Challenges with hippocampal MR spectroscopy as a surrogate for pre-radiotherapy assessment of neurocognitive impairment in patients with brain metastasis

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Aim. Patients with multiple brain metastases (BM) benefit from hippocampal-avoiding whole brain radiotherapy (HA-WBRT), the challenging and less available form of WBRT. This study explores potential of pre-radiotherapy (pre-RT) hippocampal magnetic resonance spectroscopy (MRS) measuring hippocampal neuronal density as an imaging surrogate and predictive tool for assessing neurocognitive functions (NCF).
Methods. 43 BM patients underwent pre-RT hippocampal MRS. N-acetyl aspartate (NAA) concentration, a marker for neuronal density (weighted by creatine (Cr) and choline (Cho) concentrations), and neurocognitive function (NCF) tests (HVLT and BVMT) performed by certified psychologists were evaluated. Clinical variables and NAA concentrations were correlated with pre-RT NCFs.
Results. HVLT and BVMT subtests showed pre-RT deterioration except for BVMT recognition. Significantly better NCFs were observed in women in HVLT subsets. Significantly higher NAA/Cr + Cho was measured in women (median 0.63 vs. 0.55; *P*=0.048) in the left hippocampus (no difference in the right hippocampus). In men, a positive correlation (0.51, *P*=0.018) between total brain volume and HVLT-TR, between left hippocampal NAA/Cr + Cho and HVLT-R (0.45, *P*=0.063), and between right hippocampal NAA/Cr + Cho and BVMT-recognition (0.49, *P*=0.054) was observed. In women, a borderline significant negative correlation was observed between left hippocampal NAA/Cr + Cho and BVMT-TR (−0.43, *P*=0.076) and between right NAA/Cr + Cho and HVLT-DR (−0.42, *P*=0.051).
Conclusion. Borderline statistically significant correlations were observed with speculative interpretation underlying the challenges of hippocampal MRS as a surrogate for neurocognitive impairment. Further studies need to be done to ascertain the opportunities for imaging predictors of benefit from memory sparing radiotherapy.

Key words: hippocampus, MR spectroscopy, neurocognitive function, radiotherapy

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INTRODUCTION

Radiotherapy (RT) is still the cornerstone in the management of patients suffering from brain metastases (BM). RT is indicated for almost all patients with BM, including those before/after surgery as well as for those with asymptomatic BM suitable for upfront targeted therapy or immunotherapy (deferred RT in the case of later recurrence)[1-5]. The current portfolio of widely available RT techniques for personalized RT approaches includes stereotactic radiosurgery (SRS), stereotactic fractionated radiotherapy (FSRT) to single or multiple lesions, and hippocampus avoiding whole brain radiotherapy (HA-WBRT) or whole brain radiotherapy (WBRT) alone[6-8]. All mentioned treatments may be delivered by several available RT systems[9].

According to the current ASTRO Clinical Practice Guidelines, WBRT is a reasonable option without suggested alternatives for patients with limited as well as extensive BM, who have ECOG performance status 3–4, systemic disease with poor systemic therapy options, and

with BM symptoms not controlled by steroids[4]. In the case of extensive BM, the WBRT is recommended without any other alternative also for those with ECOG performance status 3–4, absent or stable systemic disease or reasonable systemic therapy options, and with all BM smaller than 4 cm or larger in the case of contraindication to neurosurgery[10]. Nevertheless, with tremendous improvements in supportive and end-of-life care, a proportion of these patients may live after WBRT for several months, long enough to develop post-WBRT cognitive impairment.

Significant differences in the complexity of treatment preparation and administration between HA-WBRT and simple WBRT may be one of the reasons that WBRT is still recommended in the above-defined groups of patients as well as in patients who should otherwise receive HA-WBRT (ref.[11]). Even with all current tools for autosegmentation and tools enabling faster treatment planning, limitations of human resources are essential in the clinical practice in daily decision-making regarding treatment procedures. Biomarkers are urgently needed to identify patients who may derive maximal benefit from complex HA-WBRT. It is crucial to determine for whom the performance of expensive and intricate HA-WBRT techniques is most worthwhile, particularly in the context of daily routine personalized RT for patients with multiple BM diseases. This need is particularly urgent in countries with limited resources.

