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ORIGINAL ARTICLE

Hippocampal Sparing Radiotherapy in Patients with Brain Metastasis: Benefits and Risks

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Abstract

Background: Whole brain irradiation is associated with many late adverse events such as memory and learning decline due to damage of the hippocampus. The primary objective is to assess memory changes for patients treated with hippocampal sparing IMRT. The secondary objectives are to evaluate local recurrence rate within the hippocampus, response rate and assess time to radiological progression. **Methods:** Patients were randomized into two groups, the first received conventional whole brain radiotherapy and the second received hippocampal sparing whole brain IMRT, each received 30 Gy over 10 fractions. Patients had baseline memory assessment using Hopkins verbal learning test Revised before and 4 months after radiotherapy and MRI brain before treatment and every 2 months thereafter. **Results:** 41 patients were assessed, first group (n= 20) and second group (n= 21). The median follow up duration was 6 months. Regarding neurocognitive outcomes, the first group showed statistically significant decline for total and delayed recalls obtained 4 months after radiotherapy compared to the base line level (p= 0.009 and 0.001), while hippocampus sparing group had no statistically significant differences between pre and post treatment (p= 0.746 and 0.478). No statistically significant differences between both groups regarding partial response rate (40% vs 42.8%) (p= 0.5), median time to radiological progression (3 vs 4 months) (p=0.5) or acute GI– II toxicities (80% vs 61.9%) for group I and II respectively. None of group II patients relapsed within the hippocampus. **Conclusions:** Hippocampal sparing WBRT is an effective and feasible technique for preservation of neurocognitive functions while maintaining intracranial control.

Keywords: Brain metastasis; hippocampus sparing radiotherapy; whole brain radiotherapy.

INTRODUCTION

Brain metastasis is the most common intracranial tumor affecting about 20 – 40% of all cancer patients **[1]**. Treatment depends on the age of patient, performance status, primary tumor controlled or not, number of brain metastasis and control of extra cranial disease **[2]**. Generally, for patients with solitary brain metastasis, KPS > 70% and controlled primary, surgical excision or stereotactic radiosurgery with or without whole brain radiotherapy (WBRT) is the preferred treatment option. While

for patients with multiple brain metastasis, whole brain radiotherapy alone is usually considered **[3]**. The rationale for whole brain irradiation is that it can target both gross and microscopic lesions with subsequent improvement of neurological symptoms **[4]**. However, there are many late adverse events for WBRT as necrosis, leukoencephalopathy, dementia, vascular strokes and neurological deficits. Also, deterioration of the cognitive functions, such as short-term memory (i.e., verbal recall ability) in addition to concentration and learning capabilities. Early decline usually develops during the first 1– 4 months after radiotherapy **[5, 6]**.

The hypothesis for cognitive deterioration is based on that radiotherapy induces damage of the stem cells or proliferating neural progenitor cells in the hippocampus leading to deterioration of memory and learning abilities **[7]**. Hippocampus is located at the medial side of the temporal lobe that bulges into the temporal horn of the lateral ventricle. It plays an important role in spatial and episodic memory. In general, the left hippocampus predominates and primarily mediates verbal learning and memory, whereas the non- dominant right side primarily mediates nonverbal memory. Because bilateral hippocampal lesions result in amnesia, several hippocampal avoidances research have been undertaken to spare it from high dose of radiation therapy. Radiation induced neurocognitive function (NCF) decline primarily involves immediate and delayed verbal memory with/without non-verbal memory **[8, 9]**. Multiple trials for patients with primary brain tumors showed that the NCFs deterioration is directly related to the dose delivered to the hippocampus. Therefore, it is suggested that conformal hippocampal sparing during the radiotherapy course may lead to significant cognitive function preservation **[10]**. However, if metastases is located in or close to hippocampus, hippocampus avoidance radiotherapy (HA-WBRT) becomes an impossible substitute to WBRT. Also, theoretically sparing of the hippocampus may increase the risk of relapse within the hippocampal avoidance area **[11]**.

The main objectives of the present study are to assess the incidence of local recurrence rate in the hippocampal avoidance area and to assess memory changes as measured by the Hopkins Verbal Learning Test Revised (HVLT-R). The secondary objectives are to evaluate the response rate and to assess time to radiological progression.

