Comparasion of elective nodal irradiation and involved-field irradiation in esophageal squamous cell carcinoma: a meta analysis

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ABSTRACT

It is still controversial whether radical radiotherapy in patients with esophageal squamous cell carcinoma (ESCC) still requires elective nodal irradiation (ENI), or only involved-field irradiation (IFI). In this study, a meta analysis was used to compare ENI and IFI in the treatment of ESCC, in order to provide guidance for clinical practice. Methods: Literatures on ENI and IFI in treatment of ESCC were retrieved, and the last access was June 30, 2017. A meta analysis was performed to evaluate the advantage and disadvantage of ENI and IFI. Results: Nine studies with a total of 1143 patients were included in this analysis, of those 605 patients underwent radiotherapy only, and 538 underwent radiochemotherapy. There was no significant difference in 1-, 2-, 3-year local control rate between ENI and IFI, or 1-, 2-, 3-year overall survival rates. However, the incidences of ≥ 3 grade acute esophagitis and pneumonia were significantly lower in IFI group. There was no difference in the rate of out-field recurrence/metastasis in this two groups. Conclusions: Neither local control rates nor overall survival rates between ENI and IFI groups have significant differences, but in the latter group, incidences of severe radiation esophagitis and pneumonia are significantly lower. IFI is not associated with increasement of out-field recurrence/metastasis. It is noteworthy that most of the included studies are retrospective. Therefore, a large prospective randomized study is needed for further investigation and verification.

INTRODUCTION

Currently, it is still controversial whether elective nodal irradiation (ENI) or only involved-field irradiation (IFI) is required for locally advanced esophageal squmous cell carcinoma (ESCC). Dong et al found that ENI can reduce localized regional failure, improve local control rates and long-term survival in patients with radical radiotherapy [1]. However, another study indicated that few patients had out-of-field lymph node treatment failure regardless of ENI or IFI, and factors that had the most impacts on overall survival rate were primary tumor local recurrence and distant metastasis [2]. In this study, a meta-analysis was used to compare the effects of ENI and IFI on local control rate, overall survival rate and side effect in patients with ESCC, in order to provide guidance for clinial practice.

RESULTS

The retrieval results and quality evaluation

A total of 63 publications were retrieved initially, excluding 18 dissertations/conference contribution or journals not collected at Beijing university library. After reading the abstracts, twenty were excluded for repeated published data, two for using 2-dimensional technology, fouthteen for being non-case-control studies. Eventually, nine studies involing 1143 ESCC patients were included in this meta analysis [4–12]. The basic characteristics and results of included studies were shown in Tables 1 and 2.

Comparison of local control rates

The number of publications included for analysis of 1-, 2-, and 3-year local control rates was 7, 6 and 5, respectively. The fixed effect model was used due to absence of statistical heterogeneity ($P = 0.494$; $P = 0.258$; $P = 0.079$). There was no significant difference in the local control rates between ENI and IFI group at 1-, 2- and 3-year (OR = 0.759, 95% CI 0.572-1.008, $P = 0.057$; OR = 1.076, 95% CI 0.790-1.466, $P = 0.641$; OR = 0.977, 95% CI 0.726-1.315, $P = 0.879$), seen Figures 1–3.

Comparison of overall survival rates

The number of publications included for analysis of 1-, 2-, 3-year overall survival rates was 7, 7 and 6, respectively. There were no significant differences in the 1-, 2-, 3-year overall survival rates between the two groups (HR = 0.824, 95% CI 0.623-1.091, $P = 0.959$; HR = 1.030, 95% CI 0.715-1.483, $P = 0.206$; OR = 0.846, 95% CI 0.488-1.465, $P = 0.551$), seen Figures 4–6.

Evaluation of toxicity and side effects

Seven and eight publications were included to analyzed ≥3 grade acute esophagitis and ≥3 grade acute pneumonitis. The fixed effect model were used due to absence of statistical heterogeneity ($P = 0.207$; $P = 0.181$). As seen in Figures 7 and 8, the incidences of ≥3 grade acute radiation-induced esophagitis and ≥3 grade acute pneumonitis in IFI group were significantly lower than those in ENI group (OR = 0.515, 95% CI 0.341-0.778, $P = 0.002$; OR = 0.481, 95% CI 0.254-0.913, $P = 0.025$).

Out-field lymph node recurrence/metastasis

A total of 5 articles were included in analysis of out-field lymph node recurrence/metastasis between the two groups. The OR value was not significantly different between the two groups (OR = 1.629, 95% CI 0.708-3.747, $P = 0.251$), indicating that ENI did not reduce the risk of out-field recurrence/metastasis (Figure 9).

Sensitivity analysis

Literature with similar OR or HR to the combined ones were excluded, in order to detect its impact on results, seen in Table 3. It was shown that results were basically the same as before, and there was no substantial impact on the results.

