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Neurocognitive Function and Quality of Life Assessment in Patients Receiving Whole Brain Radiotherapy with Adjuvant Temozolamide and whole Brain Radiotherapy Alone: A Prospective Comparative Study

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ABSTRACT
Metastases is defined as the spread of the tumour from primary site to a distant site. Brain is the most common site of Metastases and Whole Brain radiotherapy is the mainstay of treatment in these patients. To assess the Neurocognitive function and Quality of Life in patients with brain metastasis receiving Whole Brain Radiotherapy with concurrent Temozolamide, This Double arm prospective study was conducted in Department Of Radiation Oncology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai From February-2018 till July 2019. The most common carcinoma in the control arm was Ca Breast. Histopathologically the most common tumor type is Adenocarcinoma in the control arm and least common was the melanoma. Similarly in case of treatment arm the most common subtype is the Adenocarcinoma and the least common type were the poorly differentiated carciniomas. In both the arms patients had multiple sites of involvement followed by Right Parietel region. Brain metastases symptom were present before the beginning of WBRT in about 55% and absent in 45% of patient in both arms combined. The time period between the onset of decline in cognition is about one month earlier in the control arm than in the study arm. The range of decline is also very rapid in the control arm than in the study arm. the decline in executive function in the treatment arm was late when compared to control arm although there is no significant p-value. there is statistically significant preservation of neurocognitive function in the motor skill assessment of non dominant hand and also in the visual motor scanning domain. There was also increase in overall survival of 3 months. Though all the other domains showed significant preservation of NCF but these were not statistically significant.

INTRODUCTION

Metastases is the most common tumour in the brain. It's seen in about 20-30% of all adult cancer patients. Development of imaging modalities and interventions has increased the diagnosis of brain metastases in the recent days[1].

Annual incidence of brain metastasis constitute about 1,70,000-3,00,000 world wide. Approximately 25% of patient who die with cancer are found to have brain metastases. The recent trend of increase in brain metastases may be attributed to the advent of newer diagnostic modalities, of which MRI brain and MRSA is more specific and helps in easier and earlier diagnosis Brain metastases are found to be more common with primaries of Lung, Breast, Occult primaries, Gatrointestinal tract, Melanoma and Renal cell carcinoma. Carcinoma of lung constitute about 20-50% of brain metastases, breast 5-20%, Small cell lung cancer 15%, Melanoma 7-10%,Renal cell carcinoma 4-6% and Carcinoma colon 2-5%. There has been constant decrease in brain metastases in Carcinoma Breast patient which may be attributed to the newer modalities of treatment and advent of targeted agents. The median age for diagnosis of brain metastases is about 60 years and overall clinical incidence is 20-30%[2].

The median time of diagnosis of brain metastases is 8.5 to 12 months after the diagnosis of primary cancer. The most common site for development of brain metastases in brain is the cerebral hemisphere in between the grey and white junction.

In spite of the recent advancement in the treatment facilities available for brain metastases, the median time for survival for a patient diagnosed with brain metastases ranges from 8-16 months[3].

The treatment for brain metastases ranges from surgery, Whole brain Radiotherapy, Stereotactic Radio Surgery, systemic chemotherapy, corticosteroid therapy, supportive care or a combination of these treatments.

Various trails and study designs have been published over the years comparing the effectiveness of these treatment modalities on the overall survival, local control rates and progression free survival of these patients. Studies have clearly shown that the adding any one of the treatment modalities to the patient with brain metastasis have showed significant improvement in the overall survival of these patients than observation alone.

Supportive care was the only treatment option available for patients with brain metastases until the early part of 20 th century. In 1950 Chao[4], published the first paper on the effectiveness of WBRT for multiple cerebral metastasis. Furthermore there was no difference in response to treatment in patients receiving WBRT for a radioresistant primary versus radiosensitive primary.

WBRT has been considered as an effective palliative options for patients with brain metastases for alleviating the symptoms and to decrease the use of corticosteroid to control the brain edema The effectiveness of WBRT to impact on Overall survival also depends on the Performance status and also the presence of extra cranial metastases. Due to increase in survival in these patients there has been more focus on various side effects of RT on brain such as decline in neurocognition and Quality of life in these patients and use of various agents and RT techniques such as Hippocampus sparing RT which decrease these effects on the brain.

In recent years there have been studies which show the addition of few radio sensitizers along with the conventional Whole Brain RT which not only improves the local control but also decreases the detoriation of neurocognitive function in these patients.

