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The role of deep hyperthermia in IMRT in elderly patients with esophageal cancer: a retrospective cohort study

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Abstract

Purpose This study aimed to assess the clinical utility of deep hyperthermia in elderly patients with esophageal cancer(EC) who underwent intensity-modulated radiotherapy(IMRT).

Patients and methods This retrospective analysis included 177 elderly patients with EC who underwent IMRT between 2017 and 2023, 42 of whom had combined deep hyperthermia (HT). Propensity score matching (PSM) was used to balance the covariates between the thermoradiotherapy (HTRT) group and IMRT-alone groups. Treatment outcomes and toxicities were compared between the two groups. We used the Kaplan-Meier method to estimate survival curves and the log-rank test to compare survival curves. Cox multivariate analysis was performed to analyze the prognostic factors in these patients.

Results After PSM (42 patients in each group), the HTRT group had a greater objective response rate (ORR) than the IMRT-alone group (83% vs. 62%, $P=0.028$). The HTRT group had less radiotherapy-related toxicity, including a lower incidence of leukopenia (14% vs. 33%, $P=0.040$) and RP grade ≥ 2 ($P=0.012$). However, the 1-, 2-, and 3-year overall survival (OS) rates and 1-, 2-, and 3-year disease-free survival (DFS) rates were not significantly different ($P=0.730$, 0.964). Grade ≥ 2 hypoproteinemia (odds ratio [OR] = 3.798, $P=0.004$), radiotherapy dose ≤ 60 Gy (OR = 0.445, $P=0.006$), and tumor location in the lower esophagus (OR = 0.387, $P=0.005$) were adverse prognostic factors for OS. Hypoproteinemia grade ≥ 2 (OR = 3.676, $P<0.001$) was also a crucial prognostic factor for DFS.

Conclusion Adding deep hyperthermia to IMRT can improve the ORR in elderly patients with EC. In addition, it significantly reduces radiotherapy-related toxicity. Although this approach does not improve the long-term prognosis, it is still practical and has low toxicity, making it suitable for clinical use.

Keywords Radiotherapy, Hyperthermia, Esophageal cancer, Efficacy

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Introduction

Esophageal cancer (EC) ranks sixth in overall mortality rates according to the 2020 global cancer data statistics [1]. The incidence significantly increased after the age of 60 years. Radiotherapy is the primary treatment for patients with non-operative esophageal cancer. IMRT is currently widely used. The 5-year OS rate of patients with esophageal squamous cell carcinoma who received radiotherapy alone was only 12.5% [2]. This poses a significant clinical challenge to clinicians. Although synchronous chemotherapy can improve patient survival, it is unavailable for some patients and increases radiotherapy toxicity. The development of safer and more effective combined antitumor therapeutic strategies is urgently required.

Hyperthermia is a traditional physical antitumor therapy, but its development is not stable. In recent years, several experiments and clinical studies have confirmed the synergistic effects of hyperthermia and radiotherapy. Several phase III trials have shown that combining radiotherapy with hyperthermia benefits local control in recurrent breast cancer, malignant melanoma, and nasopharyngeal cancer and improves survival in head and neck lymph node metastases and cervical carcinoma [3–6]. The underlying mechanism is beginning to be elucidated, and clinical studies of hyperthermia have regained attention. Clinical studies have been conducted on intraluminal stent thermotherapy and intrathoracic thermotherapy for EC. However, there is still a lack of research on deep hyperthermia for EC treatment [7, 8]. This study employed PSM on real-world data to mitigate bias, explored the effect of deep hyperthermia in elderly patients with EC who received IMRT, and analyzed the factors influencing patient prognosis.

Methods and materials

Patients

We searched the clinical database of thousands of patients with EC who underwent IMRT at Soochow University First Affiliated Hospital and Yixing Cancer Hospital between 2017 and 2023.

