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Clinical Efficacy and Safety of an Oral-Esophageal Thermo-Sensitive Gel for Preventing Radiation-Induced Esophagitis in Patients with Esophageal Cancer

Han Ouyang
Xiangya Hospital Central South University
Qiaojing Shi
Xiangnan University
Yingying Zhang
404376@csu.edu.com

Xiangya Hospital Central South University
Rongrong Zhou
Xiangya Hospital Central South University
Jinan Ma
Second Xiangya Hospital of Central South University
Jing Zhang
Xiangya Hospital Central South University
Zhaohua Tan
Xiangya Hospital Central South University

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1*Authors:Han Ouyang, MD,Xiangya Hospital, Central South University, Changsha, 410008, China.E-mail:1193708385@qq.com

+8615675306319

1*Qiaojing Shi ,Department of Oncology,Affiliated Hospital of Xiangnan University, Chenzhou City, Hunan423000, China. E-mail: 297012793@qq.com +8615007350610

1*：Han Ouyang and Qiaojing Shi are contributed equally to the manuscript

2*Yingying Zhang, PhD, Xiangya Hospital, Central South University, Changsha, 410008, China.E-mail:404376@csu.edu.cn.(Correspondence author)

+8613787169166

3*Rongrong Zhou,PhD, Xiangya Hospital, Central South University, Changsha, 410008, China.E-mail:zhourr@csu.edu.cn

+8613875898127

4*Jinan Ma,Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China. E-mail: 3420248369@qq.com +8613973192715

5*Jing Zhang,Xiangya Hospital, Central South University, Changsha, 410008, China.E-mail:zj782@sina.com

+8613875858026

6*Zhaohua Tan,Xiangya Hospital, Central South University, Changsha, 410008, China.E-mail:592953497@qq.com

+8613875970370

Corresponding author:
Yingying Zhang, PhD
Xiangya Hospital, Central South University,Changsha,China
Email: 404376@csu.edu.cn

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Abstract

Background and purpose:

Radiation-induced esophagitis (RIE) is a common toxicity during concurrent chemoradiotherapy (CCRT) for locally advanced esophageal cancer and may compromise quality of life and treatment adherence. This study evaluated the safety and potential clinical benefits of an oral-esophageal thermo-sensitive gel (OETG) for reducing RIE severity.

Materials and methods:

This prospective, open-label, multicentre phase II study enrolled 51 patients with locally advanced esophageal cancer receiving CCRT between June 2023 and September 2025. OETG was administered from the first day of radiotherapy until 4 weeks after treatment completion. Acute esophageal toxicity was assessed using the RTOG grading system. Secondary assessments included swallowing function, pain scores, body-weight changes, ECOG performance status, safety outcomes, and exploratory inflammatory cytokine analyses.

Results:

The cumulative incidence of RIE was 37.3% (19/51), including grade 1–2 toxicity in 33.3% and grade 3 toxicity in 3.9%; no grade 4 events occurred. RIE severity peaked at week 5 of radiotherapy and subsequently declined, with no grade ≥2 esophagitis observed at 4 weeks after treatment. Dietary tolerance worsened during radiotherapy but recovered thereafter; 64.7% of patients resumed a normal diet at follow-up week 4. Pain severity remained mild, with 90.2% of patients pain-free at the final follow-up. Mean body-weight loss improved from 3.8% at week 5 to 1.2% after treatment. Three patients experienced grade 1 adverse events potentially related to OETG, with no serious adverse events or treatment discontinuations. Exploratory cytokine analysis showed transient elevations of IL-6 and IL-8 during treatment.

Conclusion:

OETG was well tolerated and showed potential for reducing the severity of RIE and supporting functional recovery during CCRT. Further controlled studies are warranted to confirm its clinical efficacy.

Key words: locally advanced esophageal cancer; radiation-induced esophagitis; oral-esophageal thermo-sensitive gel; clinical efficacy; safety;cytokine

1 Introduction

Esophageal carcinoma remains one of the most aggressive malignancies of the gastrointestinal tract[1]. Due to its insidious onset and lack of specific early symptoms, most patients are diagnosed at locally advanced or metastatic stages[2]. Concurrent chemoradiotherapy (CRT) represents a cornerstone treatment strategy for locally advanced esophageal cancer, particularly for patients unsuitable for surgery, while neoadjuvant CRT is commonly applied in surgically eligible patients[3].

However, the esophagus is both a therapeutic target and a critical organ at risk during thoracic irradiation[4]. Radiation-induced esophagitis (RIE) is one of the most common toxicities associated with thoracic radiotherapy and may occur following irradiation for esophageal cancer, lung cancer, mediastinal tumors, and other intrathoracic malignancies[5]. Radiation exposure damages the radiosensitive esophageal epithelium, leading to mucosal inflammation, edema, and epithelial injury. With increasing cumulative radiation doses, inflammatory responses, oxidative stress, and impaired esophageal function may develop[6]. Almost all patients receiving concurrent CRT for locally advanced esophageal cancer experience varying degrees of acute esophageal mucosal injury during treatment[7]. Clinically, RIE presents with odynophagia, dysphagia, and retrosternal discomfort, with severity generally increasing with cumulative radiation exposure[6]. Severe cases may result in reduced oral intake, dehydration, nutritional deterioration, weight loss, and treatment interruption, potentially compromising therapeutic outcomes[8–10].Currently, there is no universally accepted preventive strategy for RIE. Conventional management primarily relies on symptomatic treatments, including analgesics, anti-inflammatory agents, mucosal protectants, and nutritional support[11]. However, the unique anatomical characteristics of the esophagus, including continuous peristalsis, limited drug retention, and poor local penetration, restrict the effectiveness of conventional formulations[12]. Therefore, strategies capable of providing sustained local mucosal protection during radiotherapy remain clinically needed.

