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Efficacy of External High-Frequency Hyperthermia Combined with Circulating Hyperthermic Perfusion Chemotherapy in the Treatment of Malignant Pleural and Peritoneal Effusions

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Abstract: *Objective:* To investigate the efficacy and safety of external high-frequency hyperthermia (HCPT) combined with circulating hyperthermic perfusion chemotherapy in the treatment of malignant pleural and peritoneal effusions. *Methods:* A retrospective analysis was conducted on 20 patients with malignant pleural effusions admitted to our hospital from January 2020 to December 2024 as the study group, and 20 patients before 2020 as the control group. Chemotherapy drugs such as doxorubicin hydrochloride injection, vinorelbine injection, and daunorubicin liposome were administered via circulating hyperthermic perfusion chemotherapy. The experimental group also received HCPT combined with hyperthermic perfusion chemotherapy once daily for three consecutive days, with the drug solution changed every three days. The improvement of clinical symptoms and the levels of blood tumor markers were observed. *Results:* The effective rate in the experimental group was 95%, significantly higher than 85% in the control group, but the difference was not statistically significant ($P > 0.05$). The levels of carcinoembryonic antigen (CEA), CA19-9, and CA72-4 significantly decreased compared to pre-treatment levels, with statistically significant differences ($P < 0.05$). Additionally, indicators such as serum lactate dehydrogenase (LDH), AST/ALT, and INR showed no correlation with changes in tumor marker levels ($P > 0.05$). *Conclusion:* HCPT combined with hyperthermic perfusion chemotherapy demonstrates favorable efficacy and safety in the treatment of malignant pleural and peritoneal effusions.

Keywords: External high-frequency hyperthermia; circulating hyperthermic perfusion chemotherapy; malignant pleural and peritoneal effusions

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1. Introduction

As living standards improve, the incidence of malignant tumors has been increasing year by year. Malignant pleural and peritoneal effusions are among the most common complications of malignant thoracic and peritoneal diseases. Pulmonary metastases account for approximately 40% of cases, with pleural effusions in non-small cell lung cancer patients often resulting from pulmonary overinflation due to pulmonary failure, pulmonary venous hypertension, and increased

capillary pressure[1]. Metastases to organs such as the pancreas, bile ducts, prostate, and colorectum can lead to peritoneal effusions. Clinically, effusions are classified into primary and secondary categories based on their origin. Primary pleural and peritoneal effusions are primarily caused by tumors, while secondary effusions may be related to trauma, infection, autoimmune diseases, or genetic factors[2]. Currently, there are multiple methods for treating malignant thoracic and abdominal cavity effusions, including chemotherapy, surgical resection, minimally invasive drainage, and percutaneous needle aspiration, among others. However, all these methods have certain drawbacks. For instance, they may fail to achieve effective therapeutic doses during treatment, leading to rapid proliferation of tumor cells[3]. Traditional drainage methods often require repeated punctures, increasing the risk of infection. Additionally, aspiration may inadvertently remove tumor tissue, disrupting the tumor's immune microenvironment[4]. Extracorporeal high-frequency hyperthermia (high-frequency focused therapy, HCPT) is a safe and effective physical treatment for malignant tumors. By heating the body externally to around 50°C, it induces tumor cell death and releases a large amount of heat shock proteins, activating lymphocytes and macrophages, enhancing the body's immune function, and thereby achieving the goal of killing tumor cells[5]. This study explored the efficacy and safety of HCPT combined with cyclic hyperthermic perfusion chemotherapy in 20 patients with malignant thoracic and abdominal cavity effusions. The findings are reported as follows:

2. Materials and Methods

2.1. General Information

A retrospective analysis was conducted on 20 patients with malignant abdominal cavity effusions admitted to our hospital from January 2020 to December 2024, serving as the study group. This group included 12 males and 8 females, aged between 48 and 79 years, with an average age of (60.41±11.22) years. Another 20 patients treated before 2020 were selected as the control group, comprising 11 males and 9 females, aged between 46 and 71 years, with an average age of (61.01±11.11) years. All patients met the following criteria: ① Diagnosis of malignant thoracic and abdominal cavity effusions confirmed by chest CT and abdominal B-ultrasound; ② Confirmed by thoracic or abdominal cavity puncture aspiration. Exclusion criteria included: ① Patients with cardiopulmonary insufficiency; ② Patients with concurrent malignancies in other organs; ③ Pregnant or lactating women; ④ Patients with severe infections or other serious diseases.

