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Original Article

Comparison between high-dose and low-dose intravenous methylprednisolone therapy in patients with brain necrosis after radiotherapy for nasopharyngeal carcinoma

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ABSTRACT

Background: Radiotherapy is the standard radical treatment for nasopharyngeal carcinoma (NPC) and may cause radiation-induced brain necrosis (RN). Intravenous steroids have been considered as an effective treatment for RN. However, evidence concerning the efficacy of different doses of intravenous steroid therapy remains insufficient to establish the optimal regimen for NPC patients with RN.
Methods: We retrospectively reviewed charts of 169 patients who were diagnosed with RN after radiotherapy for NPC, treated with low-dose or high-dose intravenous methylprednisolone (IVMP) and followed up for 12 months. We collected the clinical data, including the Late Effects of Normal Tissue (LENT)/Subjective, Objective, Management, Analytic (SOMA) scales score and Montreal Cognitive Assessment (MoCA) score. Magnetic resonance imaging (MRI) was performed pre- and post-treatment to define the radiographic response.
Results: There were no significant differences in the treatment response based on MRI, or changes in clinical symptoms and cognitive function between low and high-dose groups. Thirty of 93 low-dose patients (32.3%) and 21 of 76 high-dose patients (27.6%) presented effective response in MRI, with no significant differences between groups ($P = 0.515$). Neither group showed a significant difference in the effective rate based on the MoCA total score and LENT/SOMA score. The most commonly reported grade 3 adverse events in the high-dose group ($n = 76$) were infections and infestations (3 [3.9%] vs. none for low-dose group).
Conclusions: We found low-dose IVMP was not inferior to high-dose IVMP for NPC patients with RN. In addition, treatment-related infections and infestations were likewise more common with high-dose steroid than low-dose steroid.
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Nasopharyngeal carcinoma (NPC) is a common malignancy in the southern Chinese population [1]. Radiotherapy is the standard radical treatment for NPC and produces long-term effects. However, therapeutic irradiation increases the risk of neurologic injury, including radiation-induced brain necrosis (RN) [2], which is a common and serious complication among the many radiotherapy-related complications [3]. Furthermore, treatment of RN remains challenging. Treatment strategies such as anticoagulants [4], hyperbaric oxygen [5], and vitamins [6] have been reported in the past two decades, but their use is not widely accepted due to potential adverse effects and limited randomized control trials. Bevacizumab has recently been reported to be promising, but exhibits potential toxicity and has a high cost bur-

Abbreviations: RN, radiation-induced brain necrosis; NPC, nasopharyngeal carcinoma; IVMP, intravenous methylprednisolone; LENT-SOMA, the Late Effects of Normal Tissue (LENT)/Subjective, Objective Management, Analytic (SOMA) scale score; MoCA, Montreal Cognitive Assessment score; DBRN, duration between radiotherapy; DBNM, duration between RN diagnosis and methylprednisolone treatment; DBRM, duration between radiotherapy and methylprednisolone treatment; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; CPK, creatine phosphate kinase; TG, triglyceride; ApoA1, apolipoprotein A1; Hs-CRP, high-sensitivity C-reaction protein levels; ESR, erythrocyte sedimentation rate; IMRT, intensity-modulated radiotherapy; 2D-RT, two-dimensional radiotherapy; MRI, magnetic resonance imaging.

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den [7,8]. Moreover, there were 39.5% of patients presented with recurrence of RN after bevacizumab treatment in our previous study [9]. Surgical operation is one treatment option, but surgery is considered to be the last resort for those who with poor-controlled conditions, e.g. progressive symptoms despite conservative therapy, hemorrhage, and brain necrosis formation [10].

Steroids have been considered as an effective treatment for RN and used to provide prompt symptomatic relief [3,11]; steroids help reduce cytokine and inflammatory responses, which not only modify cerebral edema but also reduce risk of subsequent changes in blood vessels and inflammation [3,12]. Thus, steroids have been recommended as the front-line therapeutic strategy for decades, and pulse-dose intravenous steroids, which have been demonstrated to be more effective than oral steroids [13,14], are commonly used. However, the incidence of adverse events may go up with increasing doses of intravenous steroids, and therefore, low intravenous steroids can also be used to reduce advents events [15–19]. Furthermore, evidence concerning the safety and efficacy of different doses of intravenous steroid therapy remains insufficient to establish the optimal treatment regimen for NPC patients with RN. Since infusions of steroids are widely used to treat RN, it is important to clarify whether low-dose intravenous steroids are as safe and efficient as high-dose intravenous steroids.

We therefore undertook this study to assess the efficacy and safety of high-dose vs. low-dose intravenous methylprednisolone therapy in patients with brain necrosis after radiotherapy for nasopharyngeal carcinoma (NPC).

Methods and materials

Patients

This retrospective study was approved by the institutional review board of our hospital. A total of 169 NPC patients with history of radiotherapy admitted to the Department of Neurology at our hospital between January 2005 and December 2016 were considered. We retrospectively collected the demographic and clinical data of these patients through chart review. Patients who fulfilled the following eligibility criteria were included: (1) underwent radiation therapy at least 12 months prior to intravenous methylprednisolone administration; (2) treated using intravenous methylprednisolone (high-dose or low-dose); (3) not previously administered bevacizumab; (4) lacked evidence regarding increased intracranial pressure suggestive of brain hernia requiring surgical intervention; and (5) performed MRI before and after intravenous methylprednisolone therapy and with measurable lesions in the MRI. Patients with any of the following were excluded: NPC relapse, brain lesion resection, metastases, hepatitis, other malignances, neurovascular disease, demyelinating disease, or other diseases of the nervous system.