To address this limitation, an oral-esophageal thermo-sensitive gel (OETG) has been developed as a local mucosal barrier platform. OETG is composed of medical-grade poloxamer and carbomer and exhibits thermo-responsive sol–gel transition characteristics. The formulation remains fluid during administration and rapidly forms an adhesive gel layer upon contact with the mucosal surface, enabling prolonged retention and physical protection against mechanical and chemical irritation. Compared with conventional mucosal protectants such as sucralfate, which may have limited residence time, or topical anesthetics with transient effects, thermo-sensitive hydrogel systems provide sustained mucosal coverage and improved local retention[12].

Therefore, this prospective multicenter study aimed to evaluate the clinical efficacy and safety of OETG in patients with esophageal cancer undergoing concurrent CRT. The primary objective was to assess its effect on the incidence and severity of RIE, while secondary outcomes included swallowing function, pain control, nutritional status, and treatment-related safety. The findings may provide clinical evidence supporting thermo-sensitive mucosal protection as a novel supportive-care strategy in radiation oncology.

2 Methods

2.1 Study Population

Consecutive patients scheduled for concurrent chemoradiotherapy (CRT) at participating radiation-oncology departments between June 2023 and September 2025 were screened. After application of predefined eligibility criteria, 51 patients completed the entire treatment and follow-up protocol.(Table.1)

2.2 Inclusion and Exclusion Criteria

Patients were eligible if they met the following criteria: (1) histologically or cytologically confirmed esophageal cancer; (2) age 18–75 years; (3) planned concurrent CRT with intensity-modulated radiotherapy (IMRT) for locally advanced disease; (4) ECOG performance status 0–2; (5) expected survival ≥3 months; (6) adequate hematological, hepatic, renal, and coagulation function; (7) absence of clinically significant comorbidities affecting protocol adherence; and (8) written informed consent before enrollment.

Patients were excluded if they had: (1) esophago-airway fistula; (2) recent medications potentially affecting edema or swallowing pain assessment; (3) inability to swallow oral medication or requirement for enteral feeding support; (4) severe systemic illness affecting treatment tolerance; or (5) conditions potentially interfering with protocol adherence or outcome interpretation.

2.3 Ethics Statement

The study complied with the Declaration of Helsinki and Chinese regulations for biomedical research. The protocol was approved by the Clinical Research Ethics Committee of Xiangya Hospital, Central South University (approval No. 202303040). Written informed consent was obtained from all participants before enrollment.

2.4 Intervention

All patients received Yifutong® OETG (Maige Biomedical Co., Ltd., Hunan, China). The formulation remains liquid at room temperature and undergoes thermo-responsive sol–gel transition after administration, forming a viscoelastic protective coating on the mucosal surface.

Treatment was initiated on the first day of radiotherapy and continued until 4 weeks after radiotherapy completion. Following oral rinsing, patients swallowed 10 mL of gel (adjustable to 20 mL when clinically indicated). OETG was administered four times daily on radiotherapy days, including one dose 30 minutes before irradiation, and three times daily on non-radiotherapy days before meals.

2.5 Outcome Assessment

The primary endpoint was the cumulative incidence and severity of radiation-induced esophagitis (RIE) from the first radiotherapy fraction to 4 weeks after treatment completion. RIE severity was graded weekly using the RTOG acute esophagitis scale[13].

Secondary endpoints included swallowing function, pain intensity, nutritional status, adverse events, and ECOG performance status. Dysphagia was assessed using the Obstructive Dysphagia Score[14], pain intensity using the 11-point Numerical Rating Scale (NRS)[15], and functional status using the ECOG scale[16]. Adverse events were recorded throughout treatment and follow-up and graded according to severity and causality.

3 Results

3.1 Patient Baseline data

Males constituted 96.1% (n=49) of the cohort, with females representing 3.9% (n=2). The mean age was 62.4±10.0 years, and the mean body weight was 59.5±10.0 kg. Squamous-cell carcinoma predominated (90.2%), and the cohort included 5 patients (9.8%) with stage II disease, 14 (27.5%) with stage III disease, and 32 (62.7%) with stage IVA disease. The most common tumour location was the mid-thoracic oesophagus (47.1%). The majority of participants had an ECOG performance status of 0–1. Concurrent chemoradiotherapy was the principal treatment modality, accounting for 80.4% of cases, whereas 19.6% received neoadjuvant treatment. The

total radiation dose ranged from 40 to 50.4 Gy, and every patient completed the prescribed course. Concurrent chemotherapy regimens included TP (paclitaxel+cisplatin), TC (paclitaxel+carboplatin), capecitabine, PF (cisplatin+5-FU), EP (etoposide+cisplatin), and S-1, with or without immunotherapy. A total of 1,637 bottles of gel were consumed, with a mean of 32.1±9.7 bottles per patient(Table 1).

3.2 Incidence and evolution of RIE

The cumulative incidence of RIE was 37.3% (19/51), and the mean time to complete resolution or stabilisation was 35.6±10.9 days. These data provide the key baseline reference for gauging the therapeutic impact of the OETG and underscore the clinical importance of proactive RIE management(Table 2).

3.3 Temporal Evolution of RIE Grades

At week 1, none of the 51 patients exhibited mucosal changes. Inflammatory changes first emerged in week 3: grade 1 in 4 patients (7.8%), grade 2 in 5 patients (9.8%), and grade 3 in 2 patients (3.9%). The incidence peaked in week 5, when grade 2 toxicity was documented in 15 patients (29.4%). Thereafter, a rapid reversal was observed: during the first week of follow-up, the majority of grade-2 lesions regressed to grade 1, and by the fourth post-treatment week, only five patients (9.8%) retained grade-1 changes; no grade ≥2 esophagitis was recorded. These sequential data confirm that RIE severity parallels the radiation dose–time relationship and, critically, is reversible under the studied intervention, thereby providing a robust temporal framework for assessing the efficacy of the OETG(Figure 2.A).

