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The effect of simultaneous low-dose splenic irradiation on immune function during esophageal cancer radiotherapy

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► ***Original article***

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ABSTRACT

Background*:** The objective of this study was to examine the impact of synchronous low-dose splenic irradiation (LDSR) on immune function in patients with esophageal cancer undergoing radiotherapy. ***Materials and Methods: Twenty-one patients who were diagnosed with esophageal cancer were randomly allocated to either the control or experimental groups. The control group received routine radiotherapy alone, whereas the experimental group underwent simultaneous LDSR during radiotherapy. Low dosage radiation refers to a beam with a low linear energy transfer (LET) that delivers a dose of 0.2 Gy or less, or a high LET beam that delivers a dose of 0.05 Gy or less, while maintaining an exposure dose rate of 0.005 cGy/min. The lymphocyte subsets in the two groups were analyzed using flow cytometry at various time points during and after treatment. Additionally, complications and their occurrence times were recorded simultaneously. ***Results:*** Gradual decreases were observed in CD16+CD56+, CD3+CD4+, and CD4+/CD8+ ratios following radiotherapy in the control group ($p < 0.05$). However, no considerable differences were observed between the experimental groups in these ratios ($p > 0.05$). LDSR was found to induce immunological enhancement and counteract immune suppression caused by radiotherapy. Furthermore, the experimental group experienced larger cumulative dosages that led to problems compared to the control group, with a delayed onset. Despite receiving a higher cumulative dose, the experimental group exhibited lower levels of myelosuppression and radiation esophagitis than the control group ($p < 0.05$). Overall, the results suggest that synchronous LDSR can enhance immune function during radiotherapy in patients with esophageal cancer and reduce the adverse effects associated with routine radiotherapy. ***Conclusion:*** Synchronous LDSR may induce immunological enhancement during radiotherapy in patients with esophageal cancer, reduce adverse reactions to routine radiotherapy, and enhance tolerance.

INTRODUCTION

Radiation is a phenomenon in which energy diffuses outwards in the form of electromagnetic waves or particles. Humans are generally exposed to small amounts of natural and medical radiation. The concept of low-dose radiation (LDR) was introduced by the United Nations Scientific Committee on the Effects of Atomic Radiation in 1986. LDR is defined as a ray with a low linear energy transfer (LET) that delivers a dose of 0.2 Gy or less, or a ray with a high LET that delivers a dose of 0.05 Gy or less, while still maintaining an exposure dose rate of 0.005 cGy/min. Previous studies have shown thathigh-dose (> 1 Gy) radiation has been evaluated in the linear non-threshold (LNT) model in terms of its risk factors for the body [1], while LDR can stimulate body damage repair and promote immune function enhancement [2,3]. Recent fundamental research has demonstrated that LDR augments immune cell populations in the thymus and spleen, particularly dendritic cells (DCs), splenic macrophages, and natural killer (NK) cells. Furthermore, the cells reached a stable state [4]. The spleen, one of the most important immune organs, exhibits the most immediate immune response after exposure to LDR, and the outcome is beneficial [5]. Therefore, we investigated whether immune enhancement could be achieved equally well through LDR to the spleen in a clinical setting.

China is a high-risk area for esophageal cancer [4]. The majority of patients receive a diagnosis at the advanced stages of their condition while seeking medical advice, resulting in a 5-year survival rate of less than 30%. Most patients received different degrees of radiotherapy during their lifetime. Nutrient absorption in patients with esophageal cancer is generally poor, and long-term consumption is high. Combined with poor immune function, radiotherapy inevitably causes further damage to the immune system [6]. Further improvements in the long-term therapeutic effect in patients with esophageal cancer, reduced immunosuppression, improved prognosis, and improved survival rates have become bottlenecks in esophageal cancer treatment. To better

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observe the immunostimulatory effects of LDR and the protective effects of high-dose radiation on human esophageal cancer, the present study aimed to evaluate the concurrent impacts of low-dose splenic irradiation (LDSR) on immune function during radiotherapy for esophageal cancer. Notably, this is the first study to apply low-dose radiation to patients with esophageal cancer requiring radical radiotherapy.

