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

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ABSTRACT

It remains 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 conducted to compare ENI and IFI in the treatment of ESCC, in order to provide guidance for clinical practice. Literature on the use of ENI and IFI in the treatment of ESCC was retrieved, and the last access date was 31 December 2017. A meta-analysis was performed to evaluate the relative advantages and disadvantages of using ENI and IFI. Ten studies, involving a total of 1348 patients, were included in this analysis; of these, 605 patients underwent radiotherapy only, and 743 underwent radiochemotherapy. There was no significant difference in the 1-, 2- or 3-year local control rates between ENI and IFI, or in the 1-, 2- or 3-year overall survival rates. However, the incidences of ≥Grade 3 acute esophagitis and pneumonia were significantly lower in the IFI group. There were no differences in the rates of ≥Grade 3 myelosuppression or of out-field recurrence or metastasis between these two groups. Thus, neither local control rates nor overall survival rates differed significantly between the ENI and IFI groups, but in the latter group, incidences of severe radiation esophagitis and pneumonia were significantly lower. IFI was not associated with an increase in out-field recurrence or metastasis.

Keywords: esophageal neoplasm; three-dimensional conformal/intensity-modulated radiotherapy; involved-field irradiation; clinical target volume

INTRODUCTION

It remains controversial whether elective nodal irradiation (ENI) or only involved-field irradiation (IFI) is required for the treatment of locally advanced esophageal squamous cell carcinoma (ESCC). Dong et al. found that ENI can reduce localized regional failure, and improve local control rates and long-term survival in patients with radical radiotherapy [1]. However, there are also comprehensive studies reporting that the predominant failure pattern after IFI does not involve out-field regional failure [2, 3]. Furthermore, Li M-H et al. indicate that few patients in their study had out-of-field lymph node treatment failure, regardless of the use of ENI or IFI, and that the factors that had the most impact on overall survival rate were primary tumor local recurrence and distant metastasis [4]. In this study, a meta-analysis was conducted to compare the effects of ENI and IFI on local control rate, overall survival rate and side effects in patients with ESCC, in order to provide guidance for clinical practice.

MATERIAL AND METHODS

Sources of literature

Publications on ESCC treated with ENI and IFI were retrieved from the Chinese Biomedical Literature Database, CNKI, the Cochrane Library, PubMed and Embase. Key words were ‘esophageal carcinoma’
or ‘esophageal cancer’, and ‘elective nodal irradiation’ or ‘involved-field irradiation’ (in both English and Chinese). The last retrieval was performed on 31 December 2017.

Inclusion and exclusion criteria
Inclusion criteria: (i) subjects were ESCC patients; (ii) the radiotherapy was used three-dimensional conformal, IMRT and/or other advanced technology; (iii) detailed original data were available; (iv) the Chinese domestic literature had to have been published in the national core journals collected by Beijing University Library, and international publications had to have been published in English, in full text; (v) statistical methods were legitimate, and results were expressed clearly, such that odds ratios (ORs), hazard ratios (HRs) and their 95% confidence intervals (CIs) were presented or could be calculated.

Exclusion criteria: (i) non-ESCC patients; (ii) due to the limitations of positioning and irradiation technology in the two-dimensional age, even if the IFI included part of the high-risk lymphatic area adjacent to the lesion, cases in which two-dimensional radiotherapy was used were excluded; (iii) conference summaries, academic papers or Chinese literature that were not collected at Beijing University Library were excluded.

Quality assessment
According to the guidelines for reading case–control studies [5], every study was assessed according to the following aspects in order to determine whether there was bias and, if so, its degree of influence: (i) whether the subjects were histologically confirmed as ESCC patients, and baseline characteristics such as gender, age, and tumor location were clear; (ii) whether patients were treated with concurrent radiochemotherapy; (iii) whether proper statistical methods were used (e.g. local control and overall survival rates were calculated by the Kaplan–Meier method and Log-rank test); (iv) whether the experimental design was a prospective randomized controlled study; (v) 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 was considered to indicate reliable quality. Two researchers reviewed the literature independently according to the unified quality standard. The results were then cross-checked. In the case of disagreement, this 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, ORs, HRs and their 95% CIs were calculated. The Q test was applied for a heterogeneity test. There was considered to be heterogeneity if the P value was ≤0.05, and in those cases the random effect model could be used. There was considered to be no heterogeneity if P > 0.05, and the fixed effect model was therefore used. The Z test was used to test the significance of the combined ORs. Publications with similar ORs or HRs were then excluded before a sensitivity analysis was performed to re-assess the effects, and the results were compared with those of the analysis before the aforementioned exclusion. A funnel chart was used to assess bias: bias was considered to exist if the funnel chart was asymmetrical. Egger’s linear regression was used as a publication bias test.

