

Original Article

Effect of intrathecal injection of methotrexate and dexamethasone on quality of life and cognitive function in patients with intracranial tumors

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Abstract: Intrathecal injection therapy offers the advantages of simple operation, cost-effectiveness, and compatibility with various drugs. It can also improve brain microenvironmental conditions and cerebrospinal fluid circulation, thereby enhancing therapeutic efficacy. This retrospective study included 164 patients with intracranial malignant tumors who were treated at Jianhu County People's Hospital from January 2017 to January 2024. Patients were allocated to an experimental group (intrathecal injection of methotrexate + dexamethasone, $n = 68$) or a control group (systemic chemotherapy, $n = 96$) according to treatment regimen. After 1:1 propensity score matching, 56 patients remained in each group, and all subsequent analyses were performed based on the matched cohort. After treatment, the experimental group showed a significant improvement in Karnofsky performance status (KPS) score, increasing from 73.5 ± 8.4 at baseline to 81.2 ± 7.3 after treatment ($P < 0.001$). The effective improvement rate was significantly higher in the experimental group than in the control cohort (53.6% vs. 24.2%, $P = 0.001$). In terms of health-related quality of life (HRQoL), patients in the experimental group showed greater improvements in general physical condition, social functioning, fatigue severity, gastrointestinal adverse reactions, including nausea and vomiting, as well as tumor-associated indicators (all, $P < 0.05$). No significant difference was detected in disease control rate between the two groups ($\chi^2 = 1.423$, $P = 0.233$); however, among patients who achieved disease control, those in the experimental group exhibited more pronounced improvements in KPS and Quality of Life (QoL). No significant improvement or deterioration in cognitive function was observed in either group. In the experimental group, scores on the Symbol Digit Modalities Test (SDMT) and Trail Making Test (TMT) were significantly improved compared to baseline values after treatment ($P < 0.05$). Although the median survival time tended to be longer in the experimental group than in the control group (22.4 months vs. 20.1 months), the difference failed to reach significance ($P = 0.144$). Additionally, the experimental cohort presented a shorter average time to headache symptom relief compared to the control counterpart ($t = 7.112$, $P < 0.001$). Multivariate analysis indicated that baseline KPS score and disease control status were independent prognostic factors associated with overall survival. Furthermore, the experimental group showed a significantly lower incidence of nausea and vomiting ($P < 0.05$), with no increased risk of hematologic, hepatic, or renal toxicity. No significant difference was observed in intrathecal injection-specific adverse events between the two groups. In conclusion, as an adjuvant treatment strategy, intrathecal injection of methotrexate and dexamethasone can significantly improve KPS score and health-related QoL in patients with intracranial tumors, reduce chemotherapy-related gastrointestinal toxicity, demonstrate good safety profiles, and does not adversely affect cognitive function.

Keywords: Methotrexate, dexamethasone, intrathecal injection, intracranial tumors, cognitive function

Introduction

Brain metastatic tumors and primary malignant tumors are major types of intracranial malignant cancers. Among these malignancies, lung cancer, breast cancer, and digestive system cancers are the most common primary tumors causing intracranial metastasis. The early clinical

manifestations of brain metastatic tumors are various, commonly including headache, nausea, and neurologic symptoms of a local mass, such as frontal lobe lesions. Emotional changes may also occur in some patients [1]. In recent years, advances have been achieved in the treatment of intracranial cancers, including surgery, radiotherapy, chemotherapy, and mo-

lecular targeted therapy. However, a standardized treatment strategy has not yet been established. In addition, restricted by the blood-brain barrier (BBB), intravenous administration of antitumor agents often fails to achieve sufficient drug concentrations within intracranial lesions, while systemic toxicity and adverse effects remain major concerns, thereby restricting therapeutic efficacy [2, 3]. With the advancement in precision medicine, more emphasis has been placed on personalized treatment strategies in cancer management to optimize therapeutic outcomes. Intrathecal chemotherapy can significantly increase drug concentrations in the cerebrospinal fluid (CSF). Some agents, such as cytarabine, have a prolonged half-life, allowing intrathecal administration to enhance local drug exposure, extend drug action duration, improve therapeutic efficacy, reduce systemic chemotherapy dosage, and alleviate the economic burden on patients [4-6].

Intrathecal injection serves as an important adjuvant therapeutic approach, particularly for intracranial malignant tumors with leptomeningeal metastasis or cerebrospinal fluid dissemination. Although its application scope remains relatively limited, this approach has attracted increasing attention in recent years due to its ability to bypass the BBB and increase drug concentrations within the cerebrospinal fluid. Methotrexate, cytarabine, and thiopeta are among the most frequently used medications for intrathecal chemotherapy [7]. Previous studies have demonstrated that variations in intrathecal injection protocols, dosage regimens, and combination therapies may lead to differences in treatment efficacy due to individual patient characteristics. However, in general, the survival benefit of intrathecal chemotherapy remains limited, and treatment may be associated with significant side effects, including white matter demyelination, bone marrow suppression, and severe cerebral edema [8].

Dexamethasone is widely adopted in oncology treatment. It can effectively alleviate tumor-related complications and adverse reactions caused by antineoplastic therapy, including reducing vascular permeability, decreasing white matter edema, and relieving chemotherapy-induced nausea and vomiting. Moreover,

dexamethasone serves as an essential component of several chemotherapy regimens, such as CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone) [9]. It can effectively relieve headaches associated with intracranial tumors. Its mechanisms may involve reducing capillary permeability, improving BBB integrity, regulating cerebrospinal fluid production, and attenuating interstitial brain edema. In addition, dexamethasone may stabilize neuronal cell membranes, inhibit neuropeptide synthesis, reduce inflammatory responses and edema around of nerve roots, and regulate the synthesis of prostaglandins, thus alleviating headaches caused by intracranial lesions or bone pain associated with metastatic bone involvement [10-12].

When postoperative resectability is considered, comprehensive treatment strategies should be adopted, with surgery serving as the primary therapeutic approach. However, for patients with unresectable lesions, radiotherapy and chemotherapy remain the main treatment modalities. The specific therapeutic strategy should be individualized according to the patient's physical condition, baseline characteristics, pathologic features of both primary and metastatic lesions, available medical resources, economic status, and other factors. Intrathecal injection therapy has the advantages of simple operation, economic benefits, and can be adopted in combination with various drugs. Moreover, it can increase drug concentrations in the cerebrospinal fluid and improve cerebrospinal fluid circulation, thereby providing enhanced therapeutic effects [13].

Although intrathecal methotrexate combined with dexamethasone has been clinically applied for the treatment of intracranial malignancies, systematic evaluation regarding patient-reported outcomes, cognitive safety, and the speed of symptom relief remain limited, particularly among heterogeneous populations including both primary and metastatic intracranial tumors. To address this evidence gap, the present study systematically evaluated the impact of this regimen on quality of life and cognitive function in patients with intracranial tumors using single-center retrospective data, thereby providing additional evidence to support the clinical application of this established strategy.

Materials and methods

Study design and participants

This study was approved by the Ethics Committee of Jianhu County People's Hospital. Owing to its retrospective design, the requirement for informed consent was waived, and all clinical data were de-identified before statistical analysis.

A total of 164 patients with intracranial malignant tumors who were admitted to Jianhu County People's Hospital between January 2017 and January 2024 were retrospectively included as the initial cohort. Among them, 59 patients had primary intracranial tumors confirmed by histopathologic examination, and 105 patients had brain metastases confirmed by imaging findings or cerebrospinal fluid cytology, with the primary tumor site confirmed by pathologic examination.

According to the actual treatment regimens received, patients were categorized into two groups: (1) Intrathecal treatment group (experimental group, $n = 68$): Patients received intrathecal injection of methotrexate combined with dexamethasone in addition to necessary standard treatments. (2) Systemic chemotherapy group (control group, $n = 96$): Patients received a standard systemic chemotherapy regimen without intrathecal treatment.

