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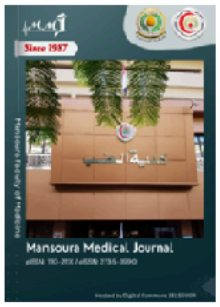

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PROSPECTIVE EVALUATION OF NEUROCOGNITIVE EFFECTS IN PATIENTS WITH BRAIN METAST/ 'ES AFTER WHOLE BRAIN RADIOTHERAPY

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ABSTRACT

Objective : The objective of the present study was to systemically evaluate the neurocognitive changes for two months after Whole brain radiotherapy (WBRT) and to evaluate time to neurocognitive failure using different reported mini-mental state examination (MMSE) cutoff score points (age/education and 23). *Patients and methods:* This study was conducted in Mansoura University Hospital (years 2007 & 2008) on 24 patients, 16 males and 8 females aged >18 years with more than 2 brain metastases. They received WBRT at a dose of 30 Gy in 10 equal daily fractions. Overall survival (OAS) measured from the date the patient first seen to the date of death or the date the patient was last known to be alive. The Folstein MMSE was done before, immediately and 2 months after WBRT to evaluate neurocognitive progression. Time to neurocognitive failure was evaluated using 2 oft-reported cutoff score points. *Results:* The median survival time was 4.5 months. The OAS was 45% at 6 month, 25% at 1 year, and 8.3% at 1.5 years. The OAS for patients <65 year-old was better than that for patients ≥ 65 year-old, however the difference was statistically insignificant (p=0.21). 79.2% of patients developed deterioration, while 12.5% showed stable and 8.3% only developed improvement of cognitive function at two month. There was mild statistically significant deterioration of basal MMSE value immediately after WBRT (p=0.047), while there was

marked deterioration 2 months after completing WBRT ($p<0.001$). On applying the MMSE cutoff point of age/ educational level, 62.5%, 70.8%, and 79.2% of patients developed neurocognitive failure before, immediately, and 2 month after WBRT, compared to 41.7%, 66.7%, 75%, respectively on applying MMSE cutoff point <23. The cumulative incidence of neurocognitive failure among patients applying MMSE cutoff ≤ age/ educational level was higher than that when applying MMSE cutoff <23, However the difference between was insignificant ($p=0.46$). *Conclusion:* Compliant patients <65 years of age had a better median survival. WBRT is associated with a steadily progressive deterioration of cognitive function. It doesn't differ whether using any of the MMSE cutoff points.

INTRODUCTION

Brain metastases, the most frequent neurological entity associated with cancer[1]. WBRT is the standard treatment for patients with brain metastases especially with multiple lesions[2]. Unfortunately, the median survival time for patients suffering from brain metastases treated by WBRT is approximately 4 months[3]. Impairment of cognition in this patient population can be attributed to several potential causes including progressive disease, sequelae of WBRT, other antineoplastic interventions, the presence of systemic cancer, and the effect of supportive agents such as anticonvulsants[4]. The objective of the present study was to systemically evaluate the neurocognitive changes before, immediately, and two months after WBRT radiotherapy putting into consideration different reported mini-mental state examination (MMSE) cutoff points of neurocognitive failure.

PATIENTS

Those eligible included: adult patients ≥18 years old, with more than two brain metastases from a histologically confirmed extracranial primary malignancy, without extracranial metastases. Before starting therapy, all patients agreed to undergo a history, physical & neurological examination and MMSE. Patients with visual, hearing, or physical impairment sufficient to interfere with neurocognitive testing and those who were uncompliant for testing were excluded from the study.

METHODS

Radiation Therapy :

All patients received WBRT to a

dose of 30 Gy in 10 equal daily fractions, with photon energies using megavoltage machines. Two parallel opposing fields with daily dose 300cGy per fraction over two weeks. The target volume included the entirety of the cranial contents, with clearance of the beam beyond skin and a minimum margin of 0.75 cm on the skull base as visualized on the simulator. The lens was shielded from the direct beam via primary collimation. Head mask was used for proper immobilization.

