

## ORIGINAL ARTICLE

# Late course accelerated hyperfractionation radiotherapy for locally advanced esophageal squamous cell carcinoma

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## Keywords

Esophageal squamous cell carcinoma; late course accelerated hyperfractionation radiotherapy; meta-analysis; randomized controlled trial.

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Received: 31 May 2012;  
accepted 11 July 2012.

doi: 10.1111/j.1759-7714.2012.00166.x

## Abstract

**Background:** Late course accelerated hyperfractionation radiotherapy (LCAHR) is used as a standard treatment option for locally advanced esophageal squamous cell carcinoma (LAESCC) in China, but concerns remain regarding its efficacy and safety. The purpose of this paper was to evaluate the efficacy and safety of LCAHR. The comparisons examined were as follows: LCAHR versus conventional fractionation radiotherapy (CFR) and LCAHR plus chemotherapy (CT) versus LCAHR alone.

**Methods:** We searched the Cochrane Library, MEDLINE, EMBASE, CENTRAL, CBMdisc, and CNKI, as well as employing manual searches. The primary end points were survival and local control. The second end point was toxicities.

**Results:** Based on search criteria, we found 29 trials involving 3187 patients. Our results showed that LCAHR, compared with CFR, improved the survival and local control, and was, thus, more therapeutically beneficial. Further analysis revealed that LCAHR plus CT proved to be better for patients' survival and local control compared to LCAHR alone. Acute toxicities were increased rather than late toxicities.

**Conclusions:** There was a significant survival and local control benefit of LCAHR over CFR, as well as LCAHR plus CT over LCAHR alone. Considering the strength of the evidence, the results of this study indicate that this regimen would be a new promising modality worth further investigation.

## Introduction

Esophageal cancer (EC) is the eighth most common malignancy and the sixth leading cause of death from cancer worldwide.<sup>1</sup> The incidence rises steadily with age and varies widely according to the country of origin.<sup>2</sup> Incidence is relatively uncommon in the United States, with 17460 new cases and 17070 deaths anticipated in 2012.<sup>3</sup> Comparatively, incidence is highest in Asia, southern and eastern Africa, and northern France, with annual mortality near 100 per 100 000.<sup>4</sup> Though progress has been achieved in EC diagnosis and treatment, the prognosis remains very poor with long-term survival rates of 20–25%.<sup>5,6</sup>

Surgical resection is a standard therapy for localized EC, but results are unsatisfactory with five-year survival rates

reported in the range of 10% to 20%.<sup>7</sup> Furthermore, most ECs are diagnosed at an intermediate to advanced stage, and, therefore, patients are not suitable candidates for curative surgical resection. Radiotherapy (RT) was considered as an alternative to surgery for the treatment of patients with EC.<sup>8</sup> However, in the arm of the landmark RTOG 85-01 trial using radiation therapy alone, all patients expired from the disease within three years.<sup>9</sup> Subsequently, there has been interest in multimodality treatment approaches for this neoplasm; usually the addition of chemotherapy (CT) to radiotherapy has been shown in randomized trials to be superior to surgery or radiotherapy alone, and concurrent chemoradiotherapy (CRT) has been well established as a standard approach to locally advanced esophageal cancer.<sup>10,11</sup> Nevertheless, local failure and distant metastasis are both common modes

of failure, generally refractory to current therapeutic approaches. In addition, the CRT-induced side effects were severe at the same time.<sup>12</sup> Therefore, in order to reduce mortality from EC, development of novel therapeutic strategies are essential, in addition to efforts geared towards primary prevention and early diagnosis.

Considerable evidence has demonstrated that tumor clonogen proliferation during conventional radiotherapy is one of the factors responsible for relapse in squamous carcinoma of the upper respiratory and digestive tracts.<sup>13</sup> Therefore, shortening the overall treatment time by accelerated fractionation, but maintaining the same total dose as that of the conventional fractionation radiotherapy (CFR) schedule could improve local failure, thereby improving survival. Based on this concept, Shi *et al.* reported that late course accelerated hyperfractionation radiotherapy (LCAHR) was used for locally advanced squamous cell carcinoma of the esophagus (LAESCC), and compared with CFR, had a five-year survival and local control rate of 34% and 55%, respectively,<sup>14</sup> resulting in LCAHR becoming the most frequently used treatment for LAESCC in China. The successor trials demonstrated that LCAHR plus cisplatin with or without fluorouracil could significantly improve the survival and local control; severe complications occurred but they were within tolerance.<sup>15–18</sup>

Though a number of randomized clinical trials indicated that LCAHR was highly beneficial for treating patients with LAESCC in China,<sup>14–18</sup> these trials had insufficient statistical power to rule out tumor protection. The purpose of this study is to use meta-analysis to evaluate the efficacy and safety of LCAHR. The comparisons examined were as follows: LCAHR versus CFR and LCAHR plus CT versus LCAHR alone. It is anticipated that this systematic review and meta-analysis will provide evidence-based information for clinical practice.

## Materials and methods

### Search strategy

Trial data available through MEDLINE, EMBASE, CBMdisk (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), was collected from January 1966 to November 2011. CENTRAL (The Cochrane Central Register of Controlled Trials) and The Cochrane Library were also used. The search was designed initially to find all trials involving terms: “esophageal cancer,” “esophagus cancer,” “esophageal neoplasm,” “esophagus neoplasm” or “EC” (and multiple synonyms for each term). No language restriction was applied. Computer searches were supplemented with a manual search of journals up to November 2011. We also manually searched the general reviews and references from published clinical trials.

### Criteria for inclusion

Acceptable publications complied with the following criteria: (1) LAESCC patients were confirmed histologically; (2) trials were described as randomized clinical trials (RCTs); (3) the comparisons examined were as follows: LCAHR versus CFR and LCAHR plus CT versus LCAHR alone; and (4) the published data of primary interest were survival and local control for calculation of the relative risk (RR) at a 95% confidence interval (CI).

