Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Optimizing Clinical Practice and Efficacy Evaluation of Radiotherapy Combined with Immunotherapy in Recurrent Esophageal Cancer: A Retrospective Cohort Study Focusing on Patient-Reported Pain Relief and Tumor Proliferation Inhibition

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Objective: To evaluate the clinical efficacy and safety of radiotherapy combined with immunotherapy in patients with recurrent esophageal cancer, with a focus on patient-reported pain relief and changes in tumor proliferation-related biomarkers.

Methods: This retrospective observational cohort study included 70 patients with recurrent esophageal cancer treated at a single center between February 2022 and June 2024. The primary endpoints were changes in patient-reported pain assessed using the Visual Analog Scale at baseline, 3 weeks, and 6 weeks, and alterations in tumor proliferation-related biomarkers. Secondary endpoints included clinical response, immune cell subsets, serum tumor markers, and treatment-related adverse events. Statistical analyses were performed using independent-samples t tests, chi-square tests, and repeated-measures analysis of variance. A two-sided P value <0.05 was considered statistically significant.

Results: Baseline characteristics and pain scores were comparable between groups. Repeated-measures analysis of variance demonstrated significant effects of group, time, and group–time interaction on pain scores (all P<0.05), with greater pain reduction at 3 and 6 weeks in the radiotherapy plus immunotherapy group. The combination therapy group showed higher overall response and disease control rates than the radiotherapy-alone group. After treatment, reductions in vascular endothelial growth factor, matrix metalloproteinase-9, Yin Yang 1, carbohydrate antigen 125, carcinoembryonic antigen, and squamous cell carcinoma antigen were observed in both groups, with more pronounced decreases in the combination therapy group. Immune profiling revealed greater increases in cluster of differentiation 3-positive and cluster of differentiation 4-positive cells and a greater reduction in cluster of differentiation 8-positive cells following combination therapy. The incidence of treatment-related adverse events, including immune-related toxicities, was comparable between groups.

Conclusion: In this retrospective observational study, radiotherapy combined with immunotherapy was associated with improved pain control and reductions in tumor proliferation-related biomarkers without an apparent increase in toxicity. These findings reflect associations and require confirmation in larger prospective studies.

Keywords: radiotherapy, immunotherapy, recurrent esophageal cancer, pain, tumor proliferation

Introduction

Esophageal cancer is one of the most common malignant tumors worldwide, with persistently high incidence and mortality rates, particularly in Asia, where its burden remains disproportionately high.[1] According to recent global cancer statistics reported by the World Health Organization and updated epidemiological analyses, esophageal cancer continues to rank among

https://doi.org/10.2147/JMDH.S563311
Received: 26 August 2025
Accepted: 17 April 2026
Published: 12 May 2026

the leading causes of cancer-related death worldwide, with an estimated incidence and mortality that remain substantial despite regional variations.[2] Despite advances in diagnosis and multimodal treatment strategies, the prognosis of esophageal cancer remains poor, especially for patients with recurrent disease, whose five-year survival rate is reported to be below 20%.[3]

The mechanisms underlying esophageal cancer recurrence are complex and multifactorial, involving tumor cell heterogeneity, immune escape, and dynamic alterations within the tumor microenvironment (TME).[4,5] Recurrent tumor cells often exhibit increased invasiveness, radioresistance, and resistance to systemic therapies, rendering conventional treatment approaches less effective.[6] Moreover, patients with recurrent esophageal cancer frequently suffer from clinically significant cancer-related pain and dysphagia, which markedly impair quality of life and impose a substantial physical and psychological burden.[7] Therefore, identifying effective and tolerable treatment strategies for recurrent esophageal cancer remains an important unmet clinical need.

Radiotherapy is a cornerstone in the management of esophageal cancer, particularly in the recurrent or palliative setting. The introduction of three-dimensional conformal intensity-modulated radiotherapy (IMRT) has substantially improved dose conformity and treatment precision, allowing enhanced tumor control while limiting toxicity to surrounding normal tissues.[8] However, radiotherapy alone often provides limited and transient benefit in recurrent disease. Emerging evidence suggests that radiotherapy can exert immunomodulatory effects beyond direct cytotoxicity, including increased tumor antigen release, enhanced antigen presentation, and remodeling of the tumor microenvironment, thereby potentially sensitizing tumors to immunotherapy.[9–11]

Immunotherapy, particularly immune checkpoint inhibition, has transformed the treatment landscape of several solid malignancies. Programmed death-1 (PD-1) inhibitors restore antitumor T-cell activity by blocking the PD-1/PD-L1 axis, thereby overcoming tumor-induced immune suppression.[12,13] Preclinical and clinical studies indicate that combining radiotherapy with PD-1 blockade may synergistically enhance antitumor immune responses through modulation of immune cell infiltration, cytokine signaling, and the immunosuppressive tumor microenvironment.[14] Camrelizumab, a PD-1 inhibitor developed in China, has demonstrated promising efficacy in multiple solid tumors, including non-small cell lung cancer, hepatocellular carcinoma, and gastric cancer.[15,16] Nevertheless, evidence regarding its combined use with radiotherapy in recurrent esophageal cancer remains limited, and existing clinical data are heterogeneous, with both encouraging and inconclusive results reported in recent trials.

Based on these considerations, we hypothesized that radiotherapy combined with immunotherapy would provide superior symptom control and biological tumor suppression compared with radiotherapy alone. The primary objective of this study was to evaluate whether the combination of IMRT and camrelizumab could reduce patient-reported pain within 6–8 weeks of treatment and decrease tumor proliferation–related biomarkers. Secondary objectives included assessment of immune response modulation, serum tumor marker changes, and treatment-related safety.