Due to the retrospective and exploratory design of this study, no *a priori* sample size estimation was performed. All eligible consecutive cases during the study period were included to minimize selection bias. A *post-hoc* power analysis based on the primary outcome, the improvement rate of the Karnofsky Performance Status (KPS), showed that the observed improvement rates were 54.8% in the experimental group and 24.2% in the control group, with statistical power exceeding 0.9, confirming that the available sample sizes were sufficient to detect a significant difference. To reduce potential selection bias due to non-randomized allocation, propensity score matching (PSM) was performed as a sensitivity analysis. Propensity scores were calculated using a logistic regression model incorporating the following covariates: age, sex, tumor type (primary/metastatic), baseline KPS score, history of radiotherapy, and history of chemotherapy. A 1:1 nearest-

neighbor matching approach was applied with a caliper width to 0.2 times the standard deviation of the logit of the propensity score.

Inclusion and exclusion criteria

Inclusion criteria: 1. Definite diagnosis of intracranial malignancy (primary intracranial tumor or brain metastasis), confirmed by histopathology or cytology combined with imaging findings. The diagnosis of intracranial malignancy was established based on the following criteria: (1) Positive CSF cytology revealing tumor cells, which was considered confirmatory; (2) Definitive histopathologic diagnosis of intracranial malignant tumor obtained via surgical biopsy or resection; (3) Intracranial metastases with evidence of a primary tumor and image confirmation; and (4) Intracranial tumor related symptoms and signs, including intracranial hypertension and focal space-occupying manifestations. Criteria (3) and (4) were auxiliary conditions for diagnosis. 2. Estimated survival > 3 months and baseline KPS score > 60 (indicating ability to manage most daily activities with occasional assistance). 3. Age < 75 years, no mental disorders, and good treatment compliance. 4. Adequate function of major organs, and absence of urgent intracranial conditions (e.g., cerebral herniation), systemic diseases that could interfere with treatment, or underlying conditions affecting cognitive function (e.g., cerebrovascular disease, Alzheimer's disease). 5. Maximum tumor diameter < 35 mm (to avoid significant mass effect). 6. Unsuitable for radiotherapy or refusal of radiotherapy.

Exclusion criteria: (1) Poor treatment compliance. (2) Mental illness precluding cooperation with treatment. (3) Pregnancy. (4) Age > 75 years. (5) KPS score < 60 . (6) Presence of life-threatening adverse reactions or complications (e.g., cerebral herniation, status epilepticus). (7) Withdrawal from treatment during the course. (8) Underlying cognitive-impairing conditions (e.g., Alzheimer's disease, cerebrovascular disease, brain atrophy). (9) Previous spinal cord radiotherapy. (10) Discontinuation of treatment or loss to follow-up for other reasons.

Interventions

Experimental group: Patients in the experimental group received four cycles of intrathecal

Table 1. Operational considerations

No.	Points to note
1	For patients with intracranial hypertension symptoms, an intravenous infusion of mannitol was administered prior to intrathecal injection. Lumbar puncture and intrathecal injection were performed after the intracranial pressure had decreased and symptoms had improved, in order to reduce the risk of cerebral herniation.
2	The drug solution must be accurately injected into the spinal canal.
3	The injection should be administered slowly during the procedure.
4	Attention should be paid to balancing the volume of cerebrospinal fluid withdrawn and the volume of drug solution injected, to avoid iatrogenic fluctuations in intracranial pressure.
5	Intrathecal injections should not be too performed too frequently, and the drug concentration should be kept within an appropriate range to minimize potential neurotoxicity.
6	In case of headache, dizziness, or serious neurologic side effects such as chemical meningitis, close clinical observation and timely symptomatic treatment should be provided as indicated.

chemotherapy according to their systemic status, metastatic lesions, and pathologic characteristics of the primary tumor. Intrathecal methotrexate combined with dexamethasone was administered once per cycle. Before each administration, lumbar puncture was performed, and an appropriate volume of CSF was collected for routine CSF analysis and cytologic examination. Methotrexate (10 mg) and dexamethasone (10 mg) were separately prepared and diluted with preservative-free normal saline to a final volume of 5 mL. After lumbar puncture, the mixture was slowly injected into the intrathecal space at a rate of approximately 1.5-2.5 mL/min, with a total injection duration of 2-3 minutes. The treatment was repeated every 3 weeks for a total of 4 cycles. The 21-day interval between consecutive injections served as the drug washout period. No additional solvents or excipients were used. All procedures were performed by experienced neurologists in accordance with the hospital's standard operating procedures. After intrathecal injection, patients were instructed to remain in a supine position without a pillow for 4-6 h to reduce the risk of potential complications associated with intracranial pressure changes (Table 1).

Control group: Patients in the control group received systemic chemotherapy and routine symptomatic interventions based on their physical condition, metastatic lesions, and pathologic features of the primary tumors.

Observation outcomes

Primary outcomes: (1) The KPS score was assessed at baseline and 1-2 weeks after completion of the fourth treatment cycle. Treatment

response based on KPS changes was categorized as improvement (an increase of ≥ 10 points from baseline), deterioration (a decrease of ≥ 10 points), or stable status (a score fluctuation within 10 points). (2) Health-related quality of life (HRQoL) was assessed using the internationally validated European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. Assessments were performed at baseline (before treatment) and 1-2 weeks after completion of the fourth treatment cycle. The EORTC Quality of Life Questionnaire Core 30 (QLQ-C30, Version 3) [14] was used as the primary assessment instrument. This generalized scale comprises 30 items and evaluates multiple dimensions of HRQoL, including five functional domains (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting), alongside a global quality of life scale. To provide a more comprehensive evaluation of symptom burden in patients with intracranial tumors, the brain tumor-specific module, the Quality-of-Life Questionnaire - Brain Neoplasm 20 (QLQ-BN20), was also used in combination with the QLQ-C30. All scores were linearly transformed according to the official EORTC scoring guidelines, with scores ranging from 0 to 100. Higher scores in functional domains and global quality of life scale indicate better functioning and improved quality of life, whereas higher scores on symptom scales and QLQ-BN20 symptom items indicate greater symptom burden [15]. (3) Tumor response after four treatment cycles was assessed according to the Response Assessment in Neuro-Oncology (RANO) criteria [16]. The evaluation criteria were as follows: Complete Response (CR):

Disappearance of all detectable tumor lesions, with stable or improved neurological function; Partial response (PR): Significant reduction in the size of all measurable lesions, with stable neurologic function; Stable disease (SD): Disease status that did not meet the criteria for PR or progressive disease (PD), with stable neurologic status. PD: Appearance of new lesions, or definite enlargement of existing lesions, or significant deterioration in neurologic function due to tumor progression. The disease control rate (DCR) was calculated as the proportion of patients achieving CR, PR and SD. All imaging assessments (contrast-enhanced cranial MRI) were independently reviewed by two experienced neuroradiologists who were blinded to patient group assignment and treatment information. In cases of disagreement, a third senior expert reviewed the images and made the final determination. (4) Overall survival (OS) was defined as the time interval from the diagnosis of primary or metastatic intracranial tumors to all-cause mortality or the final follow-up. The 6-month and 12-month survival rates were also calculated.