### Exclusion criteria

Trials were excluded if they: (1) involved animal studies or in vitro studies; (2) did not represent primary research (review articles, letters to the editor, etc.); (3) represented duplicate publications of other studies previously identified in our systematic evaluation; and (4) studies investigating local control of the disease only, without survival data.

### Data extraction

Two reviewers independently selected the trials and performed the data extraction. Discrepancies were resolved by discussion among reviewers. Information lacking in the original publications was supplemented through correspondence with the original principal investigator. Finally, the following information was extracted from each included trial: (1) the characteristics of methods (the randomization procedure, concealment of allocation, blinding procedure, withdrawal and reasons, and protection against contamination); (2) the number of patients allocated, and patient characteristics (tumor size, KPS score, and tumor position); (3) the interventional measures used (fraction dose, total dose, and antitumor drugs); and (4) outcomes, such as survival, local control, and toxicities. Survival and local control were extracted from actual numbers reported in the trials or derived from the survival curves. The toxicities were classified as acute (including gastroenterological reaction, radiation esophagitis or bronchitis, etc.) or late (including esophageal perforation or hemorrhage, esophageal stenosis, lung fibrosis, etc.), and were observed and graded according to the RTOG criteria.

### Quality assessment

The overall quality of included trials was assessed in accordance with The Cochrane Collaboration Handbook.<sup>19</sup> For each trial, the risk of bias was assessed and tabulated for each of the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Items were scored as “yes” for low risk of

bias, “unclear” for either lack of information or uncertainty over the potential for bias, and “no” for high risk of bias.

## Statistical method

We performed the meta-analysis by pooling LCAHR versus CFR and LCAHR plus CT versus LCAHR as an overall analysis. Pooled RR was presented as standard plots with 95% CIs. All P-values were two-sided and  $P < 0.05$  was considered statistically significant. First, inter-trial heterogeneity in treatment effect was evaluated using both the  $\chi^2$  statistic (significance level of  $P \leq 0.10$ ) and interpretation of the  $I^2$  statistic test.<sup>20–22</sup> Second, a fixed effect approach using the Mantel-Haenszel methods was adopted, unless there was evidence of significant unexplained heterogeneity, in which case a random effects approach using the DerSimonian and Laird methods<sup>23</sup> was used. Third, Begg and Mazumdar’s proposed adjusted rank correlation test<sup>24</sup> and Egger’s linear regression approach<sup>25</sup> were used to measure publication bias, which was shown as a funnel plot. Finally, we performed the Duval and Tweedie nonparametric “trim and fill” procedure to perform the sensitivity analysis. Analysis was performed using the statistical software Intercooled Stata version 8.2 for Windows (Stata Corporation, College station, Texas, USA).

## Results

### Common characteristics

A total of 495 trials were identified for possible inclusion in the review. After carefully reading titles and abstracts, 371 trials were excluded because of duplication or because the objective did not satisfy the inclusion criteria. A total of 124 trials were retrieved for further assessment. Of these, 19 trials were excluded for inadequate randomization methods, 52 trials were excluded because the objective did not meet the inclusion criteria, and 24 trials were excluded either because the participants and intervention or the reporting of outcomes did not meet the inclusion criteria. Ultimately, all of the trials that followed our inclusion criteria (29 trials totally 3187 patients) came from China.<sup>14–16,26–51</sup> Human trials are strongly supported by the Chinese government because there is a high level of interest in accelerated fractionation, both alone and combined with chemotherapy, for this high incidence disease. Characteristics of the included trials are listed in Tables 1 and 2.

Concerning RT, six trials employed a Cobalt-60 machine, 20 trials used a linear accelerator, and three trials employed a combination of the two. As for the fractional schedule, the CFR included daily fractions of 1.8 to 2.0 Gy, five times per week, with a total dose of 58–70 Gy, 29–38 fraction (fx), for 5.8–7.6 weeks. The LCAHR group received the same schedule as the CFR group for the first two-thirds of the treatment with

a dose of 30–43.2 Gy, 15–24 fx, for 3–4.8 weeks. This was followed by accelerated fractionation radiotherapy using reduced fields twice daily at 1.15–1.6 Gy per fraction, with a minimum interval of four to eight hours between fractions. We calculated the total dose RT based on the biologically effective dose (BED) equivalence model, which ranged from 60.7 to 74.5 Gy, so that the total dose given to the LCAHR patients was 60.7–74.5 Gy, 32–46 fx, for 5–6.6 weeks. In the LCAHR plus CT group, patients received CT separately from LCAHR, and the total dose given for LCAHR was 57.3–74.5 Gy, 35–44 fx, and for 5–6.5 weeks. The majority of included trials used a mixture of anticancer drugs. The most common anticancer drugs were cisplatin (DDP) and 5-fluorouracil (5-Fu). The most common CT interventional time included the use of CT procedure concurrent LCAHR<sup>15,16,39,40,43–47,49–51</sup> and LCAHR sandwiched between CT procedures.<sup>48</sup> (Table S1)

### Quality of included studies

In terms of quality, all included trials stated that they were “randomized,” and there were 11 trials which described the random sequence generation according to drawing lots,<sup>26,34,50</sup> random digital table,<sup>15,27,45</sup> and envelop method.<sup>31,35,38,40,42</sup> Nevertheless, no trials provided information on allocation concealment, blinding of outcome assessment, and blinding of participants and personnel. Incomplete outcome data and selective reporting were not reported in all trials. (Table 3).