Bias analysis

Egger's test was used to analyze the symmetry of the funnel graph. There was no publication bias in the literature with all P value > 0.05 (Table 4).

DISCUSSION

Radiotherapy is the primary treatment for advanced ESCC. Based on the studies that compared with two field dissection, esophageal cancer underwent three field lymph node dissection could improve local control and long-term survival [13, 14], ENI technology began to be used in radical radiotherapy. Due to the link between esophageal submucosal and muscular lymphatic network, ESCC can form a wide range of mediastinal lymph node drainage. In the routine X-ray-based simulation, the lymph nodes that are off coverage may occur and increase local failure rate. Zheng ZP et al [15] reported 988 cases of esophageal cancer using conventional radiotherapy, and the incidence of out-field lymph node metastasis as high as 30.4%.

With the continuous progress of diagnostic methods, application of three-dimensional conformal/intensity modulated radiotherapy technology and the established value of concurrent radiochemotherapy, it has been controversial whether ENI is still needed in radical radiotherapy. In 2012, a meta-analysis including 5 studies involving 405 patients showed that ENI did not improve 1-year local control and 1-year survival rate, while increased the incidence of radiation esophagitis and pneumonia [16]. Considering the facts that the number of cases has increased significantly and that multiple pulications have reported 2-, 3-year local control and survival data, the authors retrospectively reviewed the relevant publications on ENI and IFI comparison under precise irradiation, so as to provide more accurate and comprehensive guidance for clinical practice.

According to the inclusion and exclusion criteria, nine publications including 1143 patients were involved. It can be seen in Table 1 that all included studies scored 3 points or higher, indicating high quality. There were no significant differences in 1-, 2-, 3- local control rates and 1-, 2-, 3- survival rates between ENI and IFI, which may be related to that even with IFI, micrometastases near the tumor were irradiated by considerable dose [2]. Regarding the failure of ENI and IFI, this meta-analysis found no significant differences in the incidence of out-field recurrence/metastasis (OR=1.629, 95% CI

Table 1: Baseline characteristic of included studies

Author	Year	Number of patients	Stage	Irradiation range	Irradiation dose	Quality assessment				
Zhou C et al [4]	2012	57	T2~4 N0~1	IFI: CTV was defined as GTV plus a 3-5 cm margin superior and inferior to the primary tumor and a lateral margin of 0.8 cm. ENI: CTV included the CTV of the involved field plus elective nodal region in the first step; in the second step, the CTV definition was same with the CTV of IFI.	60Gy/30f, ENI: 40Gy/20f, a booster dose was further administered to up to a total dose of 60Gy	1	1	1	0	1
Li M et al [5]	2012	94	T1~4 N0~1	IFI: CTV was defined as the GTV plus a 3 cm margin superior and inferior to the primary tumor and a 0.8-1cm radial margin. ENI: based on the different locations of the primary tumor, the adjacent regional lymphatics was included in the CTV in addition to the same margins outside the primary tumor as those in IFI.	50Gy/25f, a booster dose was further administered to up to a total dose of 60-62Gy	1	0	1	1	0
Zhou ZG et al [6]	2009	87	T1~4 N0~1	IFI: CTV was defined as GTV plus a 3 cm margin superior and inferior to the primary tumor and a lateral margin of 0.8-1 cm. ENI: CTV was defined as GTV plus a 3 cm margin superior and inferior to the primary tumor and a 0.8-1 cm lateral margin and the areas at risk for elective nodal regions	54~62Gy/27~31f, or 50Gy/25f, a booster dose was further administered to up to a total dose of 60-62Gy	1	0	1	0	1
Li DJ et al [7]	2013	68	II~IV	IFI: CTV was defined as GTV plus a 3 cm margin superior and inferior to the primary tumor and a lateral margin of 0.8-1 cm. ENI: CTV was defined as GTV plus a 3 cm margin superior and inferior to the primary tumor and a 0.8-1 cm lateral margin and the areas at risk for elective nodal regions	3D-CRT: 50Gy/25f, a booster dose was further administered to up to a total dose of 60-64Gy. IMRT: 56-66Gy/28-33f	1	0	1	0	1
Zhu SC et al [8]	2014	219	T1~4 N0~2	IFI: CTV was defined as GTV plus a 1.5-2 cm margin superior and inferior to the primary tumor and a lateral margin of 0.5-0.8 cm. ENI: CTV was defined according to AJCC staging manual (6^{th} edition) of esophageal lymph node distribution.	54~66Gy/27~33f	1	0	1	0	1
Zang RK et al [9]	2013	73	T1~4 N0~1	IFI: CTV was defined as GTV plus a 3 cm margin superior and inferior to the primary tumor and a lateral margin of 0.5 cm. ENI: CTV was defined as GTV plus 3 cm craniocaudal margin with a 0.5 cm lateral margin and the areas at risk for elective nodal regions.	54Gy/30f	1	1	1	0	1
Jing W et al [10]	2015	137	T1~4 N0~1	IFI: CTV was defined as GTV plus a 2-4 cm margin superior and inferior to the primary tumor and a lateral margin of 0.8-1cm. ENI: CTV was defined as GTV plus 2-5 cm craniocaudal margin with a 0.8-1 cm lateral margin and the areas at risk for elective nodal regions	40Gy/20f, a booster dose was further administered to up to a total dose of 50-68.4Gy	1	0	1	0	1
Liu M et al [11]	2014	169	I~IV	IFI: a 1 cm margin was added around GTV, but 3cm margins in the esophageal long axis superiorly and inferiorly to encompass potential submucosal invasions. ENI: covered supraclavicular area with the upper margin at the caudal edge of cricoid cartilage, inferior margin at the sternal notch.	Doses to primary lesion and metastatic nodes were 60-68.4Gy, and 50.4~54Gy for elective node irradiation	1	1	1	0	1
Yamashita H et al [12]	2014	239	I~IV	IFI: CTV was generated by using no radial margin and 2cm longiitudinal margins to the GTV-primary, and by using no margin for the GTV-LN ENI: CTV was defined as the whole thoracic esophagus	IFI: 50.4Gy ENI: 50~50.4Gy	1	1	1	0	1