MATERIALS AND METHODS

General Information

Following approval from the Ethics Committee of the hospital, a total of 22 patients diagnosed with esophageal cancer who were admitted to the People's Hospital of Shanxi Medical University between December 2018 and August 2019 were selected. After completing the informed consent form for the clinical trial, the participants were randomly allocated to either the experimental or the control group. The experimental group received a combination of conventional radiation therapy and LDSR, whereas the control group received conventional radiation therapy. One participant in the experimental group voluntarily discontinued their participation in the study because of personal circumstances, while the remaining 21 participants successfully completed the investigation. There was no noticeable difference of general data between the two groups (table 1).

Table 1. Comparison of general data analysis between the two groups of patients.

Clinical variables		Control group (n=10)	Experimental group (n=11)	*P*
Age		67.70±8.82	72.55±6.83	0.173
Gender				
Male		6 (60.0)	7 (63.6)	0.864
Female		4 (40.0)	4 (36.4)	
Segmentation				
Upper thoracic	5 (50.0)	5 (45.5)	0.985	
Middle thoracic	2 (20.0)	3 (27.3)		
Lower thoracic	2 (20.0)	2 (18.2)		
Neck section	1 (10.0)	1 (9.1)		
Staging				
II	1 (10.0)	3 (27.3)	0.565	
III	5 (50.0)	5 (45.4)		
IV	4 (40.0)	3 (27.3)		
Length	7.50±2.07	7.18±1.99		0.723
QOL score before treatment	54.80±1.87	54.00±3.00		0.478

There were no considerable disparities in the overall attributes of the two groups.

Inclusion and exclusion criteria

All of the following criteria were met: pathology confirmed as esophageal squamous cell carcinoma; no treatment for esophageal cancer was received before treatment, such as surgery, radiotherapy, chemotherapy, targeted therapy, and immunomodulation treatment; the purpose of this treatment was to only provide local treatment of esophageal cancer, and no other part needed to receive radiation therapy at the same time; peripheral blood leukocyte count was ≥ 4.0 × 10^9/L; liver and kidney function and the electrocardiogram were almost normal; the patient and/or their family members provided informed consent and signed the corresponding consent form; and consented to participate in the follow-up process.

Patients were excluded if they fulfilled any of the subsequent conditions: severe respiratory diseases, severe liver and kidney dysfunction, hematological diseases, circulatory diseases, other immune system diseases, other diseases that have an impact on the immune system, or diagnosed with multiple primary cancers.

Methods

We used the Swedish Elekta Precise Linac (Toshiba LX-40A, Japan) to simulate localization and a full carbon-fiber frame. All patients were positioned in the supine posture. The patient's body was fixed with a thermoplastic body film and the lead point was marked using a shifting bed and laser light to determine the isocenter position. Chest enhancement CT was performed (Siemens 64-slice CT, Siemens, German). The image information was uploaded to the radiotherapy planning system (Philips Pinnacle, Netherlands) and the target area was defined and delineated. Gross tumor volume (GTV) included both the lymph nodes and primary tumor that tested positive for cancer. To determine the planning gross tumor volume (PGTV), a 5 mm expansion was applied. The clinical tumor volume (CTV) encompassed the elective nodal irradiation (ENI), and it was expanded by 5 mm to generate planning tumor volume 1 (PTV 1) (figure 1). In the experimental group, the spleen was outlined and expanded by 5 mm to generate planning tumor volume 2 (PTV 2) (figure 2), the planning organ at risk volume (PRV) was outlined, and V20 ≤ 30% was limited to both lungs, heart V40 < 30%, and spinal cord Dmax ≤ 45 Gy to evaluate the radiation dose.