3.4 Dynamic Changes in Inflammatory Cytokines (n = 24)

At baseline, abnormal elevations were relatively uncommon and were predominantly observed in IL-6 and IL-8, while IL-5 and IL-2 abnormalities were infrequent. During radiotherapy, particularly around treatment week 4–5 corresponding to the peak incidence of RIE, the proportion of abnormal IL-6 and IL-8 values increased substantially. IL-8 exhibited the most prominent elevation, with multiple patients exceeding the reference threshold (>20.6 pg/ml), including several cases with markedly elevated values. IL-6 similarly demonstrated a clear rise above the upper limit (>3.4 pg/ml) in a considerable subset of patients. IL-5 (exceeding 3.1 pg/ml) and IL-2 (exceeding 16.5 pg/ml) showed moderate transient increases during this period, though the magnitude and frequency were lower compared with IL-6 and IL-8. In contrast, TNF-α (≤16.5 pg/ml as reference upper limit) did not demonstrate a consistent or progressive elevation pattern across time points. Although isolated abnormal values were observed, there was no sustained or clustered increase at the peak RIE period, and therefore TNF-α was not identified as a dominant mediator in this cohort. At post-treatment week 4 follow-up, the majority of elevated IL-6 and IL-8 levels declined toward or returned to normal ranges, paralleling the clinical improvement in RIE grading and swallowing function. IL-5 and IL-2 abnormalities also decreased correspondingly. This temporal pattern supports the presence of a radiation dose- and time-dependent inflammatory response rather than persistent systemic cytokine activation. Overall, IL-6 and IL-8 demonstrated the strongest temporal concordance with the peak of mucosal toxicity, suggesting that these mediators may play a more prominent role in radiation-associated esophageal inflammatory injury in this study population. As shown in Table 3, IL-6 and IL-8 demonstrated the most pronounced increase in abnormal proportion at week 5, followed by IL-5 and IL-2, whereas TNF-α did not exhibit a distinct peak pattern. The decline in abnormal rates at post-treatment week 9 paralleled the improvement in clinical RIE severity(Table 3).

3.5 Temporal Changes in Dietary Tolerance Grade

At baseline, swallowing impairment was mainly related to tumour-associated luminal obstruction. According to the dietary tolerance grading system (A = normal diet; B = semi-solids; C = full liquids; D = complete obstruction), 16 patients (31.4%) required semi-solid diets and 2 patients (3.9%) required liquid diets, resulting in a baseline dysphagia rate of 35.3% (18/51). No patient had complete obstruction.During radiotherapy, dietary tolerance gradually worsened and reached its peak at week 5, when 64.7% of patients required dietary modification (grades B+C). Following completion of treatment, swallowing function progressively improved. At 4 weeks after radiotherapy, 33 patients (64.7%) resumed a normal diet, 18 (35.3%) remained on semi-solid diets, and no patient required liquid diets. Among patients who developed RIE, swallowing function improved in all cases by the end of follow-up. The temporal changes in dietary tolerance are shown in Figure B.

3.6 Temporal Evolution of NRS Pain Scores

At week 1, the vast majority were pain-free, and only two individuals reported mild discomfort. Pain intensity increased steadily with cumulative radiation dose and peaked in week 5: 28 patients (54.9%) remained pain-free (NRS 0), 17 (33.3%) had mild pain (NRS 1–3), and 6 (11.8%) recorded moderate pain (NRS 4–6); no patient experienced severe or intolerable pain (NRS ≥7). From the first follow-up week onward, a consistent downward trend was observed. By week 4 after radiotherapy, 46 of 51 subjects (90.2%) had returned to a pain-free state. Rescue analgesia was minimal: one patient received analgesics in weeks 3–4, and another required analgesia from week 3 through the first post-treatment week. These data confirm that RIE-related pain is time-dependent and closely parallels the delivered radiation dose, and they suggest that the OETG contributed materially to the subsequent resolution of pain(Figure C).

3.7 Serial Changes in Percentage Body-Weight Loss

A progressive, treatment-related decline was documented: mean weight loss was 0.9%±0.4% at week 1, increased steadily thereafter, and reached its maximum at week 5 (3.8%±0.7%). This temporal pattern closely mirrored the development of radiation-induced esophagitis, confirming that impaired swallowing was the principal driver of weight reduction. Following the cessation of radiotherapy, body mass began to recover, and by week 4 of follow-up mean weight loss had improved to 1.2%±0.5%. These data underscore the marked impact of RIE on nutritional status and suggest that the OETG mitigated treatment-associated weight loss(Figure D).

3.8 Serial ECOG Performance-Status Changes

Overall performance status remained stable: at week 1, two patients (3.9%) were fully active (score 0) and 49 (96.1%) were ambulatory and able to carry out light work (score 1). Minor fluctuations were observed thereafter, and by week 5 every patient still retained an ECOG score of 1. During follow-up, performance status gradually improved: at week 4 post therapy, 31.4% of participants had reverted to score 0, and no patient deteriorated to score ≥3. These data indicate that concurrent chemoradiotherapy was generally well tolerated and suggest that the OETG contributed to preserving patients baseline mobility(Figure E).