Materials and Methods

Study Design and Patient Population

This was a single-center retrospective observational cohort study. All data were retrospectively extracted in 2024 from electronic medical records of patients treated between February 2022 and June 2024 at Tianmen First People's Hospital.

During the study period, 83 consecutive patients were diagnosed with recurrent esophageal squamous cell carcinoma and were evaluated for further radiotherapy with or without immunotherapy. Among them, 9 patients did not meet the inclusion criteria (5 had distant organ metastases, 2 had severe organ dysfunction, and 2 had incomplete medical records), and 4 patients declined further treatment. The remaining 70 patients met all eligibility criteria and were included in the final analysis. Therefore, the study cohort represents all eligible and treated patients during the specified time period.

All clinical variables, laboratory results, imaging findings, treatment details, and follow-up information were obtained exclusively from routine medical records. No additional interventions, tests, or follow-up procedures were performed for research purposes.

Initial treatment for primary esophageal cancer included radical surgery, definitive chemoradiotherapy, or postoperative adjuvant chemoradiotherapy, according to disease stage and patient condition. The median time from

completion of initial treatment to documented recurrence was 12 months (interquartile range: 8–18 months) (Supplementary Table S1).

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Histologically confirmed esophageal squamous cell carcinoma with documented recurrence after initial treatment; (2) Age 18–75 years, regardless of sex; (3) Karnofsky Performance Status (KPS)[17] ≥70, with an expected survival of ≥6 months; (4) No evidence of distant organ metastasis; (5) Ability to tolerate radiotherapy and immunotherapy, including the ability to consume semi-liquid food without signs of esophageal perforation; (6) Meeting the clinical indications for radiotherapy with or without immunotherapy for recurrent esophageal cancer, as determined by a multidisciplinary team (MDT); (7) Availability of complete clinical and laboratory data.

Exclusion criteria included: (1) Prior exposure to immune checkpoint inhibitors; (2) Concurrent or previous malignancies other than esophageal cancer; (3) Active autoimmune disease or uncontrolled infection; (4) Severe cardiac, hepatic, or renal dysfunction; (5) Pregnancy or lactation; (6) Psychiatric illness or cognitive impairment affecting compliance; (7) Known hypersensitivity or contraindications to camrelizumab; (8) Participation in other clinical trials within 3 months prior to enrollment.

Ethics Statement

This study was approved by the Medical Ethics Committee of Tianmen First People's Hospital on August 1, 2024 (Approval No.: Ethics Review ZL-240016). Given the retrospective design, the ethics committee approved the study based on the review of existing clinical records from 2022 to 2024. All data extraction and analysis were conducted after ethical approval was granted in 2024. The requirement for written informed consent for data use was waived due to the retrospective nature of the study and anonymization of patient data.

All procedures were conducted in accordance with the Declaration of Helsinki.

Treatment Strategy

Patients were managed according to routine clinical decision-making by a multidisciplinary team (MDT) consisting of radiation oncologists, medical oncologists, and thoracic surgeons. Treatment selection (radiotherapy alone or radiotherapy combined with camrelizumab) was based on clinical factors, including: Tumor burden and recurrence pattern; Performance status; Patient comorbidities; Physician assessment of potential benefit and tolerance; Patient preference after discussion of risks and benefits; No randomization or allocation procedure was performed. Patients who received intensity-modulated radiotherapy (IMRT) alone comprised the radiotherapy-alone group (n = 35). Patients who received IMRT combined with camrelizumab comprised the radiotherapy plus immunotherapy group (n = 35).

Radiotherapy Protocol

All patients underwent IMRT using a Varian linear accelerator (Varian Medical Systems, USA). The radiotherapy equipment used in this study complies with national and international medical device regulatory standards and is routinely applied in clinical practice at our institution. Simulation was performed using large-aperture spiral CT with a slice thickness of 0.5 cm. The gross tumor volume (GTV) was delineated based on CT imaging. The clinical target volume (CTV) was generated by expanding the GTV by 0.5 cm radially and 3.0 cm cranio-caudally. The planning target volume (PTV) was created by an additional 0.5 cm margin to account for setup error and organ motion. Organs at risk (OARs), including the lungs, heart, and spinal cord, were contoured, and dose constraints were applied according to institutional protocols and international guidelines. Treatment planning ensured that at least 95% of the prescribed dose covered the PTV. A total dose of 60 Gy in 30 fractions (2 Gy per fraction, once daily, five days per week) was delivered over six weeks.

Immunotherapy Protocol

Patients in the radiotherapy plus immunotherapy group received camrelizumab (200 mg/vial; Suzhou Simcere Pharmaceutical Co., Ltd., China), administered intravenously at a dose of 200 mg every 3 weeks. Camrelizumab is an approved PD-1 inhibitor in China and was administered in accordance with its approved labeling and routine clinical

practice. Immunotherapy was initiated concurrently with radiotherapy and continued for 2–6 cycles (median: 4 cycles) unless disease progression or unacceptable toxicity occurred. None of the patients had received prior immune checkpoint inhibitor therapy. PD-L1 expression testing was not routinely performed due to the retrospective nature of this study.

Observation Indicators

Clinical Treatment Effect

Short-term efficacy was assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1),[18] including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR or PR, and the disease control rate (DCR) was defined as the proportion achieving CR, PR, or SD.

Pain Assessment

Pain scores were assessed using the Visual Analog Scale (VAS) (Cronbach's α=0.852, validity=0.834)[19] before treatment and at 3 and 6 weeks after treatment initiation. VAS scores range from 0 to 10, with higher scores indicating greater pain severity.

T-Lymphocyte Subpopulations

Before and after treatment, 10 mL of fasting venous blood was collected from the antecubital vein in the morning. A BD FACSLyric flow cytometer was used to determine the proportions of CD3+, CD4+, and CD8+ T cells.

