Review

Clinical efficacy of oral enteral nutrition in lung cancer patients receiving chemotherapy and/or radiotherapy: a systematic review of randomized controlled trials

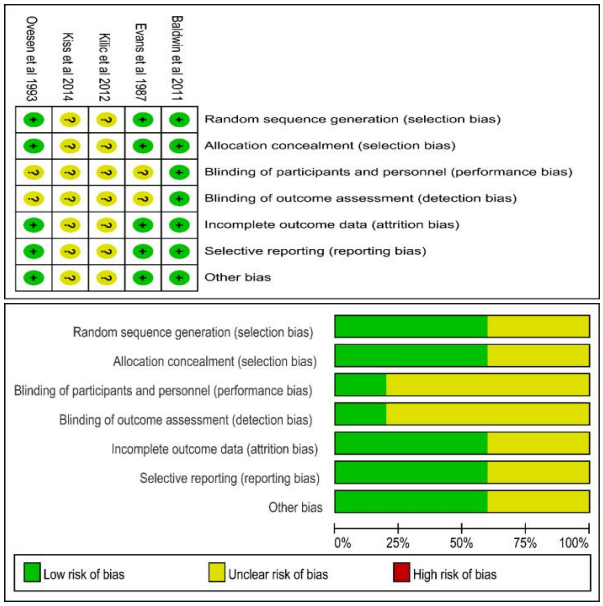
Lang Huang[1], Jian-Guo Zhou[1], Wen-Xiu Yao[2], Yu Zhang[1], Fei Wang[1], Yi Wang[1], Shui-Ping Lv[1], Hu Ma[1*]

[1]Department of Oncology, Affiliated Hospital of Zunyi Medical University, Zunyi, China. Center for Translational Medicine, Zunyi Medical University, Zunyi 563000, China. [2]Department of Oncology, Affiliated Cancer Hospital of Medical school, University of Electronic Science and Technology of China, Sichuan Cancer Hospital &Institute, The Second People's Hospital of Sichuan Province, Chengdu, 610000, Sichuan Province, China.

[#]**Correspondence to:** Hu Ma, Department of Oncology, Affiliated Hospital of Zunyi Medical University, NO.149, Dalian Road, Zunyi 563000, China. Tel: +86-0851-28609038; Fax: +86-0851-28609095; Email: mahuab@163.com

Highlights:

Oral enteral nutrition could significantly increase the energy and protein intake of lung cancer patients during chemotherapy, while no significant effects were found after the patients had received radiotherapy or chemoradiotherapy. Limited evidence is available to judge whether oral enteral nutrition could improve clinical effectiveness in lung cancer after being received chemotherapy and/or radiotherapy.



Citation: Huang L, Zhou JG, Yao WX, et al. Clinical efficacy of oral enteral nutrition in lung cancer patients receiving chemotherapy and/or radiotherapy: a systematic review of randomized controlled trials. TMR Integrative Medicine 2017, 1(1): 20-29.

DOI: 10.12032/TMRIM201701113

Submitted: 5 September 2016, **Accepted:** 23 December 2016, **Online:** 17 January 2017.

Abstract

Background and Objectives: the effects of oral enteral nutrition (EN) in lung cancer patients receiving chemotherapy and/or radiotherapy were controversial, so we made a systematic review to analyze the clinical efficacy of EN in lung cancer patients after chemotherapy and/or radiotherapy. **Methods and Study Design:** Pertinent studies were identified by searching in PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang Database, China Biomedical Literature database (CBM) and Chinese Science and Technology Periodical Database (VIP). Energy intake, protein intake, weight and other data were extracted. **Results:** Finally, 5 randomized controlled trials (RCTs) were included in this systematic review. Patients in 3 studies received chemotherapy, in 1 with radiotherapy and in 1 with chemo-radiotherapy. The combined results showed that EN significantly increased energy and protein intake in lung cancer during chemotherapy, while there was no significant effect on other results after patients had received chemotherapy and/or radiotherapy. **Conclusions:** Limited evidence is available to judge whether EN can improve clinical effect of lung cancer with or without chemotherapy and/or radiotherapy, as clinical heterogeneity and other potential variation existed in this review. Further studies are needed.
Keywords: Clinical efficacy, Enteral nutrition, Lung cancer, Chemotherapy, Radiotherapy