3.9 Device-Related Adverse Events

Among the 51 participants, three experienced mild adverse events that investigators considered “possibly related” to the gel; all were grade 1 (CTCAE v5.0) and required neither discontinuation nor specific intervention. Two patients reported mild nausea—an expected background event in esophageal cancer patients receiving concurrent chemoradiotherapy: one

receiving TP-based chemoradiotherapy and one receiving S-1-based chemoradiotherapy. One patient (with cervical esophageal cancer) experienced transient oropharyngeal and throat irritation (pain) described as a brief burning sensation; the symptom resolved after instruction to rinse with normal saline or cool boiled water before slow gargling and swallowing of the gel, and did not recur with subsequent doses. The median number of bottles used per subject was 32.1 .No new adverse events emerged during follow-up, and no grade≥2 toxicities or serious adverse events were observed, indicating that long-term topical use of the gel is well tolerated.

4 Discussion

Radiation-induced esophagitis (RIE) remains one of the most common dose-limiting toxicities during chemoradiotherapy for esophageal cancer and represents a major challenge in supportive oncology[17][18]. In this multicenter study, the incidence of RIE decreased obviously. Although direct comparison with historical data should be interpreted cautiously because of differences in patient populations and treatment protocols, these findings suggest that OETG may provide clinically meaningful protection against radiation-associated esophageal injury.

The timing of intervention may represent an important determinant of efficacy. Unlike reactive management strategies initiated after symptom onset, OETG administration was commenced from the first day of radiotherapy and continued throughout treatment. Current MASCC/ISOO clinical practice recommendations emphasize that early prophylactic application of mucosal protective approaches may preserve epithelial integrity and attenuate inflammatory amplification during radiation-induced mucosal injury[19-21]. The low incidence of severe RIE observed in this cohort suggests that early barrier protection may help interrupt the progressive cycle of epithelial damage and inflammation.Beyond toxicity grading, preservation of swallowing function represents an important clinical outcome. Dysphagia in patients with esophageal cancer results from multiple factors, including tumor-associated obstruction, radiation-induced edema, mucosal inflammation, ulceration and so on[22-23]. Severe odynophagia may reduce oral intake, cause weight loss, impair quality of life, and lead to treatment interruption[24]. In this study, swallowing function temporarily deteriorated during peak radiation exposure but subsequently recovered. These findings suggest that OETG may contribute to maintaining nutritional status and improving functional recovery. The lubricating and mucoadhesive properties of barrier therapies have previously been associated with reduced swallowing discomfort and improved nutritional maintenance during chemoradiotherapy[25].Therefore, early and continuous prophylactic application of the thermo-sensitive gel not only reduces inflammatory injury but also contributes to functional recovery and nutritional stability, supporting uninterrupted delivery of definitive radiotherapy[26].

The biological mechanism underlying RIE is closely related to radiation-induced oxidative stress and inflammatory activation. Ionizing radiation generates reactive oxygen species that damage cellular membranes, proteins, and nucleic acids, resulting in epithelial injury, endothelial dysfunction, and cytokine release[27]. Prophylactic coating of irradiated mucosa may limit direct mechanical and chemical irritation, attenuate cytokine-mediated injury, and delay the onset of clinically significant esophagitis[28-29].

Radiation dose and treatment duration are recognized determinants of RIE severity[30]. In our study, dysphagia and pain increased as treatment progressed and reached maximal severity during the latter half of radiotherapy, followed by gradual improvement after irradiation completion[31].

Importantly, preservation of nutritional status is clinically relevant because excessive body-weight loss during chemoradiotherapy has been associated with poorer outcomes in patients with unresectable esophageal cancer[32]. The limited weight loss observed in this cohort and subsequent recovery may indicate a potential benefit of improved swallowing tolerance.

Current management of RIE includes analgesics, anti-inflammatory agents, mucosal protectants, and nutritional interventions, but their efficacy is often limited by short mucosal residence time and insufficient local coverage[9][12]. Topical anesthetic preparations may provide transient symptom relief but are rapidly cleared from the esophagus, whereas conventional mucosal coating agents may have limited retention in patients with severe dysphagia[6][33]. In contrast, the thermo-sensitive gel undergoes sol–gel transition upon contact with mucosal surfaces, forming a stable mucoadhesive barrier that may prolong local protection and reduce mechanical irritation.The therapeutic characteristics of OETG are primarily attributed to its temperature-responsive gelation properties. Poloxamer and carbomer rapidly transform from a liquid formulation into an adhesive gel layer after exposure to physiological conditions, enabling prolonged mucosal coverage[34]. This protective layer may isolate damaged epithelium from mechanical and chemical stimulation to regime epithelial repair[35]. The viscoelastic properties of the hydrogel may reduce friction during swallowing and improve bolus transit, contributing to symptomatic relief[36][37]. However, further mechanistic studies are required to clarify the biological effects of OETG on inflammatory signaling, epithelial regeneration, and tissue repair.

Safety is an essential consideration for any supportive-care intervention during chemoradiotherapy. The components of OETG, including poloxamer, carbomer, have established biocompatibility profiles and are widely used pharmaceutical excipients[38-39]. Other formulation components, including trehalose, sodium bicarbonate, potassium sorbate, and sucralose, have also demonstrated favorable safety characteristics[40-43]. Peppermint oil may rarely produce mild mucosal irritation, but this is not observed at the low concentrations present in the formulation[44].Purified water is non-toxic and non-irritant. Collectively, these data indicate that the gel possesses a favorable safety margin. In this study, all gel-related adverse events were mild (CTCAE grade 1), self-limited, and resolved without sequelae, supporting the tolerability of this approach.

Radiation-induced esophagitis (RIE) ranks among the most prevalent and functionally debilitating adverse effects encountered during radiotherapy for esophageal and thoracic malignancies. Clinically, odynophagia typically develops after radiotherapy and may progress from pain during swallowing of solid food to pain on drinking liquids and, in severe cases, persistent resting pain. Therefore, current management strategies are largely based on symptom severity and supportive care(45).

