JBUON 2017; 22(4): 985-995
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Effects of javanica oil emulsion injection combined with radiotherapy versus radiotherapy alone on the efficacy and safety in patients with esophageal cancer: a pooled analysis of 1269 cases

Jing Wang*, Heng-bo Ye*, Youhong Dong

Department of Oncology, The First People's Hospital of Xiangyang, Hubei University of Medicine, XiangYang, Hubei, 441000, P.R. China.

*These authors contributed equally to this work.

Summary

Purpose: *To assess the effectiveness and safety of javanica oil emulsion injection (JOEI) when combined with radiotherapy (RT) in patients with esophageal cancer.*

Methods: *Electronic databases including EMBASE, PUBMED, the COCHRANE Library, China Academic Journals Full-text Database, Chinese Biomedical Literature Database, and Chinese Scientific Journals Database were searched. Two reviewers performed the search, identified and extracted eligible studies. Items including response rate, survival and safety were extracted and analyzed using Review Manager 5.3.*

Results: *A total of 16 clinical studies with 1269 esophageal cancer patients were included. The results showed that adding JOEI to RT could improve the complete response (CR rate) (Odds Ratio/OR 1.63; 95% confidence interval (CI), 1.27 to 2.10; p=0.0001), partial response (PR) (OR 1.25; 95% CI, 0.97 to 1.60; p=0.09), Relative Risk/RR (OR 1.42; 95% CI, 1.19 to 1.70; p<0.0001), quality of life (OR 3.01; 95% CI, 1.72 to 5.25; p=0.0001), and reduce the incidence of adverse events including nausea and vomiting (OR 0.81; 95% CI, 0.45 to 1.44; p=0.46) and radiation esophagitis (OR 0.47; 95% CI, 0.33 to 0.68; p<0.0001). The 1-, 2-, and 3-year survival rates in the JOEI group were significantly higher than those in the RT alone group (p<0.001).*

Conclusions: *JOEI in combination with RT could benefit esophageal cancer patients with improved rate of response and quality of life, prolonged survival, and reduced incidence of adverse events. However, these results should be viewed with caution due to the limited quality of the included studies.*

Key words: *esophageal cancer, javanica oil emulsion injection, meta-analysis, radiotherapy, traditional Chinese medicine*

Introduction

Esophageal cancer is one of the most serious malignancies with high rates of morbidity and mortality. In 2005, more than 400000 patients died from esophageal cancer worldwide, and nearly 500000 newly diagnosed esophageal cancer patients were reported [1]. In 2012, esophageal cancer was the fourth most common cancer in China. It is estimated that the incidence of several other kinds of tumors are expected to reduce by 2025, while the cases of esophageal cancer are about to increase by 140% [1,2]. Esophageal cancer is already a major public health concern and its overall survival of five-year is 17% [3]. Late stage at diagnosis is the main reason of poor survival outcome. Nearly half of these patients have confirmed metastatic disease, locally advanced stage is present in about 30% and

Correspondence to: Youhong Dong, MD. Department of Oncology, The First People's Hospital of Xiangyang, Hubei University of Medicine, No 15 Jienfang Road, Fancheng District, Xiangyang, Hubei, 441000, P.R. China.
Tel: +86 15997305988, E-mail: dr5q55@163.com
Received: 26/01/2017; Accepted: 06/02/2017

only 20% have a curable localized disease [3-5].

With the development and application of high-resolution CT scan, endoscopic ultrasound and FDG-PET, the evaluation of the tumor burden has been modified in recent years, thus improving the effects of treating esophageal cancer. The treatment of esophageal cancer depends on the disease stage. For non metastatic disease, esophagectomy remains the primary and basic choice for esophageal cancer patients at early stage. Indeed, this kind of malignancy is highly curable in its earliest stages when patients are operated [6]. For locally advanced tumors, it is recommended that a combination of surgery, chemotherapy and/or RT should be considered [7,8]. When the disease progresses further, non-operative treatments are usually recommended for patients who lost their chances for surgery.

Years of researches have demonstrated that the application of chemotherapy and RT could benefit patients with longer survival and lower staging of disease, especially after the emergence and development of new chemotherapeutic agents and regimens and new RT methods. In patients with locally advanced cancer of the esophagus, neoadjuvant chemoradiotherapy (CRT) but not neoadjuvant chemotherapy alone is the preferred treatment approach [9]. Recent technological advances in RT including image guided-RT, intensity-modulated RT (IMRT) and PET-CT-based RT planning, may further improve the efficacy of CRT and reduce the incidence of adverse events. However, a combination of these therapeutic options may potentially increase the risk of serious adverse events. So it is necessary to find agents which are capable of enhancing the anti-tumor effects of CRT, improving the immune function of the host, and reducing the adverse events of CRT.

Traditional Chinese Medicine (TCM), especially herbal medicine, is considered to be a part of anticancer strategy in China. A large number of cancer patients preferred to receive TCM when receiving CRT, either in the form of injection or oral administration [10].

JOEI has been widely used in the treatment of cancer in China and it is a product produced from Brucea Jen petroleum ether extracts as raw materials, and purified soybean lecithin as emulsifier [11]. Its composition is 85% triglycerides and 10% oleic acid, with the rest composed of both saturated and unsaturated fatty acids as well as some triterpenoid alcohols [12]. In recent years, it is recognized that some components of the unsaturated fatty acids of the JOEI, such as the oleic and linoleic acids, show specific affinity for tumor cell membranes and exhibit potent antitumor activity. The triglycerides, which do not directly present anticancer activity, can be hydrolyzed into oleic acid and then subsequently exerting antitumor effect [12]. Indeed, several clinical studies showed that JOEI combined with CRT could be considered as an effective and safe regimen to improve the quality of life and reduce the prevalence of adverse events [11,13].

However, most of the studies dealing with the application of JOEI in esophageal cancer lack large samples and there is no sufficient evidence to support the use of JOEI for enhancing efficacy, reducing side effects of CRT and improving the quality of life. Furthermore, there is no direct evidence to indicate that JOEI is risk-free, with regard to adverse events such as allergic reactions. So, we performed this meta-analysis to objectively assess the efficacy and safety of JOEI when combined with CRT in the treatment of patients with esophageal cancer.

Methods

Eligibility criteria

Clinical observational and randomized controlled trials comparing chemotherapy or RT with or without treatment of JOEI were potentially eligible for inclusion. Patients should have esophageal cancer regardless of different subtypes. The metaanalysis was limited to the injection of JOEI as an adjunct therapy to assist the standard anticancer therapy such as chemotherapy or RT. The primary outcomes were survival rates at different times, disease-free survival, mortality and quality of life. The secondary outcomes included complete response, partial response and adverse events such as severe neutropenia.