摘要

背景：系统评价口服肠内营养支持对接受放化疗的肺癌患者的临床疗效与可行性。

方法：计算机检索相关主要中英文数据库，并手工检索相关营养学杂志。采用 The Cochrane Collaboration’s tool for assessing risk of bias 5.1.0 进行质量评价，RevMan 5.1 软件进行统计分析。由于纳入的研究之间有明显的临床异质性和其他潜在的差异，不适合行 meta 分析，因此行简要定性分析更加合适。

结果：最终纳入 5 个随机对照试验（RCT），其中 3 个 RCT 研究对象接受化疗，1 个 RCT 研究对象接受放疗，1 个 RCT 研究对象接受放疗及化疗。综合的分析结果提示口服肠内营养仅能够显著提高接受化疗肺癌患者的能量和蛋白质摄入量，然而对于体重、营养状态、生存质量、治疗反应或者生存时间没有显著影响。

结论：现有的证据不足以证明常规口服肠内营养支持能使接受放化疗的肺癌患者获益，由于样本量少，各研究之间差异大，更多高质量的随机对照试验有待进行。
关键词：临床疗效，肠内营养，肺癌，化疗，放射治疗

Abbreviations: EN, enteral nutrition; RCTs, randomized controlled trials; CNKI, China National Knowledge Infrastructure; CBM, China Biomedical Literature database; CBM, China Biomedical Literature database; VIP, Chinese Science and Technology Periodical Database; MESH, medical subject headings.

Funding： This research was supported by NSFC (Natural Science Foundation of China) (81360351, 81660512), the Department of Science and Technology of Guizhou Province (Grant No. Qian Ke He SY [2013] 3003), High-level Innovative Talents Cultivation Program Of Guizhou Province, Start-Up Fund for Doctor of Zunyi Medical University and the Social Practice Program for Postgraduate of Zunyi Medical University(Grant No. zy-yjs2015004), Applied Basic Research Programs of Science and Technology Commission Foundation of Sichuan Province (Grant No. 2012JY0058).

Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

Executive Editor: Jian Hao, Xiao-dong Wang

Introduction

Lung cancer was one of the most commonly diagnosed and the leading cause of death in most countries [1, 2]. Approximately 1 million new lung cancer patients will be confirmed in China in 2050 [3]. Chemotherapy significantly reduced the risk of death compared with surgery or supportive care alone in lung cancer, and radiotherapy plus chemotherapy further decreased the mortality risk [4-6]. Lung cancer patients experienced more symptom distress than other cancers, meanwhile chemotherapy and radiotherapy caused severe side effects and these side effects increased the risk of weight loss and malnutrition [7, 8]. It also diminished quality of life [9,10]. Weight loss is an ominous sign predicting disease progression and shortened survival time [11-16]. Malnutrition is a common finding in lung cancer patients, but only a small part of them had received treatment [17]. Malnutrition was an independent risk factor for poor prognosis [18]. Nutrition intervention could prevent malnutrition and weight loss, and even improved the quality of life and prolong survival time of cancer patients [12-14]. Therefore, it was critical to determine the efficacy of nutrition intervention in lung cancer patients receiving chemotherapy and/or radiotherapy. Early reviews indicated that exercise and nutrition had positive effects on weight loss, physical strength, and functional performance in non-small cell lung cancer (NSCLC). But the single function of nutrition intervention was not reported. Moreover, not all participants received anticancer therapy [15]. Another review suggested that dietary counseling can improve the food-intake of lung cancer patients after chemotherapy. However, the included studies were not all randomized controlled trials (RCTs)[16]. The outcome of enteral nutrition (EN) in lung cancer patients who had received chemotherapy and/or radiotherapy based on RCTs were not quantitatively or qualitatively analyzed. Only two studies were published with new evidence. Therefore, a systematic review was carried out about it.

Methods

Search strategy

A literature search was conducted in PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang Database, China Biomedical Literature database (CBM) and Chinese Science and Technology Periodical Database (VIP) with the following medical subject headings (MESH): lung neoplasm, nutrition supplement, nutrition therapy, dietary counselling, diet therapy, randomised controlled trails. Additional studies were also manually searched in primary magazines of nutrition. All databases were searched up to September, 2015. The search work was completed by Lang Huang and Jian-Guo Zhou respectively, and the disagreements were resolved by Hu Ma. The search strategy for PubMed was summarised in Supplemental Data 1.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

(1) Participants: lung cancer patients who received chemotherapy and/or radiotherapy; Interventions: EN by oral nutrition support, dietary counselling, etc.;

(2) Comparison: control groups were used usually care, normal diet or no intervention;

(3) Outcomes: primary outcomes must include weight or dietary intake;

(4) Study types: RCTs.

