Radiotherapy and Oncology 137 (2019) 186–191

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

A prospective, three-arm, randomized trial of EGCG for preventing radiation-induced esophagitis in lung cancer patients receiving radiotherapy

Hanxi Zhao [a], Li Jia [b], Guanxuan Chen [c], Xiaolin Li [a], Xiangjiao Meng [a], Xianguang Zhao [a], Ligang Xing [a,*], Wanqi Zhu [a,*]

[a] Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University; [b] Department of Radiation Oncology, Jinan Fourth People's Hospital; and [c] Shandong Key Laboratory of Radiation Oncology, Jinan, China

ARTICLE INFO

Article history:
Received 1 August 2018
Received in revised form 9 February 2019
Accepted 27 February 2019
Available online 19 March 2019

Keywords:
EGCG
Lung cancer
Acute radiation-induced esophagitis

ABSTRACT

Background and purpose: This trial investigated whether epigallocatechin-3-gallate (EGCG), a radioprotector, could be effective in the prevention and treatment of acute radiation-induced esophagitis (ARIE).
Methods and materials: This is a phase II study of EGCG combined with chemoradiation in unresectable stage III non-small-cell lung cancer or limited stage small cell lung cancer. Patients were randomized into a prophylactic EGCG group (arm A), a therapeutic EGCG group after the occurrence of esophagitis (arm B) or conventional therapy group (arm C). Esophagitis grades, pain and dysphagia scores were recorded weekly. Adjusted esophagitis index (AEI), pain index (API) and dysphagia index (ADI) were calculated to reflect changes in esophagitis grade, pain score and dysphagia score throughout treatment.
Results: A total of 83 patients were eligible for toxicity analysis (arm A vs arm B vs arm C: $N = 28:27:28$). There was no significant difference in the baseline characteristics among three arms of the patients. The difference in the maximum esophagitis grade among three groups was statistically significant ($P = 0.004$). The maximum ARIE for patients with EGCG was significantly lower than for those with conventional therapy. The mean AEI of arm A was lower than that of arm B, while the mean AEI of arm C was the highest (arm A vs arm B, $P = 0.028$; arm B vs arm C, $P = 0.002$). Furthermore, API and ADI were significantly lower in patients receiving EGCG than in conventionally treated patients.
Conclusion: The application of EGCG could effectively alleviate acute radiation esophagitis in advanced lung cancer without obvious side effects. Prophylactic application of EGCG had a slight advantage over therapeutic use in treatment of acute esophagitis.
 Radiotherapy and Oncology 137 (2019) 186–191

Lung cancer (LC), as one of the most common malignant tumors, is the leading cause of cancer-related deaths worldwide [1]. Most patients are diagnosed with locally advanced disease and require sequential or concurrent chemoradiotherapy (CRT) [2]. However, a combination therapy often causes severe adverse events leading to prolonged treatment, unplanned treatment interruptions or ineffective doses. Acute radiation-induced esophagitis (ARIE) is a major non-hematologic toxicity of chemoradiotherapy in patients with stage III non-small cell lung cancer (NSCLC) or limited stage small cell lung cancer (LD-SCLC). ARIE compromises the quality of life of patients and affects the efficacy of anticancer treatment [3]. Indeed, severe ARIE is closely associated with the radiation dose received by a certain volume of esophagus [4]. Novel radiation techniques, such as intensity modulated radiotherapy, are used to prevent ARIE by excluding the esophagus from the radiation field. This approach is often not feasible when the esophagus is located close to the involved lymph nodes in the mediastinum.

The drugs including adrenocorticotropic hormone and certain antibiotics, such as a mixture of lidocaine, dexamethasone and gentamycin (mLDG), are the main treatments used for ARIE in China [5], although the effectiveness of mLDG has not been confirmed in clinical trials. Particular attention has been paid to the development of radioprotective agents, which are capable of preserving normal tissues without compromising anti-tumor effect [6]. EGCG has been extensively investigated in order to ameliorate radiation-induced damage [7–10]. An experiment showed that EGCG exerted protective effects against radiation-induced normal cell death in vitro [7]. It had the ability to scavenge superoxide anion, hydroxyl radical and hydrogen peroxide. In addition, EGCG

* Corresponding authors.
E-mail addresses: xinglg@medmail.com.cn (L. Xing), wanqi5145@126.com (W. Zhu).

https://doi.org/10.1016/j.radonc.2019.02.022
0167-8140/

was also able to intercalate into the DNA, protecting against radiation-induced DNA strand breaks [8].