The study involved patients aged 60 years or older who were diagnosed with esophageal squamous cell carcinoma and were either ineligible for surgery due to medical conditions or declined surgical treatment. The exclusion criteria for this study included the presence of bleeding or bleeding tendencies, severe organ dysfunction, esophageal fistula, or severe infection before or during radiotherapy; nonregional lymph node metastasis or distant metastasis; incomplete treatment; and receipt of other antitumor therapies during IMRT.

A total of 177 patients were enrolled in this study. These patients were then categorized into HTRT and IMRT-alone groups based on whether they received deep hyperthermia treatment. This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University and Yixing Cancer Hospital.

Treatment

All patients provided consent by signing a treatment form before undergoing IMRT and deep hyperthermia.

Radiotherapy

All the patients underwent IMRT. Radiotherapy was administered in the supine position using thermoplastic molds or vacuum pads for precise positioning. The total tumor volume (GTV) was defined as the tumor visible on a CT scan, endoscopy, or esophagography. GTVnd revealed highly suspicious lymph nodes. The clinical target volume (CTV) was defined as the GTV with a 3 cm expansion in the superior and inferior directions and a 0.8 cm expansion in the anterior, posterior, left, and right directions. The location of the esophageal lesion determines the lymph node drainage areas that need to be mapped. The planning target volume (PTV) was determined by expanding the CTV by 0.5 cm in all directions, followed by marking the radiotherapy center on the patient's body surface.

The prescribed radiation dose for the primary lesion and regional metastatic lymph nodes ranged from 50 to 66 Gy, whereas for lymph node drainage areas, it ranged from 45 to 54 Gy. The dose was given in fractions of 1.8–2.0 Gy per session, once daily and five times weekly, with the PTV receiving 95% of the prescribed dose. The organ at risk constraints were as follows: the mean lung dose (MLD) should not exceed 15 Gy, V20 should be less than or equal to 30%, V30 should be less than or equal to 20%, the maximum spinal cord dose should not exceed 45 Gy, the mean heart dose should not exceed 30 Gy, and the V30 of the heart should be less than 50%.

Deep hyperthermia

Deep hyperthermia involves regional heating and the heating depth can exceed 10 cm. Forty-two patients underwent deep hyperthermia treatment according to the Chinese Clinical Application Guidelines for Hyperthermia published in 2017 [9].

The hyperthermia equipment utilized was an HG 2000III external high-frequency hyperthermia machine manufactured by Zhuhai Hejia Medical Equipment Co., Ltd. The machine operates at a frequency of 13.56 MHz, boasts a maximum output power of 600 W, and has an adequate heating depth of 17–25 cm. High-frequency deep hyperthermia treatment was administered using electrode plates measuring 20 cm × 20 cm, with one positioned on the chest and another on the back. The electrode plate was placed at the treatment center on the

body surface with precise alignment to the center, maintaining a distance of 5–7 cm from the skin. Multiple surface thermometers were used for meticulous temperature control between 41 °C and 43 °C.

Hyperthermia treatment was initiated on the first day of radiotherapy and continued twice a week until the completion of radiotherapy, totaling of 10–13 sessions. The duration of each hyperthermia session was 40 min, occurring within a one-hour timeframe before radiotherapy. The time interval between two consecutive hyperthermia sessions was 72 h. During treatment, patients were positioned to ensure precise alignment of the electrode plates with the chest. Blood pressure and heart rate changes were closely monitored, and hyperthermia was promptly discontinued in the patients with abnormalities.

Data collection and follow-up

We collected data on age, sex, tumor length, tumor location, clinical stage, Karnofsky performance status (KPS), personal history of smoking, high blood pressure, diabetes status, primary lung disease status, radiotherapy dose, complete blood count, biochemical indices, X-ray/CT/esophagography results, other imaging findings, endoscopic data, and additional information from the electronic medical record system. All patients were restaged according to the staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) in 2017.

We conducted weekly reviews of complete blood counts and esophagography during radiotherapy and reviewed biochemical indicators every two weeks. After the end of treatment, we conducted follow-up evaluations one month later. We continued evaluations every three–six months for two years and every six–12 months starting in the third year. Follow-up evaluations included endoscopy, chest radiography, chest and abdominal CT scans, and hematological evaluation. Vital status was determined using medical records or telephone follow-up. The last follow-up was conducted in October 2023.