(5) Study types: RCTs.

Studies would be excluded:

(1) Studies used parenteral nutrition as the first choice or EN by tube feeding;

(2) Only focused on microelement, fatty acid, vegetable and fruit;

(3) Studies were a secondary research.

Data extraction

Titles and abstracts were screened to identify references by Jian-Guo Zhou and Yu Zhang according inclusion and exclusion criteria. Once included, the full-text was read. Name of the first author, study design, publication year, sample size, type of nutrition intervention and outcome measures were extracted by two investigators independently by using a predetermined data extraction table. Outcomes included energy intake, protein intake, weight, nutritional status, quality of life, functional status, treatment response and survival. The disagreements about the eligibility data were resolved by Hu Ma.

Quality assessment

Lang Huang and Fei Wang assessed the methodological quality using the Cochrane collaboration's tool [17]. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias were assigned a value of "high", "low" or ''unclear''. Any inconsistency was discussed with a third review author (Hu Ma).

Data synthesis

The clinical heterogeneity and other bias existed; a meta-analysis was considered inappropriately, therefore， a brief qualitative analysis was presented to describe the outcome of EN in the lung cancer patients receiving chemotherapy and/or radiotherapy.

Result

Literature research and characteristic studies

The search strategy identified 541 studies from electronic database. Finally 5 studies met the criteria were included in the systematic review [18-22]. The 5 studies contained a total of 712 patients, including 218 patients with lung cancer. All included studies were published between 1987 and 2014, and the detailed

data of one study cannot be obtained [23]. Among two of them were from Clinical Oncology Society of Australia (COSA) [18, 23]. The patients in 3 RCTs received chemotherapy , in 1 RCT with radiotherapy and in other 1 RCT received chemo-radiotherapy [5, 18, 20, 24, 23]. All studies in this review were RCTs. But only two studies focused on lung cancer without other tumor types. Three studies included other type tumors. One of these reported data by tumor type. All studies reported weight or weight change. Four studies showed survival. Three studies reported the data of nutritional status, energy and/or protein, quality of life. Treatment response was available in two studies. The detailed steps of our literature search were showed in Figure 1. The characteristics of these studies were presented in table 1.The primary outcome data of included studies were showed in table 2.

Assessing risk of bias

The blinding of participants, personnel and outcome assessment were not showed in two studies. It was assigned as "unclear". All domains were assigned as "low risk" in one study. Two meeting abstracts were assigned as "unclear" in all aspects, and no studies were assigned as "high risk". The overall methodological quality was accepted and fair. The detail of assessing risk of bias was showed in Figure 2.

Energy and protein Intake

Two studies reported the data of intake, and both studies showed a significant increase at the end of intervention after chemotherapy. Ovesen et al. reported that the intervention group was counseled to intake energy and protein by 1 megajoule (MJ) and 10g of protein per day. 1 month after the intervention, patients achieved the goal of 1MJ/d. It had a significant increase both in energy and protein intake (P<0.05) and the difference continued during the entire study period [21]. Evans et al. showed that patients in intervention group had high caloric intakes during all chemotherapy cycles (P<0.001) [22].

Weight or weight change

All studies described weight and its changes, except Kilic et al [19]. Kilic et al. found that the weight loss more prevalent in the control group than the radiotherapy group (P=0.003). None of them reported increase significant in weight in the intervention group. Baldwin et al. reported a statistically significant difference in weight change during 52 weeks (4.78±5.0Kg, 1.36±7.5Kg, P=0.04). On the contrary, because of considerable attrition, Intention-to-treat analysis was considered (0.12±5.3Kg, 0.29±5.9Kg, P>0.05) [20]. Evans et al. found overall median percent weight change during the 12 week support period did not differ significantly between the intervention and the control groups (−1.2Kg; −3.1Kg, P>0.50)[22]. Kiss et al. found no significant benefits in weight at the end of radiotherapy (3.0 kg; 95%CI: −0.8-6.8, effect size=0.7, P=0.11) and 3 months post-radiotherapy (5.5kg, 95%CI: −1.4-2.3, effect size =0.71, P=0.71) [18]. Ovesen et al reported that weight increased more in the counseled group than the control group, but the difference did not reach statistical significance after 5 months (1.0±5.6Kg, 0.1±4.7Kg, P=0.15) [21].