Our previous phase I study preliminarily showed oral administration of EGCG was feasible and safe in patients with locally advanced lung cancer receiving radiotherapy [11]. The recommended concentration was 440 μmol/L. A prospective, single-arm, phase II study was subsequently conducted to assess the effectiveness and safety of EGCG in addressing ARIE [12]. Then, we launched this prospective randomized controlled study to clinically validate the preventive and therapeutic value of EGCG in patients with ARIE.

Material and methods

This was a 3-arm, prospective, randomized, controlled clinical study designed to assess the efficacy of EGCG in the prevention and treatment of ARIE in patients receiving sequential or concurrent chemoradiotherapy. The research design was approved by the local study review and its registration number was NCT02577393 (www.clinicaltrials.gov). And an informed consent was obtained from all the subjects.

Patients

Eligible patients were required to meet the following inclusion criteria: pathologically documented LC; considered medically inoperable stage IIIA or stage IIIB or limited stage small cell lung cancer; age ≥18 years; Karnofsky's score ≥70; adequate hematologic, hepatic and renal function; FEV1 >800 cc; mean esophagus dose >20 Gy. Exclusion criteria were as follows: a known allergy or hypersensitivity to EGCG; pregnancy or lactation; prior radiation to the thorax [11,12].

Experimental dataset

All patients underwent three-dimensional conformal radiotherapy or intensity modulation radiation therapy. A repeat-fixation mask or vacuum bag was used for the CT-simulation scan. Eclipse treatment planning system® (Eclipse 8.6, Varian Medical Systems) was used for radiotherapy (RT) planning. Planning target volume included gross tumor volume and margins of 0.5–1.5 cm for metastatic regional lymph nodes, 0.8–1.5 cm for primary tumor. The total radiation dose was 50–66 Gy (1.8–2 Gy fractions once daily) or 45 Gy (1.5 Gy twice daily) for 5 days per week. The prescribed target dose was prescribed to the isocenter with a minimum target dose of 95% and a maximum dose of 107% covering 95% of PTV. For the purpose of consistency, the tissues were contoured by a team consisting of three radiation oncologist in all patients. The entire esophagus was identified and contoured on each axial plane of the planning CT scan from the inferior border of the cricoid cartilage to the gastroesophageal junction. The radiation dose limits were exactly the same as before: mean lung dose ≤18 Gy, the maximum spinal cord ≤50 Gy, total heart ≤35 Gy.

Study design and treatment

EGCG (440 μmol/L, purity ≥95% by HPLC; from NINGBO HEP Biotech Co., Ltd) or mLDG (lidocaine 0.16 mg/mL, dexamethasone 0.02 mg/mL, and gentamycin 0.16 mg/mL) dissolved in 0.9% saline solution was administered three times a day. For applications, repeated swallowing of 10 ml of the two solutions was indispensable to assure the prolonged presence of drug in the esophageal wall.

At registration, patients were randomly allocated (1:1:1) to one of the three arms through a sealed envelope system and were unaware of the treatment given. In arm A, patients received EGCG solution orally from the start of radiotherapy. Patients in arm B or C were given oral EGCG or mLDG solution respectively, and began medications as soon as grade I esophagitis occurred during radiation. The grading definition of ARIE in the Radiation Therapy Oncology Group (RTOG) scoring system was also listed in Supplementary Table S1 [13]. Three groups of patients all discontinued oral liquid preparations until two weeks after the completion of radiotherapy. Fig. 1 showed an overview of the study design.

RT was not interrupted unless persistent or worsening dysphagia was present after therapy. Other treatments were not performed until grade 4 esophagitis occurrence or radiotherapy suspension. In case of unresponsive to therapy and RT interruption, patients were supported with methylprednisolone, analgesics, antifungal therapy, or intravenous infusion as appropriate until recovery. The nasogastric or nasoduodenal tube was an option for non-responders with grade 4 toxicity lasting for at least 3 days.

