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Original Article

Circulating tumor DNA mediates the effect of intrapleural cisplatin retention on non-small cell lung cancer malignant pleural effusion

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Abstract: Objectives: To analyze the therapeutic effects of different cisplatin retention times on malignant pleural effusion and to explore whether circulating tumor DNA (ctDNA) played a mediating role in this process. Methods: A total of 207 patients with non-small cell lung cancer (NSCLC) and pleural effusion were enrolled. According to the retention time after intrapleural injection of cisplatin, patients were divided into three groups: a 1 h retention group (n=68), a 6 h retention group (n=69), and a 24 h retention group (n=70). The short-term efficacy (disease control rate, objective response rate) and long-term efficacy (progression-free survival, overall survival (OS)) were compared among the three groups, and the role of ctDNA was explored through mediation effect analysis. Results: The disease control rate in the 24 h retention group was 92.9%, significantly higher than that in the 6 h group (92.7%) and the 1 h group (80.9%) (P<0.05). Regarding survival outcomes, the median progression-free survival (PFS) in the 24 h group was 11.8 months, and the median OS was 18.5 months, both significantly longer than those in the 6 hr and 1 h groups (P<0.001). Mediation analysis showed that ctDNA concentration played a partial mediating role in the association between cisplatin retention duration and patient survival (both PFS and OS). Conclusions: 24 h intrapleural cisplatin retention significantly improves the short-term and long-term treatment outcomes in NSCLC patients with pleural effusion. Changes in ctDNA concentration play a key mediating role in this efficacy improvement, suggesting that ctDNA could serve as a novel potential biomarker for guiding personalized treatment.

Keywords: Cisplatin intrapleural injection, non-small cell lung cancer, pleural effusion, retention time, circulating tumor DNA, mediation analysis

Introduction

Lung cancer is one of the most common cancers worldwide and a leading cause of cancer-related deaths [1]. Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer, accounting for approximately 85% of all lung cancer cases [2]. The estimated 5-year survival rate for NSCLC patients is between 10% and 23% [3]. Pleural effusion is a common complication in lung cancer patients, and about half of these patients eventually develop pleural metastasis, progressing to malignant pleural effusion (MPE) [4]. The development of MPE usually indicates that the tumor has metastasized to distant sites or has progressed to an advanced stage, leading to impaired lung function and a decreased quality of life [5]. Studies have shown that MPE has an adverse effect on the prognosis of lung cancer patients, with a median survival of only 9.5 months [6, 7]. NSCLC tumors typically grow slowly and lack specific early symptoms, which often results in delayed diagnosis. Most patients are diagnosed at an advanced stage, missing the optimal time for surgical treatment. Clinically, these patients often receive radiotherapy and chemotherapy to prolong survival [8]. Intrapleural chemotherapy is an important local treatment. Cisplatin, as a first-generation platinum-based drug, can bind to the N7 site of purines to form adducts, causing changes in DNA activity and inducing apoptosis. Due to its potent anticancer activity, cisplatin has become a first-line treatment for various malignant tumors such as ovarian cancer, head and neck cancer, testicular cancer, and lung cancer [9]. However, there is currently no unified standard

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for the optimal retention time of cisplatin intrapleural injection in clinical practice, with treatment durations ranging from 1 h to 72 h [10]. Circulating tumor DNA (ctDNA) is DNA released into the bloodstream by tumor cells and is one of the most valuable plasma biomarkers for patients with various cancers, including NSCLC [11]. As a fragment of genetic material from cancer cells, ctDNA carries cancer-specific gene abnormalities and can comprehensively reflect the mutation spectrum characteristics of a patient's tumor [12, 13]. Therefore, comprehensive and accurate analysis of the characteristics of ctDNA can greatly assist in the early diagnosis of cancer, recurrence monitoring, real-time monitoring of disease progression, and postoperative residual lesion assessment [14, 15]. This retrospective cohort study clarified the correlation between different retention times of cisplatin intrapleural injection and short-term and long-term efficacy in NSCLC patients complicated with MPE. This study also introduced dynamic monitoring of ctDNA concentration for the first time and revealed its potential mediating role using a mediation effect model, providing a theoretical basis for individualized clinical treatment.