Two groups of patients were treated with 6 MV X-ray intensity-modulated radiotherapy. Both groups were prescribed the following doses for radical esophageal cancer treatment: PTV 1 DT 50 Gy/25 f/5 w, PGTV DT 60 Gy/30 f/6 w - DT66 Gy/33 f /6.6 w. The experimental group also received simultaneous LDSR using 6 MV X-rays at a dosage rate of 2 cGy/min, 6-8 hours prior to receiving radical radiotherapy on Mondays and Thursdays. The prescribed dose for LDSR was as follows: PTV 2 DT 48-52 cGy/12-13 f/6-6.2 w. The PTV1 and PTV2 dose ranges were 95% and 107%, respectively.

Observation index

Determination of immune function

A BD FACSAria II flow cytometer and IMK Kit

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reagent (BD Medical Devices Co., Ltd, China) were used to detect lymphocyte subsets in peripheral blood, including helper T cells (CD3+CD4+), NK cells (CD16+CD56+), and CD4+/CD8+ ratios, before treatment, at 3 weeks of treatment, and at the end of treatment.

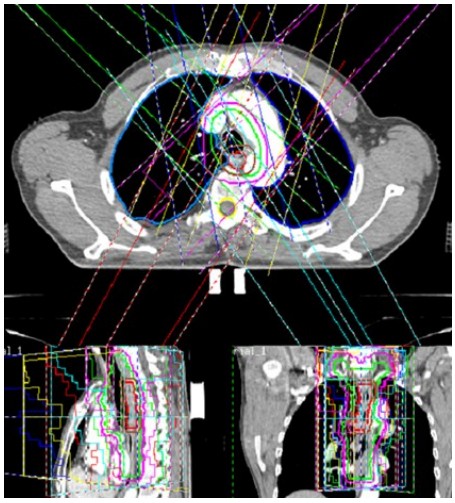

Figure 1. Target delineation and field distribution of conventional radical radiotherapy.

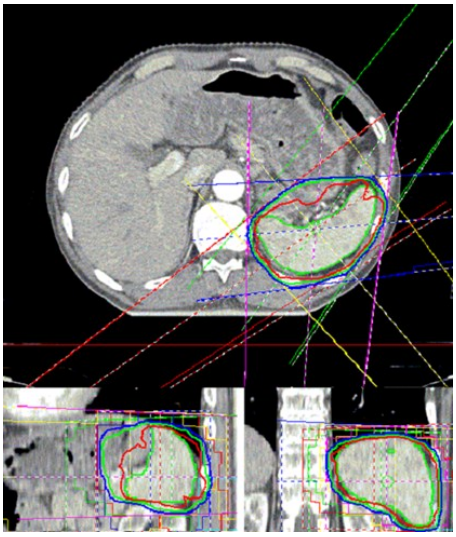

Figure 2. Target delineation and field distribution of spleen irradiation.

Adverse reactions

During treatment, patients in the two groups were observed for symptoms of acute radiation esophagitis, such as hypopharyngeal pain and retrosternal pain; skin erythema, tenderness, peeling, and other skin reaction symptoms; gastrointestinal symptoms, such as nausea and vomiting; and decreased leukocyte, neutrophil, hemoglobin, and platelet counts in the peripheral blood.

Statistical analysis

Qualitative and quantitative data are presented as percentage (number) and mean ± standard deviation (M ± SD), respectively. The independent samples t-test was employed to compare groups, whereas the paired samples t-test was used to compare within the group. The Bonferroni method was used to compare the two groups. The chi-square test was used to compare qualitative variables between groups, and the rank sum test was used for grade data and verification. Statistical analysis of the main effects and interactions of time and treatment was performed using an analysis of variance of repeated-measures design. The statistical software used was SPSS 20.0 (SPSS Inc., Chicago, IL. USA), and statistical significance was set at $p < 0.05$.