Our previous prospective magnetic resonance in-vivo spectroscopy (MRS) study described a decrease in the hippocampal concentration of N-acetylaspartate (NAA, marker of neuronal density and viability) in response to WBRT (ref.[12,13]). In the present study, patients indicated to SRS or FSRT underwent pre-RT neurocognitive function (NCF) testing and MRS focused on both hippocampi to evaluate the pre-RT NAA concentration (before RT and, thus, without bias of proven post-RT neuronal depletion). The aim is to assess the relationship between pre-RT neuronal density and pre-RT verbal and spatial memory.

MATERIAL AND METHODS

Patients‘ cohorts

Analyzed patients were enrolled in the prospective study, in which they irradiated for BM between May 2018 and May 2021, using SRS or FSRT. Inclusion criteria included measurable BM outside a 5-mm margin around either hippocampus on pre-RT contrast-enhanced T1-weighted MRI, the indication of SRS/FSRT alone for intact BM, and an indication of post-surgery SRS/FSRT. Further inclusion criteria were age ≥18 years, Karnofsky performance status ≥ 70%, and favorable survival prognosis of more than 3.8 months as predicted by the graded prognostic assessment score[14]. Patients with leptomeningeal disease, a history of neurological or psychiatric disease, patients with hippocampal MRI pathology found during pretreatment MRI, those with prior RT to the brain, patients suffering from severe active comorbidities affecting the performance of NCF testing, or having a contraindication to MRI imaging including severe claustrophobia were excluded. All patients meeting eligibility criteria were offered study registration, and after signing informed consent, patients were scheduled for pre-RT MRS and NCF testing.

This study was approved by the Institutional Ethical Committee (2017/1896/MOU), and all patients provided their written informed consent before study enrollment. This research has been performed in accordance with the Declaration of Helsinki.

Hippocampal MR Spectroscopy

Spectroscopic data by SVS (single voxel spectroscopy) technique was obtained before contrast agent administration using GE Medical Systems Discovery MR 750 3T (PRESS-SVS sequence with TE/TR =144 ms/1500 ms, 128 averages, voxel volume: 3 mL) at the Department of Medical Imaging, St. Anne's University Hospital Brno. Spectra were obtained from hippocampal areas. Postprocessing of raw spectroscopic data was performed using the LCModel for the calculation and final reporting of hippocampal total NAA absolute concentration [mM], creatine (Cr) and choline (Cho) in order to calculate the normalized ratio hippocampal-NAA/Cr + Cho as a most reproducible ratio for hippocampal MRS (ref.[15,16]).

Utilizing the same MRS study, the hippocampal volumes as a potential confounding factor for NCF were manually contoured using software EclipseTM (Varian medical systems, Palo Alto, CA, USA) with reference to RTOG hippocampal contouring online atlas[17]. Considering age and sex differences in hippocampal volumes, a corrected hippocampal volume (c-HV ratio) was calculated as a ratio of the hippocampal volume to the total brain volume (TBV) (ref.[18]).

Neurocognitive function testing

Attention was focused on verbal and visual memory impairment testing as the main affected neurocognitive domains by RT. Patients underwent the HVLT-Revised test (Hopkins Verbal Learning Test-Revised) by listening to 12 different words and repeating them for 3 consecutive attempts (total recall – TR), recalling them after 25 min (delayed recall – DR), and finally recognizing them among 24 words (recognition – R). BVMT-Revised (Brief Visuospatial Memory Test-Revised) test consisted of memorizing and drawing six geometric figures for three consecutive attempts (TR), subsequently recalling them after 25 min (DR), and finally determining them among the list of provided similar figures (recognition discrimination index DI). All cognitive tests were performed by certified psychologists. Raw data were normalized using age-specific scores to correct for age effects and expressed as individual Z-scores[19].

