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Thermal ablation combined with gemcitabine and cisplatin regimen in patients with non-small cell lung cancer

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Abstract: Objective To explore the clinical efficacy of microwave thermal ablation combined with gemcitabine and cisplatin (GP)regimen in the treatment of non-small cell lung cancer (NSCLC)and its influence on the levels of circulating tumor DNA (ctDNA)and serum exosome markers. **Methods** A total of 82 NSCLC patients admitted to Cangzhou People's Hospital from January 2022 to December 2024 were retrospectively enrolled and divided into two groups according to the treatment regimen: the control group (41 cases) was treated with GP regimen alone, while the study group (41 cases) was treated with microwave ablation on the basis of GP regimen. The clinical efficacy, levels of ctDNA, circulating tumor cells (CTCs), serum exosome markers [programmed death-ligand 1 (PD-L1), microRNA (miR)-21, miR-330], tumor markers [neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), cytokeratin 19 fragment (CYFRA21-1)] before and after treatment, and the incidence of adverse reactions during treatment were compared between the two groups. **Results** The disease control rate of the study group was higher than that of the control group (95.12% *vs* 78.05%, χ^2=5.145, *P*=0.023). After treatment, the levels of ctDNA, CTCs, CYFRA21-1, CA125 and NSE in both groups decreased, and those in the study group were lower than those in the control group (*P*<0.05). The levels of exosomal PD-L1 and miR-21 in both groups decreased, while the level of miR-330 increased, and the improvement degree of each index in the study group was better than that in the control group (*P*<0.05). The incidence of adverse reactions in the study group was lower than that in the control group (12.20% *vs* 36.59%, χ2=6.613, *P*=0.010). **Conclusion** Microwave thermal ablation combined with GP regimen in the treatment of NSCLC can improve clinical efficacy, reduce the levels of ctDNA, CTCs, exosomal PD-L1 and miR-21, increase the level of miR-330, decrease the levels of tumor markers, and reduce adverse reactions. **Keywords:** Microwave thermal ablation; Gemcitabine; Cisplatin; Non-small cell lung cancer; Circulating tumor DNA; Exosomes; Programmed death-ligand 1; MicroRNA

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Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related deaths globally. Its high heterogeneity and propensity for late-stage metastasis contribute to the limited efficacy of traditional treatment modalities [1]. Although the gemcitabine plus cisplatin (GP) regimen is one of the standard chemotherapy regimens for advanced NSCLC, its objective response rate as a single chemotherapy modality and the long-term survival benefits still face bottlenecks [2]. In recent years, local ablation techniques have gradually emerged as complementary treatment options for inoperable or locally advanced NSCLC due to their minimally invasive nature and potential to modulate the tumor microenvironment [3]. However, microwave thermal ablation, as a local treatment modality, struggles to control systemic metastatic lesions, necessitating an exploration of its synergistic mechanism with systemic chemotherapy and strategies for efficacy optimization [4]. Concurrently, the rise of liquid biopsy technology offers a new perspective for dynamic tumor monitoring and efficacy prediction. Circulating tumor DNA (ctDNA) and exosomes, as emerging biomarkers in liquid biopsy, have demonstrated potential application value in the early diagnosis of NSCLC, monitoring during treatment, and prognosis assessment [5]. Studies have confirmed that ctDNA abundance is significantly correlated with the prognosis of NSCLC patients; patients with detectable ctDNA at baseline have shorter overall survival, and its dynamic changes can reflect treatment response in real time [6]. Exosomes, as key messengers in the tumor microenvironment, regulate distant metastasis and immune escape by transmitting nucleic acids and proteins, and changes in their levels may serve as potential markers for assessing treatment sensitivity. Among these, exosomal programmed death ligand 1 (PD-L1) is a key marker in immunotherapy, while microRNA-21 (miR-21) and miR-330 have been confirmed to be closely related to the proliferation, metastasis, and prognosis of lung cancer [7]. However, systematic research on the effects of microwave thermal ablation combined with chemotherapy on ctDNA and exosomes is still relatively scarce. The GP regimen, as a classic chemotherapy combination, may enhance the anti-tumor immune response by inducing immunogenic cell death through its immunomodulatory effects [8]. Microwave thermal ablation may activate a systemic T-cell response by locally releasing tumor antigens, potentially creating an "in-situ vaccine" effect through immune synergy with the GP regimen, thereby further improving efficacy [9]. Therefore, this study aims to evaluate the clinical efficacy of microwave thermal ablation combined with the GP regimen in treating NSCLC and to explore its dynamic impact on ctDNA and exosome levels.

1 Data and Methods

1.1 General Data

A total of 82 patients with NSCLC from Cangzhou People's Hospital between January 2022 and December 2024 were selected as the study subjects, and their clinical data were retrospectively collected. This study was approved by the Ethics Committee of Cangzhou People's Hospital (Approval Number: K2024-030-02).

Inclusion criteria: (1) Meeting the diagnostic criteria for NSCLC in the *Chinese Medical Association guideline for clinical diagnosis and treatment of lung cancer (2024 edition)* [10] and confirmed by pathology or cytology; (2) Complete clinical data, including imaging examinations, laboratory test results, and follow-up information before and after treatment; (3) Karnofsky Performance Status score > 60; (4) Age ≥ 18 years.

