Efficacy of the Nordic and the MSKCC Chemotherapy Protocols on the Overall and Progression-Free Survival in intracranial PCNSL.

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Abstract

Background

To compare the Nordic and the MSKCC chemotherapy protocols for Overall Survival (OS) and Progression-Free Survival (PFS) for intracranial primary CNS lymphoma (PCNSL).

Methods

A prospective database of PCNSL was reviewed over a 12-year period (2003-2014).

Results

Overall, 79 patients with intracranial PCNSL were identified, of whom 57 received chemotherapy. MSKCC with RTX was used in 18 patients (32%) who had median OS of 46.3 months [range 9.8-131.9] and median PFS of 34.6 months [range 6.4-131.9]. The Nordic protocol was used in 14 patients (25%) who had median OS of 30.9 months [range 2.7-106.3] and PFS of 14.3 months [range 0.0-106.3]. The MSKCC was used without RTX in 25 patients (44%) who had OS of 15.2 months [range 0.7-136.5] and PFS of 12.0 months [range 0.0-117.0]. MSKCC with RTX had a significantly longer median OS ($p<0.05$) compared to the other regimens in univariate analysis. In multivariate analysis, the only prognostic factor for OS and PFS of statistical significance was deep brain involvement ($p<0.005$).

Conclusions

In univariate analysis, the MSKCC with RTX achieved significantly longer median OS compared to the Nordic protocol. However, in multivariate analysis, the only prognostic factor for survival of statistical significance was deep brain involvement.

Introduction

Despite improvements in chemotherapy protocols, patients with primary CNS lymphomas (PCNSL) still have a dismal prognosis (1, 2). Standard chemotherapy protocols which are effective for systemic non-Hodgkin lymphomas, such as CHOP or CHOD have inferior effect in PCNSL, presumably reflecting the difficulty of penetration of the blood-brain barrier (BBB) by most chemotherapeutic agents (3-5).

High-dose methotrexate (HD-MTX) is the most effective chemotherapeutic agent for PCNSL and many studies support its use as first-line therapy (5-14) and is recommended also by the guidelines of the European Association of Neuro-Oncology (5). By the addition of calciumfolinate 24 hours after a 3-4 hour MTX infusion it is possible to increase the MTX dose by a factor of 100, thus allowing the drug to penetrate the BBB by simple diffusion. The Memorial Sloan-Kettering Cancer Center (MSKCC) group demonstrated that increasing the dose of MTX and adding procarbazine and vincristine improved disease control and overall survival (OS) in patients with newly diagnosed PCNSL (10). The combination of HD-MTX with other chemotherapeutic agents, such as high dose cytarabine (HD-Ara-C), another antimetabolite, improves OS compared to HD-MTX alone (5). Ferreri et al. (13) demonstrated that addition of HD-Ara-C to HD-MTX is associated with a significant benefit in PCNSL. HD-MTX and HD-Ara-C is now considered standard drugs for first line therapy in patients aged ≤ 75 years. However, its administration should be limited or avoided in elderly patients because of nephro- and neurotoxicity.

Rituximab (RTX) improves outcome for patients with systemic diffuse large B-cell lymphoma (DLBCL) and has also shown to be efficacious in the treatment of PCNSL (15). Theroretically RTX treatment is less efficacious after restoration of the blood-brain barrier. The Nordic Lymphoma Group tested a protocol adding HD cytarabine, cyclophosphamide, ifosfamide and vindeside to HD MTX and giving RTX for the first cycle only. For patients older than 65 years, a less intensive induction phase was used, but including temozolomide in the induction and in a maintenance phase of 12 months (16). However, the optimal treatment has yet to be established and in our study, we wanted to compare the Nordic and the MSKCC chemotherapy protocols for OS and progression-free survival (PFS) for intracranial PCNSL.

Methods

Clinical setting

Oslo University Hospital (OUH) is a tertiary referral center with a catchment area of approximately 3 million inhabitants (56% of the Norwegian population).