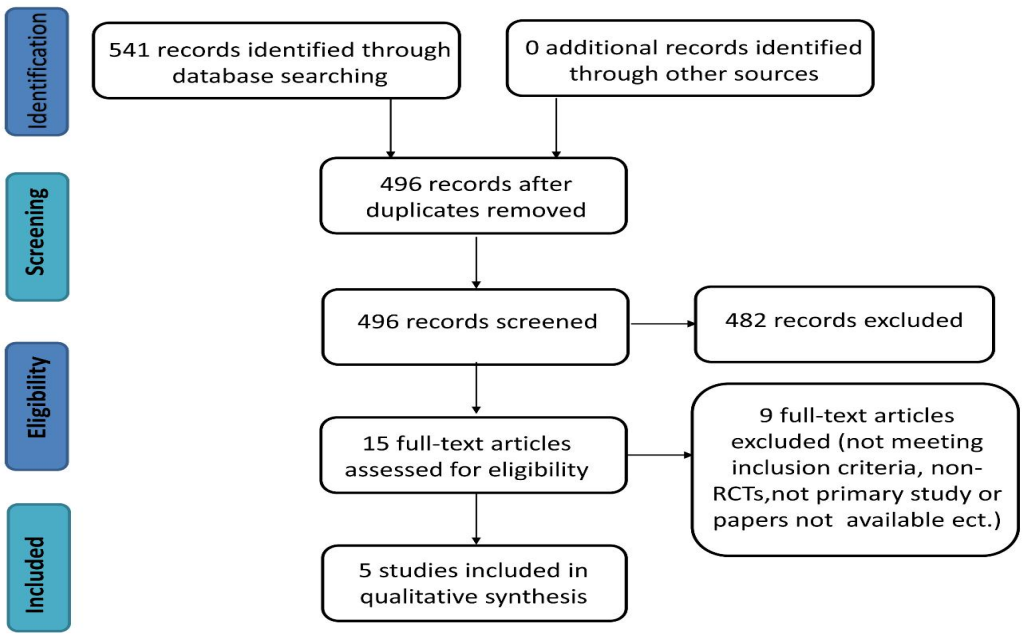


Figure 1 Flow diagram of the details of the study

Nutritional status

Three studies assessed the nutritional status by measuring the data of fat-free mass and hand grip strength. However, none of them had statistically significant difference between the intervention and the control groups. The study by Kiss et al. found dietary counselling improved fat-free mass, but there was no significant difference at the end of radiotherapy (0.6kg; 95%CI:−2.1-3.3, effect size=0.19, *P*=0.66), or three months post-radiotherapy (1.48kg; 95%CI:−0.5-3.5Kg, effect size=0.67, *P*=0.14) [18]. Baldwin et al. collected the data of grip strength of hand, while the mean changes at all time-points were no significantly different between two groups (data not shown) [20]. Ovesen et al. measured the data of fat mass from the first month to the fifth month, no significant differences were observed at any time point [21].

Quality of life

Two studies reported the quality of life by questionnaires [(European Organisation for Research and Treatment of Cancer (EORTC-C30), Functional Assessment of Cancer Therapy (FAACT), linear analog scale (LAS) and Quality-of-Life index (QL-index)]. But neither of both reported significant difference between the intervention and the control groups. Baldwin et al. collected data by using EORTC-C30 FAACT, and changes were not significantly different. However, not all participates finished the questionnaires. The data of quality of life was incomplete [20]. Ovesen et al. measured data by using LAS and QL-index. QL-index increased significantly in both groups in months. But LAS remained unchanged.

Treatment response

Two studies assessed the effects of intervention on the rate of complete remission (CR), partial remission (PR), no change (NC), and progressive disease (PD). No significantly difference between the intervention and the control groups were reported in the two studies. Ovesen et al. found the effective rate (CR+PR) and ineffective rate (NC+PD) were no significant difference in the counseled and the control groups at 3 months (65% vs 69%, *P*=0.81), and similar at 5 months (63% vs 46%, *P*=0.11) [21]. Evans et al. found no significant difference in the proportion of responders (CR+PR) and nonresponders (NC+PD) [22].