Materials and methods

Study subjects

This retrospective cohort study included 207 NSCLC patients complicated with pleural effusion, all of whom received treatment at the Baoding Fourth Center Hospital between October 2021 and October 2024.

Inclusion criteria were as follows: (1) pathologically confirmed NSCLC; (2) pleural effusion confirmed by cytological or histological examination; (3) age between 18 and 80 years; (4) intrapleural cisplatin injection therapy with a clear record of drug retention time in the medical record; (5) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2; (6) expected survival of ≥3 months; (7) complete clinical data, including pre-treatment baseline data, treatment records, and follow-up data; and (8) at least one set of ctDNA test results before and after treatment. Exclusion criteria included: (1) coexisting malignant tumors; (2) history of intrapleural chemotherapy or pleural adhesion surgery; (3) severe heart, liver, or kidney dysfunction; (4) pregnant or lactating women; (5) unable to give informed consent or refusing to participate in the study; (6) incomplete medical records, making it impossible to confirm the treatment plan or missing follow-up data.

Patients were divided into three groups based on drug retention time: a 1 h retention group (n=68), a 6 h retention group (n=69) and a 24 h retention group (n=70). This study adopted a clinically relevant treatment grouping strategy and did not stratify according to clinical stage (stage IIIb/stage IV). The intrapleural cisplatin retention time was determined by the attending physician based on the patient's overall condition, the amount of MPE, and clinical tolerance, fully reflecting real-world clinical practice.

This study was approved by the Ethics Committee of the Baoding Fourth Center Hospital. Informed consent was waived because it was a retrospective study and maintained patient privacy.

Treatment methods

We performed closed thoracic drainage using minimally invasive catheter placement techniques on all patients. After adequate drainage of pleural effusion, cisplatin was injected through the drainage tube. The cisplatin dose (80 mg/m^2) was calculated according to the Du Bois formula (body surface area = 0.20247 × [height (cm)^0.725] × [weight (kg)^0.425] [16]) and diluted with normal saline to a total volume of 50 mL. The thoracic drainage tube was then clamped and maintained in place for the duration of drug indwelling as determined by randomization.

During drug indwelling, patients were instructed to change positions cyclically (supine → right lateral decubitus → prone → left lateral decubitus), holding each position for at least 30 seconds, repeating the complete cycle every 15 minutes until the end of drug retention duration, to ensure uniform contact between cisplatin and the chest wall. After the retention duration, the drainage tube was opened for continuous drainage. The drainage tube was removed when the daily thoracic drainage volume was less than 100 mL.

Treatment was administered weekly for a maximum of three cycles, adhering to the following

standardized treatment execution and termination criteria: (1) Early termination: Complete remission of pleural effusion after 1-2 cycles, or the occurrence of grade 3/4 treatment-related adverse reactions (severe myelosuppression, renal insufficiency, severe nausea and vomiting unresponsive to symptomatic treatment); (2) Continued treatment: Partial remission or stable condition after 1-2 cycles, with good treatment tolerance (adverse reactions grade 0-2), continued treatment up to three cycles; (3) Termination of treatment: Progression of pleural effusion after any cycle of treatment.

Efficacy evaluation

Short-term efficacy was assessed according to the World Health Organization's criteria for evaluating the efficacy of pleural effusion treatment: Complete Response (CR): Complete disappearance of pleural effusion, with symptoms lasting ≥1 month; Partial Response (PR): Reduction of pleural effusion ≥50%, with symptoms lasting ≥1 month; Stable Disease (SD): Reduction of pleural effusion less than 50% or increase not exceeding 25%; Progressive Disease (PD): An increase of pleural effusion exceeding 25% or patient death. Objective response rate (ORR) is the percentage of patients achieving complete or partial remission. Disease control rate (DCR) is the percentage of patients achieving CR, PR, or SD.