Secondary outcomes: (1) Cognitive function assessment: Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), a widely validated cognitive screening tool [17]. Given that chemotherapy may cause subtle cognitive impairment, particularly in executive function and processing speed, additional neuropsychological assessments were performed using the Symbol Digit Modalities Test (SDMT) [18] to evaluate information processing speed and the Trail Making Test (TMT) [19] (comprising TMT-A and TMT-B) to evaluate executive function and task-switching ability. All cognitive assessments were conducted at baseline (before treatment) and 1-2 weeks after completion of the fourth treatment cycle. (2) Safety assessment: All adverse events occurring during the treatment period were recorded, including gastrointestinal reactions, hematologic toxicity, and other treatment-related complications. For intrathecal injection-related adverse events, the incidence, severity, and management strategies of seizures, neuralgia (including lumbodorsal and radiating pain), and chemical arachnoiditis (characterized by symptoms such as headache, neck stiffness, and fever) were documented in detail and graded according to the Common Terminology Criteria for Adverse Events (CTCAE)

version 5.0. (3) Laboratory indicators: To assess the systemic effects of treatment, peripheral blood samples were collected at baseline and 1-2 weeks after completion of the fourth treatment cycle. White blood cell (WBC) counts were measured using an automated hematology analyzer, and alanine aminotransferase (ALT) levels were determined using a biochemical analyzer, to assess changes in hematologic toxicity and liver function. (4) Time to key symptom relief: To evaluate the rapidity of symptom improvement, the time to headache relief was specifically recorded. This was defined as the number of days from treatment initiation to the time when patients reported significant improvement in headache symptoms, defined as either a $\geq 50\%$ reduction in the visual analogue scale (VAS) score or a subjective report of "significant improvement". Data were collected through daily ward rounds or telephone follow-ups.

Data collection and follow-up

This retrospective study used data sourced from the hospital's electronic medical record system, as well as outpatient and inpatient records. Follow-up information was collected through medical record review and, when necessary, telephone interviews with patients or their family members to supplement survival status information. The follow-up cutoff date was June 30, 2025. The median follow-up duration is reported in the Results section. Only patients with complete medical records and available data for key variables, including KPS score, QLQ-C30, MoCA scores, and imaging assessments, were included in the final analyses. Patients with incomplete critical data were excluded. Loss to follow-up was defined as the absence of subsequent hospital visit records in the medical record system before the follow-up cutoff date, together with failure to confirm survival status through telephone contact with the patient or their family members. Patients lost to follow-up were excluded from the survival analyses.

Statistical methods

All statistical analyses were performed using SPSS 26.0. Continuous variables following a normal distribution were presented as mean $\pm$ standard deviation, and comparisons between groups were performed using the independent-

samples t-test. For continuous variables that did not follow a normal distribution, the Mann-Whitney U test was used. For repeated measured data at two time points (before and after treatment), a two-way repeated-measures analysis of variance (ANOVA) was performed, with treatment group (experimental group vs. control group) and time point (pre-treatment vs. post-treatment) included as fixed factors to evaluate the main effects of group, time, and their interaction. When significant main effects or interaction effects were detected, *post-hoc* pairwise comparisons were performed with Bonferroni correction to control the family-wise error rate caused by multiple comparisons across different outcome scales. Categorical data were summarized as counts and percentages (n, %), and between-group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate.

Survival outcomes were analyzed using the Kaplan-Meier method, and differences in survival distributions between groups were compared using the Log-rank test.

Multivariate Cox proportional hazards regression analysis was performed to identify independent prognostic factors associated with OS. The proportional hazards assumption was tested for each covariate and for the global model using Schoenfeld residuals. A non-significant result ($P > 0.05$) indicated that the proportional hazards assumption was not violated. Variables exhibiting $P < 0.05$ in univariate analyses or those with clinical significance were included in the multivariate Cox regression model. Candidate variables included age, sex, tumor type, baseline KPS score, and treatment group.

For missing data that were assumed to be missing completely at random and accounted for $< 5\%$ of the dataset, complete-case analysis was adopted. Cases with missing values for specific variables were excluded from the corresponding analyses without imputation. All statistical tests were two-tailed, and a P -value < 0.05 was considered significant.

Results

Baseline characteristics after PSM

A total of 164 patients diagnosed with malignant intracranial tumors were included in this

study, including 68 cases in the experimental group and 96 cases in the control group. As shown in **Table 2** (original cohort), no significant intergroup differences were observed in baseline characteristics before treatment, including age, sex, tumor type (primary or metastatic), baseline KPS score, previous treatment history (radiotherapy or chemotherapy), or key laboratory indicators (all $P > 0.05$). Among patients with brain metastases, the distribution of primary tumor sites was also comparable between the two groups (all $P > 0.05$).

These findings indicated that, despite the retrospective study design, the baseline characteristics were generally balanced between the two groups, laying a solid foundation for subsequent efficacy and safety comparisons. To reduce further potential confounding effects, 56 matched pairs were generated using PSM. After matching, the standardized mean differences (SMDs) for all covariates were < 0.1 (post-matching cohort; **Table 2**), indicating satisfactory balance between the two groups.

Re-analysis based on the matched cohort showed that the KPS improvement rate (53.6% vs. 23.2%) and median overall survival (22.1 vs. 20.3 months, $P = 0.158$) were consistent with the findings from the original cohort (54.8% vs. 24.2%; 22.4 vs. 20.1 months, $P = 0.169$). The trend in quality-of-life changes also remained unchanged. These results suggested that the main conclusions were not substantially influenced by selection bias. All subsequent primary analyses were performed using the matched cohort.

Functional status (KPS)

At the end of the fourth treatment cycle, the mean KPS score in the experimental group increased from 73.5 ± 8.4 to 81.2 ± 7.3 , while that of the control group showed a slight increase from 72.9 ± 8.8 to 74.5 ± 9.1 . Two-way repeated measures ANOVA demonstrated a significant group $\times$ time interaction effect ($F = 24.36$, $P < 0.001$). *Post-hoc* pairwise comparisons with Bonferroni correction (adjusted significance threshold of $P < 0.025$ for two comparisons) showed a significant improvement in KPS scores in the experimental group (mean difference = 7.7, $P < 0.001$), while no significant change was observed in the control group (mean difference = 1.6, $P = 0.161$). The magni-

Intrathecal injection of methotrexate and dexamethasone for brain tumors

Table 2. Comparison of baseline characteristics between the two groups before and after matching

Variable	Experimental group (n = 68)	Control group (n = 96)	t/ χ^2	P	Experimental group (after matching), n = 56	Control group (after matching), n = 56	Standardization differences
Age (years)	57.2 ± 10.1	56.8 ± 9.5	0.251	0.802	57.0 ± 10.0	56.9 ± 9.6	0.03
Sex (Male/Female, n)			0.721	0.396			0.05
Male (n/%)	38/55.9	58/60.4			31 (55.4)	32 (57.1)	
Female (n/%)	30/44.1	38/39.6			25 (44.6)	24 (42.9)	
Tumor type (Primary/Metastatic) (n/%)			0.892	0.345			0.02
Primary	25/36.8	30/31.3			21 (37.5)	22 (39.3)	
Metastatic	43/63.2	66/68.8			35 (62.5)	34 (60.7)	
Baseline KPS score	73.1 ± 8.9	72.5 ± 9.3	0.412	0.681	73.0 ± 8.8	72.8 ± 9.1	0.04
Prior radiotherapy (n/%)	22/32.4	25/26.0	0.815	0.367	18 (32.1)	19 (33.9)	0.04
Prior chemotherapy (n/%)	28/41.2	35/36.5	0.392	0.531	23 (41.1)	22 (39.3)	0.05
Baseline WBC count ($\times 10^9/L$)	6.3 ± 1.6	6.5 ± 1.4	-0.873	0.384	6.3 ± 1.5	6.4 ± 1.4	0.02
Baseline ALT (U/L)	32.1 ± 8.5	31.2 ± 9.1	0.648	0.518	31.8 ± 8.4	31.5 ± 8.9	0.03
Primary tumor origin in patients with brain metastases (n/%)			0.041	0.84			0.05
Lung cancer	20/46.5	32/48.5			17 (48.6)	16 (47.1)	
Breast cancer	11/25.6	16/24.2			9 (25.7)	9 (26.5)	
Gastrointestinal tumor	7/16.3	12/18.2			5 (14.3)	6 (17.6)	
Other (Renal cancer, melanoma, etc.)	5/11.6	6/9.1			4 (11.4)	3 (8.8)	

Note: WBC: white blood cell; ALT: Alanine aminotransferase.

