·Esophageal Cancer Column·

Meta-analysis of late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy for esophageal carcinoma

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[Abstract] Background and Objective: Although there are many randomized clinical trials of late course accelerated hyperfractionated radiotherapy (LCAHFR) combined with FP chemotherapy for esophageal cancer, the efficacy and toxicity are controversial. This study was to evaluate the efficacy and toxicity of LCAHFR combined with FP chemotherapy in treating esophageal cancer. **Methods:** Reports of randomized clinical trials on LCAHFR combined with FP chemotherapy for esophageal cancer published between January 1999 and January 2009 were researched through Wanfang, CNKI, and PubMed databases. RevMan4.2 software was used for Meta-analysis. **Results:** Twenty-one reports, including 2030 patients, were included in the meta-analysis. Of the 2030 patients, 1006 underwent LCAHFR (LCAHFR group), and 1024 underwent LCAHFR combined with FP chemotherapy (combination group). Compared with those of the LCAHFR group, the 1-, 2-, 3-, 5-years survival rates and 1-, 2-, 3-year local control rates of the combination group were significant increased, and the acute toxicity was also increased, but chronic toxicity showed no significant difference. **Conclusions:** LCAHFR combined with FP chemotherapy can improve the survival rate and the local control rate of the patients with esophageal cancer. The increased acute toxicity need to be concerned, whereas the chronic toxicity needs a long-term observation.

Key words: Esophageal neoplasm, late course accelerated hyperfractionation, radiotherapy, chemotherapy, Meta-analysis

Radiotherapy is an important non-surgical treatment for esophageal cancer, but the efficacy of conventional fractionated radiotherapy is not satisfactory. In the past 30 years, the 5-year survival rate by conventional fractionated radiotherapy alone has hovered at about 10%. As the progress of radiation physics and radiation biology, people began to recognize that the accelerated re-proliferation of tumor cells in the process of fractionated radiotherapy plays an important role in local failure after treatment. Therefore, unconventional fractionated radiotherapy began to be used in radiosensitive head and neck cancer and obtained encouraging results. Later, it was found that the accelerated re-proliferation of tumor cells existed not only in head and neck cancer but also in other tumors including esophageal cancer, and then accelerated hyperfractionated radiotherapy began to be used in esophageal cancer. In 1997, Shi *et al.*[1] published firstly the results of late course accelerated hyperfractionated radiotherapy (LCAHFR) in esophageal cancer in China, and the 5-year survival and local control rates were 34% and 55% respectively, which were significantly better than those by conventional fractionation. Han *et al.*[2] reported that the 5-year survival rates were 32% by LCAHFR and 14% by conventional fractionated radiotherapy, confirming that late course accelerated fractionation was superior to conventional fractionation. Since then, LCAHFR in esophageal cancer got clinical widespread promotion in China. Meanwhile, with the publication of series research results such as RTOG 85-01, it was proved that concurrent radiotherapy and chemotherapy based on FP regimen was obviously better than radiotherapy alone, and the 5-year survival rate of radiochemotherapy group reached 26%, which laid the

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This paper was translated from Chinese into English by *CJC* Medical Translation and edited by Wei Liu.

Received: 2010-03-24; Accepted: 2010-06-11

important position of concurrent radiochemotherapy in non-surgical treatment of esophageal cancer. Currently, concurrent radiochemotherapy has become the standard non-surgical treatment of esophageal cancer. Since LCAHFR combined chemotherapy can improve the survival and local control rates as compared with radiotherapy alone, some researchers consider to combine LCAHFR with chemotherapy, and expect to achieve better clinical results. Some clinical trials showed that either LCAHFR or concurrent radiochemotherapy could increase the treatment-related toxicity as compared with radiotherapy alone. Therefore, although randomized controlled trials of LCAHFR combined with chemotherapy increase significantly, due to small sample size, single center trials with inconsistent results and toxicity, it is not clear whether LCAHFR combined with FP chemotherapy can improve survival and local control rates as well as increase acute and chronic toxicity as compared with LCAHFR alone, and its clinical value should be further explored. We conducted a Meta-analysis of randomized controlled trials on LCAHFR combined with FP chemotherapy for esophageal cancer published in recent 10 years, to assess the clinical value of LCAHFR combined with FP chemotherapy.

Materials and Methods

Databases

Searched databases were the PubMed database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM), and Wanfang database. Searched subject words: esophageal cancer, late course accelerated fractionation, and radiochemotherapy. Limits: randomized controlled trial.

The inclusion and exclusion criteria

Inclusion criteria: a randomized controlled trial; patients with pathologically confirmed esophageal cancer as study subjects; with explicit enrollment and exclusion criteria; LCAHFR combined with FP chemotherapy as experimental group, and LCAHFR alone as control group; literature quality with a Jadad score[3] of $\geqslant$ 3; evaluation indicators included survival rate, local control rate, radiation esophagitis, bronchitis, hematological and gastrointestinal toxicity. Exclusion criteria: combined with other treatment; non-FP chemotherapy; duplicate reports, and literatures with less information and unknown data.

Data processing

The Review Manager 4.2 software provided by Cochrane Collaboration was used for data processing. The 1-, 2-, 3-, 5-year survival rates, 1-, 2-, 3-year local control rates, and radiochemotherapy-related toxicities were used as statistical indicators. The Chi-square test was used for the heterogeneity test among results, the random effect model was used when a P value was less than or equal to 0.05, and the fixed effect model was used when a P value was more than 0.05. The odds ratio (OR) values of the 1-, 2-, 3-, 5-year survival rates, 1-, 2-, 3-year local control rates, and toxicities included in the Meta-analysis were taken as the abscissa axis, and the SE (LogOR) was taken as the ordinate axis to draw funnel plots, and the impact of publication bias was assessed by observing the symmetry.

Results

The included reports

A total of 21 illegible reports were included in the Meta-analysis. A total of 2030 cases were reported, of which 2022 (99.61%) had squamous cell carcinoma, and only 8 had adenocarcinoma; 1024 received LCAHFR combined with FP chemotherapy, and 1006 received LCAHFR alone. The clinical data are shown in Table 1.