Survival

Four studies reported survival analysis. However, there was no significant difference between the intervention and the control groups. Kilic et al. found that both the median overall and metastasis-free survival rates were higher in the intervention groups. But no statistically significant difference was found [19]. Baldwin et al. found that overall 1-year survival was 38.6% (95% CI: 33.3-43.9), but there were no significant difference in

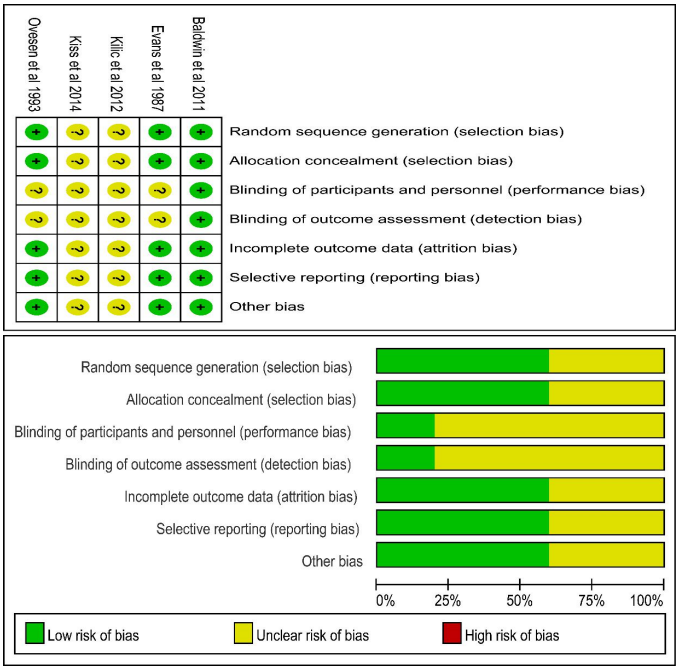


Figure 2 Appraisal risk of bias of the included trials using the Cochrane risk-of-bias tool.

overall survival (HR=0.840, 95%CI: 0.653-1.08, P<0.05). Mean weight change from baseline to 12 weeks was greater in survivors who lived beyond 26 weeks compared with those who did not (0.58±2.47kg, 0.66±3.76kg, P=0.002). It suggested that weight gain was primarily associated with survival [20]. Ovesen et al. found that there was no significant difference in the overall survival rate. The cumulative proportions surviving 1 year and 2 years were 69% and 39% respectively in the intervention group and 72% and 32% in the control group (P=0.35) [21]. Evans et al. demonstrated that the median survival time was no significant difference [22].

Discussion

Strong evidences have indicated that EN was as good as or preferable to PN. It could reduce the incidence of complication [25-27]. EN was recommended when patients were in malnutrition or the intake reducing markedly. It had been proved that the patients with gastrointestinal or head and neck tumor ~~to be~~ benefitted from EN [12]. The effect of EN in lung cancer patients receiving chemotherapy and/or radiotherapy was controversial, so it was important to ensure that whether EN in lung cancer can significant improve intake, weight, nutrition status and quality of life, even benefit in treatment response and survival or not.

Five RCTs with 241 lung cancer patients were involved in this review. Two of them were from COSA. The patients in 3 RCTs received chemotherapy, in 1 RCT with radiotherapy and in other 1 RCT received chemo-radiotherapy. Available studies indicated that EN could increase energy and protein intake in lung cancer patients undergoing chemotherapy. While limited evidence was available to judge whether EN could improve clinical effectiveness of patients received chemotherapy and/or radiotherapy or not.

Current EN guidelines recommended that intensive dietary counselling and oral nutrition supplements could increase dietary intake (grade A) in cancer patients [12,28]. But only patients with gastrointestinal or head and neck tumor could maintain weight and prevent the interruption of therapy. EN was not appropriate to the patients receiving radiotherapy (grade C) or chemotherapy (grade B). Similar to guidelines, except for energy and protein intake, other outcomes were not benefited in this review. Radiotherapy had a long and severe adverse effect on digestive system of patients with gastrointestinal or head and neck compared with lung cancer patients. It may explain why lung cancer patients could not benefit from the increase of dietary in some degree. The mechanism of different response among lung cancer, gastrointestinal tumor and head and neck tumor in the treatment of EN should be fucused on.