Statistical analysis

Patient and treatment characteristics were described using the standard summary statistics, i.e., median and interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. For the MRS and NCF testing results, mean and standard deviation (SD) were additionally considered. Depending on

the nature of the data, Fisher's exact or chi-square test for categorical variables and nonparametric Mann-Whitney test for continuous variables were used to compare differences between men and women. Spearman correlation coefficient was considered to describe the relation of NAA concentrations, NCF scores, and brain volumes. A significance level of 5% was considered, and R statistical software version 4.3.1 was used.

RESULTS

Patients and treatment characteristics

A total of 43 patients (median age 65 years, 22 women) were enrolled in this study and underwent pre-RT MRS as well as NCF testing. The most common primary diagnosis was non-small cell lung cancer (21 patients), and the majority of patients had single brain metastasis. All patients were indicated to local stereotactic RT, and

Table 1. Patients and treatment characteristics.

	Overall, n=43	**Women**, n=22	**Men**, n=21	***P***
Age (years)				0.204
Median (IQR)	65 (56–72)	63 (54–69)	68 (61–74)	
Range	29, 85	29, 85	47, 78	
>65	21 (49%)	8 (36%)	13 (62%)	0.094
KPS				0.426
70	7 (16%)	4 (18%)	3 (14%)	
80	18 (42%)	11 (50%)	7 (33%)	
90	16 (37%)	7 (32%)	9 (43%)	
100	2 (4.7%)	0 (0%)	2 (9.5%)	
Handedness				
Left	2 (4.7%)	1 (4.5%)	1 (4.8%)	
Right	41 (95%)	21 (95%)	20 (95%)	
Primary diagnosis				
NSCLC	21 (49%)	9 (41%)	12 (57%)	
Breast cancer	5 (12%)	5 (23%)	0 (0%)	
GI cancer	3 (7.0%)	2 (9.1%)	1 (4.8%)	
Melanoma	5 (12%)	3 (14%)	2 (9.5%)	
RCC	5 (12%)	0 (0%)	5 (24%)	
Other	4 (9.3%)	3 (14%)	1 (4.8%)	
Number of BM				
1	29 (67%)	13 (59%)	16 (76%)	
2	6 (14%)	3 (14%)	3 (14%)	
3	6 (14%)	5 (23%)	1 (4.8%)	
4	2 (4.7%)	1 (4.5%)	1 (4.8%)	
Sum volume of BM (cm^3)				0.648
Median (IQR)	1.6 (0.8–4.2)	1.7 (1.0–3.6)	1.2 (0.5–5.9)	
Range	0.1, 47.2	0.1, 47.2	0.2, 16.9	
Unknown	13	7	6	
GPA				0.412
Median (Range)	2.5 (1–4)	2.5 (1–4)	2 (1.5–3.5)	
Unknown	5	3	2	
Supratentorial mts	40 (93%)	20 (91%)	20 (95%)	>0.999
Temporal mts	6 (14%)	2 (9.1%)	4 (19%)	0.412
Extracranial mts	19 (44%)	9 (41%)	10 (48%)	0.658
Extracranial disease status				0.230
CR–NED	13 (30%)	8 (36%)	5 (24%)	
PD	15 (35%)	5 (23%)	10 (48%)	
PR–SD	15 (35%)	9 (41%)	6 (29%)	
Systemic treatment prior to RT	21 (49%)	13 (59%)	8 (38%)	0.169
Pre-RT surgery	22 (51%)	14 (64%)	8 (38%)	0.094
Controlled primary tumor	23 (53%)	13 (59%)	10 (48%)	0.451
Radiotherapy type				0.594
FSRT	36 (84%)	19 (86%)	17 (81%)	
SRS	4 (9.3%)	1 (4.5%)	3 (14%)	
Other	3 (7.0%)	2 (9.1%)	1 (4.8%)	
Corticosteroids during or 1 week after RT	33 (77%)	15 (68%)	18 (86%)	0.281

IQR, interquartile ratio; KPS, Karnofsky performance status; NSCLC, non-small cell lung cancer; GI, gastrointestinal; RCC, renal cell carcinoma; BM, brain metastases; GPA, graded prognostic assessment; mts, metastases; CR-NED, complete response – no evidence of disease; PD, progressive disease; PR-SD, partial response-stable disease; RT, radiotherapy; FSRT, fractionated stereotactic radiotherapy; SRS, stereotactic radiosurgery.

the majority underwent FSRT. The other basic patients, BM, and treatment characteristics are summarized in Table 1. For these variables, no significant differences were observed.