Tumor Proliferation–Related Biomarkers

Before and after treatment, serum samples were analyzed using an ADVAChemistry XPT automated biochemical analyzer to determine the concentrations of vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), and Yin Yang 1 (YY1).

Serum Tumor Markers

Serum samples were analyzed to determine the concentrations of carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and squamous cell carcinoma antigen (SCC).

Adverse Events

Adverse events during treatment were recorded, including nausea and vomiting, gastrointestinal reactions, hepatic and renal dysfunction, radiation-related reactions, and hematologic toxicity. Adverse events were graded as follows: Grade I (mild), Grade II (moderate), Grade III (severe), Grade IV (life-threatening), and Grade V (death related to an adverse event).

Statistical Analysis

GraphPad Prism 8 was used for data visualization, and SPSS 22.0 software was used for data processing. Categorical data were expressed as percentages (%) and analyzed using the χ^2-test. Continuous data were expressed as ($\overline{x} \pm s$), with independent sample t-tests used for between-group comparisons, paired t-tests for within-group comparisons, and repeated measures ANOVA for comparisons at different time points. A p-value < 0.05 was considered statistically significant.

Results

All laboratory parameters, immune cell subset measurements, tumor biomarkers, imaging findings, and adverse event data were obtained from routine clinical testing and electronic medical records. No additional laboratory assays were performed for research purposes. All biochemical and immunological measurements were conducted in the hospital's certified clinical laboratory in accordance with standard operating procedures.

Comparison of Clinical Data

A total of 82 patients were screened for eligibility during the study period. Twelve patients were excluded due to incomplete clinical data (n=5), prior immunotherapy exposure (n=4), or concurrent malignancies (n=3). Finally, 70 eligible patients were included in the analysis and categorized according to treatment into the radiotherapy-alone group (IMRT alone, n=35) and the radiotherapy plus immunotherapy group (IMRT plus camrelizumab, n=35). Baseline demographic and clinical characteristics, including sex, age, TNM stage, lesion location, lesion length, and education level, were comparable between the two groups, with no statistically significant differences (all P>0.05). Detailed baseline data are presented in Table 1.

Comparison of Clinical Treatment Outcomes

In the radiotherapy-alone group, 6 patients achieved a complete response, 10 a partial response, 10 had stable disease, and 9 showed disease progression. In the radiotherapy plus immunotherapy group, the corresponding numbers were 12, 14, 7, and 2, respectively. Both the objective response rate and disease control rate were significantly higher in the combination therapy group than in the radiotherapy-alone group (objective response rate: χ^2=5.95, df=1, P=0.01; disease control rate: χ^2=5.29, df=1, P=0.02). Results are summarized in Table 2.

Comparison of Pain Scores

Baseline Visual Analog Scale scores did not differ significantly between groups (t=0.28, df=68, P=0.78). Repeated-measures analysis of variance demonstrated significant effects of group (F(1,68)=5.72, P=0.02), time (F(2,136)=7.28, P<0.01), and group×time interaction (F(2,136)=6.46, P<0.01) on pain scores. At 3 and 6 weeks after treatment initiation, both groups showed significant reductions in pain scores compared with baseline (all P<0.05). The radiotherapy plus immunotherapy group had significantly lower pain scores than the radiotherapy-alone group at both time points (3 weeks: t=3.14, df=68, P=0.002; 6 weeks: t=4.95, df=68, P<0.001). See Table 3 and Figure 1.

Comparison of T Lymphocyte Subsets

After treatment, both groups showed increased proportions of CD3-positive and CD4-positive T cells and decreased proportions of CD8-positive T cells compared with baseline (all P<0.05). Between-group comparisons after treatment demonstrated significantly greater changes in the radiotherapy plus immunotherapy group (CD3-positive cells: t=4.15,

Table 1 Comparison of Clinical Data ($\bar{x} \pm s$, n [%])

	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	t/x^2 (df)	P
Gender	–	–	0.233 (df=1)	0.629
Male	19 (54.29)	21 (60.00)	–	–
Female	16 (45.71)	14 (40.00)	–	–
Age (years)	58.37±5.09	59.03±6.25	0.484 (df=68)	0.629
TNM Stage	–	–	0.560 (df=1)	0.454
Stage II	11 (31.43)	14 (40.00)	–	–
Stage III	24 (68.57)	21 (60.00)	–	–
Lesion Location	–	–	0.324 (df=3)	0.569
Cervical Segment	4 (11.43)	3 (8.57)	–	–
Upper Thoracic	12 (34.29)	14 (40.00)	–	–
Mid-Thoracic	10 (28.57)	11 (31.43)	–	–
Lower Thoracic	9 (25.71)	7 (20.00)	–	–
Lesion Length (cm)	6.14±0.58	6.23±0.55	0.666 (df=68)	0.507
Education Level	–	–	0.299 (df=1)	0.584
High School and Below	27 (77.14)	25 (71.43)	–	–
College and Above	8 (22.86)	10 (28.57)	–	–

Table 2 Comparison of Clinical Treatment Outcomes (n [%])

Clinical Efficacy	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	x^2 (df)	P
CR	6 (17.14)	12 (34.29)	–	–
PR	10 (28.57)	14 (40.00)	–	–
SD	10 (28.57)	7 (20.00)	–	–
PD	9 (25.71)	2 (5.71)	–	–
ORR	16 (45.71)	26 (74.29)	5.952 (df=1)	0.014
DCR	26 (74.29)	33 (94.29)	5.285 (df=1)	0.021

Abbreviations: CR, Complete Response; PR, Partial Response; PD, Progressive Disease; SD, Stable Disease; ORR, Objective Response Rate; DCR, Disease Control Rate.

