" 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 "

A DOUBLE ARM PROSPECTIVE STUDY

Dissertation submitted in partial fulfillment of

DOCTOR OF MEDICINE
RADIOTHERAPY

MD BRANCH IX
EXAMINATION - MAY 2020

DEPARTMENT OF RADIATION ONCOLOGY
MADRAS MEDICAL COLLEGE
&
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
CHENNAI – 600 003

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY
CHENNAI – 600 032
Reg No : 201719003

CERTIFICATE

This is to certify that **Dr. K. C. JYOTHISH,** has been a postgraduate student during the academic period 2017 to 2020 in the Department of Radiation Oncology , Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai - 03.

This Dissertation titled **" 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 "** is a bonafide work done by him during the study period and is being submitted to The Tamil Nadu Dr. M.G.R Medical University in partial fulfillment of M.D Branch IX Radiotherapy Examination.

Dr. R. JAYANTHI M.D.,FRCP.,[Glasg]

THE DEAN,

Madras Medical College &

Rajiv Gandhi Government General Hospital,

Chennai-600003.

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Prof. Dr. V. VISVANATHAN D.C.H., M.D.R.T.,

Head Of Department,

Department Of Radiation Oncology,

Madras Medical College &

Rajiv Gandhi Government General Hospital,

Chennai-600003.

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Prof. Dr. T. N. VIJAYASREE. D.C.H., M.D.R.T.,

Professor & GUIDE,

Department Of Radiation Oncology,

Madras Medical College &

Rajiv Gandhi Government General Hospital,

Chennai-600003.

DECLARATION

I hereby declare that the dissertation entitled **" 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 "** is a double arm prospective study done by me under the guidance and supervision of Prof. Dr. T. N. Vijayasree D.C.H., M.D.R.T is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch IX, RADIOTHERAPY is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai

Date:

Dr. K. C. JYOTHISH.,
M.D. Radiotherapy
Post Graduate Student
Department of Radiation Oncology
Madras Medical College &
Rajiv Gandhi Govt. General Hospital
Chennai -03

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Dr. VIJEY KARTHICK M.D.R.T.,

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CONTENTS

INTRODUCTION

INTRODUCTION

EPIDEMIOLOGY

Metastases is defined as the spread of the tumour from primary site to a distant site. In metastases the histopathology of both primary and the distant site tumours are the same . Metastases is the most common tumour in the brain. It's seen in about 20 to 30% of all adult cancer patients. Development of imaging modalities and interventions has increased the diagnosis of brain metastases in the recent days .

Annual incidence of brain metastasis constitute about 1,70,000 to 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 is more specific and helps in easier 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 .The median age for diagnosis of brain metastases is about 60 years and overall clinical incidence is 30% .

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 to 16 months.

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 et al , published the first paper on the effectiveness of WBRT for multiple cerebral metastasis. Furthermore there was no difference in response to treatment in

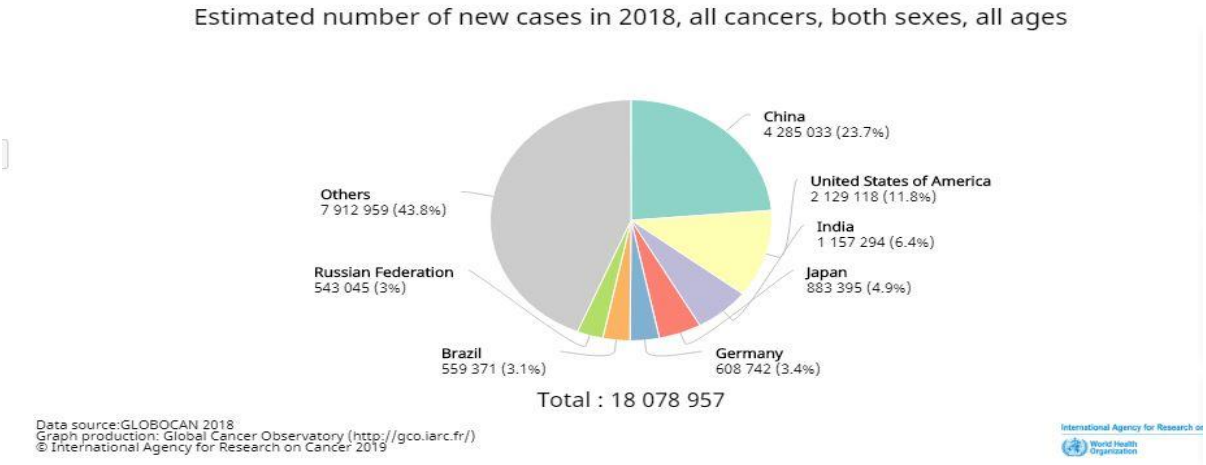
patients receiving WBRT for a radioresistant primary versus radiosensitive primary.

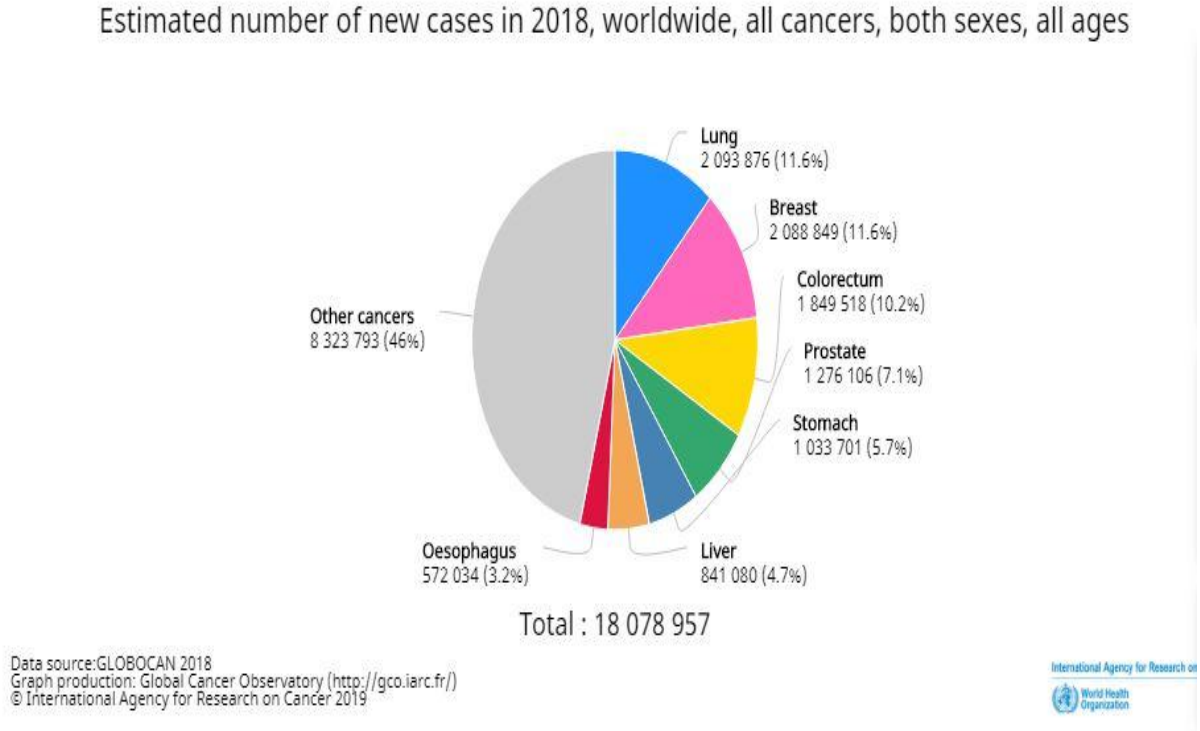
WBRT has been considered as an effective palliative options for patients with brain metastases for alleviating the symptoms and to decrease the use of corticosteroid to control the brain edema .

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.

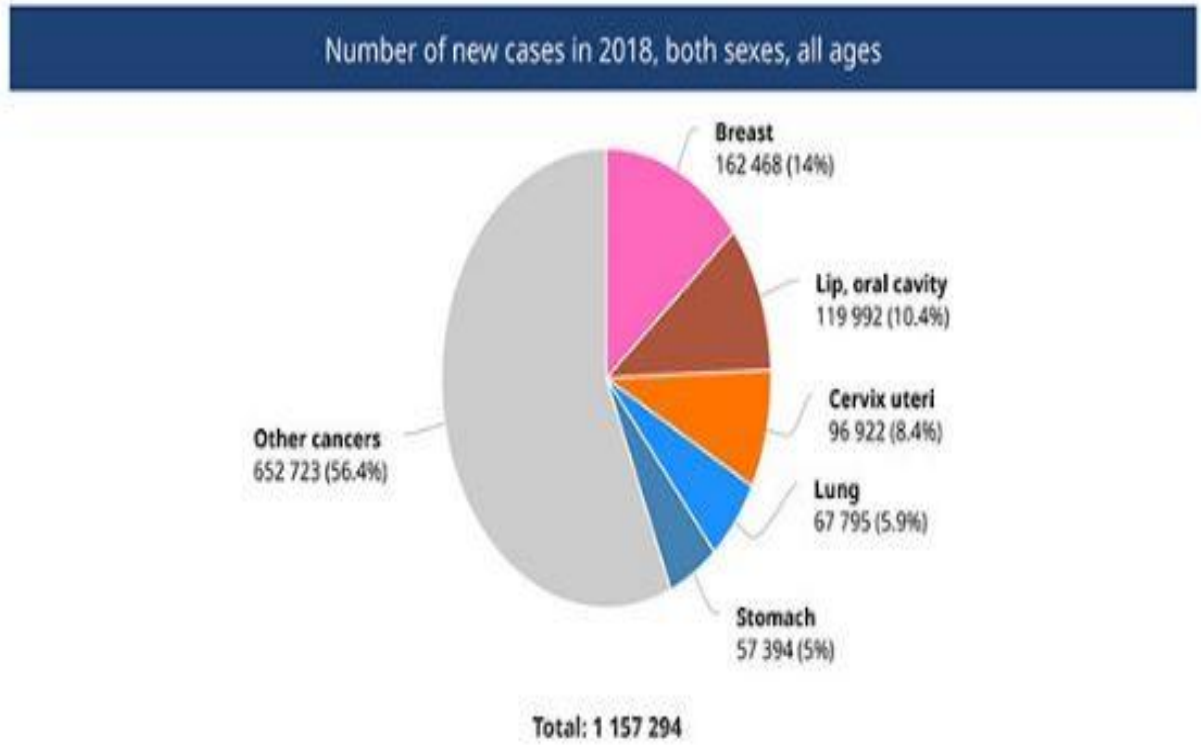
In recent years there have been studies which show the addition of few radio sensitizers along with the conventional Whole Brain RT which not only improves the local control but also decreases the detoriation of neurocognitive function in these patients.

CANCER BURDEN ACROSS THE WORLD:

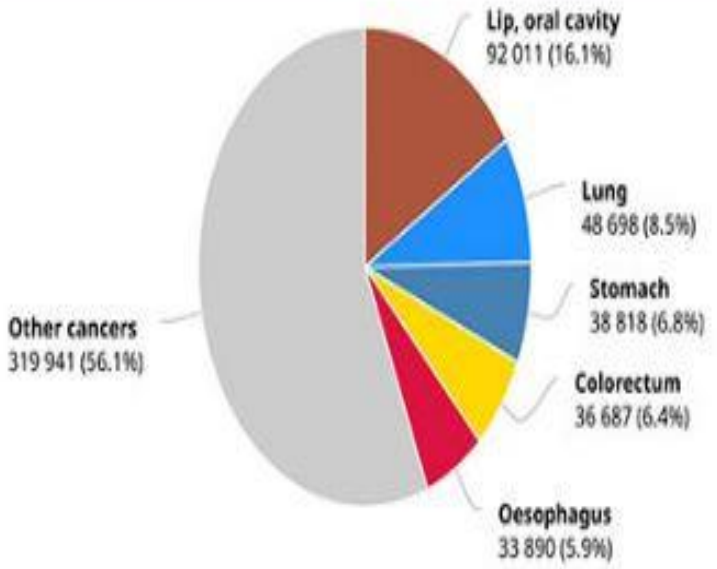




CANCER BURDEN ACROSS INDIA:

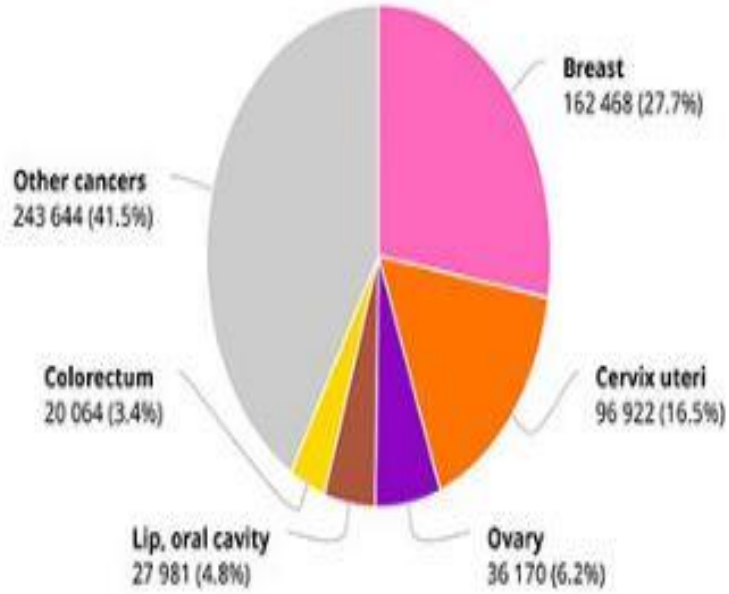


Number of new cases in 2018, males, all ages



Total: 570 045

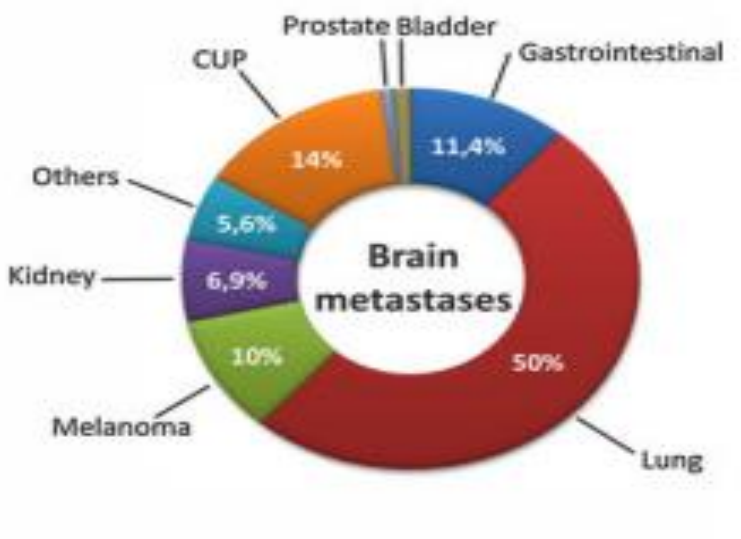
Number of new cases in 2018, females, all ages



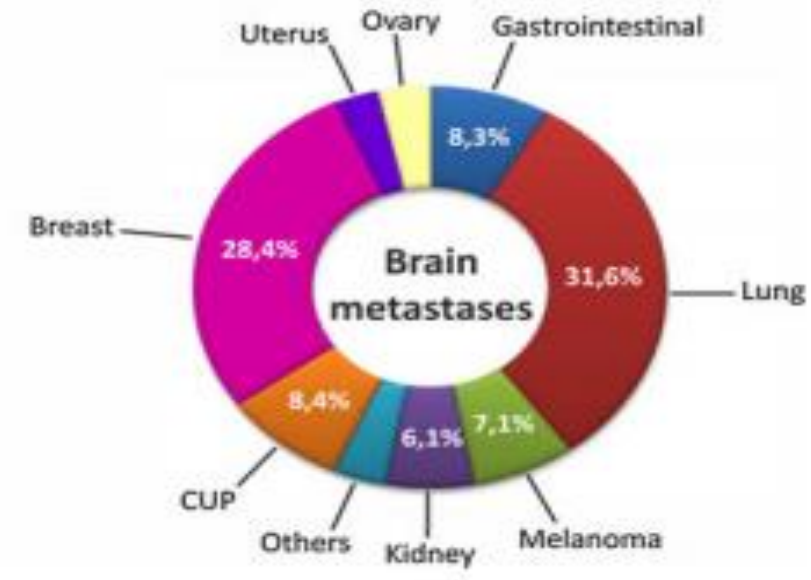
Total: 587 249

CANCER BURDEN ACROSS TAMIL NADU:

In the absence of state wide cancer registry it has been predicted that by 2018, the number of cancer cases may increase upto 7300 in Chennai alone and 60000 new cases throughout the state.In our department last year alone 289 cases of brain metastases were reported.



Relative frequency of brain metastases in Males-Worldwide.



Relative frequency of brain metastases in Females-Worldwide

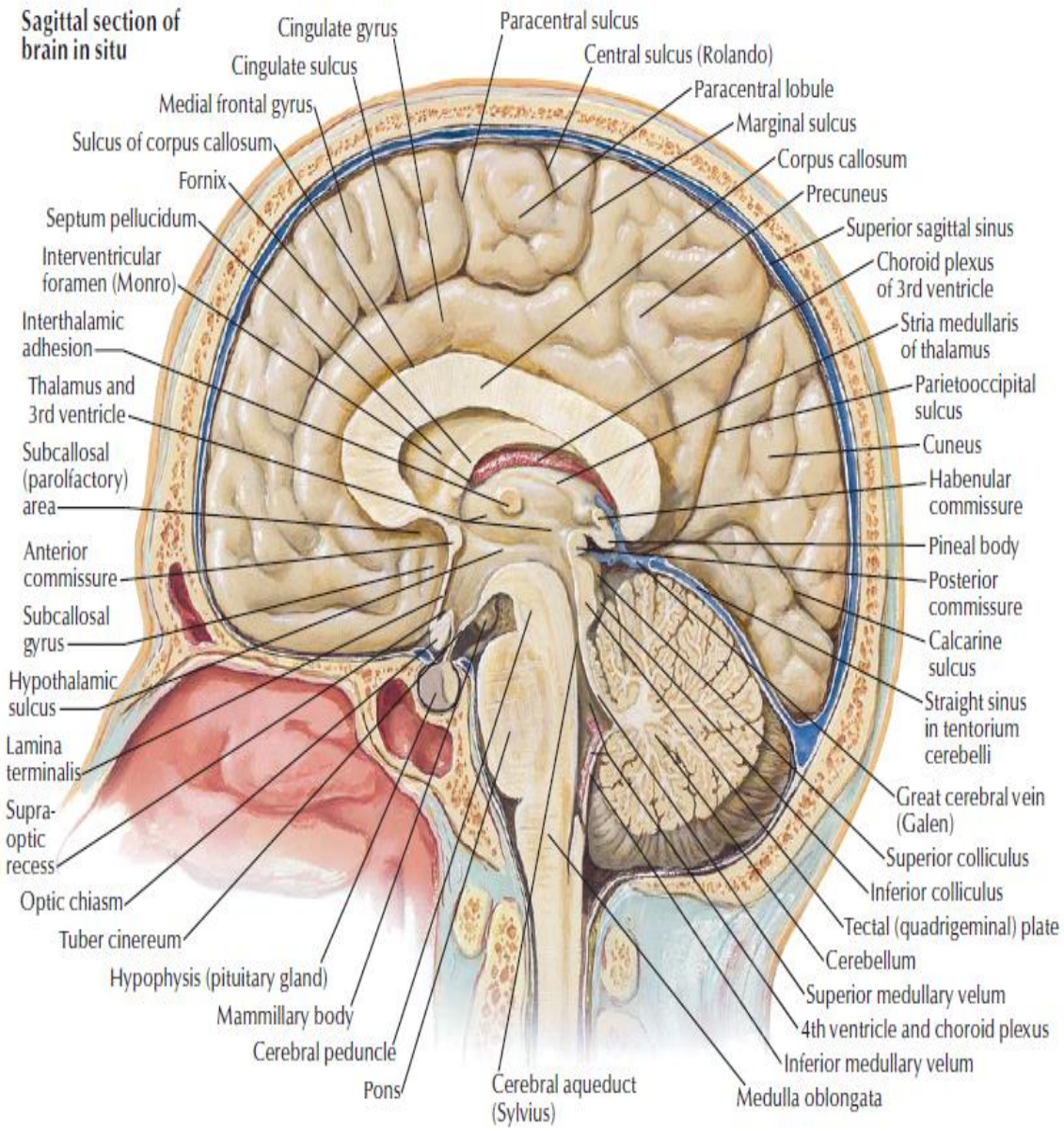
OUTLINE OF ANATOMY OF BRAIN:

Brain is the most vital organ of the body.Brain can be structurally divided into 3 parts

1) Cereberum

2) Cerebellum

3) Brain stem



Cereberum is the largest region of the brain .It can be divided into two hemispheres called Cereberal hemispheres. The outer grey region of the brain is called the Cortex and the inner white matter is called Medulla.