Long-term efficacy endpoints were assessed using progression-free survival (PFS) and overall survival (OS). PFS was the time from the start of treatment to disease progression or death from any cause. OS was the time from the start of treatment to death from any cause.

CtDNA detection

All patients underwent fasting peripheral venous blood collection (5 mL) at baseline (before treatment). Within 2 h of blood collection, plasma was separated by centrifugation at 3,000 rpm for 10 minutes at 4°C (avoiding hemolysis). The separated plasma was aliquoted and stored at -80°C (freeze-thaw cycles not exceeding 3). ctDNA was extracted using the Thermo Fisher Scientific MagMAX cell-free DNA extraction kit (product number: A29319) based on the magnetic bead method. Thermo Fisher Scientific Qubit 4.0 real-time fluorescence instrument (product number: Q33226) paired with the Qubit double-stranded DNA high-sensitivity detection kit (product number: Q32851) was used to quantify the ctDNA concentration (unit: ng/μL), with a detection range of 0.01-100 ng/μL and a detection limit of 0.01 ng/μL. The A260/A280 ratio (1.8-2.0) and A260/A230 ratio (2.0-2.5) were measured using a Nanodrop 2000 micro-volume spectrophotometer to exclude protein, ribonucleic acid, and salt ion contamination. A total of 10% of the samples were randomly selected for ctDNA fragment length analysis using an Agilent 2100 Bioanalyzer, with a target peak length of 160-180 base pairs, ensuring no sample degradation. Only samples meeting the following criteria were included in subsequent analysis: concentration ≥0.1 ng/μL, A260/A280 ratio between 1.8 and 2.0, and fragment integrity ≥80%. Unqualified samples were re-extracted (maximum of two attempts).

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x}\pm sd$) and one-way ANOVA was used for comparisons between groups. Non-normally distributed continuous data were presented as median (interquartile range (M[IQR]) and Kruskal-Wallis H test was used for comparisons between groups. Categorical data were expressed as number (percentage), and chi-square test was employed for comparisons between groups. Kaplan-Meier survival curves were plotted using the Kaplan-Meier method, and log-rank test was applied to compare differences. Cox proportional hazards regression model was used for multivariate analysis. Kolmogorov-Smirnov test showed that the PFS and OS data in the overall cohort followed a Weibull distribution (P=0.231 for PFS, P=0.185 for OS). Normality test results indicated that the ctDNA concentration data in all three groups conformed to a normal distribution (Shapiro-Wilk test, all P>0.05). Parametric survival models were applied to analyze the mediating effect of ctDNA concentration on cisplatin retention time and survival outcomes (PFS and OS). The mediating effect was assessed using a bootstrap method (5,000 replicates), and 95% confidence intervals (CI) were calculated. A two-tailed P-value <0.05 was considered statistically significant.

Table 1. Baseline characteristics of patients

Clinical features	All (n=207)	1 h Retention (n=68)	6 h Retention (n=69)	24 h Retention (n=70)	F/χ^2 value	*P*-value
Age (years)	62.39±9.68	61.75±10.24	63.05±9.27	62.34±9.57	0.313	0.732
Gender, n (%)					0.183	0.913
Male	128 (61.8)	41 (60.3)	44 (63.8)	43 (61.4)		
Female	79 (38.2)	27 (39.7)	25 (36.2)	27 (38.6)		
Pathological type, n (%)					1.851	0.763
Adenocarcinoma	151 (72.9)	46 (67.7)	53 (76.8)	52 (74.3)		
Squamous cell carcinoma	40 (19.3)	16 (23.5)	12 (17.4)	12 (17.1)		
Others	16 (7.7)	6 (8.8)	4 (5.8)	6 (8.6)		
Clinical stage, n (%)					2.099	0.350
IIIb	84 (40.6)	24 (35.3)	27 (39.1)	33 (47.1)		
IV	123 (59.4)	44 (64.7)	42 (60.9)	37 (52.9)		
ECOG score, n (%)						
0-1	165 (79.7)	55 (80.9)	54 (78.3)	52 (74.3)	0.882	0.643
2	42 (20.3)	13 (19.1)	15 (21.7)	18 (25.7)		

ECOG: Eastern Cooperative Oncology Group.