Table 3 Comparison of Pain Scores ($\bar{x} \pm s$, Points)

Pain Scores	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	t (df)	P
Before treatment	7.25±0.87	7.19±0.92	0.280 (df=68)	0.780
At 3 weeks of treatment	5.43±1.22$^{\#}$	4.49±1.28$^{\#}$	3.144 (df=68)	0.002
At 6 weeks of treatment	4.56±1.34$^{\#\Delta}$	3.05±1.21$^{\#\Delta}$	4.947 (df=68)	<0.001

Notes: Compared with the same group before treatment, $^{\#}P < 0.05$; compared with the same group at week 3 of treatment, $^{\Delta}P < 0.05$.
Abbreviation: VAS, Visual Analog Scale.

df=68, P<0.001; CD4-positive cells: t=2.87, df=68, P=0.005; CD8-positive cells: t=5.31, df=68, P<0.001). See Table 4 and Figure 2.

Comparison of Tumor Proliferation-Related Biomarkers

Serum concentrations of vascular endothelial growth factor, matrix metalloproteinase-9, and Yin Yang 1 decreased significantly after treatment in both groups (all P<0.05), with greater reductions observed in the radiotherapy plus immunotherapy group. Between-group comparisons after treatment showed statistically significant differences (vascular endothelial growth factor: t=7.45, df=68, P<0.001; matrix metalloproteinase-9: t=6.58, df=68, P<0.001; Yin Yang 1: t=6.46, df=68, P<0.001). See Table 5 and Figure 3.

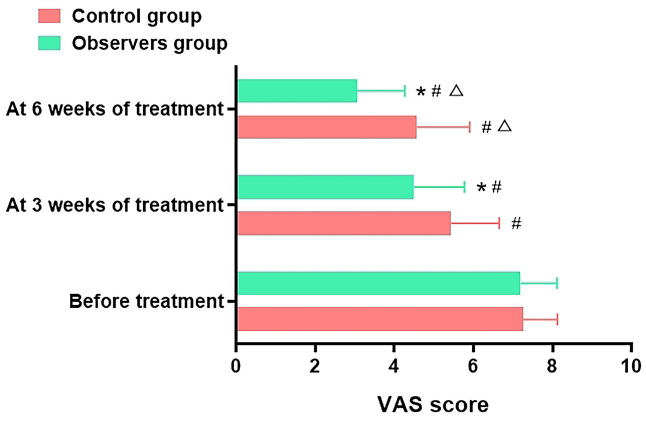

Figure 1 Comparison of Pain scores ($\bar{x} \pm s$, points).
Notes: Compared with the radiotherapy-alone group at the same time point, *P < 0.05; compared with baseline within the same group, #P < 0.05; compared with week 3 within the same group, ΔP < 0.05.
Abbreviation: VAS, Visual Analog Scale.

Table 4 Comparison of T Lymphocyte Subset Proportions ($\bar{x} \pm s$)

	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	*t (df)*	*P*
CD3+	–	–	–	–
Before treatment	59.47±2.29	59.32±2.35	0.270 (df=68)	0.787
After treatment	63.54±3.85#	67.49±4.11#	4.149 (df=68)	<0.001
CD4+	–	–	–	–
Before treatment	37.73±2.14	37.64±2.03	0.180 (df=68)	0.857
After treatment	49.78±3.23#	52.29±4.05#	2.866 (df=68)	0.005
CD8+	–	–	–	–
Before treatment	31.57±3.74	32.11±3.09	0.658 (df=68)	0.512
After treatment	24.34±3.08#	20.71±2.62#	5.310 (df=68)	<0.001

Notes: Compared with the same group before treatment, #P < 0.05. CD3+ cells (CD3+); CD4+ cells (CD4+); CD8+ cells (CD8+).

Comparison of Serum Tumor Marker Concentrations

After treatment, serum concentrations of carbohydrate antigen 125, carcinoembryonic antigen, and squamous cell carcinoma antigen were significantly reduced in both groups compared with baseline (all P<0.05). The radiotherapy plus immunotherapy group had significantly lower post-treatment concentrations than the radiotherapy-alone group (carbohydrate antigen 125: t=5.50, df=68, P<0.001; carcinoembryonic antigen: t=5.19, df=68, P<0.001; squamous cell carcinoma antigen: t=2.96, df=68, P=0.004). See Table 6 and Figure 4.