Esophagitis assessment

From the beginning of the radiation treatment to two weeks after the end of radiotherapy, esophageal toxicity was measured every week according to the RTOG scoring system. Symptoms

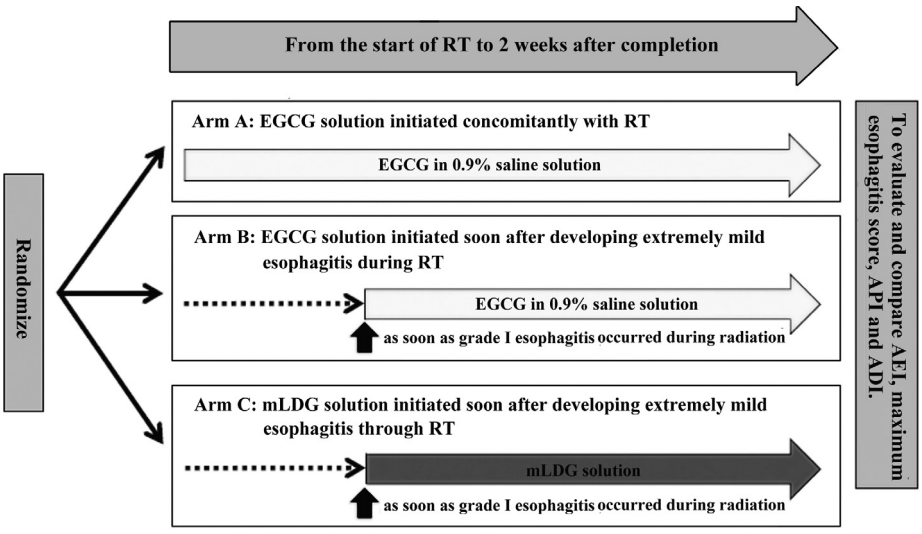

Fig. 1. An overview of the study design.

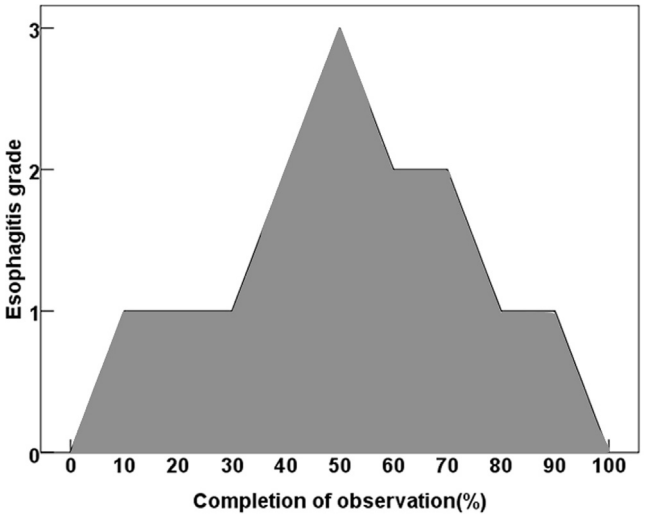

Fig. 2. Calculations of adjust esophagitis index (AEI), adjust pain index (API) and dysphagia index (ADI). The area under the curve was calculated for each patient's graph using the trapezoidal method. For example, a patient went through the changes of esophagitis over the course of trial and AEI = (0 + 1)/2 + (1 + 1)/2 * 2 + (1 + 3)/2 * 2 + (3 + 2)/2 + (2 + 2)/2 + (2 + 1)/2 + (1 + 1)/2 + (1 + 0)/2.

related to esophagitis were also measured using the numerical rating scale (NRS) weekly, including pain and dysphagia.

Esophagitis index (EI) was referred to assess therapeutic efficacy [14,15]. Esophagitis grades for each observation time point were plotted on a graph against time. Due to the different duration of individual treatment, we took a conversion method of one-percentage-mark system. The area under the curve was calculated for each patient's graph using the trapezoidal method and was defined as an adjust esophagitis index (AEI) for an example in Fig. 2. The AEI was designed to account for not only the maximum grade, but also the duration of esophagitis. The same statistical method was also used to calculate the adjusted pain index (API) and the dysphagia index (ADI) based on the NRS scores for pain and dysphagia.

A medical team consisting of two experienced physicians, unaware of the patient's clinical history and treatment allocation, conducted the routine esophagitis assessment to avoid subjective bias.

Endpoints

The primary endpoint was to evaluate the relative efficacy of EGCG to improve esophagitis grade over time during lung cancer radiotherapy compared to routine regimens. Secondary endpoints included maximum esophagitis score, API and ADI.

Statistical methods

Based on our previous experience and other documentation, the expected number of patients with AEI was estimated [15–17]. The study compared the treatment groups (arm A or B) with the control arm (arm C). Assuming a mean AEI of 5 (standard deviation = 4) in treatment groups and 10 (standard deviation = 10.5) in control arm [17], the required sample size would be 25 patients in each arm with 80% statistical power and a two-sided 5% type 1 error rate. Assuming a 10% attrition rate, a total of 83 patients would be required.

Measurement data of the different groups were expressed as mean ± standard deviation and analyzed by *t*-test. Pearson's exact tests were used for categorical variables. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL).