Toxicity reactions during treatment, such as RP, nausea, cardiac reactions, anemia, and hypoalbuminemia, were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [10]. Skin reactions, leukopenia, and thrombocytopenia were assessed according to the Radiation Therapy Oncology Group (RTOG) criteria [11]. RP refers to pneumonia occurring within six months of starting radiotherapy [12].

End-points

The primary endpoints were ORR and toxicity. The ORR was assessed within three months of radiotherapy. Efficacy assessment was based on a comprehensive evaluation of endoscopic, CT, and esophagography findings in conjunction with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [13]. Complete response (CR): The evaluation criterion was a negative esophageal biopsy finding on endoscopy. Barium ingestion results.

In an unchanged esophagus with a flexible wall and smooth barium passage. CT scans indicated less than 5 mm thickening of the esophageal wall, and the metastatic lymph nodes returned to the standard size. No new lesions were noted. Partial response (PR): Pharyngeal barium examination and chest CT revealed a $\geq 30\%$ reduction in the longest diameter of the lesion. Stable disease (SD): Both barium meal and chest CT indicated that the maximum diameter of the lesion had decreased by less than 20%. Progressive disease (PD): The patient showed an increase in the maximum diameter of the esophageal lesions by $\geq 20\%$ or the appearance of new lesions on both the esophageal barium meal and chest CT.

The secondary endpoints were OS and DFS. OS was defined as the duration of death from any cause. DFS was defined as the duration until death or the first transfer, progression, or recurrence.

Statistical analysis

The data were subjected to statistical analysis using SPSS software (version 26.0). To mitigate the influence of confounding factors across groups, PSM was employed to address confounding variables in both groups consisting of 177 patients, thereby establishing a novel study group for subsequent comparative analysis.

Quantitative data following normal distribution were presented as mean ± standard deviation($\bar{x} \pm s$). An independent sample t-test was used for the analysis. Quantitative data that deviated from a normal distribution were represented by the median (M) with interquartile range (IQR) and were subjected to analysis using the Wilcoxon rank-sum test. The chi-square or Fisher's exact probability test was used to analyze the unordered qualitative data. We used the Wilcoxon rank-sum test to analyze the ordered qualitative data. We used the log-rank test to assess disparities in survival among subgroups, and the Kaplan-Meier method to estimate DFS and OS within the groups. At the same time, the Cox proportional hazards model was applied for multivariate independent prognostic factors, considering a significance level of $P < 0.05$ as statistically significant.

Results

Patient and tumor characteristics

The HTRT and IMRT-alone groups exhibited statistically significant differences in KPS scores and radiotherapy doses ($P < 0.05$). To minimize the impact of confounding factors between different groups on the results and

to control for selection bias as much as possible, PSM was performed at a 1:1 ratio for all 177 enrolled patients, with a caliper value of 0.03. The covariates included in the analysis were age, sex, tumor length, tumor location, KPS score, tumor stage, smoking status, hypertension status, diabetes status, presence or absence of underlying lung disease, and radiotherapy dose. After PSM, 42 pairs of study participants were obtained, and no statistically significant differences were observed between the two groups in the 11 covariates ($P > 0.05$). A comparison of the case data between the HTRT and IMRT-alone groups, both before and after PSM, is presented in Table 1.

Efficacy

Following PSM, the ORR was evaluated in 84 patients in both the groups. Within the HTRT group, CR was observed in seven patients (17%), PR in 28 patients (67%), SD in six patients (14%), and PD in one patient (2%). In the IMRT-alone group, there were three cases of CR (7%), 23 cases of PR (55%), 10 cases of SD (24%), and six cases of PD (14%). The ORR (CR + PR) in the HTRT group was 83%, whereas it was 62% in the IMRT-alone group, indicating a statistically significant difference (χ^2=4.850, $P = 0.028$).

Survival

The median follow-up duration for both the groups was 44 months. During the follow-up period, 54 patients died, one patient was lost to follow-up, and 29 patients survived.