The comparison of survival rates

The OR values of merged 1-, 2-, 3-, 5-year survival rates in combination group were 1.92 (95% CI: 1.56–2.37, P < 0.001), 2.01 (95% CI: 1.61–2.49, P < 0.001), 1.90 (95% CI: 1.57–2.29, P < 0.001), and 1.85 (95% CI: 1.06–3.24, P = 0.03). The heterogeneity Chi-square test values were 19.15 (P = 0.45), 6.60 (P = 0.91), 7.54 (P = 0.98), and 0.03 (P = 0.87). The funnel plot was basically symmetric on both sides without significant publication bias (Figures 1–5).

The comparison of local control rates

The OR values of merged 1-, 2-, 3-year local control rates in combination group were 1.69 (95% CI: 1.27–2.26, P < 0.001), 1.84 (95% CI: 1.39–2.42, P < 0.001), and 1.87 (95% CI: 1.44–2.44, P < 0.001). The heterogeneity Chi-square test values were 2.75 (P = 0.99), 2.42 (P = 0.97), and 5.36 (P = 0.72) (Figures 6–8).

Acute radiation toxicity

The OR value of merged occurrence rate of grade 1–2 radiation bronchitis was 2.02 (95% CI: 1.57–2.60, P < 0.001), and the heterogeneity Chi-square test value was 17.62 (P = 0.09). The OR value of merged occurrence rate

Table 1 Clinical data of the patients with esophageal cancer included in the 21 randomized trials

Reference	Number of patients		Pathologic type		Tumor location				Dose of RT (Gy)	Chemotherapy	
	Combined group	LCAHFR group	SCC	AC	Cervical	Upper	Middle	Lower		Regimen	Cycles
Yu et al., 2003[16]	50	46	94	2	6	36	47	7	60–70	DDP 50 mg, d1–3; 5–FU 500 mg, d1–5	5
Zhou et al., 2003[28]	59	59	118	0	NR	NR	NR	NR	67–68	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	2
Li et al., 2003[23]	50	50	100	0	0	39	57	4	60	DDP 20 mg, d1; 5–FU 500 mg, d1	5
Duan et al., 2003[10]	48	47	95	0	7	30	55	3	66–70	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	2
Wu et al., 2003[29]	23	23	46	0	NR	NR	NR	NR	49–70	DDP 20 mg, 5–FU 500 mg, 2f/W	4
Ren et al., 2004[11]	49	49	98	0	8	53	37	0	55–64	DDP 20 mg, d1–5; 5–FU 500 mg, d6–10	5
Dai et al., 2004[13]	80	80	160	0	0	52	72	36	64–70	DDP 10 mg, d1–10; 5–FU 250 mg, d1–10	NR
Chen et al., 2005[18]	36	34	70	0	NR	NR	NR	NR	67–70	DDP 50 mg, d1–2; 5–FU 300 mg, d1–5	2
Hou et al., 2005[15]	81	81	156	6	21	65	59	17	63	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	2
Lu et al., 2005[25]	39	39	78	0	11	26	30	11	62.4–68.2	DDP 25 mg, d1–3; 5–FU 500 mg, d1–3	4
Liu et al., 2005[26]	30	30	60	0	0	19	37	4	64	DDP 20 mg, 5–FU 500 mg, 2f/W	4
Zhang et al., 2006[14]	24	22	46	0	NR	NR	NR	NR	60	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	2
Ye et al., 2006[17]	40	40	80	0	0	26	36	18	64–68	DDP 10 mg, d1–10; 5–FU 250 mg, d1–10	NR
Zhao et al., 2006[20]	54	57	111	0	7	30	70	4	68.4	DDP 25 mg/m^2, d1–3; 5–FU 600 mg/m^2, d1–3	4
Zhu et al., 2006[30]	38	34	72	0	11	19	33	9	65	DDP 20 mg, d1–5; carmofur 200 mg, 3f/d	NR
Zhang et al., 2006[21]	94	89	183	0	6	58	115	4	60–70	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	4
Duan et al., 2007[22]	57	58	115	0	13	37	60	5	66–70	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	2
Chen et al., 2007[27]	50	46	96	0	0	11	63	22	60	DDP 20 mg/m^2, d1–5; 5–FU 500 mg/m^2, d1–5	2
Li et al., 2008[24]	29	29	58	0	5	13	31	9	67–70	DDP 20 mg, d1–5; 5–FU 500 mg, d1–5	5
Yang et al., 2008[12]	31	30	61	0	NR	NR	NR	NR	64–68	DDP 30 mg, d1–4; 5–FU 750 mg, d1–5	2
Wang et al., 2009[19]	32	33	65	0	0	39	26	0	65.4	DDP 30 mg, d1–3; 5–FU 500 mg, d1–5	4
Xie et al. 2007[31]	30	30	60	0	NR	NR	NR	NR	65	DDP 20mg,d1–5 UFT 486mg, tid.	NR
Sum	1024	1006	2022	8	95	525	792	137			

LCAHFR, late course accelerated hyperfractionation radiotherapy; C, chemotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; NR, no report, RT, radiotherapy; DDP, cisplatin; 5–FU, 5–fluorouracil; UFT, tegarururacil. The patients in combination group were treated by LCAHFR and chemotherapy.