Result

Patient characteristics

The study was launched in April 2015 and closed in April 2018, after eighty-three consecutive patients were enrolled. The characteristics of fully eligible patients were similar in the three arms (Table 1). There are no significant differences in esophagus irradiation doses among three arms. The median age was 60 years ranging from 40 to 75. 81% of patients were male and 41% received concurrent chemoradiotherapy. The esophageal dosimetric parameters of all patients were as follows: the mean value was 31.02 ± 0.73 Gy; the maximum value was 64.36 ± 0.40 Gy; V30, V35 and V50 (percentage volume of esophagus receiving a specified dose in 30 Gy, 35 Gy and 50 Gy) was 52.24 ± 0.11, 49.10 ± 0.11 and 38.43 ± 0.12, respectively.

Treatment delivery

98.8% of patients who completed treatment were per protocol or with an acceptable deviation. Three patients gave up treatment during radiotherapy for bacterial pneumonia (arm A), mycotic infection (arm C) and medical insurance (arm C). Grade 4 neutropenia ($n = 1$) was observed only in arm B with 3 days continuous interruption of radiation. Grade 4 or 5 hematologic toxicity was not observed including anemia, thrombocytopenia and blood infection. Grade 3 non-hematologic adverse events were vomiting (seen in 5 patients) and gastrointestinal toxicity (seen in 4 patients), both of which were related to the chemotherapy. The above adverse reactions were no considered possibly, probably, or definitely related to EGCG or mLDG. Only Grade 1 nausea in one patient was considered to have a possible relationship with EGCG disagreeable taste, and gradually disappeared one week after continued medication. No other adverse effects to EGCG were noted.

Acute esophagitis

The primary objective of the study was to determine if EGCG was more effective in preventing or reducing ARIE than conventional therapy. This early radiation toxicity occurred during the third week (rang, 1–7 weeks) in most patients, and 5 patients had no ARIE. And the mean duration of treatment with EGCG or mLDG in arm A–C was 8.26 ± 0.66, 6.48 ± 0.94 and 6.27 ± 0.96, respectively. The distribution of maximum acute esophagitis grade in each treatment group was presented in Table 2. No patients had grade 4 esophagitis. The difference among the three groups was statistically significant ($P = 0.004$). Although no statistical difference in esophagitis was observed between arm A (prophylactic application) and arm B (therapeutic application), the maximum ARIE for patients with EGCG application (arm A + B) was significantly lower than that for patients with conventional therapy (arm C) ($P = 0.054$; $P = 0.036$).

The mean AEI of patients in arm A-C was 3.56 ± 2.90, 5.19 ± 2.73 and 7.46 ± 1.88, respectively. Moreover, differences were statistically apparent in the following pairwise comparisons: arm A + arm B vs arm C $P < 0.001$; arm A vs arm C, $P < 0.001$; arm B vs arm C, $P = 0.002$; arm A vs arm B, $P = 0.028$. The mean API for patients in arm C was 16.38 ± 4.45; for patients in arm A + arm B, 7.19 ± 5.07 (when compared with arm C, $P < 0.001$); for patients in arm A, 6.59 ± 6.03 (when compared with arm C, $P < 0.001$); and for patients in arm B, 7.78 ± 3.92 (when compared with arm C, $P < 0.001$). The one-way analysis of variance also revealed a statistically significant difference in ADI among arm A-C. The mean ADI of arm A + arm B, arm A, arm B to arm C was 2.07 ± 2.34, 1.41 ± 2.08, 2.74 ± 2.43 and 5.00 ± 3.03 in turn. The ADI of the two groups using EGCG was lower than that of the conventional

Table 1
Pretreatment characteristics.