PATIENTS AND METHODS

Inclusion criteria: Age more than 18 years, Karnofsky Performance Status (KPS) score ≥ 70, pathologically confirmed solid malignancy, measurable brain metastasis, Recursive partitioning analysis (RPA) class I defined as age ≤ 65 years, KPS ≥ 70%, and controlled primary tumor without extra-cranial metastases) or class II (KPS ≥70% and any other criteria).

Exclusion criteria: Lepto-meningeal metastases, metastasis in ≤ 1cm of the hippocampus, brain lymphoma, metastases of germ cell tumors or small cell lung cancer. Prior stereotactic radiosurgery (SRS) or surgical resection, previous radiation therapy to the brain, chemotherapy or targeted therapies during irradiation and patients with severe co-morbidities. Contraindication to magnetic resonance imaging (MRI) such as metallic implant or severe claustrophobia. Female patients in the childbearing period must have negative serum pregnancy test prior to study entry.

All patients had contrast enhanced MRI brain. Patients were randomized into two groups, the first one received 3-dimensional conformal whole brain radiotherapy and the second group received hippocampal sparing intensity modulated whole brain radiotherapy, each received 30 Gy / 10 fractions over two weeks.

This study was reviewed and approved by the Ethics committee, Faculty of Medicine, Alexandria University according to the Helsinki Declaration. All patients consented to participate in the study.

Treatment planning

Position and immobilization: Patients' lie in supine position with head thermoplastic mask, IV contrast CT simulation with slice thickness 1.25 mm was done. Both CT simulation and T1 weighted brain MRI scans were fused together, and target volumes and risk organs were contoured.

Target volumes:

Clinical target volume group I (CTV I): whole brain parenchyma.

Planning target volume group I (PTV I): CTV I + 2 cm.

Clinical target volume group II (CTV II): whole brain parenchyma minus the hippocampus + 5 mm volumetric expansion.
Planning target volume group II (PTV II): CTV II + 5 mm excluding hippocampal region.

Organs at risk:
Risk organs include lens, optic nerves, optic chiasma, eyes and hippocampi.

Table (1): Dose constrains for organs at risk

	Organ at risk	
HA-WBRT IMRT Planning	PTV	D2% ≤ 37.5Gy D98% ≥ 25 Gy V30 ≥ 95%
	Hippocampus	Dmin% ≤10Gy Dmax ≤17Gy
	Optic nerves and chiasm	Dmax ≤37.5Gy
	Eyes	Dmax ≤ 7Gy
	Lens	Dmax ≤ 5 Gy

HA-WBRT IMRT: hippocampal avoidance intensity modulated radiotherapy. PTV: planning target volume.

Hippocampal Contouring
T1 weighted MRI images were used to identify the gray matter in the medial temporal horn. Starting at the most inferior extent of the crescentic shaped floor of the temporal horn of the lateral ventricle and continued cranially and posteriorly along the medial edge of the temporal horn. The postero-superior extent of the hippocampus was defined by the curvilinear T1-hypointense hippocampal tail sited just antero-medially to the atrium of the lateral ventricle. Contours ended at the lateral edges of the quadrageminal cisterns prior to the emergence of the crus of the fornix.
Patients were treated by a 6-MV photons linear accelerator (L.A) with non-coplanar 7-beams using step-and-shoot IMRT.

Patients Assessments
Patients were assessed weekly during radiotherapy and every 2 months later for adverse events and time to radiological progression.
The neurocognitive function was assessed before starting treatment (base line) and then after 4 months by Hopkins Verbal Learning Test (HVLT) which tests for memory and verbal learning abilities.
The test incorporates three trials of free-recall of a 12-item. The doctor read the 12 words loudly and then the patient was asked to freely repeat them immediately (immediate recall) and after 20 minutes (delayed recall). The list was read a second and third times followed by a second and third free recall trials. The words recalled for each trial were recorded and a total recall score was calculated (range: 0–36).
Each patient will be under his/her own control. The mean, median changes in the scores between baseline and after 4 months and the standard deviations will be reported.
MRI brain with contrast was requested at 2, 4 and 6 months after radiation therapy. CNS progression is defined as at least 20% increase in the summation of the longest diameter of the contrast enhancing lesions, or the appearance of any new brain metastasis.
Statistical analysis: Statistical analysis was done using the paired t-test to compare the mean values of the same group before and after radiotherapy. An unpaired t-test compares the mean values of the two groups with a significant value of ≤ 0.05.