The median estimated OS and DFS for both the groups were 27 and 17 months, respectively. The 1-, 2-, and 3-year OS rates were 82.1%, 57.3%, and 28.7%, respectively, whereas the corresponding DFS rates were 58.6%, 31.9%, and 11.6%, respectively.

Table 1 Patient and tumor characteristics between the HTRT group and the IMRT-alone group before and after PSM

Variable	prePSM (*n* = 177)			postPSM(*n* = 84)		
	HTRT *n* = 42,n(%)	IMRT-alone *n* = 135,n(%)	P	HTRT *n* = 42,n(%)	IMRT-alone *n* = 42,n(%)	P
Age($\bar{x} \pm s$), years	76.57 ± 6.92	75.40 ± 6.91	0.339	76.57 ± 6.92	77.55 ± 5.58	0.479
V20($\bar{x} \pm s$),%	21.38 ± 3.03	20.96 ± 4.62	0.497	21.38 ± 3.03	20.71 ± 4.19	0.400
V30($\bar{x} \pm s$),%	10.53 ± 2.93	11.13 ± 3.78	0.422	10.53 ± 2.93	11.31 ± 3.95	0.312
MLD($\bar{x} \pm s$), Gy	10.79 ± 1.60	10.90 ± 1.98	0.738	10.79 ± 1.60	10.86 ± 1.88	0.866
Sex			0.645			
Male	32(76)	98(72.6)		32(76)	35(83)	0.415
Female	10(24)	37(27.4)		10(24)	7(17)	
Tumor Location			0.640			0.723
Upper thoracic esophagus	6(14)	20(14.8)		6(14)	6(14)	
Middle thoracic esophagus	16(38)	56(41.5)		16(38)	14(33)	
Lower thoracic esophagus	20(48)	59(43.7)		20(48)	22(53)	
Tumor stage			0.870			0.659
I	0 (0)	9 (6.7)		0 (0)	0 (0)	
II	24(57)	65(48.1)		24(57)	26(62)	
III	18(43)	61(45.2)		18(43)	16(38)	
KPS Score			0.017			0.671
70	16(38)	46(34.1)		16(38)	18(43)	
80	25(60)	78(57.8)		25(60)	23(55)	
90	1 (2)	11(8.1)		1(22)	1(2)	
Diabetes			1			0.457
No	39(93)	125(92.6)		39(93)	37(88)	
Yes	3 (7)	10(7.4)		3(7)	5(12)	
Smoking			0.063			1
No	20(48)	86(63.7)		20(48)	20(50)	
Yes	22(52)	49(36.3)		22(52)	22(50)	
Hypertension status			0.967			0.662
No	21(50)	68(50.4)		21(50)	19(45)	
Yes	21(50)	67(49.6)		21(50)	23(55)	
Underlying Lung Disease			0.400			0.821
No	16(38)	42(31.1)		16(38)	15(36)	
Yes	26(62)	93(68.9)		26(62)	27(64)	
Median radiotherapy dose, M(IQR), Gy	60(4)	60(6)	0.011	60(4)	61(4)	0.797
Median tumor length, M(IQR), cm	6(2)	6(3)	0.638	6(2)	5(3)	0.732

The HTRT group had a median OS of 32 months compared with 27 months in the IMRT-alone group. The 1-, 2-, and 3-year OS rates in the HTRT group were 84.7%, 56.1%, and 32.0%, respectively. At the same time, they were 82.8%, 58.6%, and 26.3% in the IMRT-alone group (χ^2=0.119, P = 0.730), indicating no statistically significant difference in survival outcomes between the two groups (Table 2).

The HTRT group had a median DFS of 19 months, whereas the IMRT-alone group had a significantly shorter DFS of only 13 months. The 1-, 2-, and 3-year DFS rates were 66.1%, 25.4%, and 8.5%, respectively, in the HTRT group, and 51.7%, 37.9%, and14.7%, respectively, in the IMRT-alone group (χ^2=0.002, P = 0.964). These results indicate no statistically significant differences between the two groups.

