult patients undergoing cancer treatment at NCCN-member institutions, no systematic review about dietary intervention specifically during RT exists. Other studies in our systematic review only involved a single study population. Champ et al. found that only four of 21 NCCN-member institutions provided nutritional guidelines - two recommended low-fat, high-carbohydrate diets with 5:1 and 6:1 carbohydrate to fat ratios, while the other two institutions recommended a 1:1 ratio of carbohydrate to fat, focusing on weight maintenance during treatment. Their findings are comparable to ours in that there is limited data and consensus of dietary recommendations for patients undergoing cancer treatment. Our work, however, expands to include micronutrient and specific RT-site recommendations as well as assesses the implementation potential of dietary interventions in RT oncology departments by reporting on acceptability, feasibility, and safety. In the "Clinical Guide to Oncology Nutrition," a chapter discusses the benefits of nutrition on radiation therapy and dis-

cusses the need for adequate caloric and protein intake, particularly focusing on supplementing a patient's specific deficiency to ameliorate or prevent side effects. The authors recommend glutamine and zinc sulfate supplementation, with evidence on minimization or prevention of mouth sores and mucositis and to help the return of taste, respectively, in head and neck cancer patients. It also discusses amifostine clinical trials that show infusions reduce the incidence of xerostomia and side effects in pelvic radiation [33].

This study is not without limitations. One limitation of this systematic review is the dearth of available literature regarding nutritional interventions for patients during RT. Only 19 papers encompassing 16 studies were published that met the inclusionary criteria for this systematic review. The included studies had small sample sizes and were predominantly limited to gynecological, head and neck, GI, and prostate cancer, with one study conducted in a breast cancer population. Individual studies varied in regards to: follow-up time, intervention type, cancer site and stage, patient demographics, and outcome measures used (i.e., quality of life is measured using different scales). Due to this heterogeneity, a meta-analysis could not be conducted and definitive conclusions cannot be drawn at this time. Further studies are needed to further elucidate the effect of various nutritional interventions on patient-reported and clinical outcomes in patients receiving chemotherapy.

Conclusion

This systematic review is the first summary of dietary interventions for cancer patients receiving RT. For patients with pelvic cancers, a high fiber diet may improve diarrhea [23]. Immunomodulating enteral nutrition formula, including proteins such as L-arginine, lipids such as eicosapentaenoic acids, glucids, and ribonucleotides may help prevent of malnutrition in head and neck cancer patients undergoing RT [17]. Lastly, vitamin C [15] and β -carotene [14] may reduce of xerostomia in head and neck cancer patients; however, the studies evaluating these vitamins included vitamin E, which increases all-cause mortality [12,13]. No dietary intervention for cancer patients receiving RT has been shown to improve survival. Future research is warranted to help establish evidence-based nutritional guidelines for oncologists and their patients with the goal of limiting RT toxicities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tipsro.2020.08.001>.

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