RESULTS

Fifty patients with pathologically confirmed malignant solid tumor were recruited from Clinical Oncology Department, Faculty of Medicine, Alexandria University Hospital between March 2017 and April 2018 in this study. 9 patients lost follow up after radiation (5 patients in group I and 4 patients in group II).
According to the primary tumor site, the most common primary site in both groups was breast

68% in group I and 72% in the group II followed by lung 32% in group I and 16% in the group II. The number of metastases ranged from 2 – 5 lesions in both groups. The mean volumes for the hippocampus, hippocampal avoidance region, whole brain and whole brain minus hippocampi avoidance regions were 7.8 cm^3 (range: 6.7–8.9 cm^3), 28.6 cm^3 (range: 24 – 34 cm^3), 1420.0 cm^3 (range: 1310–1640cm3) and 1394 (rang: 1286 – 1606) respectively. On average, the hippocampal avoidance volume occupied 2.3% (2.0–2.7%) of the whole brain (table 2).

Table (2): Patients and tumor characteristics

	WBRT (n = 20)		**HA-WBRT (n = 21)**		**χ^2**	**P**
Sex	**n**	**(%)**	**n**	**(%)**		
female	15	75.0	15	71.4	0.397	0.529
Male	5	25.0	6	28.6		
Age						
≤ 40	8	40.0	7	33.3	0.208	1.000
>40 – ≤ 60	9	48.0	11	52.4		
>60	3	12.0	3	14.3		
Primary						
Breast	15	75.0	15	71.4	3.931	0.146
Lung	4	20.0	3	14.3		
Other (kidney, colon)	1	5.0	3	14.3		
RPA class						
I II	4 16	20 80	5 16	23.8 76.2		
No of metastatic lesions						
Median Range	4 (2–5)		4 (2–5)			
Mean whole brain volume (cm^3) (range)			1420.6 (1310–1640)			
Mean hippocampi volume (cm^3) (range)			7.8 (6.7–9.8)			
Mean hippocampi avoidance volume (cm^3) (range)			28.6 (24–34)			
Mean brain – hippocampi Volume (cm^3) (range)			1394 (1286–1606)			

PRA: recursive partitioning analysis

Neurocognitive function assessment:

Total and delayed recalls were tested by Hopkins Verbal Learning Test –Revised at base line and after 4 months of radiotherapy and total recalls were calculated by the summation of trial 1+ trial 2+ trial 3. For group I (WBRT) patients there was statistically significant difference between the mean baseline value and 4 months assessments (p= 0.009 and 0.001). For group II patients (HA-WBRT) there was no significant difference between the mean baseline and after 4 months assessments (p=0.746 and 0.478), (Table 3 and 4).

Table (3): Hopkins Verbal Learning Test –Revised (total recall assessment)

HVLT R (total recall)	WBRT (n=20)	HA – WBRT (n=21)	t	p
Baseline				
Min – Max	17.0 – 36.0	25.0 – 35.0	2.578	0.014
Mean ± SD	27.92 ± 4.71	30.76 ± 2.86		
Median	28.0	31.0		
After 4 months				
Min – Max	14.0 – 31.0	23.0 – 33.0	3.471	0.001
Mean ± SD	22.32 ± 5.43	27.64 ± 3.04		
Median	20.0	26.0		
Sig. bet. periods	0.009	0.746		

t: Student t- test, t: Paired t – test between baseline and after 4 months.
p: p value for comparison between the two studied groups.
WBRT: whole brain irradiation, HA-WBRT: hippocampal avoidance whole brain irradiation

Table (4): Hopkins Verbal Learning Test –Revised (delayed recall assessment)