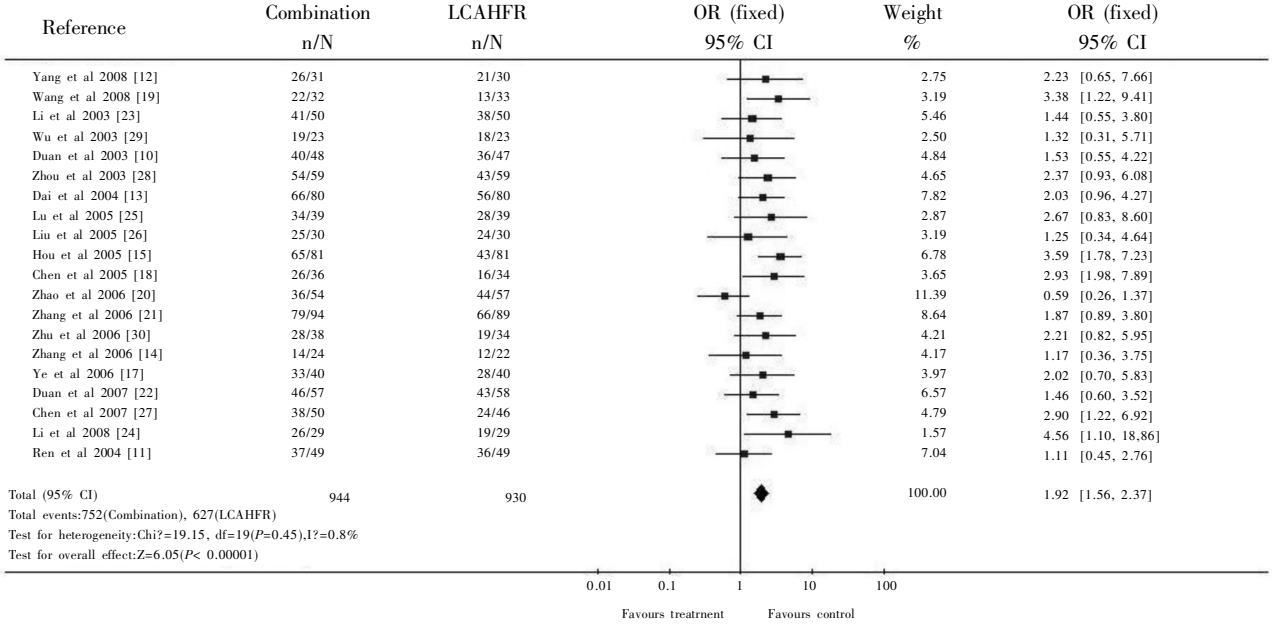

Figure 1 The comparison of 1-year survival rate between the late course accelerated hyperfractionated radiotherapy (LCAHFR) group and the combination (LCAHFR combined with chemotherapy) group

The 1-year survival rate is significantly higher in the combined group than in the LCAHFR group (Z = 6.05, P < 0.001). OR, odd ratio; N, number of group cases; n, number of incidence.

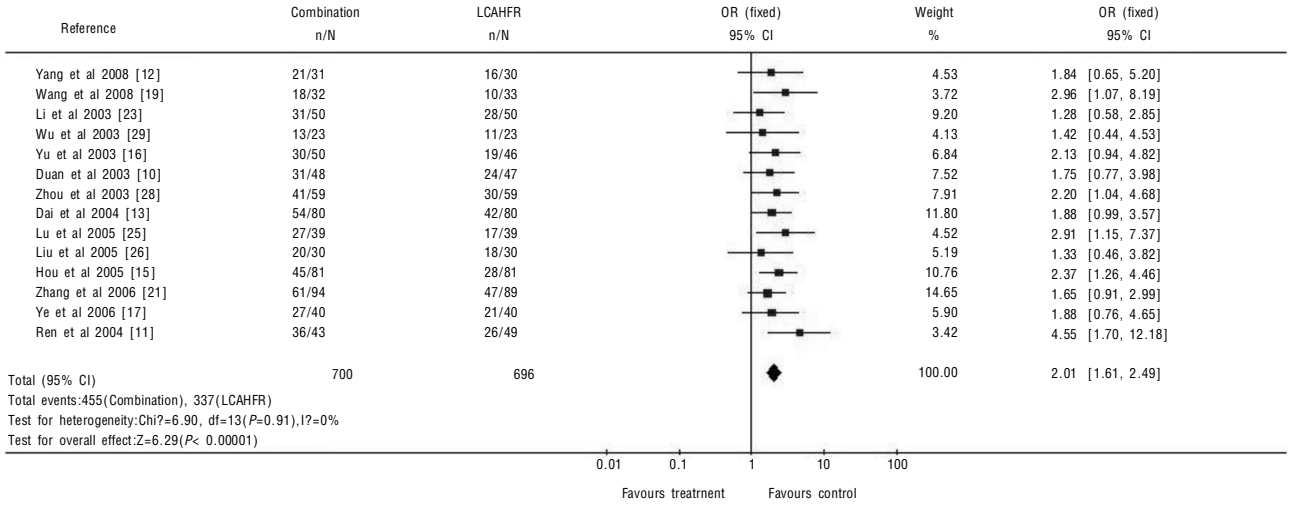

Figure 2 The comparison of 2-year survival rate between the LCAHFR group and the combination group

The 2-year survival rate is significantly higher in the combination group than in the LCAHFR group (Z = 6.29, P < 0.001).

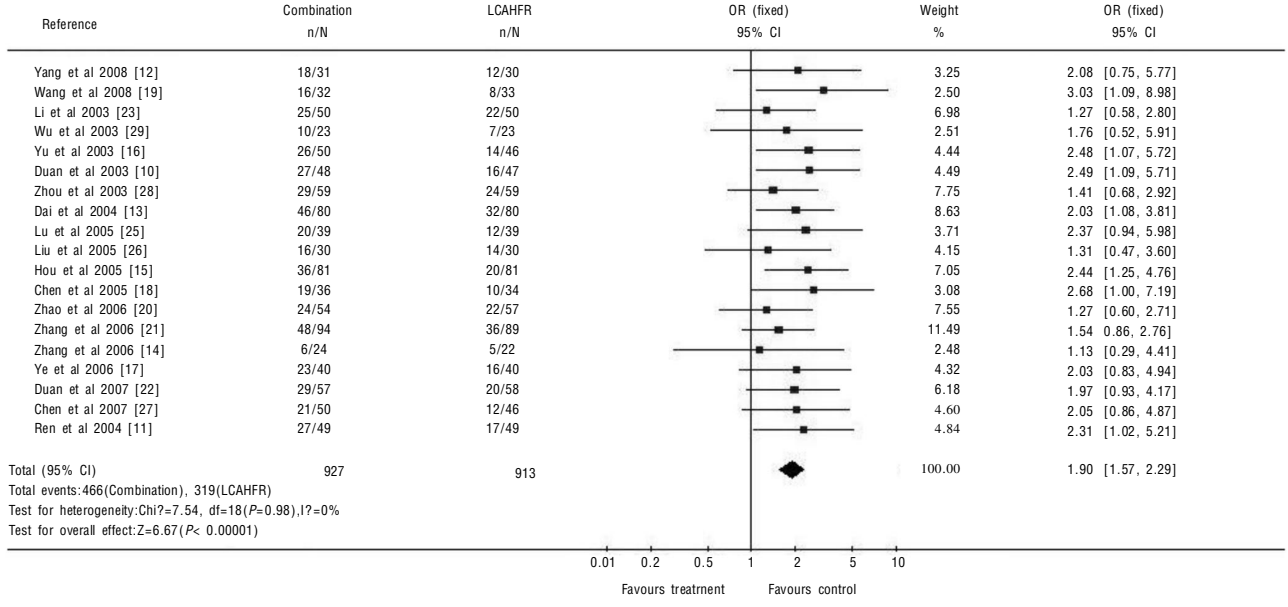

Figure 3 The comparison of 3-year survival rate between the LCAHFR group and the combination group

The 3-year survival rate is significantly higher in the combination group than in the LCAHFR group (Z = 6.67, P < 0.001).