The median total brain volume was 1371 cm^3 and was significantly larger in men than women (median 1433 vs. 1274 cm^3; $P<0.001$) with no difference in total hippocampal volume (median 4.40 vs. 4.28 cm^3) as well as in left and right hippocampi. Total c-HV ratio was slightly, but significantly, larger in women (median 0.0035 vs. 0.0031; $P=0.047$). The volume data are summarized in Table 2.

Neurocognitive function

For all patients, all HVLT and BVMT subtests showed a deterioration in pre-RT performance except for BVMT-DI (median Z-score 0.25; 95%CI −2.83, 0.50). Significantly better NCFs were observed in women. Specifically, women had higher scores for all HVLT subsets (HVLT-TR $P=0.006$, HVLT-D $P=0.005$, and HVLT-R $P=0.015$). Data are presented in Table 3.

Hippocampal MRS

A borderline significantly higher NAA/Cr + Cho ratio was measured in women (median 0.63 vs. 0.55; $P=0.048$) in the left hippocampus, with no difference between men and women in the right hippocampus ($P=0.134$). All measured data are presented in Table 4.

MRS and NCF correlation

Correlation coefficients between c-HV ratios, total brain volume, NAA/Cr +Cho ratios, and NCFs are summarized in Fig. 1. as heat maps (more detailed in Supplementary Tables S1 and S2). Particularly in women, a positive correlation was observed between subtests within HVLT or BVMT. In the cohort of men, a positive correlation (0.51, $P=0.018$) between total brain volume and HVLT-TR was observed. A slight positive correlation was also between the left hippocampal NAA/Cr + Cho ratio and HVLT-R (0.45, $P=0.063$) and between the right hippocampal NAA/Cr + Cho ratio and BVMT-recognition expressed as BVMT-DI (0.49, $P=0.054$). In the cohort of women, slight negative correlations were between the right hippocampal NAA/Cr + Cho ratio and HVLT-DR (−0.42, $P=0.051$) and between the left hippocampal NAA/Cr + Cho ratio and BVMT-TR (−0.43, $P=0.076$).

Table 2. Brain and hippocampi volumes.

	Overall, n=43	**Women**, n=22	**Men**, n=21	***P***
TBV (cm^3)				**<0.001**
Mean (SD)	1367 (121)	1285 (93)	1454 (79)	
Median (IQR)	1371 (1274–1450)	1274 (1218–1341)	1433 (1406–1496)	
Range	1090–1619	1090–1492	1323–1619	
Left HV (cm^3)				0.808
Mean (SD)	2.22 (0.62)	2.29 (0.49)	2.15 (0.74)	
Median (IQR)	2.20 (1.90–2.62)	2.09 (1.91–2.68)	2.24 (1.80–2.44)	
Range	0.60, 3.60	1.64–3.30	0.60–3.60	
Right HV (cm^3)				0.884
Mean (SD)	2.32 (0.57)	2.31 (0.55)	2.32 (0.61)	
Median (IQR)	2.17 (2.01–2.70)	2.24 (1.97–2.77)	2.10 (2.09–2.66)	
Range	1.30, 3.60	1.30–3.20	1.40–3.60	
Total HV (cm^3)				0.780
Mean (SD)	4.54 (1.11)	4.60 (0.96)	4.47 (1.26)	
Median (IQR)	4.33 (3.82–5.26)	4.28 (3.87–5.38)	4.40 (3.80–5.10)	
Range	2.20, 7.00	3.20–6.50	2.20–7.00	
Left c-HV ratio				0.157
Mean (SD)	0.0016 (0.0004)	0.0018 (0.0003)	0.0015 (0.0005)	
Median (IQR)	0.0016 (0.0015–0.0019)	0.0017 (0.0015–0.0020)	0.0016 (0.0012–0.0017)	
Range	0.0004–0.0025	0.0014–0.0025	0.0004–0.0022	
Right c-HV ratio				0.087
Mean (SD)	0.0017 (0.0004)	0.0018 (0.0004)	0.0016 (0.0004)	
Median (IQR)	0.0017 (0.0014–0.0020)	0.0018 (0.0016–0.0021)	0.0015 (0.0014–0.0018)	
Range	0.0010–0.0024	0.0010–0.0024	0.0010–0.0023	
Total c-HV ratio				**0.047**
Mean (SD)	0.0033 (0.0008)	0.0036 (0.0006)	0.0031 (0.0008)	
Median (IQR)	0.0033 (0.0028–0.0038)	0.0035 (0.0032–0.0039)	0.0031 (0.0026–0.0034)	
Range	0.0015–0.0048	0.0025–0.0048	0.0015–0.0044	