Patient cohort

Our prospective databases for brain tumors at Department of Neurosurgery and of lymphomas including PCNSL at the Department of Oncology were searched to identify all patients who underwent neurosurgery (i.e. craniotomy or biopsy) to verify the diagnosis. Inclusion criteria were histologically verified intracranial PCNSL and treatment at OUH between 2003–2014. Exclusion criteria were lymphomas in the intraorbital space, epidural space, and intra-spinal lesions. Disease outside CNS was excluded by CT neck-thorax-abdomen-pelvis and bone marrow biopsy.

Patient-related variables

The medical records of patients were reviewed retrospectively to record parameters of interest not included in the prospective databases. We recorded age, sex, time of surgery, time of death, KPS, LDH, immuno-status, and MSKCC. Time of diagnosis was set as time of surgery. Cut-off for sLDH is age-dependent: for patients ≤ 69 years, sLDH < 205 U/L is regarded as normal, while patients > 69 years has a cut-off of < 255 U/L. Immunocompromise was defined as EBV+, HIV+, TBC+, or previous organ transplantation.

Tumor-related variables

A histopathological diagnosis of PCNSL was made by a consultant pathologist at presentation. All cases were formally re-examined by a dedicated hematology pathologist (KB).

T1-weighted contrast-enhanced MRI images were reviewed by TRM and GJ. The following variables were recorded: tumor location, involvement of deep brain structures (defined as periventricular regions, basal ganglia, corpus callosum, brainstem, and/or cerebellum), maximum visible diameter of the lesion, and number of lesions.

Treatment variables

Surgery was dichotomized into a craniotomy with resection or a biopsy, be it via a biopsy craniotomy, stereotactic procedure, or endoscopic procedure.

Patients were divided into four groups by a hematology oncologist (HH) according to the treatment; Nordic protocol (16), MSKCC protocol with RTX, MSKCC protocol without RTX, and no chemotherapy or palliative treatment. Radiotherapy (RT) was performed in all patients who did not

achieve Complete Response (CR), whereas in case of unclear CR to treatment, watchful surveillance waiting for possible relapse or progression was undertaken. Radiotherapy was only given as part of the primary therapy if the patients did not achieve a remission on systemic therapy.

Outcome

All patients underwent multidisciplinary follow-up for the assessment of outcomes. Vital status and date of death were retrieved from Norwegian Population Registry at 19.12.2016. OS was calculated from time of diagnosis to time of death or censoring. PFS was calculated from time of diagnosis to time of progression or relapse, time of death or censoring.

Response evaluation

Response to treatment was assessed by neuroradiologists on T1-weighted contrast-enhanced MRI images. CR requires complete disappearance of all enhancing abnormalities on MRI in a patient who had discontinued corticosteroids for at least two weeks prior to response evaluation. Partial response (PR) was defined as $\geq 50\%$ decrease in the enhancing lesion as compared to baseline imaging and no new sites of disease. Stable Disease (SD) was defined as less than a PR but more than a progressive disease (PD). PD requires $\geq 25\%$ increase in the enhancing lesion as compared with baseline or best response, or appearance of any new lesion during or at the end of therapy. Relapsed Disease (RD) is regarded as the appearance of any new lesion (17).

Ethics

The study was approved by the Data Protection Office at OUH (2015/16840).

Statistics

Univariate statistics were calculated without assuming a Gaussian distribution using Wilcoxon's test when the variable was continuous. With categorical variables, univariate statistics were calculated using Fisher's exact test. Survival curves were generated using the Kaplan Meier estimator and the log-rank test was used to compare different survival curves. Prognostic factors for OS and PFS were identified using the Cox proportional hazards regression model. Uni- and multivariate Cox regression modeling was used for further survival analysis after ascertaining that the assumptions of proportional hazard were fulfilled. Descriptive statistics were reported as a mean with a 95% confidence interval (CI) or a median with a range, as appropriate. A p-value less than 0.05 was considered significant. For all statistical analysis, the software program JMP (version 9.03, SAS Institute Inc.) was used.