Information sources

Electronic databases including EMBASE, PUBMED, the COCHRANE Library, China Academic Journals Full-text Database, Chinese Biomedical Literature Database, and Chinese Scientific Journals Database were searched for clinical studies on the topic of JOEI plus RT or chemotherapy for treating esophageal cancer. Online searches using conference abstracts were also performed to find studies meeting the inclusion criteria.

Search

Two reviewers performed the search using the following English terms: “Yadanzi”, “Yadanziyou”, “Javanica oil emulsion injection”, “Seed Oil of Brucea javanica “, “Brucea javanica oil”, “esophageal cancer”, “esophageal tumor”, “esophageal carcinoma”, “radiotheapy”, “chemotherapy” and “chemoradiotherapy”. The Chinese searching terms includes “ Javanica oil emulsion injection”, “ esophageal cancer”, “radiotheapy”, “chemotherapy” and “chemoradiotherapy”. The searching strategy identified trials mainly in Chinese and English languages. Chinese papers were translated to ensure that they could be evaluated and analyzed for the meta-analysis.

Study selection

To identify studies suitable for inclusion, the possible eligible trials were first screened by the titles, abstracts, and keywords. After this process of selection, the remaining articles were further assessed in Full-text if they met the following criteria:

1. Enrolled patients with esophageal cancer unable and/or refused to be operated;
2. Compared the combination of conventional treatment and JOEI with conventional intervention alone;
3. Reported at least one of the relevant clinical outcomes mentioned above;
4. Studies should be randomized.

We then contacted the authors of potentially eligible trials to get more detailed information if the full-text failed.

The two reviewers had full agreement on the included studies. Excluded were studies that did not meet the criteria previously described.

Data collection process and data items

The process of data collection was performed by two reviewers independently using a well designed electronic form. Concerning items such as the number of cases participating in individual studies, treatment details, and outcome measures were extracted. The following information should be collected and recorded in the form:

1. General information: title, year of publication, authors, publication source, country, language, funding, setting, etc.
2. Study characteristics: design of trial, duration of patient enrollment, randomization, blinding, and allocation concealment.
3. Intervention(s): Chemotherapy (regimen, dose, timing), Radiotherapy (dose, timing), JOEI (dose, timing).
4. Patients: inclusion criteria, number in control and comparison groups, age, histological diagnosis, withdrawals or lost to follow up.
5. Outcomes: primary and second outcomes relevant to efficacy and safety of treatment.

After original abstracting, the information was compared and checked if there were any disagreements. For differences in data collection, a discussion was carried out. A third reviewer was consulted to solve problems of data extraction if necessary. For binary data, the total number of events in each group were collected, while the mean, standard deviation and sample size of each group were extracted for continuous data [14].

Risk of bias in individual studies

The Cochrane Handbook for Systematic Reviews of Interventions 5.3.0 was used to assess the risk of bias in each study by two reviewers independently. And the following processes or items were assessed for possible bias:

1. Selection bias: Randomization process, allocation concealment process.
2. Bias of performance and detection: blinding.
3. Bias of outcomes from loss to follow-up: incomplete outcome data.
4. Reporting bias: selective report.

Synthesis of results and statistics

Data analysis was conducted using Review Manager 5.3. The combined results were calculated using a fixed-effect model if there was no significant heterogeneity between different studies. The form of relative risk (RR) was applied for analysis of dichotomous variables, whereas mean differences (MD) were used to perform the pooled analysis of continuous data, both with 95% CI. The overall effect of RR and MD was assessed by Z-test, and it was statistically significant if the p value was less than 0.05. Chi-square and I^2 variable tests were used to assess possible heterogeneity between included trials. Statistically significant heterogeneity was accepted if $I^2 \geq 50\%$ and $p \leq 0.1$. The random effect model was selected if the heterogeneity was statistically significant.

Results

Study selection

The flow chart of study selection of the present systematic search is summarized in Figure 1.

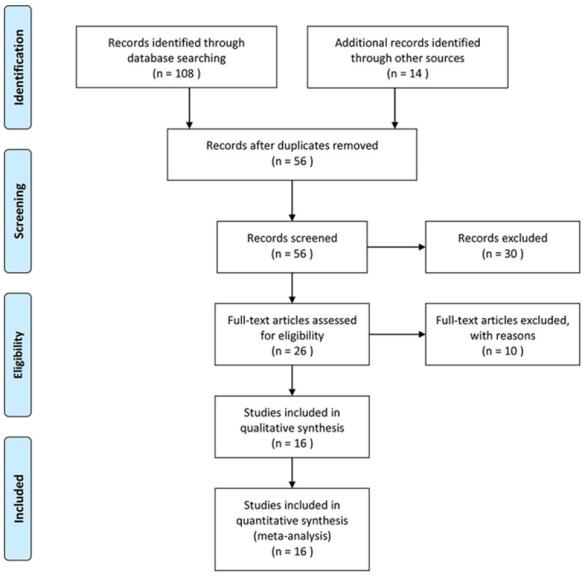

Figure 1. Flow chart of identification of eligible studies.

By using the search term presented above, a total of 122 potentially eligible references were identified from databases including EMBASE, PUBMED, the COCHRANE Library, China Academic Journals Full-text Database, Chinese Biomedical Literature Database, and Chinese Scientific Journals Database. Additional identification of possibly eligible articles was performed by checking relevant journals and reviews, and by searching conference abstracts from published meeting abstracts in China. Of the 122 identified studies from the systematic searching, 66 were discarded according to the eligibility criteria mentioned above. The full texts of the remaining 56 papers were further assessed. Thirty of them were excluded as they failed to