RESULTS

Simultaneous LDSR to reduce immunosuppressive effects during radiotherapy

The $CD16^+CD56^+$, $CD3^+CD4^+$, and $CD4^+/CD8^+$ ratios gradually decreased in the control group as radiotherapy progressed; however, these ratios did not change significantly in the experimental group. No substantial differences were observed between $CD16^+CD56^+$, $CD3^+CD4^+$, and $CD4^+/CD8^+$ cells before treatment between the two groups ($p>0.05$). The observed dissimilarities among the CD markers during and subsequent to the therapeutic intervention exhibited statistical significance (table 2).

Table 2. Comparison of lymphocyte subsets levels between the two groups at before, during, and after treatments.

Variables	Control group (n=10)	Experimental group (n=11)	*P*
$CD16^+CD56^+$			
Before treatment	0.16±0.05	0.21±0.08	0.101
During treatment	0.10±0.04	0.20±0.08	0.002
After treatment	0.07±0.03	0.19±0.07	< 0.001
CD3+CD4+			
Before treatment	0.36±0.07	0.36±0.08	0.845
During treatment	0.31±0.07	0.38±0.08	0.049
After treatment	0.26±0.05	0.37±0.07	< 0.001
CD4+/CD8+			
Before treatment	1.39±0.63	1.59±0.68	0.483
During treatment	1.12±0.38	1.77±0.71	0.018
After treatment	0.83±0.36	1.73±0.65	0.001

During the progression of radiotherapy, the CD16+CD56+, CD3+CD4+ and CD4+/CD8+ ratios gradually decreased in the control group, while remaining relatively stable in the experimental group. There were no notable differences in the CD16+CD56+, CD3+CD4+ and CD4+/CD8+ ratios between the two groups before treatment ($p > 0.05$). Statistically significant difference was observed in these indicators during and after treatment ($p < 0.05$).

Simultaneous LDSR can reduce adverse reactions to routine radiotherapy and enhance patient tolerance

Compared to the control group, simultaneous LDSR significantly reduced immunosuppression in patients treated with radiotherapy (figures 3 and 4). The changes in the blood levels of $CD16^+CD56^+$, $CD3^+CD4^+$, and $CD4^+/CD8^+$ cells in the experimental group were not statistically significant before, during, or after the intervention ($p > 0.05$). The changes in $CD16^+CD56^+$ and $CD3^+CD4^+$ cells in the peripheral blood of patients in the control group were statistically significant before, during, and after treatment ($p < 0.05$), and $CD4^+/CD8^+$ cells were not considerably different before and after intervention

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(p > 0.05). However, the changes before and during treatment were statistically significant compared to those after treatment (p < 0.05) (table 3).

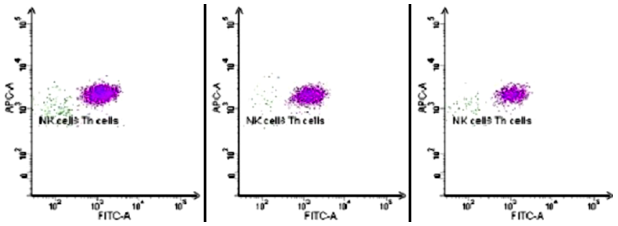

Figure 3. Changes in CD16+CD56+ and CD3+CD4+ cells before, during, and after treatment in the control group. The immunofluorescence intensity of CD16+CD56+ (NK cells) and CD3+CD4+ (Th cells) in the control group gradually decreased with the progression of radiotherapy, and the immune function was reduced.

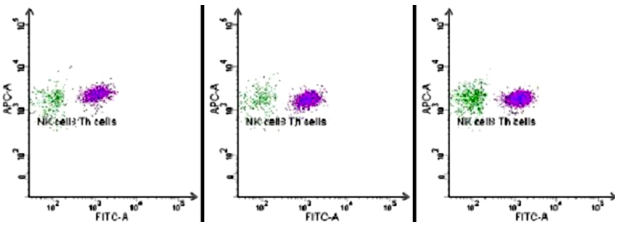

Figure 4. Changes in CD16+CD56+ and CD3+CD4+ cells before, during, and after treatment in the experimental group. The immunofluorescence intensity of CD16+CD56+ (NK cells) and CD3+CD4+ (Th cells) in the experimental group did not change much with radiotherapy, and the immune function tended to be stable.