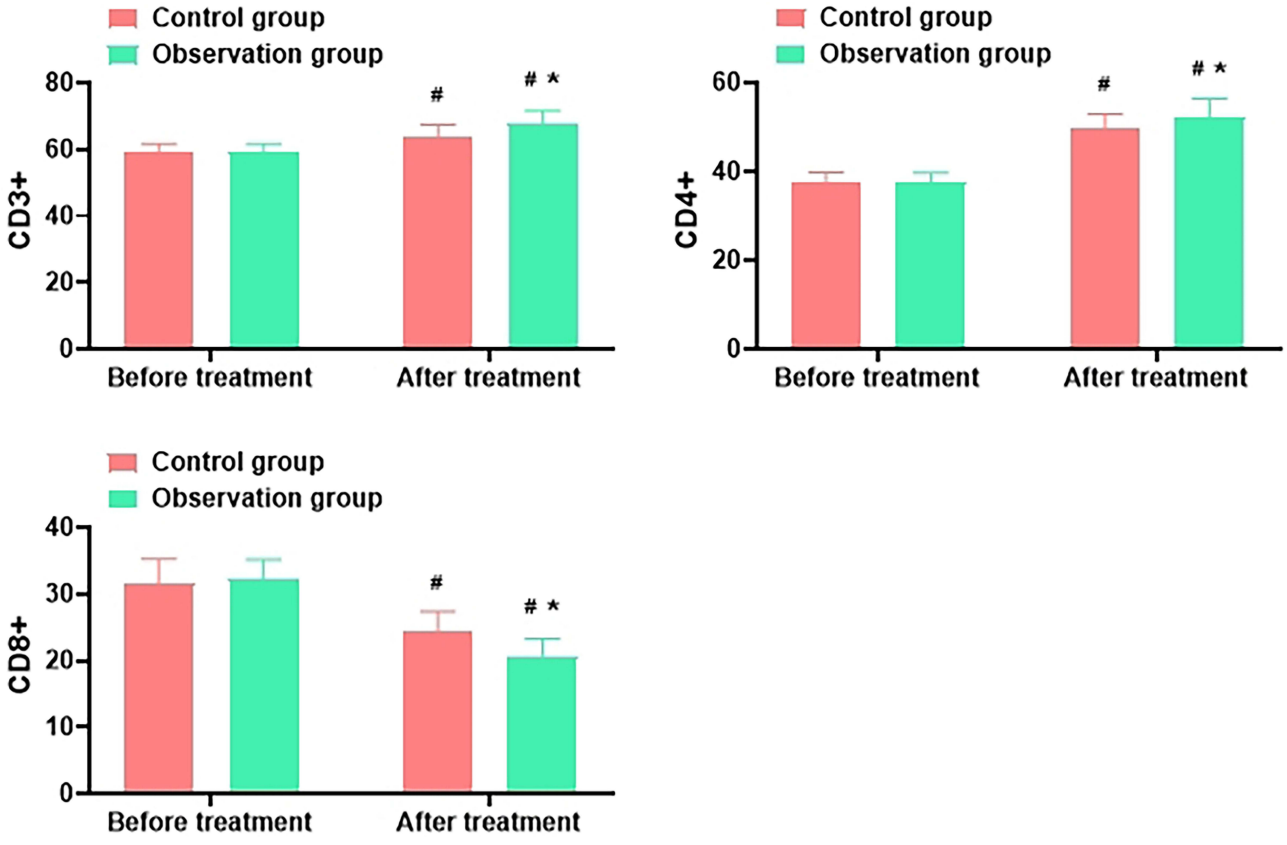

Figure 2 Comparison of T lymphocyte subset proportions ($\bar{x} \pm s$).
Notes: Compared with the radiotherapy-alone group at the same time point, *P < 0.05; compared with baseline within the same group, #P < 0.05. CD3+ cells (CD3+); CD4+ cells (CD4+); CD8+ cells (CD8+).

https://doi.org/10.2147/JMDH.S563311

Table 5 Comparison of Tumor Proliferation-Related Biomarker Concentrations ($\bar{x} \pm s$, ng/L)

	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	*t (df)*	*P*
VEGF	–	–	–	–
Before treatment	561.64±63.75	562.57±53.48	0.066 (df=68)	0.947
After treatment	159.31±35.69#	105.09±24.13#	7.445 (df=68)	<0.001
MMP-9	–	–	–	–
Before treatment	243.72±32.15	246.43±33.69	0.344 (df=68)	0.731
After treatment	93.56±32.07#	53.14±17.08#	6.581 (df=68)	<0.001
YY1	–	–	–	–
Before treatment	10.84±3.45	11.08±3.38	0.294 (df=68)	0.769
After treatment	5.21±1.43#	3.57±0.46#	6.458 (df=68)	<0.001

Notes: Compared with the same group before treatment, #P < 0.05.
Abbreviations: VEGF, vascular endothelial growth factor; MMP-9, matrix metalloproteinase-9; YY1, transcription factor Yin Yang 1.

Comparison of Adverse Reactions

No grade 3 or higher adverse events were observed in either group. The incidences of gastrointestinal, hepatic, renal, hematologic, and radiation-related adverse events were comparable between groups (all P>0.05). Immune-related adverse events in the radiotherapy plus immunotherapy group were limited to mild skin reactions, including rash and pruritus. All adverse events were manageable with symptomatic treatment, and no treatment discontinuation occurred. See Table 7.