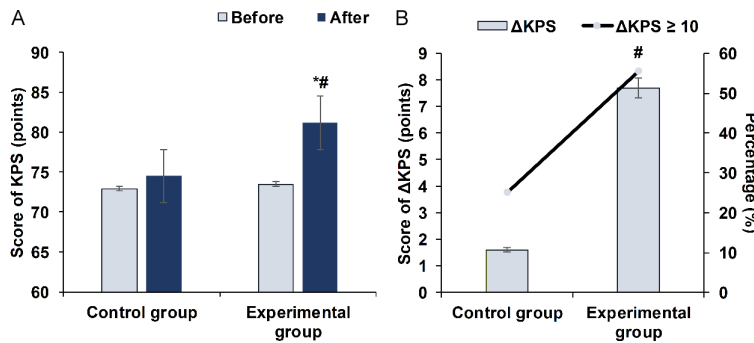


Figure 1. Changes in KPS scores before and after treatment in the two patient groups. A. Comparison of KPS scores before and after treatment in both groups; B. Comparison of the magnitude of KPS improvement (Δ KPS) and the proportion of patients with improvement (Δ KPS $\geq$ 10 points) between the two groups. * $P < 0.05$, compared with baseline levels; # $P < 0.05$, compared with the control group. KPS: Karnofsky performance status.

tude of KPS improvement (Δ KPS) in the experimental group (7.7 ± 5.1) was significantly greater than that of the control group (1.6 ± 4.9) ($P < 0.001$). According to the predefined criterion that an increase of ≥ 10 points in KPS was considered clinically meaningful improvement, 30 patients (55.4%) in the experimental group attained improvement compared with 14 cases (25.0%) in the control group ($\chi^2 = 14.023$, $P = 0.001$) (**Figure 1**).

Health-related quality of life (HRQoL)

HRQoL was comprehensively evaluated using the EORTC QLQ-C30, along with the brain tumor-specific supplementary module (QLQ-BN20) (**Table 3**). According to the EORTC QLQ-C30 results, patients in the experimental group exhibited significant improvement in global health status/quality of life (increase of 12.5 points, $t = 5.121$, $P < 0.001$), role functioning (increase of 10.2 points, $t = 3.212$, $P = 0.003$), and social functioning (increase of 9.8 points, $t = 3.021$, $P = 0.005$). Physical functioning also improved significantly (increase of 7.1 points, $t = 2.423$, $P = 0.021$).

In contrast, the control group showed no significant improvement in functional scales or overall QoL ($P > 0.05$), and role functioning significantly deteriorated (decrease of 6.3 points, $t = -2.180$, $P = 0.038$). Regarding symptom scales, the experimental group showed significant reductions in nausea/vomiting (decrease of 18.6 points, $t = -4.389$, $P < 0.001$) and fatigue (decrease of 11.4 points, $t = -3.648$, $P = 0.001$). Conversely, the control group reported signifi-

cant increases in nausea/vomiting (increase of 8.5 points, $t = 2.558$, $P = 0.016$) and fatigue (increase of 6.9 points, $t = 2.144$, $P = 0.041$).

Analysis of the QLQ-BN20 module showed that patients in the experimental group experienced significant improvements in several tumor-specific symptoms, including future uncertainty (decrease of 13.1 points, $t = -4.445$, $P < 0.001$), headache (decrease of 15.7 points, $t = -5.251$, $P < 0.001$), and somnolence (decrease of 10.9 points, $t = -3.378$, $P = 0.002$).

The control group showed no significant improvements in these domains (all $P > 0.05$), with headache and somnolence showing a worsening trend.

Disease control status based on RANO criteria

Tumor response was assessed according to the RANO criteria. DCR in the experimental group was 62.5% (35/56), which was numerically higher than that of the control group (53.6%, 30/56) ($\chi^2 = 0.892$, $P = 0.345$). No CR cases were observed in either group. PR was achieved in 5 patients (8.9%) in the experimental group and 3 patients (5.4%) in the control group; SD was observed in 30 patients (53.6%) and 27 patients (48.2%), respectively; and PD was observed in 21 patients (37.5%) and 26 patients (46.4%), respectively. The objective response rates (ORR, CR+PR) in the two groups were 8.9% and 5.4%, respectively, with no significant difference between groups ($\chi^2 = 0.535$, $P = 0.464$) (**Figure 2**).

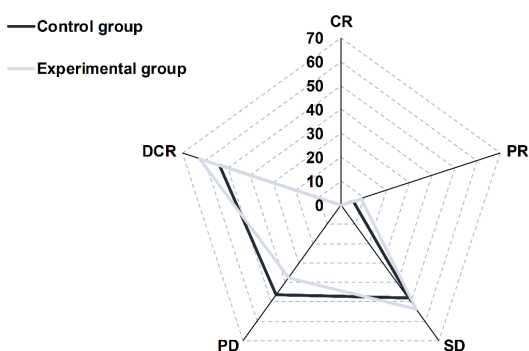
Association between tumor response and patient-reported outcome and functional status

To show the relationship between tumor response and patient-reported outcomes and functional status, improvements in QoL and functional status were compared between patients with and without disease control in both the experimental and control groups. As shown in **Table 4**, in the experimental group, patients who achieved disease control ($n = 43$) demonstrated significantly greater improvement in KPS score (Δ KPS: $+9.2 \pm 4.8$ vs. $+4.8 \pm$

Table 3. Comparison of EORTC QLQ-C30 and QLQ-BN20 scores before and after treatment between the two groups

Scale	Experimental group (n = 56)			Control group (n = 56)			P (Δ)
	Baseline	After treatment	Δ	Baseline	After treatment	Δ	
QLQ-C30							
Function	58.3 ± 12.1	70.8 ± 11.5	+12.5	56.9 ± 13.5	57.2 ± 14.1	0.3	< 0.001
Physical functioning	65.7 ± 15.2	72.8 ± 13.6	+7.1	67.1 ± 16.0	64.5 ± 17.3	-2.6	0.001
Role functioning	55.9 ± 18.4	66.1 ± 16.9	+10.2	57.4 ± 19.1	51.1 ± 20.5	-6.3	< 0.001
Emotional functioning	60.2 ± 16.8	65.9 ± 15.2	5.7	58.7 ± 17.5	61.3 ± 16.8	2.6	0.245
Cognitive functioning	68.5 ± 14.3	70.1 ± 13.7	1.6	69.2 ± 15.0	67.8 ± 14.4	-1.4	0.187
Social functioning	52.4 ± 19.7	62.2 ± 17.5	+9.8	54.0 ± 20.2	50.1 ± 21.6	-3.9	< 0.001
Symptom scales							
Fatigue	48.6 ± 16.3	37.2 ± 14.1	-11.4	46.9 ± 17.0	53.8 ± 16.2	+6.9	< 0.001
Nausea/vomiting	35.2 ± 15.8	16.6 ± 10.5	-18.6	33.5 ± 14.9	42.0 ± 15.7	+8.5	< 0.001
Pain	32.5 ± 14.1	26.8 ± 12.3	-5.7	31.1 ± 13.5	34.9 ± 14.8	3.8	0.052
QLQ-BN20							
Future uncertainty	45.8 ± 18.2	32.7 ± 15.9	-13.1	43.5 ± 17.6	46.1 ± 18.8	2.6	< 0.001
Visual disorder	28.1 ± 12.5	25.4 ± 11.7	-2.7	27.3 ± 11.9	29.5 ± 12.6	2.2	0.104
Motor dysfunction	38.4 ± 15.0	33.9 ± 13.8	-4.5	39.7 ± 14.3	41.2 ± 15.1	1.5	0.065
Difficulty in communication	25.3 ± 11.6	23.1 ± 10.9	-2.2	24.6 ± 12.1	26.3 ± 11.5	1.7	0.21
Headache	41.7 ± 14.9	26.0 ± 11.2	-15.7	39.8 ± 15.4	43.5 ± 16.1	3.7	< 0.001
Seizures	15.2 ± 8.5	13.9 ± 7.8	-1.3	14.8 ± 9.1	15.6 ± 8.4	0.8	0.451
Somnolence	50.1 ± 16.7	39.2 ± 14.0	-10.9	48.9 ± 15.8	52.7 ± 16.5	3.8	< 0.001
Itchy skin	18.5 ± 9.7	17.1 ± 8.9	-1.4	17.9 ± 10.2	18.8 ± 9.5	0.9	0.385
Hair loss	22.4 ± 10.3	58.6 ± 12.7	+36.2	21.9 ± 11.0	25.1 ± 10.5	3.2	< 0.001
Leg weakness	36.9 ± 13.8	32.1 ± 12.5	-4.8	37.5 ± 14.2	39.0 ± 13.7	1.5	0.088
Bladder control	20.7 ± 9.4	19.3 ± 8.7	-1.4	21.2 ± 10.1	22.5 ± 9.8	1.3	0.298