TBV, total brain volume; SD, standard deviation; IQR, interquartile range; HV, hippocampal volume; c-HV ratio, corrected hippocampal volume.

Table 3. Results of pre-radiotherapy NCF testing in patients with brain metastases.

	Overall, n=43	**Women**, n=22	**Men**, n=21	***P***
HVLT-TR				0.006
Mean (SD)	−1.34 (1.37)	−0.76 (1.05)	−1.95 (1.43)	
Median (IQR)	−1.26 (−2.33–−0.41)	−0.54 (−1.63–0.05)	−1.65 (−2.84–−0.88)	
Range	−5.00, 1.04	−2.58–1.04	−5.00–0.46	
HVLT-DR				0.005
Mean (SD)	−1.92 (1.71)	−1.17 (1.59)	−2.71 (1.49)	
Median (IQR)	−1.78 (−3.06–−0.83)	−1.00 (−2.11–−0.18)	−2.89 (−3.71–−1.41)	
Range	−5.44–1.22	−4.33–1.22	−5.44–−0.18	
HVLT-R				0.015
Mean (SD)	−1.88 (2.70)	−0.95 (1.95)	−2.82 (3.06)	
Median (IQR)	−1.30 (−3.79–0.25)	0.25 (−1.67–0.56)	−2.25 (−4.30–−0.56)	
Range	−12.78–0.70	−5.00–0.70	−12.78–0.70	
Unknown	1	1	0	
BVMT-TR				0.120
Mean (SD)	−0.18 (1.24)	0.20 (1.21)	−0.57 (1.18)	
Median (IQR)	−0.22 (−1.13–0.67)	−0.10 (−0.77–1.01)	−0.33 (−1.45–0.37)	
Range	−2.76–2.56	−1.49–2.56	−2.76–1.12	
Unknown	3	2	1	
BVMT-DR				0.054
Mean (SD)	−0.18 (1.08)	0.16 (0.95)	−0.53 (1.11)	
Median (IQR)	−0.15 (−1.14–0.77)	0.25 (−0.67–0.90)	−0.73 (−1.48–0.40)	
Range	−2.10–1.62	−1.62–1.62	−2.10–1.32	
Unknown	3	2	1	
BVMT-DI				0.404
Mean (SD)	−1.60 (3.35)	−1.14 (2.90)	−2.06 (3.76)	
Median (IQR)	0.25 (−2.83–0.50)	0.25 (−2.42–0.50)	−0.46 (−2.83–0.50)	
Range	−14.50–2.17	−9.50–2.17	−14.50–0.50	
Unknown	7	4	3	

HVLT-TR, Hopkins Verbal Learning Test-total recall; SD, standard deviation; IQR, interquartile range; HVLT-DR, Hopkins Verbal Learning Test-delayed recall; HVLT-R, Hopkins Verbal Learning Test–recognition; BVMT-TR, Brief Visuospatial Memory Test-total recall; BVMT-DR, Brief Visuospatial Memory Test-delayed recall; BVMT-DI, Brief Visuospatial Memory Test-discrimination index.