Toxicity

All the patients in both groups completed the planned radiotherapy dose, and there were no instances of treatment discontinuation. The 42 patients in the HTRT group did not experience any toxicity reactions, such as arrhythmia, neurological abnormalities, or skin burns during deep hyperthermia. Grade 1 nausea was observed in two patients and spontaneously resolved upon completion of hyperthermia treatment without any severe gastrointestinal reactions.

In terms of hematological toxicity from radiation therapy, the HTRT group exhibited grade 2 or higher leukopenia in 6 patients(14%). In contrast, 14 patients in the IMRT-alone group had (33%) similar disease severity (Z = 2.037, P = 0.042), indicating a statistically significant difference between the two groups. Grade 2 or higher anemia was observed in 4 patients(10%) in the HTRT group and 7(17%) in the IMRT-alone group (Z = 0.965, P = 0.335). Additionally, grade 2 or higher thrombocytopenia was found in 5 patients (12%) in the HTRT group and in only one patient (2%) in the IMRT-alone group (Z = 1.685, P = 0.092). Furthermore, hypoalbuminemia of grade 2 or higher occurred in seven patients(17%) who received HTRT and five patients (12%) who received IMRT alone (Z = 0.620, P = 0.535). No significant differences were observed among these occurrences.

The incidence of grade 2 or higher RP was significantly different between the HTRT (21%) and IMRT-alone (48%) groups (Z = 2.509, P = 0.012). The incidence of severe(≥ Grade3) RP was not significantly different between the HTRT (10%) and IMRT-alone (12%) groups (Z = 0.351, P = 0.726). The incidence of grade ≥ 2 radiation esophagitis was not significantly different between the HTRT (95%) and IMRT-alone (88%) groups (Z = 1.177, P = 0.239).

Prognostic analysis

First, we conducted univariate analysis using data from both groups. The findings summarized in Table 3 indicate that variables such as age, sex, tumor length, stage, smoking status, hypertension status, hyperthermia treatment, leukocyte reduction status, platelet reduction status, and symptom relief status were not significantly correlated with either OS or DFS (P > 0.05). Tumor location, radiotherapy dose, and hypoalbuminemia were essential factors affecting the prognosis of OS (P = 0.002, 0.006, and 0.002, respectively), whereas tumor location and hypoalbuminemia were critical factors affecting DFS (P = 0.027 and P < 0.001, respectively).

After including variables with P < 0.05, based on the univariate analysis results in the Cox multivariate regression model, we found that hypoalbuminemia (odds ratio [OR] = 3.798, P = 0.004), radiotherapy dose (OR = 0.445, P = 0.006), and tumor site (OR = 0.387, P = 0.005) significantly influenced OS. Hypoalbuminemia (OR = 3.676, P < 0.001) was identified as a critical prognostic factor for DFS (Table 2).

Discussion

Hyperthermia, recognized as the fifth primary cancer treatment modality after surgery, radiotherapy, chemotherapy, and immunotherapy, is a conventional physical antitumor intervention. Zheng et al. [3] found that the 5-year OS rate for nasopharyngeal carcinoma patients treated with chemoradiotherapy combined with whole-body hyperthermia was higher than those treated with chemoradiotherapy alone. Van et al. [5] discovered that optimal outcomes for patients with cervical cancer can be achieved by employing a short interval of hyperthermia and radiation. By maintaining a temperature range of 42–43 °C, hyperthermia targets tumor cells while minimizing toxicity to normal human tissue cells [14]. Its application has several advantages such as enhancing

Table 2 Multivariate prognostic analysis

Variable	Coefficient	Standard Error	Wald	*P*	OR	95%CI
OS						
Hypoalbuminemia ≥ Grade 2	0.868	0.425	4.175	0.041	2.381	1.036 ~ 5.473
Radiotherapy dose > 60 Gy	-0.810	0.293	7.640	0.006	0.445	0.251 ~ 0.790
Tumor location (Mid-chest compared to Lower chest)	-0.949	0.337	7.956	0.005	0.387	0.200 ~ 0.749
DFS						
Hypoalbuminemia ≥ Grade 2	1.302	0.334	15.212	< 0.001	3.676	1.911 ~ 7.072