MATERIALS AND METHODS

This Double arm prospective study was conducted in Department Of Radiation Oncology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai From February-2018 till July 2019. Among Patients with brain metastasis receiving Whole Brain RT (300cGy/10#/30Gy) treated with concurrent Temozolamide are evaluated for Neurocognitive Function and Quality of life. Tumor response to therapy is assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, prior and post WBRT at every month for first 6 months and then for 3 months for rest of their lives. Treatment is to be delivered using a Telecobalt 60 machine.

Inclusion Criteria:

- Patients with histology proven cancers with evidence of brain metastasis.
- Karnofsky's performance status >60%.
- Age-between 18-65 years.
- Hemoglobin >10gm%.
- Total WBC count >4000/mm3.
- Platelets >1,00,000 cells/mm3.
- Previously not exposed to Tyrosine Kinase Inhibitors.
- No previous Brain Irradiation.
- ECOG Status: 1-2.
- No previous history of mental illness, drug or substance abuse.
- No uncontrolled co morbid illness like Diabetes Mellitus or Hypertension.

Exclusion Criteria:

- Patient with KPS <60.
- Deranged hepatic and renal functions (>twice the upper limit), reduced bone marrow reserve.

- Patient not co-operating at any point in the treatment.
- Previously received any treatment for any other malignancy.
- Interrupted treatment.
- Patient who died within one month of starting radiotherapy.

Sample Size: Two arms One arm with 30 Patients receiving Whole brain RT with concurrent Temozolamide and followed by adjuvant Temozolamide for 6 cycles And another arm with 30 patients treated with Whole brain RT alone.

Data Collection and Methods:

- The primary endpoint is the neurological progression in both Arms, secondary end point being the response assessment to WBRT and its effect on overall survival.
- Neuro cognitive function and Quality of Life assessment all are made monthly for first 6 months and every 3 months until death during the follow up visit of the patient to our OP.
- Response and disease progression are observed clinically weekly during treatment.
- Assessments included complete history, neurological examination, biochemical parameters, complete blood counts and quality of life assessments.
- Post Treatments patients are evaluated every month for first 6 months and every 3 months from then until death. Evaluations included physical examination , neurological examination, complete blood counts, liver function test, Xray chest, CT brain or MRI brain as and when needed.
- Patients are subjected to battery of tests assessing neuro cognitive function and quality of life pre treatment at baseline and post treatment at various time intervals as mentioned above.

This study involves the use of 4 questionnaires and one peg board for the assessment of NCF. The Cognitive domain is examined using Modified Mini Mental Status examination questionnaire. This tests Orientation, Registration Attention and Calculation, Recalling and Language and Praxis The questions and the scoring is explained

The assessment using MMSE questionnaire is done on time periods as mentioned earlier and the mean of response is calculated as the decline in MMSE scores over the period of time

Executive Function Testing: This is done by using COWAT and Trail B testing.

COWAT analysis (Controlled Oral Word Association Test) tests verbal fluency in which the patient is allowed to make verbal association of the alphabet by saying all the words beginning with that alphabet . This test requires a pen, paper and a stopwatch.

Three letters with progressive increase in associative difficulty is given a stimuli. The level of difficulty is determined by the relative frequency of words in that language. In case of Tamil three letters were used.

These words were chosen for COWAT assesment by consulting with the Department of Speech and Audiopathology, RGGGH , Madras Medical College. The number of words told for each letter in every 60seconds is calculated . The total number of words told for all 3 alphabets in that 60 secs each was considered as the score.

Neuro Cognitive Function Assessment: Assessment of NCF was grouped into four domains

- **Cognitive Function Test:** Cognitive function is tested using Mini Mental State Examination (MMSE)
- Executive function Test. This will be evaluated by COWA (Controlled Oral Word Association Test), Trail Making B Test.
- Fine motor testing, will be done using Pegboard Non Dominant Hand Test, Pegboard Dominant Hand Test.
- Visual Motor Scanning Speed Test will be done using Trail making Test A.

Quality Of Life Assesment:

- Quality Of Life Assessment will be done by EORTC QLQC 30 questionnaire translated in Tamil officially available in the web page.

Response Assessment:

- Tumor response to therapy is assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, prior and post WBRT
- All assessments made monthly for first 6 months and every 3 months until death.