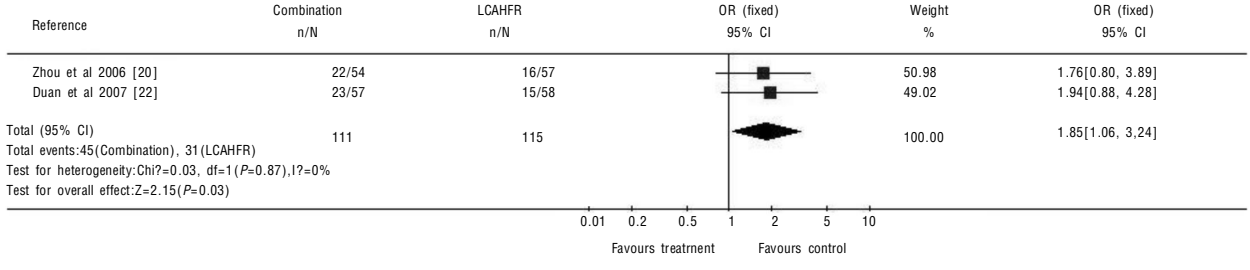

Figure 4 The comparison of 5-year survival rate between the LCAHFR group and the combination group

The 5-year survival rate is significantly higher in the combination group than in the LCAHFR group (Z = 2.15, P = 0.03).

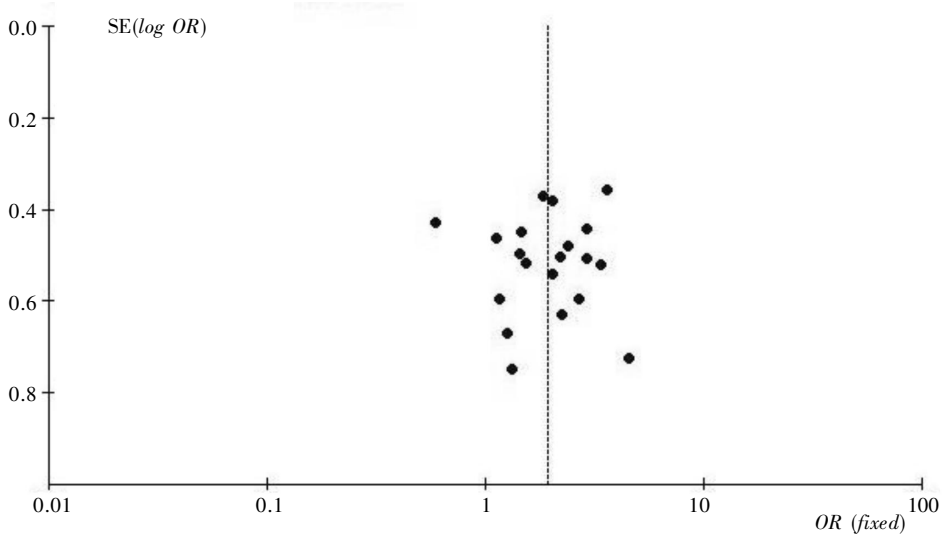

Figure 5 An example of the funnel plots which indicated that there was no evidence of heterogeneity between trials for 3-year survival rate.

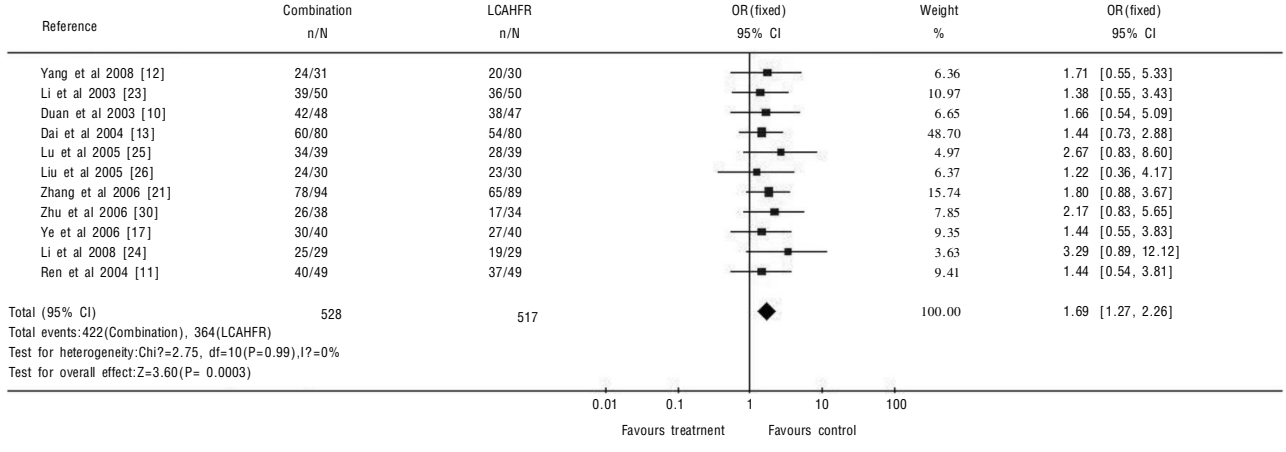

Figure 6 The comparison of 1-year local control rate between the LCAHFR group and the combination group

The 1-year local control rate is significantly higher in the combination group than in the LCAHFR group (Z = 3.60, P < 0.001).