Table 2: Specific results of the included studies

Author	Group	Local control rate %			Overall survival rate %			≥3 grade acute esophagitis	≥3 grade acute pneumonitis
		1-year	2-year	3-year	1-year	2-year	3-year		
Zhou C et al [4]	IFI	-	-	-	-	48	-	7.41	0
	ENI	-	-	-	-	46	-	4.17	0
Li M et al [5]	IFI	72.4	59.4	54.5	66.9	55.4	36.2	6.12	2.04
	ENI	69.5	58.4	46.0	68.6	48.4	35.5	15.56	0
Zhou ZG et al [6]	IFI	75	57	-	67	43	-	12	2
	ENI	72	45	-	69	40	-	18	9
Li DJ et al [7]	IFI	66	48	-	59	41	-	-	5
	ENI	68	49	-	61	39	-	-	12
Zhu SC et al [8]	IFI	63	-	39.1	67.6	-	24.9	-	-
	ENI	70.5	-	53.3	73.7	-	45.1	-	-
Zang RK et al [9]	IFI	93	71.6	71.5	71.8	44.7	25.7	11.4	2.86
	ENI	87	80	80	66.1	60	45.4	39.5	13.16
Jing W et al [10]	IFI	43.8	23.6	21	59	30.7	21.7	18.5	7.4
	ENI	52.1	36.6	20.6	68.5	41	26.4	6	12
Liu M et al [11]	IFI	-	-	-	-	-	49	6	2
	ENI	-	-	-	-	-	47	6	4
Yamashita H et al [12]	IFI	73	61	55.5	70.8	58.7	51.6	10.1	0
	ENI	58.9	51.3	44.8	65.8	45.8	34.8	23.3	5.83

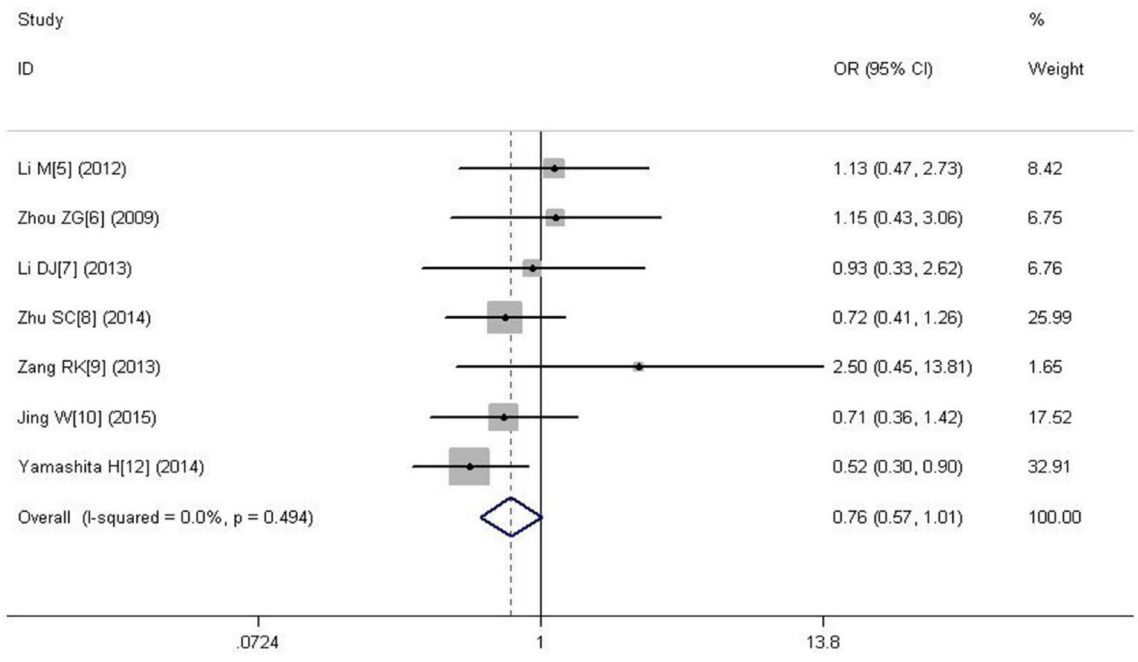

Figure 1: Forest plot of 1-year local control rate.