RESULTS AND DISCUSSIONS

In this study, both control arm and the treatment arm had 17 males and 13 females each. The most common carcinoma in the control arm was Ca Breast and least common were Unknowm pimary, Ca anorectum and RCC. The most common carcinoma in the treatment arm was Ca lung followed by equally distributed cases of ca Rectum, Unknowm pimary, Ca anorectum and RCC.

Control Arm: Histopathologically the most common tumor type is Adenocarcinoma in the control arm and least common was the melanoma, Similarly in case of treatment arm the most common subtype is the

Adenocarcinoma and the least common was the poorly differentiated.

Distribution of Metastases: In both the arms the most common location of brain metastases were multiple in location followed by Right Parietel region combining both arms. The least site for loaction was the CP angle metastases

In both the arms about 52.5% completed treatment to the primary before occurrence of metastases and 46.5% did not complete the primary treatment in both arms combined.

Brain metastases symptom were present before the beginning of WBRT in about 55% and absent in 45% of patient in both arms combined.

Assessment of Mini Mental Status Exam: In the treatment arm the average mean value corresponding to impairment in cognitive function begins after 3rd cycle of chemotherapy (Mean 17.55±3.87) and the maximum impairment of cognition is observed after 3 months of treatment (mean=11.50±0.71).

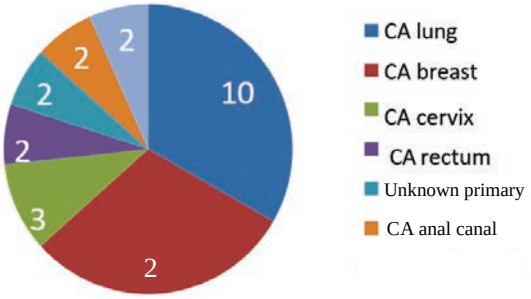

Fig. 1: Site wise Distribution

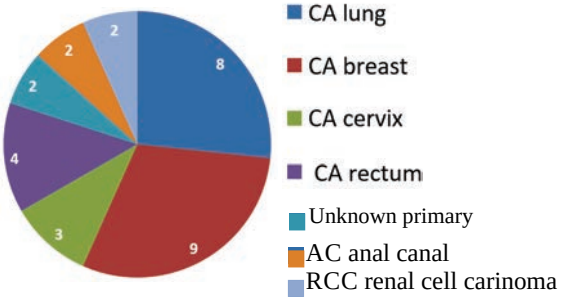

Fig. 2: Treatment ARM

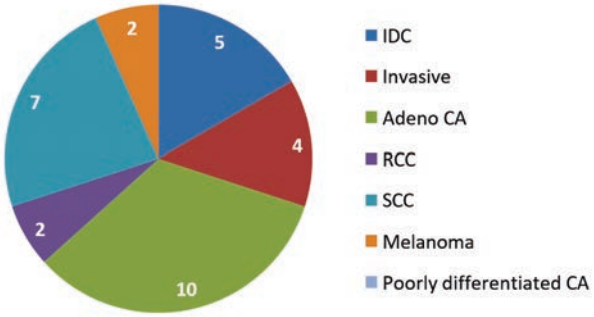

Fig. 3: Control ARM

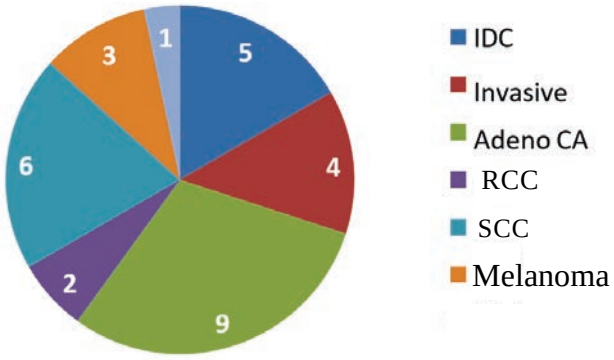

Fig. 4: Control ARM

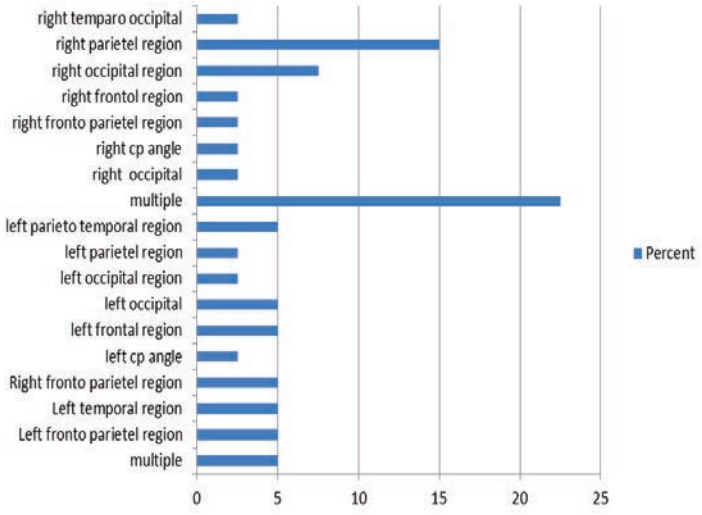

Fig. 5: Location of Secondaries in Brain

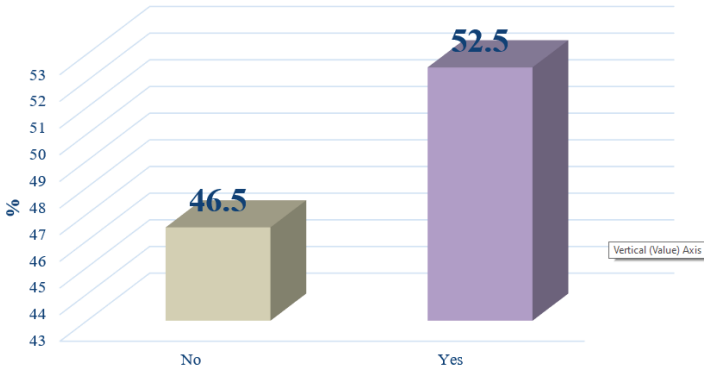

Fig. 6: Completion of Treatment to Primary

