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RESEARCH ARTICLE
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EVALUATING ROLE OF MRI IN DIFFERENTIATING RECURRENT/RESIDUAL TUMOR FROM RADIATION INJURY IN A CASE SERIES OF RADIOTHERAPY TREATED CASES OF BRAIN TUMORS

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Abstract
Differentiating radiotherapy induced changes from residual/recurrent tumor is the mainstay challenge in neuro-oncoradiology. Contrast enhanced MRI is the current mainstay for evaluation of treatment response in brain tumors. However both shows similar clinical symptoms and post contrast enhancement. Conventional MRI sequences provides only anatomical information, newer sequences also provides information regarding tumor microenvironment , metabolic and hemodynamic function. The aim of our study was to evaluate the diagnostic effectiveness of MR spectroscopy and MR perfusion images to differentiate recurrent/residual tumor and radiation injury using parameters like Cho/NAA, Cho/Creat, NAA/Creat ratios and rCBV. In our hospital based observational study, Contrast MRI with advanced sequences eg. MR spectroscopy, DSC Perfusion MRI were performed using 3T MRI Machine. Total 40 cases of radiotherapy treated brain tumors were analyzed. In our study we found that mean value of Cho/NAA were significantly higher in residual/recurrent lesion (5.4), compared to radiation injury(0.33). Mean value of Cho/creat were significantly higher in residual/recurrent lesion(2.9), compared to radiation injury(1.01). Mean value of NAA/Creat were significantly lower in residual/recurrent lesion(0.45) compared to in radiation injury(4.2). Mean value of rCBV in a contrast enhancing lesion were significantly higher in residual/recurrent lesion(713), compared to in radiation injury(129). Mean value of rCBV ratio in lesion compared to contralateral normal white matter were significantly higher in residual/recurrent lesion(3.4), compared to in radiation injury(0.49). MR Spectroscopy and MR Perfusion may increase the accuracy of differentiating recurrent/residual tumor from radiation injury in radiotherapy treated cases of brain tumors and can help avoid unnecessary invasive procedures like biopsy.

Introduction
Differentiating radiotherapy induced injury from recurrent/residual tumor is the mainstay challenge in neurooncoradiology.Contrast enhanced MRI is the current mainstay for evaluating treatment

response in brain tumors, however tumor and radiation injury both can show similar clinical symptoms and even similar appearance on contrast MRI images. Differentiating treatment induced injuiry from recurrent/residual tumor is very crucial for diagnosis and treatment planning, and for this surgical biopsy with re-operation is often required. It is for this reason much efforts has been put to develop non invasive methods to differentiate between these two. Conventional MRI sequences like T1, T2, FLAIR, GRE images provides only anatomical information. Newer sequences like Diffusion images, MR spectroscopy and Perfusion images also provides information regarding tumor microenvironment, metabolic and hemodynamic information.The aim of our study was to evaluate the diagnostic effectiveness of MR spectroscopy and MR perfusion images to differentiate recurrent/residual tumor and radiation injury using parameters like Cho/NAA, Cho/Creat, NAA/Creat ratios and rCBV.

AIMS AND OBJECTIVE:

- To evaluate role of MR spectroscopy and Perfusion imaging in differentiating residual/recurrent brain tumor vs radiation injury in radiotherapy treated cases of brain tumors
- To evaluated new areas of contrast enhancement at the site of previously treated brain tumors
- To guide neurosurgeon regarding treatment planning and biopsy site if there is recurrent/residual lesion.

MATERIAL AND METHODS:

It is and hospital based observational study conducted at GCRI, Ahmedabad in the month of April and May 2023. Contrast MRI with advanced sequences eg. MR spectroscopy, DSC Perfusion MRI was performed using SIEMENS MAGNATOM SKYRA 3T MRI Machine.

INCLUSION CRITERIA:

- Treated cases of Brain tumors who have received at least Radiotherapy.
- Treated cases of brain tumors in which MRI showing new areas of contrast enhancement

EXCLUSION CRITERIA:

- Patient who have allergy from contrast media
- Patient having general contraindication for MRI

Clinical, Neuroradiological and Pathological follow up was used to establish identity of the lesion.

Lesion was regarded as recurrent/residual tumor if it met the following criteria:

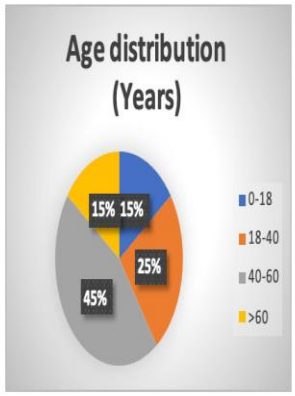
1. HPE confirmation after Biopsy or Surgical resection or Autopsy
2. Continuing progression on subsequent MRI in a manner consistent with tumour growth.