For prophylaxis, several mucosal protective agents have been used in clinical practice, including mucosal repair agents and antioxidant compounds. Oral preparations such as Kangfuxin solution (Periplaneta americana extract) (46)have been employed to promote mucosal healing, whereas free-radical scavengers have been investigated for their potential radioprotective effects(47). However, the therapeutic efficacy of these agents is often limited by rapid esophageal transit and short mucosal retention time(12). To prolong local exposure, various viscous formulations or slurry preparations have been empirically developed to improve adherence to the esophageal mucosa.

Once odynophagia develops, management is primarily symptom-directed and may include

topical analgesics, anti-inflammatory agents, proton pump inhibitors, and nutritional support(9). Patients with mild symptoms may benefit from oral mucosal analgesics and anti-inflammatory medications. For moderate esophagitis associated with pain on liquid intake, compounded oral solutions containing local anesthetics, corticosteroids, antibiotics, or mucosal coating agents are frequently used to facilitate oral intake. Severe cases characterized by resting pain often require escalation to intravenous antibiotics, systemic corticosteroids, opioid analgesics, enteral tube feeding, or parenteral nutritional support.Systemic radioprotectors such as amifostine have demonstrated inconsistent clinical benefit and are often limited by adverse effects including hypotension and nausea, restricting their widespread application(47)(48). Antioxidant-based interventions have similarly shown variable efficacy and lack robust evidence for preventing clinically significant esophagitis.

In contrast, OETG represents a localized, non-systemic, and physically protective strategy that directly targets the irradiated mucosal surface. By undergoing in situ thermogelation, OETG forms a stable mucoadhesive barrier that prolongs esophageal residence time and provides sustained mucosal coverage. This mechanism addresses one of the major limitations of conventional topical therapies, namely their inability to remain in contact with the esophageal mucosa for a sufficient duration.Moreover, OETG has the potential to serve as a multifunctional delivery platform. Beyond providing physical shielding, the hydrogel matrix may be engineered to incorporate anti-inflammatory agents, antioxidants, or mucosal repair compounds, thereby combining mechanical protection with localized pharmacological intervention. Such a dual-function strategy could further enhance mucosal resilience, attenuate inflammatory amplification, and promote epithelial regeneration while minimizing systemic toxicity.Therefore, rather than merely alleviating symptoms after tissue injury has occurred, OETG acts upstream by preventing the initial epithelial insult and may ultimately shift the management paradigm of RIE from reactive symptom control toward proactive mucosal protection and targeted local therapy.

The results of this investigation carry significant implications for clinical practice. Early commencement of OETG from the initial day of radiotherapy appears critical, supporting the concept that cumulative mucosal injury begins early during treatment and may be preventable if adequate barrier protection is provided consistently.

Reduction in both incidence and severity of RIE has the potential to improve treatment adherence, reduce unplanned interruptions, and enhance the overall therapeutic ratio of chemoradiotherapy. Given its favorable safety profile, ease of administration, and non-invasive nature, OETG represents a promising candidate for integration into routine supportive care for patients undergoing thoracic radiotherapy.

Several limitations should be acknowledged. First, this was a prospective but non-randomized study with a relatively limited sample size, and the absence of a concurrent control group prevents definitive conclusions regarding efficacy. Randomized controlled trials are required to validate the clinical benefit of OETG. Second, follow-up duration was limited, and longer observation is necessary to determine whether OETG influences late radiation-associated esophageal complications or long-term quality of life. Third, this cohort mainly included patients with esophageal squamous cell carcinoma, and the efficacy of OETG in other tumor types requires further investigation.Despite these limitations, the findings suggest that thermo-sensitive mucosal protection may represent a promising supportive-care strategy during thoracic radiotherapy.

Beyond these limitations, several important questions remain unresolved. The optimal dosing

frequency, timing strategy, and duration of administration remain to be defined. In particular, whether intensified application during peak-dose radiation periods could further enhance protective efficacy warrants investigation.Furthermore, the anatomical extent of protection—whether full esophageal coverage or selective high-dose region targeting—is currently unknown and may benefit from integration with radiotherapy dose distribution maps[49].

Although this study focused on esophageal cancer, radiation-induced esophageal injury constitutes a frequently encountered complication across various thoracic malignancies. Patients with mediastinal neoplasms, including lung cancer and breast cancer, who receive internal mammary or mediastinal irradiation commonly experience incidental esophageal exposure[23][50].

Therefore, OETG may have broader applicability beyond esophageal cancer. However, differences in radiation dose distribution, fractionation schedules, concurrent systemic therapy, and baseline nutritional status may influence efficacy and require dedicated validation in disease-specific settings.

The thermosensitive hydrogel system described herein may represent a platform technology for mucosal protection rather than a disease-specific intervention[51][52]. Potential applications may extend to other radiation-sensitive mucosal organs[53], including: These include the oral cavity (radiation-induced oral mucositis)[25],the rectum (pelvic radiotherapy-induced proctitis[54],and the gastrointestinal tract in upper abdominal irradiation fields[55].

However, organ-specific physiological conditions such as pH, enzymatic degradation, mechanical stress, and microbiome composition may significantly influence gel stability and retention, necessitating tailored formulation optimization for each anatomical site[12]. Beyond its function as a purely physical barrier, the temperature-responsive gel system investigated herein may additionally function as a localized drug delivery vehicle, enabling a dual-function strategy that combines mechanical mucosal protection with pharmacological intervention. Poloxamer-based thermoresponsive hydrogels possess intrinsic advantages as drug reservoirs, including high aqueous compatibility, injectable/oral applicability, and temperature-triggered in situ gelation, which together allow sustained and localized drug release at the target mucosal surface. This raises the possibility that OETG could be further engineered as a drug-loaded multifunctional platform, rather than a passive protective material. From a translational perspective, incorporation of bioactive agents into OETG may enhance its protective efficacy through complementary mechanisms. For example, anti-inflammatory compounds (such as corticosteroids or non-steroidal anti-inflammatory agents), antioxidants (such as N-acetylcysteine), or epithelial-protective substances (such as epidermal growth factor analogs or mucosal repair peptides) could theoretically attenuate radiation-induced oxidative stress, suppress NF-κB–mediated inflammatory signaling pathways, and accelerate epithelial regeneration.