Characteristic	Arm A (n = 28)	Arm B (n = 27)	Arm C (n = 28)	P
Age (years)				
Mean ± SD	59.32 ± 7.98	58.63 ± 9.46	59.05 ± 8.68	0.954
Sex (n)				
Male	25	22	20	
Female	3	5	8	0.236
KPS score (n)				
70	1	0	0	
80	10	11	13	
90	16	16	15	
100	1	0	0	0.837
Smoking index (years * root)				
Mean ± SD	700.00 ± 614.03	551.85 ± 559.79	578.57 ± 545.25	0.594
Stage (n)				
IIIA	6	6	10	
IIIB	22	21	18	0.398
Pathology (n)				
Squamous	13	4	6	
Adenocarcinoma	3	9	9	
Small cell cancer	12	14	13	0.053
Total dose (Gy)				
Mean ± SD	58.80 ± 3.48	58.17 ± 3.31	58.12 ± 3.55	0.716
Treatment scheme (n)				
Concomitant CRT	14	17	18	
Sequential CRT	14	10	10	0.488
Dose of esophagus				
Mean value (Gy)				
Mean ± SD	29.30 ± 7.02	32.11 ± 6.94	31.70 ± 5.92	0.239
Maximum value (Gy)				
Mean ± SD	64.70 ± 3.75	64.43 ± 3.78	63.94 ± 3.60	
V30 value (%)				0.742
Mean ± SD	49.13 ± 0.13	54.79 ± 0.11	53.29 ± 0.10	
V35 value (%)				0.163
Mean ± SD	45.91 ± 0.13	51.37 ± 0.11	50.11 ± 0.10	0.175
V50 value (%)				
Mean ± SD	35.29 ± 0.10	40.86 ± 0.13	39.23 ± 0.11	0.194

Table 2
Distribution of maximum acute radiation-induced esophagitis grade and tumor response by treatment group.

	arm A	arm B	arm C	Total	P value
Maximum acute radiation-induced esophagitis grade					
0	5(19%)	0(0%)	0(0%)	5(6%)	
1	18(67%)	24(89%)	17(65%)	59(74%)	
2	4(15%)	3(11%)	8(31%)	15(19%)	
3	0(0%)	0(0%)	1(4%)	1(1%)	P = 0.004
Response					
Complete response	2(7%)	2(7%)	1(4%)	5(6%)	
Partial response	19(70%)	20(74%)	19(73%)	58(73%)	
Stable disease	3(11%)	2(7%)	3(12%)	8(10%)	
Progressive disease	3(11%)	3(11%)	3(12%)	9(11%)	
Overall response	21(78%)	22(81%)	20(77%)	63(79%)	P = 0.998

treatment group (arm A + arm B vs arm C, $P < 0.001$; arm A vs arm C, $P < 0.001$; arm B vs arm C, $P = 0.002$). However, no statistical difference was observed between arm A and arm B in API or ADI ($P = 0.375$ or $P = 0.057$). Fig. 3 showed the detailed distribution of maximum esophagitis grades, pain score and dysphagia score for the different treatment groups during the course.

Response rates

Three patients who terminated protocol treatment were excluded from the analysis owing to unevaluable response. Overall, 78% of patients had an objective response at computed tomography (CT) evaluation within three weeks after completing study treatment (Table 2). There was no significant difference in response rates among the three groups.

Discussion

Although most studies showed concurrent chemoradiotherapy or higher radiation doses or hyperfractionation schemes could prolong the survival of patients with lung cancer, better outcomes were accompanied by an increase in the incidence of ARIE [18–20]. Continuous improvements in treatment planning and techniques were used to reduce radiation toxicity. The 3DCT planning enabled investigators to minimize esophageal dose–volume

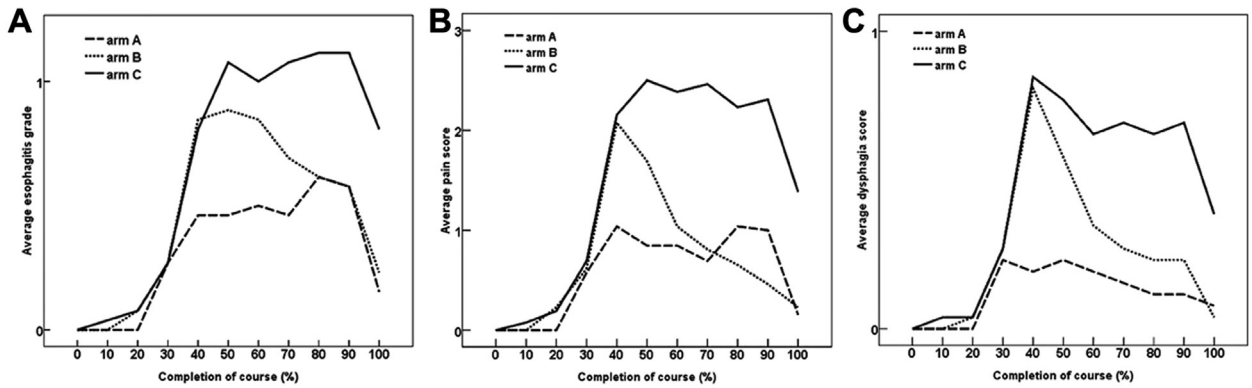

Fig. 3. The detailed distribution of maximum esophagitis grades, pain score and dysphagia score in different treatment groups during the course. arm A: patients received EGCG from the start of radiotherapy to two weeks after the end of radiotherapy; arm B: patients received EGCG from initiated soon after developing mild esophagitis to two weeks after the end of radiotherapy; arm C: patients received mLDG from immediately after the documentation of developing mild esophagitis to two weeks after the end of radiotherapy. Panels A–C show esophagitis grades, pain score and dysphagia score over time according to trial schedule.