0.708-3.747, $P = 0.251$). This may be due to the accuracy of delineating mediastinal metastatic lymph nodes such as CT simulation and PET/MRI were significantly improved. Consequently, the probability of off-coverage could be reduced obviously. Meanwhile, more and more clinical studies mainly used concurrent radiochemotherapy, which was helpful to treat subclinical lesions. As a result, the use of IFI mode was not associated with higher probability of recurrence/ metastasis.

The scope of lymph node metastasis of ESCC is extremely extensive and complex. There is not only regional metastasis, but also jumping metastasis. In addition to the lesion location, lymph node metastasis may be also affected by tumor depth, lesion length, pathological general classification, differentiation and many other factors [17]. In view of ENI is based on the lesion site with a relatively fixed range of irradiation. it still cannot ensure coverage of all the regional lymph nodes. Therefore, IFI based on imaging data is more in line with the principle of individualized intervention. The incidences of ≥3 grade acute radiation-induced esophagitis and ≥3 grade acute pneumonitis in the IFI group were significantly lower due to the decrease of irradiation volume (OR=0.515, 95% CI 0.341-0.778, $P = 0.002$; OR=0.481, 95% CI 0.254-0.913,

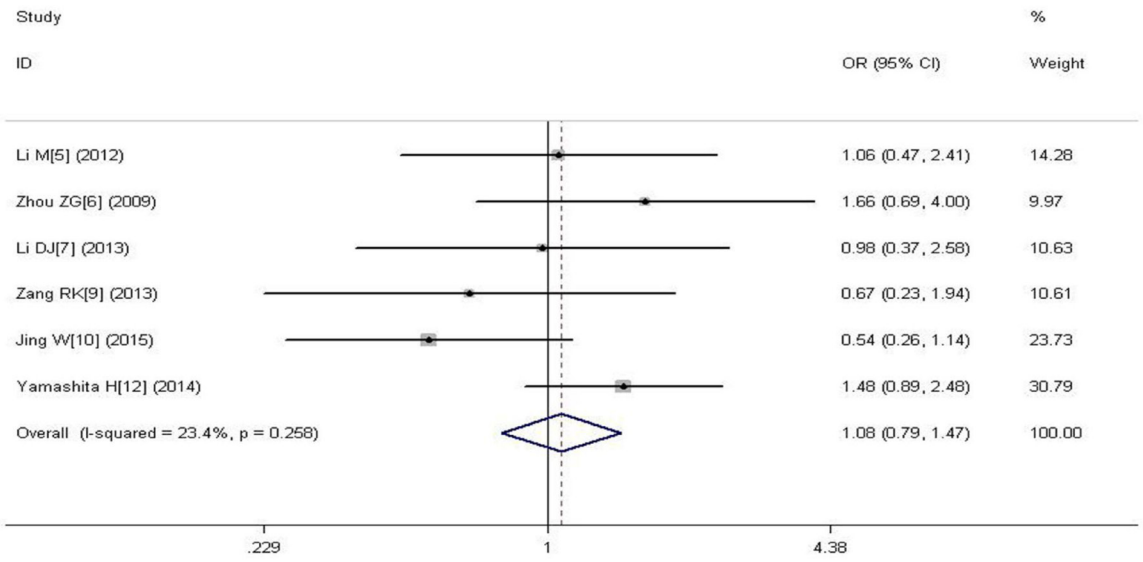

Figure 2: Forest plot of 2-year local control rate.