Cortex is further divided into Neocortex and much smaller Allocortex. The two hemispheres are connected by commisural nerve tracts. The largest of these commisural neuronal tract is the Corpus Collosum. Each cerebral hemisphere is divided into four lobes:

1)Frontal Lobe

2)Parietel Lobe

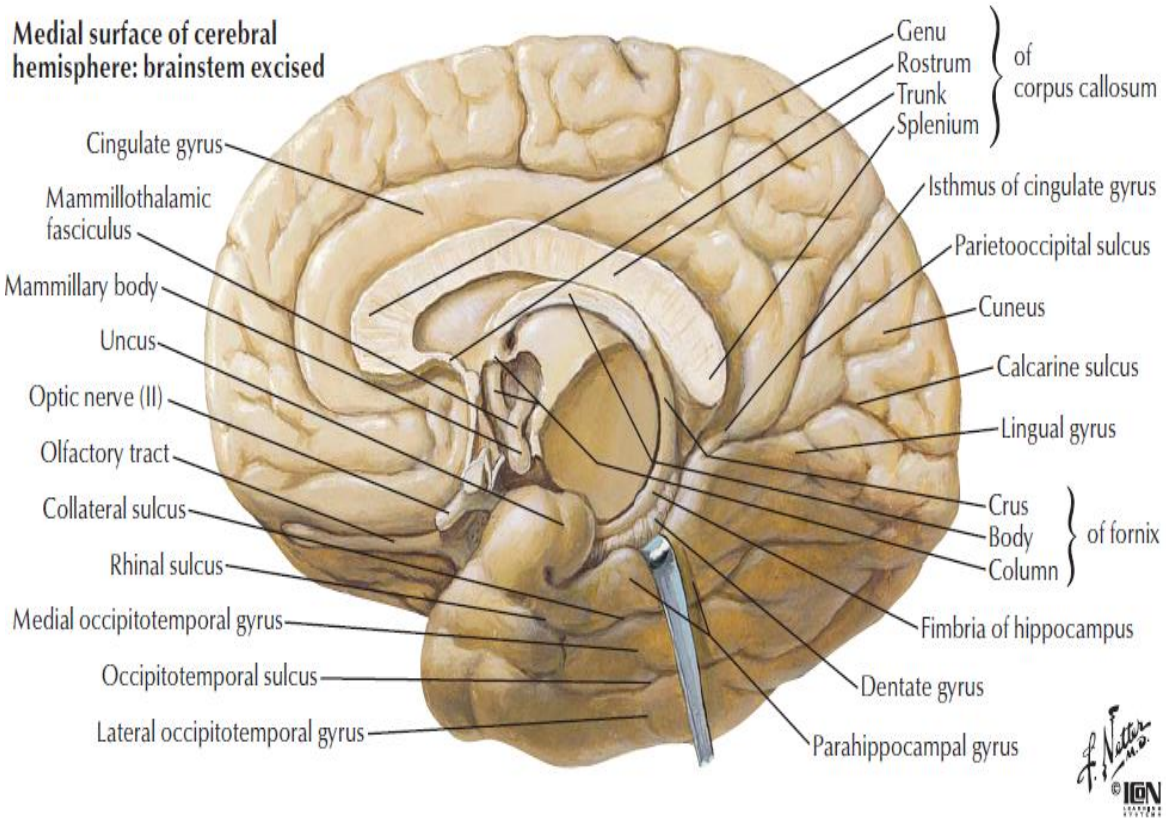
3)Temporal Lobe

4)Occipital Lobe

Cereberum contains the ventricles which helps in the production and circulation of CSF within the brain. Located deep with in the cereberum is the structure called basal ganglia also known as basal nuclei. Largest component of basal nuclei is striatum. Other structure includes substantia niagra, subthalmic nucleus and globus pallidus. Located below and in front of the striatum are number of basal forebrain structures.

They are nucleus accumbens , diagonal band of Boraca ,nucleus basalis, medial septal nucleus and substatia inominata.

The major function of these region is the production pf neurotransmitter Acetylcholine. Nucleus Basalis is the major cholinergic output.



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Cerebellum lies in the posterior region of cranial cavity,beneath the occipital lobe and is divided into

1)Anterior Lobe

2)Posterior Lobe

3) Floconodular Lobe

Anterior and the posterior lobes are connected by Vermis. Beneath the anterior and the posterior lobe is the Floconodular lobe . Its connectede to the

mid brain by the superior cerbellar peduncle, pons by middle cerebellar peduncle and the medulla by inferior cerebellar peduncle.

Brain stem consists of Midbrain, Pons and Medulla oblangata. Brain stem is connected to cerebellum by means of pairs of tracts. Below the several cortex are various important structures like thalamus, epithalamus, pineal gland, hypothalamus, pitutary gland,subtahlamus, amygdyla,hippocampus,(parts of limbic system .

Histologically the cells in the brain are called neuronal cells and the supporting cells of the brain is called as glial cells.

DIFFERENT LOBES AND FUNCTIONS

Frontal Lobe:

Its responsible for higher cognitive functions which includes

spontainety,

problem solving,

memory,

language ,

motivation,

impulse control ,

judgement,

social and sexual behaviour

Prefrontal cortex mediates the mood and personality of the individual

Temporal Lobe:

Temporal lobe contains the language area " Boracas Area" of the brain.Temporal lobe plays a vital role in

Emotional response,

Smelling,

Tasting,

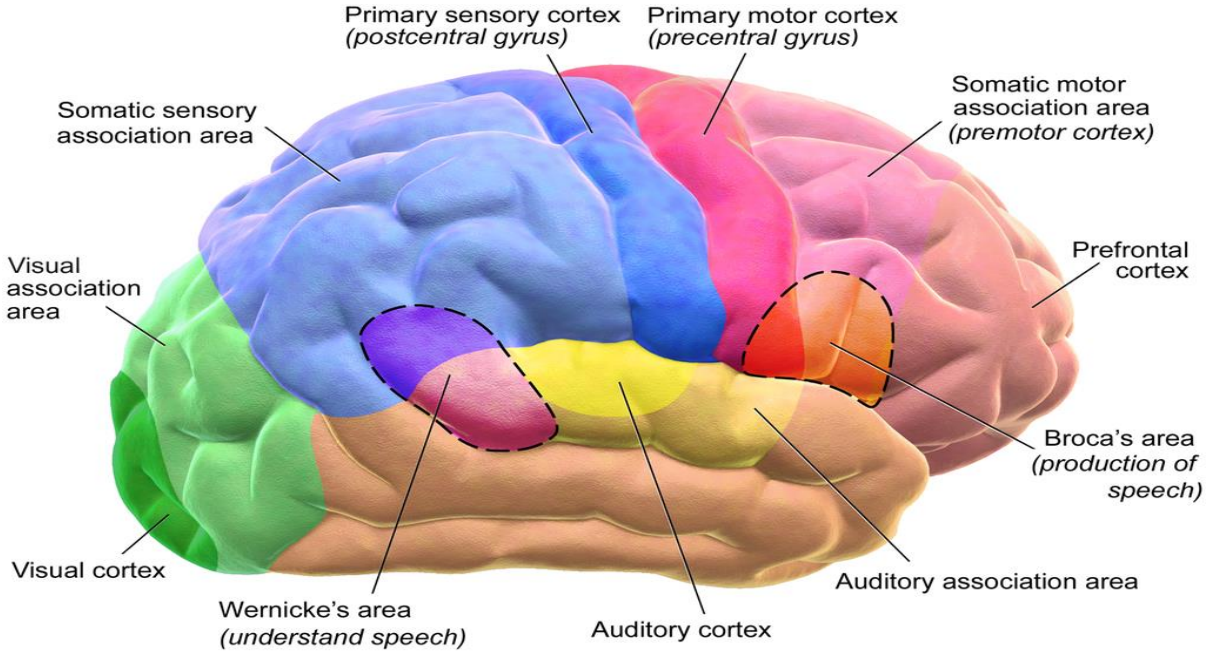
Perception,

Memory,

Understanding Music,

Agressiveness

Sexual Behaviour



Parietal Lobe:

This lobe contains the “Wernickes Area” of the brain which is responsible for matching of written words with sound of speech that is spoke. Its also responsible for

Sensations such as touch, smell and taste,

Spatial Awareness

Hand-eye coordination movements

Arcuate Fasciculus is a part of white matter, which connects the Brocas area and Wernickes area through thge temporal , frontal and parietal lobe. Allows coordinated and comprehensive speech

Occipital Lobe:

Located in the rear area of the brain.Visual cortex is located in the Occipital lobe and controls

Vision and

Recognition

Limbic Lobe and the Limbic System:

Limbic Lobe is located deep in the brain and forms the limbic system.Limbic system is the area of the brain responsible emotion and

memory.It connects the lower and higher brain fuctions. The Limbic system is made up of

Cingulate gyrus

Amygdala

Anterior Thalamic nuclei

Hypothalmus

Hippocampus

Thalamus is the gateway were all the sensory inputs of the brain pass through it to the higher levels. Hypothalmus is under the thalamus and controls major bodily functions which includes

Control for Autonomic system

Centre for emotional response and Body behaviour

Regulates Body Temprature

Regulates Food Intake

Regulates water balance and thirst

Controls Sleep and wake cycles

Controls Endocrine System

Medulla Oblangata:

It controls many of the involuntary reflexes of human body like

Regulation of cardio vascular and respiratory activity

Swallowing

Sneezing

Coughing

Vomiting

Medulla is the site of orgin of many cranial nerves

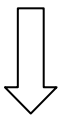
Pons acts as a bridge between the cerebellum to rest of the brain. It helps in modifying the respiratory output in medulla

MECHANISM OF BRAIN METASTASES

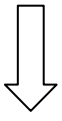
The exact mechanism of brain metastases is still exactly not clear.Although various theories have been proposed over the years. Some of the major hypothesis on brain metasatses includes “Seed and Soil Hypothesis” , “Metastatic cascade theory” etc. The Metastatic cascade theory has been accepted worldwide by various authors.

The general proposed mechanism of brainmetastases involves the following steps

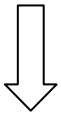
Dissemination of tumor cells from the primary tumor



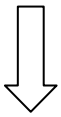
Attachment to the microvascular endothelium



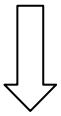
Extavasation of the tumor cells into the brain parenchyma



Interaction of the extravasated cells with the local environment



Intiating angiogenesis caused by various local and systemic responses



Finally, intiation of proliferation

SEED AND SOIL HYPOTHESIS:

According to this theory the metastases to a distant organ does not occur by a matter of chance.Its due to the affinity of particular tumor cell (seed), towards the mileu of certain organ (soil) which is mediated by several trophic factors

METASTATIC CASCADE THEORY:

Metastases usually occurs in the late stage of the disease inmost of the case. But in some tumors this occurs even in the early stage of disease.

According to this theory theprimary tumor spreads to a site A and further metastases to another site B is from site A.

SPREAD OF METASTASES TO BRAIN:

In general its belived that metastases to the brain is mainly via the arterial blood dissemination. This is supported by the fact that most of the brain tumors are locatedin the Grey-White matter junctions and also around the terminal water shed areas of the terminal regions of major intracranial arteries.

Retroperitoneal tumors such as GIT, Uteres, Kidney and Bladder shows retrograde dissemination via th Batson plexus.Intra medullary spread via the spinal cord is rare and lympathic spread does not happen in brain as brain do not have any lymphatics.Retrograde pattern of spread will have metastases in the posterior fossa region of the brain.

PENETRATION INTO BRAIN

Blood brain barrier is the protective mechanism which prevents the deposition of the metastases into the brain. Inspite of this protective mechanism the adhesion of tumor cells and their migration into the brain parenchymaoccurs due to a complex molecular level interaction. In depth molecular level interaction in the development of brain metastases still under study.

But however with the data availableit has been reported that the attachment of tumor cells to the brain endothelial cells occurs due to interaction of tumor cell receptors with the endotheleial cell molecules such as integrins,selectins and chemokines

SELECTINS:

These are carbohydrate binding molecules and are divided into 3 subtypes: P selectin expressed over activated endothelial cells and platelets, L-Selctin expressed over the leukocytesand E selectin that is expressed over activated endothelial cells. The tumor cells expresses the selectin ligand which attaches with the selectin molecule and uses leukocyte migratory molecule for tumor migration and this mechanismis called “leukocyte mimicry”

INTEGRINS:

These are hetrodimeric transmembrane glycoprotein that help in the cell to cell, cell to extracellular matrix adhesion and cell migration. It has 18 alpha and 10 beta integrin subunit that can assemble into atleast 24 combinations. Examples are fibronectin, complement factors, collagen, fibrinogen, C-reactiveprotein and others. Alpha-v-Beta 5, Alpha 3 beta, Beta 4 are someof the examples of integrins which play a vital role in the metastases of various tumors from the primary. Integrins increases VEGF production , this results in the

decrease in the integerity of vasuclar endothelial cells of the bloodvessels in the brain and causing the transmigration of these cells into the brain. Inhibition of these integrin molecules has been used in targeted therapies of various cancer with brain metastases

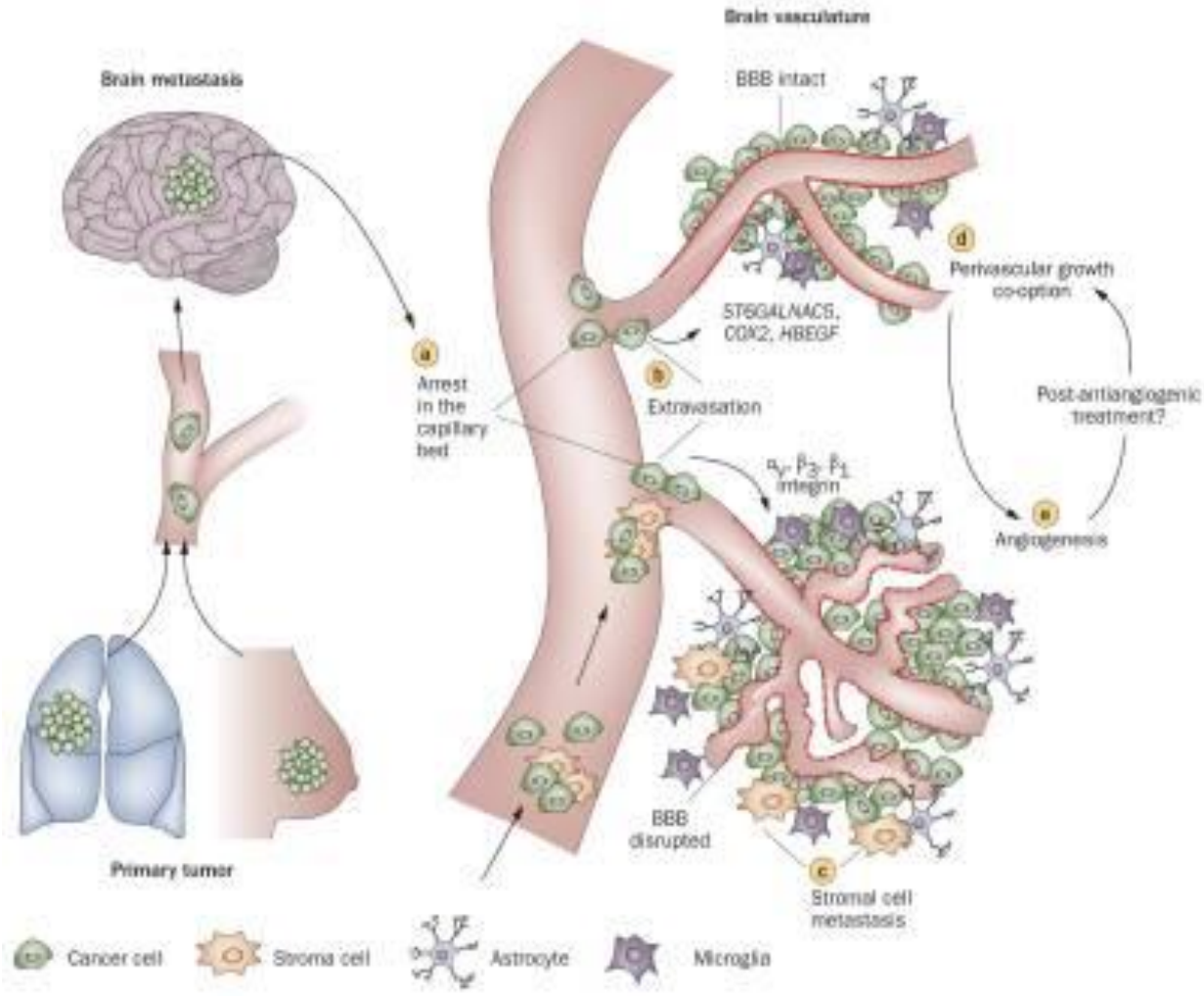
CHEMOKINES:

These are cytokines that guides the cell migration and thereby promoting selective tropism. Examples include CXCR4, CXCL12. Both of them have been expressed in breast cancers and small cell carcinoma of Lung, enabling them to be the targets for immunotherapy.

Few other factors like prostagladin synthesising Cyclo-oxygenase 2, Heparin binding epidermal growth factor have also been found to have associated in the mechanism of brain metastases of few cancers.

DIFFERENCE IN TUMOR COLONISATION:

Its found that different tumors exhibit different pattern of spread within the brain. Melanomas show a typical perivascular tumor cell growth which may be due to its interaction with integerin beta subunit along the endothelial cell lines. Carcinoma Lung shows a nodular growth pattern with early signs of angiogenesis.



Fraction of both melanoma and Ca Lung enter into a dormant phase and lies as a single cell in the perivascular spaces which manifest late as brain metastases.

INTERACTION OF TUMOR CELLS WITH ECM:

Extra Cellular matrixis the acellular component which supports the cellular architecture. Its made up of water, proteins , polysaccharides. Some ECM components such as fibronectin and collagen are absent in brain parenchyma whereas proteoglycans are abundant.ECM components form the

‘perineural nets’ of reticular networks encomposing the neuronal bodies and proximal dendrites. Cancer colonisation requires degradation of ECM by components like heparanase and Matrixmetaloproteinase(MMP).

HEPARANASE:

Heparanase is the only functional mammalian endoglycosides degrades heparin sulphate that is present of the cell surface and ECM. In Her2 Neu positive Breast cancers its shown that heparanse moves to the nucleolus and cofunctions with Topioisomerase-1 upon the activation of Her2 Neu receptor activation, which points towards the possibility of targeted therapy in brain metastases of Her 2 Neu positive Ca Breast. Suramin , a poly sulfanated napthylurea used in the treatment of sleeping sickness and trynosomiasis has been found to be an effective inhibitor of Heparanase.

MATRIXMETTALOPROTEASE:

This is a zinc dependent endopeptidase plays a important role in destruction of ECM and cancer invasiveness. Breast cancer clones with increased levels of MMP are found to have increased tendency to metastases including colonization in the brain. Furthermore paracrine signalling by the astrocytes of brain is found to increase the expression of MMP in metastatic brain cancer cells.

TUMOR CELL INTERACTION WITH BRAIN GLIAL CELLS:

ASTROCYTES:

These are the cells that are faced by the tumor cells immediatedly when they cross the blood brain barrier. Its also shown that secondary brain tumors are accompanied by reactive gliosis. Several studies have shown that astrocytes have proneoplastic properties and increase the invasiveness by degrading the ECM by Heperanase production.