Table 3 Univariate prognostic analysis

Variable	Cases No.(%)	Median OS (months)	1-Year OS Rate(%)	2-Year OS Rate(%)	3-Year OS Rate(%)	χ2	*P*	Median DFS (months)	1-Year DFS Rate(%)	2-Year DFS Rate(%)	3-Year DFS Rate(%)	χ2	*P*
Age						1.526	0.217					0.002	0.965
≤ 76 years	29	30	74.0	69.0	40.6			11	49.5	28.9	14.5		
> 76 years	55	25	82.3	51.3	22.5			17	63.5	33.5	9.8		
Sex						0.004	0.951					0.814	0.367
Male	67	27	80.7	57.7	25.3			15	52.8	30.8	9.2		
Female	17	28	88.2	56.6	45.3			22	81.4	35.5	23.7		
Tumor Length						0.318	0.573					0.340	0.560
≤ 6 cm	63	28	79.5	56.4	33.4			18	61.4	29.6	12.7		
> 6 cm	21	27	90.0	60.0	15.2			16	50.4	39.2	8.2		
Tumor Location						12.189	0.002					7.199	0.027
Upper	12	38	83.3	71.4	57.1			23	75.0	38.1	9.5		
Middle	30	32	92.9	76.4	38.2			22	75.5	46.2	20.5		
Lower	42	21	73.6	38.1	12.8			11	40.5	19.9	5.3		
Tumor Stage						0.957	0.328					0.026	0.872
Stage II	50	28	84.9	61.2	31.6			16	59.6	28.2	14.8		
Stage III	34	27	78.2	52.1	24.8			21	57.0	36.6	8.1		
KPS Score						0.821	0.093					3.055	0.080
70	34	24	75.3	46.8	21.2			14	54.0	25.4	4.9		
80–90	50	29	86.8	65.2	34.3			21	61.4	36.5	16.6		
Diabetes						2.915	0.088					1.3	0.254
No	76	27	81.6	54.6	23.6			17	58.1	28.6	9.1		
Yes	8	41	87.5	87.5	87.5			29	62.5	62.5	31.3		
Smoking						0.022	0.881						
No	40	28	84.0	53.7	38.4			21	71.1	37.8	18.9	2.099	0.147
Yes	44	27	80.3	59.9	24.0			12	46.9	26.1	7.8		
Hypertension						0.123	0.726					0.001	0.980
No	40	24	76.9	49.8	21.1			18	58.5	28.1	9.4		
Yes	44	28	86.1	63	34.1			16	58.3	34.5	13.2		
Underlying Lung Disease						3.541	0.060					0.090	0.764
No	31	22	86.2	47.7	7.9			20	69.6	29.7	5.9		
Yes	53	29	80.0	62.8	39.5			14	52.7	32.7	14		
Hyperthermia						0.119	0.730					0.002	0.964
No	42	27	82.8	58.6	26.3			13	51.7	34.7	14.7		
Yes	42	32	81.8	56.1	32.0			19	66.1	25.4	8.5		
Radiotherapy dose						7.418	0.006					1.908	0.167
≤ 60 Gy	45	25	72.9	54.2	10.8			16	57.2	27.4	3.4		
> 60 Gy	39	32	92.0	60.9	49.2			18	60.1	36.6	21.3		
Leukopenia						0.113	0.737					0.028	0.867

Table 3 (continued)