Table 1. Baseline characteristics of included studies

First author, year	Patients		Sex		Age		Regimen		Outcomes
	I	C	M	F	I	C	I	C	
Liang, 2002	33	33	48	18	40-74	36-73	RT+JOEI: RT, 60-70Gy/6-7weeks; JOEI, 60 ml/d, 30 days	RT: 60~70Gy/6-7weeks	CR, PR, RR, 1-y SR, 3-y SR, 5-y SR, adverse events,
Kong, 2004	30	30	47	13	NA	NA	RT+JOEI: RT, 2 Gy/d, 5 t/w, 60-70Gy in total; JOEI, 30 ml/d, 21 days	RT: 2 Gy/d, 5 t/w, 60-70Gy in total	CR, PR, RR, 1-y SR, 2-y SR, adverse events
Chen, 2007	44	48	65	27	NA	NA	RT+JOEI: RT, 64-70Gy/32-35; JOEI, 10~20 ml/d, 42 days	RT: 64-70Gy/32-35	adverse events
Jia, 2008	76	72	116	32	36-70	36-70	RT+JOEI: RT, 60-68Gy in total; JOEI, 30-50 ml/d, 30 days	RT: 60-68Gy in total	CR, PR, RR, 1-y SR, 2-y SR, 3-y SR, QOL, adverse events, immune function
Ma, 2008	40	40	56	24	44-68	45-69	RT+JOEI: RT, 2 Gy/d, 5 t/w; JOEI, 30 ml/d, 21 days	RT: 2 Gy/d, 5 t/w	CR, PR, RR, adverse events
Jiang, 2009	35	34	41	28	42-68	39-66	RT+JOEI: RT, 1.8~2.0 Gy/d, 60-70Gy in total; JOEI, 30 ml/d, 42 days	RT: 1.8-2.0 Gy/d, 60-70Gy in total	CR, PR, RR, adverse events
Liu, 2010	28	28	39	17	30-78	30-78	RT+JOEI: RT, 2 Gy/d, 5 t/w, 60-70Gy in total; JOEI, 30 ml/d, 21 days	RT: 2 Gy/d, 5 t/w, 60-70Gy in total	CR, PR, RR, QOL, adverse events
He, 2010	35	35	63	7	52-78	52-78	RT+JOEI: RT, 2 Gy/d, 5 t/w, 60-70Gy in total; JOEI, 30 ml/d, 18-21 days	RT: 2 Gy/d, 5 t/w, 60-70Gy in total	CR, PR, RR, QOL, adverse events
Yue, 2010	100	100	134	66	NA	NA	CT+RT+JOEI: CT, FP; RT, 2 Gy/d, 5 t/w, 60~66Gy in total; JOEI, 30mgl/d, 28 days	CT+RT: CT, FP; RT, 2 Gy/d, 5 t/w, 60-66Gy in total	CR, PR, RR, 1-y SR, 2-y SR, 3-y SR, adverse events
Li, 2011	28	28	37	19	31-71	29-74	RT+JOEI: RT, 4.2-4.8 Gy/d, 3 t/w, 50-60Gy in total; JOEI, 30 ml/d, 21 days	RT: 2 Gy/d, 5 t/w, 60-70Gy in total	CR, PR, RR, 1-y SR, 2-y SR, 3-y SR, 5-y SR, adverse events
Xie, 2011	40	40	51	29	60-78	60-78	CT+RT+JOEI: CT, FP; RT, 2 Gy/d, 5 t/w, 60-66Gy in total; JOEI, 30mgl/d, 28 days	CT+RT: CT, FP; RT, 2 Gy/d, 5 t/w, 60-66Gy in total	CR, PR, RR, 1-y SR, 2-y SR, 3-y SR, adverse events
Liao, 2012	44	44	61	27	60-78	60-78	RT+JOEI: RT, 2 Gy/d, 5 t/w, 60-62Gy in total; JOEI, 60 ml/d, 21 days	RT: 2 Gy/d, 5 t/w, 60-62Gy in total	CR, PR, RR, 1-y SR, 2-y SR, 3-y SR, adverse events, VEGF level
Lu, 2012	29	29	43	15	36-74	38-73	CT+RT+JOEI: CT, FOLFOX4; RT,60~64Gy in total; JOEI, 30mgl/d, 28 days	CT+RT: CT, FOLFOX4; RT, 60-64Gy in total	CR, PR, RR, QOL, adverse events
Li, 2013	25	25	36	14	48-73	48-73	RT+JOEI: RT, 2 Gy/d, 5 t/w, 60Gy in total; JOEI, 30 ml/d, 21 days	RT: 2 Gy/d, 5 t/w, 60-62Gy in total	CR, PR, RR, 1-y SR, adverse events
Liu, 2013	23	23	29	17	40-73	40-68	T+RT+JOEI: T, 60mg/m2, qw, 6 weeks; RT, 1.8 Gy/d, 5 t/w, 50.4Gy in total; JOEI, 30 mg/d, 5 t/w, 6 weeks	T+RT: T, 60mg/m2, qw, 6 weeks; RT, 1.8 Gy/d, 5 t/w, 50.4Gy in total	CR, PR, RR, MS, 3-y SR
Mi, 2015	25	25	31	19	38-81	38-81	RT+JOEI: RT, 2 Gy/d, 5 t/w, 64Gy in total; JOEI, 30 ml/d, 21 days	RT, 2 Gy/d, 5 t/w, 64Gy in total	CR, PR, RR, QOL, adverse events

I: intervention, C: control, M: male, F: female, T: taxol, RT: radiotherapy, JOEI: Javanica oil emulsion injection, CT: chemotherapy, CR: complete response, PR: partial response, RR: response rate, MS: median survival, SR: survival rate, 1-y: 1-year, 2-y: 2-year, 3-y: 3-year, t/w: times per week, QoL: quality of life, NA: not available, FP: 5-FU + cisplatin

meet the requirements of the inclusion criteria. The main reasons were that studies did not provide sufficient enough data of efficacy for patients treated in the treatment and control group; review papers; case reports; unable to show clear information about the treatment regimen. Finally, the remaining 16 trials were qualified for the systematic review and could provide enough data for inclusion in the meta-analysis.

Study characteristics

A total of 16 clinical studies with 1269 esophageal cancer patients were included for the final analysis, and 635 patients were randomized to the JOEI-containing treatment group and 634 cases were included in the control group. The characteristics of included studies are listed in Table 1. Briefly, the 16 eligible studies evaluated the efficacy of JOEI combined with chemotherapy and/or RT in patients with esophageal cancers [15-30]. All studies were released in full publication and the main outcomes were available. We contacted the investigators to collect additional unpublished information as much as possible. Most of the studies were single-center reportings.

The age of patients in the included studies ranged from 29 to 79 years and the median age in each study varied. There were inclusion criteria in each of the included studies. The trials recruited esophageal cancer patients without regarding tumor subtype. All patients received chemotherapy and/or RT, and patients in the intervention group were additionally treated with JOEI. The dose and duration of RT varied, with dose ranging from 50.4 to 70 Gy and duration ranging from 30 to 49 days. The chemotherapy administered included all classical regimens (Table 1). Only 8 studies reported survival rates at 1, 2 and 3 years. One study showed changes in the VEGF level before and after treatment with JOEI, and one study reported improvement of immune function with JOEI.

The risk of bias within studies is presented in Figure 2. Briefly, we used the Cochrane Handbook for Systematic Reviews of Interventions 5.3.0 to assess the risk of bias in each study. Since the studies reported the application of randomization, it was likely that there were low risk of bias selection. However, we could not evaluate the methodological quality as the details were not always fully presented in the included studies. With regard to another allocation bias, none of them reported or declared that the method of blinding was used, because it was difficult to conceal treatment regimen, schedules, infusion time and adverse events. Few studies reported the lost to follow up information, making it hard to provide complete outcome data. Not all of the included studies had a low bias selection of reporting as some trials only reported data of overall response rate but not complete response or partial response rate. Besides, the incidence of adverse events such as nausea and vomiting were also not well described in accurate numbers in a few number of studies.