Results

Patient characteristics

Overall, 79 patients with intracranial PCNSL were identified. The female-to-male ratio was 1:1.6, with 30 females (38%) and 49 males (62%). The median age of the cohort was 65.3 years [range 18.9-80.7]. Immunocompromise was present in 10 patients (13%). Twenty-six (33%) patients had elevated sLDH, while 44 patients (56%) had normal sLDH. Eighteen patients (23%) had a KPS of 100, while 22 (28%) had ≤ 50 (Table 1A).

Tumor characteristics

Data on histology of lymphoma was available for every patient. Seventy-seven patients (97%) had a B-cell lymphoma and 2 (3%) had a T-cell lymphoma. Thirty-two patients (40%) had one lesion, 45 patients (60%) had two or more lesions. The mean size of lesions was 40.3 mm (CI 43.7-36.9 mm). Involvement of deep brain structures was shown in 63 patients (80%). (Table 1A).

Treatment

Twenty-two patients received either no chemotherapy or only palliative therapy and were analyzed for OS only (Figure 1). Fifty-seven patients received chemotherapy. The MSKCC protocol with RTX was used in 18 patients (32%). Four patients received only MTX and because of the paucity of cases in this group, the patients were joined to the MSKCC without RTX group (n=25, 44%) for analysis purposes. The Nordic protocol was used in 14 patients (25%) (Figure 1, Table 1B). RT was performed in 6 patients (11%) among subjects treated with chemotherapy, while in the palliative therapy group 7 patients (32%) were irradiated.

Response to treatment

Altogether, 42 patients (74%) achieved a CR after first chemotherapy. Of those, 11 patients underwent Nordic protocol, 17 patients got MSKCC with RTX, and 14 patients received MSKCC without RTX or only MTX. In patients who achieved CR, median OS and median PFS were 46.3 months [range 7.2-157.7] and 34.3 months [range 5.0-157.7], respectively.

Fourteen patients (25%) progressed after first line chemotherapy; 3 from Nordic protocol, 1 patient from MSKCC + RTX, and 10 patients from MSKCC without RTX/only MTX. In patients with PD, median OS and median PFS were 3.9 months [range 0.7-51.3] and 0.0 months [range 0.0-11.8], respectively. In addition, one patient (2%) treated with MSKCC without RTX/only MTX achieved SD (Figure 1).

The 22 patients with biopsy proven PCNSL who received no chemotherapy had a median OS of 1.3 months [range 0.2-9.4] (Table 2).

OS and PFS

We analyzed survival according to active treatment regimens (Figure 2, 3; Table 2). Patients who received the Nordic protocol had OS and PFS of 30.9 months [range 2.7-106.3] and 14.3 months [range 0.0-106.3], respectively. Patients receiving MSKCC with RTX had a median OS of 46.3 months [range 9.8-131.9] and a median PFS of 34.6 months [range 6.4-131.9]. Patients who got MSKCC without addition of RTX or only MTX had an OS of 15.2 months [range 0.7-136.5] and a PFS of 12.0 months [range 0.0-117.0] (Table 2). Lastly, our analysis also showed significantly improved OS ($p<0.05$) in patients treated with RTX versus those who did not. Conversely, prolongation of the PFS was not significant (Figure 4, 5; Table 2).

Prognostic factors for OS and PFS

According to our univariate analysis, sex, deep brain location, chemotherapy regimen, and the addition of RTX to chemotherapy were significant for OS in the cohort of actively treated patients (Table 2). Furthermore, only deep brain involvement was highly significant for both OS and PFS (OS: $p<0.0005$; PFS: $p<0.0001$). All other parameters were not significant. In multivariate analysis, the only prognostic factor for OS and PFS of statistical significance was deep brain involvement ($p<0.005$) (Table 2).