Exclusion criteria: (1) Patients with other concurrent malignant tumors; (2) Presence of severe dysfunction of vital organs such as the liver, kidneys, heart, or lungs; (3) Inability to tolerate microwave thermal ablation or chemotherapy due to physical condition.

Patients were divided into two groups based on the treatment regimen. The 41 patients treated with the GP regimen served as the control group, and the 41 patients treated with the GP regimen plus microwave ablation served as the study group. There were no statistically significant differences in baseline data between the two groups (P>0.05). See **Table 1**.

Tab.1 Comparison of general data between two groups (n=41)

Group	Gender (case)		Age (years, $\bar{x}\pm s$)	BMI (kg/m^2,$\bar{x}\pm s$)	Tumor classification (case)		Tumor diameter (%)	
	Male	Female			Adenocarcinoma	Squamous cell carcinoma	⩽3 cm	>3 cm
Control group	25	16	59.84±5.01	21.36±3.02	17	24	12	29
Study group	26	15	61.48±4.95	22.57±3.13	19	22	10	31
t/χ^2 value	0.052		1.491	1.781	0.198		0.248	
P value	0.820		0.140	0.078	0.656		0.618	

1.2 Methods

1.2.1 Control Group

The control group was treated with the GP regimen, as follows: On days 1 and 8 of the chemotherapy cycle, gemcitabine 1,250 mg/m² (Jiangsu Hansoh Pharmaceutical, Approval Number: H20030104) was mixed with normal saline and administered intravenously over approximately 30 minutes. On days 1 to 3, cisplatin 75 mg/m² (Qilu Pharmaceutical, H37021358) was mixed with normal saline and administered intravenously over approximately 1 hour. Each treatment cycle lasted 3 weeks, for a total of 4 cycles.

1.2.2 Study Group

The study group received microwave ablation treatment in addition to the GP regimen used in the control group. The specifics were as follows: Two days after chemotherapy, microwave ablation was performed by an experienced surgeon in collaboration with a CT physician. First, CT localization was performed, followed by local anesthesia using 2% lidocaine. Under CT guidance, the microwave ablation needle was inserted percutaneously or through a surgical incision into the tumor tissue, ensuring the needle tip was positioned at the center or an appropriate location within the tumor. Ablation parameters were set based on factors such as tumor size and location, with ablation power ranging from 50 to 70 W and duration depending on tumor size and the desired ablation margin, typically 5 to 10 minutes. During the ablation process, changes in the ablation zone were monitored using CT to ensure the ablation coverage encompassed the entire tumor while minimizing damage to surrounding normal tissue. After ablation was completed, the ablation needle was removed, pressure was applied to the puncture site for hemostasis, and the site was bandaged. The patient's vital signs and local condition were observed, and necessary symptomatic supportive care was provided. To confirm complete tumor ablation, a CT scan with contrast was performed after ablation. If complete ablation was not achieved, ablation was repeated.

1.3 Observation Indicators

1.3.1 Clinical Efficacy

Clinical efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [11], as follows:

Complete response: Disappearance of all lesions, sustained for ≥4 weeks.

Partial response: ≥30% decrease in the sum of the diameters of target lesions, sustained for ≥4 weeks.

Stable disease: Changes in lesions did not meet the above criteria.

Progressive disease: ≥20% increase in the sum of the diameters of lesions or the appearance of new lesions.

Disease control rate = (number of complete response cases + number of partial response cases + number of stable disease cases) / total number of cases × 100%.

1.3.2 ctDNA and Circulating Tumor Cell (CTC) Levels

The following tests were performed

(1) CTC negative enrichment and flow cytometry detection: Whole blood samples were incubated with a mixture of red blood cell-specific antibodies (CD235a) and white blood cell-specific antibodies (CD45/CD14/CD66b). Through antigen-antibody coupling combined with density gradient centrifugation (Ficoll separation solution, 1.077 g/mL), red and white blood cells were removed to obtain a CTC-enriched solution. A Beckman Coulter CytoFLEX flow cytometer (excitation wavelength 488 nm, detection channel FL1/FITC) was used for quantitative analysis using EpCAM/CK18 as CTC markers.

(2) ctDNA extraction and quantification: Plasma samples were centrifuged at 2,000 r/min for 10 minutes in a horizontal rotor with a radius of 13.5 cm to remove cell debris. Circulating free DNA was extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Germany). After digestion with lysis buffer (containing proteinase K), Buffer ACB and an ethanol mixture were added sequentially. ctDNA was purified by silica membrane adsorption, washed with AW1/AW2 buffers, and then eluted. ctDNA concentration was detected using quantitative real-time polymerase chain reaction (PCR) (primers targeting the ALU sequence, fragment size: 115 bp), and copy numbers were calculated using the standard curve method.

1.3.3 Exosomal PD-L1, miR-21, and miR-330 Levels

Before and after treatment, 5 mL of fasting venous blood was collected from patients. After standing for 30 minutes, the blood was centrifuged to separate the serum. Serum samples were stored in a -20 °C freezer for subsequent use. From 1 mL serum samples, exosomes were extracted using an Exosome Rapid Extraction Kit (Cusabio, Catalog No.: CSB-EI0102). Exosomal PD-L1 levels were detected using enzyme-linked immunosorbent assay. Total RNA was extracted from exosomes using Trizol reagent (Beyotime Biotechnology, Catalog No.: R0016). RNA purity was determined using a UV spectrophotometer (Shimadzu, Model: UV-1800). Total RNA was reverse transcribed into cDNA using a reverse transcription kit (Takara Bio, Catalog No.: RR037A). Subsequently, PCR amplification was performed using a real-time quantitative PCR instrument (Hongshi Medical Technology, Shanghai, Model: SLAN-96P). The reaction system was 20 μL, containing SYBR Green Master Mix and 10 μmol/L primers. The amplification program was set as follows: pre-denaturation at 95 °C for 10 min; 40 cycles of denaturation at 95 °C for 15 s / annealing and extension at 60 °C for 1 min. U6 was used as the internal reference gene, and the relative expression levels of miR-21 and miR-330 were calculated using the $2^{-\Delta\Delta Ct}$ method. Primer sequences are shown in **Table 2**.