Note: Negative values (-) indicate a reduction/improvement in symptoms, while positive values (+) indicate an increase in symptoms. All pre- and post-treatment comparisons were based on repeated measures ANOVA with Bonferroni correction, and the corrected significance threshold was set to $P < 0.003$ (0.05/15). EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-BN20: Quality of Life Questionnaire - Brain Neoplasm 20.


Figure 2. Comparison of disease control rate between the two groups. CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; DCR: Disease control rate.

4.1, $P < 0.001$) compared to those failed to achieve disease control ($n = 25$). In terms of QoL, patients with disease control also showed

significantly greater improvements in EORTC QLQ-C30 global health status (+15.1 points vs. +7.9 points, $P = 0.011$), role functioning (+13.5 points vs. +4.8 points, $P = 0.003$), and social functioning (+12.9 points vs. +4.5 points, $P = 0.007$). Moreover, they experienced significantly greater reductions in symptom scores for future uncertainty (-16.3 points vs. -7.8 points, $P = 0.009$) and headache (-18.6 points vs. -10.9 points, $P = 0.019$) on the QLQ-BN20 scale.

However, in the control group, no significant differences were observed in the KPS improvement or most QoL-related outcomes between patients with disease control ($n = 52$) and those without ($n = 44$). Significant differences were observed only in the degree of decline in role functioning (-4.1 points vs. -9.1 points, $P = 0.021$) and the change in fatigue scores (+5.1

Table 4. Correlation analysis of disease control status with patient functional and QoL improvements in each group

Index	Experimental group (n = 56)			Control group (n = 56)		
	DCR (n = 36)	Non-DCR (n = 20)	P	DCR (n = 34)	Non-DCR (n = 32)	P
ΔKPS (points)	+9.2 ± 4.8	+4.8 ± 4.1	< 0.001	+2.1 ± 5.0	+0.9 ± 4.7	0.234
EORTC QLQ-C30						
ΔTotal score	+15.1 ± 11.2	+7.9 ± 10.5	0.011	+1.5 ± 13.9	-1.2 ± 14.3	0.341
ΔRole functioning	+13.5 ± 16.1	+4.8 ± 15.3	0.003	-4.1 ± 19.8	-9.1 ± 20.5	0.021
ΔSocial functioning	+12.9 ± 16.8	+4.5 ± 17.0	0.007	-2.9 ± 20.1	-5.1 ± 19.8	0.298
ΔFatigue	-14.1 ± 15.3	-6.9 ± 14.8	0.018	+5.1 ± 16.5	+11.3 ± 17.1	0.033
ΔNausea/vomiting	-21.5 ± 15.1	-13.2 ± 14.5	0.009	+6.8 ± 14.9	+10.5 ± 15.3	0.105
EORTC QLQ-BN20						
ΔFuture uncertainty	-16.3 ± 15.2	-7.8 ± 16.0	0.009	+1.8 ± 17.5	+4.1 ± 18.2	0.267
ΔHeadache	-18.6 ± 13.5	-10.9 ± 14.1	0.019	+2.5 ± 15.8	+5.2 ± 16.4	0.189

Note: DCR: Disease control rate; Non-DCR: Non-disease control rate (i.e., progressive disease). Negative values (-) indicate a reduction/improvement in symptoms, while positive values (+) indicate an increase in symptoms. EORTC: European Organisation for Research and Treatment of Cancer; KPS: Karnofsky performance status; QLQ-C30: EORTC Quality of Life Questionnaire Core 30; QLQ-BN20: Quality of Life Questionnaire - Brain Neoplasm 20; QoL: Quality of Life.

points vs. +11.3 points, $P = 0.033$) (all $P > 0.05$).

Cognitive function

At baseline, the mean MoCA scores were 22.5 ± 3.1 in the experimental group and 23.1 ± 3.4 in the control group, with no significant inter-group difference ($P = 0.298$). After treatment, the mean MoCA score increased to 23.8 ± 3.3 in the experimental group, whereas the control group had a mean score of 22.9 ± 3.6 .

Within-group analyses revealed a borderline improvement in cognitive function in the experimental group ($t = -1.982$, $P = 0.052$), and no evident alterations were observed in the control group ($t = 0.487$, $P = 0.628$). Furthermore, no significant difference in post-treatment MoCA scores was identified between the two cohorts ($t = 1.492$, $P = 0.138$).

Further SDMT and TMT assessment results showed that the number of correct SDMT responses in the experimental group increased significantly after treatment compared to baseline (from 42.3 ± 8.5 to 45.1 ± 8.1 ; $P = 0.043$), whereas no significant change was observed in the control group (41.9 ± 9.2 vs. 42.3 ± 9.0 , $P = 0.621$). TMT-A (reflecting processing speed) decreased by an average of 3.2 seconds in the experimental group ($P = 0.038$), while no significant improvement in TMT-A was seen in the control group ($P > 0.05$). TMT-B (reflecting executive function and task switching) decreased by

an average of 4.5 seconds in the experimental group ($P = 0.027$), whereas no significant change was observed in the control group ($P > 0.05$) (**Figure 3**).

Overall survival

At the follow-up cutoff date of June 30, 2025, the median follow-up duration was 18.6 months (range: 3.2-48.5 months). At the final follow-up, 26 deaths were recorded in the experimental group, and 29 deaths were recorded in the control group. Kaplan-Meier survival analysis demonstrated that the median OS was 22.4 months (95% CI: 19.8-25.0) in the experimental group and 20.1 months (95% CI: 17.5-22.7) in the control group. The Log-rank test revealed no significant difference in overall survival between the two cohorts ($\chi^2 = 1.892$, $P = 0.169$), indicating similar survival outcomes between the two groups (**Figure 4**). The survival rates at specific time points were also analyzed. The 6-month and 12-month survival rates were 92.9% and 78.6% in the experimental group and 89.3% and 71.4% in the control group, respectively, with no significant differences observed between groups ($P > 0.05$).