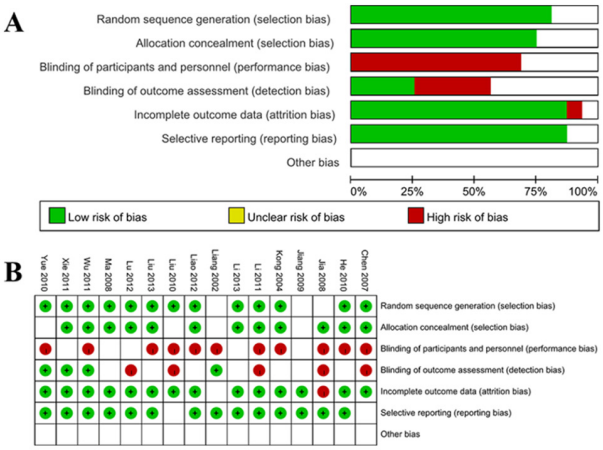

Figure 2. Risk of bias. **A:** review of authors' judgements about each risk of bias item for each included study; **B:** review of authors' judgements about each risk of bias item presented as percentages across all included studies.

Efficacy of JOEI

Survival rate

Eight trials reported the data of survival rate at 1, 2 and 3 years. After pooled analysis (Figure 3), we found that the application of JOEI could significantly reduce the risk of mortality. At 1 year after treatment, the risk ratio was 1.32 with a 95% CI ranging from 1.18 to 1.49 (p<0.00001), which could be explained as the patients in the intervention group had a higher rate of survival. This was also found at 2-year (RR, 1.37; 95% CI, 1.17 to 1.61; p=0.0001) and 3-year (RR, 1.62; 95% CI, 1.26 to 2.07; p=0.0002) results after intervention of JOEI (Table 2).

Table 2. Summary of pooled results

Items	*Pooled RR*	*95%CI*	*Z*	*p*
1-year survival	1.32	1.18, 1.49	4.78	<0.00001
2-year survival	1.37	1.17, 1.61	3.85	0.0001
3-year survival	1.62	1.26, 2.07	3.76	0.0002
CR	1.57	1.21, 2.02	3.43	0.0006
PR	1.40	1.17, 1.67	3.67	0.0002
Quality of life	3.07	1.75, 5.38	3.92	<0.0001
Nausea and vomiting	0.81	0.45, 1.44	0.73	0.46
Neutropenia	0.57	0.36, 0.91	2.36	0.02
Radioactive esophagitis	0.52	0.35, 0.77	3.33	0.0009

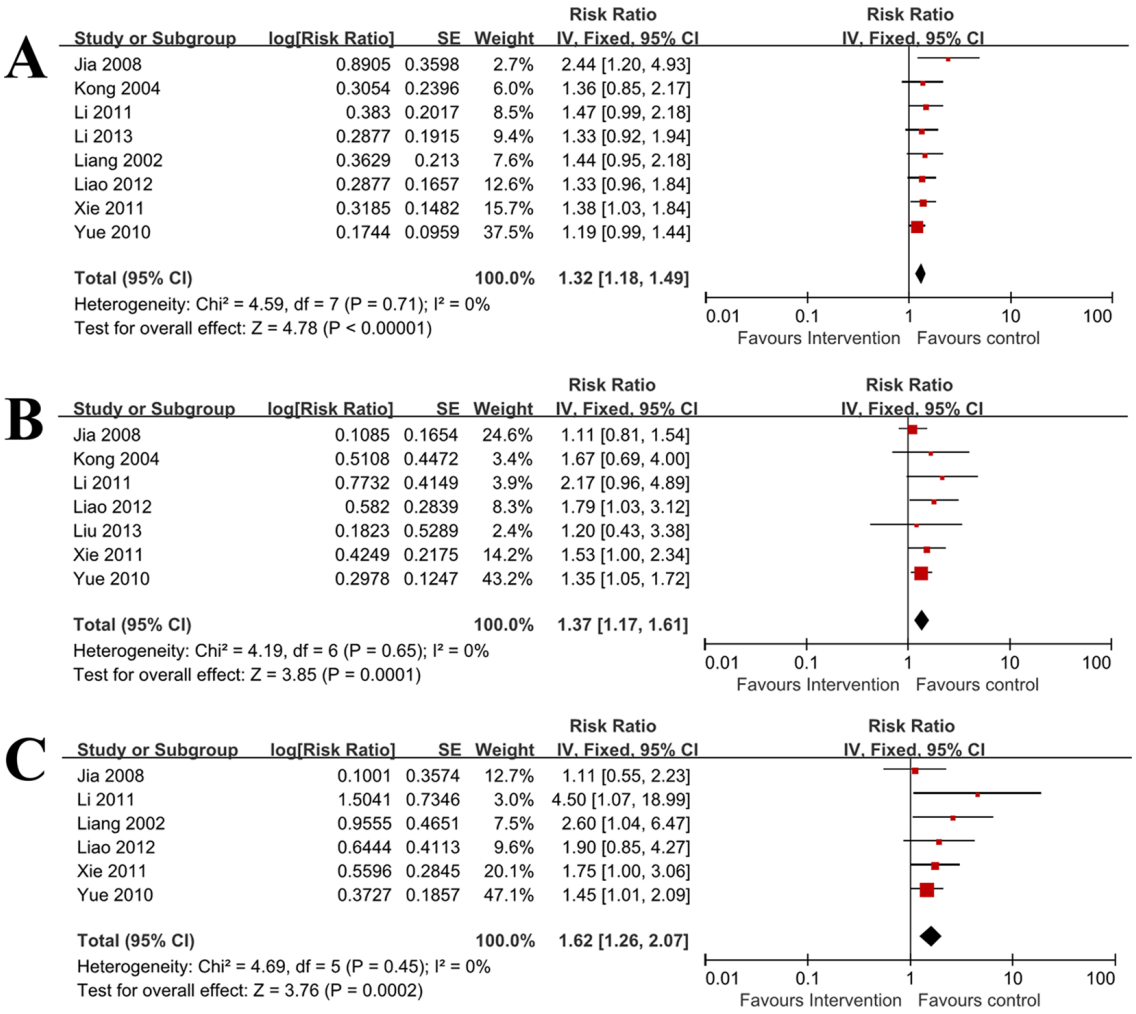

Figure 3. Meta-analysis of the effect of JOEI on the survival after treatment at different years. **A:** 1-year survival; **B:** 2-year survival; **C:** 3-year survival.