Table 2. Comparison of short-term efficacy

Group	CR (n, %)	PR (n, %)	SD (n, %)	PD (n, %)	ORR (CR+PR, n, %)	DCR (CR+PR+SD, n, %)
1 h Retention	10 (14.7)	22 (32.4)	23 (33.8)	13 (19.1)	32 (47.1)	55 (80.9)
6 h Retention	22 (31.9)	27 (39.1)	15 (21.7)	5 (7.3)	49 (71.0)	64 (92.7)
24 h Retention	25 (35.7)	26 (37.1)	14 (20.0)	5 (7.2)	51 (72.9)	65 (92.9)
χ^2 *value*					12.288	6.573
P-value					0.002	0.037

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

Results

Comparison of baseline characteristics

There were no statistically significant differences in baseline characteristics (including age, gender, pathological type, clinical stage, and ECOG performance status score) among the three groups (all $P>0.05$), indicating comparability (**Table 1**).

Comparison of short-term efficacy

The CR rate in the 24 h retention group was 35.7% (25/70), significantly higher than that in the 6 h retention group (31.9%, 22/69) and the 1 h retention group (14.7%, 10/68) ($P<0.05$). Regarding the ORR, the 24 h retention group achieved 72.9% (51/70), the 6 h retention group 71.0% (49/69), and the 1 h retention group 47.1% (32/68) ($P<0.05$). For the DCR, the 24 h retention group was 92.9% (65/70), the 6 h retention group was 92.7% (64/69), and the 1 h retention group was 80.9% (55/68), ($P<0.05$) (**Table 2**).

Comparison of long-term efficacy

Kaplan-Meier survival analysis showed that the median PFS in the 24 h retention group was 11.8 months (95% *CI*: 9.08-14.52 months), significantly longer than that in the 6 h retention group (10.0 months, 95% *CI*: 7.78-12.22 months) and the 1 h retention group (7.00 months, 95% *CI*: 5.33-8.68 months) (Log-rank test, $P<0.001$) (**Figure 1A**). The median OS in the 24 h retention group was 18.5 months (95% CI: 15.53-21.47 months), significantly longer than that in the 6 h retention group (16.2 months, 95% *CI*: 12.95-16.45 months) and the 1 h retention group (11.7 months, 95% *CI*: 8.99-14.41 months) (Log-rank test, $P<0.001$) (**Figure 1B**). Regarding the 1-year survival rate, the 24 h

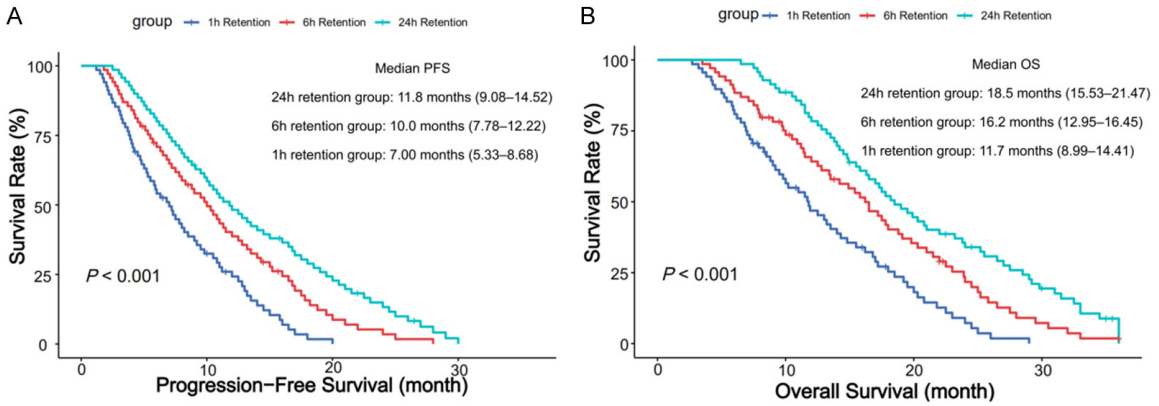

Figure 1. Comparison of long-term efficacy. A. Kaplan-Meier curves of PFS among the three groups. B. Kaplan-Meier curves of OS among the three groups. PFS: Progression-Free Survival; OS: Overall Survival.