Prognostic factors for OS

To identify independent prognostic factors associated with OS among patients with malignant intracranial tumors, variables including age, sex, tumor type, baseline KPS score, previ-

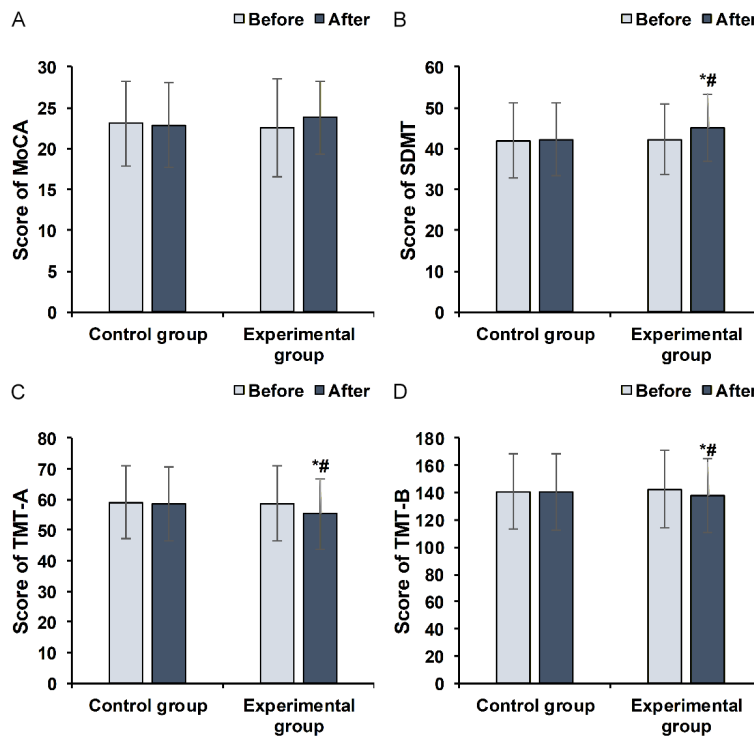


Figure 3. Changes in cognitive function before and after treatment in the two groups. A. Comparison of MoCA scores; B. Comparison of SDMT scores; C. Comparison of TMT-A scores; D. Comparison of TMT-B scores. * $P < 0.05$, compared with baseline levels; # $P < 0.05$, compared with the control group. MoCA: Montreal Cognitive Assessment; SDMT: Symbol Digit Modalities Test; TMT-A: Trail Making Test-A; TMT-B: Trail Making Test-B.

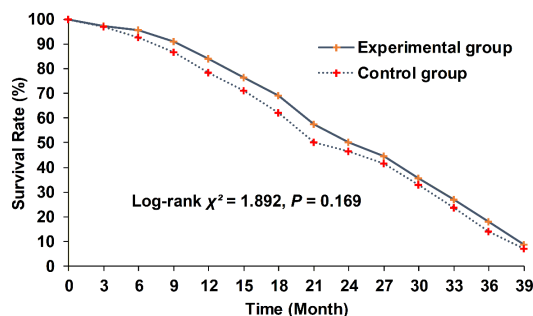


Figure 4. Kaplan-Meier survival curves for the two groups. Log-rank test result: $\chi^2 = 1.892$, $P = 0.169$.

ous radiotherapy history, previous chemotherapy history, treatment group, and DCR were entered into the Cox proportional hazards regression model. Univariate analysis revealed that elevated baseline KPS score (HR = 0.96, 95% CI: 0.94-0.99, $P = 0.007$), assignment to the experimental group (HR = 0.75, 95% CI: 0.58-0.97, $P = 0.028$), and favorable DCR (HR = 0.62, 95% CI: 0.48-0.81, $P < 0.001$) were associated with improved OS and were identified as

protective factors. Conversely, metastatic tumor type was associated with an increased risk of mortality (HR = 1.52, 95% CI: 1.11-2.08, $P = 0.009$). Variables with $P < 0.1$ in univariate analysis were subsequently incorporated into the multivariate Cox regression model. Before multivariate Cox analysis, the proportional hazards assumption was evaluated using Schoenfeld residuals. The global test showed no significant violation of the proportional hazards assumption ($\chi^2 = 3.42$, $P = 0.491$), and none of the individual covariates demonstrated significant deviation from the assumption (all $P > 0.05$). Multivariate Cox regression analysis further demonstrated that a higher baseline KPS score (HR = 0.97, 95% CI: 0.94-0.99, $P = 0.048$) and favorable DCR (HR = 0.65, 95% CI: 0.50-0.85, $P = 0.001$) remained independent protective factors associated with prolonged OS (Table 5).

Changes in laboratory indicators

Changes in key laboratory indicators before and after treatment were compared between the two cohorts. In the experimental group, the WBC count decreased from $6.3 \pm 1.6 \times 10^9/L$ at baseline to $5.8 \pm 1.4 \times 10^9/L$ after treatment, whereas the control group showed a decrease from $6.5 \pm 1.4 \times 10^9/L$ to $5.9 \pm 1.3 \times 10^9/L$. No significant intergroup difference was detected between the two groups ($P = 0.215$).

Regarding ALT levels, the experimental group showed a decrease from $32.1 \pm 8.5 U/L$ to $29.8 \pm 7.2 U/L$, while the control group decreased from $31.2 \pm 9.1 U/L$ to $30.5 \pm 8.3 U/L$, with no significant difference between the groups ($P = 0.387$) (Figure 5).

Time to symptom relief

The mean duration required for headache relief was 3.2 ± 1.5 days in the experimental group, which was significantly shorter than 5.8 ± 2.1

Table 5. Univariate and multivariate Cox regression analyses of factors affecting OS

Variable	Category	Univariate analysis		Multivariate analysis		
		HR (95% CI)	P	Adjusted HR (95% CI)	P	β (SE)
Age	Per 1-year increase	1.00 (0.99-1.02)	0.741	-	-	-
Gender	Male vs. Female	1.08 (0.84-1.39)	0.553	-	-	-
Tumor Type	Metastatic vs. Primary	1.52 (1.11-2.08)	0.009	1.31 (0.95-1.81)	0.099	0.270 (0.164)
Baseline KPS	Per 1-point increase	0.96 (0.94-0.99)	0.007	0.97 (0.94-0.99)	0.048	-0.030 (0.015)
Previous Radiotherapy History	Present vs. absent	1.18 (0.89-1.57)	0.247	-	-	-
Previous Chemotherapy History	Present vs. absent	1.15 (0.89-1.49)	0.281	-	-	-
Treatment Group	Experimental group vs. control group	0.75 (0.58-0.97)	0.028	0.82 (0.63-1.07)	0.142	-0.198 (0.136)
DCR	Yes vs. no	0.62 (0.48-0.81)	< 0.001	0.65 (0.50-0.85)	0.001	-0.431 (0.132)

Note: HR: Hazard ratio; CI: Confidence interval; KPS: Karnofsky performance status; DCR: Disease control rate; OS: Overall survival.

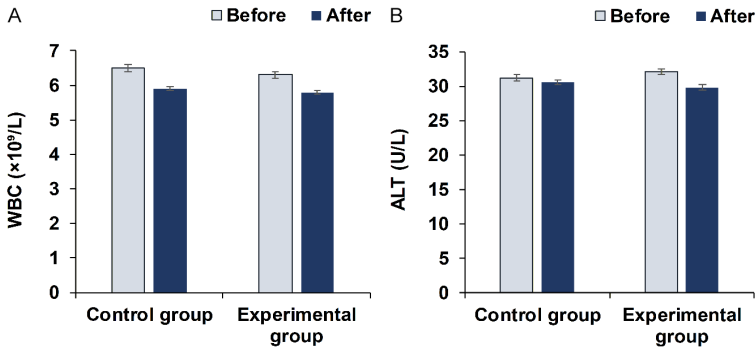


Figure 5. Comparison of laboratory indicator before and after treatment between the two groups. A. WBC: white blood cells; B. ALT: Alanine amino-transferase.