## Meta-analysis outcomes

### LCAHR versus CFR

#### Survival

We identified 18 trials<sup>14,26–42</sup> with outcome measurements of one-year survival; 12 trials<sup>14,26–29,34–45</sup> with two-year survival; 18 trials<sup>14,26–42</sup> with three-year survival; and ten trials<sup>14,26,30,31,33,36,37,39,41,42</sup> with five-year survival. The fixed-effects model was used, as there was no intertribal heterogeneity of the results of trials. LCAHR significantly improved one-year, two year, three-year, and five-year survival compared with CFR ( $P = 0.0001$ ). (Table 4)

#### Local control

We identified 12 trials<sup>14,27–29,31,34,35,38–42</sup> with outcome measurements of one-year local control; 11 trials<sup>14,27–29,34,35,38–42</sup> with two-year local control; 12 trials<sup>14,27–29,31,34,35,38–42</sup> with three-year local control; and four trials<sup>14,31,41,42</sup> with five-year local control. The fixed-effects model was used, as there was no intertribal heterogeneity of the results of trials, with the exception of the one-year local control. LCAHR significantly

**Table 1** Late course accelerated hyperfractionation radiotherapy versus conventional fractionated radiotherapy for locally advanced esophageal squamous cell carcinoma

Study	Author (Year)	Arms	No. of patients	Size (cm)	TP (U/M/L)	Survival rate (%)					Local control rate (%)					Acute toxicities (%)					Late toxicities (%)			
						1 year	2 years	3 years	5 years	1 year	2 years	3 years	5 years	GIR	RE	RB	EP	H	ES	LF				
Han C (1997) <sup>26</sup>	LCAHR	CFR	50	3–9	19/30/1	84.0	56.0	48.0	32.0	NA	NA	NA	NA	16.0	16.0	NA	0	0	NA	NA	NA	0	0	NA
			50	3.5–9	20/26/4	62.0	34.0	22.0	14.0	78.0	57.0	43.0	NA	20.0	12.0	NA	0	0	NA	NA				
Sheng XF (1998) <sup>27</sup>	LCAHR	CFR	51	≤8	0/51/0	75.0	51.0	41.0	NA	78.0	57.0	43.0	NA	NA	88.0	NA	NA	3.9	NA	NA	NA	0	0	NA
			53	≤8	0/53/0	56.0	36.0	23.0	NA	58.0	36.0	26.0	NA	NA	72.0	NA	NA	0	NA	NA				
Guo JQ (1998) <sup>28</sup>	LCAHR	CFR	21	≤8	3/16/2	81.0	76.1	57.1	NA	71.4	66.6	61.9	NA	NA	38.0	28.5	NA	4.8	NA	NA	NA	0	0	NA
			21	≤8	2/16/3	47.6	33.3	19.0	NA	43.8	33.0	28.5	NA	NA	19.0	19.0	NA	0	NA	NA				
Shi XH (1999) <sup>14</sup>	LCAHR	CFR	43	≤8	12/30/1	72.1	55.8	41.9	34.0	67.4	60.5	58.1	55.0	NA	34.9	27.9	0	7.0	4.6	NA	NA	0	0	NA
			42	≤8	11/30/1	47.5	26.2	19.0	15.0	38.1	31.9	28.6	21.0	NA	14.3	14.3	2.4	0	0	0				
Zhang KL (2000) <sup>29</sup>	LCAHR	CFR	40	≤8	12/20/8	75.0	57.5	42.5	NA	75.0	67.5	52.5	NA	NA	37.5	17.5	0	0	10.0	NA	NA	0	0	NA
			40	≤8	10/21/9	52.5	32.5	20.0	NA	37.5	30.0	25.0	NA	NA	30.0	15.0	0	0	10.0	NA				
Jiang JD (2001) <sup>30</sup>	LCAHR	CFR	48	NA	10/31/7	81.0	NA	44.1	26.8	NA	NA	NA	NA	NA	27.1	18.8	NA	NA	0	NA	NA	0	0	NA
			48	NA	11/32/5	61.7	25.1	16.9	NA	78.9	NA	66.1	40.7	NA	16.7	12.5	NA	NA	0	0				
Zhou XF (2002) <sup>31</sup>	LCAHR	CFR	76	≤10	21/45/10	78.9	NA	64.0	31.0	78.9	NA	66.1	40.7	NA	NA	13.2	NA	NA	NA	NA	NA	0	0	NA
			76	≤10	16/44/16	76.3	29.4	8.4	NA	69.7	NA	29.0	10.9	NA	19.1	16.2	0	0	NA	NA				
Li AE (2002) <sup>32</sup>	LCAHR	CFR	68	3–12	19/39/10	85.3	NA	45.6	NA	NA	NA	NA	NA	NA	16.8	14.9	0	0	NA	NA	NA	0	0	NA
			67	3–11	20/36/11	52.3	20.9	NA	NA	NA	NA	NA	NA	NA	35.0	19.0	NA	NA	NA	NA				
Liu YC (2003) <sup>33</sup>	LCAHR	CFR	100	≤8	36/54/6	85.0	NA	46.5	30.9	NA	NA	NA	NA	NA	24.0	13.0	NA	NA	NA	NA	NA	0	0	NA
			100	≤8	34/58/4	63.0	23.5	11.5	NA	72.5	55.0	40.0	NA	27.5	20.0	NA	0	0	NA	NA				
Cheng GH (2003) <sup>34</sup>	LCAHR	CFR	40	≤9	10/26/2	75.0	50.0	42.5	NA	72.5	55.0	40.0	NA	27.5	20.0	NA	0	0	NA	NA	NA	0	0	NA
			40	≤9	10/25/3	55.0	34.0	22.5	NA	50.0	32.5	25.0	NA	25.0	15.0	NA	0	0	NA	NA				
Yang LQ (2003) <sup>35</sup>	LCAHR	CFR	41	3.1–10	13/28/0	73.2	42.2	39.4	NA	68.3	45.0	45.0	NA	70.7	80.4	NA	NA	NA	NA	NA	NA	0	0	NA
			41	3.1–10	14/27/0	61.0	31.7	26.8	NA	52.6	30.1	27.4	NA	56.1	48.8	NA	NA	NA	NA	NA				
Wang JZ (2004) <sup>36</sup>	LCAHR	CFR	68	NA	18/40/10	75.0	NA	35.3	26.5	NA	NA	NA	NA	NA	86.8	88.2	NA	NA	NA	NA	NA	0	0	NA
			68	NA	12/46/10	61.8	25.0	14.7	NA	72.5	55.0	40.0	NA	27.5	20.0	NA	0	0	NA	NA				
Qiao XY (2004) <sup>37</sup>	LCAHR	CFR	41	≤10	16/21/4	57.5	NA	29.3	24.4	NA	NA	NA	NA	NA	41.5	NA	7.3	NA	NA	NA	NA	0	0	NA
			40	≤10	23/15/2	57.5	22.5	14.1	NA	81.3	63.8	53.8	NA	NA	22.5	7.7	NA	NA	NA	NA				
Hu LH (2005) <sup>38</sup>	LCAHR	CFR	80	≤8	25/41/14	83.8	61.3	41.3	NA	81.3	63.8	53.8	NA	NA	26.3	28.8	1.3	1.3	2.5	NA	NA	0	0	NA
			75	≤8	19/39/17	54.7	42.7	25.3	NA	54.7	46.7	30.7	NA	NA	20.0	20.0	1.3	2.7	2.7	NA				
Li XM (2003) <sup>39</sup>	LCAHR	CFR	50	≤8	20/28/2	76.0	56.0	44.0	34.0	72.0	60.0	56.0	NA	16.0	76.0	26.0	4.0	6.0	8.0	2.0	NA	0	0	NA
			50	≤8	19/30/1	54.0	30.0	18.0	12.0	40.0	32.0	26.0	NA	12.0	56.0	18.0	2.0	4.0	4.0	0				
Wang TJ (2006) <sup>40</sup>	LCAHR	CFR	40	≤8	10/28/2	71.0	49.0	40.0	NA	70.0	58.0	53.0	NA	15.0	80.0	27.5	2.5	5.0	7.5	2.5	NA	0	0	NA
			40	≤8	9/30/1	50.0	28.0	17.0	NA	38.0	31.0	25.0	NA	10.0	60.0	17.5	0	2.5	2.5	2.5				
Wang MM (2007) <sup>41</sup>	LCAHR	CFR	63	≤8	27/26/10	82.0	62.0	50.0	18.2	83.0	78.5	58.0	18.0	NA	NA	11.0	0	0	0	0	NA	0	0	NA
			63	≤8	29/22/12	79.8	50.4	24.3	12.0	79.0	52.5	15.0	10.0	NA	NA	6.0	0	0	0	0				
Zhang Q (2007) <sup>42</sup>	LCAHR	CFR	60	≤10	20/23/17	65.0	51.0	36.0	32.0	78.0	74.0	64.0	61.0	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA
			60	≤10	18/26/16	53.0	47.0	19.0	15.0	59.0	38.0	30.0	26.0	NA	NA	NA	NA	NA	NA	NA				