Data collection

The following demographic, clinical, and laboratory data before methylprednisolone administration were retrieved from the clinical notes: age, sex, body weight, NPC stage, high-sensitivity C-reactive protein levels (hs-CRP), total radiation dose of the neck and temporal lobe, radiation approaches (intensity-modulated radiotherapy [IMRT] vs. conventional), duration between radiotherapy and RN diagnosis (DBRN), duration between RN diagnosis and methylprednisolone treatment (DBNM), duration between radiotherapy and methylprednisolone treatment (DBRM), the Late Effects of Normal Tissue (LENT)/Subjective, Objective, Management, Analytic (SOMA) scale score, and Montreal Cognitive Assessment (MoCA) score. The 7th edition of the AJCC/UICC staging system was used for clinical staging at presentation.

Methylprednisolone regimens

Before 2009, patients with brain necrosis after radiotherapy for NPC were treated with low-dose methylprednisolone [15,20]. Low-dose methylprednisolone was administered as an intravenous infusion of 1 mg/kg/day for 5 consecutive days, then 40 mg for 5 days, then oral prednisone 30 mg per day, gradually tapering by 5 mg/week to a maintenance dose of 10 mg daily for 3 months. All patients with brain necrosis after radiotherapy for NPC were generally treated with high methylprednisolone after 2009 [21]. High-dose methylprednisolone was administered as an intravenous infusion of 500 mg for 3 consecutive days, 80 mg for 4 days, 40 mg for 4 days, then oral prednisone 30 mg/day, gradually tapering by 5 mg/week to a maintenance dose of 10 mg daily for 3 months.

Clinical and radiological measurements

MRI scan

The RN volume was detected using T2-weighted fluid-attenuated inversion recovery (FLAIR) and T1-weighted gadolinium contrast-enhanced MRI 3 days before methylprednisolone administration (F0) and at 3 (F1) and 12 months (F2) of follow up; images were independently assessed by two radiologists who were masked to the treatment. For lesion measurement, radiologists identified the outline of the lesion manually and semi-automatically, and the total RN volume was estimated with Volume Viewer 2 software (GE Healthcare, AW Suite 2.0 6.5.1. z) on T2-weighted FLAIR images. The methylprednisolone response rate was defined as the percentage decrease in brain edema volume shown on T2-weighted FLAIR and T1-weighted gadolinium contrast-enhanced images at F1 or F2, compared with images at F0. The effective response was defined as $\geq$25% reduction in RN volume at F1 and F2 compared with the volume at F0 [9].

Progressive disease was defined as either (1) more than a 10% increase in the volume of the lesions on MRI (2) the appearance of any new lesion/site on MRI or (3) clear clinical worsening, and progression-free survival (PFS) was defined as the time from the start of steroid therapy to disease progression. We measured overall survival (OS) from the date of initiation of steroid treatment until death, and we censored patients who were alive at the time of the last data cutoff at the time of the last follow-up.

LENT-SOMA assessment

Clinical symptoms and signs were evaluated using the LENT/SOMA scale at F0 and F1; the total LENT/SOMA score was a summary of the Subjective, Objective, and Management (SOM) characteristics [22–24]; a reduction $\geq$1 in the total LENT/SOMA score was defined as clinical improvement [21].

MoCA assessment

MoCA, which consists of seven cognitive domains, visuospatial and executive abilities, naming, attention, language, abstraction, delayed recall memory, and orientation [25], was performed to assess cognitive function at F0 and F1. A total score >25 indicated normal cognitive function, and scores <20 and 20–24 indicated significant and mild cognitive impairment likely to impair function, respectively [26]. Changes in MoCA total score were compared between groups. Improvement was defined as a change (i) from mild or significant cognitive impairment to normal cognitive function or (ii) from significant to mild cognitive impairment. Deterioration was defined as a change (i) from normal cognitive function to mild cognitive impairment or significant cognitive impairment or (ii) from mild to significant cognitive impairment.

Safety assessments included the frequency and severity of adverse events (AEs), we graded adverse event severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03).

Statistical analysis

Variables were summarized using proportions for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Student's *t* test was used to compare between-group differences for normally distributed variables, the Mann–Whitney *U* test was used to compare non-parametric variables, and the chi-squared or Fisher's exact tests were used to compare categorical variables. Progression-free survival (PFS) and overall survival (OS) curves were plotted using the Kaplan–Meier method, and comparisons were performed using the log-rank test. All tests were two-sided, and $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using R version 3.3.2 for Windows (R Foundation).

Results

Demographic and clinical characteristics

A patient flowchart is shown in Fig. 1. The two groups had similar demographic and clinical characteristics (Table 1). There were 169 RN patients who were treated with intravenous methylprednisolone, including 137 males (81.1%) and 32 females (18.9%). The median age was 49 years, with a range of 25–70 years. There were no significant differences between the two groups regarding age, sex, duration between radiotherapy and RN, duration between RN diagnosis and methylprednisolone treatment, duration between radiotherapy and methylprednisolone treatment, LENT/SOMA scores, MoCA scores, high-sensitivity C-reaction protein levels (hs-CRP), total radiation dose of neck, radiation approaches (IMRT/conventional), NPC stage, the brain volume of edema, and necrosis at baseline.

Radiotherapy characteristics

Of the 169 patients, 149 (88.2%) and 20 (11.8%) received conventional two-dimensional radiotherapy and IMRT, respectively. In the low-dose group, 93 patients developed RN after a median latency of 41.3 months (IQR, 34.6–68.4 months) from commencement of the primary course of radiotherapy; in the high-dose group, 76 patients developed RN after a median latency of 40.1 months (IQR, 33.7–60.7 months) (Table 1). The overall distribution of patients with stages II, III, IV, and IVA NPC in the low- and high-dose groups was 3.2%, 44.1%, 26.9%, and 25.8% and 7.9%, 43.4%, 31.6%, and 17.1%, respectively.