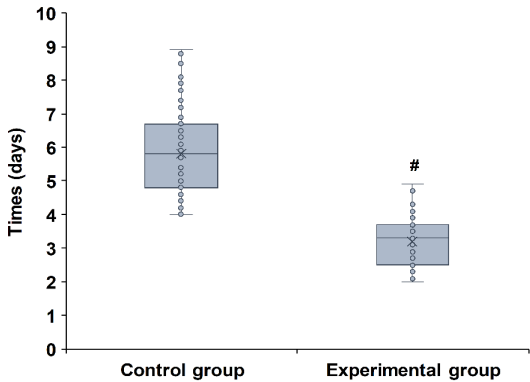


Figure 6. Comparison of time to headache relief between the two groups. # $P < 0.05$, compared to the control group.

days in the control group ($t = 7.112$, $P < 0.001$) (Figure 6).

Treatment-related adverse reactions

During the treatment period, the overall incidence of severe adverse reactions (Grade III/

IV) was comparable between the two groups (Table 6). No Grade IV hepatic or renal dysfunction occurred in either group, and no significant changes in hepatic or renal function were observed before and after intervention ($P > 0.05$). Regarding gastrointestinal toxicity, Grade III/IV nausea and vomiting occurred in 5 patients (8.9%) in the experimental group, including 3 cases (5.4%) of Grade IV vomiting. In the control group, 9 patients (16.1%) experienced Grade III/IV nausea and vomiting, including 5 cases (8.9%) of Grade IV vomiting. Regarding hematologic toxicity, the experimental group included one case (1.8%) of Grade IV hemoglobin reduction and one case (1.8%) of Grade IV thrombocytopenia. No Grade IV hemoglobin reduction or Grade IV thrombocytopenia was observed in the control group. No significant differences were observed between the two groups in the incidence of leukopenia, hemoglobin reduction, or thrombocytopenia across all grades. Regarding intrathecal injection-related adverse events, seizure occurred in 2 patients (3.6%; Grade I-II) in the experimental group, neuralgia occurred in 7 patients (12.5%, including one case Grade III), and chemical arachnoiditis in 4 patients (7.1%; Grade I-II). In the control group, seizures occurred in 1 patient (1.8%), neuralgia in 4 patients (7.1%), and chemical arachnoiditis in 3 patients (5.4%).

No significant differences were identified between the two groups in either the incidence or

Table 6. Adverse reactions of patients [n (%)]

Group	Adverse reaction	0	I	II	III	IV
Experimental group (n = 56)	Leukopenia	31 (55.4)	13 (23.2)	8 (14.3)	4 (7.1)	0 (0.0)
	Hemoglobin reduction	30 (53.6)	10 (17.9)	12 (21.4)	3 (5.4)	1 (1.8)
	Thrombocytopenia	33 (58.9)	12 (21.4)	8 (14.3)	2 (3.6)	1 (1.8)
	Hepatic dysfunction	37 (66.1)	11 (19.6)	6 (10.7)	2 (3.6)	0 (0.0)
	Renal dysfunction	40 (71.4)	9 (16.1)	5 (8.9)	2 (3.6)	0 (0.0)
	Nausea and vomiting	29 (51.8)	12 (21.4)	10 (17.9)	2 (3.6)	3 (5.4)*
	epilepsy	54 (96.4)	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
	neuralgia	49 (87.5)	4 (7.1)	2 (3.6)	1 (1.8)	0 (0.0)
	Chemical arachnoid inflammation	52 (92.9)	2 (3.6)	2 (3.6)	0 (0.0)	0 (0.0)
Control group (n = 56)	Leukopenia	30 (53.6)	12 (21.4)	9 (16.1)	5 (8.9)	0 (0.0)
	Hemoglobin reduction	29 (51.8)	11 (19.6)	12 (21.4)	4 (7.1)	0 (0.0)
	Thrombocytopenia	32 (57.1)	12 (21.4)	9 (16.1)	3 (5.4)	0 (0.0)
	Hepatic dysfunction	36 (64.3)	11 (19.6)	7 (12.5)	2 (3.6)	0 (0.0)
	Renal dysfunction	38 (67.9)	9 (16.1)	6 (10.7)	3 (5.4)	0 (0.0)
	Nausea and vomiting	23 (41.1)	12 (21.4)	12 (21.4)	4 (7.1)	5 (8.9)*
	Epilepsy	55 (98.2)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Neuralgia	52 (92.9)	2 (3.6)	1 (1.8)	1 (1.8)	0 (0.0)
	Chemical arachnoid inflammation	53 (94.6)	2 (3.6)	1 (1.8)	0 (0.0)	0 (0.0)

Note: * represents obvious statistical distinction between two groups ($P < 0.05$).

severity distribution of these adverse events. All adverse events were resolved with symptomatic management, and no patient discontinued treatment or died due to adverse events.

Discussion

Intrathecal combination therapy with methotrexate and dexamethasone for intracranial malignancies is not a novel therapeutic approach and has been used in clinical practice for decades. However, its actual effectiveness in improving patients' quality of life, preserving cognitive function, and providing rapid symptom relief-particularly compared to systemic chemotherapy alone-has not been fully evaluated in mixed populations comprising both primary and metastatic intracranial tumors. Based on single-center retrospective data, this study provides complementary evidence regarding the effects of this strategy on clinically meaningful outcomes. Furthermore, PSM was performed as a sensitivity analysis, demonstrating that the main findings were not significantly affected by selection bias.

Methotrexate is an effective antineoplastic agent that inhibits dihydrofolate reductase, thereby blocking the conversion of dihydrofolate to tetrahydrofolate. This process subsequently interferes with nucleotide synthesis,

particularly pyrimidine nucleotide synthesis, thereby reducing DNA synthesis and inhibiting tumor cell proliferation [20, 21]. Methotrexate also exerts inhibitory effects on thymidylate synthase; however, its effects on RNA and protein synthesis are relatively limited [22]. Given the barrier effect of the BBB, conventional intravenous administration of chemotherapeutic agents may fail to achieve sufficient drug concentrations within the central nervous system to effectively control intracranial malignant tumors. HD-MTX chemotherapy can increase drug concentrations in the cerebrospinal fluid; however, it requires intensive supportive management, including hydration, urine alkalinization, folinic acid rescue, and plasma drug concentration monitoring. In addition, patient tolerance to intravenous chemotherapy varies considerably. Therefore, the therapeutic efficacy of methotrexate in intracranial malignancies further investigation and validation [23-25]. Intrathecal administration offers the advantage of directly delivering drugs into the cerebrospinal fluid, thereby achieving higher local drug concentrations and potentially improving therapeutic efficacy in intracranial malignant tumors, while reducing systemic toxic side effects. Because intrathecal methotrexate administration is less affected by systemic toxicities such as myelosuppression, it can be combined with

systemic chemotherapy regimens to enhance therapeutic outcome [26, 27].

A retrospective study conducted in Indonesia investigated the efficacy of high-dose dexamethasone (mean daily dose: 16.8 mg) in patients with brain tumors. The results demonstrated that high-dose dexamethasone significantly decreased peripheral blood lymphocyte counts and increased the systemic immune-inflammation index (SII), suggesting its potent immunomodulatory and anti-inflammatory effects [28]. In addition, dexamethasone can also be used for the prevention and management of adrenal insufficiency caused by hypothalamic or peri-pituitary malignant tumors. Concurrent administration of dexamethasone with intrathecal chemotherapy may reduce adverse effects, including the incidence of chemical arachnoiditis [29, 30].

Although dexamethasone exerts therapeutic benefits in tumor management, its adverse effects should also be noted. Dexamethasone exerts immunosuppressive effects by reducing T lymphocytes, monocytes, and eosinophils, inhibiting the synthesis and release of interleukins, decreasing the binding affinity between immunoglobulins and cell surface receptors, inhibiting the transformation of T lymphocytes into lymphoblasts, and suppressing cellular immune responses [31-33]. Dexamethasone can indeed alleviate certain chemotherapy-induced toxicity; nevertheless, T cell-mediated adaptive immune responses remain an important component of tumor-related immune regulation [34]. Accordingly, clinical application of dexamethasone requires close monitoring of potential adverse effects to maintain an appropriate balance between therapeutic benefits and immunosuppressive risks. Prolonged or excessive administration of dexamethasone may impair host immunity and potentially affect anti-cancer immune responses. Therefore, long-term high-dose use should be avoided unless clinically indicated.