CFR, Conventional fractionated radiotherapy; Cm, Centimetre; EP, Esophageal perforation; ES, Esophageal stenosis; GIR, Gastroenterological Reaction including nausea and vomit; H, Haemorrhage; LCAHR, Late course accelerated hyperfractionation radiotherapy; LF, Lung fibrosis; NA, not recorded or available; RB, Radiation bronchitis including chest pain, dry cough, even dyspnoea *et al.*; RE, Radiation esophagitis including chest pain and dysphagia *et al.*; RT, Radiotherapy; TP, Tumor position (Upper thoracic/ Middle thoracic/ Lower thoracic).

**Table 2** Late course accelerated hyperfractionation radiotherapy plus chemotherapy versus late course accelerated hyperfractionation radiotherapy alone for locally advanced esophageal squamous cell carcinoma

Study Author (Year)	Arms	No. of Patients	Size (cm)	TP (U/M/L)	Survival rate (%)				Local control rate (%)				Acute toxicities (%)				Late toxicities (%)			
					1 year	2 years	3 years	5 years	1 year	2 years	3 years	5 years	GIR	RE	RB	EP	H	ES	LF	
					1 year	2 years	3 years	5 years	1 year	2 years	3 years	5 years	GIR	RE	RB	EP	H	ES	LF	
Gao XS (2002) <sup>17</sup>	LCAHR+CT	40	3–10	11/24/5	80.7	NA	40.0	NA	77.1	60.1	48.0	NA	NA	92.5	NA	0	0	NA	NA	
	LCAHR	41	3–10	11/24/6	73.2		34.2		71.4	47.6	34.4			80.4		0				
	LCAHR+CT	59	2–10	NA	86.4	69.5	49.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		
	LCAHR	59	3–10		72.9	50.8	40.7													
Duan YJ (2003) <sup>44</sup>	LCAHR+CT	48	≤10	20/27/1	83.3	64.6	56.3	NA	87.5	77.1	66.7	NA	NA	75.0	37.5	NA	NA	NA		
	LCAHR	47	≤10	17/28/2	76.5	51.1	34.0		80.9	61.7	42.5			63.8	31.9					
	LCAHR+CT	50	3–9	36/14/0	86.0	78.0	NA	NA	82.0	72.0	NA	NA	50.0	50.0	NA	NA	NA	NA		
	LCAHR	50	3–9	36/14/0	78.0	66.0			60.0	40.0			50.0	50.0						
Cheng HH (2003) <sup>45</sup>	LCAHR+CT	50	≤8	19/29/2	82.0	62.0	50.0	38.0	78.0	66.0	60.0	50.0	42.0	92.0	36.0	4.0	4.0	8.0	4.0	
	LCAHR	50	≤8	20/28/2	76.0	56.0	44.0	34.0	72.0	60.0	56.0	48.0	16.0	76.0	26.0	4.0	6.0	8.0	2.0	
	LCAHR+CT	23	6–10	NA	82.7	56.6	43.5	NA	NA	NA	NA	NA	NA	100	NA	NA	NA	NA	NA	
	LCAHR	23	6–10		78.3	47.8	30.8							65.2						
Ren BZ (2004) <sup>47</sup>	LCAHR+CT	49	≤8	31/18/0	76.0	73.0	55.0	NA	82.0	76.0	69.0	NA	71.4	95.9	59.0	NA	NA	10.2	2.0	
	LCAHR	49	≤8	30/19/0	73.0	53.0	35.0		76.0	59.0	49.0		16.3	77.6	42.8		8.1	6.1		
	LCAHR+CT	54	2–9	16/36/2	67.0	59.3	44.0	40.0	84.0	NA	74.0	67.0	11.1	24.1	5.6	NA	NA	3.7	14.8	
	LCAHR	57	1–10	21/34/2	77.0	49.1	39.0	28.0	82.0	NA	63.0	59.0	1.8	19.3	3.5		10.5	17.5		
Chen GR (2005) <sup>48</sup>	LCAHR+CT	36	3–10	NA	71.0	NA	51.6	29.1	NA	NA	NA	NA	NA	14.0	NA	NA	NA	NA	NA	
	LCAHR	34	2–12		48.1		30.0	10.2						47.0						
	LCAHR+CT	40	≤8	10/29/1	77.0	58.0	47.0	NA	76.0	63.0	54.0	NA	45.0	100	37.5	2.5	5.0	7.5	5.0	
	LCAHR	40	≤8	10/28/2	71.0	49.0	40.0		70.0	58.0	53.0		15.0	80.0	27.5	2.5	5.0	7.5	2.5	
Ye HX (2006) <sup>49</sup>	LCAHR+CT	40	≤8	12/18/10	82.5	67.5	57.5	NA	75.0	70.0	65.0	NA	NA	75.0	85.0	NA	NA	NA	NA	
	LCAHR	40	≤8	14/18/8	70.0	52.5	40.0		67.5	60.0	52.5			50.0	27.5					
	LCAHR+CT	94	<9	35/57/2	84.0	65.0	52.0	NA	83.0	73.0	65.0	NA	44.7	64.9	44.7	NA	NA	NA	NA	
	LCAHR	89	<9	29/58/2	74.0	53.0	41.0		73.0	55.0	49.0		18.0	53.9	33.7					
Zhu ZS (2006) <sup>51</sup>	LCAHR+CT	38	≤10	15/18/5	73.7	NA	NA	NA	68.4	NA	NA	NA	42.1	89.5	36.8	NA	NA	NA	NA	
	LCAHR	34	≤10	15/15/4	55.9				50.0				14.7	73.5	26.5					

Cm, Centimetre; EP, Esophageal perforation; ES, Esophageal stenosis; GIR, Gastroenterological Reaction including nausea and vomit; H, Haemorrhage; LCAHR, Late course accelerated hyperfractionation radiotherapy; CT, Chemotherapy; LF, Lung fibrosis; NA, not recorded or available; RB, Radiation bronchitis including chest pain, dry cough, even dyspnoea *et al.*; RE, Radiation esophagitis including chest pain and dysphagia *et al.*

**Table 3** The risk of bias in included studies

Study [Year, Reference]	Quality Assessment					
	Rand. Seq. Gen†	All. Con‡	Blind. Part§	Blind. out¶	Incompt††	Free of select‡‡