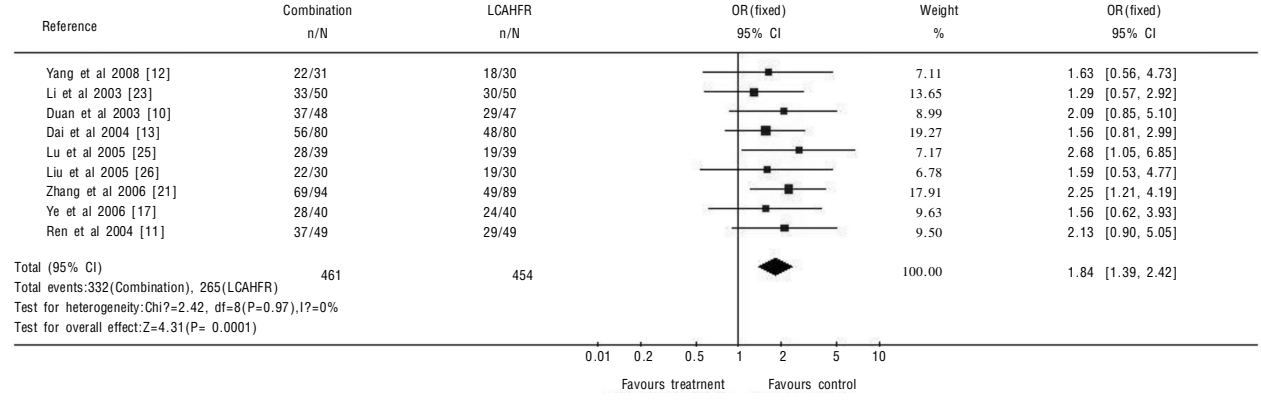

Figure 7 The comparison of 2-year local control rate between the LCAHFR group and the combination group

The 2-year local control rate is significantly higher in the combination group than in the LCAHFR group (Z = 4.31, P < 0.001).

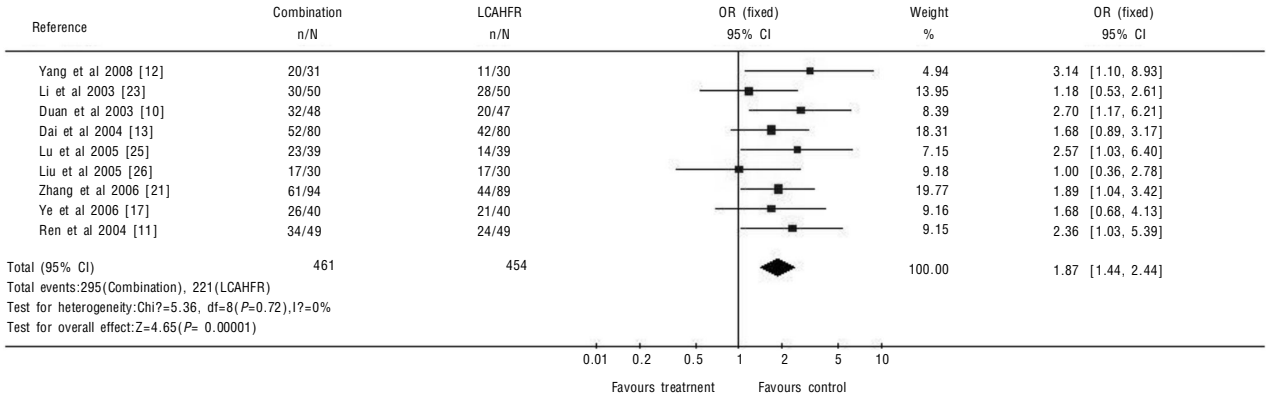

Figure 8 The comparison of 3-year local control rate between the LCAHFR and the combination group

The 3-year local control rate is significantly higher in the combination group than in the LCAHFR group (Z = 4.65, P < 0.001).

of grade 3–4 radiation bronchitis was 3.01 (95% CI: 1.33–7.24, P = 0.009), and the heterogeneity Chi-square test value was 1.43 (P = 0.96).

The OR value of merged occurrence rate of grade 1–2 radiation esophagitis was 1.82 (95% CI: 1.17–2.84, P = 0.008), and the heterogeneity Chi-square test value was 4.49 (P < 0.001), thus the random effect model was used. The OR value of merged occurrence rate of grade 3–4 radiation esophagitis was 2.60 (95% CI: 1.69–4.00, P < 0.001), and the heterogeneity Chi-square test value was 9.29 (P = 0.51).

The OR value of merged occurrence rate of myelosuppression with leukopenia as the main manifestation was 3.57 (95% CI: 2.67–4.78, P < 0.001), and the heterogeneity Chi-square test value was 11.29 (P = 0.19).

Gastrointestinal toxicities mainly manifested as nausea, vomiting, and diarrhea, of which the OR value of merged occurrence rate was 5.34 (95% CI: 3.72–7.66, P < 0.001), and the heterogeneity Chi-square test value was 5.74 (P = 0.33) (Figures 9–14).

Chronic radiation toxicity

The chronic radiation toxicity in the combination group mainly manifested as esophageal stenosis and pulmonary fibrosis, which were only reported in 3 papers. The OR value of merged occurrence rate of esophageal stenosis was 1.00 (95% CI: 0.42–2.40, P = 1.00), and the heterogeneity Chi-square test value was 0.34 (P = 0.84) (Figure 15). The OR value of merged occurrence rate of pulmonary fibrosis was 1.12 (95% CI: 0.46–2.76, P = 0.80), and the heterogeneity Chi-square test value was 1.54 (P = 0.46) (Figure 16).

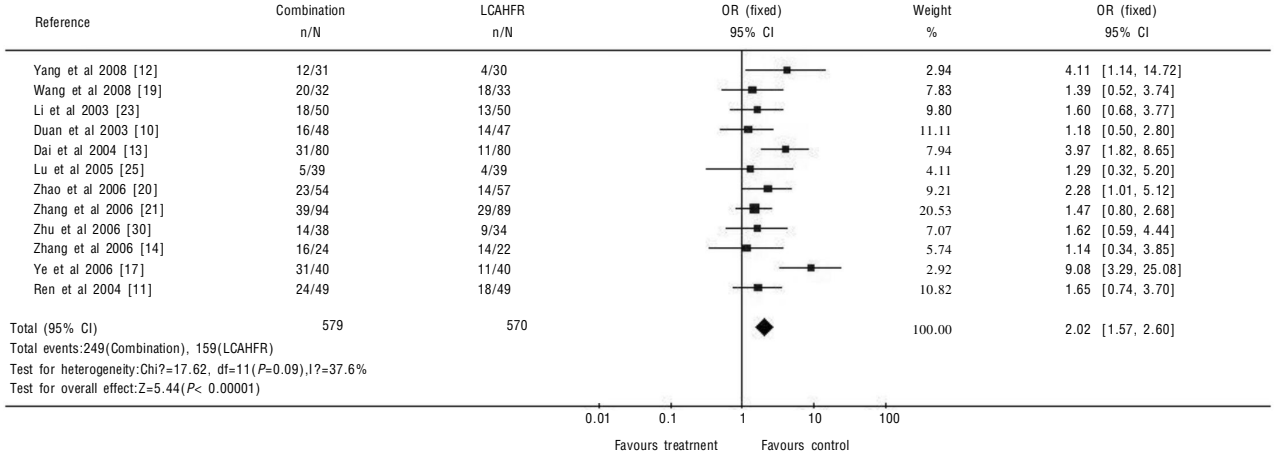

Figure 9 The comparison of acute grade 1–2 acute trachitis between the LCAHFR group and the combination group

Trachitis was evaluated according to the EORTC reverse event criteria (version 3.0). The occurrence rate of grade 1–2 acute trachitis was higher in the combination group than in the LCAHFR group (Z = 5.44, P < 0.001).