Table 4. Pre-radiotherapy single voxel hippocampal MRS measurement results in patients with brain metastases.

	Overall, n=43	**Women**, n=22	**Men**, n=21	***P***
NAA/Cr + Cho left H				0.048
Mean (SD)	0.59 (0.11)	0.63 (0.12)	0.56 (0.09)	
Median (IQR)	0.58 (0.50–0.67)	0.63 (0.54–0.71)	0.55 (0.48–0.63)	
Range	0.41–0.84	0.41–0.84	0.44–0.76	
Unknown	5	2	3	
NAA/Cr + Cho right H				0.134
Mean (SD)	0.64 (0.14)	0.67 (0.15)	0.60 (0.11)	
Median (IQR)	0.61 (0.54–0.72)	0.65 (0.56–0.74)	0.58 (0.53–0.66)	
Range	0.43–0.98	0.44–0.98	0.43–0.89	
Unknown	2	0	2	

NAA/Cr + Cho, N-acetyl aspartate, creatine and choline ratio; H, hippocampus; SD, standard deviation; IQR, interquartile range.

DISCUSSION

In this study, we aimed to assess the potential of hippocampal MRS in predicting the status of NCFs before RT. We observed borderline significant correlations between hippocampal NAA/Cr + Cho ratio and some NCF tests, with the opposite manner in men (positive correlation between left hippocampal MRS and HVLT and between right hippocampal MRS and BVMT, respective) and women (negative correlations). Altogether, the interpretation of these observations is self-limited by numerous confounding factors, which are natural for this study population of patients suffering from pre-treated advanced cancer disease with BM. On the other hand, to the best of our knowledge, our study constitutes the largest cohort of patients with BM, who underwent baseline NCF