Our review may have more convinced results than the previous reported review [16]. Firstly, we had a more comprehensive search strategy. Secondly, to the best of our knowledge, this was the first systematic review to focus on EN in lung cancer patients received chemotherapy and/or radiotherapy based on RCTs. Finally, methodological quality was assessed. The overall quality of involved studies was good. Some potential limitations were also needed to resolve in this review. First of all, the clinical heterogeneity and other variation were existed. Quantitative analysis were not conducted in this review. Then, only a small number of eligible studies were included, and other type tumors were included in this review. Lung cancer patients had more chances to experience weight loss and malnutrition than other type tumors when they received chemotherapy and/or radiotherapy. So the data may not be extremely convinced. Moreover, the amount of dietary intake in the control group was not unified. Current studies existed huge variation in this field. Primarily, the target caloric and protein intake in intervention groups were different. Additionally, only a part of participators reached the intake goals. Furthermore, the time of follow-up were different. Finally, the time and frequency of assessment results were also various. Therefore, it would be better if consensuses could be reached about intervention and evaluation in further studies.

Conclusion

In conclusion, this review suggested that dietary and nutritional counselling could significantly improve the energy and protein intake in lung cancer patients receiving chemotherapy. But there was insufficient evidence indicating the clinical effectiveness. Current literatures demonstrated that it was not feasible to recommend EN as a routine treatment for lung cancer patients undergoing chemotherapy and/or radiotherapy. However, limitations had existed in this review. We should interpret with caution. Malnutrition and weight loss occurred frequently in lung cancer patients, especially after they had received chemotherapy and/or radiotherapy, and associated with poor prognosis [11,12,29-33]. In addition, It was demonstrated that EN had positive effect in patients with gastrointestinal, head and neck tumor. So, unless strong evidence proved that EN had no effect on lung cancer patients undergoing chemotherapy and/or radiotherapy, further high quality RCTs should be conducted.

Table 1 Characteristic of included studies

Study ID	Participants (n)	Nutrition intervention/ Comparison	Outcome	Results
Kiss et al 2014 Study design: RCT COSA	lung cancer(24)receiving (chemo)radiotherapy	1.NI(12):intensive, individualized nutritional management up to 6 weeks following radiotherapy 2. UC(12):study didn't show	Weight Fat-free mass Quality of life	Study dietary counselling improved weight, fat-free mass, fatigue and functional outcomes in lung cancer patients receiving(chemo)radiotherapy
Kilic et al 2012 Study design: RCT COSA	Lung(45) cancer patients at locally advanced stage undergoing radiotherapy	Gr 1: normal diet Gr 2: immune-enriched ONS Gr 3: Standard ONS	Weight Malnourish TNFa and IL-6 Esophagitis Toxicity Quality of life Survival rates	Immune-enriched oral nutritional supplementation was found its effective to decrease the RT-related esophagitis via reducing systemic inflammation without any effect on survival
Baldwin et al 2011 Study design: RCT	Gastrointestinal (277) cancer and lung (81) cancers receiving chemotherapy	Gr1(96):No intervention, weekly phone call from dietician Gr2(90):Dietary advice alone, an additional 2510 kJ (600 kcal) intake per day by selecting four items daily from booklet Gr3(86):Nutritional supplement alone, receiving a supplement sachet （ScandiShake or Calshake）to provide 2460 kJ (588 kcal) plus full-cream milk，multivitamin and mineral supplement Gr4(86): increase food intake by250 kJ (600 kcal) per day and one sachet of the nutritional supplements and vitamin preparations were given to groups 2, 3Intervention groups received weekly phone encouragement by a dietitian	Survival Quality of life Dietary increased Weight	Oral nutritional interventions based on dietary advice or supplements had no effect on nutritional status or quality of life
Evans et al 1987 Study design: RCT	NSCLC (96) and colorectal(84) cancer patients during chemotherapy	Gr1:an adliboral diet without specific nutritional counselling Gr2: to meet 10%±TCI with 12.5% form protein and RDA of vitamins	Weigh Dietary intake Treatment response	Nutritional support has no benefit in terms of tumor response, toxicity, or survival duration

		and minerals Gr3: to meet 10%±TCI with 25% form protein and RDA of vitamins and minerals plus 150 mg Zn and 266 mg Mg	Survival	
Ovesen et al 1993 Study design: RCT	Breast cancer(19); ovarian cancer(45); lung cancer(41) Undergoing Chemotherapy	Gr1:ad lib diet Gr2:dietary counseling from a dietitian with or without ONS to achieve an intake that met or exceeded calculated energy and protein requirements 1.5 to 1.7 X basal energy expenditure protein intake of 1.0 to 1.2 g/kg body weight	Weight Dietary intake Nutritional status (anthropometry) Quality of life Treatment response Survival	Nutritional counseling effectively increased energy and protein intake, but no significant increase was seen in weight, lean body mass, or survival.