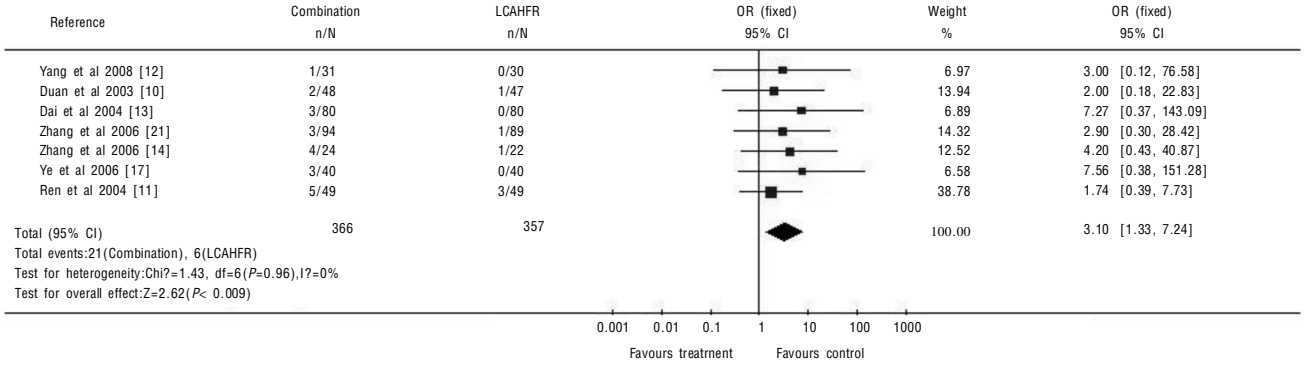

Figure 10 The comparison of grade 3–4 acute trachitis between the LCAHFR group and the combination group

The occurrence rate of grade 3–4 acute trachitis was higher in the combination group than in the LCAHFR group (Z = 2.62, P < 0.009).

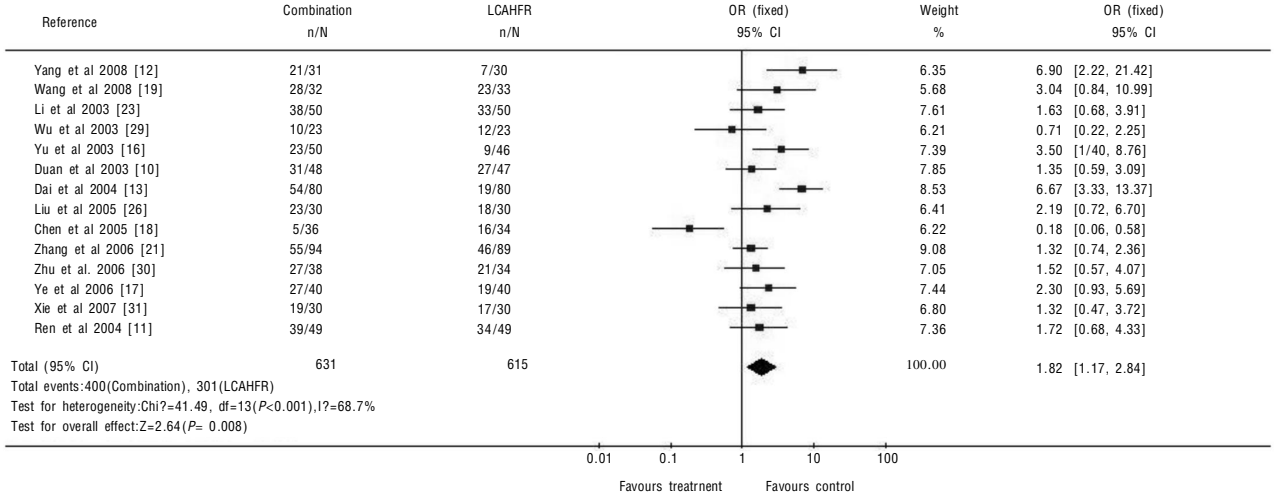

Figure 11 The comparison of grade 1–2 acute esophagitis between the LCAHFR group and the combination group

Esophagitis was evaluated according to the EORTC reverse event criteria (version 3.0). The occurrence rate of grade 1–2 acute esophagitis was higher in the combination group than in the LCAHFR group (Z = 2.64, P < 0.008).

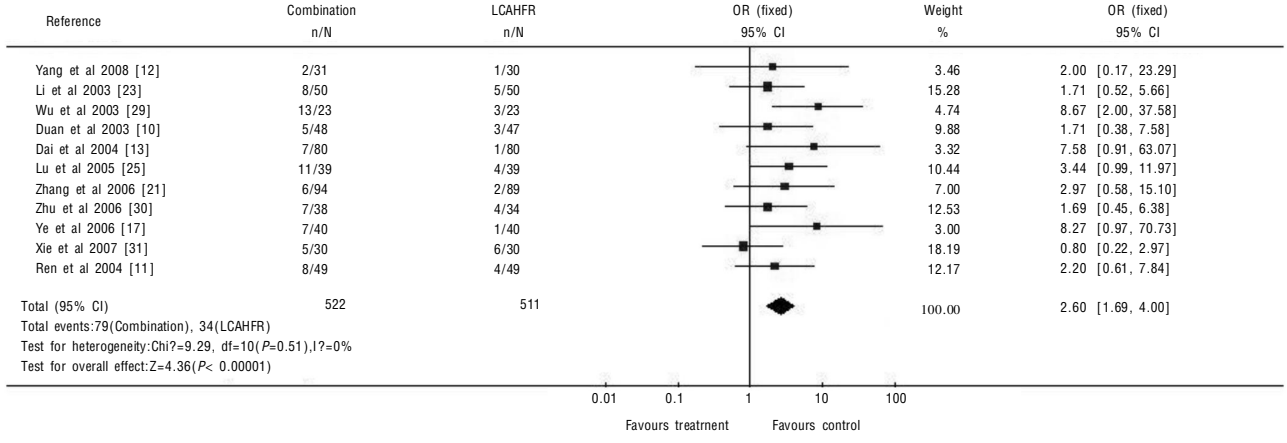

Figure 12 The comparison of grade 3–4 acute esophagitis between the LCAHFR group and the combination group

The occurrence rate of grade 3–4 acute esophagitis was higher in the combination group than in the LCAHFR group (Z = 4.36, P < 0.008).