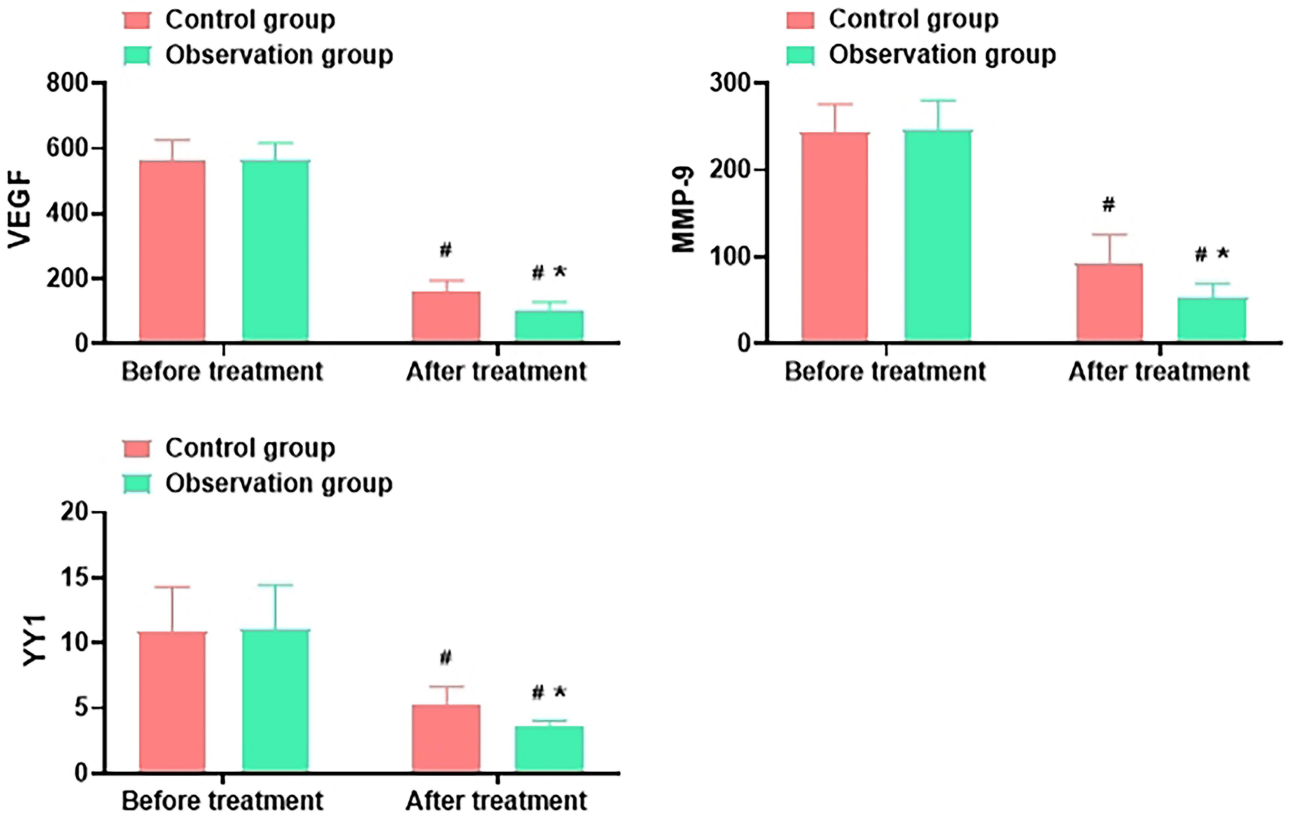

Figure 3 Comparison of Tumor Proliferation-Related Biomarker Concentrations ($\bar{x} \pm s$, ng/L).
Notes: Compared with the radiotherapy-alone group at the same time point, *P < 0.05; compared with baseline within the same group, #P < 0.05.
Abbreviations: VEGF, vascular endothelial growth factor; MMP-9, matrix metalloproteinase-9; YY1, transcription factor Yin Yang 1.

https://doi.org/10.2147/JMDH.S563311

Table 6 Comparison of Serum Tumor Marker Concentrations ($\bar{x} \pm s$)

	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	*t (df)*	*P*
CA125 (IU/mL)	–	–	–	–
Before treatment	81.54±24.27	82.23±25.19	0.116 (df=68)	0.907
After treatment	49.21±10.26#	35.87±10.05#	5.495 (df=68)	<0.001
CEA (mg/L)	–	–	–	–
Before treatment	9.75±2.14	9.85±1.79	0.212 (df=68)	0.832
After treatment	3.13±1.06#	2.07±0.58#	5.190 (df=68)	<0.001
SCC (μg/L)	–	–	–	–
Before treatment	1.94±0.53	1.95±0.47	0.083 (df=68)	0.933
After treatment	0.67±0.24#	0.52±0.18#	2.958 (df=68)	0.004

Notes: Compared with the same group before treatment, #P < 0.05.
Abbreviations: CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma antigen.

Discussion

Synergistic Effects of Radiotherapy and Immunotherapy and the Role of the Tumor Microenvironment

The combined application of radiotherapy and immunotherapy is not merely a simple addition but an enhancement of antitumor effects through multilevel synergistic mechanisms. First, radiotherapy induces immunogenic cell death (ICD) in tumor cells, leading to the release of numerous tumor antigens (such as HMGB1 and ATP). These antigens are captured by antigen-presenting