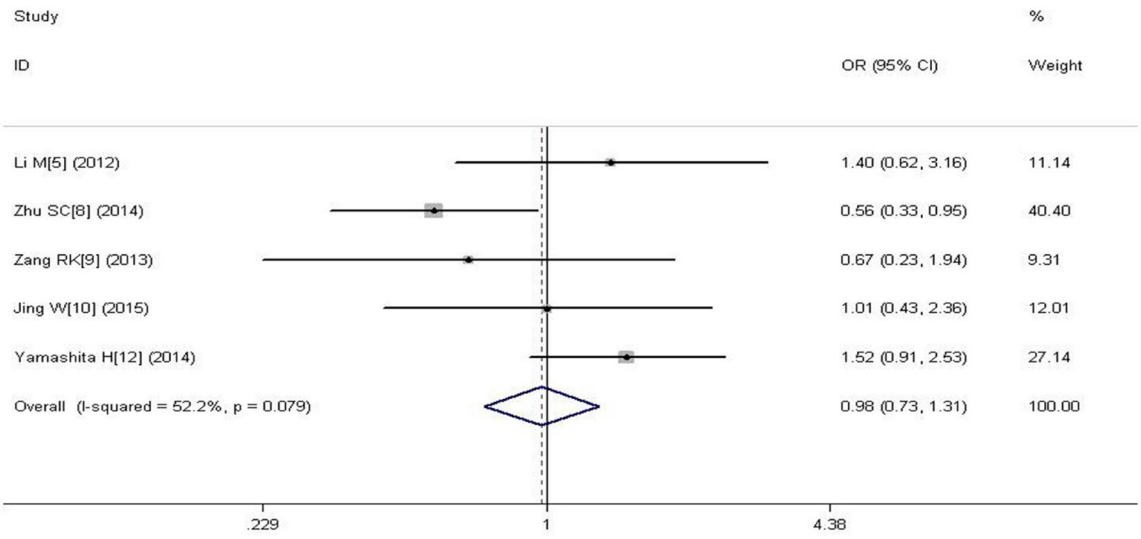

Figure 3: Forest plot of 3-year local control rate.

P = 0.025). Considering the side effects of concurrent radiochemotherapy and prophylactic exposure further affects patients' tolerance, ENI may lead to more severe radiation esophagitis and pneumonia.

The literature with similar OR or HR to the combined ones were excluded, in order to detect its impact on results, seen in Table 3. It was shown that results were basically the same as before, and there was no substantial impact on the results.

Original publication bias exists in a certain extent and may affect the reliability of results. Egger analysis showed that the funnel plot was symmetrical (P>0.05), indicating the bias was small. The potential bias had no substantial influence on the final conclusion, and it further increased the reliable conclusion. A limitation of this meta-analysis is that the publications included were mostly retrospective studies. In addition, the range of exposure and radiation dosage in ENI groups were not consistent. Non-surgical

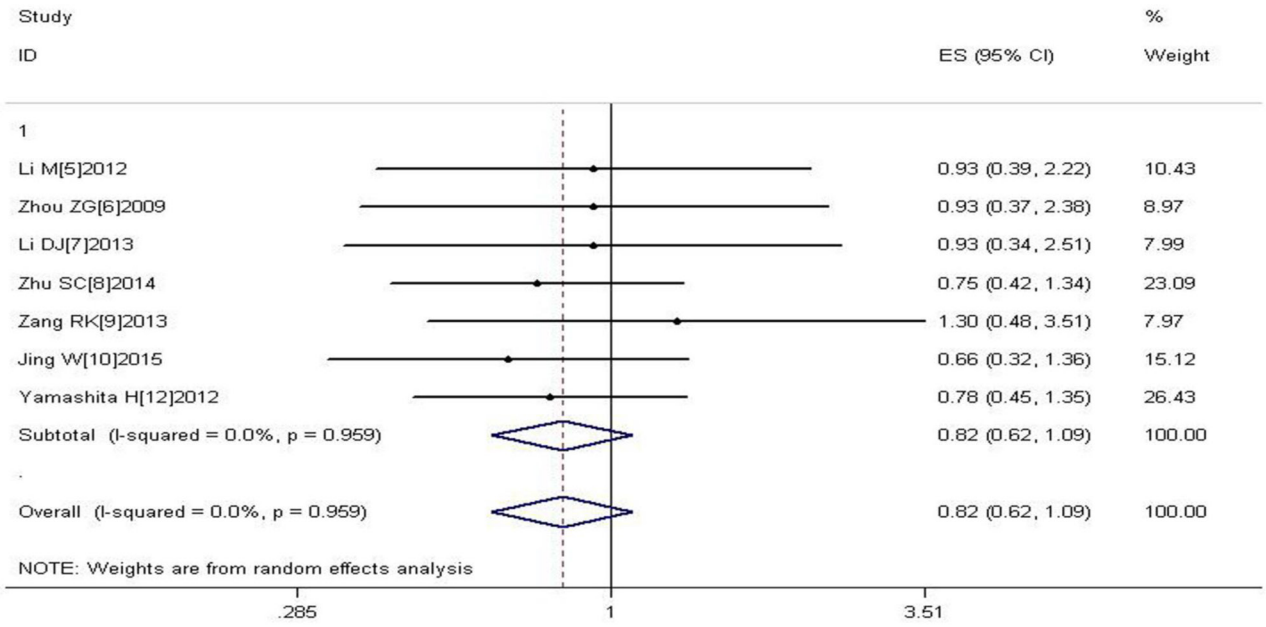

Figure 4: Forest plot of 1-year overall survival rate.