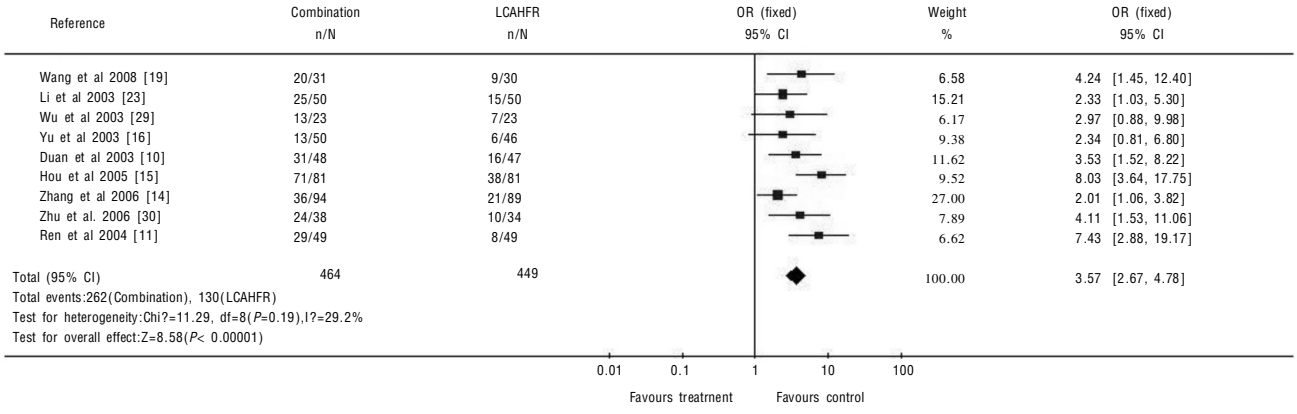

Figure 13 The comparison of bone marrow suppression between the LCAHFR group and the combination group

The occurrence rate of bone marrow was higher in the combination group than in the LCAHFR group (Z = 8.58, P < 0.001).

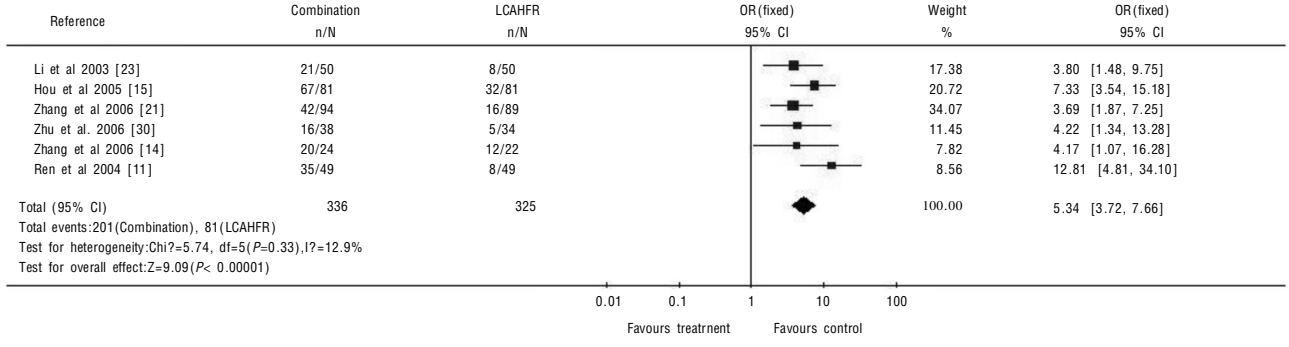

Figure 14 The comparison of intestinal disturbance between the LCAHFR group and the combination group

The occurrence rate of intestinal disturbance was higher in the combination group than in the LCAHFR group (Z = 9.09, P < 0.001).

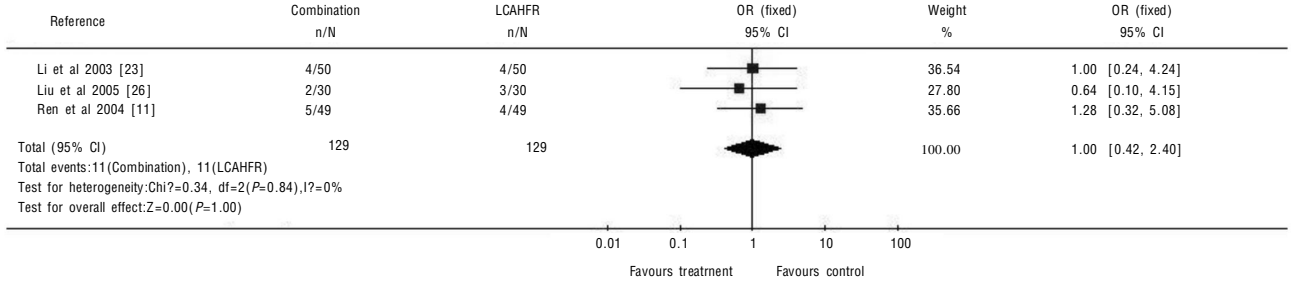

Figure 15 The comparison of esophagostenosis between the LCAHFR group and the combination group

No significant difference shows between the two groups (Z < 0.01, P = 1.00).