Tab.2 PCR primer sequences of miR-21, miR-330, and U6

Target	Sequence
miR-21	Forward primer: 5'-GCTTATCAGACTTATGTTGACTG-3'
	Reverse primer: 5'-CAGCCCATCGACTGGTG-3'
miR-330	Forward primer: 5'-TTTGGCGATCACTGCCTCTC-3'
	Reverse primer: 5'-CTCTCTGCAGGCCGTGTG-3'
U6	Forward primer: 5'-CGAGATCCCTCCAAAATCAA-3'
	Reverse primer: 5'-TTCACACCCATGACGAACAT-3'

1.3.4 Tumor Marker Levels

Before and after treatment, using the same serum samples as above, the levels of neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), and cytokeratin fragment 19 (CYFRA21-1) were detected using enzyme-linked immunosorbent assay. Kits were produced by Elabscience, and the detection procedures were strictly followed according to the kit instructions.

1.3.5 Adverse Reactions

The occurrence of adverse reactions during treatment was recorded for both groups, including leukopenia, liver function damage, nausea and vomiting, myelosuppression, and renal function damage.

1.4 Statistical Methods

SPSS 25.0 software was used for data analysis. Measurement data with a normal distribution were expressed as $\bar{x} \pm s$ and compared between groups using the *t*-test. Count data were expressed as case(%) and compared between groups using the chi-square test. $P<0.05$ was considered statistically significant.

2 Results

2.1 Comparison of Clinical Efficacy

The disease control rate in the clinical efficacy comparison study group was higher than that in the control group ($P<0.05$). See **Table 3**.

2.2 Comparison of ctDNA and CTCs Levels

Before treatment, there was no statistically significant difference in ctDNA and CTCs levels between the two groups ($P>0.05$). After treatment, ctDNA and CTCs levels decreased in both groups, and the levels in the study group were lower than those in the control group ($P<0.05$). See **Table 4**.

2.3 Comparison of Exosomal PD-L1, miR-21, and miR-330 Levels

Before treatment, there was no statistically significant difference in exosomal PD-L1, miR-21, and miR-330 levels between the two groups ($P>0.05$). After treatment, exosomal PD-L1 and miR-21 levels decreased in both groups, while miR-330 levels increased in both groups. The degree of improvement in all indicators was better in the study group than in the control group ($P<0.05$). See **Table 5**.

Tab.3 Comparison of clinical efficacy between two groups [n=41, case(%)]

Group	Complete response	Partial response	Stable disease	Progressive disease	Disease control rate (%)
Control group	6 (14.63)	12 (29.27)	14 (34.15)	9 (21.95)	78.05
Study group	10 (24.39)	16 (39.02)	13 (31.71)	2 (4.88)	95.12
χ^2 **value**					5.145
***P* value**					0.023

Tab.4 Comparison of ctDNA and CTCs levels between two groups (n=41, $\bar{x} \pm s$)

Group	ctDNA(ng/μL)		CTCs($\times10^{-5}$)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	4.39±1.16	3.59±1.09[a]	17.68±2.58	9.98±1.63[a]
Study group	4.46±1.22	2.46±1.13[a]	17.62±2.47	5.69±1.26[a]
***t* value**	0.266	4.609	0.108	13.333
***P* value**	0.791	<0.001	0.915	<0.001

Note: a, compared with pre-treatment, $P<0.05$.

2.4 Comparison of Serum Tumor Marker Levels

Before treatment, there were no significant differences in CYFRA21-1, CA125, and NSE levels between the two groups (P>0.05). After treatment, CYFRA21-1, CA125, and NSE levels decreased in both groups, and the levels in the study group were lower than those in the control group (P<0.05). See **Table 6**.

2.5 Comparison of Adverse Reactions

The incidence of adverse reactions in the study group was 12.20%, which was lower than the 36.59% in the control group (P<0.05). See **Table 7**.

Tab.5 Comparison of PD-L1, miR-21, and miR-330 levels in exosomes between two groups (n=41, $\bar{x}\pm s$)

Group	PD-L1 (pg/mL)		miR-21		miR-330	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	334.21±14.83	262.74±12.69[a]	1.36±0.21	1.09±0.18[a]	0.51±0.13	0.59±0.11[a]
Study group	330.26±13.45	233.71±11.26[a]	1.39±0.24	0.86±0.15[a]	0.52±0.19	0.66±0.15[a]
t value	1.263	10.957	0.602	6.285	0.278	2.410
P value	0.210	<0.001	0.549	<0.001	0.782	0.018

Note: a, compared with pre-treatment, P<0.05.