HVLTR (delayed recall)	WBRT (n=20)	HA WBRT (n=21)	t	p
Baseline				
Min – Max	7.0 – 10.0	7.0 – 11.0	1.355	0.182
Mean ± SD	10 ± 1.17	10.76 ± 0.86		
Median	9.0	10.0		
After 4 months				
Min – Max	6.0 – 10.0	8.0 – 11.0	3.183	0.003
Mean ± SD	7.32 ± 1.77	8.64 ± 1.08		
Median	8.0	10.0		
Sig. bet. periods	0.001	0.478		

t: Student t- test, t: Paired t – test between baseline and after 4 months.
p: p value for comparison between the two studied groups.
WBRT: whole brain irradiation, HA-WBRT: hippocampal avoidance whole brain irradiation

Radiological Assessment:

MRI brain was done at 2, 4 and 6 months after radiotherapy and compared to the pretreatment study. The median duration of follow up was 6 months (range 3 – 12 months).

No complete response was observed in both groups, 8/20 (40%) patients in group I had partial response compared to 9/21 (42.8%) patients in group II without statistically significant differences (p=0.54). 7/20 patients (35%) had stable disease compared to 8/21 patients (38.1%) in group II with no statistically significant difference (p= 0.6). Progressive disease was observed in 5 patients (25%) group I compared to 4 patients (19%) in group II with no statistically significant differences (p= 1.00). None of the patients in both groups developed metastasis within the hippocampal avoidance area during the follow up period. The median time for radiological progression was 3 months for group I compared to 4 months for group II without statistically significant differences (p=0.5)

Acute adverse events:

Sixteen out of twenty patients (80%) in group I have reported various GI – II acute side effects (alopecia, erythema, otitis, xerostomia, headache, lethargy, nausea, vomiting or worsening of neurological deficit) compared to 13/21 patients (61.9%) who received whole brain radiotherapy with hippocampal sparing, however this difference didn't have statistical significance (p=0.09).

DISCUSSION

Improvements in systemic treatments with prolongation of patients overall survival increase the frequency of brain metastases. The standard and

the most widely used treatment option for patients with multiple brain metastases is whole brain radiotherapy with significant improvement of median survival from 1–2 months to 4 – 6 months or more. However, it carries the risks of acute and late adverse events. Deterioration of NCF may be due to metastasis itself and/or a late adverse event of brain irradiation **[12]**.

Hippocampus has a key role in learning, remembering, creating memories and relaying information from short-term to long-term memory together with the ability of remembering information. It was hypothesized that; hippocampal sparing could decrease or defer the onset and severity of NCF decline as assessed by clinical neurocognitive measures **[13]**. **Chang et al. [14]** conducted a phase III single-institution study that evaluated the NCF decline in patients treated with stereotactic radiosurgery (SRS) with or without WBRT for patients with one to three brain metastases. Neurocognitive function decline was defined as a >5 point drop 4 months from baseline using the HVLT-R as a neurocognitive measurement for learning and memory. The trial was stopped early due to an interim observation of a two-fold increase in the mean incidence of NCF decline (49%, SRS+WBRT, versus 23%, SRS alone) in patients who received whole brain irradiation **[14]**. RTOG 0933, a single arm nonrandomized phase II trial assessed the benefit of conformal hippocampal avoidance during WBRT, using the 'Hopkins Verbal Learning Test (HVLT). The results showed significant preservation of memory and quality of life compared to a historical series of patients who received standard WBRT **[15]**.