retention group was 70.0% (49/70), the 6 h retention group was 55.1% (38/69), and the 1 h retention group was 39.7% (27/68) (P<0.05). Regarding the 2-year survival rate, the 24 h retention group was 27.1% (19/70), the 6 h retention group was 17.4% (12/69), and the 1 h retention group was 7.4% (5/68) (P<0.05).

Cox regression analysis

We first included variables that might affect PFS and OS in univariate regression analysis, and then included variables with P<0.1 in the univariate analysis in multivariate analysis. To explore the potential impact of differences in clinical stage distribution on the correlation between cisplatin retention time and efficacy, we constructed an interaction term between clinical stage and grouping. After adjusting for confounding factors, with the 1 h retention group as the reference, the 6 h retention group (hazard ratio [HR]=0.586, 95% *CI*: 0.411-0.835, P=0.003) and the 24 h retention group (HR=0.351, 95% *CI*: 0.240-0.513, P<0.001) remained independent protective factors for PFS (**Table 3**). For OS, 6 h retention (HR=0.570, 95% *CI*: 0.397-0.817, P=0.002) and 24 h retention (HR=0.332, 95% *CI*: 0.226-0.487, P<0.001) were considered independent protective factors (**Table 4**).

Mediating effect of ctDNA on cisplatin retention duration and PFS

To investigate the mediating role of ctDNA concentration, we conducted a mediation effect analysis. A significant mediating effect of ctDNA concentration was found between cisplatin retention duration and PFS, with an effect size of 0.217 (95% *CI*: 0.068, 0.403) (P<0.001) (**Table 5** and **Figure 2**).

Mediating effect of ctDNA on cisplatin retention duration and OS

To investigate the mediating role of ctDNA concentration, we conducted a mediation effect analysis. A significant mediating effect of ctDNA concentration was found between cisplatin retention duration and OS, with an effect size of 0.183 (95% *CI*: 0.056, 0.311) (P<0.001) (**Table 6** and **Figure 3**).

Comparison of safety

Adverse events of varying degrees occurred in all three groups during treatment, mainly including nausea, vomiting, myelosuppression, and renal impairment. Nausea and vomiting had the highest incidence, while renal impairment had a relatively low incidence. Overall, there were no statistically significant differences in the incidence and severity of adverse events among the three groups (P>0.05), indicating that prolonged cisplatin retention time does not significantly increase the risk of adverse events (**Table 7**).

Discussion

MPE refers to the accumulation of fluid in the pleural cavity accompanied by the presence of malignant cells, indicating that the cancer has progressed to an advanced stage [17]. Among lung cancers complicated with MPE, NSCLC is the most common. The mechanism by which