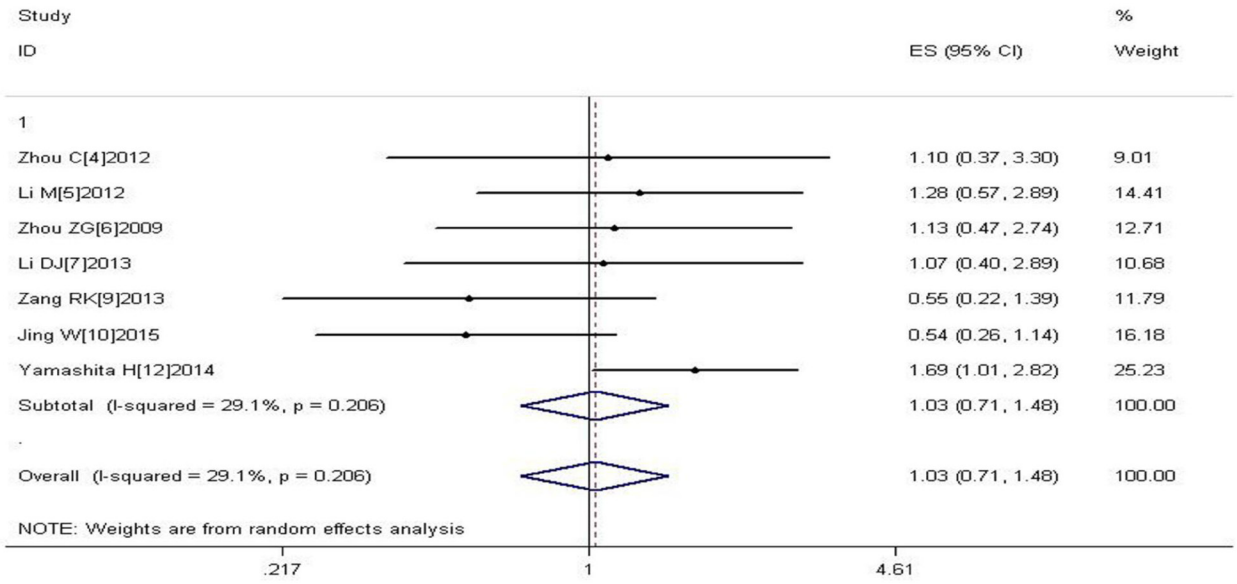

Figure 5: Forest plot of 2-year overall survival rate.

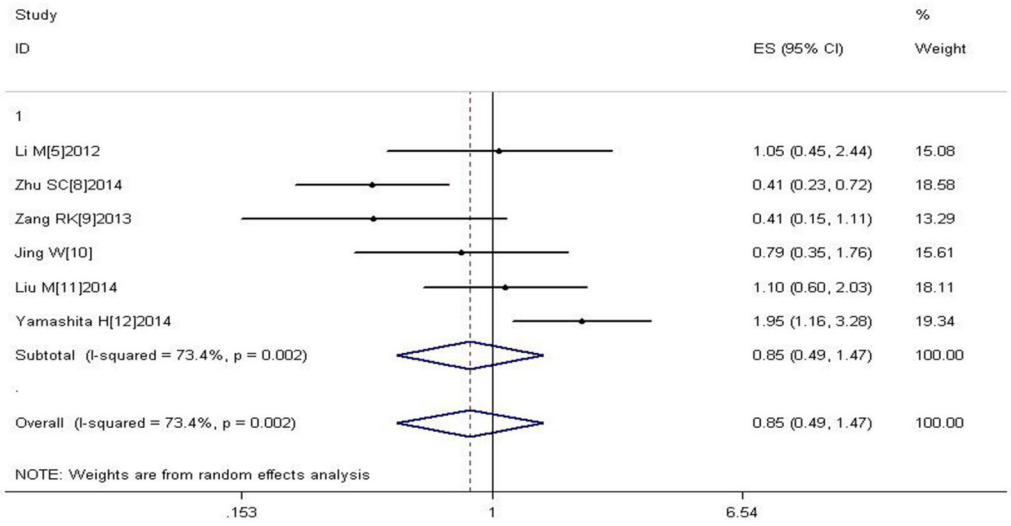

Figure 6: Forest plot of 3-year overall survival rate.