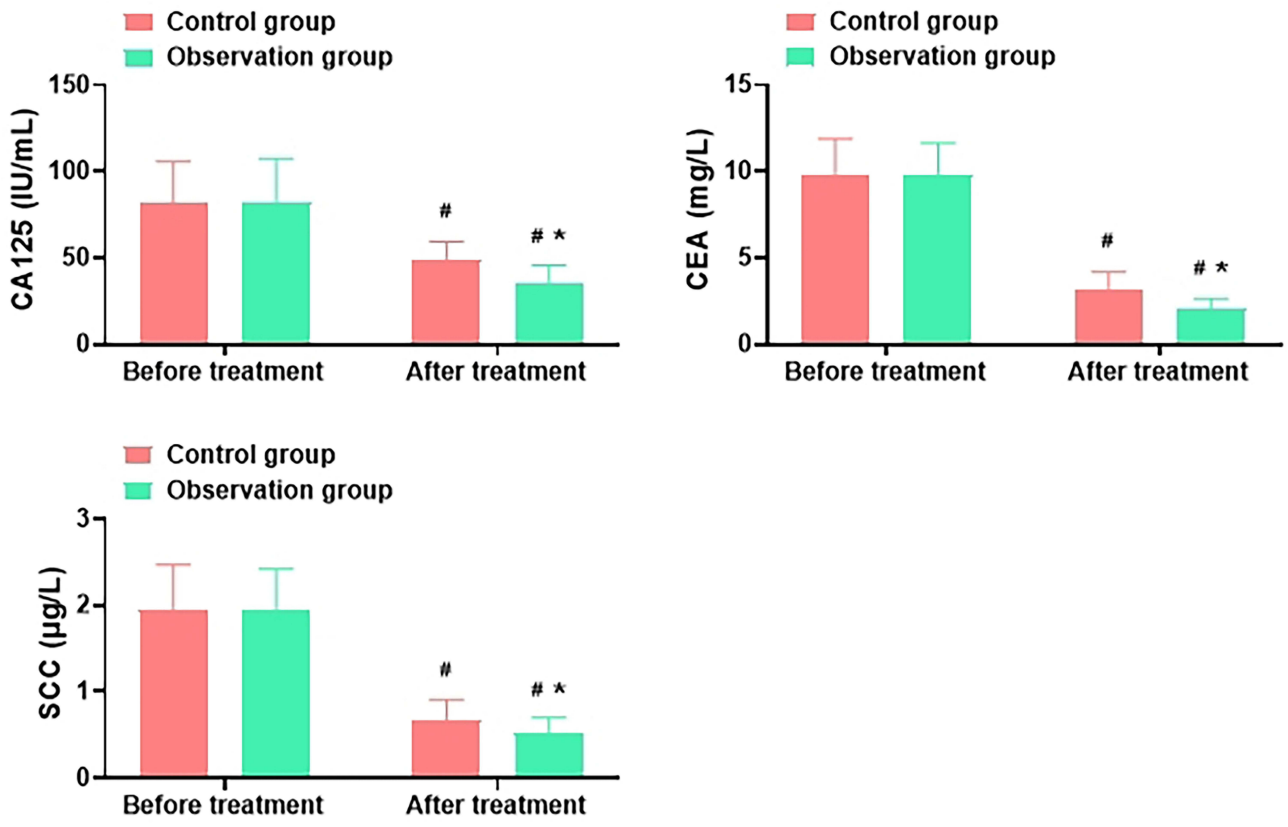

Figure 4 Comparison of Serum Tumor Marker Concentrations ($\bar{x} \pm s$).
Notes: Compared with the radiotherapy-alone group at the same time point, *P < 0.05; compared with baseline within the same group, #P < 0.05.
Abbreviations: CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma antigen.

https://doi.org/10.2147/JMDH.S563311

Table 7 Comparison of Adverse Reaction Incidence (n [%])

Adverse Reactions	Radiotherapy-Alone Group (n=35)	Radiotherapy Plus Immunotherapy Group (n=35)	x^2 (df)	P
Gastrointestinal reactions	–	–	–	–
Nausea	12 (34.29)	14 (40.00)	0.264 (df=1)	0.613
Vomiting	9 (25.71)	11 (31.43)	0.293 (df=1)	0.597
Diarrhea	4 (11.43)	5 (14.29)	0.135 (df=1)	0.729
Hepatic dysfunction	–	–	–	–
ALT elevation	6 (17.14)	7 (20.00)	0.097 (df=1)	0.768
AST elevation	5 (14.29)	6 (17.14)	0.106 (df=1)	0.756
Renal dysfunction	–	–	–	–
Creatinine elevation	4 (11.43)	5 (14.29)	0.132 (df=1)	0.724
Hematologic toxicity	–	–	–	–
Leukopenia	7 (20.00)	8 (22.86)	0.087 (df=1)	0.786
Anemia	8 (22.86)	9 (25.71)	0.076 (df=1)	0.795
Thrombocytopenia	3 (8.57)	4 (11.43)	0.153 (df=1)	0.703
Radiation-related reactions	–	–	–	–
Radiation esophagitis	4 (11.43)	3 (8.57)	0.000 (df=1)	1.000
Radiation dermatitis	3 (8.57)	4 (11.43)	0.156 (df=1)	0.704
Immune-related adverse events	–	–	–	–
Skin rash	–	5 (14.29)	–	–
Pruritus	–	4 (11.43)	–	–

cells (such as dendritic cells) and presented to T cells, thereby activating a systemic antitumor immune response.[20] This mechanism, known as the "abscopal effect" of radiotherapy, implies that radiotherapy not only exerts a local cytotoxic effect on tumors but also suppresses distant metastases through immune system activation. Second, radiotherapy remodels the tumor microenvironment by increasing the number of tumor-infiltrating lymphocytes (TILs) and promoting the release of pro-inflammatory cytokines (such as IFN-γ and TNF-α). These cytokines enhance T cell activity and function, thereby creating favorable conditions for immunotherapy.[21] Additionally, radiotherapy upregulates PD-L1 expression on tumor cell surfaces, while PD-1 inhibitors (such as camrelizumab) block the PD-1/PD-L1 pathway, relieving tumor-induced T cell suppression and enhancing T cell antitumor activity.[22] Recent studies further suggest that dynamic interactions among immune cells, cytokines, and tumor-associated factors within the tumor microenvironment play a critical role in modulating responsiveness to immune checkpoint blockade, highlighting the complexity of TME regulation in immunotherapy outcomes.[23–25] In this study, the ORR and DCR in the radiotherapy plus immunotherapy group were significantly higher than those in the radiotherapy-alone group, and T lymphocyte subsets showed marked improvement, suggesting an association between combined radiotherapy and immunotherapy and enhanced antitumor immune activity. However, given the retrospective and non-randomized nature of this study, these findings should be interpreted with caution, and causality cannot be definitively established.

Clinical Significance of Pain Relief

Pain is one of the most common symptoms in patients with recurrent esophageal cancer and severely impacts their quality of life.[26] In this study, patients in the radiotherapy plus immunotherapy group had significantly lower VAS scores at weeks 3 and 6 of treatment compared to the radiotherapy-alone group, indicating that radiotherapy combined with immunotherapy was associated with faster and more effective pain relief. This outcome may be related to the following mechanisms: (1) Tumor burden reduction: Immunotherapy inhibits tumor growth by activating the immune system, thereby reducing tumor compression and infiltration into surrounding tissues, leading to pain relief. (2) Regulation of inflammatory factors: Both radiotherapy and immunotherapy modulate inflammatory factor concentrations in the tumor microenvironment, reducing the release of pro-inflammatory cytokines,[27] thus alleviating pain. (3) Neuroimmune interactions: Immunotherapy may regulate neuroimmune interactions, reducing pain signal transmission. It should be noted that although pain relief is a clinically meaningful endpoint,

the present study did not formally analyze correlations between biomarker changes and pain outcomes, and the observed associations warrant further investigation in prospective studies.