Importantly, this strategy would allow spatiotemporally controlled drug delivery, ensuring that therapeutic agents are concentrated at the irradiated esophageal mucosa while minimizing systemic exposure and associated toxicity. This is particularly relevant in patients receiving concurrent chemoradiotherapy, where systemic drug escalation is often limited by cumulative toxicity.

Moreover, a dual-function OETG system may shift the current paradigm from a purely protective barrier toward an active mucosal conditioning platform, in which the gel not only prevents direct radiation injury but also actively modulates the local microenvironment to promote tissue resilience and repair.

However, several key challenges must be addressed before clinical translation. These include (1) drug–polymer compatibility and stability within the hydrogel matrix, (2) release kinetics under dynamic esophageal conditions (peristalsis, saliva flow, and pH fluctuations), (3) maintenance of gelation properties after drug incorporation, and (4) optimization of dosing schedules to synchronize drug release with radiation-induced injury kinetics[56].

Future studies should systematically evaluate different drug candidates and loading strategies, as well as explore whether sequential or sustained-release formulations provide superior protection compared with barrier function alone. In addition, integration with radiobiological endpoints and mucosal microenvironment profiling will be essential to fully characterize the therapeutic synergy of this combined approach.

The OETG substantially decreases both the incidence and severity of radiation-induced esophagitis among patients with esophageal carcinoma. Its clinical benefit is attributable to a unique temperature-triggered film-forming mechanism, high mucosal permeability, and prolonged residence time. The formulation is well tolerated, with no serious adverse events reported. Further research should focus on long-term efficacy, differential responses across histological subtypes and disease stages, and the feasibility of additive or synergistic combination regimens to optimise patient outcomes.