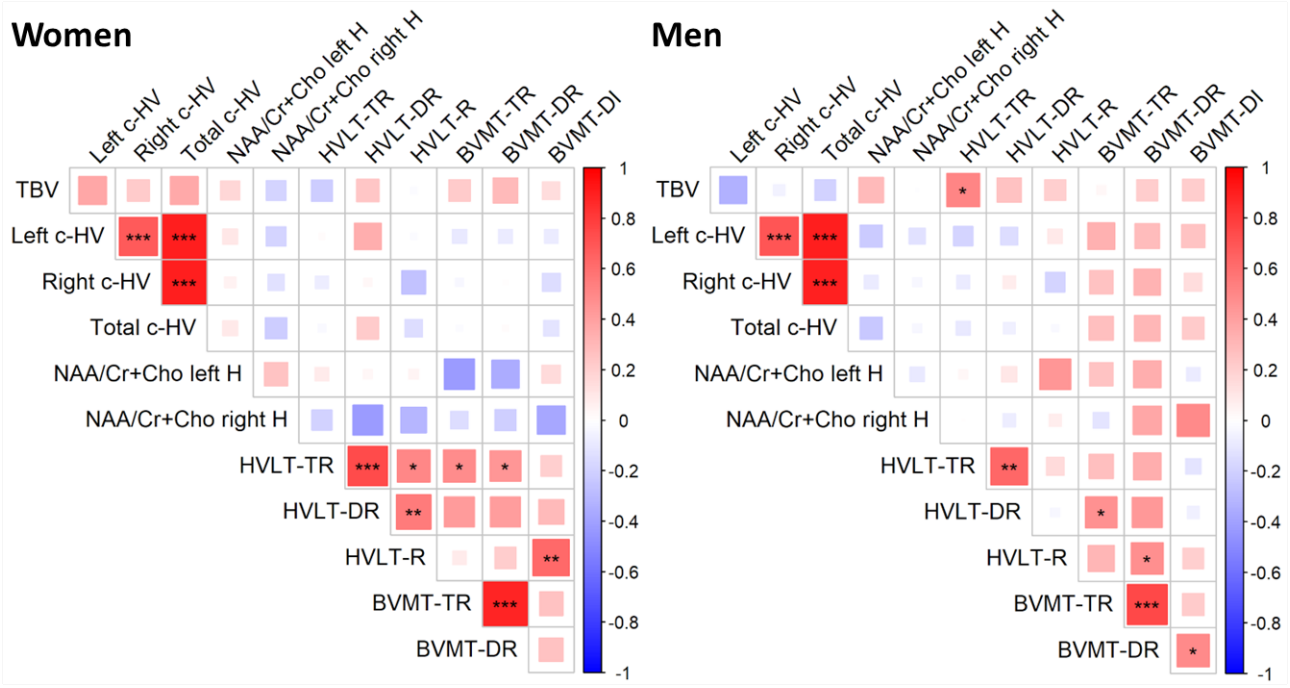

Fig. 1. Correlation of hippocampal and total brain volumes, NAA/Cr + Cho ratios, and NCFs separately for women and men. The size and color intensity of the square correspond to the correlation coefficient. The stars determine the statistical significance of the correlations (*P<0.05, **P<0.01, ***P<0.001) TBV, total brain volume; c-HV, corrected hippocampal volume ratio; NAA/Cr + Cho, N-acetyl aspartate, creatine and choline ratio; H, hippocampus; HVLT-TR, Hopkins Verbal Learning Test-total recall; HVLT-DR, Hopkins Verbal Learning Test-delayed recall; HVLT-R, Hopkins Verbal Learning Test–recognition; BVMT-TR, Brief Visuospatial Memory Test-total recall; BVMT-DR, Brief Visuospatial Memory Test-delayed recall; BVMT-DI, Brief Visuospatial Memory Test-discrimination index.

measurements (performed by certified psychologists) and hippocampal MRS prior to RT, thereby minimizing potential biases associated with post-radiation NCF alterations. For this reason, we also enrolled patients with limited BM indicated to local targeted RT to avoid potential bias of NCF alteration related to multiple BM. Consequently, our cohort stands as a unique model for exploring potential correlations, just as in the presented study.

Quality of life and cognitive function are currently considered the most important outcomes in the palliative therapy of BM. In fact, these are the primary outcomes in pivotal phase III studies that define the current standard of care, with survival outcomes considered secondary ones. For patients with multiple BM, the HA-WBRT is currently recommended based on the results of the CC001 study, where the HA-WBRT combined with the N-methyl-D-aspartate (NMDA) receptor antagonist memantine was associated with a significantly lower risk of cognitive failure (adjusted hazard ratio, 0.74; P=0.02) comparing to WBRT+memantine[20]. According to these results, the complex HA-WBRT technique should be considered for all patients with multiple BM, who are unsuitable for targeted stereotactic radiotherapy, especially those with an estimated survival of at least 4 months, as indicated by the observed NCF decline curve separation in CC001 trial. However, it's important to emphasize that in routine clinical practice in treating multiple brain metastases, HA-WBRT is not frequently used, possibly due to its complexity compared to simple whole-brain radiotherapy[21-25]. Barriers to integrating these modern techniques into routine clinical practice were currently described by Jairam et al. in their online survey of all American Society for Radiation Oncology-registered radiation oncologists (excluding trainees), regarding their practice patterns and attitudes toward employing memantine and HA-WBRT. Out of 417 respondents, almost one-third do not offer hippocampal avoidance for patients indicated to WBRT. Common reasons for not offering HA-WBRT included resource-intensive treatment planning, treatment delay, and concern about obtaining prior authorization[26].