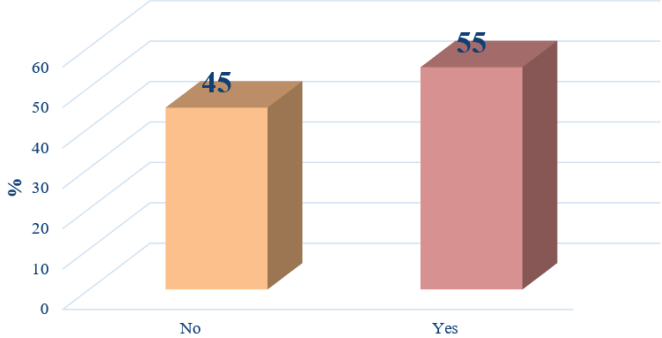

Fig. 7: Brain Metastases Symptom Present Before the Beginning of WBRT

Table 1: Score and Interpretation

Score	Interpretation
53 or above	Superior
45-52	High average
34-44	Average
24-33	Low average
20-23	Deficient
<20	Very Deficient

In case of control arm the mean value corresponding to the maximum decline is seen at C2 (mean 16.15±2.96) and most severe after C6(mean=9.0).
This shows that the time period between the onset of decline in cognition is about one month earlier in the control arm than in the study arm. The range of decline is also very rapid in the control arm than in the study arm.

Assessment of Executive Functioning
COWA (Controlled Oral Word Association Test): In this, the treatment arm, the range which corresponds to decline of COWAT function began at C3 (mean 19.80±5.92) and it was least after 6 months of completing treatment (mean 6.0) In case of the control arm the deficient results in COWA began at C2 (mean 18.89±27.33) and touched the least value at C6.

Trail B Test: In the treatment arm the value corresponding to decline in executive funtion began at C5 (mean 281.4±71.33). and reached minimum after 6 months after treatment. In case of control arm the decline in the executive function began at C3 itself and reached the least level after C5 Both these tests show that the decline in executive function in the treatment arm was late when compared to control arm although there is no significant p-value.

Assessment of Finemotor Testing:
Pegboard-Non Dominant Hand: In the treatment arm the value corresponding to the decline in motor function began at C3 (mean: 102.8±35.11) and reached the minimum after 3 months after treatment. In case of control arm the decrease in motor function in the non dominant hand began at C2. (Mean: 92.90±13.79) and reached the least value at C5 (209.80±36.7).