COSA: Clinical Oncology Society of Australia; TCI: target caloric intake

Table 2 The primary outcome data of included studies

Reference	Outcome	Intervention group	Control group	*P* value
Baldwin et al 2011 Study design: RCT	One survival rate	HR 0.840 (0.653-1.08)	1.00	>0.05
	Mean (SD) change (kg)	Baseline 70.3kg (13.0)	Baseline70.0kg (13.4)	>0.05
		6 weeks 0.16 (3.1)	6 weeks 0.36 (3.3)	>0.05
		52weeks 0.12 (5.3)	52weeks 0.29 (5.9)	>0.05
Evans et al 1987 Study design: RCT	Median percent weight change (N)	4wk -0.6%(57)	-2.1%(33)	0 .06
		Overall -1.2%(45)	-3.1%(20)	>0.50
	Caloric Intake(N)	Baseline 67(59)	62 (33)	0.13
		4wk 89 (59)	68 (34)	0.001
		12wk 90 (48)	61 (23)	0.004
		Overall 91 (58)	62 (34)	<0.001
	response rate	27.5%	14.7%	>0.05
Ovesen et al 1993 Study design: RCT	Weight change(Kg)	5m 1.0 ± 5.6	5m 0.1 ± 4.7	0 .15
		1m -0.7 ± 2.7	1m -0.6 ± 2.6	-
	Energy intake(MJ/d)	5m 0.6 ± 2.3	5m -0.3 ± 2.0	<0.05
		1m 1.1 ± 2.6	1m 0.3 + 2.7	<0.05

	Protein intake(g/d)	5m	8 ± 21	5m	-1 ± 22	<0.05
		1m	12 ± 23	1m	2±21	<0.05
	CR+PR(n)	5m	36	5m	22	0.11
		3m	37	3m	33	0.83
	Survival rate	1year	69%	72%		<0.05
		2year	39%	32%		<0.05
Kiss et al 2014	Weight change	1m	3.0 kg	95%CI −0.8, 6.8		0.11
Study design: RCT		3m	5.5 kg	95%CI −1.4, 12.3		0.71
	fat-free mass	1m	0.6 kg	95%CI −2.1, 3.3		0.66
COSA		3m	1.48kg	95%CI −0.5, 3.5		0.14
Kilic et al 2012	Weight loss was detected in Gr 1					0.03
Study design: RCT	100%, 17% and 60% of patients were malnourished in Gr 1, 2 and 3					<0.001
	Esophagitis 27%, 87% and 80% in Gr 1, 2 and 3					<0.002
COSA	Better functional scores were detected in Gr 2					>0.05
	median overall- and metastasis-free survival rates were higher for Gr 2					>0.05
	TNFa and IL-6 were higher Gr 2					<0.05

Reference

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016, 66(1): 7-30.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016, 66(2): 115-132.
3. Chen WQ, Zheng RS, Zhang SW, et al. The incidences and mortalities of major cancers in China, 2010. Chin J Cancer 2014, 33(8): 402-405.
4. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2000, 2: Cd002139.
5. De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, et al. Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. Ann Oncol 2006, 17(4): 543-552.
6. Pijls-Johannesma M, De Ruysscher D, Vansteenkiste J, et al. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. Cancer Treat Rev 2007, 33(5): 461-473.
7. Cooley ME. Symptoms in adults with lung cancer: A systematic research review. J Pain Symptom Manage 2000, 19(2): 137-153.
8. Khalid U, Spiro A, Baldwin C, et al. Symptoms and weight loss in patients with gastrointestinal and lung cancer at presentation. Support Care Cancer 2007, 15(1): 39-46.
9. Sarna L, Evangelista L, Tashkin D, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. Chest 2004, 125(2): 439-445.
10. Fox SW, Lyon DE. Symptom clusters and quality of life in survivors of lung cancer. Oncol Nurs Forum 2006, 33(5): 931-936.
11. Kiss N, Isenring E, Gough K, et al. The prevalence of weight loss during (chemo) radiotherapy treatment for lung cancer and associated patient- and treatment-related factors. Clin Nutr 2014, 33(6): 1074-1080.
12. Arends J, Bodoky G, Bozzetti F, et al. ESPEN guidelines on enteral nutrition: non-surgical