Response rate

A total of 14 studies provided the data on CR rate and the pooled analysis revealed that patients who received treatment with JOEI had a significantly higher chance of achieving CR (OR, 1.63; 95% CI, 1.27 to 2.10; p=0.0001) than patients in the control group. However, as illustrated by Figure 4, there was no significant difference between intervention and control groups with regard to PR (OR, 1.25; 95% CI, 0.97 to 1.60; p=0.09). Overall, by combining data of CR and PR, we found that patients treated with JOEI could have a better performance in overall response than patients without treatment of JOEI (OR, 1.42; 95% CI, 1.19 to 1.70; p<0.0001).

Quality of life

Esophageal cancer patients usually have poor quality of life due to the malignant disease itself and its treatment. We performed this test to show whether JOEI could significantly improve the quality of life in such patients. After selection, 4 studies were eligible for analysis. It was clear that treatment with JOEI was capable of improving the quality of life (OR, 3.01; 95% CI, 1.72 to 5.25; p=0.0001).

Safety

Toxic effects of CRT have been well investigated and were expected to be reduced by using protective agents. In this study, we mainly assessed the protective effect of JOEI on reducing the incidence of severe adverse events including nausea and vomiting, neutropenia, and radiation esophagitis. Of the 16 included studies, 6 reported grade 3 or 4 nausea and vomiting, 5 showed grade 3 or 4 neutropenia, and 10 studies reported radiation esophagitis cases. The systematic analysis showed that the administration of JOEI reduced, but not significantly, the incidence of nausea and vomiting (OR, 0.81; 95% CI, 0.45 to 1.44; p=0.46), neutropenia (OR, 0.81; 95% CI, 0.45 to 1.44; p=0.46), while radiation esophagitis was significantly reduced (OR, 0.47; 95% CI, 0.33 to 0.68; p<0.0001) (Figure 6).

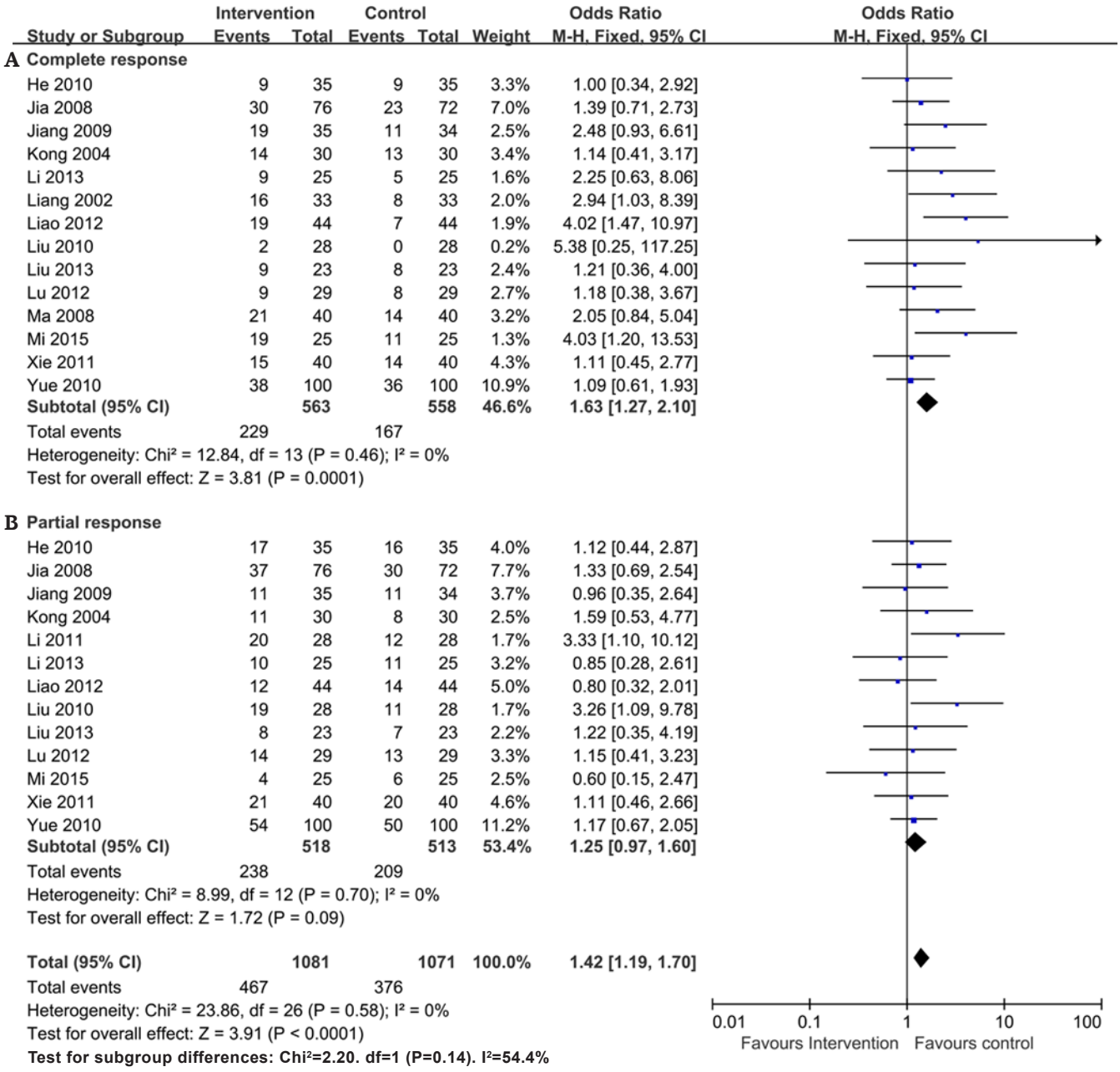

Figure 4. Meta-analysis of the effect of JOEI on the complete and partial response. **A:** complete response; **B:** partial response.

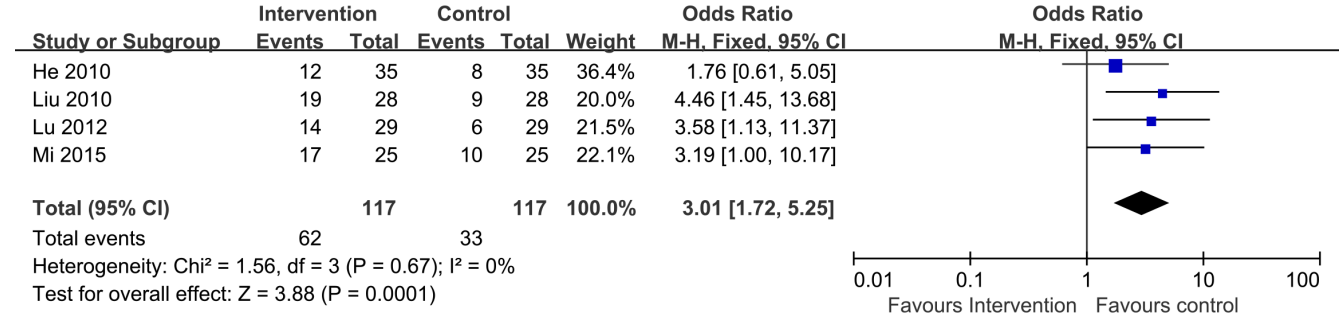

Figure 5. Pooled analysis of the effect of JOEI on the improvement of quality of life.