MRI characteristics of brain necrosis

The median volume of brain edema lesions in T2-weighted FLAIR images in the low- and high-dose groups was 18.4 cm^3 (IQR, 4.2–45.4 cm^3) and 14.7 cm^3 (IQR, 5.2–52.4 cm^3), respectively ($P = 0.744$). The median volume of brain necrotic lesions in T1-weighted contrast-enhanced images in the low and high-dose groups was 1.5 cm^3 (IQR, 0.4–4.3 cm^3), and 1.9 cm^3 (IQR, 0.5–5.0 cm^3) ($P = 0.350$), respectively. Bilateral brain edema lesions were detected in 127 patients, and 42 patients showed unilateral radiological abnormalities ($P = 0.265$), with no significant differences between groups at the sides of lesions in the brain edema and brain necrotic lesions (Table 2).

Brain necrotic lesions were present in 72 out of 93 (77.4%) and 65 out of 76 (85.5%) patients in low-dose and high-dose groups, respectively. Cysts occurred in 14 (15.1%) and seven patients (9.2%) in the low and high-dose groups, respectively ($P = 0.252$).

Clinical assessment

Changes in MRI

As shown in Table 3, the improvement of RN volume, cognitive function, and clinical symptoms and signs at the different time points of the study in the two groups of patients are reported.

At F1, the total effective rate of intravenous methylprednisolone on T2-weighted FLAIR images was 30.2% in 169 patients; in addition, 30 and 21 patients in the low and high-dose groups, respectively, exhibited radiological improvement on T2-weighted FLAIR images at F1 (32.3% vs. 27.6%, $P1 = 0.515$). Notably, patients in both groups showed an improvement of the treatment response rate based on T1-weighted gadolinium enhanced MRI (low-dose group, 31.2%; high-dose group, 40.8) (Table 3), but it did not reach the statistical difference between the two groups ($P1 = 0.278$). The percentage change in brain lesions size for all assessable patients is shown in Fig. 2.

At F2, the total effective rate of intravenous methylprednisolone on T2-weighted FLAIR images was 37.9% in 169 patients; in addi-

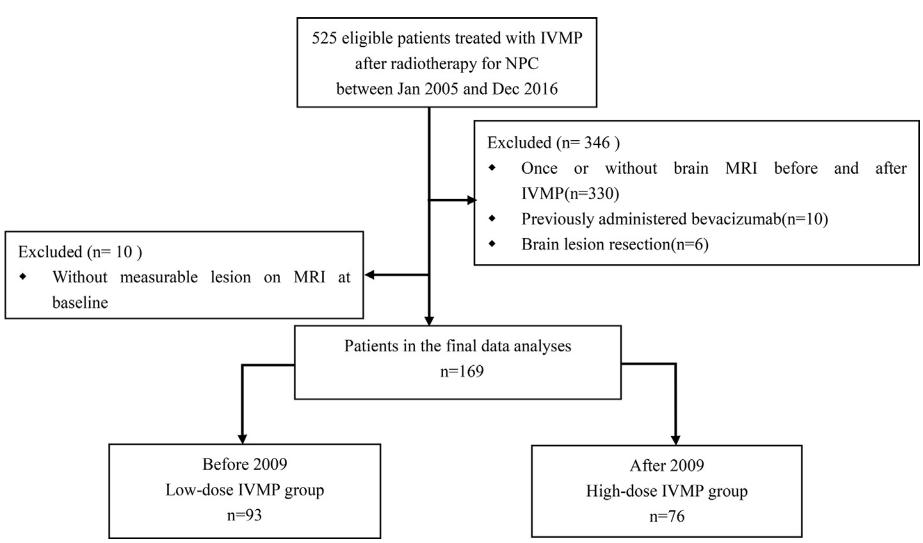

Fig. 1. Flow chart of study cohort selection. Abbreviations: NPC = Nasopharyngeal Carcinoma; IVMP = intravenous methylprednisolone; MRI = magnetic resonance imaging; RN = radiation-induced brain necrosis.

Table 1
Patient baseline characteristics by group.

	Low-dose group (n = 93)	High-dose group (n = 76)	P value
Demographic and clinical characteristics			
Age, years	49.0 (44.0–56.0)	49.0 (43.8–54.0)	0.977
Sex			0.303
Male	78 (83.9)	59 (77.6)	
Female	15 (16.1)	17 (22.4)	
DBRN, months	41.3 (34.6–68.4)	40.1 (33.7–60.7)	0.461
DBRM, months	59.5 (30.6–93.6)	49.7 (12.3–73.4)	0.119
DBNM, months	10.8 (0.2–38.6)	6.3 (0.1–22.4)	0.085
Biochemical characteristics			
AST (U/L)	20.0 (18.0–24.0)	21.0 (16.3–25.0)	0.753
ALT (U/L)	20.0 (14.0–28.0)	17.0 (13.0–25.0)	0.246
BUN (mg/dL)	4.4 (3.8–5.3)	4.4 (3.5–5.2)	0.643
TG (mmol/L)	1.1 (0.7–1.5)	0.9 (0.6–1.4)	0.069
ApoA1 (g/L)	1.2 (1.0–1.3)	1.1 (1.1–1.3)	0.790
CPK (U/L)	87.0 (55.5–132.0)	82.0 (61.0–110.0)	0.688
Hs-CRP (mg/L)	3.2 (1.4–7.9)	2.2 (1.1–6.7)	0.208
ESR (mm/h)	15.0 (12.0–26.0)	15.0 (7.5–31.5)	0.638
Radiotherapy characteristics			
Nose-dose, Gy	70.0 (68.0–74.0)	70.0 (70.0–72.0)	0.712
Neck-dose, Gy	60.0 (56.0–64.0)	62.0 (60.0–64.5)	0.099
Temporal lobe, Gy	68.6 (66.7–72.5)	68.6 (68.6–70.6)	0.846
Radiation approaches			0.998
Conventional 2D-RT	82 (88.2)	67 (88.2)	
IMRT	11 (11.8)	9 (11.8)	
NPC-associated characteristics			
NPC type			0.375
Undifferentiated	55 (59.1)	50 (65.8)	
Poorly differentiated	38 (40.9)	26 (34.2)	
NPC stage			0.252
II	3 (3.2)	6 (7.9)	
III	41 (44.1)	33 (43.4)	
IV	25 (26.9)	24 (31.6)	
IVA	24 (25.8)	13 (17.1)	