Variable	Cases No.(%)	Median OS (months)	1-Year OS Rate(%)	2-Year OS Rate(%)	3-Year OS Rate(%)	χ2	*P*	Median DFS (months)	1-Year DFS Rate(%)	2-Year DFS Rate(%)	3-Year DFS Rate(%)	χ2	*P*
< Grade 2	64	28	83.1	57.8	25.3			19	59.9	34.8	9.2		
≥Grade 2	20	27	80.0	56.0	36.3			13	55.0	25.0	15.0		
Thrombocytopenia						1.429	0.232					1.903	0.168
< Grade 2	78	28	82.0	58.3	31.4			17	60.4	33.1	12.9		
≥Grade 2	6	15	83.3	41.7	20.8			7	33.3	16.7	0		
Anemia						3.717	0.054					3.102	0.078
< Grade 2	73	29	85.4	60.4	31.3			19	0.611	0.335	13.8		
≥Grade 2	11	18	60.6	36.4	12.1			12	41.6	20.8	0		
Hypoalbuminemia						9.761	0.002					18.144	< 0.001
< Grade 2	72	29	86.4	63.2	31.0			21	65.9	36	13.9		
≥Grade 2	12	14	58.3	16.2	16.2			7	16.7	8.3	0		
Remission Status						0.023	0.880					0.314	0.575
No	23	27	76.5	53.3	26.6			11	41.4	36.3	18.1		
Yes	61	28	84.2	59.0	29.4			19	65.1	31.0	9.9		

tumor blood flow and perfusion, ameliorating tumor cell hypoxia, and augmenting tumor cell sensitivity. Hyperthermia also amplifies DNA damage induced by radiation and suppresses the activity of DNA repair enzymes. It modulates cytotoxic T cell activity and augments tumor immunogenicity to activate the immune system. Additionally, hyperthermia induces heat shock proteins (HSPs) to facilitate antitumor responses [15–18].

Datta et al. [19] conducted a systematic analysis of 38 studies involving 3,478 patients, including EC patients. Their findings revealed that the CR rates were significantly higher in the HTRT group than in the IMRT-alone group (54.9% vs. 39.8%, $P<0.001$). Gani et al. [20] confirmed the feasibility of deep hyperthermia. In our study, all 84 patients had locally advanced disease after PSM, and our CR evaluation criteria were more stringent, resulting in a lower CR rate (16.6%) in the HTRT group. However, consistent with the findings of Datta et al., our study confirmed that hyperthermia combined with IMRT can significantly improve the ORR of patients with EC.

In addition, our study compared the survival of the two groups of patients. The median DFS and OS were better in the HTRT group (19 months vs. 13 months; 32 months vs. 27 months), the 1- and 2-year survival rates were similar to those in the IMRT-alone group, and the 3-year OS rate improved (32.0% vs. 26.3%). Overall, the two groups did not differ significantly in OS ($P=0.730$). The same was true for DFS ($P=0.964$). The small sample size may explain this inconsistency, with some improvements in the long-term survival of patients with hyperthermia. In our univariate and multivariate prognostic analyses, we did not find that hyperthermia affected the prognosis of elderly patients with EC. Owing to the diversity of current treatments for esophageal cancer, OS depends more on treatment measures taken after progression. This may be the main reason why hyperthermia has not been found to improve the long-term prognosis. Similarly, our study revealed no significant associations between age, sex, tumor length, tumor stage, smoking status, hypertension status, hyperthermia treatment, leukocyte reduction therapy, platelet reduction therapy, ORR, OS, or DFS.

Univariate analysis revealed that tumor location was a significant prognostic factor for both DFS ($P=0.027$) and OS ($P=0.002$). Patients with lower thoracic EC have a worse prognosis than those with middle thoracic EC, possibly because of the increased tumor mobility and limited reproducibility of esophageal targets affecting treatment outcomes.

After conducting univariate and multivariate analyses ($P=0.002$,0.006), we determined that receiving a radiotherapy dose greater than 60 Gy was a favorable prognostic factor for OS. As a result, there has been an improvement in the 1-year, 2-year, and 3-year survival

rates and an extension of the median survival. Li et al. studied the survival rate of patients with advanced esophageal squamous cell carcinoma in China from 2002 to 2018. They found significant differences in survival between the ≥60 Gy group and the 50–59.9 Gy group ($P < 0.001$), which is consistent with our research findings [21].