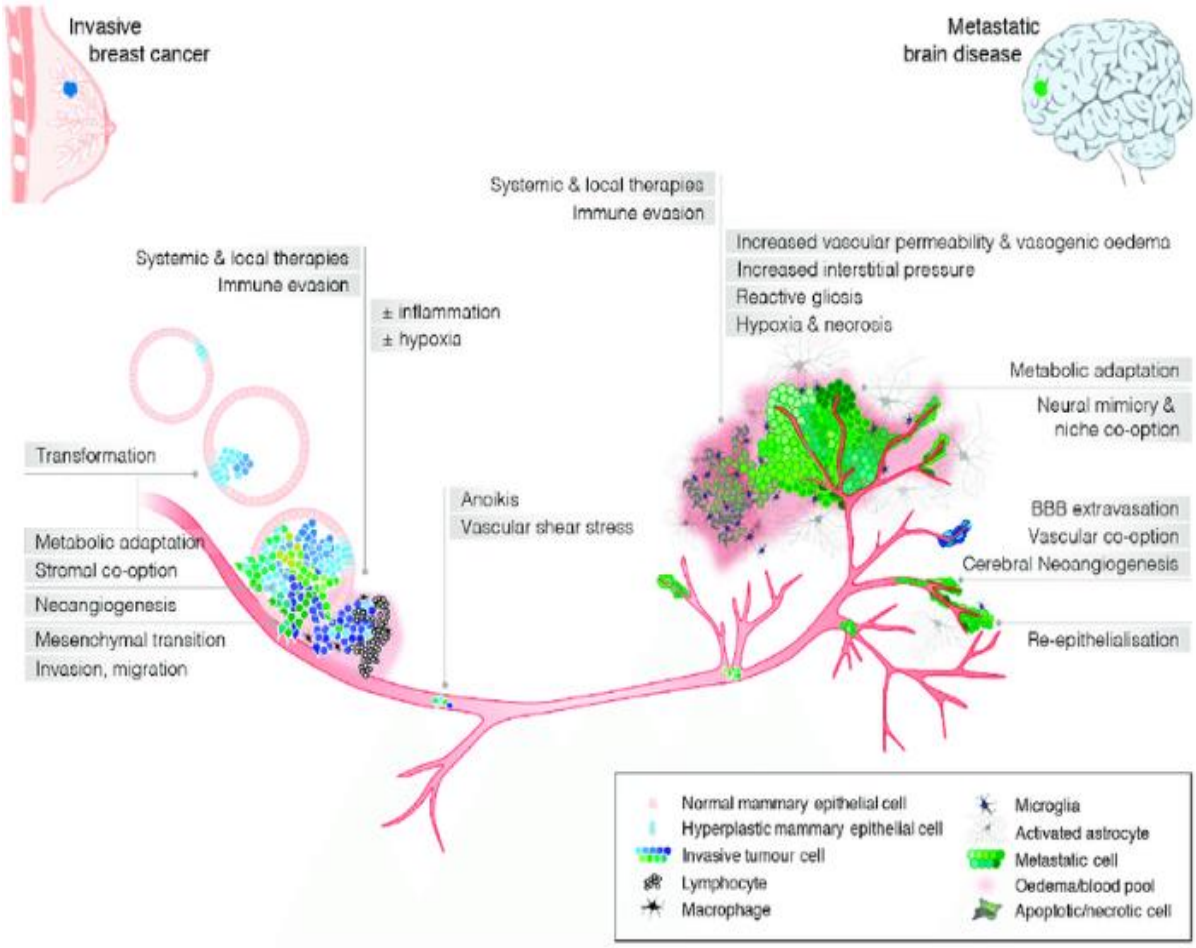
The increase in production of cytokines by astrocytes also found to enable favourable environment for metastases deposition in brain by paracrine signaling. Astrocytes have been found to play a role in therapy resistance especially by inhibiting the apoptosis of chemo treated cancer cells. This mechanism has been obeserved more in melanomas in vitro studies

MICROGLIAL CELLS:

Microglial cells are considered to be the main immune protectors of the brain. These are found to be effectively activated in various brain conditions like stroke, infection, cancer and neuro degeneration.

The mechanism of recriutment in the damaged site is not clear but may be attributable to Hypoxia Induced Factor -Alpha1 and CXCR4. Generally its believed that activated microglial cells are tumoricidal and lyse the cancer cells by releasing Nitrous Oxide. But in case of brain metastases microglial cells

increase the colonisation of cancer cells in the brain. Several invitro studies have shown that microglial cells precede the tumor cells in the brain parenchyma and prepares the parenchyma for tumor deposition and colonisation.



PARACRINE SIGNALING:

NEUTROPHINS:

Neutrophins including the prototypic Neural growth factors are a group of protiens expressed mainly in the brain. These proteins simualte and control neurogenesis by pro mitotic, anti apoptotic and chemotactic pathways.

ANGIOGENESIS:

This is the most important step in the tumor depostion and progression in the brain parenchyma. This is mainly activated by Vascular Endothelial Growth Factors (VEGF). Hence using of VEGF inhibitors decreases tumor brain metastatic deposition and tumor spread.

VASCULAR PARAMETERS FOR DIFFERENT TUMORS:

Its shown that different tumor cells exhibit different pattern of vasculature during brainmetastases. Most of the tumor cells induce neoangiogenesis for their depostion and early expansion. But some tumor types grows independently of the new vessel formation in the neuroparenchyma. Example being melanomas.

Melanomas tend to grow in region with significant lower microvascular densities and tend to grow along the lines of existing cerebral vasculature.

However in Lung cancer cells tend to produce angiogenesis in their proliferating nodule after they reach the critical diameter of about 150-200 micro meters. Glomeuroid bodies resembling that of renal glomeruli is common finding in Small Cell Lung Cancer brain metastases.

PATTERN OF BRAIN METASTASES IN CA BREAST:

It occurs in about 10-16% of Carcinoma breast. Autopsies have shown that more than 30% of cancer breast patients have brain metastases. Development of brain metastases related to young age, Her 2 Neu positive, Triple negative disease.

HER2 NEU POSITIVE CA BREAST:

It is found in about 16% of Breast Ca. Its generally found to be associated with poor prognosis, and increasedincidence of brain metastases especially before the advent of targeted therapy. It has been stated that development of brain metastases in Her2 neu positive cases is found to be 26-39%. But the reasons for development is unclear , probably multifactorial. One reason may be that Her 2 overexpression may increase the brain metastases by direct biological effect.

Another possible reason may be that treatment with Trastuzumab which is used for the targeted therapy of Her2 neu positive Ca breast. Trastuzumab has been found to have lower CNS penetration and do not have a significant role in prevention of brain metastases in Her 2 neu positive Ca Breast and makes brain the possibke “sanctuary site” of metastases

Poor CNS penetration of Trastuzumab is seen even after WBRT and even in leptomeingeal metastases. Various randomized studies have shown that

increase in Brain metastases in Trastuzumab treated Her2 positive patients. Another possible increase in brain metastases in these patients may be due to increase in survival time given by Trastuzumab treatment, which increases the chance of developing brain metastasesin these patients. Further newer agents like Laptinib have found to have an impact in Her2 positive Ca Breast and their incidence of Brain metastases.

Lapatinib is a dual Tyrosine Kinase Inhibitor with targets both EGFR and Her2 Neu. The efficacy of single agent lapatinib in treatment in Her2 Neu postive ca breast has been well established.

Studies showing the combination of laptanib with other cytotoxic agents like Capacetabine along with WBRT in Brain metastases of Her 2 positive Breast Ca have been promising . These studies showed some first line or secondline activity in Her 2 positive Metastatic Ca Breast.

TRIPLE NEGATIVE CA BREAST:

Triple Negative Breast cancers are commonly found in young age and African descent. These tumors are found to show aggressive behaviour and higher incidence of metastases especially visceral metastases. Gene profiling of these cancers have shown that they are hetrogenous and comprise molecular distinct subtype which increase the chance of brain metastases. PARP (poly adenosine diphosphate ribose polymerase) are a family DNA repair enzymes. PARP inhibitors are found to be effective in the triple negative breast cancers

and BRCA mutated breast and ovarian cancers.Examples include Olparib, velaparib and Iniparib. These drugs also found to increase the cytotoxic effects of other chemo agentswhen used in combinations.

But the effectiveness of these drugs in brain metastases has not been well understood. Several phase 2 trails on their way to show the efficacy of these drugs in TNBC brain metastases.

SPECIFIC TARGETS OF METASTASES:

Polo-like kinase 1(Plk-1) is an molecular target that has been found in dividing cells than in normal cells. Plk-1 is upregulated in several tumor cells. Plk-1 mRNA expression was higher in brain metastases than in systemic metastases in Ca Breast.Hence giving scope for newer target for agents in the therapy for brain metastases.

CA LUNG AND PATTERN OF BRAIN METASTASES :

Brain metastases is found in about 10-25 % of carcinoma lung patients during initial diagnosis itself and 40-50% Ca Lung patient develop brain metastases during the course.The two major types of Ca Lung included Non small cell Lung Cancers(NSCLC) and Small Cell lung Cancers(SCLC). NSCLC constitutes of 80-85% of Ca Lung and remaining includes SCLC. The incidence

of brain metastases is found to be higher in Small cell than in Non Small cell variant.

NON SMALL CELL LUNG CANCERS:

Brain metastases in NSCLC had been related many features including

- Large primary tumor
- Lymphovascular space invasion
- Presence of largelymphnodal metastases
- Hilar space involvement
- Females
- Non squamous histology especially Adenocarcinoma
- High LDH levels
- High CEA levels
- Longer overall survival
- Preoperative chemotherpy administration
- Response to Neoadjuvant Chemotherapy

EGFR mutation is seen in 10-25% of carcinoma lungs especially associated with adenocarcinoma. Oral Tyrosine kinase inhibitors like Erlotinib and Geftinb are approved for the use in NSCLC. Geftinib is being routinely

used in NSCLC with EGFR mutations were as Erlotinib is used in locally advanced or metastatic NSCLC that has been shown to fail atleast one first line of chemotherapy.

Meta Analysis by Zheng et al have shown that the use of Erlotinib or Geftinib in NSCLC with EGFR mutation along with Whole Brain RT has improved outcomes when compared with WBRT in these patients. Erlotinib have higher CNS concentrations when compared with Geftinib, hence preffered than Geftinib in Brain metastases. It has also been showed that resistance to EGFR inhibitor is due to the Mesenchymal epithelial transistion factor(MET) amplification. Hence recent data suggests that usage of MET inhibitors along with EGFR inhibitors found to improve outcome in CNS treatment of NSCLC.

Anaplastic Lymphoma Kinase (ALK) gene activation due to oncogenic fusion of ALK and Echinoderm associated microtubule protein 4 (EML-4) gene is seen in about 4 % of NSCLC.

Its more common in younger patients and patients who are non or light smokers and also in adeno carcinoma. Its shown that Crizotinib an ALK and Met inhibitor is found to be effective in these patients with ALK mutation. But however effectiveness of Crizotinib in brain metastases has not been very effective due to its poor CNS penetration and CSF concentrations.

PATTERN OF BRAIN METASTASES IN MELANOMA :

10% of melanoma patients end up having brain metastases and 73% of patients with disseminated cutaneous melanoma show brain metastases in their autopsies. The molecular determinnants in the formation of brain metastases in case of melanoma is not very clear but different cell lines exhibit different propensity of attraction towards brain parenchyma. But as mentioned earlier, brain parenchyma invasion in melanoma is independent of neoangiogenesis, enabling easy spread within the brain parenchyma.

BRAF INHIBITORS:

60% melanomas are found to have mutation of Serine threonine kinase v-RAF murine sarcoma viral oncogene homolog B1(BRAF). BRAF mutations are found in many human cancers but high levels are found in melanomas.Vermurafenib is an effective agent of BRAF inhibitor used in the systemic therapy as well as in brainmetastases of melanomas.

Although intial studies show promising results with BRAF inhibitors but patients develop secondary resistance to these drugs during course of treatment , this may be attributed to platelet derived growth factor upregulation or acquisition of NRAS or MET mutation

CLINICAL MANIFESTATION OF BRAIN METASTASES:

The clinical manifestation of brainmetastases is mainly due to

- Symptoms due the space occupying effect of tumor and raised intracranial pressure
- Symptoms with respect to the location in the brain and inhibition of function of their respective function.

Headache is the most common presenting symptom in patients with brain metastases. This is due to obstuctive hydrocephalus, edema within closed space and diffuse parenchymal edema.

Headache is usually mor e in the morning which is due to hypoventilation during sleep casing increased cerebral edema and often wakes up the patient from sleep. Its worst with coughing and sneezing and may cause personality or behavourial changes.

Normal intracranial pressure ranges from 7-15mm of Hg and in ranges of 20-25 mm of Hg may need intervention. Patient is generally alert till 25-40mm of Hg and when ICP elevates beyond 40-50mm of Hg there is alteration in the level of consiousness.

Pressures of more than 200 mm of Hg can cause life threatening herniation syndromes. Uncal herniation syndrome ,is more common in lesions arising from the temporal brain. Uncus is a region located in the middle

temporal lobe, in the supratentorial region and communicates with the subtentorial compartment via tentorial notch . The increase in ICP causes herniation of brain matter from one compartment of brain to another,and impingment of this tentorial notch.

The structures located near the notch includes midbrain, cranial nerves, superior and posterior cerbellar arteries and cerebellum is located posterior to this structure.

The impingment of these structures result in pupillary dilatation , abducens palsy and Cushings traid. Cushing traid includes increased systolic Blood pressure, decreased Heart Rate(bradycardia) and widened pulse pressure along with abnormal pattern in respiration. The earliest and most consistent sign with elevated ICP is unilateral dilatation of the pupil. This is due to the occulomotor nerve compression near the tentorial notch. The compression of posterior cerebellar arteriesmay result in homonymous hemianopia .

Ipsilateral or contralateral hemiparesis may also been found with Uncal herniation syndrome. Patients affected with Uncal herniation syndrome may be awake initially and progress to rapid loss of consiousness, coma and death.

Normally vomiting associated with increased ICP does not accompany nausea. Its sudden projectile vomiting which is the characterictic of

raised ICP. Other symptoms associated with raised ICP includes gait abnormalities, slowing down of psychomotor functions,seizures, personality changes and somnolence.

In many occasions slowness of psychomotor activity, change in behaviourial pattern might be the only sign of raised ICP, This should not be confused with depression in older adults. Seizures are more common in supratentorial tumors.

MONRO-KELLIE HYPOTHESIS:

Monro-Kellie suggested that there exists a pressure volume relationship between Intracranial pressure, volume of Cerebro spinal fluid, blood,brain tissue and Cerebral Perfusion Pressure(CPP).

According to this hypothesis, cranial compartments are inelastic and the volume of cranium is fixed. Any increase in volume of any of the constituents of the brain like CSF, Blood or brain tissue is compensated by the decrease of the other. This forms the basis for cereberal herniation

The specific lobewise function for each lobe is mentioned below:

FRONTAL LOBE:

- Personality change
- Lack of inhibition
- Inattentiveness
- Lethargy
- Slowing of movements of hand on C/L side
- Spastic contralateral Hemiplegia
- Aparaxia (If dominant lobe is involved)
- Loss of intiation
- Speech (Speaking and Writing-Boracos area)

TEMPORAL LOBE:

- Understanding Language(Wernicke's Area)
- Memory
- Emotions
- B/L hemiparesis
- Spasticbulbar palsy
- Dementia
- Primitive Grasp, suck and snout reflex

- Mood
- Dominant lobe:

  -Minor perceptual problem

  -Spatial disorientation
- Non Dominant lobe

  -Dysnomia

  -Fluency-Wernicke like aphasia

  -Impaired perception in verbal commands

PARIETAL LOBE:

- Mild hemiparesis
- Visual inattention
- Mild to moderate sensory loss(touch, pain,tempearture)
- Homonymous Hemianopia
- Dominant lobe

  -Alexia

  -Dysgraphia

  -Other forms of Apraxia
- Non Dominant lobe

  -Perceptual abnormalaties

-Anosognosia

-Apraxia of Self Dressing

OCCIPITAL LOBE:

- Visual abbretions
- C/L Homonymous Heminopia
- B/L Lobe involvement: Cortical Blindness

THALAMUS:

- Relay station of cortex
- Also pays a role in attention, pain sensation,memory and alertness

BASAL GANGLIA:

- This includes the glabus pallidus, caudate and putamen.
- Nuclei located here works along with the cerebellum in coocrdinating fine motions like movement of finger tips

LIMBIC SYSTEM:

- This includes cingulate gyri, hypothalamus, amygdala (emotional reactions) and hippocampus (memory).
- This region is responsible for Memory,emotion and learning Hence the recent advancement of Hippocampal Avoidance RT in improving Neurocognitive function.

INVESTIGATIONS

The detection of brain metastases is important in intial staging of the disease itself. In other cases the pressence of neurological symptoms during or after treatment, may warrant neurological imaging and management varies accordingly.

NON CONTRAST ENHANCED CT(NECT)

Prehaps the first investigation encountered by any patients with neurological symptoms. This is because it can be easily acquired and also rapidly obtained and well tolerated. It helps in immediate identification of life threating conditions like hemorrhage, hydrocephalus and significant mass effect.

CT VS MRI

As discuused earlier, the location of brain metastases is in the grey white matter junction ,water shed areas of major arterial territories. Most common location of metastases is at cereberum (80%), cerebellum(15%), Basal ganglia(3%), sometimes they may also be located in the posterior fossa, choroid plexus and leptomeninges. The location of secondaries have also been seen in pitutary gland , but this is very rare and difficult to distingush from a secretory pitutary adenoma. In some cases of lymphoma , metastases can spread along or inside the cereberal vessel

Brain metastases can be solitary or multiple. Brain metastasess is usually solitary in

- Ca Breast
- Ca Thyroid
- Renal Cell Carcinoma
- Ca Colon

Multiple metastases are usually seen in

- Ca Lung
- Melanoma

But usually the number of lesions don’t suggest the type of primary which the metastases had taken place.

Metastases can also be hemorrhagic and non-hemorrhagic metastases. Hemorrhagic metastases is commonly seen in

- Choriocarcinoma
- Renal Cell Carcinoma

} Classically hemorrhagic

- Ca Thyroid
- Ca Lung
- Ca Breast

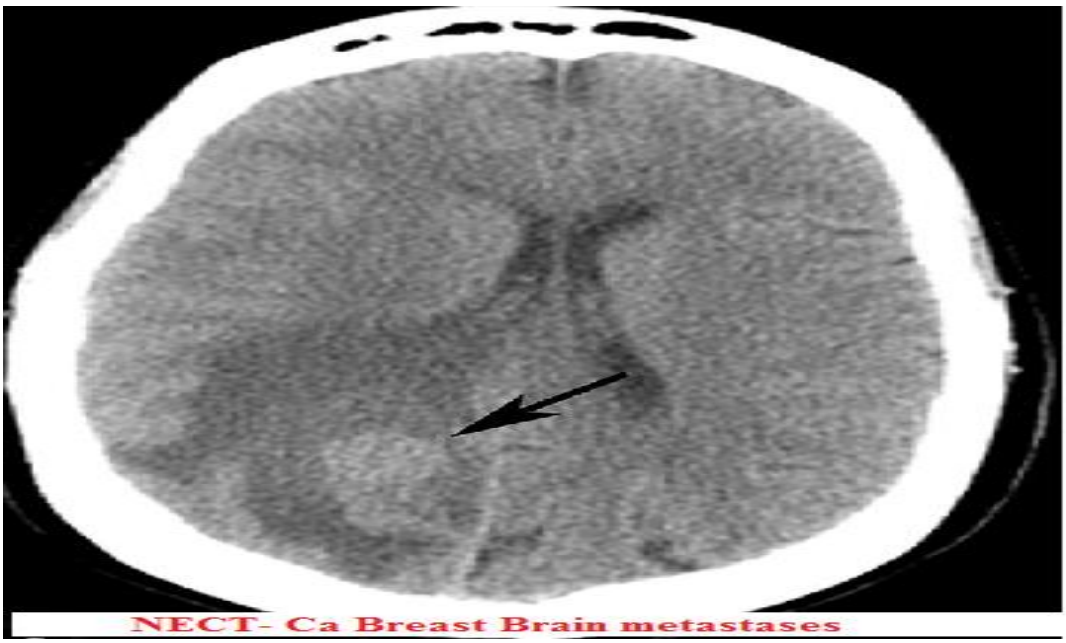
COMPUTED TOMOGRAPHY:

In case of brain metastases Contrast enhanced CT is used only whem MRI is unavailable or contraindicated(due to metal prosthesis or pacemakers).Fewer studies in late 1980s have shown that the usuage of CECT may be equivalent to MRI. This may be due to the thicker slices from MRI that were obtained earlier. But datas after that clearly show an advantage of MRI over CECT. Brain metastases in CECT may be single or multiple with varying degree of vasogenic edema around the lesion. In general its iso,hypo or hyper dense with the surrounding brain parenchyma in the absence of hemorrhage.