Neuropsychological Assessment:

The Folstein MMSE[5] was used to determine neurocognitive progression. It was performed for all patients one time before starting, another time immediately after and a third time two months after radiotherapy (RT). Because the MMSE is affected by age and years of education, cutoff levels for both parameters were used to define patients with possible cognitive dysfunction. Table 1 displays cutoff scores from the MMSE in relation to age and educational level. Although the maximum score is uniformly 30, patients with scores falling at or below the specified adjusted value as depicted in the matrix were considered to be neurocognitively impaired "cognitive failure". In addition the frequently reported cutoff of 23[3] was used to evaluate neurocognitive failure in parallel analyses that were run. The cumulative incidence mode was used to analyze time to neurocognitive failure.

Statistical Consideration:

The GraphPad Prism v 5.02 was used for analysis. Chi-square test and student's t-test were used for categorical and non-categorial variables respectively. OAS and Cumulative incidence of patients regarding time to neurocognitive failure, measured by MMSE using 2 cutoff values, were estimated by Kaplan Myer method. Log-rank test was used to analyze the difference between the curves. P value <0.05 was considered statistically significant. Overall survival (OAS) was measured from the date the patient first seen to the date of death or the date the patient was last known to be alive.

RESULTS

The present study was performed in Mansoura University Hospital (years 2007 & 2008) on 24 patients, 16 (66.7%) males, and (33.3%) females with mean age 61.13±11.60. The primary malignant site was the

lung in 12, the breast in 8, the kidney in 2 and unknown in 2 patients. The median survival time for these patients was 4.5 months. The OAS was 45% at 6 month, 25% at 1 year, and 8.3% at 1.5 years figure (1). The OAS for patients <65 years old was better than that for patients≥65 years old however the difference was statistically insignificant (p=0.21) Fig (2).

Our results revealed- 2 months after WBRT- that 19 patient (79.2 %) developed deterioration, while 3 (12.5 %) showed stable and 2 only (8.3%) showed improvement of cognitive function by increase of their raw MMSE scores by more than 1.5 times SD (z-score) table (2).

There was mild statistically significant deterioration of basal MMSE value immediately after WBRT {(mean ± SD=24.33±2.87 vs 22.38±3.74) (p=0.047)}, while there was marked deterioration 2 months after completing WBRT {mean±SD=19.71±4.23 (p<0.0001)}. Applying the MMSE cutoff age/educational level, 62.5%, 70.8%, and 79.2% of patients develleped neurocognitive failure before, immediately , and 2 month after WBRT, compared to 41.7%, 66.7%, 75%, respectively on applying MMSE cutoff <23 table (3).

Figure (3) graphs the time to neurocognitive failure among patients employing MMSE criteria based on cutoff age/educational level compared to absolute cutoff 23. The cumulative incidence of neurocognitive failure among patients applying MMSE cutoff ≤ age/educational level was higher than that when applying MMSE cutoff < 23, However the difference between the 2 curves was insignificant (p=0.46).

Table (1): Cutoff scores for MMSE (from RTOG 0118)

Age	Up to grade 8	Some high school Did not graduate	Graduated high school Or received GED	Attended college or technical school after high school
< 55	26	28	28	29
55-59	26	28	28	28
60-64	26	27	27	28
65-69	25	26	27	27
70-74	24	25	26	27
75-79	23	24	25	26
80-84	23	23	24	24
85-89	23	23	23	24
90-95	23	23	23	23

Table (2): Neurocognitive assessment 2 months after WBRT

Neurocognitive Assessement	NO	%	P value
Deteriorated	19	79.2	0.000
Stable	3	12.5	
Improved	2	8.3	
Total	24	100	

Table (3): Cognitive failure using different cutoff points

MMSE Cutoff point	Before WBRT N (%)	Immediately after WBRT N (%)	2 month after WBRT N (%)
≤Age/Educational level	15/24(62.5)	17/24(70.8)	19/24(79.2)
< 23	10/24(41.7)	16/24(66.7)	18/24(75)