RESULTS
The retrieval results and quality evaluation
A total of 64 publications were retrieved initially, excluding 18 dissertations/conference contributions/journals not collected at Beijing University Library. After reading the abstracts, 20 of these publications were excluded for repeating published data, 2 for using 2-dimensional technology, and 14 for being non-case–control studies. Eventually, 10 studies involving 1348 ESCC patients were included in this meta-analysis [6–15]. The basic characteristics and the results of the included studies are shown in Tables 1 and 2.

Comparison of local control rates
The numbers of publications included for analysis of the 1-, 2- and 3-year local control rates were 7, 6 and 5, respectively. The fixed effect model was used in the case of absence of statistical heterogeneity (P = 0.494; OR = 0.258; P = 0.079). There was no significant difference in the local control rates between the ENI and IFI groups at 1-, 2- or 3- years (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), as seen in Figs 1–3.

Comparison of overall survival rates
The numbers of publications included for analysis of the 1-, 2- and 3-year overall survival rates were 8, 8 and 7, respectively. There were no significant differences in the 1-, 2- or 3-year overall survival rates between the two groups (HR = 0.840, 95% CI 0.646–1.093, P = 0.194; HR = 1.082, 95% CI 0.803–1.459, P = 0.604; HR = 0.901, 95% CI 0.571–1.423, P = 0.655), as seen in Figs 4–6.

Evaluation of toxicity and side effects
Eight, nine and three publications were included to analyze ≥Grade 3 acute esophagitis, ≥Grade 3 acute pneumonitis and ≥Grade 3 myelosuppression, respectively. The fixed effect model was used in the case of absence of statistical heterogeneity (P = 0.201; OR = 0.253; P = 0.498). As seen in Figs 7 and 8, the incidences of ≥Grade 3 acute radiation-induced esophagitis and ≥Grade 3 acute pneumonitis in the IFI group were significantly lower than those in ENI group (OR = 0.467, 95% CI 0.319–0.683, P = 0.000; OR = 0.464, 95% CI 0.264–0.817, P = 0.008), while there was no significant difference with respect to ≥Grade 3 myelosuppression (OR = 0.683, 95% CI 0.410–1.137, P = 0.143), as seen in Fig 9.

Out-field lymph node recurrence or metastasis
A total of six articles were included in the analysis of out-field lymph node recurrence or metastasis between the two groups. The OR value did not differ significantly between the two groups (OR = 1.373, 95% CI 0.766–2.460, P = 0.287), indicating that ENI did not reduce the risk of out-field recurrence or metastasis (Fig 10).

Sensitivity analysis
Literature with similar ORs or HRs were excluded, in order to detect their impact on the results, as seen in Table 3. We found that
| Author          | Year | Number of patients | Stage | Irradiation range | Irradiation dose | Quality assessment |
|-----------------|------|--------------------|-------|-------------------|------------------|--------------------|
| Zhou et al.     | 2012 | 57                 | T2–4  | 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. | 60 Gy/30 fr, ENI: 40 Gy/20 fr, a booster dose was further administered up to a total dose of 60 Gy | 1 1 1 0 1          |
| Li et al.       | 2012 | 94                 | T1–4  | IFI: CTV was defined as the GTV plus a 3 cm margin superior and inferior to the primary tumor and a 0.8–1 cm 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. | 50 Gy/25 fr, a booster dose was further administered to up to a total dose of 60–62 Gy | 1 0 1 1 0          |
| Zhou et al.     | 2009 | 87                 | T1–4  | 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 | 54–62 Gy/27–31 fr, or 50 Gy/25 fr, a booster dose was further administered up to a total dose of 60–62 Gy | 1 0 1 0 1          |
| Li et al.       | 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: 50 Gy/25 fr, a booster dose was further administered up to a total dose of 60–64 Gy, IMRT: 56–66 Gy/28–33 fr | 1 0 1 0 1          |
| Zhu et al.      | 2014 | 219                | T1–4  | 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 (6th edition) of esophageal lymph node distribution. | 54–66 Gy/27–33 fr | 1 0 1 0 1          |
| Zang et al.     | 2013 | 73                 | T1–4  | 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. | 54 Gy/30 fr | 1 1 1 0 1          |
the results were basically unchanged, i.e. there was no substantial impact on the results. Since only three articles about myelosuppression were available, sensitivity analysis could not be performed.

Bias analysis
Egger’s test was used to analyze the symmetry of the funnel graphs. There was no publication bias found in the literature, with all P values being >0.05 (Table 4).