Discussion

Esophageal cancer is a common malignant tumor in China, and radiotherapy is an important treatment of esophageal cancer, but the 5-year survival rate of the patients with esophageal cancer treated by conventional fractionated radiotherapy was less than 10% [4]. In 1980s, because of the progress in radiation biology, it was found that the accelerated re-proliferation of tumor cells was an important reason of local treatment failure, and accelerated hyperfractionated radiotherapy was firstly used in head and neck cancer, then better results were achieved with significantly improved local control rate and survival rate [5,6]. In China, Shi *et al.* [1] reported the long-term efficacy of

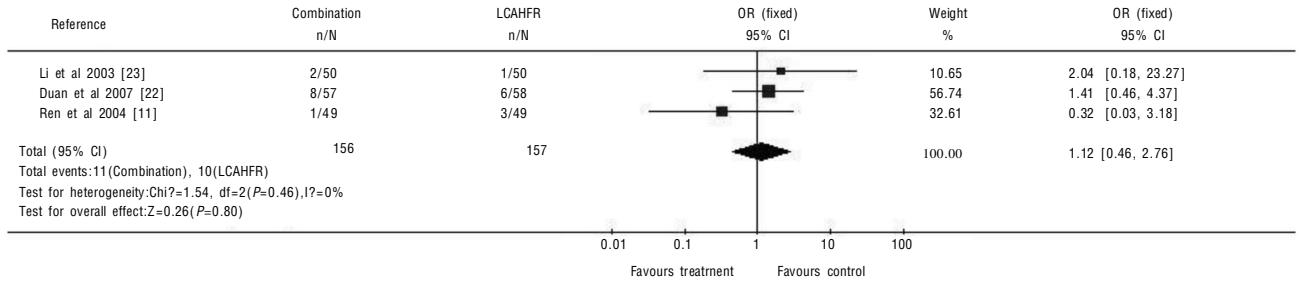

Figure 16 The comparison of chronic pulmonary fibrosis between the LCAHFR group and the combination group
No significant difference shows between the two groups (Z = 0.26, P = 0.80).

LCAHFR on esophageal cancer, and the 1-, 3-, 5-year survival rates were 67.4%, 58.1%, and 55.8%, which were significantly higher than those by conventional fractionation. In 2001, Zou *et al.*[7] reported a Meta-analysis of LCAHFR in esophageal carcinoma, with 6 randomized trials included, and the results showed that the 1-, 3-year survival rates were significantly higher than those of the conventional fractionation group. Hence, LCAHFR was considered worthy of clinical application. Since then, LCAHFR of esophageal cancer was widely used in clinical practice.

With the results of RTOG 85-01 study published [8], concurrent radiochemotherapy based on FP program became the standard non-surgical treatment of locally advanced esophageal squamous cell carcinoma. Some researchers began to study LCAHFR combined with chemotherapy in esophageal cancer. Gao *et al.* [9] reported the results of LCAHFR alone or in combination with cisplatin in esophageal cancer, the median survival time increased from 25.4 months to 32.6 months, the 1-, 3-year survival rates were 73.2% vs. 80.7% and 34.2% vs. 40%, and the 1-, 3-year local control rates were 71.4% vs. 77.1% and 34.4% vs. 48% , but all P values had no statistical significance; whereas the incidence of acute esophagitis and gastrointestinal toxicities increased significantly in the combination group. Zhao *et al.* [10] reported the results of a stage III clinical trial on LCAHFR combined with FP chemotherapy, and the 1-, 3-, 5-year survival rates were 67%, 44%, 40% in combination group, and 77%, 39%, 28% in radiotherapy alone group, with a P value of 0.310; whereas the incidence of grade 3–4 toxicities were 42% and 25% , with a P value less than 0.05. They concluded that LCAHFR combined with chemotherapy had the trend of improving survival rate, but with significantly increased toxicities.

From 2003 to 2009, many randomized trials on LCAHFR combined with FP chemotherapy were reported[10-31], but most of them were single center trials with a small sample size. The 1-year survival rate in the combination group varied from 58% to 89.6% , the 3-year survival rate varied from 24% to 57.5%, and the 5-year survival rate was fewer reported, up to 40% in only 2 reports. Inconsistent toxicities were reported, and in the combination group the incidence of grade 1–2 radiation bronchitis was 12.8% –66.7% , grade 3–4 radiation bronchitis was 3.2% –17.5% , grade 1–2 radiation esophagitis was 43.5% –87.5% , grade 3–4 radiation esophagitis was 1.3%–13.0%, myelosuppression was 26%–86.6%, gastrointestinal toxicities was 42%–82.5%, esophageal stenosis was 6.7%–10.2%, and pulmonary fibrosis was 2%–14%. Meta-analysis showed that LCAHFR combined with FP chemotherapy could significantly improve 1-, 3-, 5-year survival rates and 1-, 3-year local control rates as compared with LCAHFR alone, with short-term toxicities significantly increased, especially grade 3–4 acute radiation toxicities, which were noteworthy, and long-term toxicities such as esophageal stenosis and pulmonary fibrosis had no difference between the two groups in a few reports, which needed further investigation.

The radiation dose used in the trials included in our Meta-analysis varied from 49 to 70 Gy, with the accelerated fraction dose from 1.3 to 1.5 Gy. The RTOG 94-05 clinical trial compared the efficacy of 50.4 Gy and 64 Gy radiotherapy combined with chemotherapy, and found that the survival and local control rates had no difference between the two groups, but toxicity in the high dose group was increased. Therefore, the subsequent clinical trials in Europe and America used 50.4 Gy as radiation dose. In China, high dose of 65–70 Gy is commonly used. Because three-dimensional conformal radiotherapy was not used in RTOG 85-01 and 94-05 trials, the radiation field was large with great radiation-related toxicity, and the rate and frequency of radiotherapy interruption increased significantly, which might affect the efficacy of radiotherapy and require a further comparative study. Although FP regimen was used in the trials, the doses and chemotherapy cycles were quite different. Some trials did not describe the chemotherapy cycles and subsequent treatment, which might lead to differences in the results. Currently, there is no standard chemotherapy regimen for concurrent radiochemotherapy. Lin *et al.* [32] conducted a trial on dose escalation FP chemotherapy combined with conventional fractionated

radiotherapy, and found that the maximum tolerated dose for Chinese people was cisplatin 52.5 mg/m^2, d1 and 5-FU 500 mg/m^2, d1–5. The appropriate chemotherapy regimen and cycles for LCAHFR combined with chemotherapy have not been reported. Hence, the appropriate concurrent chemotherapy regimen and subsequent treatment need to be determined in order to standardize clinical treatment. The combination of LCAHFR with new cytotoxic drugs such as taxol and targeted therapy drugs may further improve the efficacy on esophageal cancer, which is worth waiting.

This Meta-analysis based on current data indicates that LCAHFR combined with FP chemotherapy can improve the survival rate and local control rate of esophageal cancer as compared with LCAHFR alone, with short-term toxicities significantly increased, and long-term toxicities not increased but needing more observation.

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