Table 3. Cox regression analysis of PFS

Variables	Univariate analysis					Multivariate analysis				
	β	S.E	Z	*P*	HR (95% CI)	B	S.E	Z	*P*	HR (95% CI)
Group										
1 h Retention					1.000 (Reference)					1.000 (Reference)
6 h Retention	-0.554	0.180	9.490	0.002	0.575 (0.404-0.818)	-0.548	0.179	9.307	0.002	0.578 (0.407-0.822)
24 h Retention	-0.967	0.189	26.174	<0.001	0.380 (0.262-0.551)	-0.972	0.189	26.335	<0.001	0.378 (0.261-0.548)
Age	0.026	0.008	11.756	<0.001	1.026 (1.011-1.042)	0.026	0.007	12.375	<0.001	1.027 (1.012-1.042)
Gender										
Male					1.000 (Reference)					
Female	0.053	0.151	0.124	0.725	1.055 (0.785-1.417)					
Pathological type										
Adenocarcinoma					1.000 (Reference)					
Squamous cell carcinoma	-0.099	0.187	0.281	0.596	0.906 (0.628-1.306)					
Others	-0.002	0.281	0.000	0.993	0.998 (0.575-1.730)					
Clinical stage										
IIIb					1.000 (Reference)					
IV	0.049	0.147	0.109	0.741	1.050 (0.787-1.401)					
ECOG score										
0-1					1.000 (Reference)					
2	0.101	0.175	0.330	0.566	1.106 (0.784-1.560)					
Clinical stage*Group										
IIIb*1 h Retention					1.000 (Reference)					
IV*6 h Retention	-0.215	0.379	0.322	0.570	0.807 (0.384, 1.694)					
IV*24 h Retention	-0.141	0.372	0.144	0.704	0.868 (0.419, 1.801)					

ECOG: Eastern Cooperative Oncology Group.

Table 4. Cox regression analysis of OS

Variables	Univariate analysis					Multivariate analysis				
	β	S.E	Z	*P*	HR (95% *CI*)	B	S.E	Z	*P*	HR (95% *CI*)
Group										
1 h Retention					1.000 (Reference)					1.000 (Reference)
6 h Retention	-0.583	0.183	10.133	0.001	0.558 (0.390-0.799)	-0.568	0.182	9.696	0.002	0.567 (0.396-0.810)
24 h Retention	-1.004	0.19	27.811	<0.001	0.366 (0.252-0.532)	-1.003	0.19	27.839	<0.001	0.367 (0.253-0.532)
Age	0.026	0.008	11.756	<0.001	1.026 (1.011-1.042)	0.027	0.008	12.661	<0.001	1.027 (1.012-1.043)
Gender										
Male					1.000 (Reference)					
Female	0.089	0.153	0.341	0.559	1.093 (0.811-1.474)					
Pathological type										
Adenocarcinoma					1.000 (Reference)					
Squamous cell carcinoma	-0.086	0.189	0.205	0.65	0.918 (0.0633-1.330)					
Others	-0.054	0.291	0.035	0.853	0.947 (0.536-1.675)					
Clinical stage										
IIIb					1.000 (Reference)					
IV	0.023	0.15	0.024	0.876	1.024 (0.764-1.372)					
ECOG score										
0-1					1.000 (Reference)					
2	0.13	0.178	0.533	0.465	1.138 (0.804-1.613)					
Clinical stage*Group										
IIIb*1 h Retention					1.000 (Reference)					
IV*6 h Retention	-0.151	0.384	0.155	0.694	0.860 (0.405, 1.826)					
IV*24 h Retention	-0.135	0.377	0.128	0.720	0.874 (0.417, 1.829)					

ECOG: Eastern Cooperative Oncology Group.

Table 5. Mediation analysis of PFS

Path Relationship	Effect Type	Effect Value (β)	BootSE	BootLLCI	BootULCI
Retention group → PFS	Total Effect (c)	0.504	0.039	0.267	0.728
Retention group → FPS	Direct Effect (c')	0.287	0.104	0.071	0.393
Retention group → ctDNA	Path a	-0.496	0.144	-0.578	-0.409
ctDNA → PFS	Path b	-0.437	0.252	-0.622	-0.246
Retention group → ctDNA → PFS	Indirect Effect (a×b)	0.217	0.072	0.068	0.403

ctDNA: circulating tumor DNA; PFS: Progression-Free Survival.