LCAHR versus CFR	—	—	—	—	—	—
Han C (1997) <sup>26</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Sheng XF (1998) <sup>27</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Guo JQ (1998) <sup>28</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Shi XH (1999) <sup>14</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhang KL (2000) <sup>29</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Jiang JD (2001) <sup>30</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhou XF (2002) <sup>31</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Li AE (2002) <sup>32</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Liu YC (2003) <sup>33</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Cheng GH (2003) <sup>34</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Yang LQ (2003) <sup>35</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Wang JZ (2004) <sup>36</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Qiao XY (2004) <sup>37</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Hu LH (2005) <sup>38</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Li XM (2003) <sup>39</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang TJ (2006) <sup>40</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Wang MM (2007) <sup>41</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhang Q (2007) <sup>42</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
LCAHR+CT versus LCAHR	—	—	—	—	—	—
Gao XS (2002) <sup>15</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Zhou SB (2003) <sup>43</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Duan YJ (2003) <sup>44</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Cheng HH (2003) <sup>45</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Li XM (2003) <sup>39</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Wu JT (2003) <sup>46</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Ren BZ (2004) <sup>47</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhao KL (2005) <sup>16</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Chen GR (2005) <sup>48</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang TJ (2006) <sup>40</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Ye HX (2006) <sup>49</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhang H (2006) <sup>50</sup>	Yes	Unclear	Yes	Yes	Yes	Yes
Zhu ZS (2006) <sup>51</sup>	Unclear	Unclear	Yes	Yes	Yes	Yes

† = random sequence generation; ‡ = allocation concealment; § = Blinding of participants and personnel; ¶ = Blinding of outcome assessment. †† = Incomplete outcome data; ‡‡ = Free of selective reporting. "Yes" indicated low risk of bias, "No" indicated high risk of bias. CFR, conventional fractionated radiotherapy; CT, Chemotherapy; LCAHR, Late course accelerated hyperfractionation radiotherapy.

improved one-year, two year, three-year, and five-year local control compared with CFR ( $P = 0.0001$ ). (Table 4)

### Acute toxicities and late toxicities

We identified five trials<sup>26,34,35,39,40</sup> with outcome measurements of gastroenterological reaction; 15 trials<sup>14,26–30,32–40</sup> with radiation esophagitis; 12 trials<sup>14,28–33,36,38–41</sup> with radiation bronchitis; five trials<sup>14,37–40</sup> with esophageal perforation; six trials<sup>14,27,28,38–40</sup> with hemorrhage; five trials<sup>14,29,38–40</sup> with esophageal stenosis; and two trials<sup>39,40</sup> with lung fibrosis. The fixed-effects model was used, as there was no intertribal heterogeneity of the results of trials. LCAHR significantly increased acute toxicities ( $P = 0.0001$ ), rather than gastroenterological reaction ( $P = 0.24$ ) and late toxicities (esophageal perforation,  $P = 0.83$ ; hemorrhage,  $P = 0.24$ ; esophageal

stenosis,  $P = 0.30$ ; lung fibrosis,  $P = 0.62$ , respectively), compared with CFR. (Table 4)