Tab.6 Comparison of serum tumor marker levels between two groups (n=41, $\bar{x}\pm s$)

Group	CYFRA21-1 (ng/mL)		CA125 (U/mL)		NSE (ng/mL)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	5.12±1.24	3.11±1.08[a]	267.39±21.23	67.48±9.12[a]	30.17±4.08	19.64±3.44[a]
Study group	4.87±1.36	2.26±1.04[a]	266.47±20.94	59.26±8.16[a]	31.02±4.16	15.23±2.87[a]
t value	0.870	3.630	0.198	4.301	0.934	6.303
P value	0.387	<0.001	0.844	<0.001	0.353	<0.001

Note: a, compared with pre-treatment, P<0.05.

Tab.7 Comparison of adverse reactions between two groups [n=41, case(%)]

Group	Decreased WBC	Liver dysfunction	Nausea and vomiting	Myelosuppression	Renal dysfunction	Total
Control group	5(12.20)	2(4.88)	3(7.32)	2(4.88)	3(7.32)	15(36.59)
Study group	2(4.88)	1(2.44)	1(2.44)	0	2(4.88)	5(12.20)
χ^2 value						6.613
P value						0.010

3 Discussion

NSCLC is one of the most prevalent types of malignant tumors worldwide, with its incidence and mortality rates remaining at high levels, posing a significant public health challenge [12]. Although traditional chemotherapy regimens such as the GP regimen play an important role in the treatment of NSCLC, the efficacy of chemotherapy alone still has certain limitations [13]. In recent years, microwave thermal ablation technology, as a local treatment modality, has gradually gained attention in the comprehensive treatment of NSCLC. The treatment model combining microwave thermal ablation with the GP regimen aims to leverage the synergistic effects of the two therapeutic approaches to enhance clinical treatment efficacy, reduce tumor marker levels, and mitigate adverse reactions. The study results showed that compared with the disease control rate of 78.05% in the control group, the disease control rate in the study group was significantly improved, reaching 95.12%, suggesting that microwave thermal ablation can reduce tumor burden through local ablation and enhance the killing effect of chemotherapeutic drugs on residual tumor cells [14]. Research by Shao *et al.* [15] indicated that dendritic cell-cytokine-induced killer cell immunotherapy combined with the GP regimen could increase the disease control rate to 86.67%, suggesting that the synergistic effect of local immunotherapy and systemic chemotherapy may be achieved through immune modulation. Furthermore, tumor cell necrosis induced by microwave thermal ablation may release tumor antigens, activating dendritic cells and T cells, thereby enhancing the systemic anti-tumor immune response [16]. Concurrently, after treatment, ctDNA and CTCs levels in the study group were significantly lower than those in the control group, indicating that microwave thermal ablation may reduce the shedding of tumor cells into the circulatory system by directly clearing the primary lesion and micro-metastases [17]. Additionally, dynamic changes in ctDNA can serve as a monitoring indicator for minimal residual disease, and its decrease may predict a reduced risk of long-term recurrence [18]. Meanwhile, exosomal PD-L1 and miR-21 levels were significantly reduced in the study group, while miR-330 levels increased. PD-L1 is an immune checkpoint protein, and its high expression in exosomes may mediate immune escape by inhibiting T cell function [19]. Microwave thermal ablation may reduce the release of PD-L1 exosomes by disrupting the tumor microenvironment, thereby reversing the immunosuppressive state [20]. As an oncogenic factor, the downregulation of miR-21 may inhibit tumor proliferation and metastasis [21]; whereas miR-330 suppresses tumor invasiveness by targeting the MAPK/ERK pathway [22]. In this study, tumor marker levels were lower in the study group, suggesting that microwave thermal ablation combined with chemotherapy can more effectively eliminate tumor cells and inhibit their activity. This result is consistent with the findings of Zhu *et al*. [23] on low molecular weight heparin combined with

the GP regimen in treating NSCLC; the decrease in marker levels in this study may reflect the comprehensive regulation of tumor biological behavior by the combined therapy [24]. The incidence of adverse reactions in the study group (12.20%) was significantly lower than that in the control group (36.59%). This may be due to the combined application of microwave thermal ablation and the GP regimen, while enhancing the therapeutic effect, can reduce the dosage or frequency of chemotherapeutic drug administration, thereby mitigating potential damage to non-tumor tissues [14]. Furthermore, as a local treatment modality, microwave thermal ablation itself carries a low risk of complications, further improving the safety profile of the treatment [25]. Research on local hyperthermia by Sun *et al.* [26] also showed that thermal ablation treatment in patients with papillary thyroid carcinoma did not significantly increase grade 3 or higher adverse reactions, suggesting that the safety advantages of thermal ablation are broadly applicable.

In conclusion, microwave thermal ablation combined with the GP regimen demonstrates significant clinical advantages in treating NSCLC. It not only improves the disease control rate but also effectively reduces the levels of tumor markers and circulating tumor-related biomarkers, while decreasing the occurrence of adverse reactions. Future multicenter studies with larger sample sizes are needed to further validate its clinical translational value.