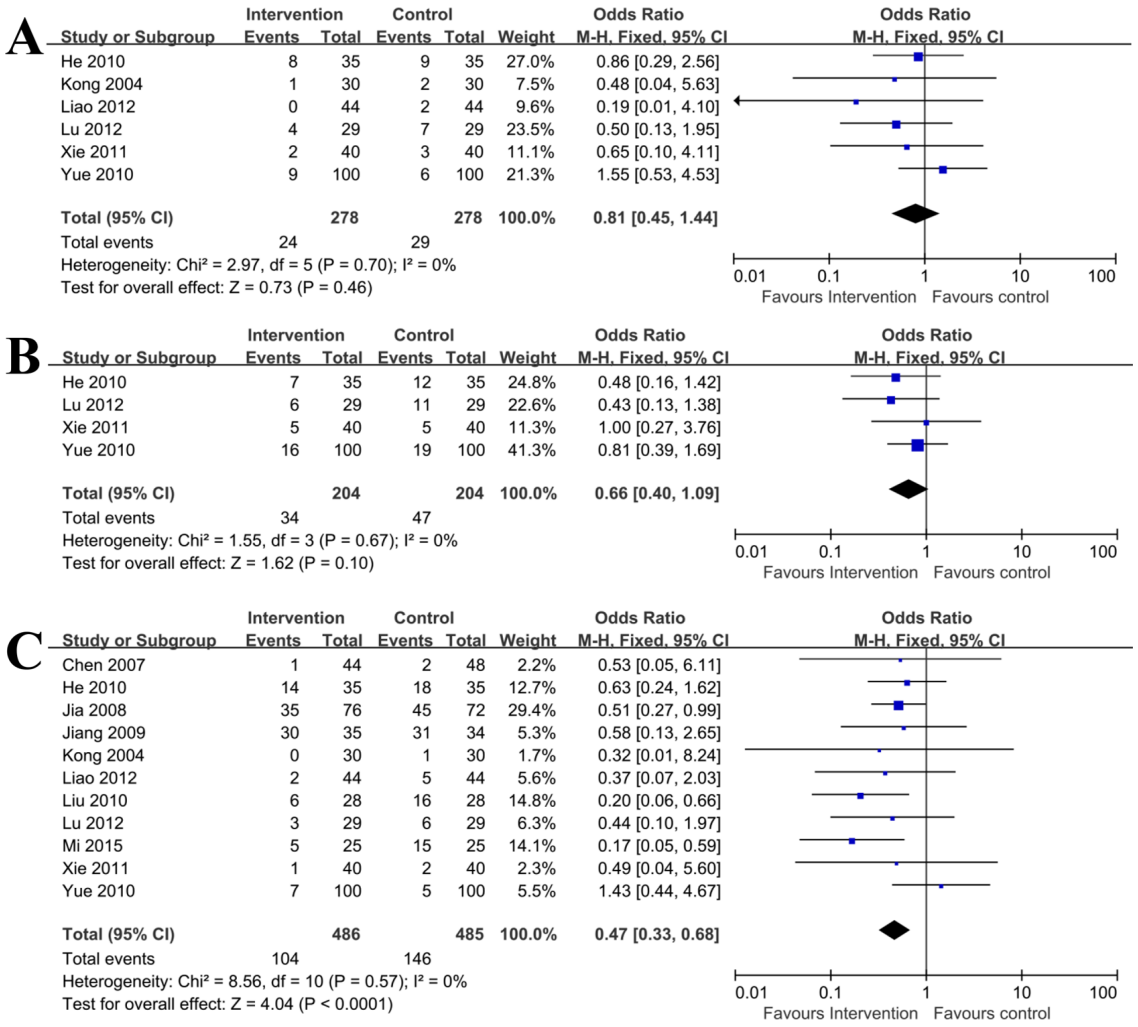

Figure 6. Meta-analysis of the effect of JOEI on preventing adverse events. **A:** nausea and vomiting; **B:** neutropenia; **C:** radiation esophagitis.

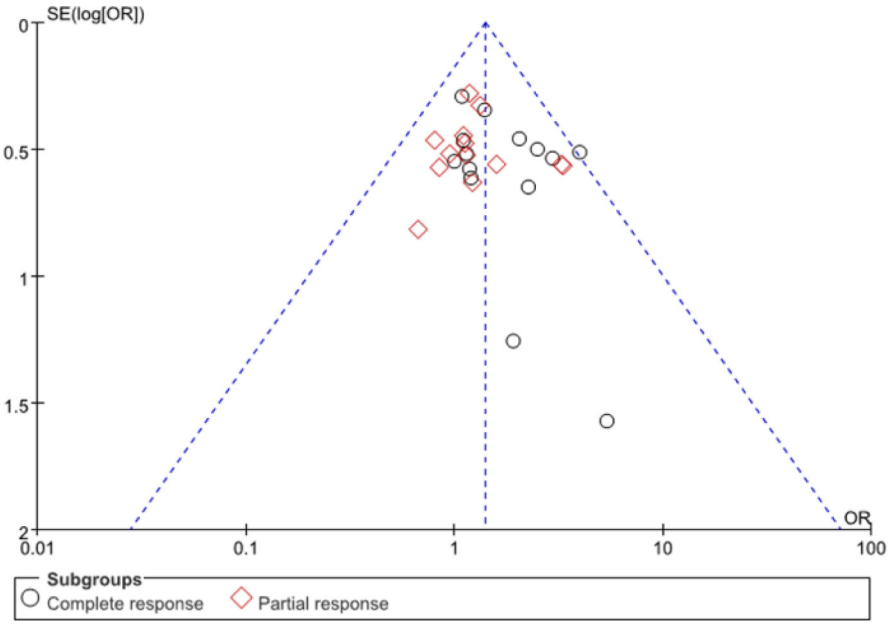

Figure 7. Publication bias of the included studies shown by funnel plot.

Risk of bias across studies

Treatment-related deaths were not common for both JOEI-containing and JOEI-free groups. Three studies reported cases of loss to follow-up during treatment. By calculating I^2, we found that there was low to moderate risk of bias across studies (Figures 3-6). We also performed an additional analysis to detect if there was any possibility of publication bias, something that the funnel plot results denied (Figure 7).