DISCUSSION
Radiotherapy is the primary treatment for advanced ESCC. In studies of esophageal cancer, compared with two-field dissection, three-field lymph node dissection was shown to improve local control and long-term survival [16, 17], and ENI technology began to be used in radical radiotherapy. Due to the link between the esophageal submucosal and muscular lymphatic networks, ESCC can affect a wide range of mediastinal lymph node drainage. In routine X-ray–based simulation, recurrence in lymph nodes that are out of field may occur and increase the local failure rate. Zheng et al. [18] reported on 988 cases of esophageal cancer treated using conventional radiotherapy, and the incidence of out-field lymph node metastasis was as high as 30.4%.

With the continuous progress in diagnostic methods, the 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 five studies, involving 405 patients, showed that ENI did not improve the 1-year local control or 1-year survival rates, while it increased the incidence of radiation esophagitis and pneumonia.
Considering the fact that the number of cases has increased significantly, and that multiple publications have reported 2- and 3-year local control and survival data, the authors retrospectively reviewed the relevant publications comparing ENI and IFI with precise irradiation, so as to provide more accurate and comprehensive guidance for clinical practice. This study was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement guidelines [20].

According to the inclusion and exclusion criteria, 10 publications, including 1348 patients, were involved. It can be seen in Table 1 that all included studies scored 3 points or higher, indicating that they are of high quality. Most of the studies had compared two groups of patients who had or had not received chemotherapy, and there was no statistical difference in the numbers of patients who received chemotherapy compared with those who did not. There were no significant differences in the 1-, 2- or 3-year local control rates or the 1-, 2- or 3-year survival rates between the ENI and IFI groups, which may be related to the fact that, even with IFI, micrometastases near the tumor were irradiated by a considerable dose [4]. Regarding failure of ENI and IFI, this meta-analysis found no significant differences in the incidence of out-of-field recurrence or metastasis between the two groups (OR = 1.373, 95% CI 0.766–2.460, P = 0.287). This may be due to the accuracy of delineating the mediastinal metastatic lymph nodes with CT simulation and PET/MRI being significantly improved, and thus the probability of out-of-field recurrence being reduced. In addition, more and more clinical studies are using concurrent radiochemotherapy, which is helpful for treating subclinical lesions. As a result, the use of IFI mode was not found to be associated with a higher probability of recurrence or metastasis.

The scope of lymph node metastasis of ESCC is extremely extensive and complex. There is not only regional metastasis, but

| Author          | Group | Local control rate (%) | Overall survival rate (%) | ≥Grade 3 acute esophagitis | ≥Grade 3 acute pneumonitis | ≥Grade 3 myelosuppression |
|-----------------|-------|------------------------|---------------------------|----------------------------|---------------------------|--------------------------|
| Zhou et al. [6] | IFI   | 48                     | 7.41                      | 0                          | 33.5                      |                          |
|                 | ENI   | 46                     | 4.17                      | 0                          | 64.3                      |                          |
| Li et al. [7]   | IFI   | 72.4                   | 59.4                      | 54.5                       | 66.9                      | 55.4                     | 36.2                      | 6.12                      | 0                          | 2.04                      |
|                 | ENI   | 69.5                   | 58.4                      | 46.0                       | 68.6                      | 48.4                     | 35.5                      | 15.56                     | 0                          |
| Zhou et al. [8] | IFI   | 75                     | 57                        | 67                         | 43                        | 12                       | 2                         |
|                 | ENI   | 72                     | 45                        | 69                         | 40                        | 18                       | 9                         |
| Li et al. [9]   | IFI   | 66                     | 48                        | 59                         | 41                        | 5                        |                          |
|                 | ENI   | 68                     | 49                        | 61                         | 39                        | 12                       |                          |
| Zhu et al. [10] | IFI   | 63                     | 39.1                      | 67.6                       | 24.9                      |                          |
|                 | ENI   | 70.5                   | 53.3                      | 73.7                       | 45.1                      |                          |
| Zang et al. [11] | IFI  | 93                     | 71.6                      | 71.5                       | 71.8                      | 44.7                     | 25.7                      | 11.4                      | 2.86                      | 0                        |
|                 | ENI   | 87                     | 80                        | 80                         | 66.1                      | 60                       | 45.4                      | 39.5                      | 13.16                     | 5.3                      |
| Jing et al. [12] | 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 et al. [13] | IFI   | 49                     | 6                         | 2                          |                           |                          |
|                 | ENI   | 47                     | 6                         | 4                          |                           |                          |
| Yamashita et al. [14] | 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                      |
| Lyu et al. [15] | IFI   | 83.6                   | 62.1                      | 44.5                       | 4.8                       | 3.8                      | 27.9                      |
|                 | ENI   | 84.1                   | 57.3                      | 39.4                       | 15.8                      | 8.9                      | 32.7                      |
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 [21]. In view of ENI being based on the lesion site and having a relatively fixed range of irradiation, it 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 ≥Grade 3 acute radiation-induced esophagitis and ≥Grade 3 acute pneumonitis in the IFI group were significantly lower due to the decrease in irradiation volume and dose (OR = 0.467, 95% CI 0.319–0.683, P = 0.000; and OR = 0.464, 95% CI 0.264–0.817, P = 0.008, respectively), while there was no significant difference in ≥Grade 3 myelosuppression (OR = 0.683, 95% CI 0.410–1.137, P = 0.143). The side effects of...
concurrent radiochemotherapy and prophylactic exposure further affect the patient’s tolerance, so ENI may lead to more severe radiation esophagitis and pneumonia. One retrospective study provided data on subsequent salvage treatments in IFI and ENI groups, and only 1 patient (14%) in the ENI group received salvage radiotherapy after failure, while 5 patients (63%) in the IFI group received salvage chemotherapy.