Both univariate and multivariate analyses indicated that hypoalbuminemia of grade ≥ 2 was a key factor affecting the prognosis (both OS and DFS) of older EC patients receiving IMRT. Hypoalbuminemia often arises from a reduced nutritional intake or excessive nutrient loss. In patients with EC, particularly those with lower thoracic tumors, the risk of hypoalbuminemia increases owing to factors such as dietary obstruction, pain, and tumor consumption. These patients frequently experience significant malnutrition, compromised immune function, decreased tolerance to radiation therapy, and impaired recovery from adverse treatments. Consequently, their DFS and OS rates were lower than those of the well-nourished patients. Therefore, close attention to the nutritional status of EC patients is crucial. A comprehensive assessment of dietary risk before radiotherapy and early initiation of enteral or parenteral nutrition may improve patient prognosis.

The main toxicities associated with deep hyperthermia include cardiac reactions, skin burns, and tissue hardening. All patients in the study completed hyperthermia treatment, with only two patients experiencing mild nausea during the procedure. However, these symptoms were relieved after therapy, indicating favorable tolerance to hyperthermia without significant toxicity reactions.

In contrast, the addition of hyperthermia significantly mitigated radiotherapy toxicity, including grade ≥ 2 leukopenia. The reduction in leukopenia was consistent with the findings of a meta-analysis conducted by Hu et al. [22]. In contrast to Hu et al., our study revealed no significant effect of hyperthermi, either beneficial or harmful, on the reduction of radiation esophagitis. This was due to the exclusion of patients with esophageal fistula to prevent interference with the assessment of RP, which may have led to a potential statistical bias in the incidence of radiation esophagitis. According to conventional wisdom, higher temperatures result in a faster blood flow. Therefore, further discussion is required regarding the impact of deep hyperthermia on radiation esophagitis. Our study did not find a significant correlation between high fever and the occurrence or severity of anemia, thrombocytopenia, or hypoalbuminemia.

Interestingly, hyperthermia reduced symptomatic RP(≥ 2 RP). This was found in a recent multifactorial analysis of RP [23]. This could be because increasing the temperature can lead to the upregulation of heat shock proteins, which have cellular protective and anti-apoptotic properties that prevent and reverse heat-induced protein misfolding and repair heat-induced cell damage through chaperone activity [16]. HSP27, HSP90, HSP70, and small molecule HSPs in the HSP family have anti-inflammatory effects in various ways [24, 25]. Hyperthermia also improves blood flow, biofilm permeability, and metabolism. Additionally, some researchers have shown that the levels of high-sensitivity C-reactive protein (hsCRP) and inflammatory factors such as hsCRP, TNF-α, IL-6, and TGF-β significantly decrease after hyperthermia, indicating that hyperthermia can reduce the inflammatory response to RP [26, 27]. The incidence of severe RP was low, ranging from 10 to 12%. As a result, no effect of hyperthermia on severe RP was observed.

IMRT combined with deep hyperthermia offers a new treatment option for EC patients who are unable to undergo surgery or chemotherapy. It has a good safety profile and reduces the incidence of radiation-induced pneumonia and leukopenia. However, this was a retrospective study, and although PSM balanced some confounding factors, a selection bias was unavoidable. For example, our study excluded patients who failed to complete the treatment to better assess the treatment efficacy. Moreover, the sample size was limited. Therefore, further validation and well-designed prospective studies in larger populations are required to validate our findings.

Conclusion

In conclusion, combining deep hyperthermia with IMRT improves tumor response rates and reduces radiotherapy-induced toxicity. Although this approach does not improve the long-term prognosis, it is still practical and has low toxicity, making it suitable for clinical use.

Author contributions

Wang MJ and Yang J were responsible for the design, execution, and writing of the paper. Wang MJ, Wang DF, and Wang LL contributed to the data analysis. Zhou JY and Qin SB provided valuable clinical insights. The report was supervised by Wang LL and Jiao Y.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study involving human participants was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Ethics Research Society No. 227, 2023) and Yixing Cancer Hospital (LL20240201). The study was conducted retrospectively and did not require informed consent from the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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