Discussion

The present systematic review and meta-analysis strongly supports that the application of JOEI as part of the tumor killing strategy for unresectable esophageal cancer in patients with intermediate or advanced disease stage provides a statistically significant improvement in 1-, 2-, and 3-year survival rates, in health-related quality of life, and the overall response rate without increasing the risk of adverse events. In these cases the RR or OR for 1-, 2-, 3-year survival, and overall response were 1.32, 1.37, 1.62, and 1.40, favouring the use of JOEI as part of the treatment strategy when compared with control regimens that did not include JOEI.

There were 16 trials with a total of 1269 esophageal cancer patients (635 in the intervention group and 634 in the control group) included in this review, making it adequate to draw reasonalbe results and conclusions. A few studies did not have a good performance during follow up, however, it seemed that the pooled Hazard Ratio (HR) was not significantly affected by this situation. The heterogeneity between included articles was not statistically significant. The reviewers found that at least 2 studies were ongoing and there could be more unreleased studies which may be eligible for inclusion in this review. And some results from the study by Liang et al. [28] were excluded as they did not publish efficacy related number of events in intervention and control groups. The funnel plots indicated that there was no significant publication bias favoring significant data which could overestimate the effect of intervention [28].

The findings of this study are in accordance with the results of the previously published article by Nie et al. [31] and Wang et al. [32], though these studies were designed to assess the effectiveness and safety of JOEI plus CRT to alleviate symptoms of lung cancer patients. The study of Nie et al. [31] included 21 randomized controlled trials involving more than 1600 patients. The pooled analysis revealed that JOEI in combination with CRT was superior in improving complete response rate ($p<0.01$) and quality of life ($p<0.01$). Besides, it was found that the use of JOEI was capable of increasing the survival time, enhancing the immune function, and decreasing the incidence of adverse events. They concluded that JOEI may have positive effects on lung cancer patients concerning the response rate, improvement of quality of life, and reducing the prevalence of some adverse effects when compared to CRT alone. However, the results were moderate due to the low quality of included studies. Another meta-analysis by Wang et al. [32] included 22 randomized controlled trials and their results showed that the combination of JOEI and chemotherapy could enhance the short-term therapeutic effect (RR=1.31, 95% CI:1.18-1.45, $p<0.00001$), improve the quality of life (RR=1.78, 95% CI:1.51-2.09, $p<0.00001$), the myelosuppression (OR=0.37, 95% CI:0.27-0. 51, $p<0.00001$) and the gastrointestinal reactions (OR=0.59, 95% CI:0.44-0.80, $p=0.0007$), with an improvement in immune function. Their study indicated that JOEI could enhance the chemotherapeutic efficacy in lung cancer patients, improve the quality of life and reduce adverse effect of platinum-containing chemotherapy regimens and thus it is worth using it in the clinical treatment of cancer. Although the subjects in our study were patients with esophageal cancer, we found similar results to what Wang et al. found after the systematic analysis. JOEI in combination with RT could benefit esophageal cancer patients with improved rate of response and quality of life, prolonged survival, and reduced incidence of adverse events.

Overall, JOEI-containing treatments exhibited expected efficacy and acceptable toxicities. In the past, it was difficult to clarify how the JOEI exerts its antitumor effect due to its complicated components. In recent years, it is recognized that the oleic and linoleic acids, important components of the JOEI, show specific affinity for tumor cell membranes and exhibit potent antitumor activity. The triglycerides, also components of the JOEI, can be hydrolyzed into oleic acid and then subsequently revealing antitumor activity [12]. Nowadays, several mechanisms of tumor inhibiting or killing effects of JOEI have been revealed in several types of cancer such as bladder cancer, lung cancer, and leukemia [33-35]. The study of Lou et al. [33] proved that brucea javanica oil induces apoptosis in bladder cancer cells via increasing the expressions of caspase-3, caspase-9, and inhibition of NF-kappaB and COX-2 levels. Xu and his colleagues [34] demonstrated that Brucea javanica oil (BJO) can inhibit the expression of VEGF mRNA and secretion of VEGF in A549 lung cancer cells in

a dose-dependent manner, which may be one of the mechanisms of its antitumor effect. Another study by Zhang et al. [35] investigated the antileukemic potential of JOEI in human acute myeloid leukemia cell lines (AML) U937 and HL-60 *in vitro* and in a mouse U937 xenograft tumor model. The results revealed that BJO induced AML cell apoptosis through activation of caspase-8 and modulation of apoptosis-related proteins. Meanwhile, the inhibition of survivin and XIAP increased the cytotoxicity of BJO. BJO also increased subG1 phase cells and caused PARP cleavage in AML leukemia cells, with weak cytotoxicity found in peripheral blood lymphocytes (PBLs) of healthy volunteers. In addition, the authors found that oleic acid and linoleic acid were the active components of BJO. Furthermore, intravenous injection of BJO significantly inhibited U937 tumor growth *in vivo*. The above studies may explain how the BJO has several therapeutic roles in the treatment of cancer.

All trials eligible for inclusion in this meta-analysis were released in the past few years and some of them could be classified as well designed articles, which may be a reflection of increasingly emphasis on high quality clinical trials by authors, reviewers and editors. In fact, after assessing the quality of included studies, we found that nearly half of them were of low to moderate quality. Most of them only reported short-term response rates but not survival rates, possibly for quick publication or lack of knowledge of statistics. Few studies reported the survival rates at 1, 2, and 3 years, and numbers of cases lost to follow-up. There were also potential biases in the process of reviewing. Although it has been demonstrated in many studies the benefit of JOEI, there may still be uncertainty about its dose and treatment duration. The doses and duration of JOEI varied between different studies, so the most effective strategy of using JOEI could not be identified in our meta-analysis. Trials with significant publication bias might partially have an influence on the results of the present study, overestimating the effect of JOEI. Another reason of overestimation of the treatment efficacy of JOEI could possibly be due to publication bias of favoring significant results. Although we tried to avoid potential biases, this study may still contain some of them.

Conclusions

The present study strongly suggests the use of JOEI as part of the treatment strategy for esophageal cancer aiming at improving both survival, response rate and quality of life, and reducing the toxicities of chemotherapy and/or RT. Although a JOEI-containing treatment regimen should be considered for patients with esophageal cancer, the dose and duration of the intervention needs to be well investigated as there is still lack of applicable evidence. So, ongoing and future clinical trials are required to define the most effective use of JOEI when combined with chemotherapy and/or RT for patients with cancer.

Conflict of interests

The authors declare no confict of interests.