LDSR had different effects on immune enhancement before, during, and after treatment

The statistical analysis revealed that low-dose spleen irradiation and treatment time delay had a significant effect on the change in $CD16^{+}CD56^{+}$ cells (p = 0.01). However, there was no considerable interaction between these two variables (p > 0.05). Additionally, the analysis showed that the low-dose spleen irradiation and time had a statistically significant effect on $CD3^{+}CD4^{+}$ and $CD4^{+}/CD8^{+}$ (p < 0.05) and there was also an interaction effect (p < 0.01) (table 4).

Synchronous LDSR reduces the level of radiotherapy complications and delays their occurrence.

During the therapeutic intervention, there was no noticeable difference in the grades of cutaneous and gastrointestinal responses between the two groups (p > 0.05). Additionally, the experimental group experienced significantly less myelosuppression and radiation-induced inflammation of the esophagus compared to the control group (p < 0.05) (table 5). In the experimental group, the cumulative doses causing skin reactions, digestive tract reactions, myelosuppression, and radiation esophagitis were found to be higher compared to the control group, which meant that the occurrence time was delayed, patient tolerance was better, and the difference between myelosuppression and radiation esophagitis was significant (p < 0.05) (table 6).

Table 3. Comparison of lymphocyte subsets levels between the two groups at different time points.

Variables	Control group		Experimental group	
	t	*P*	*t*	*P*
$CD16^{+}CD56^{+}$				
Before treatment: during treatment	19.391	<0.001	1.653	0.129
Before treatment: after treatment	15.507	<0.001	1.333	0.212
During treatment: after treatment	5.782	<0.001	0.209	0.838
$CD3^{+}CD4^{+}$				
Before treatment: during treatment	5.847	<0.001	0.807	0.438
Before treatment: after treatment	6.550	<0.001	0.328	0.749
During treatment: after treatment	4.321	0.002	0.426	0.679
$CD4^{+}/CD8^{+}$				
Before treatment: during treatment	1.899	0.090	2.068	0.065
Before treatment: after treatment	3.984	0.003	1.643	0.131
During treatment: after treatment	5.581	<0.001	1.140	0.281

In the experimental group, there were no notable alterations in the blood levels of CD16+CD56+, CD3+CD4+ and CD4+/CD8+ cells in patients before, during, and after radiotherapy, as indicated by the lack of statistical significance (p > 0.05). In contrast, the peripheral blood of patients in the control group showed statistically significant changes in CD16+CD56+ and CD4+/CD8+ levels before, during, and after treatment (p < 0.05). Additionally, CD4+/CD8+ levels before and during treatment were considerably significant compared to those after treatment (p < 0.05).

Table 4. Variance analysis in each group of patients at different time points using repeated measurement design.

Variables	SS	df	MS	F value	P value
$CD16^{+}CD56^{+}$					
Low-dose splenic irradiation	0.182	1	0.182	17.097	0.001
Time	0.010	2	0.005	9.273	0.001
Low-dose splenic irradiation × time	0.002	2	0.001	1.491	0.238
Difference between groups	0.203	19	0.011		
Intragroup difference	0.021	38	0.001		
$CD3^{+}CD4^{+}$					
Low-dose splenic irradiation	0.059	1	0.059	5.066	0.036
Time	0.021	2	0.011	7.153	0.002
Low-dose splenic irradiation × time	0.028	2	0.014	9.570	< 0.001
Difference between groups	0.220	19	0.012		
Intragroup difference	0.056	38	0.001		
$CD4^{+}/CD8^{+}$					
Low-dose splenic irradiation	5.326	1	5.326	5.613	0.029
Time	0.510	2	0.255	5.534	0.008
Low-dose splenic irradiation × time	1.275	2	0.638	13.834	< 0.001
Difference between groups	18.029	19	0.949		
Intragroup difference	1.752	38	0.046		