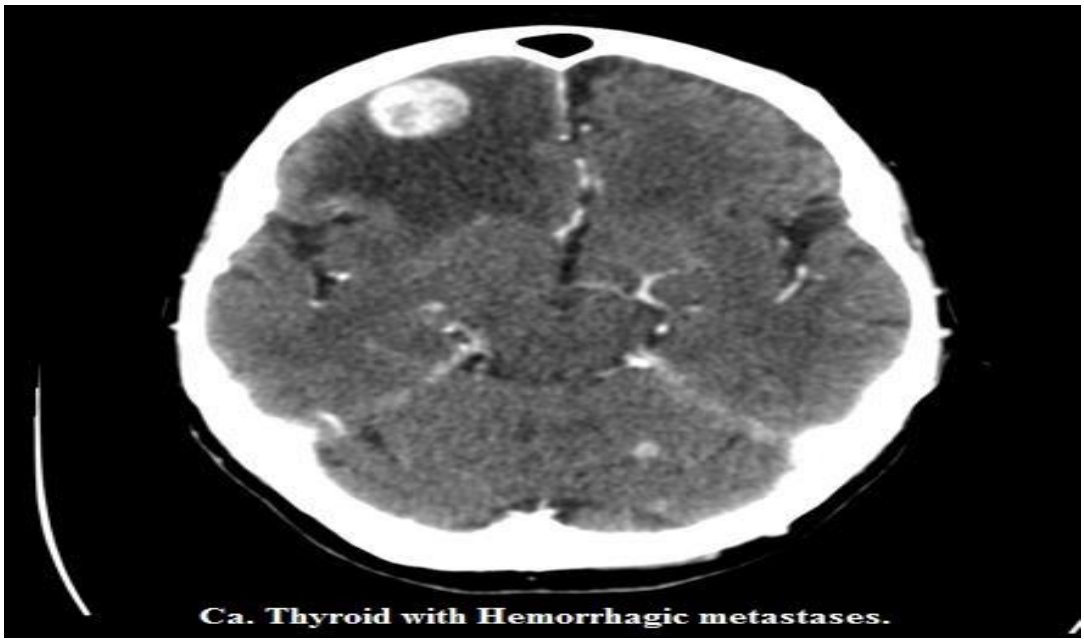
Hemorrhagic brain metastases appears to be hyperdense.Further more metastases fro melonoma appears to be hyperdense even without

hemorrhage. Usually brain metastases donot calcify or calcification of lesion in brain suggestive of someother pathology.

Iodinated contrast plays a vital role in the identification of brian metastases. On using iodinated contrast brain metastases shows ring,nodular or solid enhancement.Further on using iodinated contrast several studies showed delayed imaging should be done inorder to achieve better results



NECT- Ca Breast Brain metastases



Ca. Thyroid with Hemorrhagic metastases.

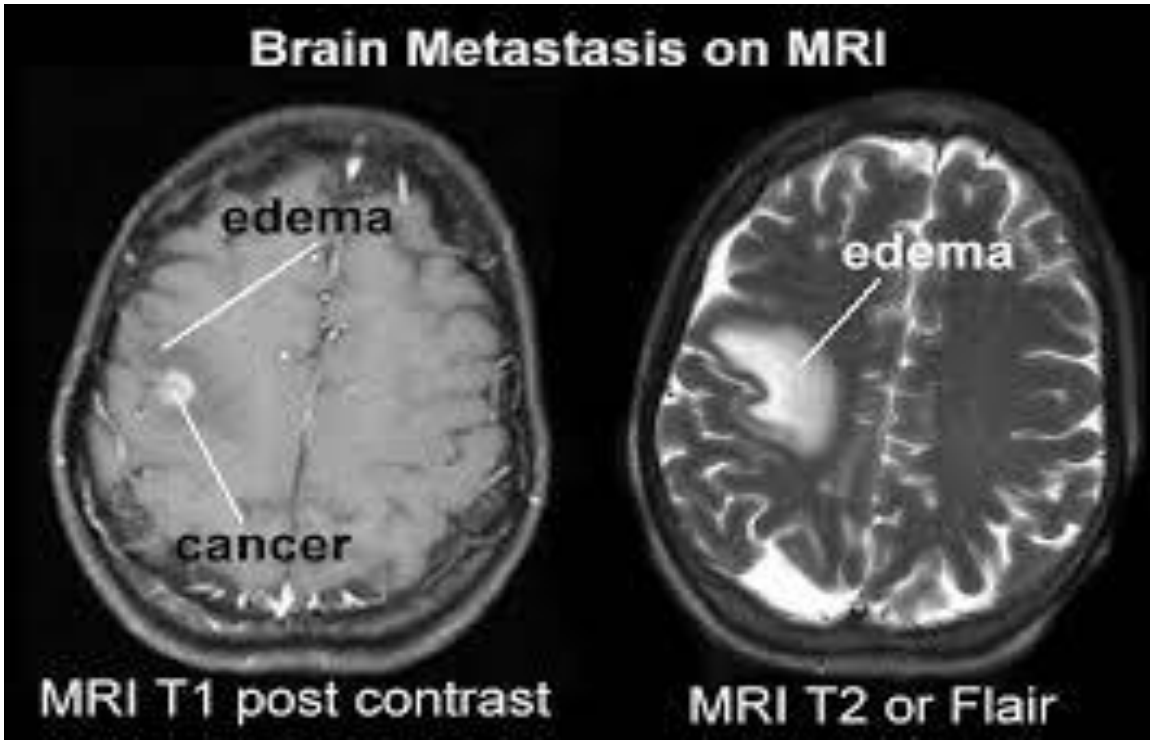
CONVENTIONAL MRI:

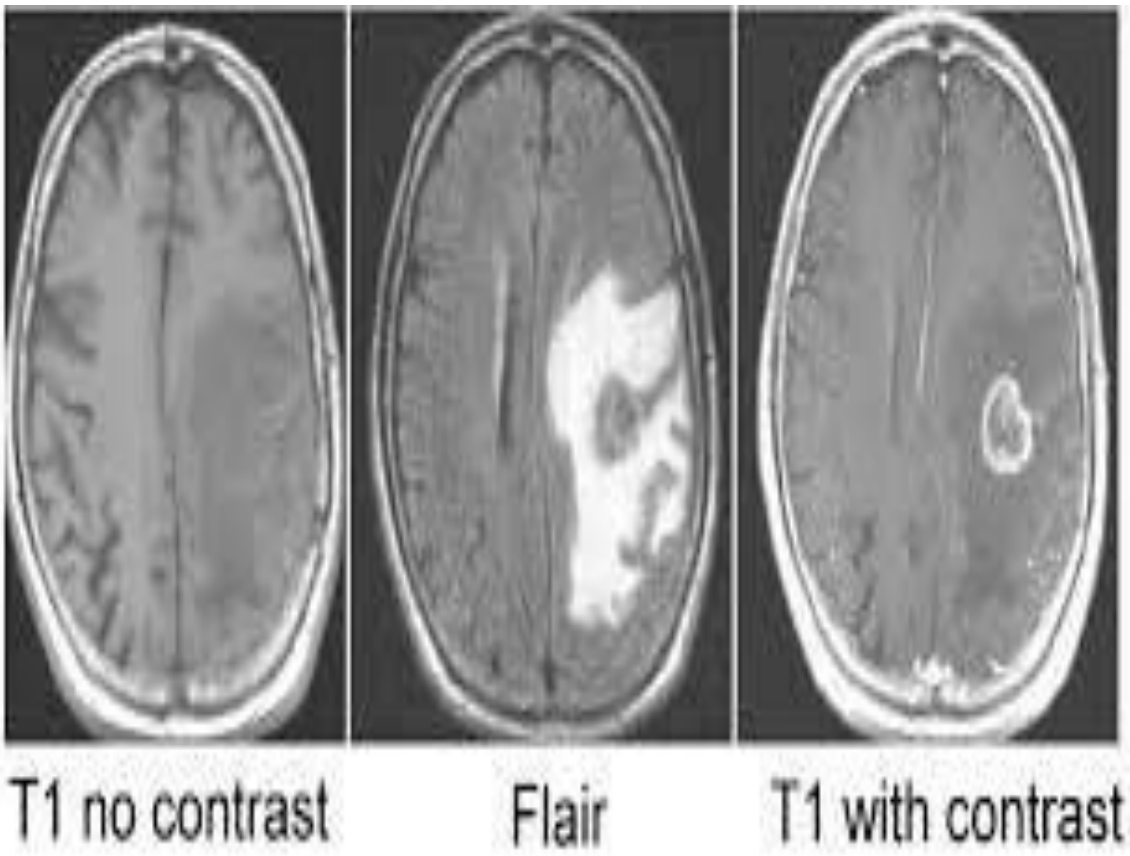
Magnetic Resonance Imaging is the most sensitive tool in detecting brain metastases. In MRI metastases is usually isointense, hypointense in T1,Hyperintense in T2 and show avid enhancement. In case ofmelanoma metastases is hyperintense even in T1 that is due to the paramagnetic properties in melanin. Hemorrhagic metastases shows T1 Hyperintense but depend upon the age of hemorrhage.

Diffuse Weighted Imaging usually demonstrated facilated diffusion , that is bright on Apparent Diffusion Coefficient(ADC) mapping rather than diffusion restriction.

Gadolinium contrast is a very important tool in detecting metastases especially in smaller lesions. Contrast administration may help in distingushing nonneoplastic white matter such as in microvascular ischemia. Thin slice (2.4 mm or less) spoiled gradient recalled echo (SPGR) post contrast

MRI is used in SRS planning and improves the dectection of small brain metastases when compared with standard T1 spin echo weighted imaging.


Brain Metastasis on MRI
edema
cancer
edema
MRI T1 post contrast
MRI T2 or Flair


T1 no contrast
Flair
T1 with contrast

MR SPECTROSCOPY:

This helps in distinushing between neoplastic from a non-neoplastic brain lesion.This can be used with a single voxel or multiple voxels. However multi voxels provides better spatial resolution and greater coverage which allows evaluation of different components of heterogenous masses.Metabolites commonly evaluated includes:

- Choline at 3.2ppm marker for cell membrane turnover
- N-AcetylAspartate(NAA) 2.0 ppm marker for neural integrity
- Lactate at 1.3 ppm marker for Anaerobic metabolism
- Lipid between 0.9 -1.4ppm marker for byproduct of necrosis
- Creatine 3.0ppm marker for energy metabolism. This is often used as a internal control for comparison of other markers.

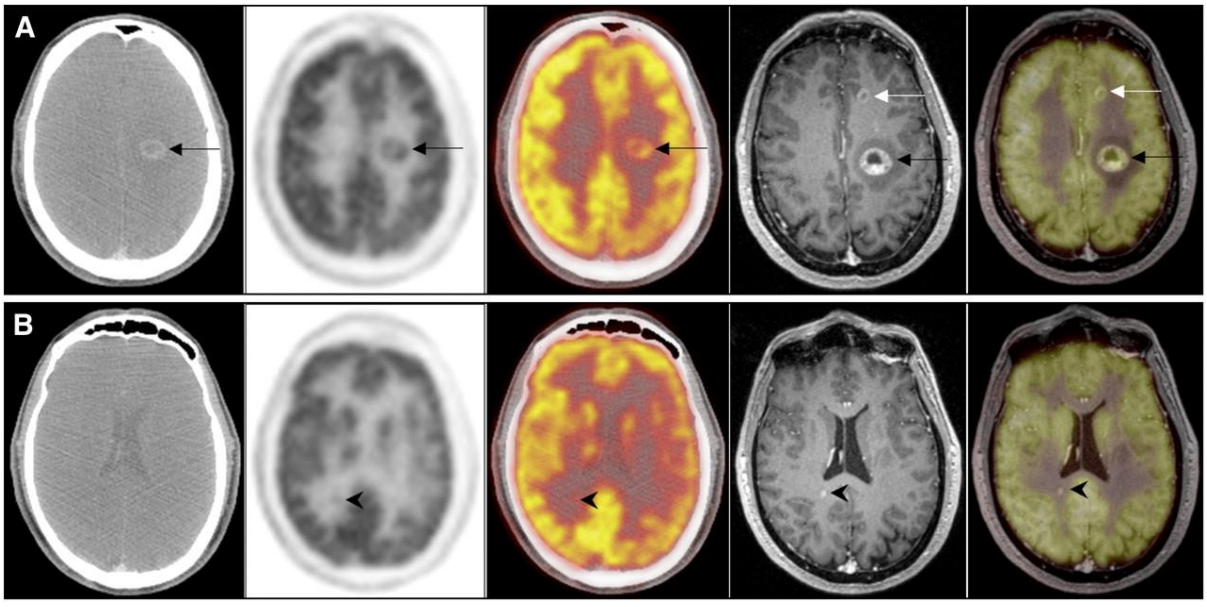
Commonly used ratios in the brain neoplasms includes :

- Choline/ creatine ratio
- Choline/NAA ratio

The enhancing components present in both choline/creatine ratio is elevated both in primary high grade gliomas and Metastatic lesions when

compared to normal brain parenchyma.Similarly lipids and lactate levels in primary high grade gliomas and metastases is no different as both exhibits necrosis. But , the enhancing T2 Hyperintense area around the increasing mass has shown to differentiate between a primary high grade glioma and brian metastases. The pathology behind this is the infiltrating nature of gliomas compared to that of the brain metastases. Furthermore, T2 Hyperintense region surrounding brain metastases shows pure vasogenic edema whereas in high grade gliomas its a combination both vasogenic and infiltrative edema.

Various other components of MRI such as Diffuse Tensor Imaging(DTI), Diffuse Weighted Imaging (DWI) and other modalaties like Angiography can also be used in detecting brain secondaries. FDG PET on combination with CTscans or MRI can provide a better deliniation of tumor volume since it provides both physiological and structural anatomy of the disease.



GENERAL MANAGEMENT OF BRAIN METASTASES:

There are various treatment modalities in the management of brain metastases. These may include

- Corticosteroids
- Anticonvulsants
- Anti edema measures
- Surgery
- Whole brain Radiotherapy
- Stereotactic Radiosurgery
- WBRT + Concurrent Radiosensitizers
- Anticonvulsants

Studies have shown improvement in overall survival when WBRT is combined with SRS.

CORTICOSTEROIDS:

Its shown that prompt starting of steroids may provide appropriate anti-edema measures, and decreases neurological deficit in about $2/3^{rd}$ of patients with brain metastases when started within 24 to 48hours.

Vecht et al compared the usage of steroids in patient with brain metastases where 2 successive groupof patients were selected. In group 1 patients were treated with 8 mg of i.v Dexamethasone vs 16 mg of i.v

dexamethasone and initial dose of dexa is tappered over 4 weeks. In the 2nd group 4mg i.v dexamethasone vs 16 mg i.v dexamethasone with continuation of these doses until 28 days and then tappering.

All these patients were subjected to WBRT and inj Rantac in both the groups. The group with maximum improvement in KPS score was the 16mg per day arm and when the dose was tappered over 4 weeks.

Velch et al, however demonstrated that usage of 4 mg/day dexa was sufficient in select patients with minimal mass effect. Its said that 10 mg iv bolus followed by 4 to 6 mg iv every 8 hours along with PPIs is an effective corticosteroid regimen in the treatment of brain metastases.

WHOLE BRAIN RADIOTHERAPY:

This continues to be the standard of care in patient with brain metastases. It improves local neurological symptoms in more than 70% of patients. But however there is disagreement regarding the optimal dose and the fractination schedule to be used.

The table below shows various fractionation schedule used at various institutions and their effectiveness in the treatment.

Author/Study Group (Reference)	Dose/Fractions	*N*	Median Survival	*P*
Borgelt et al./RTOG[18]				
First study (1971–1973)	30 Gy/10	233	21 wk	NS
	30 Gy/15	217	18 wk	
	40 Gy/15	233	18 wk	
	40 Gy/20	227	16 wk	
Second study (1973–1976)	20 Gy/5	447	15 wk	NS
	30 Gy/10	228	15 wk	
	40 Gy/15	227	18 wk	
Haie-Meder et al./French (1986–1989)[19]	25 Gy/10	110	4.2 mo	NS
	36 Gy/6[a]	106	5.3 mo	
Priestman et al./Royal College of Radiology (1990–1993)[20]	30 Gy/10	263	84 day	.04
	12 Gy/2	270	77 day	
Murray et al./RTOG-91-04 (1991–1995)[21]	30 Gy/10	213	4.5 mo	NS
	54.4 Gy/34[b]	216	4.5 mo	
Graham et al./Australia (1996–2006)[22]	40 Gy/20[c]	57	6.1 mo	NS
	20 Gy/4	56	6.6 mo	

[a]18 Gy/3 split course with another 18 Gy/3 within 1 month.
[b]32 Gy in 1.6 Gy twice a day hyperfractionation to the whole brain followed by boost of 22.4 Gy in 1.6 twice a day hyperfractionation to visible lesions with a 2-cm margin.
[c]40 Gy in 1.0 Gy twice a day hyperfractionation for the entire course of therapy.
NS, not significant; RTOG, Radiation Therapy Oncology Group.

Inspite of various fractionisation schedule world wide the standard 30Gy/10#/300cGy/# or 37.5 Gy/15# continues to be the standard treatment of care.However in patients with poor perfomance status 400cGy/#/5#/20Gy Cn be used

TARGETED AGENTS AS AN REPLACEMENT TO WBRT:

Systemic chemotherapy for the control of NSCLC in brain metastases has been limited due to the poor penetration of these agents across the blood brain barrier. ALK mutations and EGFR rearrangements has been found to be in 15-20% of NSCLC and had been commonly targeted in the disease.

SURGERY:

The advantage of surgery over Whole Brain RT is that

- Pathological specimen is available for further investigation
- Immediate relief from mass effect
- Particularly considered in easily acessible lesion without extensive systemic disease or reducing symptomatic mass effect for tumors generally >3 cm
- Useful in lesions failed treatment by SRS and radiation necrosis.
- Controversial in lesions with multiple metastases

Various trails showing advantage of surgery includes:

Patchell et al./University of Kentucky (n = 48)[37]			
Primary end point	**Surgery + RT**(36 Gy/12 fx)	**RT Alone**(36 Gy/12 fx)	
Overall survival	40 wk	15 wk	<.01
Secondary end points			
Local control			
Local failure	20%	52%	<.02
Time to local failure	>59 wk	21 wk	<.0001
Time to neurologic death	62 wk	26 wk	<.0009
KPS ≥ 70 maintenance	38 wk	8 wk	<.005
Noordijk et al./Dutch (n = 63)[38]	**Surgery + RT** (40 Gy/20 fx)[a]	**RT Alone** (40 Gy/20 fx)[a]	
Primary end points			
Overall survival	10 mo	6 mo	.04
FIS[1b]	7.5 mo	3.5 mo	.06
Mintz et al./Canadian (n = 84)[39]	**Surgery + RT** (30 Gy/10 fx)	**RT Alone** (30 Gy/10 fx)	
Primary end point			
Overall survival	5.6 mo	6.3 mo	NS
Secondary end points			
FIS (proportion of days, mean)[2b]	32%	32%	NS
Quality of life (Spitzer score)			
1–3 months (mean)	6.38	5.36	NS
4–6 months (mean)	6.32	6.15	NS

[a]40 Gy total in 2 Gy twice a day hyperfractionation for the entire course of therapy.
[b]Functionally independent survival as defined by:
[1]WHO performance status ≤ 1 and neurologic condition ≤ 1.
[2]KPS ≥ 70.
fx, fraction number; KPS, Karnofsky performance score; RT, whole-brain radiotherapy; WHO, World Health Organization.

STEROTACTIC RADIOSURGERY:

Sterotactic Radiosurgery is an alternative to surgery in well demarcated disease**.**which does not have mass effect by accurate direction of beams with rapid dose fall off. SRS boost in addition to WBRT in patients with upto three lessions significantly improves intracranial control ratesas compared with WBRT alone, however there is no survival benefits with multiple metatstases.