The baseline pre-RT state of NCFs may be crucial in determining the most appropriate RT technique for individual patients with multiple BM. While evaluating the quality of life using questionnaires is relatively efficient and easy for data collection and interpretation, conducting a more comprehensive assessment of neurocognitive functions, particularly regarding the most important verbal and spatial memory, can be more demanding for both patients and medical personnel. Therefore, the search for surrogates and predictive tools of these NCF tests remains of significant clinical relevance. On the other hand, any such surrogate test should be simple to perform and not burden patients too much. For that reason, we focused on single-voxel MRS rather than more complex MRS techniques such as Multi-voxel Chemical Shift Imaging. It is challenging for patients with brain metastases to pass various NCF tests. Even in the frame of motivated patients participating in the prospective study (let alone in routine

clinical practice), nearly half of the patients from CC001 trial evaluated at 12 months post-RT refused consent or did not complete the HVLT (at 12 months, a total of 114 completed WBRT, 307 died, and 97 did not complete the HVLT) (ref.[8]).

Several secondary analyses derived from the phase II RTOG 0933 study[18], that preceded CC001, were conducted with the intent to disclose possible NCF surrogates, similar to our study. Abraham et al. evaluated baseline hippocampal volume with NCF and observed that larger c-HV ratio was positively associated with improved performance at baseline and 4-month HVLT-R scores in patients with brain metastases undergoing HA-WBRT, but was not associated with change in NCF (ref.[18]). In our study, with comparable volumes of brain and c-HV ratio, but with different study population, no unambiguous and across different domains correlation was observed between hippocampal volumes and NCF. Another secondary analysis of RTOG 00933 evaluated the initial volume of MRI-determined white matter injury when a larger volume of this damage predicted memory impairment after HA-WBRT, suggesting a mechanism of RT-induced neurocognitive toxicity may also be independent of hippocampal stem cell radiosensitivity[27]. However, the depletion of neuronal stem cells localized in the hippocampal region is still considered one of the most important causes of sequential neurocognitive deterioration after RT and provides the basis for current HA-WBRT techniques[28]. Therefore, we focused our study on changes in the hippocampal region.

Given the multitude of possible confounding factors involved in neurocognitive functioning in cancer patients, the interpretation of our and all other similar observations is burdened with a variety of biases and, as such, is always speculative. Consistent with the assumption that the left hippocampus is more involved in processes associated with verbal memory and the right hippocampus with spatial memory, we observed a borderline significant positive correlation in men between neuronal depletion in the respective hippocampi and the impairment in the HVLT or BVMT, respectively[29]. Women in our cohort performed better pre-RT NCF in all evaluated domains as well as in NAA/Cr + Cho in the left and right hippocampus. This may reflect the much greater mechanisms of preserved brain plasticity and general coping strategies in the women in our study (who were also younger, albeit non-significantly so, than the men). For example, based on our observations, one might infer that the decline in the right hippocampal pool of neurons in women was associated with compensatory enhancement of other memory components, specifically memory associated with BMVT tests. Higher possible hippocampal plasticity in women compared to men enrolled in our study may also be expressed by surprisingly larger c-HV ratio, because correction to total brain volumes is employed to mitigate possible gender changes in brain subvolumes.

However, more evaluated patients to weigh possible confounding factors would be needed to fully understand pre-RT hippocampal MRS utility as a non-invasive surrogate of pre-RT NCF testing. Despite the essentially negative nature of this study, with no clear and consistent pattern in pre-RT hippocampal MRS and pre-RT NCF, we have identified several crucial factors that warrant further research and development in the field of palliative RT for BM. Similar efforts to identify patients suitable for complex HA-WBRT techniques will be even more timely with the results of the ongoing NRG BN009 trial, NCT04588246, that compare salvage SRS alone or salvage SRS plus hippocampal avoidance WBRT and memantine.

CONCLUSION

In conclusion, hippocampal MRS focused on non-invasive evaluation of hippocampal neuronal pool was evaluated in patients indicated to stereotactic radiotherapy for limited BM. Our study aimed to evaluate a possible association between pre-RT hippocampal MRS and baseline NCF to provide a non-invasive and easy-to-use surrogate for NCF estimation. Borderline statistically significant correlations were observed with speculative interpretation. Similar imaging studies evaluating predictors of baseline pre-RT NCF status in BM patients should be included in all ongoing studies evaluating different RT techniques in BM patients.

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