### LCAHR plus CT versus LCAHR alone

#### Survival

We identified 13 trials<sup>15,16,39,40,43–51</sup> with outcome measurements of one-year survival; 10 trials<sup>15,39,40,43–47,49,50</sup> with two-year survival; 11 trials<sup>15,16,39,40,43,44,46–50</sup> with three-year survival; and three trials<sup>15,39,48</sup> with five-year survival. The fixed-effects model was used, as there was no intertribal heterogeneity of the results of trials. LCAHR plus CT significantly improved survival (one-year,  $P = 0.002$ ; two-year,  $P = 0.0001$ ; three-year,  $P = 0.0001$ ; five-year,  $P = 0.045$ ), compared with LCAHR alone. (Table 5)

**Table 4** Late course accelerated hyperfractionation radiotherapy versus conventional fractionated radiotherapy for locally advanced esophageal squamous cell carcinoma: a meta-analysis of survivals, local controls, acute toxicities, and late toxicities

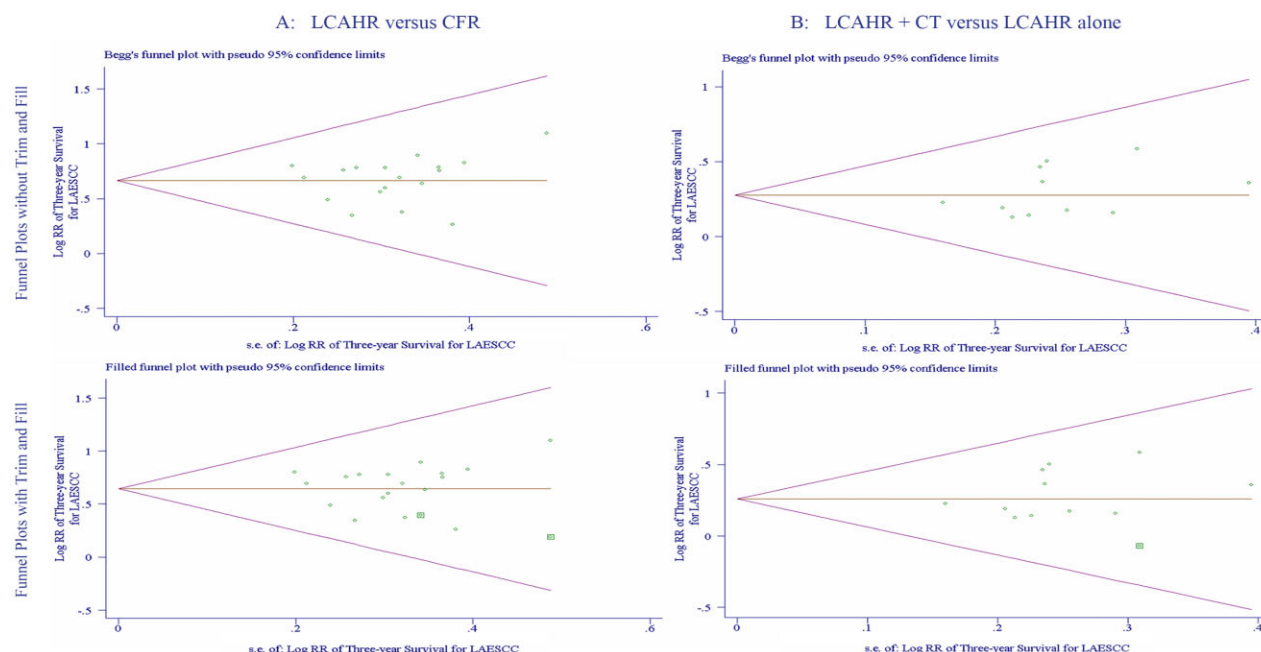
End points	No. of Studies	No. of Patients	RR	Significance		Publication Bias (BT)		Heterogeneity	
				Z	P	Z	P	$\chi^2$	I <sup>2</sup> (%)
Survivals	—	—	—	—	—	—	—	—	—
One-year survival	18	1953	1.30	8.42	P = 0.0001	1.17	P = 0.24	24.34	P = 0.11
Two-year survival	12	1153	1.50	6.18	P = 0.0001	2.47	P = 0.01	9.21	P = 0.60
Three-year survival	18	1953	1.95	9.66	P = 0.0001	0.57	P = 0.57	6.62	P = 0.99
Five-year survival	10	1196	2.24	6.48	P = 0.0001	-0.45	P = 0.66	5.98	P = 0.74
Local controls	—	—	—	—	—	—	—	—	—
One-year local control	12	1205	1.41	5.13	P = 0.0001	2.33	P = 0.02	24.48	P = 0.01
Two-year local control	11	1053	1.72	8.40	P = 0.0001	1.32	P = 0.19	4.08	P = 0.94
Three-year local control	12	1205	2.17	9.77	P = 0.0001	-1.03	P = 0.30	7.33	P = 0.77
Five-year local control	4	483	2.50	5.86	P = 0.0001	—	—	2.30	P = 0.51
Acute and late toxicities	—	—	—	—	—	—	—	—	—
Gastroenterological reaction	5	442	1.19	1.18	P = 0.24	—	—	1.38	P = 0.85
Radiation esophagitis	15	1555	1.50	6.81	P = 0.0001	1.04	P = 0.30	13.38	P = 0.50
Radiation bronchitis	12	1407	1.74	5.31	P = 0.0001	0.96	P = 0.34	10.85	P = 0.46
Esophageal perforation	5	501	1.12	0.22	P = 0.83	—	—	1.23	P = 0.87
Haemorrhage	6	566	1.75	1.17	P = 0.24	—	—	1.93	P = 0.86
Esophageal stenosis	5	500	1.56	1.05	P = 0.30	—	—	1.64	P = 0.80
Lung fibrosis	2	180	1.67	0.50	P = 0.62	—	—	0.27	P = 0.61

BT, Begg's test; CI, Confidence interval; RR, Relative risk.