Randomized and retroprospective studies also suggest that SRS alone a reasonable option in a subset ofpatients with less than equal to four lessions. SRS alonewith close follow up should be considered for higher functioning patients who wish to preserve neurocognitive fumctions. These patients should be properly explained regarding followup with regular physical examinations ,neurocognitive assesments and also regular neuroaxial imaging. If one feels that patient has poor compliance to followup then SRS +WBRT is the treatment of choice. SRS dose guidelines have been made out by RTOG to minimise the radiation necrosis besides the size , location and histology of the lesion

SL.NO	DIAMETER OF THE LESION	DOSE IN GY
1	</= 2cm	24
2	2.1-3.0cm	18
3	3.1-4.0 cm	15

RADIOSURGERY BOOST IN BRAIN METASTASES

Author/Study Group (Reference)				*P*
Andrews/RTOG 95-08 (*n* = 333; 1–3 lesions)[40]	**RT** (37.5 Gy/10 fx)	**RT Alone** (37.5 Gy/10 fx)		
Primary end point (overall survival)				
1–3 lesions	5.7 mo	6.5 mo		NS
Single brain metastasis (planned subgroup analysis)	6.5 mo	4.9 mo		.04
Secondary end points				
Local control (1 yr)	82%	71%		.01
Neurologic death rate	28%	31%		NS
Performance outcome				
KPS stable/improve				
At 3 mo	50%	33%		.02
At 6 mo	43%	27%		.03
Mental status				NS
Unplanned subgroup analysis (overall survival)				
Largest tumor > 2 cm	6.5 mo	5.3 mo		.04
RPA class I	11.6 mo	9.6 mo		.05
Squamous/NSCLC	5.9 mo	3.9 mo		.05
Other outcomes				
Response rate (3 mo)				
Tumor	73%	62%		.04
Edema	70%	47%		.002
Kondziolka et al./University of Pittsburgh (*n* = 27; 2–4 lesions)[41]	**RT** (30 Gy/12 fx)	**RT Alone** (30 Gy/12 fx)		
Primary end point				
Local control (1 yr)	92%	0%		.0016
Time to local failure	36 mo	6 mo		.005
Time to any brain failure	34 mo	5 mo		.002
Secondary end points				
Overall survival	11 mo	7.5 mo		NS
Treatment morbidity	0	0		
Progression-free survival	Not reported			
Need for retreatment	Not reported			
Chougule et al./Brown University (*n* = 109; 1–3 lesions)[42]	**RT + SRS**	**RT Alone**	SRS Alone	
End points (abstract only)	(30 Gy/10 fx + 20 Gy SRS)	(30 Gy/10 fx)	(30 Gy SRS)	
Overall survival	5 mo	9 mo	7 mo	Not reported
Local control	91%	62%	87%	Not reported
New brain lesions	19%	23%	43%	Not reported

fx, fraction number; KPS, Karnofsky performance score; NS, not significant; NSCLC, non–small-cell lung cancer; RPA, recursive partitioning analysis; RT, whole-brain radiotherapy; SRS, stereotactic radiosurgery.

SRS can be delivered using Gamma knife , LINAC based system or protons. LINAC can be adapted to deliver SRS within mechanical tolreance with physics quality assurance. Various trails which suggest advantage of SRS boost have been explaied below. Variations in terms of doses and response assesment is given.

PROGNOSTIC FACTORS:

Various prognostic indices are used inorder to determine the overall survival with the various treatment modalities . These include Recursion Partitioning Analysis by RTOG, Graded Prognostic assesment scores (GPA score)and Score Index for Surgery (SIR)

Recurssion Partitioning Analysis(Gasper et al 1997)

SL.NO	CLASS	RPA	MEDIAN SURVIVAL
1	I	KPS≥ 70 <65 years Controlled primary with no extracaranial metastases	7.1 months

2	II	Remaining populice	4.2 months
3	III	KPS<70	2.3 months

Survival in terms of types of treatment is given by

RPA	WBRT	SURGERY	SRS
I	7.1 months	14.8 months	16.1 months
II	4.2 months	9.9 months	10.3 months
III	7.3 months	6.0 months	8.9 months

Graded prognostic index is the newer form of scotring system on the basis of RTOG database

SL.NO	PARAMETER	0	0.5	1
1	Age in years	>60	50-59	<50
2	KPS	<70	70-80	>80
3	No. of Brain mets	>3	2-3	1
4	Extra cranial metastases	Present	Not Applicable	None

GPA scores in terms of survival

SL.NO	GPA	Median Survival(in Months)
1	3.5-4	11
2	3	6.9
3	1.5-2.5	3.8
4	0-1	2.8

Site specific GPA score gives an information regarding the estimated median survival in various organs

Score Index Radiosurgery is an alternative prognostic scoring system used for patients undegoing Radiosurgery.

SL. NO	PARAMETER	0	1	2
1	Age (years)	≥ 60	51-59	≤50
2	KPS	≥ 50	60-70	80-100
3	Systemic disease	Progressive	Stable	Complete Response
4	No of lesions	≥3	2	1
5	Volume in ml	>13	5-13	<5

CONCURRENT RADIOSENSITIZERS:

The newer advent of techniques had definetly imroved the overall survival in patients with WBRT or SRS.The addition of radiosensitizers alonf with WBRT has been attempted to improve treatment outcomes. The addition of Radiosensitizers have not shown any improvements in terms of overall survival but increase in response rates have been shown.

Author/Study Group (Reference)	Arms	Response Rate (%)	P	Median Survival	P
Komarnicky et al./RTOG 79-16[62] (*n* = 859)	RT (30 Gy/10 fx)	45[a]	NS	4.5 mo	NS
	RT + misonidazole	42[a]	NS	3.9 mo	NS
	RT (30 Gy/6 fx)	42[a]		4.1 mo	
	RT + misonidazole	45[a]		3.1 mo	
Ushio et al./Japan[69,b] (*n* = 88)	RT (40 Gy/20 fx)	36	<.05	27 wk	NS
	RT + nitrosourea	69		29 wk	
	RT + nitrosourea + tegafur	74		30.5 wk	
Phillips et al./RTOG-89-05[63] (*n* = 72)	RT (37.5 Gy/15 fx)	50[d]	NS	6.1 mo	NS
	RT + BrdUrd	63[d]		4.3 mo	
Guerrieri et al./Australia[70,b] (*n* = 42)	RT (20 Gy/5 fx)	10	NS	4.4 mo	NS
	RT + carboplatin	29		3.7 mo	
Antonadou et al./Greece[64] (*n* = 52)	RT (40 Gy/20 fx)	67	.017	7.0 mo	NS
	RT + temozolomide	96		8.6 mo	
Verger et al./Spain[65] (*n* = 82)	RT (30 Gy/10 fx)	54[c]	.03	3.1 mo	NS
	RT + temozolomide	72[c]		4.5 mo	
Mehta et al./SMART Trial[66] (*n* = 401)	RT (30 Gy/10 fx)	51	NS	4.9 mo	NS
	RT + MGd	46		5.2 mo	
Suh et al./REACH Trial[67] (*n* = 515)	RT (30 Gy/10 fx)	38	NS	4.4 mo	NS
	RT + efaproxiral	46		5.4 mo	
Knisely et al./RTOG-01-18[68] (*n* = 175)	RT (37.5 Gy/15 fx)			3.9 mo	NS
	RT + thalidomide			3.9 mo	

[a]Percentage of survival time in KPS 90–100 range.
[b]Only lung cancer patients.
[c]Ninety-day freedom from brain metastasis.
[d]Overall complete and partial response rate.
BrdUrd, bromodeoxyuridine; fx, fractions; KPS, Karnofsky performance score; MGd, motexafin gadolinium; NS, not significant; RT, wholebrain radiotherapy; RTOG, Radiation Therapy and Oncology Group; SWOG, South West Oncology Group.

NEUROCOGNITIVE FUNCTION AND WHOLE BRAIN RT

Whole Brain RT has been found to have decrease the neurocognitive fucnction and is found to be the major cause of neurocognitive decline in cancer patients. The study done by Memorial Sloan-Kettering Cancer Centre experince was published by DeAngelis et al. reported a 11% increased risk in radiation induced dementia in patient receiving WBRT. This figure is often misleading. Of the 47 patients who survived,5 patient developed dementia. All these 5 patient who developed dementia, were treated in ways which increase neurocognitive decline which include high dose per fraction ranging from 5-6 Gy/#, where as one patient received 6 Gy/# along with Adriamycin. Of these 5 patients only one patient received conventional fractionation but however even this patient received radiosensitizer. Further these studies did not explore the underlying disease progression and its effect on Neurocognitive decline.

Li et al. have attempted the actual effect of neurocognitive decline associated with Whole Brain RT while controlling for brain metastases response. In his study all the patients were treated with Whole brain Radiotherpay for 300cGy/10#/30Gy in 2 weeks .

Neurocognitive function in domains of memory , verbal fluency and executive function was assesed every month for the first 6 months post treatment, then every 3 months until death. The treatment response was

calculated by the summation of greatest dimension of 6 brain metastases. The size of increase of greater than 45% indicated poor response were as less than 45 % indicated good response. It was shown that volume regression was associated with the preservation of NCF in the domain of executive function and fine motor coordination and weaker association with preservation of memory domain.

RTOG 0933 and RTOG 0614 assessed the role of avoidance of Hippocampal Avoidance Whole Brain RT (HA-WBRT) and role of memantine respectively in the preservation of neurocognitive function. In RTOG 0933 it showed that the HA-WBRT the mean decline of Human Verbal Learning Test scores of 7% which was significantly lower than the control arm without hippocampal sparing which had a decline of 30%

In case of RTOG 0614 WBRTof 37.5 Gy/15# along with and without 24 weeks of Memantine. Primary endpoint was that the delayed recall in 24 weeks (although statistically not significant),favoured for memantine.

These results have lead to the ongoing trail ,NRG-CC001 which assesed the neurocognitive function in patients with or without Hippocampal sparing WBRT,all of whom recieved Memantine.

AIMS AND OBJECTIVES

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PRIMARY OBJECTIVES:

To assess the Neurocognitive function and Quality of Life in patients with brain metastasis receiving Whole Brain Radiotherapy with concurrent Temozolamide

SECONDARY OBJECTIVES:

To describe the Objective Response Rate(ORR) ,Progression Free survival(PFS),Disease Control Rate(DCR), Overall Survival(OS) and Disease Free Survival(DFS) in patients with brain metastasis treated with whole brain radiotherapy .

STUDY CENTRE:

Department Of Radiation Oncology,

Rajiv Gandhi Government General Hospital,

Madras Medical College,

Chennai-03.

DURATION OF THE STUDY:

From February -2018 till July 2019

STUDY DESIGN:

Double arm prospective study

SAMPLE SIZE:

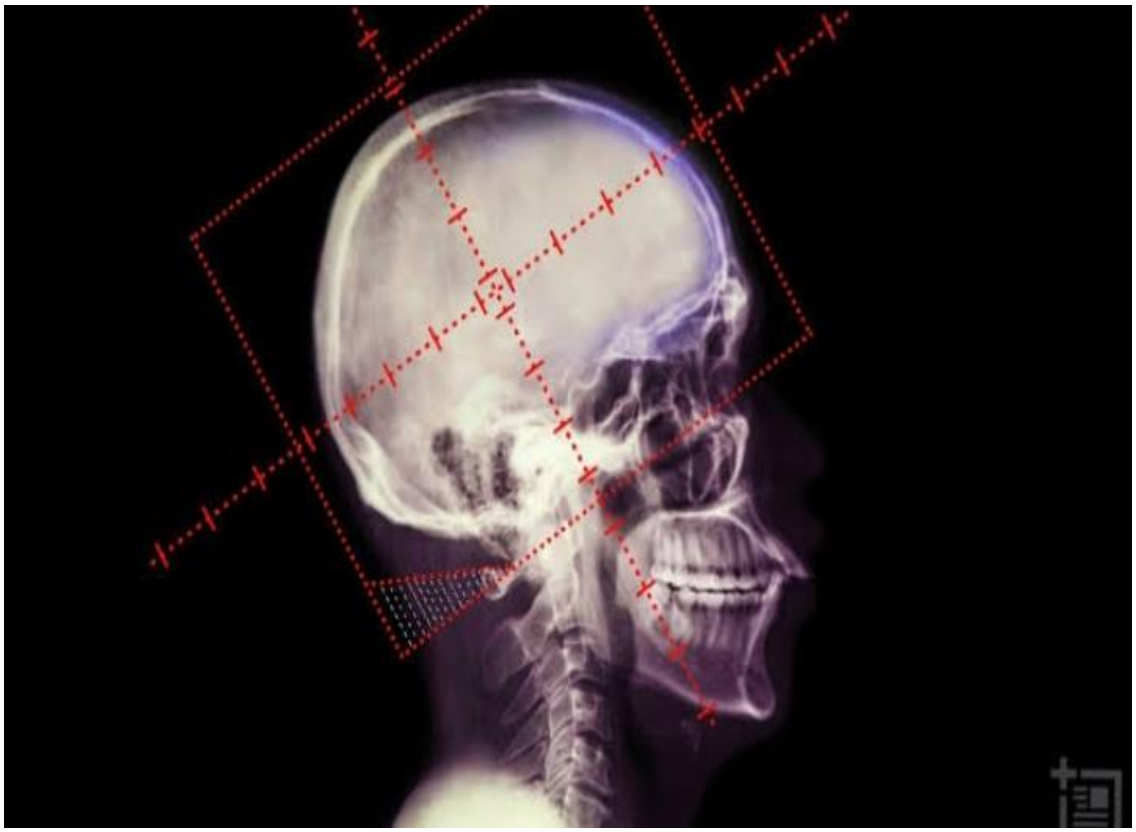
30 cases in each arm , total of 60 cases included in the study

MATERIALS & METHODS

MATERIALS & METHODS

- 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.

FIELD BORDERS:



Simulation film of WBRT 2D planning

Position :

Supine

Borders :

- SUPERIOR BORDER: Air
- POSTERIOR BORDER: Air
- ANTERIOR BORDER: Air
- INFERIOR BORDER : Line joining Supra orbital ridge via tragus to C2 Vertebrae or the base of skull.

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.

Response Assessment according to RECIST1.1:

Complete response	Disappearance of all target lesions, plus reduction in short-axis diameter of pathologic lymph nodes to <10 mm
Partial response	≥30% decrease in the sum of the longest diameters of target lesions
Stable disease	Neither partial response nor progressive disease
Progressive disease	≥20% increase (≥5 mm absolute increase) in the sum of the longest diameters, in comparison with the smallest sum of the longest diameters recorded since treatment started

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(more than twice the upper limit), reduced bone marrow reserve.
- Patient not co-operating at any point in the treatment.
- Pregnant and lactating women
- Any Previous Malignancy
- 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.

Investigation Details :

- Biopsy from tumour lesion
- Complete blood count, Liver function tests, Renal function tests, Viral markers.
- CT scan Brain – Plain and Contrast pre-treatment and post treatment (after 4weeks) or MRI brain pre and post treatment
- Chest X ray – PA view, ECG ,blood grouping
- Weekly CBC during RT

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 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
- If a patient did not attempt or complete a test due to the primary cause as a result of disease progression, will be recorded and included in progression of analysis

- 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

QUESTIONNARIES AND ANALYSIS:

This study involves the use of 5 questionnaries and one peg board for the assesment of NCF. The Cognitive domain is examined using Modified Mini Mental Status examination questionnarie.This tests Orientation, Registration Attention and Calculation, Recalling and Language and Praxis The questions and the scoring is explained below.

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions:** Ask the questions in the order listed. Score one point for each correct response within each question or activity.*

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Instructions for administration and scoring of the MMSE

Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

SCORING

24-30	No Cognitive Impairment
18-23	Mild Cognitive Impairment
0-17	Severe cognitive Impairment

The assesment using MMSE questionnarie is done on time periods as mentiond 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 as stimuli. The level of ddiifficulty is determined by the relative frequency of words in that language. In case of Tamil three letters ‘த’, ‘ப’ ,’க’ 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.The COWAT questionnarie is given below

The scoring system for COWAT is shown as

SL NO.	SCORE	INTERPRETATION
1	53 or above	Superior
2	45-52	High average
3	34-44	Average
4	24-33	Low average
5	20-23	Deficient
6	Less than 20	Very Deficient

COWAT QUESTIONNARIE:

All the instructions were translated in local language (Tamil) and explained to the patient

HABC Enrollment ID #	Acrostic	Year and Quarter of Interview
H		15Q1 15Q2 15Q3 15Q4 16Q1 16Q2 16Q3 16Q4 17Q1 17Q2 17Q3 17Q4 18Q1 18Q2 18Q3 18Q4 19Q1 19Q2 19Q3 19Q4 20Q1 20Q2 20Q3 20Q4

Health ABC

CONTROLLED ORAL WORD ASSOCIATION

I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words you can think of that begin with that letter. You may say any word at all except proper names such as the names of people or places. So you would not say "Rochester" or "Robert." Also, do not use the same words again with a different ending, such as "run" and "running." For example, if I say R you could say rat, river, or run. Can you think of any other words beginning with the letter R? ***Wait for the participant to give a word, indicate if the word is correct, and ask the participant to give another word beginning with the letter R.***

35. Can you tell me another word that begins with R?

(Examiner Note: If participant says another appropriate word that begins with R, tell participant "That is fine," mark "Sample Completed," and go on to timed test.)

○ Sample completed ○ Unable to complete sample ○ Refused ○ Unable to test

Do NOT go on to timed test. Do not score. Go to Page 17, Question # 39.

36. Now I'm going to give you another letter, and again, say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up. You will have a minute for each one. The first letter is C. Ready, go.

(Examiner Note: Start the stop watch when the participant provides the first word. If after 15 seconds the participant gives no words, start stopwatch, and repeat the basic instructions and the letter. No extension on the time limit is made in the event that the instructions are repeated. Stop the participant after 60 seconds.)

1.	7.	13.	19.
2.	8.	14.	20.
3.	9.	15.	21.
4.	10.	16.	22.
5.	11.	17.	23.
6.	12.	18.	24.

Number correct words ☐☐

37. Now I am going to give another letter. Tell me as many words as you can that begin with F. Tell me as many words as quickly as you can that begin with F. Ready, go.

(Examiner Note: See instructions above. Stop the participant after 60 seconds.)

1.	7.	13.	19.
2.	8.	14.	20.
3.	9.	15.	21.
4.	10.	16.	22.
5.	11.	17.	23.
6.	12.	18.	24.

Number correct words ☐☐

38. Now I am going to give another letter. Tell me as many words as you can that begin with L. Tell me as many words as quickly as you can that begin with L. Ready, go.

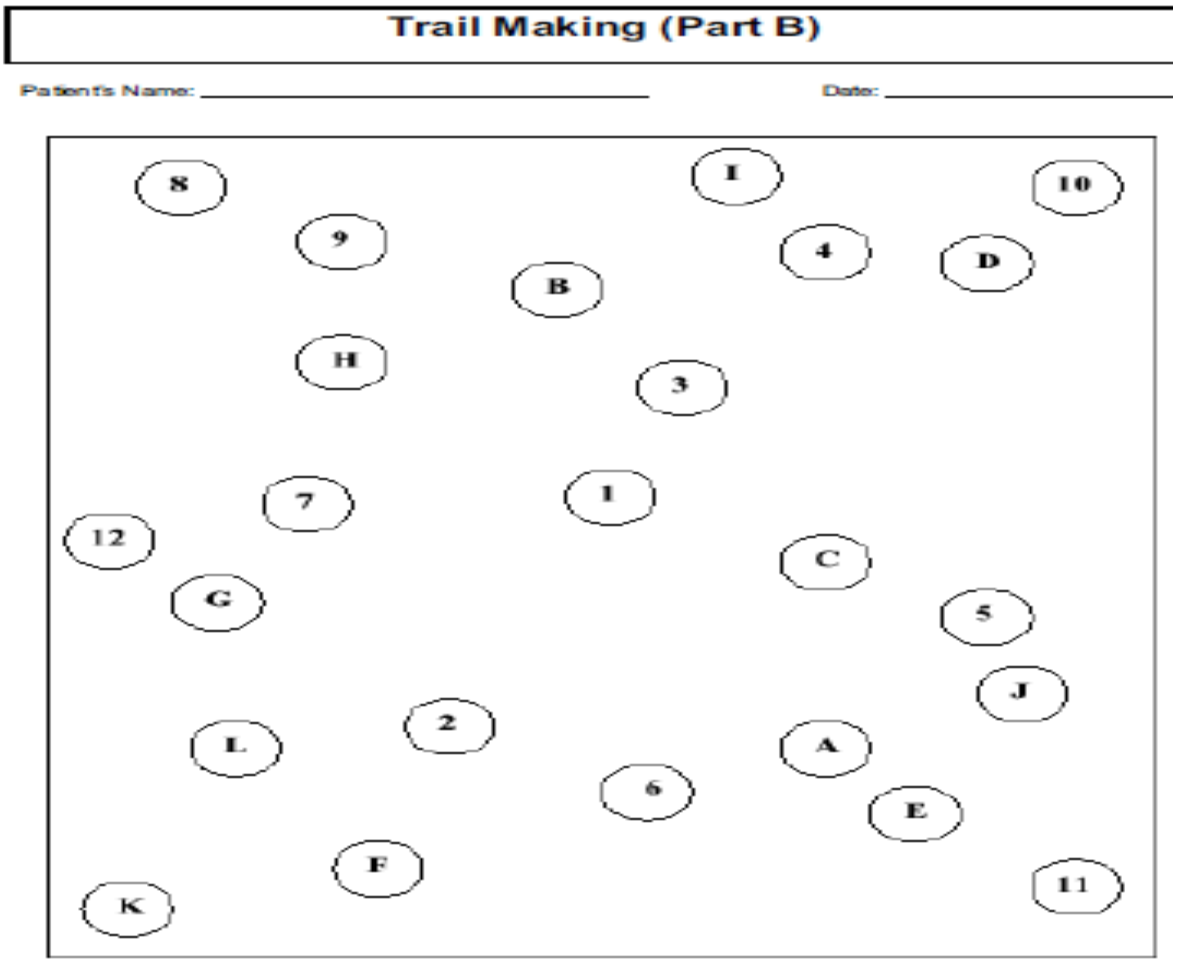
(Examiner Note: See instructions above. Stop the participant after 60 seconds.)