Pegboard-Dominant Hand: In the treatment arm the value corresponding to the decline in motor function of dominant hand began at C1 (mean: 82.8±17.71) and reached the minimum after 3 months after treatment (mean: 262.22±115.51). In case of control arm the decrease in motor function in the dominant hand began at C1. (Mean: 92.90±13.79) and reached the least value at C5 (209.80±36.7).
This suggest that the decline in motor fucntion in NDH was lesser and the preservation of function was statstically significant ($p<0.05$), were as no stastically significant preservation of motor function in the treatment arm in the dominant hand.

Visual Motor Scanning Speed test Trail A Test: In the treatment arm the value corresponding to the decline in visual motor scanning began at C5 (mean: 79±7.27) and reached the minimum after 3 months after treatment (mean: 86.25±9.81). In case of control arm the decrerase in visual motor scanning was observed at C2. (Mean: 95±36.20) and reached the least value at C4 (169.22±99.29).
The above test showed though the visual motor scanning was preserved for more time in the treatment arm this was statistically significant with $p<0.01$.

Quality of Life Assessment: In the treatment arm the value corresponding to the decline in <50% of baseline QOL began at C3 (mean: 36.05±9.70) and reached the minimum after 6 months after treatment (mean:17±7.07). In case of control arm the value corresponding to the decline in <50% of baseline QOL began at C2. (Mean: 39.90±9.46) and reached the least value at C5 (17.20±4.66).
These results clearly indicate that although there is improvement in Quality of Life in the treatment arm there is no significance in the p value.

Overall Survival: When comparing both the arms the over all survival in the treatment arm after completion of treatment was 9.15 months and 6.35 months in the control arm. This was statistically significant with $p<0.01$.
The other secondary end point such as Objective Response Rate (ORR), Progression Free survival (PFS), Disease Control Rate (DCR) and Disease Free Survival (DFS) could not be assessed. This is because of the difficulty in imaging these ill and debilitating patients especially when they are detoriating. With the data which was obtained is not enough to determine a significant sample size to assess the above results.
In the study done by Deng[5]. The efficacy and roles of combining temozolomide (TMZ) with whole brain radiotherapy (WBRT) in protection neurocognitive function (NCF) and improvement quality of life (QOL) were investigated and compared with WBRT alone in the treatment of NSCLC patients with BMⅡ.
In this study the same regimen of temozolamide as used in our study was used. However, the Neurocognitive function was assessed by variety of scales including Human Verbal Learning test-R, COWA and Trail making test were used.
The Quality of life was assessed using Functional Assessment of Cancer Treatment for Lung, Chinese version was used. This study showed that there was improvement in Objective Response Rate and Disease

Control Rate. There was also improvement in the NCF and QOL at 5 months between the treatment arm and the control arm.

Another study done by Liao[6]. was a metanalysis of various studies from MEDLINE, EMBASE, Cochrane Library, etc. about the WBRT along with temozolamidein the treatment of NSCLC. This study showed that there was a stastically significant improvement in Objective Response without much imorovement in the OS. There were also significant myelosupression that was seen in elderly patients above 65 years.

Further more meta analysis done by Bai[7]. Eligible RCTs demonstrated that both WBRT and TMZ significantly improves the ORR and over all survival (Statistically insignificant). However there was an increase in the incidence of GI toxicity and myelosuppression was significant for all-grades.

The dosage of Temozolamide used in this studies varied and the above side effects were seen more when used in adjuvant dosage of 250mg/m^2 and there was a slight decrease in toxicity when the dosage of temozolamide was decreased.

A phase 3 trial were-Whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1-3 brain metastasesII is done by RTOG 0320. This study showed that the addition of TMZ or ETN to WBRT+SRS in NSCLC patients with 1-3 brain metastases did not improve survival and possibly had a deleterious effect.

The study done by Deng *et al* published is the basic model in which this study has been designed, however additional parameter of motor functioning namely Peg board analysis has been added in this study.

CONCLUSION

The above study-Neurocognitive function and Quality of life assessment in patients receiving whole brain radiotherapy with adjuvant Temozolamide and whole brain radiotherapy alone had shown that there is statistically significant preservation of neurocognitive function in the motor skill assessment of non dominant hand and also in the visual motor scanning domain. There was also increase in overall survival of 3 months which was statistically significant. Though all the other domains showed significant preservation of NCF but these were not statistically significant.

In future there must be single tests which assess all the domains of function in the patient decreasing the effort put by the patient in attending these questionnaires. The location of the primary tumor, the basic tumor characteristics and the response to treatment may also decrease the NCF along with the toxicity profile which can be considered in future in determining the final outcome.

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