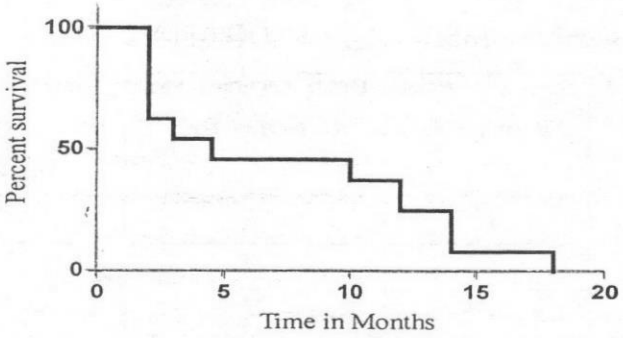


Figure (1): Overall Survival for all patients

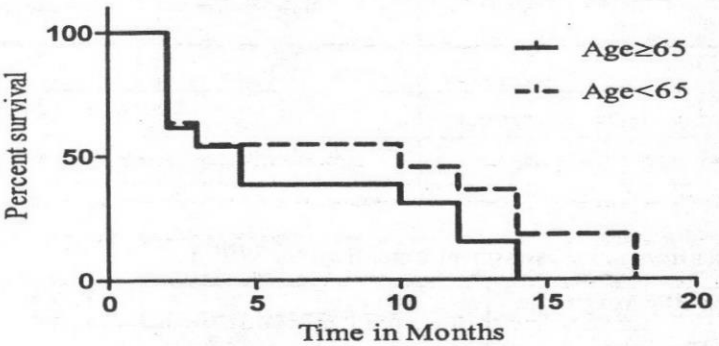
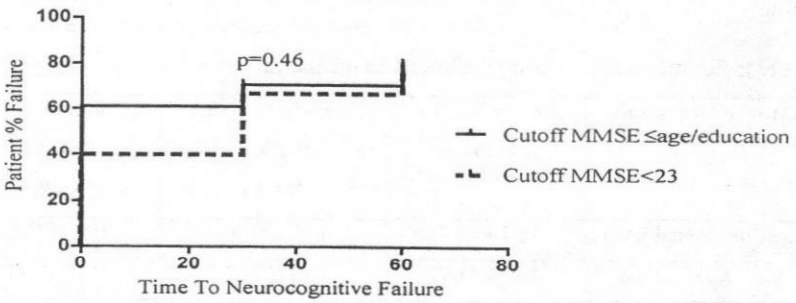


Figure (2) OAS in patient groups regarding age



Figur (3): Time to neurocognitive failure applying different MMSE cutoff points

DISCUSSION

We investigated cognitive function before, immediately, and 2 months after WBRT in patients with brain metastases. First, even before the start of radiotherapy, the basal cognitive performance of 62.5 % of patients ranged below the test norms. These findings are in accordance with those of several other studies reporting on cognitive impairment in cancer patients before radiotherapy[6]. Others [7] studied the short-term effects of therapeutic cranial irradiation in patients with brain metastases and reported a significant deterioration in memory score (the retroactive interference, delayed recall and recognition scores), however, memory scores showed some improvement at the end of radiotherapy. Nearly similar to our results that revealed that 19 (79.2 %) of patient developed deterioration, while 3 (12.5 %) showed stable and 2 (8.3%) only showed improvement of cognitive function by increase of more than 1.5 times SD in MMSE score. Early memory impairment after WBRT may be related to the sensitivity of the hippocampus to radiation-induced damage[8]. In our study there was mild significant deterioration of cognitive function immediately after the WBRT (p=0.048). It doesn't matter using different MMSE cutoff points (age/education vs 23) for evaluating time to neurocognitive failure. Radiation techniques that spare the hippocampus or agents that prevent hippocampal damage may help preserve memory and reduce the risk and severity of radiation-induced dementia[9]. One study[10] reported a median survival time of 3.9 month and OAS of 34%, 19%, and 13% at 6, 12, and 18 months respectively. Other studies[11, 12, 13] reported a median survival time of 4, 4.5 and 4.9 months. These results were nearly similar to our results. Another study (14) reported a median survival of 6.7 months for patients ≤65 years old and 4.6 months for patients >65 years. In our study the median survival was 10 months for patients <65 year-old and 4.5 months for patients ≥65 years. The OAS for patients ≥65 years was significantly less than that for patients<65 years old (p=0.21).

CONCLUSION

Compliant patients under 65 year-old had a better median survival time. WBRT is associated with a steadily progressive deterioration of cognitive function. It doesn't differ whether using either MMSE cutoff point ≤ age/education or absolute cut-

off point of 23 to evaluate neurocognitive failure.

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