Discussion

In this study, we compared the Nordic and the MSKCC chemotherapy protocols for OS and PFS for intracranial PCNSL. Fifty-seven consecutive patients included in this study received chemotherapy and their median OS and PFS were 35.4 months and 15.7 months, respectively (Table 2). These values are in line with those reported by other authors such as Houillier et al (18) and Ghesquierès et al (19), as well as with the largest randomized phase III study on PCNSL (G-PCNSL-SG-1) by Korfel et al (20).

Age is a well-known negative prognostic factor for PCNSL (21, 22) and in our cohort, 33% of patients were ≥ 70 years. Ney et al. (23) in a large series of patients ≥ 65 years reported an OS similar to ours (median OS 25 months). The encouraging results reported by this author remind us that although the outcome is worse in older patients, this should not preclude the use of chemotherapy since the majority of patients do respond and improve clinically. On the other hand, the cohort presented by Ney et al (23) consisted of selected patients and might not reflect accurately the elderly population in the community. Indeed, the older patients' series reported by Welch et al (24) had far lower survival rates (median OS 7.9 months; median PFS 6.5 months). This effect on survival rates is presumably due to the median age of this cohort which was peculiarly advanced (median age 82 years). However, most patients tolerated therapy well, and despite low baseline creatinine clearance, no significant renal toxicity was noted. Moreover, 3 patients lived more than 4 years after diagnosis. These results suggest that aggressive chemotherapy based on HD-MTX and other well-known chemotherapeutic agents, such as vincristine, temozolomide and procarbazine, may be feasible also in elderly cohorts (65-75 years of age). In the Nordic trial, the elderly patients did as well as the younger ones, presumably due to temozolomide maintenance chemotherapy (15), although this result may be due to a selection bias.

Both MSKCC and IELSG prognostic scoring systems include age (25, 26). However, in multivariate analysis, the only prognostic factor for OS and PFS of statistical significance was deep brain involvement ($p < 0.005$) (Table 2), indicating that the significant difference between the treatment regimens seen in univariate analysis could be due to inequalities in the treatment groups with respect to age or other risk factors. Indeed, 50% of patients who received the Nordic protocol were in MSKCC risk group 3 (worst prognosis) but no patient was in risk group 1 (best prognosis) versus 22% and 17% of those treated with MSKCC with RTX in risk group 3 and 1, respectively (Table 1B). With regard to age, we assume that the lack of statistical significance reported in our study is due to the heterogeneity of the cohort and that a proportion of the elderly are not included in the analysis as they only received palliative treatment. In fact, there are obvious difficulties of administering full systemic PCNSL treatment to elderly patients and to those with comorbidities. Nephrotoxicity and other side-effects can be the cause of postponing chemotherapy courses, or forcing premature treatment interruption. Therefore, this may offer a plausible explanation for why new treatments have not translated into a

survival benefit in the group of PCNSL (27). Furthermore, it is likely that the different types of treatment approaches and also the presence of immunocompromised patients played a role as confounding factors in our analysis.

In our univariate analysis, we found a significant effect of sex on the OS (Table 2). As far as we know, this has not been previously noted in the literature regarding PCNSL. On the other hand, the prognostic impact of sex in B-cell NHL is controversial. Hasselblom et al (28) found in a large series comprising 535 de novo DLBCL patients that male sex had a negative impact on both OS and PFS, independent of International Prognostic Index. In accordance to these findings, a recently published meta-analysis about DLBCL treated with RTX-containing regimens highlighted male gender to be associated with poor prognosis (29). On the other hand, authors questioned the prognostic power of gender in DLBCL. Riihijärvi et al (30) compared two groups of B-cell NHL. Hundred and sixty patients were treated with traditional chemotherapy, while 327 were treated with immunochemotherapy. No difference in survival between the genders was found in the chemotherapy-treated group, while female patients had a better PFS in the immunochemotherapy cohort. These results support the idea that women seem to respond better to RTX, presumably due to a faster RTX clearance in males than in females (31). This conclusion is in contrast to the study published by Takahashi et al (32) who found sex not to be a prognostic factor among DLBCL patients receiving uniform R-CHOP therapy.