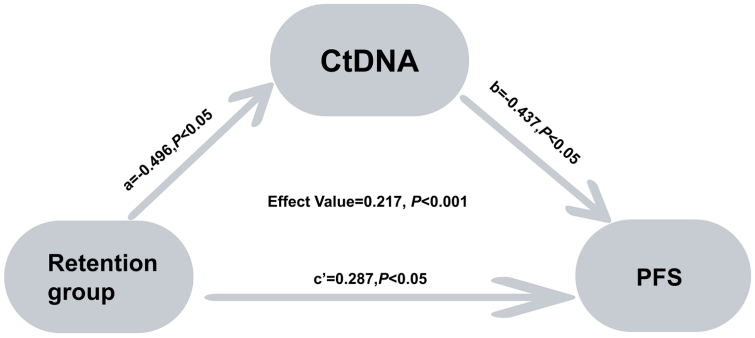

Figure 2. Mediation analysis of PFS. ctDNA: circulating tumor DNA; PFS: Progression-Free Survival.

lung cancer induces MPE is directly associated with pleural invasion. Tumor cells primarily metastasize to the visceral pleura via the hematologic system, and then spread to the parietal pleura through tumor adhesion or free tumor cells [18]. Compared with NSCLC patients without MPE, the median OS of those with even minimal MPE is significantly shortened [19]. Cisplatin is a classic intrapleural infusion drug for the treatment of MPE, and its efficacy is regulated by various factors such as dosage and route of administration. However, the clinical value of the key parameter of retention time has not been fully elucidated. This study retrospectively analyzed 207 NSCLC patients complicated with pleural effusion, systematically explored the correlation between different retention times of cisplatin intrapleural perfusion and the short-term and long-term efficacy of patients, and for the first time analyzed the mediating role of ctDNA concentration in this process. The results showed that a 24 h retention of cisplatin intrapleural perfusion significantly improved the short-term efficacy and long-term survival of patients, and the change in ctDNA concentration played an important mediating role in this process.

This study found that the pleural disease control rate of patients in the 24-hour retention group was 92.9%, which was significantly higher than that of the 6 h retention group (92.7%) and the 1 h retention group (80.9%). The results of this study verified the effective rate range of cisplatin intrapleural perfusion therapy (46.2%-97.3%) in earlier literature [10]. The complete remission rate of the 24 h retention group was 35.7%, which was also significantly higher than that of the other two groups. The above results imply that prolonging the drug retention time may enhance the therapeutic effect, and its mechanism of action may be to prolong the contact time between the drug and the pleura, thereby increasing the local drug concentration. In terms of long-term efficacy, the median PFS was 11.8 months and the median OS was 18.5 months in the 24 h retention group, both of which were significantly better than the other two groups. This result holds important clinical significance. Previous studies have shown that the median survival of NSCLC patients with pleural effusion is typically only 4 to 7 months [20, 21], while the median OS of patients in the 24 h retention group in this study was close to 20 months, indicating that optimizing the cisplatin retention time may be an important strategy to improve patient prognosis.

CtDNA is derived from tumor cells and carries the genetic information of the tumor genome. When macrophages phagocytose apoptotic or necrotic tumor cells, they produce ctDNA fragments, which are released into the peripheral blood circulation via exosomes [22]. Due to degradation by DNase in the circulatory system, clearance by the kidneys, and uptake by the liver or spleen, the half-life of ctDNA is short, ranging from 16 minutes to 2.5 hours

Table 6. Mediation analysis of OS

Path Relationship	Effect Type	Effect Value (β)	BootSE	BootLLCI	BootULCI
Retention group → OS	Total Effect (c)	0.427	0.079	0.261	0.722
Retention group → OS	Direct Effect (c')	0.244	0.086	0.067	0.452
Retention group → ctDNA	Path a	-0.496	0.144	-0.578	-0.409
ctDNA → OS	Path b	-0.368	0.103	-0.649	-0.323
Retention group → ctDNA → OS	Indirect Effect (a×b)	0.183	0.069	0.056	0.311

ctDNA: circulating tumor DNA; OS: Overall Survival.