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Registry

Trial registration number:MR-43-23-019720

Date of registration:2023-06-26

Funding declaration

Not applicable

Figure Legend

Graphic Abstract

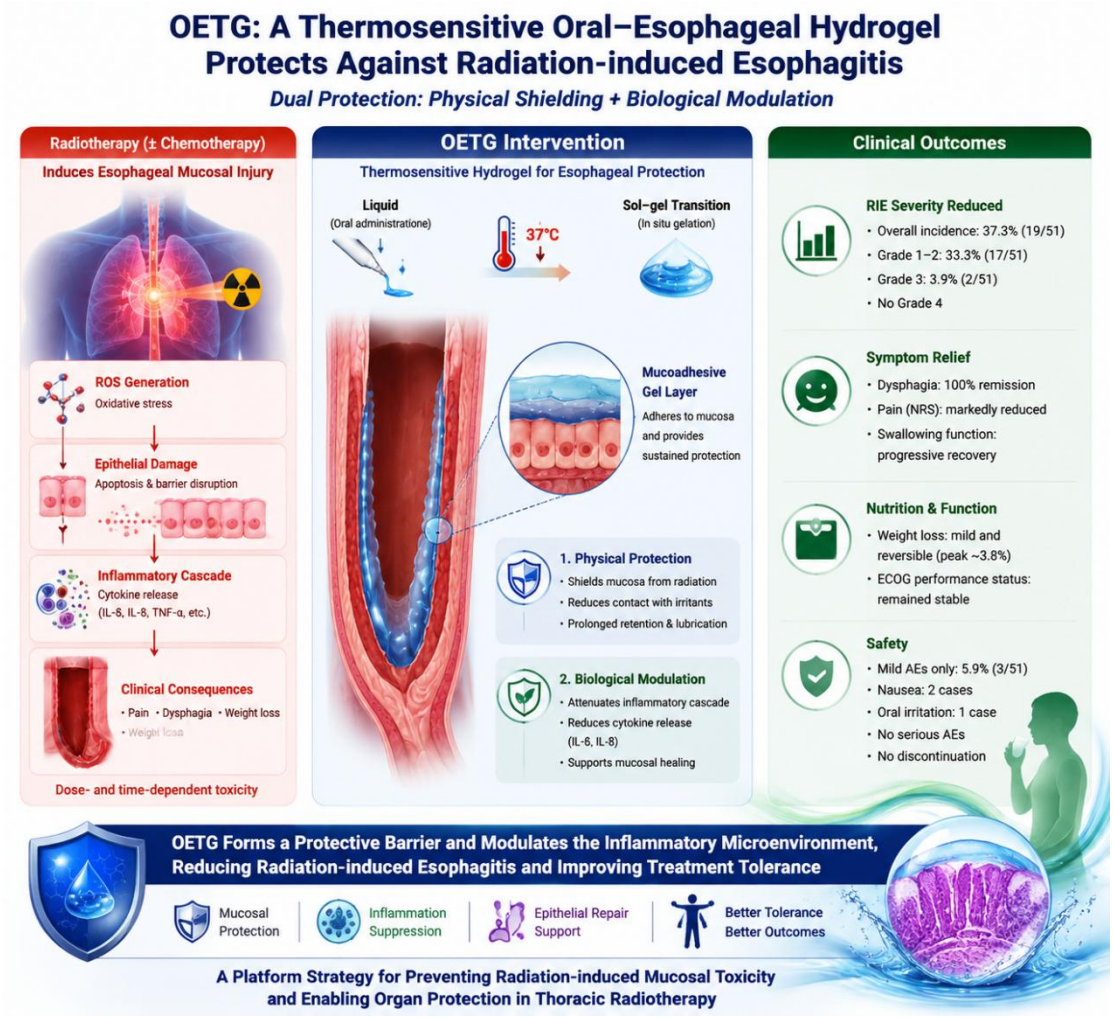


Figure1.Overall flow of the OETG research

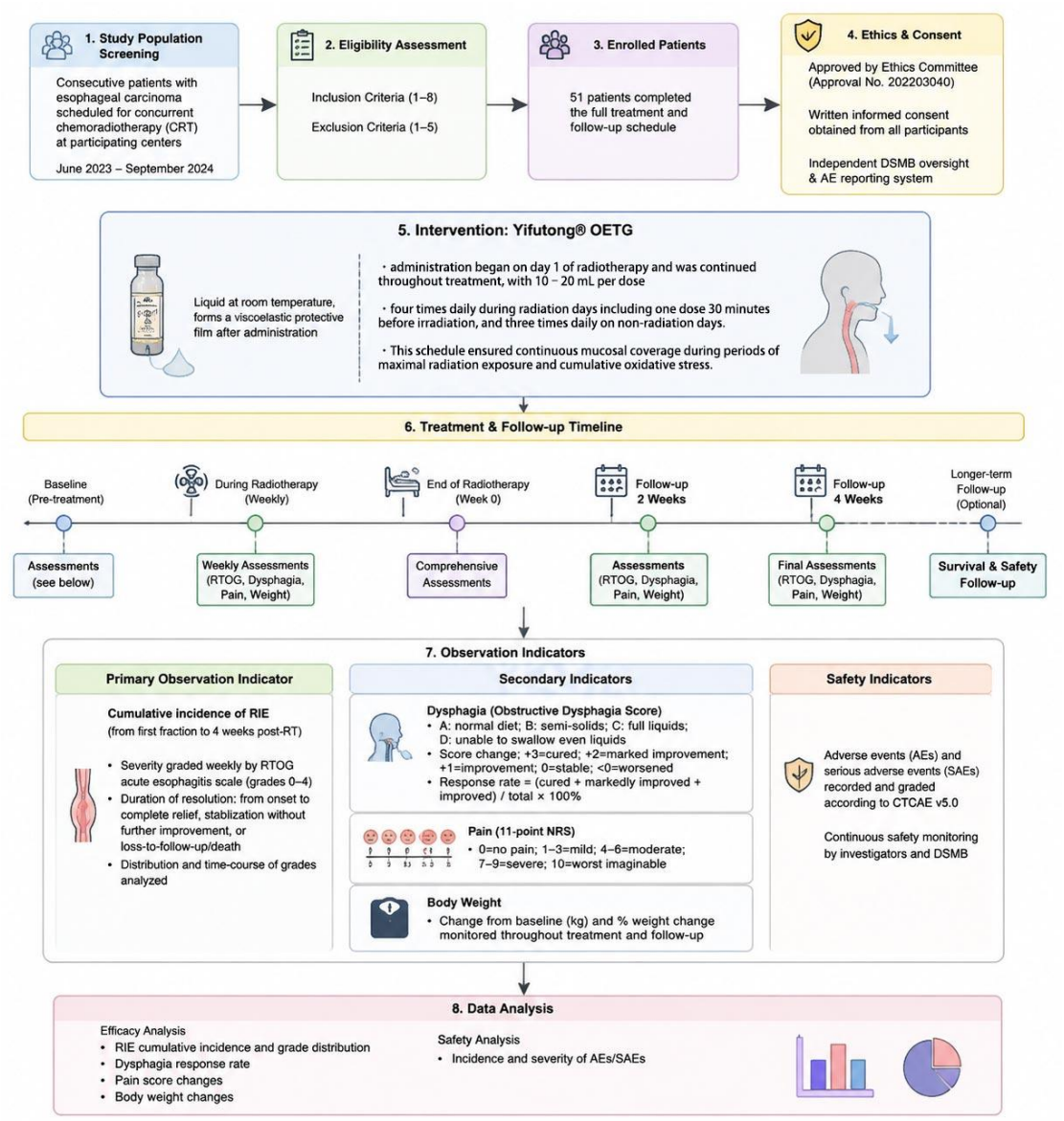
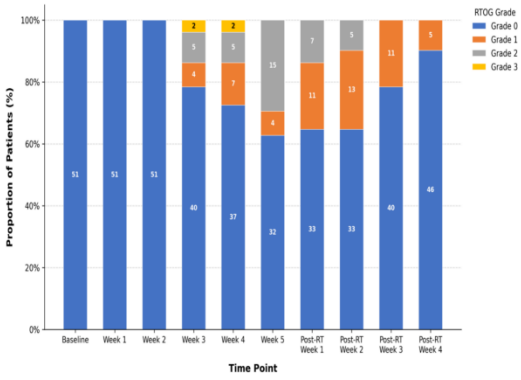
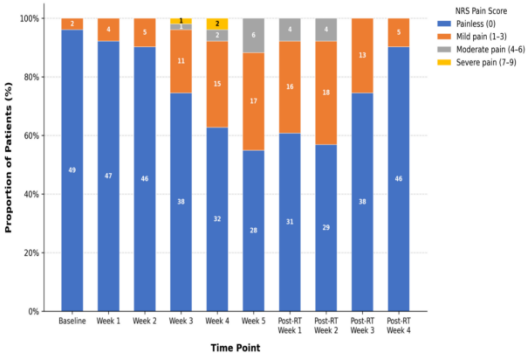


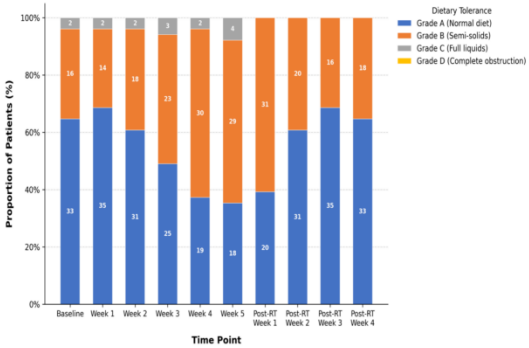
Figure2.Primary endpoint and secondary results of the OETG research