According to our analysis, the MSKCC protocol with RTX was superior to the Nordic protocol with respect to OS. However, the most relevant difference was found between MSKCC with RTX and MSKCC without RTX (Figure 2 and 3). The only difference between these two regimens is the addition of the anti-CD20 monoclonal antibody. Interest in adding RTX to standard chemotherapy protocols arose because of its strong activity against DLBCL. Although some authors raised doubts about the capability of RTX of crossing the BBB (13, 18), two recent series (33, 34) showed promising results when RTX was used as first-line treatment in addition to MTX-based-chemotherapy and our results are in accordance with these studies. In fact, in our patients, addition of RTX to MSKCC improved significantly the OS (Figure 4). Furthermore, many protocols nowadays incorporate RTX as a component of the first-line treatment for PCNSL (8). Noteworthy, RTX could be an efficacious treatment also in elderly patients (34). These results are in line with Morris et al. (35) and also other authors support the efficacy of RTX in treating PCNSL (33, 34).

Conclusions

In univariate analysis, the MSKCC with RTX achieved significantly longer median OS compared to the Nordic protocol. However, in multivariate analysis, the only prognostic factor for survival of statistical significance was deep brain involvement.

Strengths and limitations of the study

Our prospective cohort represents one of the largest single-center series available in literature and has complete follow-up for all patients. Moreover, due to the centralized administration of chemotherapy, our data on treatment are homogeneous. However, the patients received various treatment protocols due to the length of the inclusion period (2003-2014) and the treatment was not randomized. Data about systemic and neurological toxicity of treatments were incomplete and thus not included in this study. Due to the paucity of patients (5%) who received only MTX, these patients were joined to the MSKCC without RTX group (n=25, 31%) for analysis purposes, something that may have exaggerated the difference between the MSKCC with RTX and MSKCC without RTX protocols. Despite being a large series, the number of patients in the statistical analyses is low and may give source to type II statistical errors. Recent data support the inclusion of tiotepa in the chemotherapy regimen, which was not used for our patients (36). Lastly, autologous stem-cell transplantation, which allows for more aggressive treatment with high-dose chemotherapy (37-39), were not studied.

Compliance with ethical standards

Informed consent: For this type of study formal consent is not required.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Conflict of Interest and Sources of Funding Statement

The authors declare that they have no conflict of interest.

Only in-house sources were used.

List of legends

Figure 1. Patient treatments and responses.

CR: complete response; MSKCC: Memorial Sloan-Kettering Cancer Center; MTX: methotrexate; PD: progressive disease; RT: radiotherapy; RTX: rituximab; SD: stable disease. Values for median with range in brackets.

Figure 2. Overall Survival by active treatment protocol.

MTX: methotrexate; OS: Overall Survival; RTX: rituximab.

Figure 3. Progression-Free Survival by active treatment.

MTX: methotrexate; PFS: Progression-Free Survival; RTX: rituximab.

Figure 4. Overall Survival by Rituximab

OS: Overall Survival; RTX: rituximab.

Figure 5. Progression-Free Survival by Rituximab.

PFS: Progression-Free Survival; RTX: rituximab.

Table 1A. Overall patient and tumor characteristics.

KPS: Karnofsky performance status; MSKCC: Memorial Sloan-Kettering Cancer Center.

Table 1B. Patient and tumor characteristics by chemotherapy regimen.

KPS: Karnofsky performance status; MSKCC: Memorial Sloan-Kettering Cancer Center.

Table 2. Univariate and multivariate analyses.

ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan-Kettering Cancer Center; MTX: methotrexate; NS: not significant; OS: Overall Survival; PFS: Progression-Free Survival; RTX: Rituximab.