No obvious intergroup differences were observed between the two groups based on MoCA scale assessments. However, the experimental group showed significant improvement from baseline in SDMT and TMT performance after treatment, indicating better preservation of information processing speed and executive function compared to the control group. These

findings are consistent with recent studies investigating the neurocognitive safety of intrathecal chemotherapy. Mshaymesh et al. [35] mentioned in a review that the mechanisms underlying methotrexate-associated neurotoxicity are complex, possibly involving folate metabolism disruption, oxidative stress, and inflammatory responses. Previous studies have suggested that methotrexate exposure may elevate cerebrospinal fluid homocysteine levels. As a glutamatergic agonist, homocysteine may cause neuronal excitotoxicity, possibly contributing to cognitive impairment [36]. The overall stability of MoCA scores and the observed improvements in SDMT and TMT performance in this study may be related to the concurrent use of dexamethasone. Through its potent anti-inflammatory effects, dexamethasone may alleviate neuroinflammatory reactions induced by intrathecal injection and tumor-related processes, thereby potentially reducing methotrexate-associated neurotoxicity [37]. Clinical reports have also indicated that early steroid administration, including intrathecal dexamethasone, is associated with the resolution of methotrexate-related neurotoxicity [38]. A Phase I open-label study investigating intrathecal methotrexate for progressive multiple sclerosis also reported relatively stable cognitive function. Patients showed no significant cognitive decline over a 1-year follow-up period based on SDMT assessment, and the treatment was generally well tolerated [39]. Unlike previous studies that relied primarily on MoCA, the present study incorporated the SDMT and TMT to capture subtle chemotherapy-related cognitive changes. The findings suggested that intrathecal treatment may preserve cognitive function and may even provide benefits in specific cognitive domains, including information processing speed and executive function.

Additionally, the experimental group in this study showed significant improvement across multiple dimensions of the KPS score, EORTC QLQ-C30, and QLQ-BN20, especially in role functioning, social functioning, fatigue, and symptoms such as nausea and vomiting. Further analysis revealed that patients in the experimental group who achieved disease control experienced significantly greater improvements in QoL and functional status than those who did not, suggesting that the QoL benefits of intrathecal treatment are partly attributable to local

control of intracranial disease. Moreover, the prognostic factor analysis of OS provides important insight into the key variables affecting patient outcomes. Multivariate Cox regression analysis confirmed that a higher baseline KPS score and achievement of disease control are independent protective factors for prolonged OS. This finding is highly consistent with clinical consensus, emphasizing the core importance of good baseline patient condition and effective disease control in achieving long-term survival. These results align with recent reports on intrathecal therapy for leptomeningeal metastasis and symptom control. For example, in patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis, intrathecal chemotherapy (including methotrexate and pemetrexed) has been shown to improve neurological symptoms and delay disease progression [40]. Dexamethasone as an adjuvant agent, plays a well-established role in reducing peritumoral edema [41], attenuating inflammatory responses [42], and alleviating chemotherapy-related nausea and vomiting [43]. The significantly lower incidence of nausea and vomiting in the experimental group in this study may be partly attributed to the antiemetic and anti-inflammatory effects of dexamethasone. Moreover, compared to systemic chemotherapy, intrathecal administration can bypass the BBB, delivering higher drug concentrations directly to the cerebrospinal fluid while minimizing systemic exposure and related toxicities, a property confirmed by recent physiologically based pharmacokinetic (PBPK) model studies and clinical research [44]. This pharmacokinetic advantage further supports the preservation of patients' QoL and functional status. This study, along with several recent studies, demonstrated that intrathecal injection of methotrexate and dexamethasone has a controllable safety profile when administered in accordance with strict indications and operational standards. Specific adverse events related to intrathecal injection, including seizures (3.6% in the experimental group), neuralgia (12.5%), and chemical arachnoiditis (7.1%), were documented, and their incidence did not differ significantly compared to the control group. For example, Kolb et al. (2025) [39] reported no serious neurotoxic events in their study, indicating good tolerability of intrathecal methotrexate administration. Another retrospective study showed that intrathecal methotrexate combined with

dexamethasone improved recurrence-free survival with a favorable safety profile, supporting its use as a controllable adjuvant therapy [45]. The present study further confirms the favorable safety profile and rapid symptom relief advantages of the intrathecal methotrexate and dexamethasone regimen. Laboratory safety indicator analysis revealed that WBC counts and ALT levels showed only mild declines after treatment compared with baseline in both groups, with no statistically significant intergroup differences. These results clearly indicate that, compared to systemic chemotherapy, intrathecal injection does not impose additional risk of myelosuppression or hepatic impairment, and its safety profile remains controllable, which is consistent with the pharmacokinetics of this therapy that can minimize systemic drug exposure [44]. Particularly noteworthy was the significant effect of intrathecal therapy on rapid symptom relief observed in this study. In the time-to-symptom-improvement analysis, patients in the experimental group achieved markedly faster headache alleviation compared to those in the control group. This rapid response may be partly due to the potent and prompt action of dexamethasone in reducing peritumoral edema and intracranial pressure [41]; it is also inseparable from the direct delivery of high-concentration drugs to the cerebrospinal fluid via intrathecal administration, enabling more direct and rapid control of central nervous system lesions. This rapid headache relief is corroborated by a significant improvement in headache scores on the QLQ-BN20 scale, collectively accounting for the substantial QoL gains observed in the experimental group, especially in role and social functioning.

Although neither this study nor most retrospective analyses have demonstrated that intrathecal therapy can significantly prolong OS, it has shown potential value in improving DCR, maintaining stable neurological function, and enhancing QoL. Therefore, intrathecal therapy serve as an important component of palliative or comprehensive treatment for intracranial malignancies, especially for patients with leptomeningeal metastasis or those who respond poorly to conventional treatment. It provides a locally feasible treatment option for patients who are unsuitable for systemic intensified che-

motherapy or have progressed after standard radiotherapy.

However, several limitations should be acknowledged. This was a single-center retrospective study with a fixed intrathecal dosing regimen (methotrexate 10 mg + dexamethasone 10 mg) without individualization based on body surface area, age, or renal function, which may have introduced interindividual variability in efficacy and toxicity. Future prospective studies with pharmacokinetics-guided dose adjustment are warranted. Furthermore, although the present study incorporated SDMT and TMT to assess cognitive function, evaluation was still limited to two time points. Future research could combine multimodal MRI and cerebrospinal fluid biomarker analyses to explore the effect of treatment on cognitive networks from multiple dimensions. In addition, genetic background (e.g., gene polymorphisms in genes encoding enzymes involved in methotrexate metabolism) may influence individual susceptibility to treatment-related neurotoxicity, and future precision-medicine-oriented stratified studies are encouraged.

Conclusion

Intracranial malignant tumors are life-threatening diseases that require multidisciplinary treatment, yet their prognosis is not ideal, especially for metastatic tumors. Active intervention is therefore crucial for improving QoL in affected patients. This study shows that intrathecal injection of methotrexate combined with dexamethasone, as an adjuvant therapy, can effectively relieve tumor-related symptoms such as headache, significantly improve the KPS score, and enhance health-related QoL, while maintaining a favorable safety profile. Nevertheless, given the single-center retrospective study using fixed dosing strategy, it is necessary to conduct multicenter prospective trials with individualized dosing regimens to validate these findings.

Disclosure of conflict of interest

None.

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