Abbreviations: DBRN, duration between radiotherapy and radiation-induced brain necrosis (RN) diagnosis; DBNM, duration between RN diagnosis and methylprednisolone treatment; DBRM, duration between radiotherapy and methylprednisolone treatment; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; CPK, creatine phosphate kinase; TG, triglyceride; ApoA1, apolipoprotein A1; Hs-CRP, high-sensitivity C-reaction protein levels; ESR, erythrocyte sedimentation rate; Nose-dose, total radiation dose of nasopharynx; Neck-dose, total radiation dose of neck; IMRT, intensity-modulated radiotherapy; 2D-RT, two-dimensional radiotherapy.
Data are shown as numbers (%) or medians (interquartile ranges). No difference was found between the low dose group and high dose group regarding either the clinical characteristics or the follow-up data (P = 0.099–0.998).

Table 2
MRI characteristics of temporal lobe necrosis at baseline.

	Low dose group (n = 93)	High dose group (n = 76)	P value
RN volume at baseline (cm^3)			
White-matter lesions	18.4 (4.2–45.4)	14.7 (5.2–52.4)	0.744
Contrast-enhanced lesions	1.5 (0.4–4.3)	1.9 (0.5–5.0)	0.350
White-matter lesions			
Number of flair lesions			0.464
Single	20 (21.5)	20 (26.3)	
Multiple	73 (78.5)	56 (73.7)	
Side of flair lesions			0.265
Unilateral	20 (21.5)	22 (28.9)	
Bilateral	73 (78.5)	54 (71.1)	
Contrast-enhanced lesions			
Number of enhancing lesions			0.379
None	21 (22.6)	11 (14.5)	
Single	20 (21.5)	20 (26.3)	
Multiple	52 (55.9)	45 (59.2)	
Side of enhancing lesions			0.397
None	21 (22.6)	11 (14.5)	
Unilateral	28 (30.1)	24 (31.6)	
Bilateral	44 (47.3)	41 (53.9)	
Cysts			0.252
None	79 (84.9)	69 (90.8)	
Yes	14 (15.1)	7 (9.2)	

Abbreviations: MRI, magnetic resonance imaging; RN, radiation-induced brain necrosis
Data are shown as numbers (%) or medians (interquartile ranges). No difference was found between the low dose group and high dose group regarding either the clinical characteristics or the follow-up data (P = 0.252–0.744).

tion, 36 and 28 patients in the low and high-dose groups, respectively, exhibited radiological improvement on T2-weighted FLAIR images (38.7% vs. 36.8%, $P2$ = 0.803). Moreover, patients in both groups showed an improvement of the treatment response rate based on T1-weighted gadolinium enhanced MRI in 137 patients (low-dose group, 24.7%; high-dose group, 30.3%), but it did not reach the statistical difference between the two groups ($P2$ = 0.373).

LENT/SOMA and MoCA assessment

At F1, 25 (26.9%) and 20 (26.3%) cases in the low and high-dose groups, respectively, showed improvement in cognitive function. Meanwhile, 26 of 93 patients (28.0%) in the low-dose group improved by at least one point on the LENT/SOMA score compared to 26 of 76 patients (34.2%) in the high-dose group. Neither group showed a significant difference in the effective rate based on the MoCA total score and LENT/SOMA score.

Survival outcomes

Twenty-two patients (12 on high-dose group and 10 on low-dose group) presented new neurologic symptoms during follow up, and cranial MRIs showed progression of RN in these patients. In the log-rank test, progression-free survival (PFS) during follow up was similar between groups (P = 0.474; Fig. 3). And we found the actual 5-year overall survival in the low-dose group and in the high-dose group was 68.6% and 59.0%, respectively, but it did not reach the statistical difference between the two groups ($P2$ = 0.599; Fig. 4).

Safety and tolerability

Adverse events (any grade) were reported by 41 (44.1%) of 93 patients who received low-dose steroids and by 48 (63.2%) of 76 patients who received high-dose steroids. The most common adverse events reported by patients who received low-dose steroids were flushing (10 [10.8%] of 93), hyperglycemia (6 [6.5%]), gastritis (5 [5.4%]), and insomnia (5 [5.4%]; Table 4). No cases of Infections and infestations were reported for low-dose steroids. The most common adverse events reported by patients who received high-dose steroids were flushing (11 [14.5%] of 76), hyperglycemia (7 [9.2%]), gastritis (7 [9.2%]; Table 4). No grade 4 adverse events deemed related to treatment were observed between the two groups, but the most commonly reported grade 3 adverse event was insomnia for low-dose group (2 [2.2%], vs. 1 [1.3%] for high-dose steroids), and for high-dose group they were infections and infestations (3 [3.9%] vs. none for low-dose group), gastritis (1 [1.3%] vs. none).