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Table 1A – Overall Patient and Tumor Characteristics

	n	%
Patient characteristics		
Sex		
Male	49	62
Female	30	38
Age		
<50 years	6	8
≥50 years	73	92
≥60 years	55	70
≥70 years	26	33
Immunodeficiency		
Yes	10	13
No	69	87
sLDH		
Elevated	13	17
Not elevated	57	72
ECOG		
0	18	23
≥1	61	77
KPS		
≥70	39	49
<70	40	51
IELSG score		
0	5	6
1	12	15
2	21	27
3	28	35
4	3	4
5	0	0
MSKCC score		
Risk group 1	6	8
Risk group 2	35	44
Risk group 3	38	48
Tumor characteristics		
Histology		
B-Cell lymphoma	77	97
T-Cell lymphoma	2	3
Multiplicity		
1	32	40
2-4	38	48
≥5	7	9
Size		
≤30 mm	23	29
>30 mm	51	65
>40 mm	36	46
>50 mm	21	27
Deep brain structures		
Involved	63	80
Not involved	16	20

Table 1B –Patient and Tumor Characteristics by Chemotherapy Regimen

	MSKCC with RTX	MSKCC without RTX	Nordic	All protocols
Patient characteristics	18 (32%)	25 (44%)	14 (25%)	57 (100%)
Sex				
Male	7 (39%)	22 (88%)	8 (57%)	37 (65%)
Female	11 (61%)	3 (12%)	6 (43%)	20 (35%)
Age				
<50 years	3 (17%)	2 (8%)	0 (0%)	5 (9%)
≥50 years	15 (83%)	23 (92%)	14 (100%)	52 (91%)
≥60 years	8 (44%)	19 (76%)	9 (64%)	36 (63%)
≥70 years	3 (17%)	8 (32%)	1 (7%)	12 (21%)
Immunodeficiency				
Yes	5 (28%)	1 (4%)	0 (0%)	6 (11%)
No	13 (72%)	24 (96%)	14 (100%)	51 (89%)
sLDH				
Elevated	8 (44%)	5 (20%)	5 (36%)	18 (32%)
Normal	10 (56%)	20 (80%)	9 (64%)	39 (68%)
ECOG				
0	6 (33%)	4 (16%)	6 (43%)	16 (28%)
≥1	12 (67%)	21 (84%)	8 (57%)	41 (72%)
KPS				
≥70	13 (72%)	14 (56%)	7 (50%)	34 (60%)
<70	5 (28%)	11 (44%)	7 (50%)	23 (40%)
IELSG score				
0	3 (17%)	1 (4%)	1 (7%)	5 (9%)
1	4 (22%)	5 (20%)	2 (14%)	11 (19%)
2	4 (22%)	8 (32%)	4 (29%)	16 (28%)
3	6 (33%)	10 (40%)	7 (50%)	23 (40%)
4	1 (6%)	1 (4%)	0 (0%)	2 (4%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MSKCC score				
Risk group 1	3 (17%)	2 (8%)	0 (0%)	5 (9%)
Risk group 2	11 (61%)	10 (40%)	7 (50%)	28 (49%)
Risk group 3	4 (22%)	13 (52%)	7 (50%)	24 (42%)
Tumor characteristics				
Histology				
B-Cell lymphoma	18 (100%)	25 (100%)	14 (100%)	57 (100%)
T-Cell lymphoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiplicity				
1	11 (61%)	19 (76%)	8 (57%)	38 (67%)
2-4	4 (22%)	1 (4%)	3 (21%)	8 (14%)
≥5	3 (17%)	5 (20%)	3 (21%)	11 (19%)
Size				
≤30 mm	6 (33%)	3 (12%)	5 (36%)	14 (25%)
>30 mm	12 (67%)	19 (76%)	9 (64%)	40 (70%)