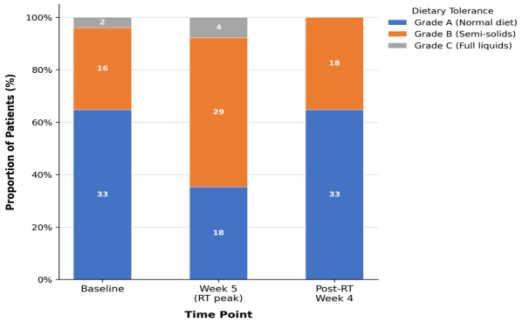
A.Grading Changes of RIE (n=51)



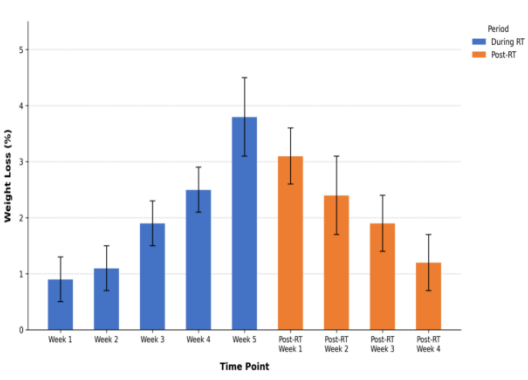
C.Changes in NRS pain score(n=51)



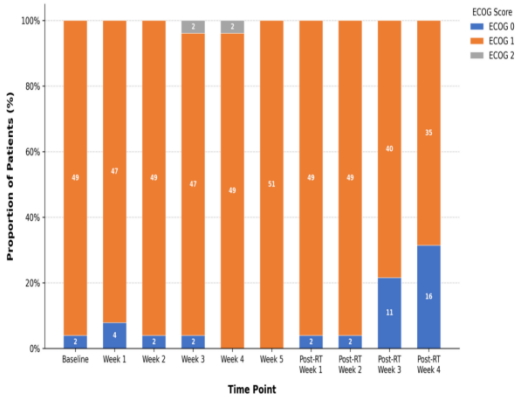
B-1.Temporal Changes in Dietary Tolerance Grade



B-2.Comparative Analysis of Dysphagia Status at Key Time Points (n=51)



D.Changes in the proportion of patients' weight loss (%)



E.Changes in ECOG score (n=51)

Table

Table 1 Baseline Characteristics

Variables	Patients with esophageal cancer (n=51)
Mean age ($\bar{x}$±s, year)	62.4±10.0
Gender [n (%)]	
Male	49（96.1%）
Female	2（3.9%）
Body weight ($\bar{x}$±s, kg)	59.5±10.0
TNM stage [n (%)]	
Stage II	5 (9.8%)
Stage III	14 (27.5%)
Stage IVA	32(62.7%)
Tumour location [n (%)]	
Upper thoracic	5 (9.8%)
Mid-thoracic	24 (47.1%)
Lower thoracic	15 (29.4%)
Multiple segments (including cervical)	7 (13.7%)
Histological type [n (%)]	
Squamous-cell carcinoma	46 (90.2%)
Adenocarcinoma	2 (3.9%)
Small-cell neuro-endocrine carcinoma	3 (5.9%)
ECOG Score [n (%)]	
0	2 (3.9%)
1	49 (96.1%)
Treatment modality [n (%)]	
Neoadjuvant	10 (19.6%)
Concurrent chemoradiotherapy	41（80.4%）
Total radiation dose / fractionation [n (%)]	
50.4Gy/1.8Gy*28 fractions	21(41.1%)
50Gy/2Gy*25 fractions	20 (39.2%)
44Gy/2Gy*22 fractions	5 (9.8%)
42Gy/2Gy*21 fractions	3 (5.9%)
40Gy/2Gy*20 fractions	2 (3.9%)
Total gel consumption (bottles)	1637
Mean gel consumption per patient ($\bar{x}$±s, bottles)	32.1±9.7

Table 1 presents the baseline demographic and clinical characteristics of the 51 enrolled esophageal cancer patients, thereby provides a comprehensive demographic, pathological, and therapeutic baseline profile for the cohort, serving as the reference frame for all subsequent efficacy and safety analyses.

Table 2 Indicators related to RIE in patients

Variables	Patients with esophageal cancer (n=51)
Incidence rate [n (%)]	19 (37.3%)
The mean time to complete resolution or stabilisation ($\bar{x}$±s, days)	35.6±10.9

Table 2 summarises the RIE-related parameters in the 51 esophageal-cancer patients.

Table 3 Abnormal Proportion of Inflammatory Cytokines at Key Time Points (n = 24)

Cytokine	Baseline n (%)	Week 5 n (%)	Post-RT Week 4 n (%)
IL-6	4 (16.7%)	11 (45.8%)	5 (20.8%)
IL-8	5 (20.8%)	13 (54.2%)	6 (25.0%)
IL-5	2 (8.3%)	7 (29.2%)	3 (12.5%)
IL-2	1 (4.2%)	6 (25.0%)	2 (8.3%)
TNF-α	2 (8.3%)	3 (12.5%)	2 (8.3%)

Table 3 shows that abnormal proportion was defined as the percentage of patients whose serum cytokine concentrations exceeded the predefined reference upper limits at each assessment time point. Cytokine measurements were performed at baseline, during radiotherapy (week 5), and at 4 weeks after completion of radiotherapy. IL, interleukin; TNF-α, tumour necrosis factor-alpha; RT, radiotherapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Graphicabstract.jpeg