Conflict of Interest None

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·肺癌专题·论著·

热消融联合吉西他滨+顺铂方案治疗非小细胞肺癌

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摘要：目的　探讨微波热消融联合吉西他滨+顺铂（GP）方案治疗非小细胞肺癌（NSCLC）的临床疗效及其对循环肿瘤DNA（ctDNA）及血清外泌体标志物水平的影响。**方法**　回顾性纳入2022年1月至2024年12月沧州市人民医院82例NSCLC患者，按治疗方案分为两组，对照组（41例）采用GP方案治疗，研究组（41例）在此基础上联合微波消融。比较两组临床疗效，治疗前后ctDNA与循环肿瘤细胞（CTCs）水平、血清外泌体标志物[程序性死亡配体1（PD-L1）、微小RNA（miR）-21、miR-330]水平、肿瘤标志物[神经元特异性烯醇化酶（NSE）、糖类抗原125（CA125）、细胞角蛋白19片段（CYFRA21-1）]水平以及治疗期间不良反应发生情况。**结果**　研究组疾病控制率高于对照组（95.12% *vs* 78.05%，χ^2=5.145，*P*=0.023）。治疗后，两组ctDNA、CTCs、CYFRA21-1、CA125、NSE水平均降低，且研究组低于对照组（*P*<0.05）。两组外泌体PD-L1、miR-21水平均降低，miR-330水平均升高，且研究组各项指标改善程度优于对照组（*P*<0.05）。研究组不良反应发生率低于对照组（12.20% *vs* 36.59%，χ^2=6.613，*P*=0.010）。**结论**　微波热消融联合GP方案治疗NSCLC可提高临床疗效，降低ctDNA、CTCs及外泌体PD-L1、miR-21水平，提高miR-330水平，降低肿瘤标志物水平，减少不良反应。

关键词：微波热消融；吉西他滨；顺铂；非小细胞肺癌；循环肿瘤DNA；外泌体；程序性死亡配体1；微小RNA

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Thermal ablation combined with gemcitabine and cisplatin regimen in patients with non-small cell lung cancer

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Abstract: Objective　To explore the clinical efficacy of microwave thermal ablation combined with gemcitabine and cisplatin (GP) regimen in the treatment of non-small cell lung cancer (NSCLC) and its influence on the levels of circulating tumor DNA (ctDNA) and serum exosome markers. **Methods**　A total of 82 NSCLC patients admitted to Cangzhou People's Hospital from January 2022 to December 2024 were retrospectively enrolled and divided into two groups according to the treatment regimen. The control group (41 cases) was treated with GP regimen alone, while the study group (41 cases) was treated with microwave ablation on the basis of GP regimen. The clinical efficacy, levels of ctDNA, circulating tumor cells (CTCs), serum exosome markers [programmed death ligand 1 (PD-L1), microRNA (miR)-21, miR-330], tumor markers [neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), cytokeratin 19 fragment (CYFRA21-1)] before and after treatment, and the incidence of adverse reactions during treatment were compared between the two groups. **Results**　The disease control rate of the study group was higher than that of the control group (95.12% *vs* 78.05%, χ^2=5.145, *P*=0.023). After treatment, the levels of ctDNA, CTCs, CYFRA21-1, CA125 and NSE in both groups decreased, and those in the study group were lower than those in the control group (*P*<0.05). The levels of exosomal PD-L1 and miR-21 in both groups decreased, while the level of miR-330 increased, and the improvement degree of each index in the study group was better than that in the control

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group (P<0.05). The incidence of adverse reactions in the study group was lower than that in the control group (12.20% *vs* 36.59%, χ^2=6.613, P=0.010). **Conclusion** Microwave thermal ablation combined with GP regimen in the treatment of NSCLC can improve clinical efficacy, reduce the levels of ctDNA, CTCs, exosomal PD-L1 and miR-21, increase the level of miR-330, decrease the levels of tumor markers, and reduce adverse reactions.

Keywords: Microwave thermal ablation; Gemcitabine; Cisplatin; Non-small cell lung cancer; Circulating tumor DNA; Exosomes; Programmed death ligand 1; MicroRNA

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非小细胞肺癌(non-small cell lung cancer, NSCLC)是全球恶性肿瘤死亡的主要原因之一,其高异质性和晚期易转移的特性导致传统治疗手段疗效有限[1]。尽管以顺铂为基础的吉西他滨+顺铂(gemcitabine plus cisplatin, GP)方案是晚期NSCLC的标准化疗方案之一,但其单一化疗的客观缓解率与长期生存获益仍面临瓶颈[2]。近年来,局部消融技术因其微创性和对肿瘤微环境的调控潜力,逐渐成为不可手术或局部晚期NSCLC的补充治疗选择[3]。然而,微波热消融作为局部治疗手段,难以控制全身性转移病灶,亟需探索其与系统性化疗的协同作用机制及疗效优化策略[4]。与此同时,液体活检技术的兴起为肿瘤动态监测和疗效预测提供了新视角。循环肿瘤DNA(circulating tumor DNA, ctDNA)和外泌体作为液体活检的新兴标志物,在NSCLC的早期诊断、治疗过程的监测以及预后评估方面,展现出潜在的应用价值[5]。研究证实,ctDNA丰度与NSCLC患者的预后显著相关,基线可检测ctDNA的患者总生存期更短,且其动态变化可实时反映治疗反应[6]。外泌体作为肿瘤微环境的关键信使,通过传递核酸和蛋白调控远处转移与免疫逃逸,其水平变化可能成为评估治疗敏感性的潜在标志物。其中外泌体程序性死亡配体1(programmed death ligand 1, PD-L1)是免疫治疗中的关键标志物,而微小RNA(microRNA, miR)-21和miR-330则被证实与肺癌的增殖、转移、预后等密切相关[7]。然而,目前关于微波热消融联合化疗对ctDNA和外泌体影响的系统性研究仍较匮乏。GP方案作为经典化疗组合,其免疫调节作用可能通过诱导免疫原性细胞死亡,增强抗肿瘤免疫反应[8]。微波热消融则可能通过局部释放肿瘤抗原,激活全身性T细胞应答,与GP方案的免疫协同效应形成"原位疫苗"作用,进一步提升疗效[9]。因此,本研究旨在评估微波热消融联合GP方案治疗NSCLC的临床疗效,并探讨其对ctDNA和外泌体水平的动态影响。