1.	7.	13.	19.
2.	8.	14.	20.
3.	9.	15.	21.
4.	10.	16.	22.
5.	11.	17.	23.
6.	12.	18.	24.

Number correct words ☐☐

TRAIL B TEST:

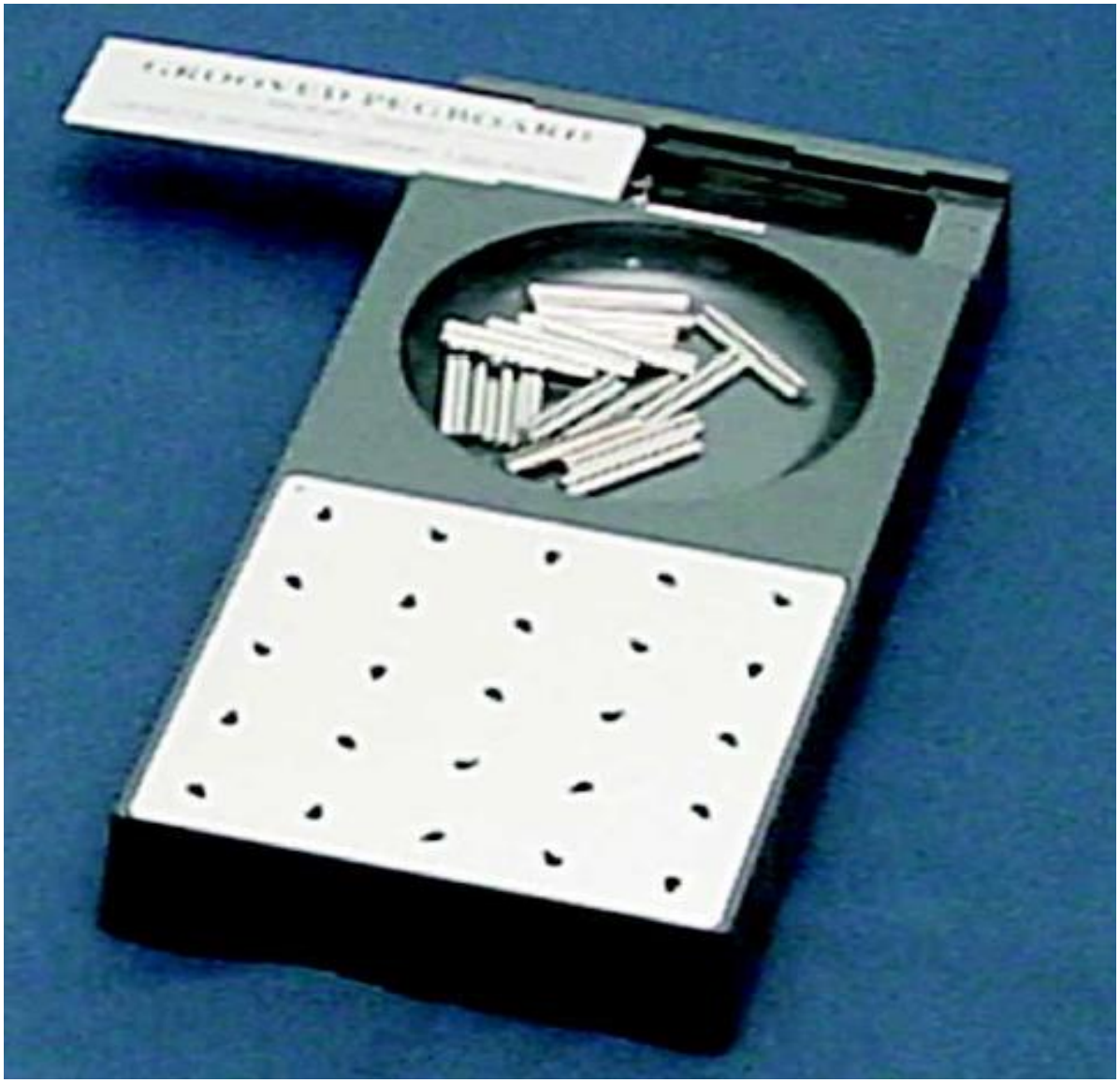
In this test paper consisting of both alphabets and numbers is used. The patient is asked to draw a line connecting the number ‘1’ to letter ‘A’ and follwed by number ‘2’ to letter ‘B’ and continue till the last alphabet. In our test we prepared a chart containing alphabets of tamil language. The time taken for completion is noted.



Scoring in Trail B is Average time for completion is 75 secs and neurological deficit isobserved when the score is above 273 secs

FINE MOTOR TESTING :

This test is done by assesing the time taken in the Peg Board Test. In this test the time taken for arranging the pegs on holes in the board by both dominant and the dominant hand is calculated. This is the most difficult test to perform because in almost all patients with brain metastases developed some sort of motor deficiency during the cousre of the survival. The following is the picture of the pegboard used in this study.



SCORING:

In case of peg board analysis the maximum time that could be waited for the completion of test is 300 seconds .Age wise average time taken and the standard deviation is shown below

Sl.no	Peg board	Non dominant Hand	Dominant Hand
1	40-49 years	69.05 +/- 9.80secs	63.5+/-7.2 secs
2	50-59 years	74.70 +/_10.5 secs	68.10+/_9.42 secs
3	60+ years	87.95 +/_26.20secs	82.70 +/_ 18.7 secs

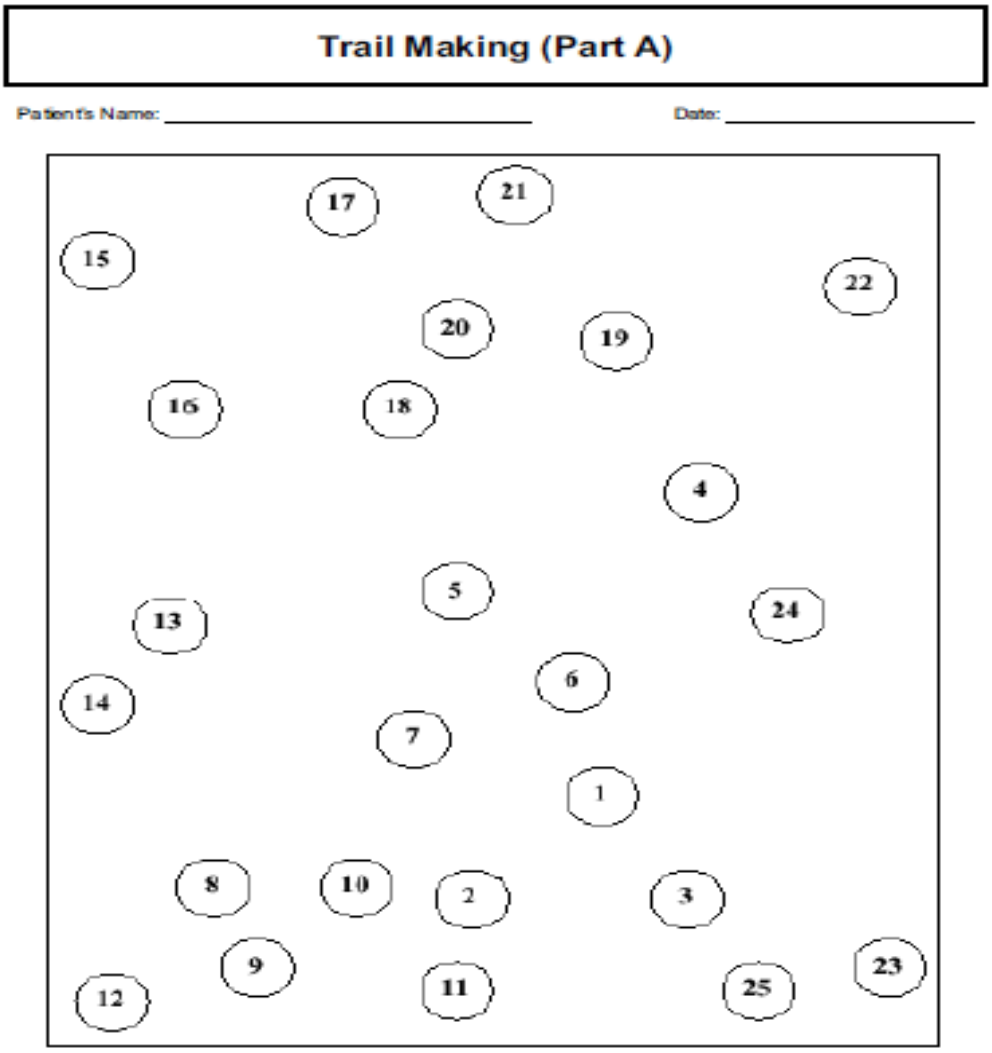
The scores above this values were considered to be deficient.

VISUAL MOTOR SCANNING SPEED:

TRAIL A:

This is done by using Trail A.Instructions similar to that of Trail B has been followed. But Trail A chart contains only numbers starting from ‘1’. This

is done by drawing a line connecting these numbers in the ascending chronology.



SCORING:

The average time taken for the completion of Trail B is 28 secs and if the time exceeds 78 secs its considered to be deficient.

QUALITY OF LIFE ASSESSMENT:

The Quality of life assesment scale was done on the basis of EORTC Qlqc-30. Version 3.0 questionnarie which is used to assess the general quality

of life in cancer patients. Various assessment of daily day to day activities to overall general well being of the patient was assesed. The result are interrupted in the software provided by the EORTC group for Qlqc-30. Version 3.0 interpretation.The questionnarie is as follows

TAMIL

EORTC QLQ - C30 (version 3)

நாங்கள் உங்களையும், உங்கள் ஆரோக்கியத்தையும் பற்றி சில விஷயங்களை அறிய ஆர்வமாய் உள்ளோம். தயவு செய்து எல்லாக் கேள்விகளுக்கும் நீங்களே பதில் தாருங்கள். உங்களுக்கு உள்ள அளவில் பொருந்தும் எண்ணைச் சுற்றி வட்டமிடவும். "சரியான" அல்லது "தவறான" பதில்கள் கிடையாது. நீங்கள் தரும் விபரம் கண்டிப்பாக ரகசியமாக இருக்கும்.

தயவு செய்து உங்கள் பெயரின் முதல் எழுத்துகளை இட்டு நிரப்பவும். _____

உங்களது பிறந்த தேதி (நாள், மாதம், வருடம்) _____

இன்றைய தேதி _____

		இல்லவே இல்லை	ஒரு சிறிது	கணிசமாக	மிக அதிக அளவு
1	நீங்கள் ஒரு கனமான கடைச் சாமான்களை அல்லது ஒரு கைப் பெட்டியைத் தூக்குவது போன்ற கடினமான வேலைகள் செய்கையில் ஏதாவது தொல்லை அனுபவிக்கிறீர்களா?	1	2	3	4
2	நீண்ட நேர நடை எடுக்கையில் நீங்கள் ஏதாவது தொல்லை கொண்டுள்ளீர்களா?	1	2	3	4
3	வீட்டுக்கு வெளியில் சின்ன நடை எடுக்கையில் நீங்கள் ஏதேனும் தொல்லை கொண்டுள்ளீர்களா?	1	2	3	4
4	பகலில் படுக்கை மீது அல்லது ஒரு நாற்காலியில் இருக்கும்படி நீங்கள் தேவையை உணர்கிறீர்களா?	1	2	3	4
5	நீங்கள் சாப்பிட, உடுத்த, குளிக்க அல்லது கழிப்பிடத்தைப் பயன்படுத்த உதவி தேவைப்படுகிறதா?	1	2	3	4
	கடந்த வாரத்தின் போது:				
6	நீங்கள் உங்கள் வேலையையோ அல்லது மற்ற ஒவ்வொரு நாள் நடவடிக்கைகளையோ செய்கையில் வரம்புக்குள் இருந்தீர்களா?	1	2	3	4
7	நீங்கள் உங்களது பிடித்த பொழுது போக்குகள் அல்லது பிற ஓய்வு நேர நடவடிக்கைகளைத் தொடரும் போது வரம்புக்குள் இருந்தீர்களா?	1	2	3	4
8	நீங்கள் மூச்சுத் திணறலுடன் இருந்தீர்களா?	1	2	3	4
9	நீங்கள் உடலில் வலி கொண்டிருந்தீர்களா?	1	2	3	4
10	நீங்கள் ஓய்வு எடுக்கத் தேவைப்பட்டதா?	1	2	3	4
11	நீங்கள் தூங்குவதில் தொல்லை கொண்டிருந்தீர்களா?	1	2	3	4
12	நீங்கள் பலவீனமாக உணர்ந்து இருந்தீர்களா?	1	2	3	4

தயவு செய்து அடுத்த பக்கத்திற்குப் போகவும்

	கடந்த வாரத்தில் போது:	இல்லவே இல்லை	ஒரு சிறிது	கணிசமாக	மிக அதிக அளவு
13	நீங்கள் பசி வெடுக்கது இல்லாது இருந்தீர்களா?	1	2	3	4
14	நீங்கள் குமட்டுவது போல உணர்ந்தீர்களா?	1	2	3	4
15	நீங்கள் வாந்தியெடுத்துள்ளீர்களா?	1	2	3	4
16	நீங்கள் மலச்சிக்கல் கொண்டிருந்தீர்களா?	1	2	3	4
17	நீங்கள் தொடர்ந்து வயிற்றுப் போக்கு கொண்டிருந்தீர்களா?	1	2	3	4
18	நீங்கள் களைப்படைந்தீர்களா?	1	2	3	4
19	வலி உங்களது தினசரி நடவடிக்கைகளில் இடையூறு செய்ததா?	1	2	3	4
20	நீங்கள் ஒரு செய்திதாள் வாசிப்பது அல்லது தொலைக்காட்சி பார்ப்பது போன்ற விஷயங்கள் மேல் கவனம் செலுத்துவதில் கஷ்டம் கொண்டிருந்தீர்களா?	1	2	3	4
21	நீங்கள் பதற்றமான இருக்கதை உணர்ந்தீர்களா?	1	2	3	4
22	நீங்கள் கவலைப்பட்டீர்களா?	1	2	3	4
23	நீங்கள் எரிச்சல் பட்டீர்களா?	1	2	3	4
24	நீங்கள் மன அழுத்தம் உணர்ந்தீர்களா?	1	2	3	4
25	நீங்கள் பொருட்களை ஞாபகம் கொள்வதில் கஷ்டப்பட்டிருந்தீர்களா?	1	2	3	4
26	உங்கள் உடல் நிலையும் அல்லது மருத்துவச் சிகிச்சை உங்களது குடும்ப வாழ்க்கையோடு குறுக்கிட்டுப் பாதித்து இருக்கிறதா?	1	2	3	4
27	உங்கள் உடல் நிலையும் அல்லது மருத்துவச் சிகிச்சை உங்களது நண்ப நடவடிக்கைகளோடு குறுக்கிட்டுப் பாதித்து இருக்கிறதா?	1	2	3	4
28	உங்கள் உடல் நிலையும் அல்லது மருத்துவச் சிகிச்சை உங்களுக்கு நிதிக் கஷ்டங்களை உண்டாக்கி உள்ளதா?	1	2	3	4

பின்வரும் கேள்விகளுக்கு 1லிருந்து 7 முடிய உங்கள் எண்களில், உங்களது நிலைக்கிற்கு உச்ச அளவில் பொருந்தும் எண்ணைச் சுற்றி தயவு செய்து வட்டமிடவும்.

29 கடந்த வாரத்தின் போது, பொதுவாக உங்களுடைய ஆரோக்கியத்தை நீங்கள் எவ்வாறு மதிப்பீடு செய்வீர்கள்?

1 2 3 4 5 6 7

(மிக மோசம்) (சிறப்பாக)

30 கடந்த வாரத்தின் போது, பொதுவாக உங்களுடைய வாழ்க்கைத் தரத்தை நீங்கள் எவ்வாறு மதிப்பீடு செய்வீர்கள்?

1 2 3 4 5 6 7

(மிக மோசம்) (சிறப்பாக)

This questionnarie has been oficially translated by EORTC into more than 100 languages. Patients were allowed to take the help of the attenders in filling up this questionnarie as its not time bound.

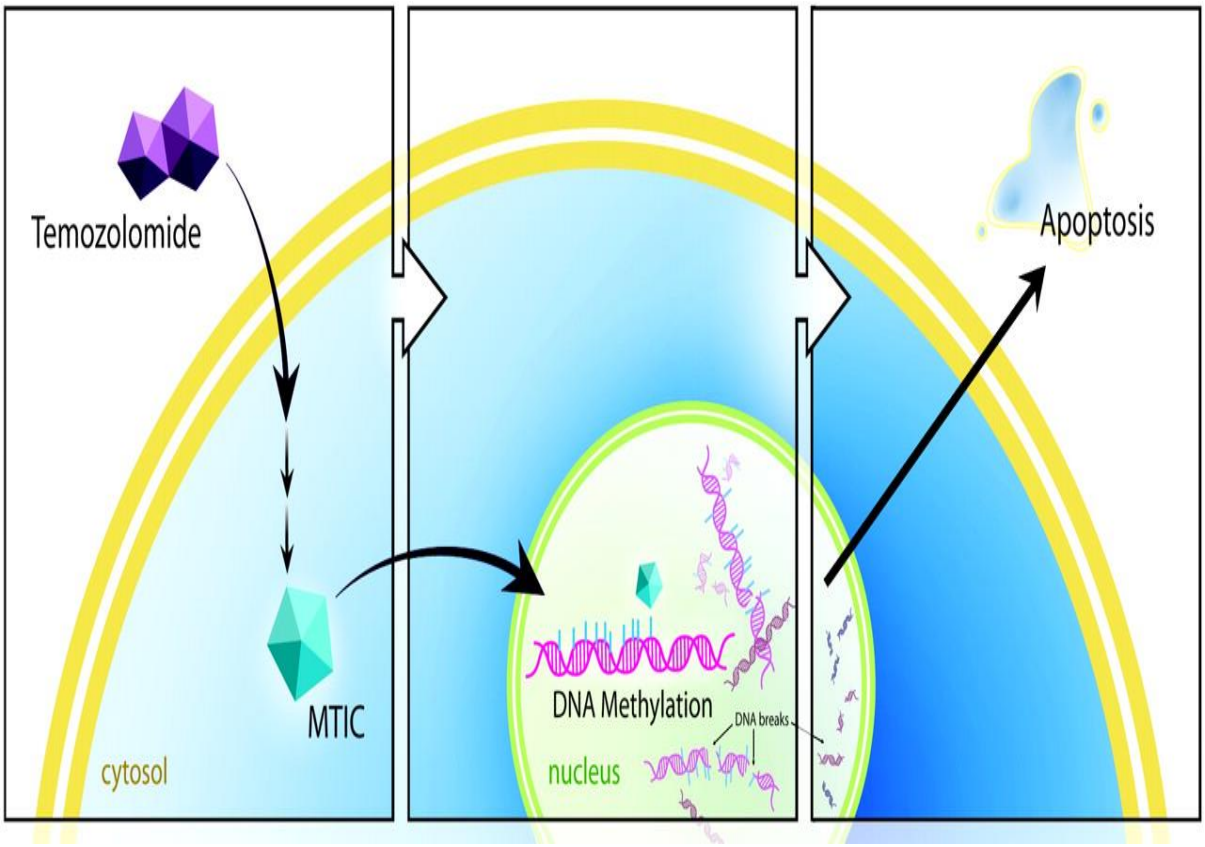
DISCUSSION

DISCUSSION

TEMOZOLAMIDE:

Temozolamide is an oral alkylating agent which is mainly used as a radiosensitizer in the traetment of High grade gliomas and few low grade tumors.Its an imidazotetrazene analog that is structurally andfunctionally similar to that of dacarbazine..