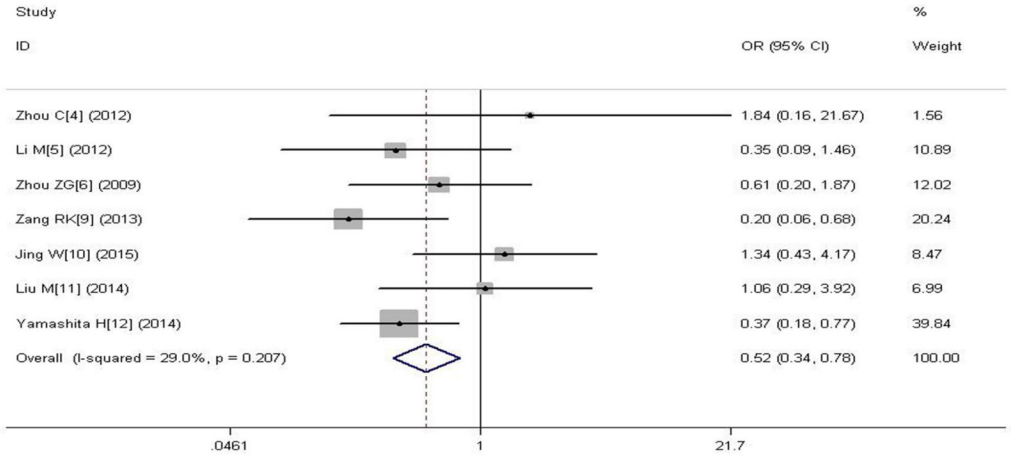

Figure 7: Forest plot of ≥3 grade acute radiation-induced esophagitis.

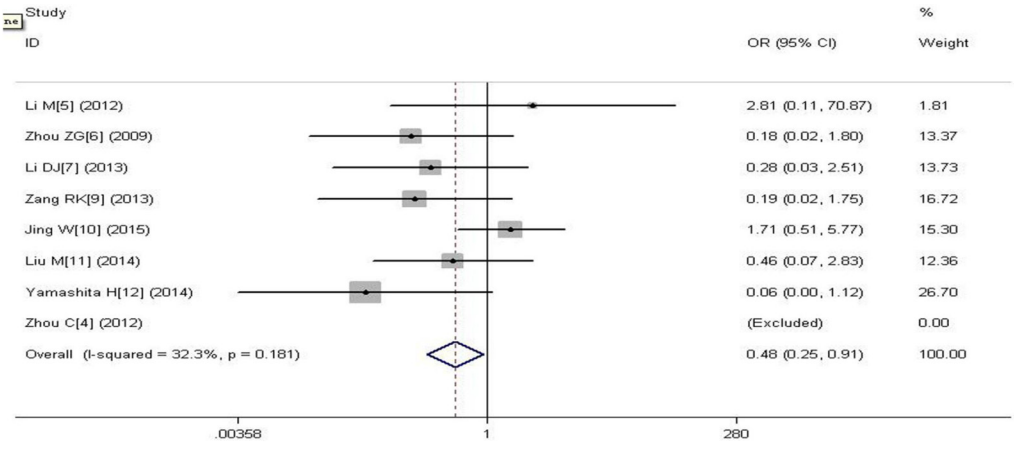

Figure 8: Forest plot of ≥3 grade acute radiation-induced pneumonitis.

Table 3: Results of sensitivity analysis

Evaluation index	Literature removed	OR or HR	95% CI		*P* value	Whether the same as before removal
1-year local control rate	Jing et al [10]	0.769	0.563	1.050	0.098	yes
2-year local control rate	Jing et al [10]	1.243	0.884	1.749	0.211	yes
3-year local control rate	Jing et al [10]	0.973	0.709	1.336	0.866	yes
1-year overall survival rate	Yamashita et al [12]	0.840	0.606	1.165	0.295	yes
2-year overall survival rate	Li DJ et al [7]	1.010	0.662	1.542	0.962	yes
3-year overall survival rate	Jing et al [10]	0.852	0.443	1.636	0.630	yes
≥3 grade acute esophagitis	Zhou ZG et al [6]	0.503	0.322	0.783	0.002	yes
≥3 grade acute d pneumonitis	Liu M et al [11]	0.484	0.244	0.959	0.038	yes
Out-field lymphatic reccurence/metastasis	Liu M et al [11]	2.365	0.799	7.000	0.120	yes

staging method was not uniform. Some studies used radiotherapy alone rather than concurrent radiochemotherapy. Consequently, it is a challenge to draw more detailed and persuasive stratified analysis results. Large prospective randomized controlled studies are needed to further evaluate the efficacy and adverse reactions of ENI and IFI.

In summary, this meta-analysis shows that local control rates, survival rates in IFI group are similar to those in ENI group, while incidences of severe acute radiation esophagitis and pneumonia are significantly lower. IFI is not associated with increasement of out-field lymph nodes recurrence/metastasis.