Interpretation of Tumor Proliferation–Related Biomarkers

Studies[28] have shown that tumor proliferation-related factors play a crucial role in tumor growth, invasion, and metastasis. VEGF is a key factor in tumor angiogenesis, and its reduction may inhibit tumor blood supply, thereby limiting tumor growth.[29] MMP-9 contributes to extracellular matrix degradation, promoting tumor invasion and metastasis; its decreased expression may reduce tumor invasiveness.[30] YY1 is highly expressed in various tumors and participates in tumor cell proliferation and apoptosis regulation; its downregulation may suppress tumor growth.[31] In this study, after-treatment concentrations of VEGF, MMP-9, and YY1 in the radiotherapy plus immunotherapy group were significantly lower than those in the radiotherapy-alone group, suggesting that radiotherapy combined with immunotherapy not only directly kills tumor cells but also achieves multidimensional tumor control by inhibiting the expression of tumor proliferation-related factors. However, these biomarker changes primarily reflect biological associations, and their direct relationship with clinical efficacy or symptom improvement was not specifically examined in this study.

Serum Tumor Markers and Treatment Response

Furthermore, serum tumor markers are essential indicators for assessing tumor burden and therapeutic efficacy. CA125 is a widely used serum biomarker for various malignancies (such as ovarian, esophageal, and gastric cancers), and elevated serum concentrations are typically associated with tumor progression and poor prognosis.[32] CEA is a glycoprotein highly expressed in multiple epithelial tumors, with elevated serum concentrations often linked to tumor invasiveness and metastasis.[33] SCC is a tumor marker highly expressed in squamous cell carcinoma (such as esophageal and cervical cancers), and increased serum concentrations are generally correlated with tumor progression and poor prognosis.[34] In this study, after treatment, serum concentrations of CA125, CEA, and SCC in the radiotherapy plus immunotherapy group were significantly lower than those in the radiotherapy-alone group, further supporting a potential association between combined therapy and reduced tumor burden. Nevertheless, the prognostic implications of these changes require validation through long-term follow-up and survival analysis.

Safety Considerations

In terms of safety, although the incidence of adverse reactions in the radiotherapy plus immunotherapy group was slightly higher than that in the radiotherapy-alone group, the difference was not statistically significant, and all adverse reactions were mild to moderate and alleviated after symptomatic treatment. Common adverse reactions included nausea, vomiting, gastrointestinal reactions, liver and kidney function impairment, and hematological toxicity. These adverse reactions were consistent with those reported in previous studies.[35,36] Given the limited sample size, rare but severe immune-related adverse events may not have been captured in this cohort, and safety conclusions should therefore be interpreted cautiously. This is consistent with findings from larger studies evaluating immune checkpoint inhibitors combined with radiotherapy.[37,38]

Limitations

Despite the promising findings of this study, several limitations should be acknowledged. First, the sample size was relatively small, with only 70 patients included, which may limit the generalizability of the results. Second, this was a retrospective, non-randomized study, and treatment allocation was based on routine clinical practice, which may introduce selection bias. Third, follow-up observation was limited, and long-term outcomes such as overall survival, progression-free survival, and late adverse events could not be evaluated. Future studies should incorporate longer follow-up periods to assess sustained efficacy and long-term safety. Finally, this study primarily focused on clinical efficacy and selected biological indicators, and mechanistic exploration was limited. Further studies are warranted to elucidate the molecular and immunological mechanisms underlying the combination of radiotherapy and immunotherapy.

Conclusion

In conclusion, in the current study cohort, radiotherapy combined with camrelizumab-based immunotherapy was associated with pain relief, improvement in immune-related parameters, and reductions in tumor proliferation–related

biomarkers in patients with recurrent esophageal cancer. These findings provide preliminary and exploratory signals suggesting potential clinical benefit of the combined treatment approach. However, given the retrospective and non-randomized nature of this study, these observations should be interpreted with caution and require confirmation in larger, prospective studies incorporating biological markers and survival endpoints.

Abbreviations

VAS, Visual Analog Scale; VEGF, Vascular Endothelial Growth Factor; MMP-9, Matrix Metalloproteinase-9; YY1, Yin Yang 1; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen; SCC, Squamous Cell Carcinoma Antigen; CD3, Cluster of Differentiation 3; CD4, Cluster of Differentiation 4; CD8, Cluster of Differentiation 8; RT, Radiotherapy; PD-1, Programmed Death-1; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; ECOG, Eastern Cooperative Oncology Group; ANOVA, Analysis of Variance; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; ORR, Objective Response Rate; DCR, Disease Control Rate; IMRT, Intensity-Modulated Radiotherapy; GTV, Gross Tumor Volume; CTV, Clinical Target Volume; PTV, Planning Target Volume; OARs, Organs at Risk; KPS, Karnofsky Performance Status; MDT, Multidisciplinary Team; RECIST, Response Evaluation Criteria in Solid Tumors; TME, Tumor Microenvironment.

Funding

Funding Clinical Research on Circulating Tumor DNA Combined with Low-dose Spiral CT in Early Screening of Lung Cancer;Fund Name: Joint Fund of Key Laboratory of Occupational Hazard Identification and Control in Hubei Province; Project Number:JF2024-Y23.

Disclosure

The authors report no conflicts of interest in this work.

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