histogram (DVH) parameters associated with esophagitis, such as mean esophagus dose and V50 [21–22]. With the advent of novel technologies such as intensity modulated radiation therapy, 4DCT, gating and image guided radiation therapy, studies focused on how to deliver lethal doses to cancer while reducing treatment-related toxicity. However, ARIE was still inevitable due to the physical properties of X-rays and the genetic susceptibility of patients [23]. In the meta-analyses and prospective trials, the incidence of grade 3–4 acute esophagitis caused by concurrent chemoradiotherapy was usually about 20–30% [24–26]. The proportion of high-grade esophagitis was lower in our study, even in the mLDG-treated group. This was probably an effect of efficacity of supportive care. Other possible explanations might not be excluded, such as the presence of sequential CRT, novel radiation technologies, the differences in chemotherapy regimens, the small sample sizes and the low total doses.

Radiation protective chemical/biological agents were applied as the other main method for the prevention and treatment of ARIE. Radiation protectants, including sulfhydryl compounds, nitroxides, antioxidant compounds and non-antioxidant radioprotectors, had been tried orally or intravenously with some success [27]. Established clinical efficacy, no tumor protection, and acceptable toxicity were the important considerations for developing these agents [28]. EGCG and honey, which a traditional Chinese medicine called the drug homologous food, had been tested as a way to reduce radiation-induced normal tissue toxicity and complications recently. A retrospective study showed that a skin care program containing tea extracts helped to restore skin integrity for Grade $\geq$2 skin lesions in the head and neck and pelvic regions [29]. A randomized phase II trial of prophylactic manuka honey during the treatment of lung cancer (NRG Oncology RTOG 1012) showed honey was not superior to best supportive care in preventing radiation esophagitis. And the active species in the agent were incompletely known [30].

This trial supported the hypothesis that EGCG was more effective than conventional therapy (mLDG) in preventing or minimizing radiation-induced dermatitis. There was an overall difference in prevention or duration of radiation-induced dermatitis between EGCG and mLDG. The data also showed the earlier EGCG was applied, the more benefits patients had for AEI. The severity of esophagitis in group A was lower than that in group B, and five patients in arm A had no esophagitis. No significant differences were found due to relatively small number of patients. This study also showed that the use of EGCG can improve the patient's dysphagia and pain symptoms. Instead of progression of its severity, a rapid regression of esophagitis was noted in most cases in arm B, which was consistent with our previous research. The area under grade-duration curve was similar in arm A and B, but patients in arm A had less pain and dysphagia. These might mean a better quality of life and a medication adherence. EGCG was generally considered a safe food like honey, and only few patients were allergic to it. All of the reported events with large-quantity application were rated as mild events, such as excess gas, nausea, heartburn, abdominal pain [31]. The adverse events associated with EGCG were also mild in this study. Previous studies on NSCLC and SCLC with concurrent radiotherapy reported an ORR of 63–76% and 77–90%, respectively [32–35]. In our study, concurrent radiotherapy yielded an ORR of 78%. However, the results of these studies might be not necessarily comparable due to differences in patient selection, staging procedures, chemotherapy, CRT timing and schedules, and response evaluation.

From what had been discussed above, ECGC could be safely used as a radioprotectant for patients undergoing radiotherapy and occupationally exposed individuals. However, some limitations of this study should be emphasized. Firstly, no Kuwahata's endoscopic grade of esophagitis was obtained, and the esophagitis scores and treatment interruption were mainly according to the clinical symptoms. However, invasive procedure would worsen the condition of esophagitis and compromise the interests of human subjects. Secondly, a wide range of total radiation doses, loss of appropriate sample stratification and large ranges of esophageal doses might also have an impact on the demonstrated findings, although there was no statistical difference in all the pretreatment characteristics among the three groups. Thirdly, Similar to most double blinded trials on other radio-protective agents, an unconscious bias toward experimental agents might be not completely excluded [36]. In addition, the impact of EGCG on survival would be evaluated in further researches.