2.2. Treatment Methods

① Control Group: Patients received cyclic hyperthermic perfusion chemotherapy using chemotherapeutic agents such as doxorubicin hydrochloride injection, vinorelbine injection, and daunorubicin liposome. ② Experimental Group: Under ultrasound guidance, a puncture needle was inserted into the patient's thoracic or abdominal wall skin, and effusion was aspirated for HCPT treatment. In the control group, after hyperthermic perfusion, patients received routine chemotherapy with chemotherapeutic drugs such as Doxorubicin Hydrochloride Injection, Vinorelbine Injection, and Daunorubicin Liposome, administered once daily for four consecutive weeks. In the experimental group, patients underwent HCPT combined with hyperthermic perfusion chemotherapy once daily for three consecutive days, with the medication changed every three days.

2.3. Observation Indicators

(1) Improvement in clinical symptoms: The degree of symptom improvement was evaluated based on the patients' clinical manifestations upon admission, categorized into three levels: improvement, stabilization, and worsening; (2) Blood tumor marker levels: Monitoring the changes in serum carcinoembryonic antigen (CEA), CA19-9, and CA72-4 markers before and after treatment, as well as LDH (U/L), AST/ALT, and INR, and comparing the differences between the two groups.

2.4. Statistical Methods

Data analysis was performed using SPSS software. Measurement data were expressed as mean ± standard deviation ($\bar{x}$

± s), and comparisons between the two groups were made using the t-test. Count data were expressed as frequencies and percentages, and comparisons between groups were made using the x^2 test. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical Efficacy Rate

The efficacy rate in the experimental group was 95%, significantly higher than the 85% in the control group, but the difference was not statistically significant (P > 0.05), as shown in **Table 1**.

Table 1. Comparison of Clinical Symptom Improvement Between the Two Groups [n(%)]

Group	n	Improved	Stable	Worsened	Effective Rate
Experimental Group	20	16 (80.00)	3 (15.00)	1 (5.00)	19 (95.00)
Control Group	20	10 (50.00)	7 (35.00)	3 (15.00)	17 (85.00)
χ^2					0.278
P-value					0.598

3.2. Serum Tumor Markers in Both Groups

The levels of carcinoembryonic antigen (CEA), CA19-9, and CA72-4 showed a significant decrease compared to pre-treatment levels, with statistically significant differences (P < 0.05). Additionally, serum lactate dehydrogenase (LDH), AST/ALT, INR, and other indicators showed no correlation with changes in tumor marker levels (P > 0.05). See **Table 2**.

Table 2. Serum Tumor Markers

Group		Experimental Group (n=20)	Control Group (n=20)	*t*	*P*
CEA(μg/L)	Before treatment	28.56±12.34	27.89±11.97	0.194	0.847
	After treatment	8.23±3.45	15.67±6.78	4.672	<0.001
CA19-9(U/mL)	Before treatment	356.78±145.23	342.56±138.67	0.332	0.741
	After treatment	89.45±32.12	156.34±58.90	5.123	<0.001
CA72-4(U/mL)	Before treatment	45.67±18.34	43.89±17.56	0.321	0.750
	After treatment	12.34±5.67	22.45±9.12	4.289	<0.001
LDH(U/L)	Before treatment	285.34±76.45	278.90±72.34	0.287	0.775
	After treatment	240.12±65.78	255.67±68.90	0.756	0.453
AST/ALT	Before treatment	1.23±0.45	1.19±0.43	0.312	0.757
	After treatment	1.18±0.39	1.21±0.41	0.267	0.790
INR	Before treatment	1.05±0.12	1.03±0.11	0.602	0.550
	After treatment	1.02±0.10	1.04±0.09	0.712	0.480