Remarks: CD16+CD56+ spherical test statistic w = 0.820, p = 0.167, satisfied spherical symmetry; CD3+CD4+ spherical test statistic w = 0.840, p = 0.207, satisfied spherical symmetry; and CD4+/CD8+ spherical test statistic w = 0.857, p = 0.250, satisfied spherical symmetry. The effect of low-dose spleen irradiation and treatment time delay on the change in CD16+CD56+ in the experiment was statistically significant (p = 0.01), but there was no interaction between the two variables (p > 0.05). The effect of low-dose spleen irradiation and time on CD4+/CD8+ and CD4+/CD8+ was not only statistically significant (p < 0.05) but there was also an interaction effect (p < 0.01).

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Table 5. Comparison of complications during treatment between both groups.

Complications	Control group (n=10)	Experimental group (n=11)	*Z*	*P*
Acute radiation esophagitis				
Level 1	2 (20.0)	7 (63.6)	2.303	0.021
level 2	5 (50.0)	4 (36.4)		
Level 3	3 (30.0)	0 (0.0)		
Skin reaction				
Level 0	7 (70.0)	8 (72.7)	0.135	0.893
Level 1	3 (30.0)	3 (27.3)		
Digestive tract reaction				
Level 0	4 (40.0)	5 (45.5)	0.702	0.482
Level 1	4 (40.0)	6 (54.5)		
Level 2	2 (20.0)	0 (0.0)		
Myelosuppression				
Level 0	0 (0.0)	1 (9.1)	2.231	0.026
Level 1	2 (20.0)	6 (54.5)		
level 2	6 (60.0)	4 (36.4)		
Level 3	2 (20.0)	0 (0.0)		

The experimental group exhibited remarkably reduced levels of acute radiation esophagitis and myelosuppression in comparison to the control group, as indicated by the statistical analysis ($p < 0.05$).

Table 6. Comparison of cumulative doses of radiotherapy complications between the two groups.

Complication	Control group	Experimental group	*t*	*P*
Acute radiation esophagitis	15.00±4.83	21.45±4.91	3.033	0.007
Skin reaction	46.67±9.02	54.00±4.00	0.314	0.267
Digestive tract reaction	22.67±6.28	30.67±14.01	1.276	0.243
Myelosuppression	15.80±6.43	22.00±6.11	2.211	0.040

The experimental group exhibited a higher cumulative dose at which adverse reactions such as skin reactions, gastrointestinal reactions, bone marrow suppression, and radiation esophagitis occurred compared to the control group, indicating a delayed onset of adverse reactions.

DISCUSSION

Esophageal carcinoma is a prevalent malignancy that affects the digestive tract. Approximately 400,000 people die each year from esophageal cancer [7], the low 5-year survival rate of esophageal cancer is not only due to the less obvious nature of its early symptoms, leading to delays in treatment time, but also due to the complex anatomical structure around the esophagus and its biological behavior. The esophageal wall and lymphatic tissues are abundant, and lymphatic metastasis is the main pathway of esophageal cancer metastasis, lymphatic tissue destruction reduces patient immunity. The thymus is an important central immune organ, located behind the sternum and close to the heart, and is inevitably exposed to different degrees of irradiation during radiotherapy for esophageal cancer. Myelosuppression after sternal, rib, and vertebral radiotherapy results in varying degrees of damage to the cellular and humoral immunity. Therefore, for patients with esophageal cancer who choose to receive radiation therapy, inhibition of immune function is undoubtedly one of the main poor prognostic factors.