**Fig. 3. Forest plot of 3-year local control rate.**

**Fig. 4. Forest plot of 1-year overall survival rate.**
Fig. 5. Forest plot of 2-year overall survival rate.

Fig. 6. Forest plot of 3-year overall survival rate.
group had salvage radiotherapy. It is necessary to investigate this further.

A publication with similar ORs or HRs to the combined ones was excluded, in order to detect its impact on the results, as seen in Table 3. It was shown that results were basically unchanged by excluding any single publication.

Original publication bias exists to a certain extent and may affect the reliability of the results. However, Egger’s analysis...
showed that the funnel plot was symmetrical ($P > 0.05$), indicating that the bias was small and that the potential bias had no substantial influence on the final conclusion. A limitation of this meta-analysis was that the publications included were mostly retrospective studies. In addition, the type of radiation exposure and radiation dosage in the ENI groups were not consistent, and the non-surgical staging method was not uniform. Some studies used radiotherapy alone rather than concurrent radiochemotherapy. Because the frequency of lymph node metastasis affects tumor invasion, it is difficult to evaluate the treatment outcomes for each stage. Consequently, further stratified analysis is difficult. Nine out of ten studies were from China, and the remaining one was from Japan, so this meta-analysis has indicated that IFI may be useful for Asian patients.

In summary, this meta-analysis has shown that the local control rates and survival rates in the IFI group were similar to those in the ENI group, while the incidences of severe acute radiation esophagitis and pneumonia were significantly lower in the IFI group. IFI

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**Fig. 9. Forest plot of ≥Grade 3 myelosuppression.**

**Fig. 10. Forest plot of out-field lymph node recurrence/metastasis.**
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. [12]   | 0.769    | 0.563        | 1.050   | 0.098                             | Yes                                |
| 2-year local control rate            | Jing et al. [12]   | 1.243    | 0.884        | 1.749   | 0.211                             | Yes                                |
| 3-year local control rate            | Jing et al. [12]   | 0.973    | 0.709        | 1.336   | 0.866                             | Yes                                |
| 1-year overall survival rate         | Yamashita et al. [14] | 0.859    | 0.636        | 1.158   | 0.318                             | Yes                                |
| 2-year overall survival rate         | Li et al. [9]      | 1.068    | 0.762        | 1.497   | 0.703                             | Yes                                |
| 3-year overall survival rate         | Jing et al. [12]   | 0.914    | 0.542        | 1.542   | 0.737                             | Yes                                |
| ≥Grade 3 acute esophagitis           | Yamashita et al. [14] | 0.513    | 0.327        | 0.803   | 0.004                             | Yes                                |
| ≥Grade 3 acute pneumonitis           | Liu et al. [13]    | 0.464    | 0.256        | 0.842   | 0.011                             | Yes                                |
| Out-field lymphatic recurrence/metastasis | Lyu et al. [15]   | 1.629    | 0.708        | 3.747   | 0.251                             | Yes                                |

Table 4. Publication bias of the involved literature

| 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         | 2.44    | −0.002       | 2.908   | 0.05  |
| 2-year overall survival rate         | −1.52   | −5.496       | 1.286   | 0.180 |
| 3-year overall survival rate         | −1.09   | −11.631      | 4.704   | 0.325 |
| ≥Grade 3 acute esophagitis           | 1.01    | −2.295       | 5.272   | 0.358 |
| ≥Grade 3 acute pneumonitis           | 1.26    | −4.251       | 1.357   | 0.254 |
| Out-field lymphatic recurrence/metastasis | 1.27    | −1.048       | 2.823   | 0.272 |

was not found to be associated with an increase of out-field lymph node recurrence or metastasis.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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