Discussion

We retrospectively assessed the effect of low-dose vs. high-dose intravenous methylprednisolone therapy in patients with brain necrosis after radiotherapy for NPC, based on MRI and changes in clinical symptoms and cognitive function. Few studies have evaluated the efficacy of different doses of intravenous steroid therapy in patients with brain necrosis. We found that high-dose intravenous methylprednisolone showed no additional benefit above that of low-dose intravenous methylprednisolone in the treatment

Table 3
Efficacy of improvement based on LENT/SOMA score, MoCA score, and MRI findings at the different study time points.

Therapeutic effect	Low dose group (*n* = 93) Baseline	3 months	12 months	High dose group (*n* = 76) Baseline	3 months	12 months	*P1*†	*P2*‡
RN volume (cm^3)								
White-matter lesions							0.515	0.803
Effective		30 (32.3)	36 (38.7)		21 (27.6)	28 (36.8)		
Non-effective		63 (67.7)	57 (61.3)		55 (72.4)	48 (63.2)		
Contrast-enhanced lesions							0.278	0.373
Effective		29 (31.2)	23 (24.7)		31 (40.8)	23 (30.3)		
Non-effective		43 (46.2)	49 (52.7)		34 (44.7)	42 (55.3)		
MoCA								
Degree of cognitive impairment							0.252*	
Normal	29 (31.2)	37 (39.8)		25 (32.9)	26 (34.2)			
Mild	60 (64.5)	52 (55.9)		43 (56.6)	46 (60.5)			
Significant	4 (4.3)	4 (4.3)		8 (10.5)	4 (5.3)			
Treatment response rate							0.996	
Improved		25 (26.9)			20 (26.3)			
Stable		50 (53.8)			41 (54.0)			
Deteriorated		18 (19.4)			15 (19.7)			
LENT-SOMA								
Domain								
Subjective	1 (0–2)	0 (0–1)		0 (0–1)	0 (0–1)			
Objective	1 (0–2)	1 (0–2)		1 (0–1)	0 (0–1)			
Management	4 (4–4)	4 (4–4)		4 (4–4)	4 (4–4)			
Analytic	3 (2–3)	3 (2–3)		3 (2–3)	3 (2–3)			
Total score#	6 (5–7)	5 (5–7)		5 (4–6)	5 (4–6)		0.182*	
Treatment response rate							0.382	
Improved		26 (28.0)			26 (34.2)			
Ineffective		67 (72.0)			50 (65.8)			

Abbreviations: LENT-SOMA, the Late Effects of Normal Tissue (LENT)/Subjective, Objective, Management, Analytic (SOMA) scale score; MoCA, Montreal Cognitive Assessment score; RN, radiation-induced brain necrosis.
Data are shown as numbers (%) or medians (interquartile ranges). *P1*†, low-dose group vs. high-dose group at 3 months; *P2*‡, low-dose group vs. high-dose group at 12 months. *, low-dose group vs. high-dose group at baseline; #, summary grade of the Subjective, Objective, and Management (SOM) characteristics.

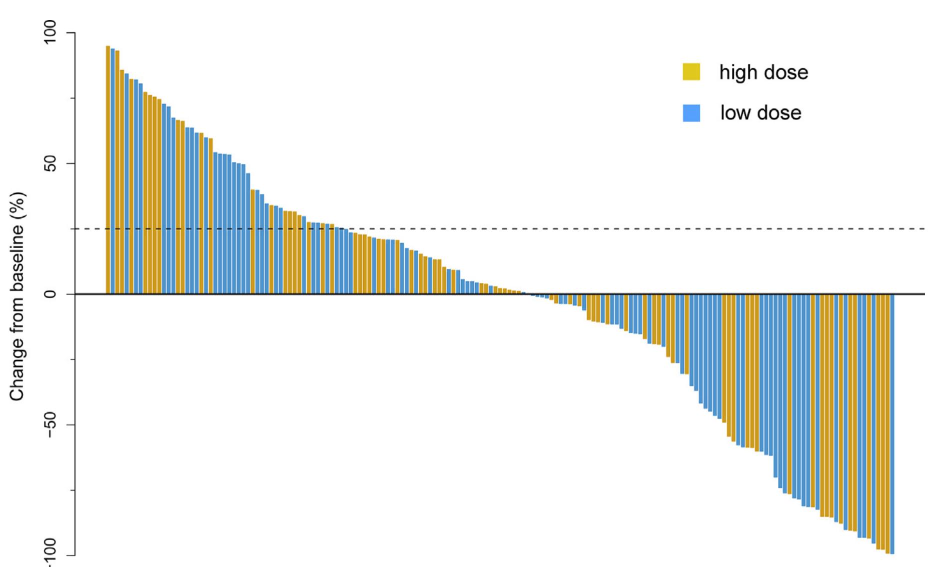

Fig. 2. Waterfall plot. The changes of the lesion sizes in the MRI for 169 evaluable patients.

response rate based on MRI or changes in clinical symptoms and cognitive function. The mechanisms of RN corresponding to clinical manifestations are not fully understood. One important pathological feature of RN is radiation-induced damage of endothelial and glial cells and vascular injury, which initiates brain necrosis; vascular endothelial cell damage results in fibrinoid necrosis of the small arteries, accompanied by increased capillary permeability, leading to focal coagulative necrosis and oligodendrocyte damage and demyelination [27]. Methylprednisolone reduces cytokine and inflammatory responses, which reduces vasogenic edema as well as subsequent changes in blood vessels and inflammation [12]. Besides, steroids may also result primarily in the restoration of the endothelial junctions within the cerebral microvasculature and consequent reduction in cerebral edema [28]. Thus, steroids have long been used in treatment of RN and to provide prompt symptomatic relief [3]. Eyster et al. first reported on