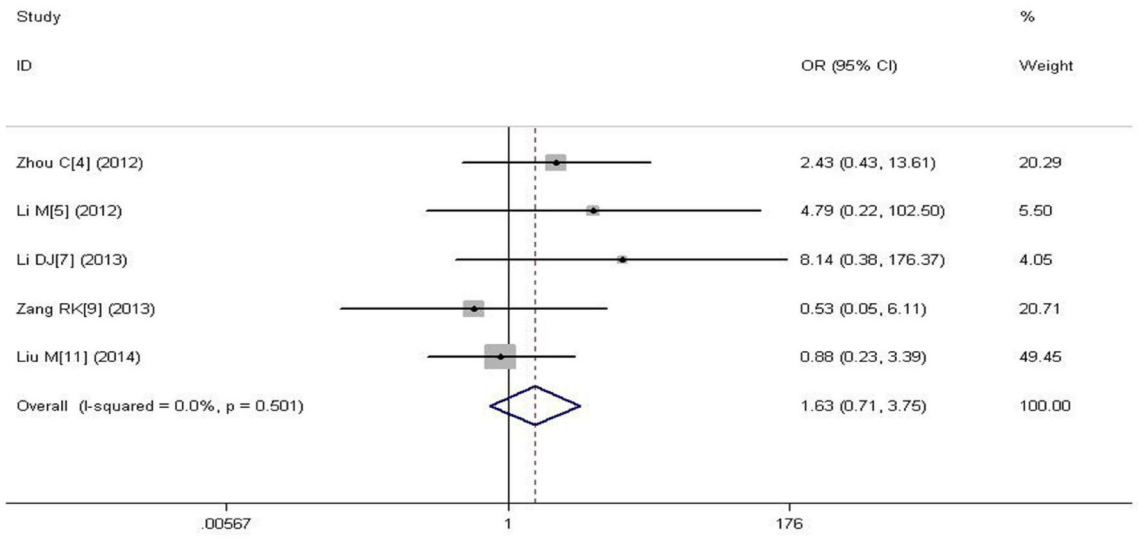

Figure 9: Forest plot of out-field lymph node recurrence/metastasis.

Table 4: Publication bias of the involved literatures

Evaluation index	*T* value	95% CI		*P* value
1-year local control rate	4.92	1.193	3.806	0.104
2-year local control rate	-1.04	-7.016	3.200	0.358
3-year local control rate	-0.12	-9.067	8.394	0.910
1-year overall survival rate	2.36	-0.130	2.983	0.065
2-year overall survival rate	-1.37	-6.567	2.010	0.230
3-year overall survival rate	-0.89	-13.536	6.967	0.424
≥3 grade acute esophagitis	1.01	-2.295	5.272	0.358
≥3 grade acute d pneumonitis	-1.76	-5.469	1.023	0.139
Out-field lymphatic reccurence/metastasis	1.26	-2.285	5.263	0.298

MATERIALS AND METHODS

Sources of literature

Publications on ESCC treated with ENI and IFI were retrieved from Chinese Biomedical Literature Database, CNKI, Cochrane Library, Pubmed and EMbase. Key words were "esophageal carcinoma" or "esophageal cancer", "elective nodal irradiation" or "involved-field irradiation" (in both English and Chinese). The last retrieval was on June 30, 2017.

Inclusion and exclusion criteria

Inclusion criteria: (1) Subjects were ESCC patients; (2) Radiotherapy was used three-dimensional conformal, IMRT and/or other advanced technology; (3) Detailed original data were available; (4) Chinese domestic literatures must be published in the national core journals collected by Beijing university library, and international publications must be published in English, in full-text; (5) Statistical methods were proper, and results were expressed clearly. Odds ratio (OR), harzard ratio (HR) and their 95% confidence intervals (CI) were presented or could be calculated.

Exclusion criteria: (1) Subjects included non-ESCC patients; (2) Due to the limitations of positioning and irradiation technology in two-dimensional age, even the IFI included part of high-risk lymphatic area adjacent to the lesion, two-dimensional radiotherapy was excluded; 3) Conference summary, academic papers or Chinese literatures were not collected at Beijing university library.

Quality assessment

According to the guidelines for reading case-control studies [3], every research was assessed by the following aspects in order to determine if there was bias and its degree of influence: (1) The subjects were histologically confirmed as ESCC patients, and baseline characteristics such as gender, age, tumor location were clear; (2) Whether patients were treated with concurrent radiochemotherapy; (3) Whether proper statistical methods were used, for example, local control and overall survival rates were calculated by Kaplan-Meier method and Log-rank test; (4) Whether experimental design was prospective randomized controlled study; (5) Whether the existence of bias was discussed. One point was assigned for each of the five aforementioned five items matched. A total score of ≥ 3 points indicates reliable quality. Two researchers reviewed the literatures indepently according to the unified quality standard. The results were then crosschecked. In case of disagreement, it was resolved through discussion or by enlisting help from a third researcher.

Statistical methods

Stata 11.0 statistical software provided by the Cochrane collaboration was used in this meta analysis. As an effect size, OR, HR and their 95% CIs were calculated. Q test was applied for heterogeneity test. There was heterogeneity if P value was 0.05 or less, and it needed to use random effect model. Otherwise, there was no heterogeneity if $P > 0.05$, and fixed effect model was therefore used. Z test was used for significance test of combined OR. Publications with similar OR or HR were then excluded before a sensitivity analysis was performed to re-estimate the effects and the results were compared with those of the analysis before the aforementioned exclusion. Funnel chart was used to assess bias in that bias may exist if the funnel chart was asymmetrical. Egger linear regression was used for publication bias test.

CONFLICTS OF INTEREST

The authors declares no conflicts of interest.

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