LDR stimulates cell proliferation, reverses tissue damage, and enhances immunity. LDR has a long history. In 1967, Johnson *et al.* [8] applied LDR to non-Hodgkin's lymphoma and confirmed the antitumor ability of LDR; however, they could not determine the reason for this phenomenon. Until the 1980s, the introduction of the LDR excitatory effect (hormesis) led to a peak in LDR research [9]. LDR stimulation of cell proliferation is manifested in two parts: normal tissue cells and immune-related cells. Chen et al. showed that a protein emerged in the cytoplasm of thymocytes 4-8 hours after LDR, inducing the proliferation of splenocytes and increasing the expression of CD16+CD56+ and CD3+CD4+, which was in agreement with the present findings [10]. Liu *et al.* combined conventional radiotherapy and LDR in a synthetic mouse model of breast and colon cancer. They found that LDR improved the immune microenvironment by altering the CD4+CD8+ T-cell infiltration status [11], which is consistent with the increase in CD4+CD8+ T cells observed in this study. Additionally, some studies have shown that LDR has a positive effect on the proliferation of neural stem cells and hematopoietic stem cells [12,13]. Increased proliferation of normal cells, particularly stem cells, is strongly associated with tissue repair, suggesting that LDR plays a potential role in tissue repair. In figures 3 and 4, we similarly observed that LDR was utilized to irradiate the spleen, and we also observed an immunostimulatory effect of LDR. In innate immunity, LDR can increase the cytotoxicity of macrophages, stimulate the p38-MAPK pathway to improve the activity of NK cells, facilitate the release of cytokines by DCs, and enhance their antigen-presenting ability [14-16]. In the present study, tables 2 and 3 show that circulating levels of CD16+CD56+, CD3+CD4+, and CD4+/CD8+ cells remained stable before and after treatment in patients who underwent LDR. By contrast, these levels continued to decrease in the control group. This confirmed the stimulatory proliferative impact of LDR on NK and T cells. LDR stimulates positively associated cytokines, including IFN-γ, TNF-α, and IL-2 [17,18], inhibits negatively associated cytokines, and regulates the release of T cells and cytokines, such as IL-10 and TGF-β [19-21], thereby simultaneously augmenting the body's immune surveillance and cytotoxicity towards malignant tumors while concomitantly suppressing the progression and metastasis of malignant cells. Subsequently, we will further investigate the mechanism of LDR immunoexcitation by using other models.

This study found that in patients with esophageal cancer undergoing radiotherapy, simultaneous LDSR could ameliorate the reduction in peripheral blood immune-related cells and induce

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immune enhancement. The elimination of immunosuppression is more conducive to the body's immune mechanism to secondarily kill tumor cells. Thus, the efficacy of radiotherapy has been further improved and consolidated. In addition, as shown in tables 5 and 6, the experimental group in this study showed a lower level of complications, which are not only related to the stability of immune function, but also to the promotion of cell proliferation and tissue repair by LDR. Simultaneous LDSR can alleviate adverse reactions to conventional radiotherapy and improve patient tolerance. At present, basic research on LDR at home and abroad is more advanced, and most studies have confirmed that LDR can induce immune enhancement, and can stimulate cell proliferation and tissue repair. However, few clinical trials have been conducted on LDR. Our aim was to provide additional research data on the clinical application of LDR to inform future clinical practices.

CONCLUSION

Concurrent administration of LDSR along with LDR and conventional radiotherapy has the potential to induce immune enhancement during radiotherapy in patients with esophageal cancer, thereby diminishing the adverse effects of conventional radiotherapy and augmenting patient tolerance. However, owing to the small number of cases in this study, further clinical trials are necessary to improve clinical treatment.

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Availability of data and materials: All data produced or examined during this investigation are encompassed within this published publication. Furthermore, data can be obtained by interested researchers upon contact with the relevant author.

Ethics approval and consent to participate: This study was approved by Shanxi Provincial People's Hospital (No.20170612). All patients provided consent by signing a form that authorized secondary utilization of their medical records.

Authors' contributions: XS conceived and designed the study, analyzed data, interpreted data, and wrote the paper; YG and XL reviewed articles; XN performed data analysis; and XZ and JR collected data. All authors read and approved the final manuscript.

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