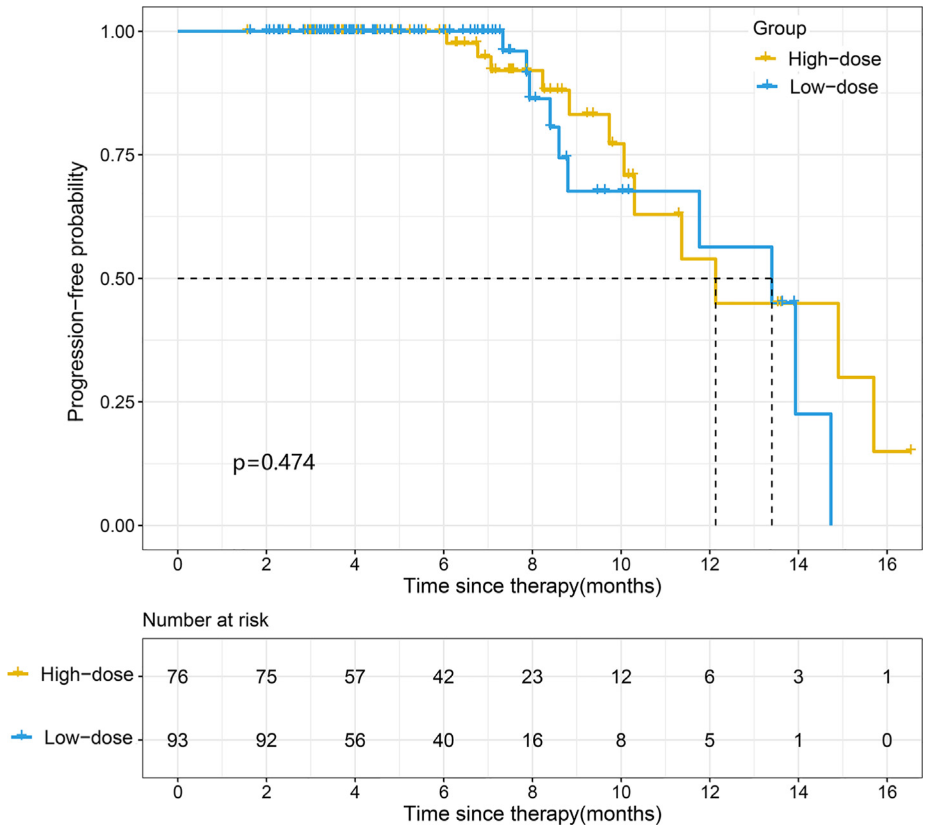

Fig. 3. Progression-free survival is illustrated in patients who underwent high-dose IVMP vs. low-dose IVMP.

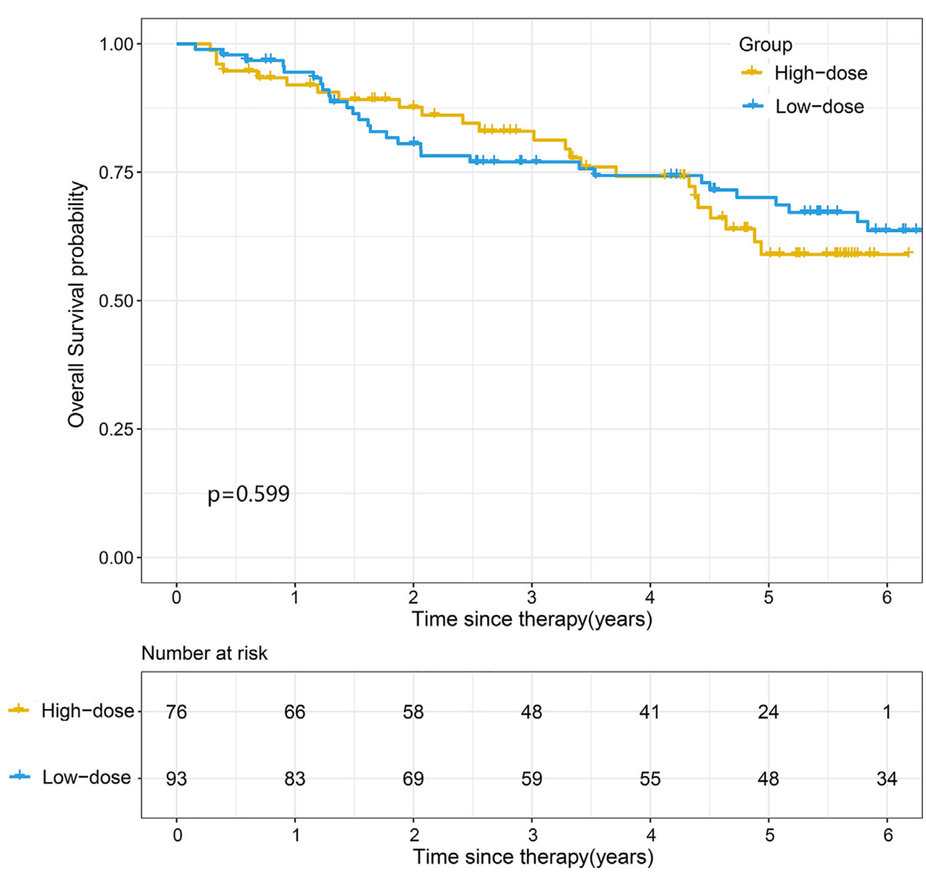

Fig. 4. Overall survival is illustrated in patients who underwent high-dose IVMP vs. low-dose IVMP.

treatment with steroids and suggested that steroids might have a retarding influence on the progressive pathologic process, in addition to symptomatic relief via the anti-edema effect [29].