Conclusion

EGCG as prescribed within this protocol was superior to a traditional treatment in preventing radiation esophagitis. Prophylactic EGCG application for reducing radiation-induced esophagitis was superior to therapeutic one. Further studies are warranted to determine if patients with chronic esophagitis would benefit from EGCG, and whether EGCG applications would alleviate radiation mucositis or dermatitis.

Financial Support:

This work funded by National Natural Science Foundation of China (81572970), Shandong Provincial Natural Science Foundation (No. ZR2016HM35) and the grants from Shandong

Provincial key scientific and technological project of China (2018GSF118232)

Conflict of interest

We hereby confirm that none of the authors has any conflict of interest relevant to the present work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.022.

References

[1] Cadranel J, Park K, Arrieta O, Pless M, Bendaly E, Patel D, et al. Characteristics, treatment patterns, and survival among ALK+ non-small cell lung cancer (NSCLC) patients treated with crizotinib: a chart review study. Lung Cancer 2016;98:9–14.
[2] Stinchcombe TE, Zhang Y, Vokes EE, Schiller JH, Bradley JD, Kelly K, et al. Pooled analysis of individual patient data on concurrent chemoradiotherapy for stage III non-small-cell lung cancer in elderly patients compared with younger patients who participated in US National Cancer Institute Cooperative Group Studies. J Clin Oncol 2017;35:2885–92.
[3] Lopez Guerra JL, Wei Q, Yuan X, Gomez D, Liu Z, Zhuang Y, et al. Functional promoter rs2868371 variant of HSPB1 associates with radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with radio(chemo)therapy. Radiother Oncol 2011;101:271–7.
[4] Zhang Z, Xu J, Zhou T, Yi Y, Li H, Sun H, et al. Risk factors of radiation-induced acute esophagitis in non-small cell lung cancer patients treated with concomitant chemoradiotherapy. Radiat Oncol 2014;9:54.
[5] Shen L, Li X, Shan B, Zhang L, Gong Y, Dong Z, et al. Therapeutic effect of compound of White Peony Root Oral Liquids on radiation-induced esophageal toxicity via the expression of EGF and TGF-β1. Biomed Rep 2013;1:308–14.
[6] Khan AA, Paget JT, McLaughlin M, Kyula JN, Wilkinson MJ, Pencavel T, et al. Genetically modified lentiviruses that preserve microvascular function protect against late radiation damage in normal tissues. Sci Transl Med 2018;10.
[7] Richi B, Kale RK, Tiku AB. Radio-modulatory effects of green tea catechin EGCG on pBR322 plasmid DNA and murine splenocytes against gamma-radiation induced damage. Mutat Res 2012;747:62–70.
[8] Yoshioka H, Kurosaki H, Yoshinaga K, Saito K, Yoshioka H. Beta ray-induced scission of DNA in tritiated water and protection by a green tea percolate and (−)-epigallocatechin gallate. Biosci Biotechnol Biochem 1997;61:1560–3.
[9] Zhu W, Jia L, Chen G, Zhao H, Sun X, Meng X, et al. Epigallocatechin-3-gallate ameliorates radiation-induced acute skin damage in breast cancer patients undergoing adjuvant radiotherapy. Oncotarget 2016;7:48607–13.
[10] Zhao H, Zhu W, Jia L, Sun X, Chen G, Zhao X, et al. Phase I Study of topical Epigallocatechin-3-gallate (EGCG) in patients with breast cancer receiving adjuvant radiotherapy. Br J Radiol 2016;89:20150665.
[11] Zhao H, Zhu W, Xie P, Li H, Zhang X, Sun X, et al. A phase I study of concurrent chemotherapy and thoracic radiotherapy with oral epigallocatechin-3-gallate protection in patients with locally advanced stage III non-small-cell lung cancer. Radiother Oncol 2014;110:132–6.
[12] Zhao H, Xie P, Li X, Zhu W, Sun X, Sun X, et al. A prospective phase II trial of EGCG in treatment of acute radiation-induced esophagitis for stage III lung cancer. Radiother Oncol 2015;114:351–6.
[13] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[14] Werner-Wasik M, Axelrod RS, Friedland DP, Hauck W, Rose LJ, Chapman AE, et al. Preliminary report on reduction of esophagitis by amifostine in patients with non-small-cell lung cancer treated with chemoradiotherapy. Clin Lung Cancer 2001;2:284–9.
[15] Machin D. Sample size tables for clinical studies. 2nd ed. Oxford, England: Blackwell Science; 1997.