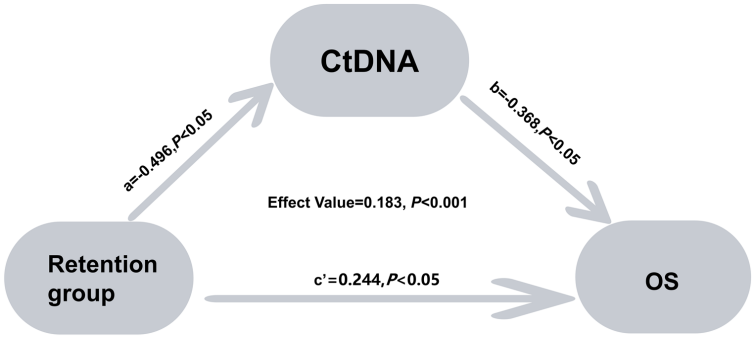

Figure 3. Mediation analysis of OS. ctDNA: circulating tumor DNA; OS: Overall Survival.

Table 7. Safety analysis

Group	Nausea and Vomiting	Myelosuppression	Renal impairment
1 h Retention	38 (55.9%)	13 (19.1%)	5 (7.4%)
6 h Retention	39 (56.5%)	19 (27.5%)	4 (5.8%)
24 h Retention	43 (61.4%)	21 (30.0%)	6 (8.6%)
χ^2 *value*	0.525	2.347	0.399
P-value	0.769	0.309	0.819

[23]. Therefore, ctDNA can serve as a source of information reflecting the tumor status in real time through simple blood sampling [24]. In addition, ctDNA can also predict clinical efficacy. The number or relative abundance of variations in baseline ctDNA is negatively correlated with overall survival, while patients whose oncogene-related ctDNA is cleared have significantly prolonged overall survival [25]. CtDNA has high specificity and dynamic monitoring capabilities, making it a biomarker with great clinical application value, and it can also directly provide a basis for the calculation of tumor-related prognostic indicators [26]. This study found that ctDNA levels could partially explain the association between cisplatin retention time and therapeutic efficacy, suggesting that the effect of retention time on treatment efficacy may involve two different pathways. As a classic chemotherapeutic drug, cisplatin can directly form adducts with DNA, inhibiting DNA repair, causing DNA damage accumulation, inducing apoptosis, and ultimately improving clinical prognosis [27, 28]. In addition, cisplatin induces DNA damage and apoptosis, promoting the release of DNA fragments into the bloodstream, resulting in an early increase and rapid decrease in ctDNA levels. This clearance phenomenon is associated with prolonged PFS and a reduced risk of recurrence [29].

The main adverse reactions of intrapleural cisplatin injection include nausea, vomiting, bone marrow suppression, and renal impairment, which are generally well tolerated by patients [30]. In this study, the incidence of adverse reactions was similar in the three groups, with no significant difference, indicating that prolonged cisplatin retention time in the body does not increase drug toxicity.

This study has certain limitations. This study is a retrospective analysis and may be subject to selection bias, which is consistent with clinical practice - clinicians will individualize the drug retention time based on the patient's condition and tolerance. The detection of ctDNA is easily affected by various factors such as tumor burden and the sensitivity of the detection method. Some studies have shown that ctDNA levels in pleural effusion may be higher and easier to detect [31], but this study mainly used plasma

samples to detect ctDNA. Furthermore, due to limitations in technology and resources, this study did not analyze the tumor-specific mutations (such as epidermal growth factor receptor and anaplastic lymphoma kinase) carried by ctDNA, which made it difficult to clarify the causal relationship of "cisplatin retention → tumor cell damage → ctDNA release → improved efficacy". Moreover, the sample size of the study is relatively small, and a multi-center, large-sample study is needed to verify the above conclusions. Therefore, it is urgent to conduct a large-sample prospective randomized controlled trial to further verify the results of this study and explore personalized treatment strategies based on ctDNA.

Conclusion

This study confirms that a 24 h intrapleural cisplatin retention can significantly improve the short-term and long-term prognosis of patients, and the ctDNA level plays an important mediating role between cisplatin retention time and treatment efficacy. The results of this study are helpful in optimizing treatment plans and are expected to become a new biomarker for personalized treatment.

Disclosure of conflict of interest

None.

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