A phase III NRG Oncology CC001 trial randomized 518 adult patients with brain metastases during the period between July 2015 and March 2018 to memantine plus HA-WBRT or memantine plus WBRT. Memantine is an N-methyl-D-aspartate (NMDA) receptor agonist which has established use for dementia in patients with Alzheimer's disease. Time to cognitive function deterioration was the primary end point. The secondary objectives include overall survival (OS), intracranial progression-free survival (PFS) and toxicity. After a median follow up duration of 7.9 months, the risk of cognitive failure was significantly lower after HA-WBRT plus memantine versus WBRT plus memantine (adjusted hazard ratio, 0.74; 95% CI, 0.58 to 0.95; P = .02). There were no significant differences in PFS or OS **[16]**. Hippocampal sparing technique carries the risk of decreasing the benefit of WBRT due to increased risk of missing metastatic disease within the hippocampal avoidance region. Within the brain, metastases tend to develop at the junction between gray and white matter, where the terminal "watershed regions" of arterial circulation reside. The most common sites of metastasis are the cerebral hemispheres (80%), cerebellum (15%), and brainstem (5%) **[17]**. A study conducted by **Ghia et al. [18]** evaluated the incidence and sites of brain metastasis in relation to hippocampal avoidance region. One hundred patients with 272 metastases were included and analyzed, 3.3% of metastases were within 5 mm of the hippocampi (n=9); 4.0 % of metastases were between 5 to 10 mm from the hippocampi (n=11); and 6.2% of metastases lay between 10 and 15 mm from the hippocampi (n=17) with 86.4% an overall incidence of metastases greater than 15 mm from the hippocampi (n=235). No metastases occurred within the hippocampi **[18]**. Another study by **Gondi et al. [19]** investigated the risk of detecting a metastatic lesion within 5 mm of the hippocampi at the time of presentation. 371 patients with 1,133 total metastases were included and founded that only 8.6% of patients presented with a tumor inside the hippocampal avoidance region (5mm expansion around the hippocampi). Therefore, it was concluded that HA-WBRT can be possible an effective treatment option for 91.4% of patients with brain metastasis **[19]**. **Yi Rong et al. [20]** published a dosimetric study that compared Intensity Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), and Helical Tomotherapy for Hippocampal-Avoidance whole brain radiotherapy. Regarding PTV coverage, V30 (>95%) was 94.4% for tomotherapy, 94.8% for IMRT without statistically significant difference (p=0.17) and 95.5% for Rapid Arc which was significant compared to the 2 other modalities (p= <0.001 and < 0.05). Significantly higher homogeneity index for tomotherapy 0.15 ± 0.03 compared to the two other modalities 0.28 ± .04 for IMRT (p= <0.005) and 0.22 ± 0.03, (p < .005) for the Rapid Arc.

Concerning the treatment time, Rapid Arc has an average delivery time of 2.5 min compared to 15 minutes for IMRT and 18 minutes for Tomotherapy. For Hippocampal avoidance, significantly higher mean D100% (D-min) for both IMRT (8.7 Gy), and

Rapid Arc (8.6 Gy) compared to tomotherapy (8.0 Gy) ($p<0.001$ and <0.001). No significant difference between IMRT and Rapid Arc ($p=0.596$). The average hippocampal maximum dose (D-max) of IMRT was (14.9 Gy), Tomotherapy was (15.1 Gy) and Rapid Arc was (13.6 Gy) which had a statistically significantly lower D-max than both Tomotherapy ($p < .001$) and IMRT ($p < .05$). There was no significant difference between Tomotherapy and IMRT ($p= 0.762$). The average D-max of the optic nerves and chiasm, for IMRT was (36.6 Gy) which is significantly higher than both Tomotherapy (33.9 Gy) ($p < .005$) and Rapid Arc (34.4 Gy) ($p < .005$), while there was no significant difference between Rapid Arc and Tomotherapy ($p= 0.22$) **[20]**. An ongoing phase II study (NOA-14, ARO2015-3, DKTK-ROG) evaluates the efficacy and safety of dose escalation with the simultaneous integrated boost (SIB) on metastases/resection cavities combined with hippocampal avoidance whole brain radiotherapy (HIPPORAD). The rationale is that the local control rate of WBRT is poor (40 – 60%) and is associated with a deterioration in neurocognitive function (NCF). Patients are randomized into two treatment groups: HA-WBRT+SIB and WBRT+SIB. WBRT dose 30 Gy/12 daily fractions, the SIB dose 51 Gy/ 12 fractions for metastases and 42 Gy/12 fractions for resection cavities **[21-23]**. Still waiting for the results that may change the treatment strategy for multiple brain deposits.

The sum of the above studies and our results suggest that HA-WBRT achieves gross and microscopic brain lesions control with preservation of memory-related NCF without compromising local control rate and the intracranial progression free survival.

CONCLUSIONS

Significant advances in radiotherapy techniques have enhanced the effectiveness and safety of hippocampus avoidance whole brain irradiation for patients with brain metastasis. It significantly preserves the neurocognitive functions as compared to whole brain irradiation without compromising local tumor control or intracranial progression free survival. Hippocampal or peri-hippocampal brain metastases are not eligible for this treatment technique. Inclusion of more patients with longer follow-up is recommended.

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