**Table 5** Late course accelerated hyperfractionation radiotherapy plus chemotherapy versus late course accelerated hyperfractionation radiotherapy alone for locally advanced esophageal squamous cell carcinoma: a meta-analysis of survival, local control, acute toxicities, and late toxicities

End points	No. of Studies	No. of Patients	RR	Significance		Publication Bias (BT)		Heterogeneity	
				Z	P	Z	P	$\chi^2$	I <sup>2</sup> (%)
Survival	—	—	—	—	—	—	—	—	—
One-year survival	13	1234	1.11	3.15	P = 0.002	0.49	P = 0.63	8.95	P = 0.71
Two-year survival	10	1011	1.24	4.14	P = 0.0001	-0.27	P = 0.79	1.60	P = 1.00
Three-year survival	11	1062	1.32	3.97	P = 0.0001	1.48	P = 0.14	4.15	P = 0.94
Five-year survival	3	281	1.46	2.00	P = 0.045	—	—	2.20	P = 0.33
Local control	—	—	—	—	—	—	—	—	—
One-year local control	10	1000	1.12	3.25	P = 0.001	1.70	P = 0.09	5.21	P = 0.82
Two-year local control	8	817	1.27	4.39	P = 0.0001	0	P = 1.00	5.21	P = 0.63
Three-year local control	8	828	1.27	3.91	P = 0.0001	0.49	P = 0.62	4.06	P = 0.77
Five-year local control	2	211	1.05	0.41	P = 0.69	—	—	0.38	P = 0.54
Acute and late toxicities	—	—	—	—	—	—	—	—	—
Gastroenterological reaction	7	744	2.22	3.27	P = 0.001	—	—	38.53	P = 0.0001
Radiation esophagitis	12	1116	1.18	4.21	P = 0.0001	-1.10	P = 0.27	16.33	P = 0.13
Radiation bronchitis	8	809	1.51	4.29	P = 0.0001	1.48	P = 0.14	8.99	P = 0.25
Esophageal perforation	2	180	1.00	0	P = 1.00	—	—	0	P = 1.00
Haemorrhage	2	180	1.00	0	P = 1.00	—	—	0.09	P = 0.76
Esophageal stenosis	4	389	0.83	0.52	P = 0.60	—	—	1.71	P = 0.64
Lung fibrosis	4	389	0.86	0.37	P = 0.71	—	—	1.73	P = 0.63

CI, Confidence interval; RR, Relative risk.



**Figure 1** Funnel plots with and without Trim and Fill. (○ = Identified studies; □ = Estimated missing studies after adjustment for publication bias).

### Local control

We identified 10 trials<sup>15,16,39,40,44,45,47,49–51</sup> with outcome measurements of one-year local control; eight trials<sup>16,39,40,44,45,47,49,50</sup> with two-year local control; eight trials<sup>15,16,39,40,44,47,49,50</sup> with three-year local control; and two trials<sup>15,39</sup> with five-year local control. The fixed-effects model was used, as there was no intertribal heterogeneity of the results of trials. LCAHR plus CT significantly improved local control at one-year ( $P = 0.001$ ), two-year ( $P = 0.0001$ ), and three-year ( $P = 0.0001$ ), with the exception of five-year ( $P = 0.69$ ), compared with LCAHR alone. (Table 5)

### Acute toxicities and late toxicities

We identified seven trials<sup>15,39,40,45,47,50,51</sup> with outcome measurements of gastroenterological reaction; 12 trials<sup>15,16,39,40,44–51</sup> with radiation esophagitis; eight trials<sup>15,39,40,44,47,49–51</sup> with radiation bronchitis; two trials<sup>39,40</sup> with esophageal perforation and hemorrhage, respectively; and four trials<sup>15,39,40,47</sup> with esophageal stenosis and lung fibrosis, respectively. The fixed-effects model was used, as there was no intertribal heterogeneity of the results of trials, with the exception of gastroenterological reaction. LCAHR plus CT significantly increased acute toxicities (gastroenterological reaction,  $P = 0.001$ ; radiation esophagitis,  $P = 0.0001$ ; radiation bronchitis,  $P = 0.0001$ , respectively), rather than late toxicities (esophageal perforation,  $P = 1.00$ ; hemorrhage,  $P = 1.00$ ; esophageal stenosis,  $P = 0.60$ ; lung fibrosis,  $P = 0.71$ , respectively), compared with LCAHR alone. (Table 5)

### Publication bias

Review of funnel plots could not rule out the potential for publication bias for either analysis. Publication bias was not evident when the Begg rank correlation method ( $P = 0.57$  for three-year survival in LCAHR versus CFR, and  $P = 0.14$  for three-year survival in LCAHR plus CT versus LCAHR alone) and Egger's Weighted regression method ( $P = 0.79$  for three-year survival in LCAHR versus CFR, and  $P = 0.27$  for three-year survival in LCAHR plus CT versus LCAHR alone), were used. (Fig. 1)

### Sensitivity analysis

A sensitivity analysis was performed to explore the influence of trial quality on the statistical effect size. We undertook a sensitivity analysis using the trim and filled method,<sup>52</sup> which conservatively imputes hypothetical negative unpublished studies to the positive studies that cause funnel plot asymmetry. The pooled RR and 95% CI incorporating the hypothetical studies continued to show statistical significance at three-year survival (RR = 1.90; 95% CI 1.67–2.17;  $P = 0.0001$ ) for LCAHR versus CFR and (RR = 1.29; 95% CI 1.13–1.48;  $P = 0.0001$ ) for LCAHR plus CT versus LCAHR alone.