1　资料与方法

1.1　一般资料　选取2022年1月至2024年12月沧州市人民医院82例NSCLC患者作为研究对象,回顾性收集其临床资料,本研究已通过沧州市人民医院伦理委员会审批(审批号:K2024-030-02)。纳入标准:(1)符合《中华医学会肺癌临床诊疗指南(2024版)》[10]中NSCLC的诊断标准,且经病理学或细胞学确诊;(2)临床资料完整,涵盖治疗前后的影像学检查、实验室检查结果及随访信息;(3)卡氏功能状态评分>60分;(4)年龄≥18岁。排除标准:(1)合并其他恶性肿瘤;(2)存在肝、肾、心脏或肺部等重要器官的严重功能障碍;(3)因身体状况无法耐受微波热消融或化疗。根据治疗方案的不同,将患者分为两组。采用GP方案治疗的41例为对照组,在此基础上联合微波消融的41例为研究组。两组患者的基线资料比较差异无统计学意义(P>0.05)。见表1。

表1　两组基线资料比较　(n=41)

Tab.1　Comparison of general data between two groups　(n=41)

组别	性别(例)		年龄(岁, $\bar{x}\pm s$)	身体质量指数(kg/m^2, $\bar{x}\pm s$)	肿瘤分型(例)		肿瘤直径(例)	
	男	女			腺癌	鳞癌	≤3 cm	>3 cm
对照组	25	16	59.84±5.01	21.36±3.02	17	24	12	29
研究组	26	15	61.48±4.95	22.57±3.13	19	22	10	31
χ^2/t值	0.052		1.491	1.781	0.198		0.248	
P值	0.820		0.140	0.078	0.656		0.618	

1.2　*方法*

1.2.1　对照组　采用GP方案治疗,具体如下。化疗周期第1天和第8天,给予吉西他滨1 250 mg/m^2(江苏豪森药业,国药准字H20030104),与生理盐水混合后静脉滴注,持续约30 min;第1~3天,给予顺铂75 mg/m^2(齐鲁制药,国药准字H37021358),与生理盐水混合后静脉滴注,持续约1 h。每3周为1个治疗周期,共4个周期。

1.2.2　研究组　在对照组的GP方案治疗基础上,联合应用微波消融治疗,具体如下。化疗2 d后,由经

验丰富的手术医生与CT医生协作实施微波消融。首先进行CT定位，随后使用2%的利多卡因进行局部麻醉。在CT引导下，将微波消融针经皮穿刺或通过手术切口插入肿瘤组织内，确保针尖位于肿瘤中心或适当位置。根据肿瘤的大小、位置等因素设定消融参数，消融功率在50~70 W，时间根据肿瘤大小和消融范围而定，为5~10 min。消融过程中，通过CT监测观察消融区域的变化，确保消融范围覆盖整个肿瘤，同时尽量减少对周围正常组织的损伤。消融结束后，拔除消融针，对穿刺点进行压迫止血和包扎，观察患者生命体征和局部情况，给予必要的对症支持治疗。为确认肿瘤完全消融，消融结束后进行CT造影检查，若未完全消融则再次进行消融。

1.3　观察指标

1.3.1　临床疗效　依据实体瘤临床疗效评价标准1.1版[11]（Response Evaluation Criteria in Solid Tumors，RECIST）进行评估，具体如下。完全缓解：所有病灶消失，持续≥4周；部分缓解：目标病灶直径总和缩小≥30%，持续≥4周；疾病稳定：病灶变化未达到以上标准；疾病进展：病灶直径总和增大≥20%或出现新病灶。疾病控制率=（完全缓解例数+部分缓解例数+疾病稳定例数）/总例数×100%。

1.3.2　ctDNA与循环肿瘤细胞（circulating tumor cells，CTCs）水平　分别于治疗前后进行以下检测。（1）CTCs阴性富集与流式检测：取全血样本经红细胞特异性抗体（CD235a）及白细胞特异性抗体（CD45/CD14/CD66b）混合孵育，通过抗原-抗体偶联结合密度梯度离心（Ficoll分离液，1.077 g/mL）去除红、白细胞，获取CTCs富集液；采用贝克曼库尔特CytoFLEX流式细胞仪（激发波长488 nm，检测通道FL1/FITC），以EpCAM/CK18作为CTCs标记物进行定量分析。（2）ctDNA提取与定量：取血浆样本于半径13.5 cm的水平转子中以2 000 r/min离心10 min去除细胞碎片。采用QIAamp循环核酸试剂盒（德国Qiagen）提取血浆游离DNA，裂解液（含蛋白酶K）消化后，依次加入结合缓冲液（Buffer ACB）及乙醇混合液，通过硅胶膜吸附法纯化ctDNA，经AW1/AW2缓冲液洗涤后洗脱；采用荧光定量聚合酶链反应（polymerase chain reaction，PCR）（引物针对ALU序列，片段大小：115 bp）检测ctDNA浓度，以标准曲线法计算拷贝数。