[16] Al-Sunduqchi Mahdi S. Determining the appropriate sample size for inferences based on the Wilcoxon statistics Ph.D. dissertation under the direction of William C. Guenther. Laramie, Wyoming: Dept. of Statistics, University of Wyoming; 1990.
[17] Werner-Wasik M, Pequignot E, Leeper D, Hauck W, Curran W. Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy. Int J Radiat Oncol Biol Phys 2000;48:689–96.
[18] Rodríguez N, Algara M, Foro P, Lacruz M, Reig A, Membrive I, et al. Predictors of acute esophagitis in lung cancer patients treated with concurrent three-dimensional conformal radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 2009;73:810–7.
[19] Atagi S, Mizusawa J, Ishikura S, Takahashi T, Okamoto H, Tanaka H, et al. Chemoradiotherapy in elderly patients with non-small-cell lung cancer: long-term follow-up of a randomized trial (JCOG0301). Clin Lung Cancer 2018.
[20] Pöttgen C, Eberhardt W, Graupner B, Theegarten D, Gauler T, Freitag L, et al. Accelerated hyperfractionated radiotherapy within trimodality therapy concepts for stage IIIA/B non-small cell lung cancer: Markedly higher rate of pathologic complete remissions than with conventional fractionation. Eur J Cancer 2013;49:2107–15.
[21] Chen C, Uyterlinde W, Sonke JJ, de Bois J, van den Heuvel M, Belderbos J. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. Radiother Oncol 2013;108:337–41.
[22] Zhu J, Zhang ZC, Li BS, Liu M, Yin Y, Yu JM, et al. Analysis of acute radiation-induced esophagitis in non-small-cell lung cancerpatients using the Lyman NTCP model. Radiother Oncol 2010;97:449–54.
[23] Reuther S, Szymczak S, Raabe A, Borgmann K, Ziegler A, Petersen C, et al. Association between SNPs in defined functional pathways and risk of early or late toxicity as well as individual radiosensitivity. Strahlenther Onkol 2015;191:59–66.
[24] Verma V, Simone 2nd CB, Werner-Wasik M. Acute and late toxicities of concurrent chemoradiotherapy for locally-advanced non-small cell lung cancer. Cancers (Basel) 2017;9:E120.
[25] Pan Y, Brink C, Knap M, Khalil AA, Nyhus CH, McCulloch T, et al. Acute esophagitis for patients with local-regional advanced non small cell lung cancer treated with concurrent chemoradiotherapy. Radiother Oncol 2016;118:465–70.
[26] Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116–25.
[27] Devine A, Marignol L. Potential of amifostine for chemoradiotherapy and radiotherapy-associated toxicity reduction in advanced NSCLC: a meta-analysis. Anticancer Res 2016;36:5–12.
[28] Lawrence YR, Paulus R, Langer C, Werner-+Wasik M, Buyyounouski MK, Komaki R, et al. The addition of amifostine to carboplatin and paclitaxel based chemoradiation in locally advanced non-small cell lung cancer: long-term follow-up of Radiation Therapy Oncology Group (RTOG) randomized trial 9801. Lung Cancer 2013;80:298–305.
[29] Pajonk F, Riedisser A, Henke M, McBride WH, Fiebich B. The effects of tea extracts on proinflammatory signaling. BMC Med 2006;4:28.
[30] Fogh SE, Deshmukh S, Berk LB, Dueck AC, Roof K, Yacoub S, et al. A randomized phase 2 trial of prophylactic manuka honey for the reduction of chemoradiation therapy-induced esophagitis during the treatment of lung cancer: results of NRGOncologyRTOG1012. Int J Radiat Oncol Biol Phys 2017;97:786–96.
[31] Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults – results of a systematic review. Regul Toxicol Pharmacol 2018;95:412–33.
[32] Kawano Y, Sasaki T, Yamaguchi H, Hirano K, Horiike A, Satouchi M, et al. Phase I/II study of carboplatin plus nab-paclitaxel and concurrent radiotherapy for patients with locally advanced non-small cell lung cancer. Lung Cancer 2018;125:136–41.
[33] Vokes EE, Herndon 2nd JE, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007;25:1698–704.
[34] Spiro SG, James LE, Rudd RM, Trask CW, Tobias JS, Snee M, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. J Clin Oncol 2006;24:3823–30.
[35] Halvorsen TO, Sundstrøm S, Fløtten Ø, Brustugun OT, Brunsvig P, Aasebø U, et al. Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small cell lung cancer. Acta Oncol 2016;55:1349–54.
[36] White IR. Uses and limitations of randomization-based efficacy estimators. Stat Methods Med Res 2005;14:327–47.