In our study, the total effective rate of intravenous methylprednisolone on T2-weighted FLAIR images was 30.2% in 169 patients. This is consistent with a previous report in which approximately one-third of patients in the early phase of RN benefitted from steroid therapy [3]. In a recent study, high-dose steroid treatment, which has better tolerance and may minimize long-term steroid-induced side effects, was compared to oral steroids in the treatment of RN in NPC patients; 20% of patients receiving pulse steroids experienced radiological improvement as opposed to 3.2% of those receiving conventional oral steroids [13]. Our study further demonstrated that high dose intravenous methylprednisolone showed no benefit while comparing with low dose intravenous methylprednisolone; this finding might be related to the mechanism of steroid. High-dose intravenous methylprednisolone has commonly been used in the acute and progressive stages of autoimmune diseases such as multiple sclerosis [30] and myasthenia gravis [31], supporting the concept that autoimmunity plays a major role in the pathogenesis of diseases. However, in our study, all patients exhibited late delayed injury whose primary pathogenesis is that vascular injury initiates the process of necrosis, mostly presenting as a chronic onset; therefore, we speculate that this is why low-dose intravenous methylprednisolone may be as effective as high-dose intravenous methylprednisolone.

The consistent efficacy of different doses of intravenous methylprednisolone is also manifested in the improvement of cognitive function and clinical symptoms. The mechanisms underlying radiation-induced cognitive impairment remain ill-defined. Cognitive impairment due to brain necrosis has been explored in several studies, and a decline in the cognitive function of patients with brain lesions due to radiation generally has been reported [32]. A study also demonstrated a significant association between the volume of brain necrosis and the level of cognitive impairment after radiotherapy in evaluated patients [33]. Our study demonstrated neither group showed a significant difference in the effective rate based on the MoCA total score, it is tempting to speculate that this might be related to brain necrosis. There was no statistical difference in the treatment response rate in the T1-weighted gadolinium enhancement between the two groups; therefore, there was also no difference in the treatment response rate of cognitive function.

Nevertheless, high steroid treatment is associated with numerous side effects such as increased number of infections, gastrorrhagia, hyperglycemia, cataracts, osteoporosis, peptic ulcer disease, liver damage and aseptic necrosis of the bones [17–19]. There are numerous case-series reports on the potential serious hepatic risks of the intravenous glucocorticoid administration modality, and the extent and outcome of severe liver damage seems to be dose dependent [16,34]. Safety and tolerability in our study favored low-dose steroid compared with high-dose steroid, with a reduction in the frequency of overall adverse events reported and a reduction in grade 3 adverse events. Furthermore, treatment-related infections and infestations were likewise more common with high-dose steroid then low-dose steroid, probably related to the induced immunodepression, and the adverse event profile was in line with the profile reported previously.

In conclusion, there were no significant differences in the efficacy of high-dose vs. low-dose intravenous methylprednisolone treatments for NPC patients with RN, and treatment-related infections and infestations were likewise more common with high-dose steroid than low-dose steroid. This observation may have important clinical implications that low-dose is superior to high-dose intravenous methylprednisolone therapy since the adverse effects of low-dose intravenous methylprednisolone therapy might be significantly reduced, while an increase in methylprednisolone dose may increase the incidence of adverse effects.

The present study has several limitations that need to be addressed for accurate interpretation of the results. First, given the retrospective nature of this study, our data may exhibit attrition bias due to missing documentation and loss to follow-up. LENT/SOMA scales and MoCA scales at 12 months were not integrally recorded in our study. Second, due to the sample size of our study, further prospective investigations with a larger cohort

Table 4
Treatment-related adverse events.

Adverse event, *n* (%)	Low dose group (*n* = 93)		High dose group (*n* = 76)	
	Grades 1–2	Grade 3	Grades 1–2	Grade 3
Total adverse events	39 (41.9)	2 (2.2)	43 (56.6)	5 (6.6)
Gastrointestinal disorders				
Gastritis	5 (5.4)	0	7 (9.2)	1 (1.3)
General disorders and administration site conditions				
Fatigue	4 (4.3)	0	3 (3.9)	0
Infections and infestations				
Lung infection	0	0	2 (2.6)	1 (1.3)
Meningitis	0	0	0	1 (1.3)
Urinary tract infection	0	0	0	1 (1.3)
Investigations				
Weight gain	4 (4.3)	0	4 (5.3)	0
Metabolism and nutrition disorders				
Hyperglycemia	6 (6.5)	0	7 (9.2)	0
Nervous system disorders				
Dizziness	2 (2.2)	0	1 (1.3)	0
Psychiatric disorders				
Insomnia	5 (5.4)	2 (2.2)	2 (2.6)	1 (1.3)
Respiratory, thoracic and mediastinal disorders				
Nasal hemorrhage	1 (1.1)	0	1 (1.3)	0
Skin and subcutaneous tissue disorders				
Rash acneiform	0	0	2 (2.6)	0
Vascular disorders				
Flushing	10 (10.8)	0	11 (14.5)	0
Hypertension	2 (2.2)	0	3 (3.9)	0

Abbreviation: Data are shown as numbers (%).

are needed to confirm our findings. Third, this was a single-center, retrospective study, thus the results should be further validated in other cohorts to improve generalizability.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