References

1. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol 2014;6:112-120.
2. Lambert R, Hainaut P. The multidisciplinary management of gastrointestinal cancer. Epidemiology of oesophagogastric cancer. Best practice & research. Clin Gastroenterol 2007;21:921-945.
3. D'Journo XB, Thomas PA. Current management of esophageal cancer. J Thor Dis 2014;(6 Suppl 2):S253-264.
4. Falk GW. Risk factors for esophageal cancer development. Surg Oncol Clin North Am 2009;18:469-485.
5. Zhang Y. Epidemiology of esophageal cancer. J Gastroenterol 2013;19:5598-5606.
6. Clark GW, Peters JH, Ireland AP et al. Nodal metastasis and sites of recurrence after en bloc esophagectomy for adenocarcinoma. Ann Thor Surg 1994;58:646-653; discussion 653-644.
7. Gebski V, Burmeister B, Smithers BM et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 2007;8:226-234.
8. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681-692.
9. Fokas E, Weiss C, Rodel C. The role of radiotherapy in the multimodal management of esophageal cancer. Digestive Dis (Basel, Switzerland) 2013;31:30-37.
10. Liu J, Li X, Liu J, Ma L, Li X, Fonnebo V. Traditional Chinese medicine in cancer care: a review of case reports published in Chinese literature. Forschende Komplementarmedizin 2011;18:257-263.
11. Lu YY, Huang XE, Cao J et al. Phase II study on Java-

nica oil emulsion injection (Yadanzi(R)) combined with chemotherapy in treating patients with advanced lung adenocarcinoma. Asian Pac J Cancer Prev 2013;14:4791-4794.

12. Yang F, Yu XH, Qiao F et al. Formulation and characterization of Brucea javanica oil microemulsion for improving safety. Drug Develop Indust Pharm 2014;40:266-277.
13. Liu J, Huang XE, Tian GY et al. Phase II study on safety and efficacy of Yadanzi(R) (Javanica oil emulsion injection) combined with chemotherapy for patients with gastric cancer. Asian Pac J Cancer Prev 2013;14:2009-2012.
14. Wei X, Chen Z, Yang X, Wu T. Chinese herbal medicines for esophageal cancer. The Cochrane database of systematic reviews: CD004520, 2009.
15. Chen S, Wang D, Jiang Q, Zhu G. Chinical effect of Javanica oil emulsion injection in advanced esophageal cancer patients treated with radiotherapy. J Pract Tradit Chinese Intern Med 2007;21:78-79.
16. Chunying Xie SL, Xiaodong Luo. Brucea javanica oil emulsion injection in combination with chemoradiation therapy for the treatment of 40 elderly patients with esophageal cancer. Chin J Gerontol 2011;31:3408-3409.
17. Dezhi Li GL, Shimin Wen. Clinical observation of three-dimensional conformal radiotherapy combined with Brucea javanica oil emulsion injection in the treatment of 28 cases with esophageal carcinoma. Chongqing Med J 2011;40:170-171.
18. He Lijia LH, Xiang Li. Efficacy of Brucea Javanica Oil Emulsion Combined radiotherapy on Treating Advanced Esophageal Cancer. Chin J Experim Tradit Med Formulae 2010;16:212-214.
19. Jianbo Liu WS. Clinical practice of paclitaxel plus Javanica oil emulsion injection and three dimensional conformal radiotherapy in the treatment of locally advanced esophageal cancer. Asian Pac Tradit Med 2013;9:146-147.
20. Jingfeng Lu YC. Clinical observation of brucea Javanica oil emulsion injection combined with concomitant chemoradiation therapy for patients with advanced esophageal cancer. J Pract Tradit Chin Med 2012;28:753-753.
21. Kong Xiangming XL, Hang Ni. Clinical Observation on Treating Advanced Esophageal Cancer with Emulsion Injection of Seminal Oil plus Radiotherapy. Zhejiang J Integr Tradit Chin Western Med 2004;14:339-340.
22. Liao J. The effect of Javanica oil emulsion injection on the level of serum VEGF and treatment outcome in patients with esophageal cancer. Chin J Gerontol 2012;32:4535-4536.
23. Ma Jianguang HCQL, Jia Yanmin. Clinical observation of brucea javanica oil combination with radiotherapy for advanced esophageal cancer. Chin J Pract Med 2008;33:2174-2176.
24. Ping Liang JL, Zhendong Su, Yu Huang. Clinical observation of radiotherapy plus Javanica oil emulsion injection in patients with esophageal cancer. J Youjiang Med College for Nationalities 2002;24:33-34.
25. Qing Li SD, Ping Chen. Intensity-modulated radiotherapy combined with Brucea Javanica Oil Emulsion for the treatment of recurrent esophageal cancer. ShanXi Med J 2013;42:86-87.
26. Xiaoxue Liu HZ. Brucea Javanica Oil Emulsion combined with radiotherapy for 28 cases of Esophageal Carcinoma. JiangXi ZhongYiYao 2010;41:42-43.
27. Yongshi Jia SW, Shiliang Lv, Liping Zhang, Liping Xu. Clinical observation of Javanica oil emulsion injection plus Radiotherapy for advanced esophageal cancer. J Chinese Materia Medica 2008;33:2174-2176.
28. Yuren Yue QS, Hui Liang, Ningbo Wu. Clinical research of Brucea javanica oil emulsion combined with chemoradiation therapy for esophageal cancer. Clin J Tradit Chin Med 2010;22:18-20.
29. ShengXia JXH. Clinical study of yadanzi oil emulsion injection improving efficacy on radiotherapy in treatment of esophageal cancer. World Health Digest Med Periodical 2009;8:35-36.
30. Zhetao M, Zhifang Z, Xiufu Z. Effect of brucea javanica oil emulsion combined with radiotherapy for the treatment of patients with esophageal cancer. Cancer Res Clinic 2015;27:627-629.
31. Nie YL, Liu KX, Mao XY, Li YL, Li J, Zhang MM. Effect of injection of brucea javanica oil emulsion plus chemoradiotherapy for lung cancer: a review of clinical evidence. J Evidence-based Med 2012;5:216-225.
32. Wang Q, Wang M, He X et al. [Meta-analysis on treatment of non-small cell lung cancer with brucea javanica oil emulsion in combination with platinum-contained first-line chemotherapy]. China J Chin Materia Medica 2012;37:2022-2029.
33. Lou GG, Yao HP, Xie LP. Brucea javanica oil induces apoptosis in T24 bladder cancer cells via upregulation of caspase-3, caspase-9, and inhibition of NF-kappaB and COX-2 expressions. Am J Chin Med 2010;38:613-624.
34. Xu X, Xu DH, Jiang B, Lv QH. [Effects of brucea javanica oil on expression of vascular endothelial growth factor in A549 cell line]. China J Chin Materia Medica 2008;33:2517-2520.
35. Zhang H, Yang JY, Zhou F et al. Seed Oil of Brucea javanica Induces Apoptotic Death of Acute Myeloid Leukemia Cells via Both the Death Receptors and the Mitochondrial-Related Pathways. Evidence-based Complem Altern Med : eCAM 2011: 965016, 2011.