1.3.3　外泌体PD-L1、miR-21、miR-330水平　分别于治疗前后，取患者空腹时肘静脉血5 mL，放置30 min后，离心分离血清，血清样本在−20 ℃冰箱中保存，以备后续使用。取1 mL血清样本，使用外泌体快速提取试剂盒（武汉华美生物工程，货号：CSB-EI0102）提取外泌体，采用酶联免疫吸附法检测外泌体PD-L1水平。采用Trizol试剂（碧云天生物技术，货号：R0016）提取外泌体中的总RNA，应用紫外分光光度计[岛津（Shimadzu），型号：UV-1800]测定RNA纯度，利用反转录试剂盒（宝生物工程，货号：RR037A）将总RNA反转录为cDNA，随后使用实时荧光定量PCR仪（上海宏石医疗科技，型号：SLAN-96P）进行PCR扩增，反应体系为20 μL，包含SYBR Green Master Mix和10 μmol/L引物。扩增程序设置为：预变性95 ℃ 10 min；40个循环的95 ℃ 15 s变性/60℃ 1 min退火延伸。采用U6作为内参基因，通过$2^{-\Delta\Delta Ct}$法计算miR-21、miR-330的相对表达量。引物序列见表2。

1.3.4　肿瘤标志物水平　分别于治疗前后，取同上血清样本，采用酶联免疫吸附法检测神经元特异性烯醇化酶（neuron-specific enolase，NSE）、糖类抗原125（carbohydrate antigen 125，CA125）、细胞角蛋白19片段（cytokeratin fragment 19，CYFRA21-1）水平。试剂盒产自Elabscience，检测流程严格按照试剂盒说明书操作。

1.3.5　不良反应发生情况　记录两组患者治疗期间的不良反应，包括白细胞减少、肝功能损伤、恶心与呕吐、骨髓抑制、肾功能损伤等。

1.4　统计学方法　采用SPSS 25.0软件进行数据分析。呈正态分布的计量资料采用$\bar{x}\pm s$表示，并通过t检验进行组间比较；计数资料采用例（%）表示，并通过χ^2检验进行组间比较。P<0.05为差异有统计学意义。

2　结　果

2.1　临床疗效比较　研究组疾病控制率高于对照组（95.12% *vs* 78.05%，P<0.05）。见表3。

2.2　ctDNA与CTCs水平比较　治疗前，两组ctDNA与CTCs水平比较差异无统计学意义（P>0.05）；治疗

表2　miR-21、miR-330和U6的PCR引物序列

Tab.2　PCR primer sequences of miR-21, miR-330 and U6

目标基因	序列
miR-21	正向引物：5′-GCT TAT CAG ACT TAT GTT GAC TG-3′
	反向引物：5′-CAG CCC ATC GAC TGG TG-3′
miR-330	正向引物：5′-TTT GGC GAT CAC TGC CTC TC-3′
	反向引物：5′-CTC TCT GCA GGC CGT GTG-3′
U6	正向引物：5′-CGA GAT CCC TCC AAA ATC AA-3′
	反向引物：5′-TTC ACA CCC ATG ACG AAC AT-3′

后，两组ctDNA与CTCs水平均降低，且研究组低于对照组（P<0.05）。见表4。

2.3　外泌体PD-L1、miR-21及miR-330水平比较　治疗前，两组外泌体PD-L1、miR-21及miR-330水平比较差异无统计学意义（P>0.05）；治疗后，两组外泌体PD-L1、miR-21水平均降低，miR-330水平均升高，且研究组各项指标改善程度均优于对照组（P<0.05）。见表5。

2.4　血清肿瘤标志物水平比较　治疗前，两组CYFRA21-1、CA125、NSE水平比较差异无统计学意义（P>0.05）；治疗后，两组CYFRA21-1、CA125、NSE水平均降低，且研究组低于对照组（P<0.05）。见表6。

2.5　两组不良反应情况比较　研究组不良反应发生率为12.20%，低于对照组的36.59%（P<0.05）。见表7。

表3　两组临床疗效比较　［n=41，例(%)］

Tab.3　Comparison of clinical efficacy between two groups ［n=41, case(%)］

组别	完全缓解	部分缓解	疾病稳定	疾病进展	疾病控制率(%)
对照组	6(14.63)	12(29.27)	14(34.15)	9(21.95)	78.05
研究组	10(24.39)	16(39.02)	13(31.71)	2(4.88)	95.12
χ^2值					5.145
P值					0.023

表4　两组ctDNA及CTCs水平比较　(n=41, $\bar{x}\pm s$)

Tab.4　Comparison of ctDNA and CTCs levels between two groups　(n=41, $\bar{x}\pm s$)

组别	ctDNA(ng/μL)		CTCs($\times10^{-5}$)	
	治疗前	治疗后	治疗前	治疗后
对照组	4.39±1.16	3.59±1.09[a]	17.68±2.58	9.98±1.63[a]
研究组	4.46±1.22	2.46±1.13[a]	17.62±2.47	5.69±1.26[a]
t值	0.266	4.609	0.108	13.333
P值	0.791	<0.001	0.915	<0.001

注：与治疗前比较，[a]P<0.05。

表5　两组外泌体PD-L1、miR-21及miR-330水平比较　(n=41, $\bar{x}\pm s$)

Tab.5　Comparison of PD-L1, miR-21 and miR-330 levels in exosomes between two groups　(n=41, $\bar{x}\pm s$)