[1] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] Crossen JR, Garwood D, Glatstein E, et al. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol 1994;12:627–42.
[3] Lee AW, Ng SH, Ho JH, et al. Clinical diagnosis of late temporal lobe necrosis following radiation therapy for nasopharyngeal carcinoma. Cancer 1988;61:1535–42.
[4] Glantz MJ, Burger PC, Friedman AH, et al. Treatment of radiation-induced nervous system injury with heparin and warfarin. Neurology 1994;44:2020–7.
[5] Lin HY, Ku CH, Liu DW, et al. Hyperbaric oxygen therapy for late radiation-associated tissue necroses: is it safe in patients with locoregionally recurrent and then successfully salvaged head-and-neck cancers? Int J Radiat Oncol Biol Phys 2009;74:1077–82.
[6] Chan AS, Cheung MC, Law SC, et al. Phase II study of alpha-tocopherol in improving the cognitive function of patients with temporal lobe radionecrosis. Cancer 2004;100:398–404.
[7] Jeyaretna DS, Curry WJ, Batchelor TT, et al. Exacerbation of cerebral radiation necrosis by bevacizumab. J Clin Oncol 2011;29:e159–62.
[8] Furuse M, Kawabata S, Kuroiwa T, et al. Repeated treatments with bevacizumab for recurrent radiation necrosis in patients with malignant brain tumors: a report of 2 cases. J Neurooncol 2011;102:471–5.
[9] Li Y, Huang X, Jiang J, et al. Clinical variables for prediction of the therapeutic effects of bevacizumab monotherapy in nasopharyngeal carcinoma patients with radiation-induced brain necrosis. Int J Radiat Oncol Biol Phys 2018;100:621.
[10] Li Y, Shi X, Rong X, et al. Neurosurgery and prognosis in patients with radiation-induced brain injury after nasopharyngeal carcinoma radiotherapy: a follow-up study. Radiat Oncol 2013;8:88.
[11] Shaw EG, Robbins ME. The management of radiation-induced brain injury. Cancer Treat Res 2006;128:7–22.
[12] Tada E, Matsumoto K, Kinoshita K, et al. The protective effect of dexamethasone against radiation damage induced by interstitial irradiation in normal monkey brain. Neurosurgery 1997;41:209–17. 217–219.
[13] Lam T, Wong FCS, Leung T, et al. Clinical outcomes of 174 nasopharyngeal carcinoma patients with radiation-induced temporal lobe necrosis. Int J Radiat Oncol Biol Phys 2012;82:e57–65.
[14] Genc M, Genc E, Genc BO, et al. Significant response of radiation induced CNS toxicity to high dose steroid administration. Br J Radiol 2006;79:e196–9.
[15] Goodkin DE, Kinkel RP, Weinstock-Guttman B, et al. A phase II study of i.v. methylprednisolone in secondary-progressive multiple sclerosis. Neurology 1998;51:239–45.
[16] Le Moli R, Baldeschi L, Saeed P, et al. Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in Graves' ophthalmopathy. Thyroid 2007;17:357–62.
[17] Perez A, Jansen-Chaparro S, Saigi I, et al. Glucocorticoid-induced hyperglycemia. J Diabetes 2014;6:9–20.
[18] de S Queiroz L, da Cruz Neto JN. Late pseudotumoral brain necrosis following irradiation of a scalp neoplasm. Case report. J Neurosurg 1976;45:581–4.
[19] Jiang CL, Liu L, Li Z, et al. The novel strategy of glucocorticoid drug development via targeting nongenomic mechanisms. Steroids 2015;102:27–31.
[20] Beck RW, Cleary PA, Trobe JD, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. The Optic Neuritis Study Group. N Engl J Med 1993;329:1764–9.
[21] Tang Y, Rong X, Hu W, et al. Effect of edaravone on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma after radiotherapy: a randomized controlled trial. J Neurooncol 2014;120:441–7.
[22] LENT SOMA scales for all anatomic sites. Int J Radiat Oncol Biol Phys 1995;31:1049–91.
[23] Rubin P, Constine LR, Fajardo LF, et al. EORTC Late Effects Working Group. Overview of late effects normal tissues (LENT) scoring system. Radiother Oncol 1995;35:9–10.
[24] Davidson SE, Burns MP, Routledge JA, et al. Assessment of morbidity in carcinoma of the cervix: a comparison of the LENT SOMA scales and the Franco-Italian glossary. Radiother Oncol 2003;69:195–200.
[25] Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.
[26] Webb AJS, Pendlebury ST, Li L, et al. Validation of the montreal cognitive assessment versus mini-mental state examination against hypertension and hypertensive arteriopathy after transient ischemic attack or minor stroke. Stroke 2014;45:3337–42.
[27] Gutin PH, Leibel SA, Sheline GE, et al. Radiation injury to the nervous system. New York: Raven Press; 1992.
[28] Shaw PJ, Bates D. Conservative treatment of delayed cerebral radiation necrosis. J Neurol Neurosurg Psychiatry 1984;47:1338–41.
[29] Eyster EF, Nielsen SL, Sheline GE, et al. Cerebral radiation necrosis simulating a brain tumor. Case report. J Neurosurg 1974;40:267–71.
[30] Milligan NM, Newcombe R, Compston DA. A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 1. Clinical effects. J Neurol Neurosurg Psychiatry 1987;50:511–6.
[31] Arsura E, Brunner NG, Namba T, et al. High-dose intravenous methylprednisolone in myasthenia gravis. Arch Neurol 1985;42:1149–53.
[32] Cheung M, Chan AS, Law SC, et al. Cognitive function of patients with nasopharyngeal carcinoma with and without temporal lobe radionecrosis. Arch Neurol 2000;57:1347–52.
[33] Cheung MC, Chan AS, Law SC, et al. Impact of radionecrosis on cognitive dysfunction in patients after radiotherapy for nasopharyngeal carcinoma. Cancer 2003;97:2019–26.
[34] Marinó M, Morabito E, Brunetto MR, et al. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. Thyroid 2004;14:403.