oncology. Clin Nutr 2006, 25(2): 245-259.
13. Isenring E, Zabel R, Bannister M, et al. Updated evidence-based practice guidelines for the nutritional management of patients receiving radiation therapy and/or chemotherapy. Nutr Diet 2013, 70(4): 312-324.
14. De Waele E, Mattens S, Honore PM, et al. Nutrition therapy in cachectic cancer patients. The Tight Caloric Control (TiCaCo) pilot trial. Appetite 2015, 91: 298-301.
15. Payne C, Larkin PJ, McIlfatrick S, et al. Exercise and nutrition interventions in advanced lung cancer: a systematic review. Curr Oncol 2013, 20(4): E321-E37.
16. Kiss NK, Krishnasamy M, Isenring EA. The Effect of Nutrition Intervention in Lung Cancer Patients Undergoing Chemotherapy and/or Radiotherapy: A Systematic Review. Nutr Cancer 2014, 66(1): 47-56.
17. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library 2008.
18. Kiss N, Isenring E, Gough K, et al. Outcomes from a pilot randomised controlled trial of early and intensive dietary counselling in lung cancer patients receiving (chemo) radiotherapy. Asia-Pacific J Clin Oncol 2014, 10(6): 129.
19. Kilic D, Iren S, Bagriacik U, et al. The impact of nutritional support on treatmen trelated complications, qol and survival in lung cancer patients undergoing radiotherapy: A randomized, controlled study. Clin Nutr, Supplement 2012, 7(1): 164.
20. Baldwin C, Spiro A, McGough C, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. J Hum Nutr Diet 2011, 24(5): 431- 440.
21. Ovesen L, Allingstrup L, Hannibal J, et al. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. J Clin Oncol 1993, 11(10): 2043-2049.
22. Evans WK, Nixon DW, Daly JM, et al. A randomized study of oral nutritional support versus ad lib nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. J Clin Oncol 1987, 5(1): 113-124.
23. Kilic D, Iren S, Bagriacik U, et al. The impact of nutritional support on treatmentrelated complications, qol and survival in lung cancer patients undergoing radiotherapy: A randomized, controlled study. Clin Nutr, Supplement 2012, 7(1): 164.
24. Evans WK, Nixon D, Daly J, et al. A randomized study of oral nutritional support versus ad lib nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. J Clin Oncol 1987, 5(1): 113-124.
25. Miyata H, Yano M, Yasuda T, et al. Randomized study of clinical effect of enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer. Clin Nutr 2012, 31(3): 330-336.
26. Bozzetti F, Braga M, Gianotti L, et al.. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. Lancet 2001, 358(9292): 1487-1492.
27. Mercadante S. Parenteral versus enteral nutrition in cancer patients: indications and practice. Support Care Cancer 1998, 6(2): 85-93.
28. Isenring E, Zabel R, Bannister M, et al. Updated evidence‐based practice guidelines for the nutritional management of patients receiving radiation therapy and/or chemotherapy. Nutr Diet 2013, 70(4): 312-324.
29. Kisner DL. Malnutrition In Lung-Cancer - Incidence, Prognostic Implications, And Pathogenesis. Recent Results Cancer Res 1982, 80: 240-245.
30. Buccheri G, Ferrigno D. Importance of weight loss definition in the prognostic evaluation of non-small-cell lung cancer. Lung Cancer 2001, 34(3): 433-440.
31. Ovesen L, Hannibal J, Mortensen EL. The Interrelationship Of Weight-Loss, Dietary-Intake, And Quality-Of-Life In Ambulatory Patients With Cancer Of The Lung, Breast, And Ovary. Nutr Cancer 1993, 19(2):159-167.
32. Hebuterne X, Lemarie E, Michallet M, et al. Prevalence of Malnutrition and Current Use of Nutrition Support in Patients With Cancer. JPEN J Parenter Enteral Nutr 2014, 38(2): 196-204.
33. Norman K, Lochs H, Pirlich M. Malnutrition as prognostic factor. Chir Gastroenterol 2004, 20: 175-180.