组别	PD-L1(pg/mL)		miR-21		miR-330	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照组	334.21±14.83	262.74±12.69[a]	1.36±0.21	1.09±0.18[a]	0.51±0.13	0.59±0.11[a]
研究组	330.26±13.45	233.71±11.26[a]	1.39±0.24	0.86±0.15[a]	0.52±0.19	0.66±0.15[a]
t值	1.263	10.957	0.602	6.285	0.278	2.410
P值	0.210	<0.001	0.549	<0.001	0.782	0.018

注：与治疗前比较，[a]P<0.05。

表6　两组血清肿瘤标志物水平比较　(n=41, $\bar{x}\pm s$)

Tab.6　Comparison of serum tumor marker levels between two groups　(n=41, $\bar{x}\pm s$)

组别	CYFRA21-1(ng/mL)		CA125(U/mL)		NSE(ng/mL)	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照组	5.12±1.24	3.11±1.08[a]	267.39±21.23	67.48±9.12[a]	30.17±4.08	19.64±3.44[a]
研究组	4.87±1.36	2.26±1.04[a]	266.47±20.94	59.26±8.16[a]	31.02±4.16	15.23±2.87[a]
t值	0.870	3.630	0.198	4.301	0.934	6.303
P值	0.387	<0.001	0.844	<0.001	0.353	<0.001

注：与治疗前比较，[a]P<0.05。

表7　两组不良反应情况比较　［n=41, 例(%)］

Tab.7　Comparison of adverse reactions between two groups ［n=41, case(%)］

组别	白细胞减少	肝功能损伤	恶心、呕吐	骨髓抑制	肾功能损伤	合计
对照组	5(12.20)	2(4.88)	3(7.32)	2(4.88)	3(7.32)	15(36.59)
研究组	2(4.88)	1(2.44)	1(2.44)	0	1(2.44)	5(12.20)
χ^2值						6.613
P值						0.010

3　讨　论

NSCLC是国际上广泛存在的恶性肿瘤类型之一，其发病率与死亡率均维持在较高水平，构成严峻的公共卫生挑战[12]。尽管传统的化疗方案如GP方案在NSCLC的治疗中发挥了重要作用，但单一化疗的疗效仍存在一定的局限性[13]。近年来，微波热消融技术作为一种局部治疗手段，在NSCLC的综合治疗中逐渐受到关注。本研究旨在通过结合微波热消融及GP方案的治疗模式，发挥二者的协同效应，以期达到提升临床治疗效果、降低肿瘤标志物水平及减轻不良反应的目的。本研究结果显示，相较于对照组的疾病控制率78.05%，研究组的疾病控制率显著提升，达到了95.12%，提示微波热消融可通过局部消融减少肿瘤负荷，增强化疗药物对残余肿瘤细胞的杀伤作用[14]。邵汉成等[15]的研究表明，树突状细胞-细胞因子诱导的杀伤细胞免疫治疗联合GP方案可将疾病控制率提升至86.67%，提示局部免

疫治疗与全身化疗的协同作用可能通过免疫调节实现。此外，微波热消融诱导的肿瘤细胞坏死可能释放肿瘤抗原，激活树突状细胞和T细胞，从而增强全身抗肿瘤免疫反应[16]。同时，治疗后研究组ctDNA和CTCs水平显著低于对照组，表明微波热消融可能通过直接清除原发灶及微转移灶，减少肿瘤细胞脱落进入循环系统[17]。此外，ctDNA动态变化可作为微小残留病灶的监测指标，其降低可能预示远期复发风险减少[18]。同时，外泌体PD-L1和miR-21水平在研究组显著降低，而miR-330水平升高。PD-L1是免疫检查点蛋白，其在外泌体中的高表达可能通过抑制T细胞功能介导免疫逃逸[19]。微波热消融可能通过破坏肿瘤微环境减少PD-L1外泌体的释放，从而逆转免疫抑制状态[20]。miR-21作为促癌因子，其下调可能抑制肿瘤增殖和转移[21]；而miR-330则通过靶向MAPK/ERK通路抑制肿瘤侵袭性[22]。本研究中，研究组肿瘤标志物水平更低，提示微波热消融联合化疗可更有效地清除肿瘤细胞并抑制其活性。这一结果与朱晶等[23]的低分子肝素联合GP方案治疗NSCLC的结果一致，本研究中标志物水平的下降可能反映联合治疗对肿瘤生物学行为的综合调控[24]。研究组不良反应发生率(12.20%)显著低于对照组(36.59%)，这可能是由于微波热消融与GP方案联合应用时，在增强治疗效果的同时，减少了化疗药物的使用剂量或频次，进而减轻了对非肿瘤组织的潜在伤害[14]。此外，微波热消融作为一种局部治疗手段，其本身具有较低的并发症风险，进一步提高了治疗的安全性[25]。孙豪等[26]的局部热疗研究中也显示，热消融治疗甲状腺乳头状癌患者未明显增加3级以上不良反应，提示热消融的安全性优势具有广泛适用性。

综上所述，微波热消融联合GP方案在治疗NSCLC方面展现了显著的临床优势，不仅提高了疾病控制率，还有效降低了肿瘤标志物和循环肿瘤相关生物标志物的水平，同时减少了不良反应的发生。未来需通过多中心大样本研究进一步验证其临床转化价值。

利益冲突　无

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