>40 mm	7 (39%)	16 (64%)	7 (50%)	30 (53%)
>50 mm	2 (11%)	11 (44%)	4 (29%)	17 (30%)
Deep brain structures				
Involved	13 (72%)	19 (76%)	11 (79%)	43 (75%)
Not involved	5 (28%)	6 (24%)	3 (21%)	14 (25%)

Table 2 – Univariate and Multivariate Analyses

	n	Overall Survival in months (median [range])	P-value for OS	Progression-Free Survival in months (median [range])	P-value for PFS
Overall	79	16.4 [0.2-157.7]		9.8 [0.0-157.7]	
Active therapy	57	35.4 [0.7-136.5]		15.7 [0.0-131.9]	
No chemotherapy	22	1.3 [0.2-9.4]		-	
Sex					
Male	37	24.3 [0.7-136.5]	<0.05	12.9 [0.0-117.0]	NS
Female	20	57.6 [7.2-131.9]		44.3 [0.0-131.9]	
Age					
<50 years	5	72.9 [0.9-131.9]	NS	63.4 [0.0-131.9]	NS
≥50 years	52	34.3 [0.7-136.5]		13.6 [0.0-117.0]	
<60 years	21	35.4 [0.9-131.9]	NS	28.5 [0.0-131.9]	<0.05
≥60 years	36	35.0 [0.7-136.5]		11.3 [0.0-90.7]	
<70 years	45	33.9 [0.7-136.5]	NS	15.7 [0.0-131.9]	NS
≥70 years	12	38.3 [1.2-69.4]		24.9 [0.0-67.3]	
Immunodeficiency					
Yes	6	71.1 [3.9-131.9]	NS	55.4 [3.2-131.9]	NS
No	51	33.9 [0.7-136.5]		13.8 [0.0-117.0]	
sLDH					
Elevated	18	30.5 [0.9-108.9]	NS	14.6 [0.0-108.9]	NS
Normal	39	39.8 [0.7-136.5]		15.7 [0.0-131.9]	
ECOG					
0	16	54.9 [0.7-131.9]	NS	41.1 [0.0-131.9]	<0.05
≥1	41	27.6 [0.9-136.5]		12.4 [0.0-108.9]	
Deep brain structures					
Involved	43	24.3 [0.7-136.5]	<0.0005	11.8 [0.0-117.0]	<0.0001
Not involved	14	64.9 [15.2-131.9]		63.5 [13.8-131.9]	
Multiplicity					
1	38	37.0 [0.7-136.5]	NS	14.8 [0.0-131.9]	NS
2-4	8	68.3 [16.4-88.0]		55.4 [7.4-88.0]	
≥5	11	24.3 [1.2-79.1]		12.9 [0.0-56.4]	
Size					
<30 mm	14	26.0 [5.6-108.9]	NS	19.5 [3.7-108.9]	NS
≥30 mm	40	39.2 [0.7-136.5]		14.5 [0.0-131.9]	
≥40 mm	31	39.8 [0.7-108.9]		15.7 [0.0-131.9]	
≥50 mm	17	39.8 [3.0-136.5]		15.7 [0.0-117.0]	
Active therapy protocol					
Nordic	14	30.9 [2.7-106.3]	<0.05	14.3 [0.0-106.3]	NS
MSKCC + RTX	18	46.3 [9.8-131.9]		34.6 [6.4-131.9]	
MSKCC – RTX/only MTX	25	15.2 [0.7-136.5]		12.0 [0.0-117.0]	
RTX					
Yes	32	41.6 [2.7-131.9]	<0.05	24.7 [0.0-131.9]	NS
No	25	15.2 [0.7-136.5]		12.0 [0.0-117.0]	

Multivariate analysis		
Age	NS	NS
KPS	NS	NS
Deep brain structures	<0.005	<0.01
Active treatment regimens		
Nordic	NS	NS
MSKCC + RTX	NS	NS
MSKCC - RTX	NS	NS

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5