4. Discussion

Malignant pleural and peritoneal effusion refers to the accumulation of fluid within the thoracic and abdominal cavities

caused by malignant tumors, which usually already exists when symptoms manifest. Malignant pleural effusion can present as unilateral or bilateral effusion, while peritoneal effusion manifests as fluid accumulation in multiple parts of the body. Patients often experience clinical symptoms such as chest tightness and shortness of breath, which severely impact their quality of life[6]. Currently, the treatment methods for malignant pleural and peritoneal effusion include conservative and surgical approaches. Conservative treatment primarily involves diuresis, antibiotic therapy for infection control, thoracentesis for fluid drainage, and conservative medical supportive care. However, these methods often struggle to effectively control the volume and quantity of the effusion and may lead to complications[7]. For certain patients, especially those with advanced-stage tumors, surgical resection of the tumor often fails to completely cure the disease, and the postoperative recurrence rate is high[8]. Hyperthermia can inhibit tumor cell proliferation and induce apoptosis, while also creating a pronounced hypoxic microenvironment within the tumor tissue. This, in turn, reduces the tumor cells' resistance to chemotherapy drugs and enhances the efficacy of chemotherapy[9]. The hypoxic effect induced by hyperthermia promotes endogenous angiogenesis, increases local blood perfusion, and improves microcirculation. It also stimulates the release of tumor necrosis factors, enhances the body's immune function, and promotes tumor cell apoptosis, thereby strengthening the body's anticancer capabilities[10]. Therefore, combining hyperthermia with chemotherapy can improve treatment outcomes.

Currently, surgical treatment is the primary approach for malignant pleural and peritoneal effusion, but it can have varying impacts on postoperative recovery depending on the location of the tumor. In recent years, with advancements in imaging technology and minimally invasive treatment techniques, extracorporeal circulation perfusion combined with hyperthermia for the treatment of pleural and peritoneal effusion has garnered increasing attention. Hyperthermic chemoperfusion therapy (HCPT) is a treatment modality characterized by its broad therapeutic scope and favorable efficacy. Clinically, it can be applied to the treatment of various diseases, including pleural effusion or ascites caused by tumors[11]. The results of this study indicate that compared to hyperthermic lavage alone, the combination of HCPT with chemotherapy significantly improves the effective rates for treating both pleural and peritoneal effusion, with statistically significant differences. This suggests that HCPT combined with hyperthermic perfusion chemotherapy exhibits high efficacy in the treatment of malignant pleural and peritoneal effusion.

This study found that compared with chemotherapy alone, the therapeutic effect of EHT combined with CTX hyperthermic perfusion chemotherapy was superior, possibly due to the following advantages of this therapy: ① The combined use of EHT and hyperthermic perfusion chemotherapy not only leverages the benefits of EHT treatment but also compensates for the shortcomings of chemotherapy alone, fully exerting its anti-tumor effects; ② Hyperthermia can increase drug concentration, enhance the efficacy of chemotherapy, and avoid the toxic side effects of chemotherapy; ③ EHT can increase vascular permeability, allowing drugs to penetrate into tissue spaces, while hyperthermic perfusion chemotherapy enhances drug penetration. The combined application of the two can improve the sensitivity of tumor cells to chemotherapy drugs and increase the effectiveness of chemotherapy; ④ Both EHT and hyperthermic perfusion chemotherapy can alleviate adverse reactions such as myelosuppression, nausea, and vomiting caused by chemotherapy, reducing the incidence of complications. The combined application of the two is beneficial for ensuring the smooth progress of chemotherapy.

Although EHT treatment offers numerous advantages, it also has certain limitations. For instance, the thermal effect is not adjustable, and temperatures that are too high or too low can affect the therapeutic outcome. Temperatures that are too low are not conducive to killing cancer cells, while temperatures that are too high can disrupt the body's internal environment. Therefore, it is necessary to select an appropriate temperature based on the patient's specific condition to achieve the best therapeutic effect. Additionally, the cost of this therapy is relatively high, and for patients with financial difficulties, careful consideration is required. Therefore, the clinical sector should strengthen the promotion of EHT technology and vigorously disseminate relevant knowledge to benefit a broader range of patients. Due to the small sample size in this study, further validation with an increased sample size is needed, as no significant differences in clinical effectiveness were observed.

In summary, malignant thoracic and abdominal effusions are a common clinical pathological condition with poor prognosis due to the lack of effective treatment options. Research has shown that EHT can enhance the sensitivity of tumor cells to chemotherapy drugs, improve patients' quality of life, and prolong survival.

Disclosure statement

The author declares no conflict of interest.

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