It’s a cell-cycle nonspecific agent. It requires metabolic activation to its active form 5-(3-Methyltriazen-1-yl)imidazole-4-carboxamide(MITC). It crosses blood brain barrier with its CNS concentration reaching 30% of plasma concentration.



MECHANISM OF ACTION:

The proposed mechanism of action of Temozolomide is by its ability to deposit methyl groups in guanine bases of DNA.The oral drug when given is absorbed in the intestine ,readily crosses the blood brain brain because of its lipophilic natue and smaller size and gets converted in the cytosol to its active form MITC via hydrolysis.

MITC methylates large number of bases in the DNA ,especially the guanine base.This results in a nick in the DNA,which cannot be repaired and leads to apoptosis causing inhibition of RNA and protein synthesis and donot allow cross linking of DNA stands

PHARMACOLOGY:

This drug is rapidly absorbed in the tissue with a oral bioavailabity reaching almost 100%. Maximum plasma concentrations are reached within 1 hour and T1/2 is about 2 hours. Food reduces the rate and extent of absorbtion

METABOLISM:

This drug is primarily metabolized by non enzymatic hydrolysis at physiological pH. It gets converted into MITC which further hydrolysis to AIC,

a known intermediate in the purine denova pathway and methylhydrazine the peresumed active alkylyting species. Liver cytochrome P-450 plays a minor role in the metabolism of temozolamide. The elimination T1/2 is about 2 hours and 40-50% of parent drug is excreted out of urine within 6 hours of administration. In kidneys Tubular excretion is the predominant methodof excretion.

SPECIAL CONSIDERATION DURING TEMOZOLOMIDE ADMINISTRATION:

- Moderately emetogenic and hence agresssive use of anti emetics before drug administration is necessary.
- No dose reduction is needed in case of mild to moderate renal or hepatic dysfunction
- Patient should be warned of photodermatitis from sun exposure during and several days after treatment
- Should be used in patient in elderly patients (>65 yrs) with caution since increases chance of myelo suppression
- Patient should be closely monitored for Pnemocystis Carni infection and all patients receiving Temozolomide and RT should be given PCP prophylaxis Tab.Septran
- Pregnancy category D. Breast Feeding to be discontinued

TOXICITY:

- Myelosupreesion is the dose limiting toxicity . Both leukopenia and thrombocytopenia are commonly seen
- Nausea and vomiting starts 1-3 hours after administration and lasts for 12 hours after administration
- Headache and fatigue
- Mild elevation of hepatic transaminase
- Photosensitivity
- Tertogenic , Mutagenic and Carcinogenic

In the study done by Deng et al. –"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 BM".

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 K et al. 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 et al. 18 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/m2 . There was slightly decreased toxicity when the temozolamide dosage 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 to 3 brain metastases" is done by RTOG 0320. This study showed that the addition of TMZ or ETN to WBRT + SRS in NSCLC patients with 1 to 3 brain metastases did not improve survival and possibly had a deleterious effect.

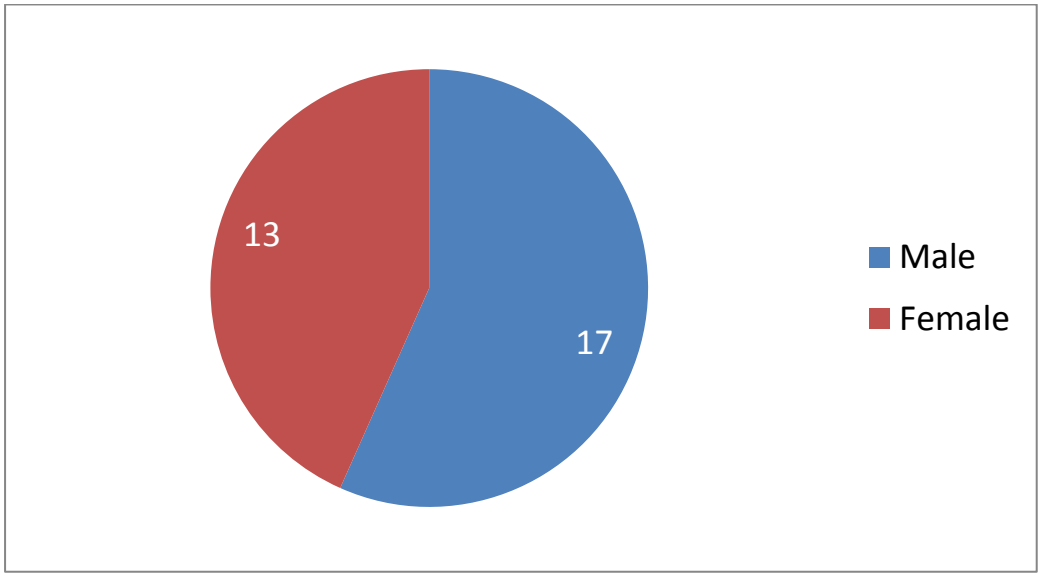
The study done by Deng et al published is the basic model in which this study has been designed , however additional parameter of motor functioning namely Peg board analysis has been added in this study

RESULTS

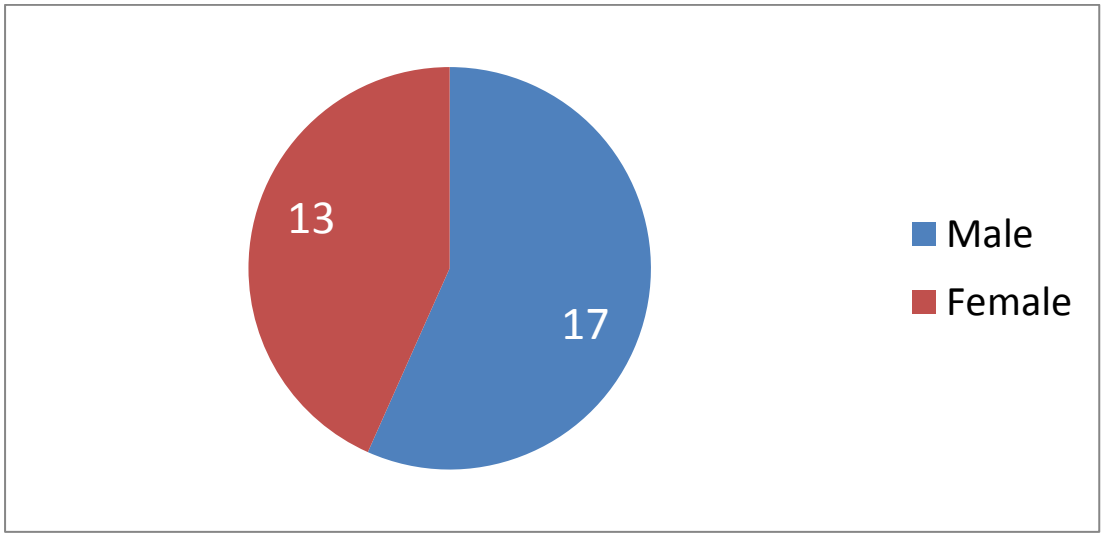
Results

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.

SEX –WISE DISTRIBUTION:

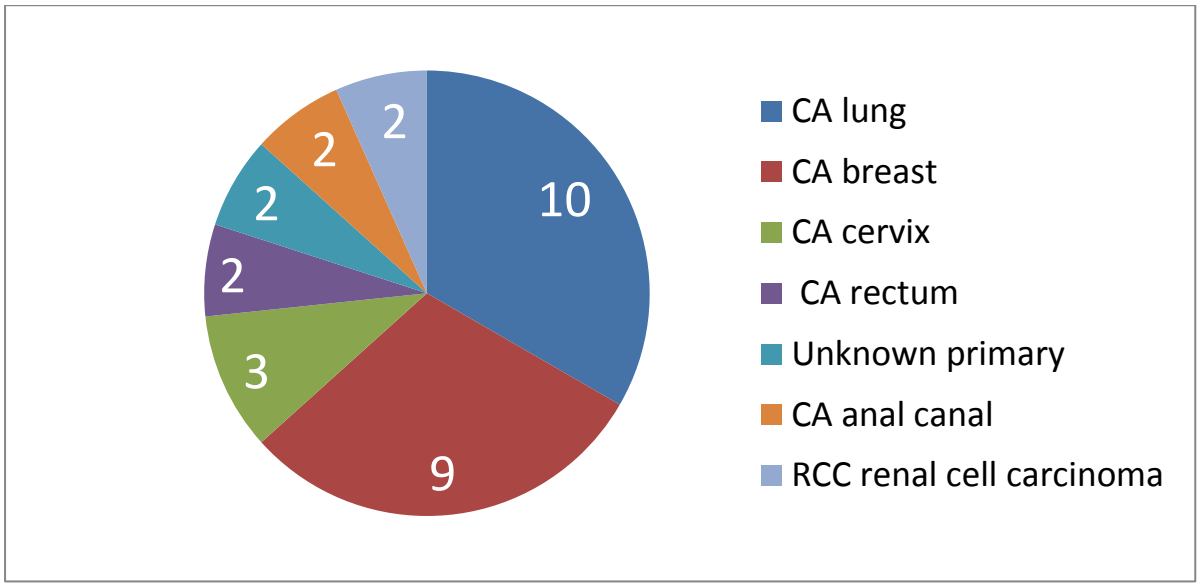


TREATMENT ARM

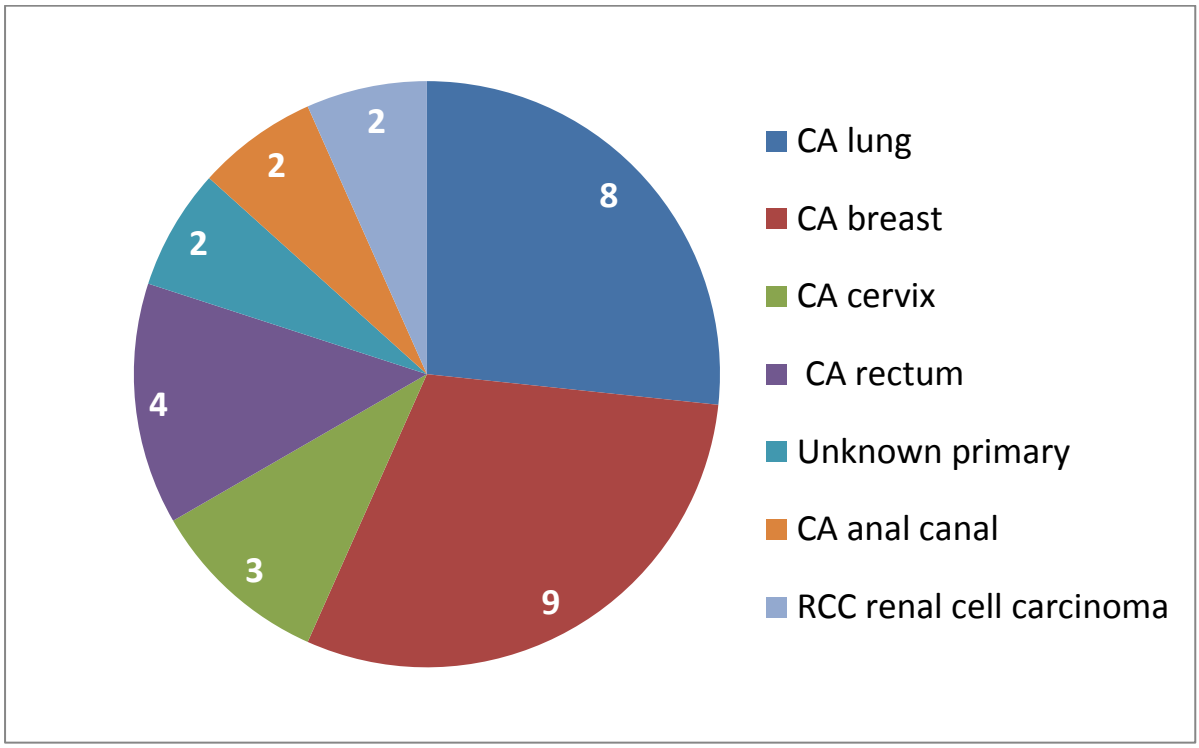


CONTROL ARM

SITE WISE DISTRIBUTION

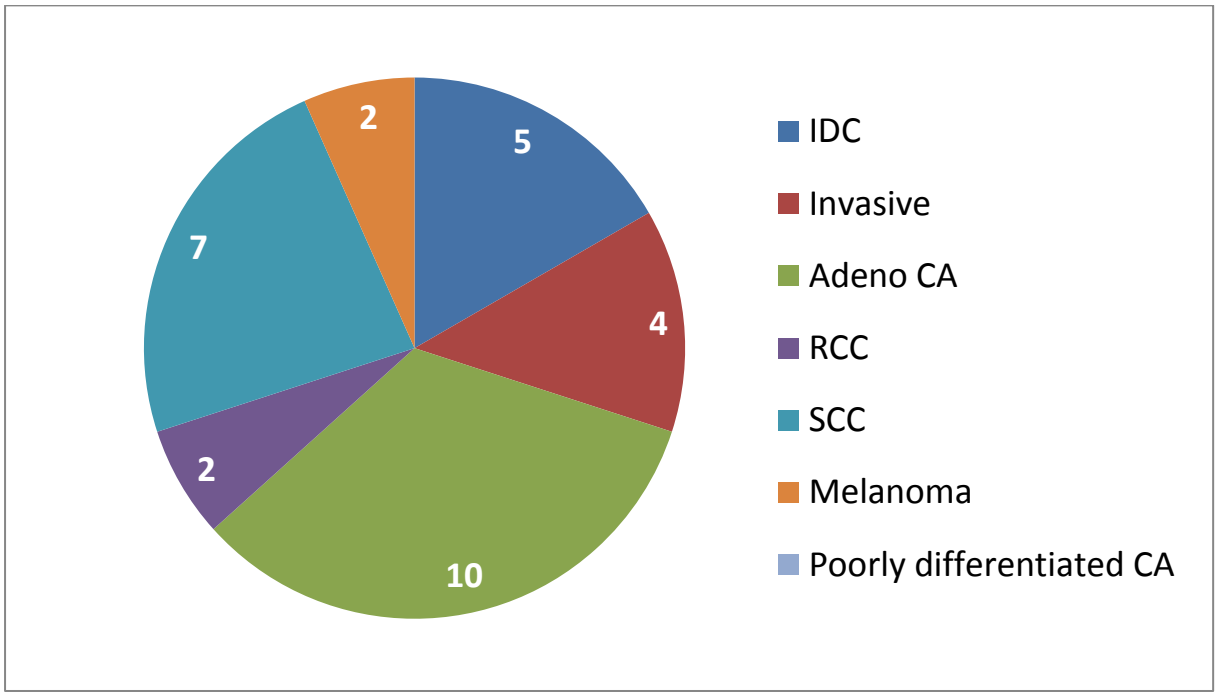


TREATMENT ARM

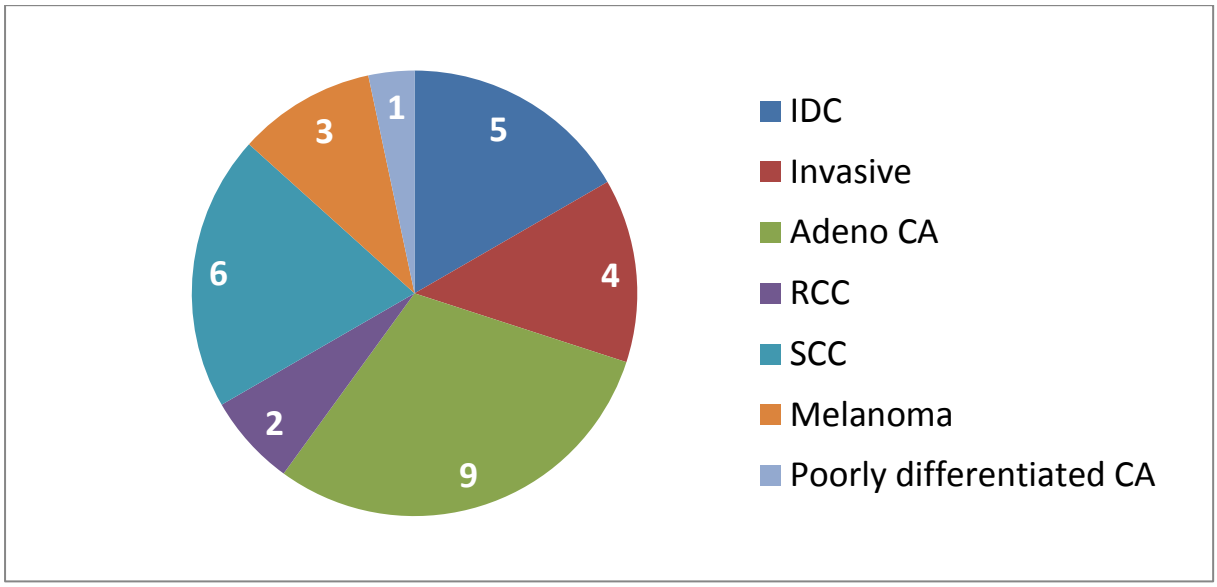


CONTROL ARM

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.