### Discussion

In the current study, LCAHR was shown to significantly improve survival and local control, compared with CFR. We also demonstrated a survival and local control advantage for

LCAHR plus CT over LCAHR alone, with the exception of five-year local control, which may be related to the smaller sample size; however, a similar trend of five-year local control was noted in LCAHR plus CT. Importantly, LCAHR with or without CT did not increase late toxicities, with the exception of acute toxicities.

Concurrent CRT is recommended as the non-surgical treatment of choice for EC in Western countries, which has resulted in a two-year local control rate of 55% and a five-year survival rate of 25%.<sup>53</sup> Historically, attempts to improve the survival rate of patients with EC have included increased radiation doses and intensification of chemotherapy, based on the series of RTOG studies, but the outcomes were uniformly disappointing. The RTOG 85-01 trial reported the rate of local recurrences to be as high as 45% without improvement in survival outcome.<sup>9</sup> Subsequently, an insignificant difference in local control and overall survival was found between the group treated with intensified chemotherapy and a higher radiation dose, compared with the standard group, demonstrated in the RTOG 90-12,<sup>54</sup> prospective RTOG 92-07,<sup>55</sup> and randomized RTOG 94-05 studies.<sup>6</sup> These results could imply that the larger radiation volume may have offset the benefit of a higher radiation dose and resulted in greater acute radiation toxicities and prolonged overall radiation time.

In order to improve the prognosis of patients with EC, development of novel radiation therapeutic strategies have been adopted in different countries.<sup>56–58</sup> In China, EC has unique geographical and pathologic features, with the morbidity and mortality relatively high, and squamous cell carcinoma as the major pathologic type, which are different factors compared with Western countries.<sup>59</sup> Supportive therapy in China is not comparable with those used for Western patients as a result of economic issues. These differences, together with racial difference, make it unclear whether the National Comprehensive Cancer Network (NCCN) would recommend the same therapy for Chinese patients.

Fortunately, the development of radiobiology and radiation physics, enables us to have a comprehensive understanding of the accelerated repopulation of tumor clonogenes during the course of RT. Withers HR and colleagues observed that with shorter total treatment times, an increase in local control has been demonstrated in head and neck cancer, and speculated that clonogen repopulation in squamous cell carcinoma accelerates only after a lag period of the order of  $4 \pm 1$  weeks after the initiation of RT.<sup>60</sup> Subsequently, this phenomenon was also found in esophageal cancer.<sup>61</sup> Laing *et al.*<sup>62</sup> have reported that human esophageal cancer has a median potential doubling time (Tpot) of 5.2 days. Furthermore, several previous studies were consistent with the results of our outcomes, which showed that LCAHR can improve survival and local control compared to CFR.<sup>63,64</sup> It is presumed that these reasons may improve the efficacy of LCAHR

according to linear quadratic (LQ) theory. First, with a decrease in fractionated doses, total doses increased, as did the radiation tolerance of late reactions; the demand for oxygen was reduced, thereby, the elimination of hypoxic tumor cells increased. Second, radiation twice a day prompts the cell from the insensitive phase into the sensitive phase by cell cycle distribution, which is conducive to secondary tumor cell destruction. Third, the reparatory capacity of radiation injury of normal tissues is better than for tumor cells, therefore, the opportunity of repair increased with the increase in exposition.<sup>65</sup>

As to why LCAHR plus CT can improve the local control and survival rate compared to LCAHR alone, the mechanisms of how CT and RT interact to improve outcomes has been extensively studied in several ways. RT may primarily control local disease, while CT may address disease outside the RT area. CT may target radioresistant cell populations such as hypoxic cells. RT and CT may synergistically enhance one another's effects on a molecular level.<sup>4</sup> CT may blunt the increased tumor proliferation that may occur late in the course of radiation,<sup>66</sup> and there may be a simple additive effect.

With regards to the toxicities, the comparative analysis showed that the acute toxicities were significantly increased in the LCAHR with/without CT groups, but they were within tolerance and all patients completed the whole course of treatment without any cessations. It is noteworthy that the ranges of acute toxicity rates seem to be quite different; the possible reasons for this include novel radiation strategy, as well as individual differences in patients in these studies. On the contrary, late toxicities remained at relatively stable levels. Overall, these results indicated that LCAHR increased acute toxicities to a certain extent, but did not increase late toxicities.

## Limitations

This study has potential weaknesses that may impact on the possibility of drawing meaningful conclusions. First, as mentioned above, there were some trials that did not provide information on random sequence generation. And there was indeed some heterogeneity among trials, which shows the weakness of the materials. Despite the fact that we cannot demonstrate which factors account for the differences according to current data, we can apply random effects models to perform the meta-analysis, because the use of random effects model to calculate CIs results in wider intervals and is thus a more conservative estimate of treatment effects, compared with a fixed effects model. Second, we cannot determine the efficacy and safety of LCAHR plus CT compared to CFR plus CT because there were no cases reported in the literature, therefore, this contention also needs further investigation.

## Conclusion

In conclusion, LCAHR with or without CT resulted in worse acute toxicities than any other form of treatment, however the response and survival rates were very encouraging. Considering all of the drawbacks related to these literature-based meta-analyses, credible evidence has been presented that the administration of LCAHR is worthy of additional study. Therefore, rigorously designed, multi-center, large, randomized, double blind, controlled trials are required.

## Acknowledgements

We wish to thank Yao-Li Cui, MD, PhD, Intensive Care Unit, Tianjin First Center Hospital, for his contribution to the manuscript. We also wish to thank the anonymous referee for his/her very helpful comments, which significantly improved the quality of this paper.

## Disclosure

No authors report any conflict of interest.

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## Supporting information

Additional supporting information may be found in the online version of this article.

**Table S1.** Technical features for treatment of locally advanced esophageal squamous cell carcinoma.