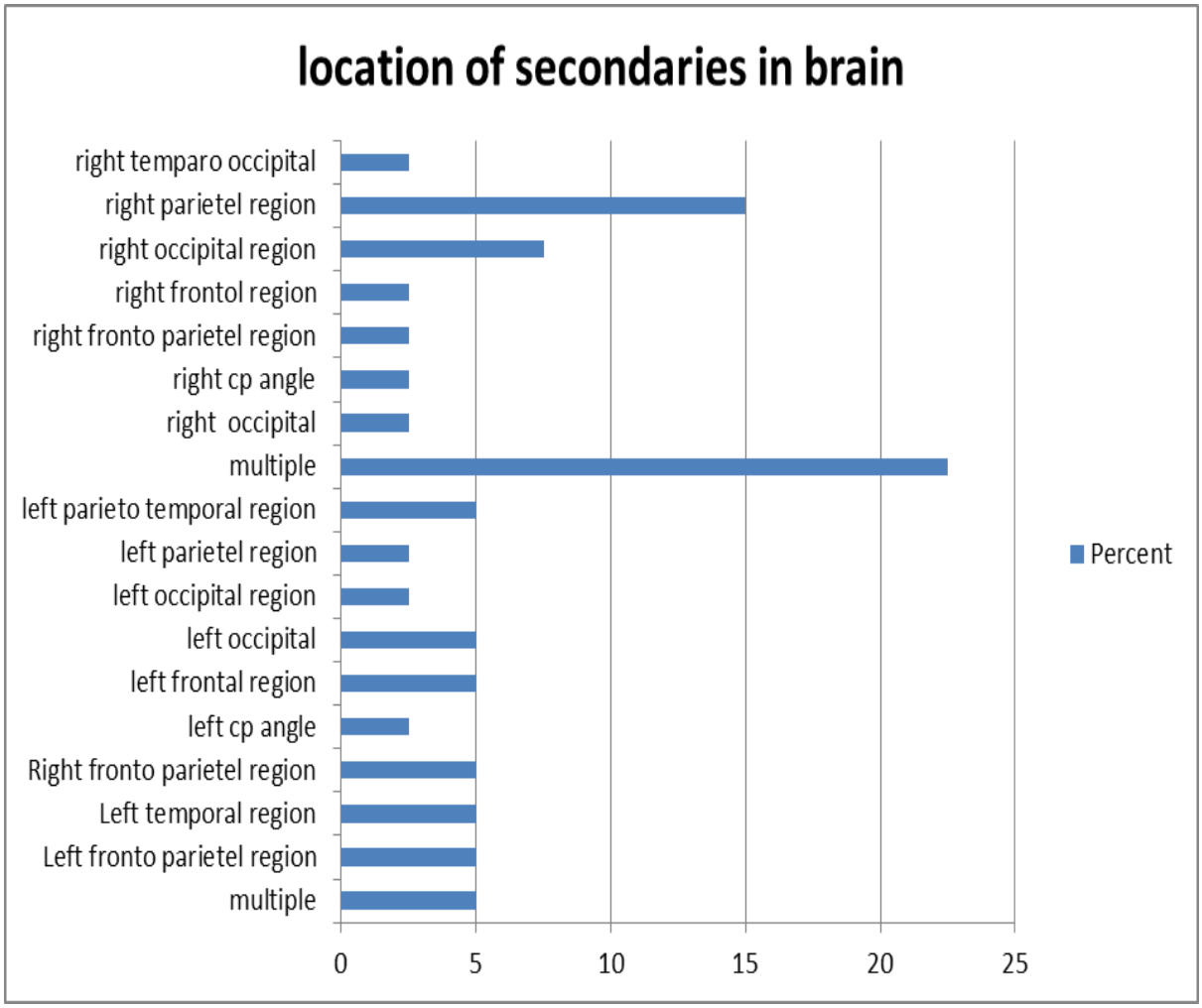


CONTROL ARM

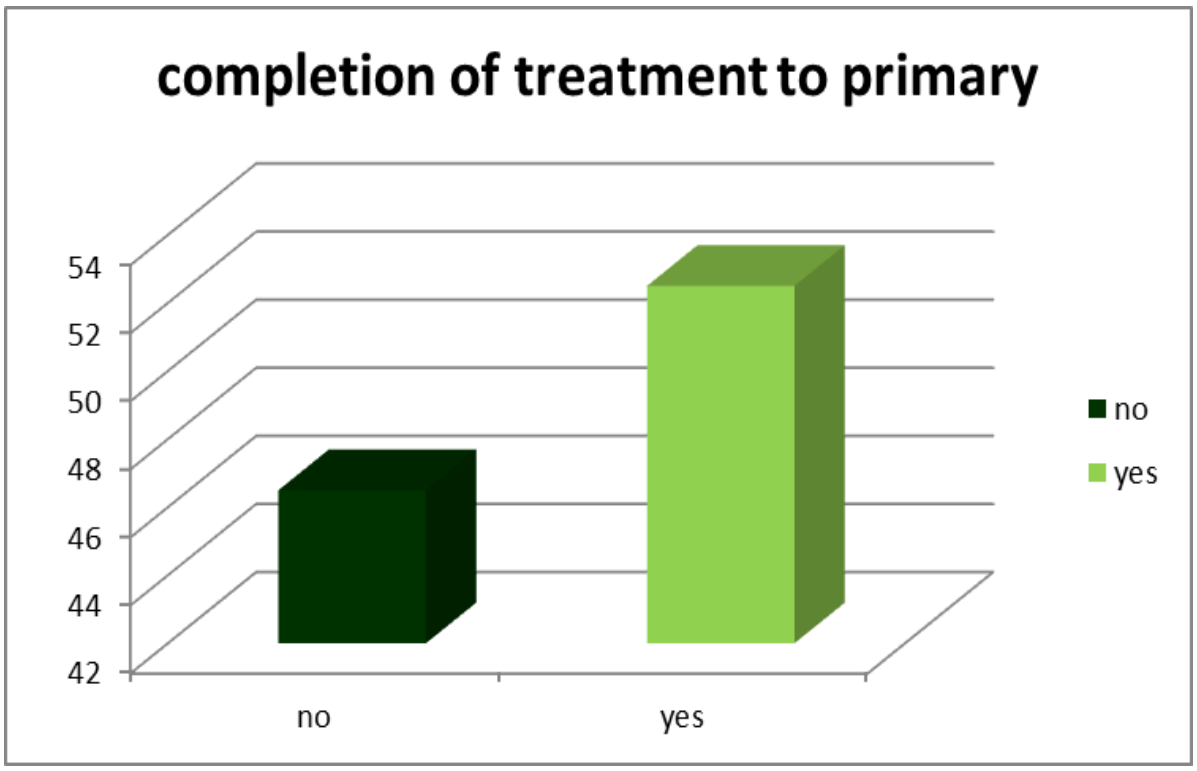


DISTRIBUTION OF METASTASES:

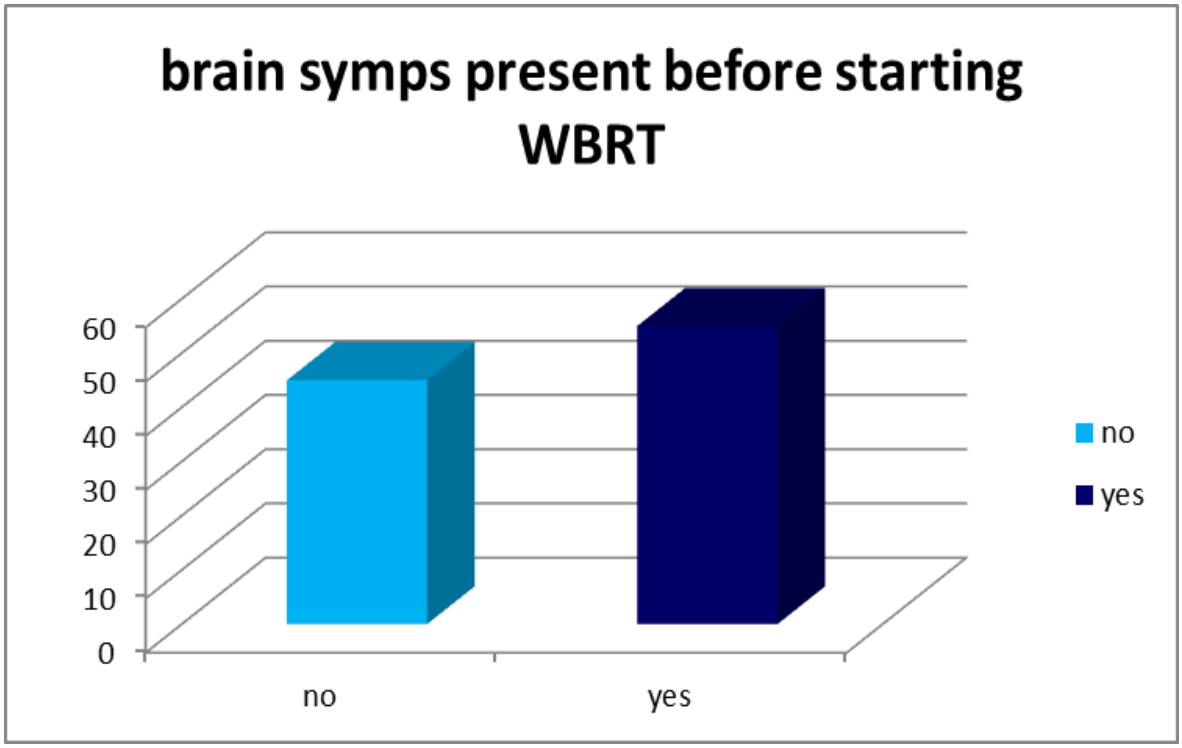
In both the arms the most common location of brain metastases were multiple in locationfofllowed by Right Parietel region combining both arms. The least site for loaction was the CP angle metastases



In both the arms about 52.5% completed treatment to the primary before occurrence of metastases and 46.5% did not complete theprimary 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 6 months of followup (mean=11.50 ± 0.71)

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 decrerase 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 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 decrerase in motor function in the non 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

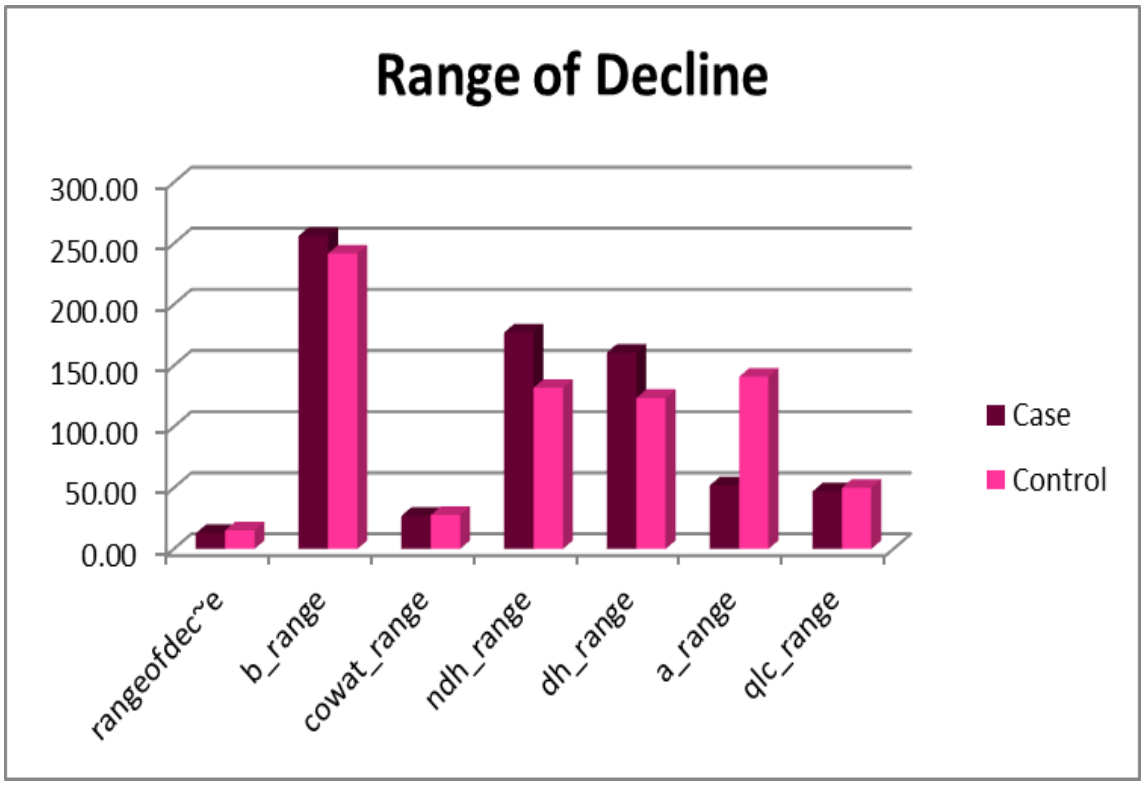
In the treatment arm the value corresponding to the decline in visual motor scanning began at C5(mean: 79 ± 7.27) and reached the minimum after 3 months after treatment(mean:86.25 ± 9.81). In case of control arm the decrerase in visual motor scanning was observed at C2.(Mean: 95 ± 36.20) and reached 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 less than 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 less than 50% of baseline QOL began at C2.(Mean: 39.90 ± 9.46) and reached the least value at C5(17.20 ± 4.66)

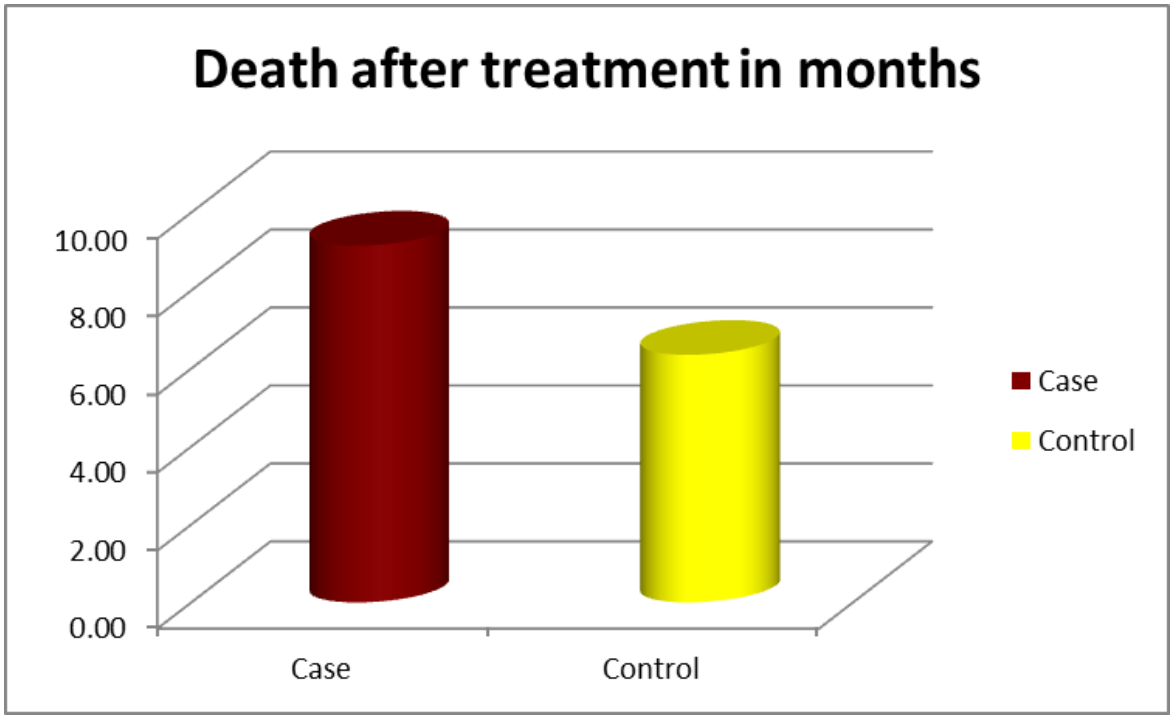
These results clearly indicate that although there is improvement in Quality of Life in the treatment arm there is no significance in the p value.



OVERALL SURVIVAL:

When comparing both the arms the over all survival in the treatment arm 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 assesed . This is because of the difficulty in imaging these ill and deblitating 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.



CONCLUSION

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.

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 which can be considered in future in determining the final outcome.

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13).Temozolomide and unusual indications: Review of literature

ZuzanaTatarab1EmilieThivatcdEloisePlanchatc1PierreGimberguesc1EmilieGadeac1CatherineAbrialcd1XavierDurandoace1; Cancer Treatment Reviews

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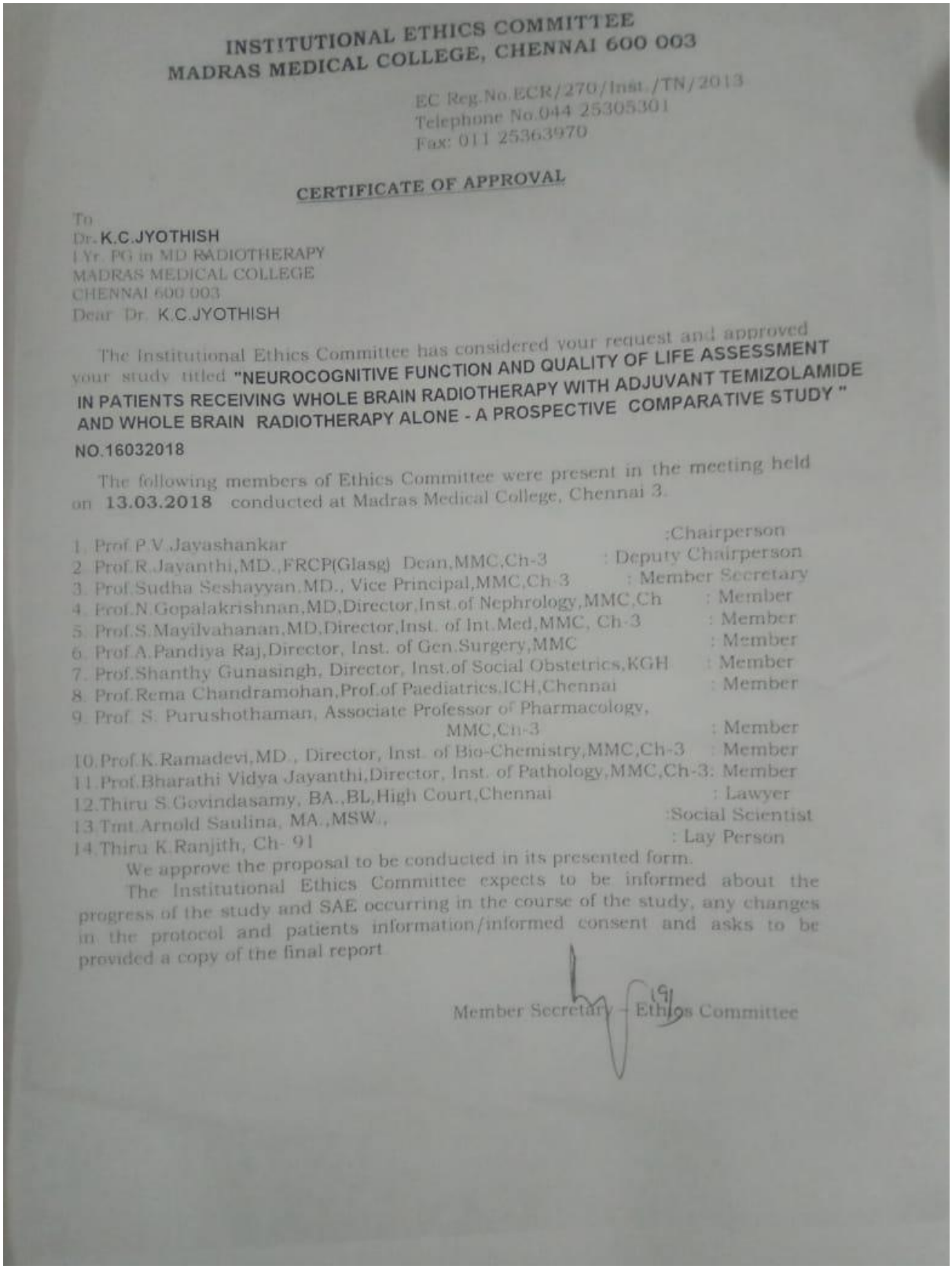
Annexures

Annexure I

IEC Approval :



INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr. K.C.JYOTHISH
I Yr. PG in MD RADIOTHERAPY
MADRAS MEDICAL COLLEGE
CHENNAI 600 003

Dear Dr. K.C.JYOTHISH

The Institutional Ethics Committee has considered your request and approved your study titled **"NEUROCOGNITIVE FUNCTION AND QUALITY OF LIFE ASSESSMENT IN PATIENTS RECEIVING WHOLE BRAIN RADIOTHERAPY WITH ADJUVANT TEMIZOLAMIDE AND WHOLE BRAIN RADIOTHERAPY ALONE - A PROSPECTIVE COMPARATIVE STUDY "**

NO.16032018

The following members of Ethics Committee were present in the meeting held on **13.03.2018** conducted at Madras Medical College, Chennai 3.

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3 : Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch : Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3 : Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC : Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH : Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
9. Prof. S. Purushothaman, Associate Professor of Pharmacology, MMC,Ch-3 : Member
10. Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3 : Member
11. Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3: Member
12. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
13. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
14. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report

Member Secretary - Ethics Committee

Annexure II

Tamil Consent Form :

சுயஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு: முழு மூளை கதிர் வீச்சுடன் டெமிசோலமைடு மற்றும் முழு மூளை கதிர் வீச்சு சிகிச்சை மட்டும் பெறும் நோயாளிகளுக்கு நரம்பியல் செயல்பாடு மற்றும் உயிர் மதிப்பீட்டின் தரம் ஆகியவை -ஒரு முன்நிலை ஒப்பீட்டு ஆய்வு

இடம்:

கதிர் வீச்சு துறை,

சென்னை மருத்துவ கல்லூரி மற்றும் ராஜீவ் காந்தி அரசு மருத்துவமனை

சென்னை-600003.

பங்குபெறுபவரின் பெயர் :

பங்குபெறுபவரின் வயது :

பங்குபெறுபவரின் எண் :

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளல்லாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில்பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன்.

இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு

உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

இடம் :

தேதி :

Annexure III

Abbreviations :

WBRT - Whole Brain Radio therapy

Her 2 Neu - Human Epidermal Growth factor Receptor 2

MMSE - Mini Mental Scale Examination

NCF - Neurocognitive Function

COWA - Controlled Oral Word Association Test

NDH - Non Dominant Hand

DH - Dominant Hand

ECOG - European Cooperative Oncology Group

RTOG - Radiation Therapy Oncology Group

CERTIFICATE

This is to certify that the dissertation entitled **"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 "** of the candidate **Dr. K. C. JYOTHISH** with the **Registration Number : 201719003** for the award of M.D Degree in the Branch of Radiotherapy is personally verified by me in the urkund.com website for the purpose of plagiarism check.

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