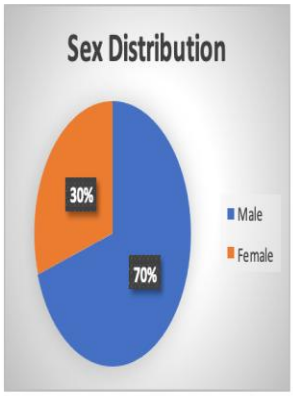
Lesion classified as radiation injury if met either of the following criteria:

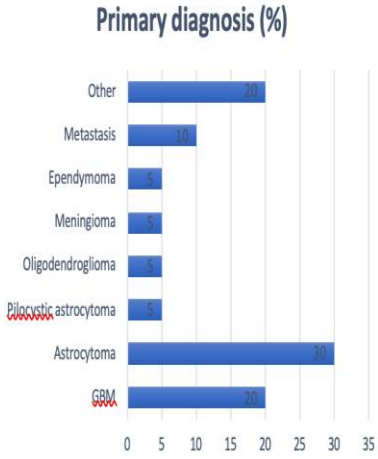
1. HPE confirmation after Biopsy or Surgical resection
2. MRI follow up images showing prolonged stability or spontaneous regression unaccompanied by clinical worsening.

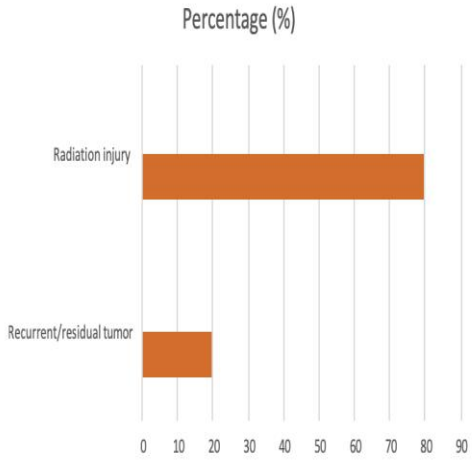
Observations and Analysis:

A total of 40 cases of radiotherapy treated brain tumors were analyzed.

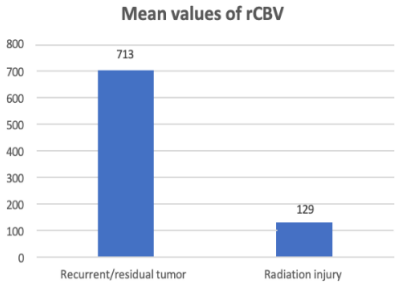


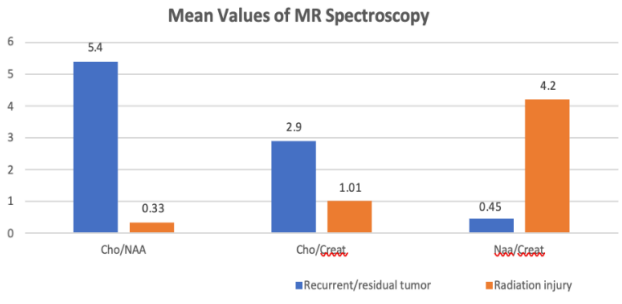


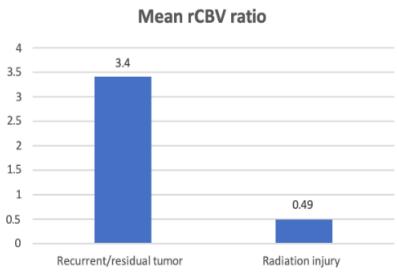




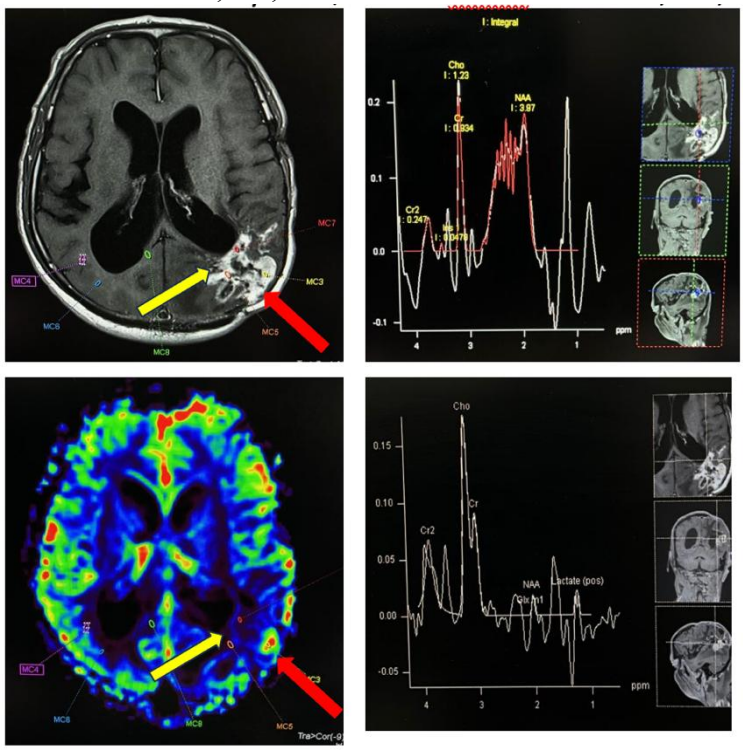
MEAN VALUES	Cho/ NAA	Cho/ Creat	Naa/ Creat	rCBV	rCBV ratio
Recurrent / residual tumor	5.4	2.9	0.45	713	3.4
Radiation Injury	0.33	1.01	4.2	129	0.49







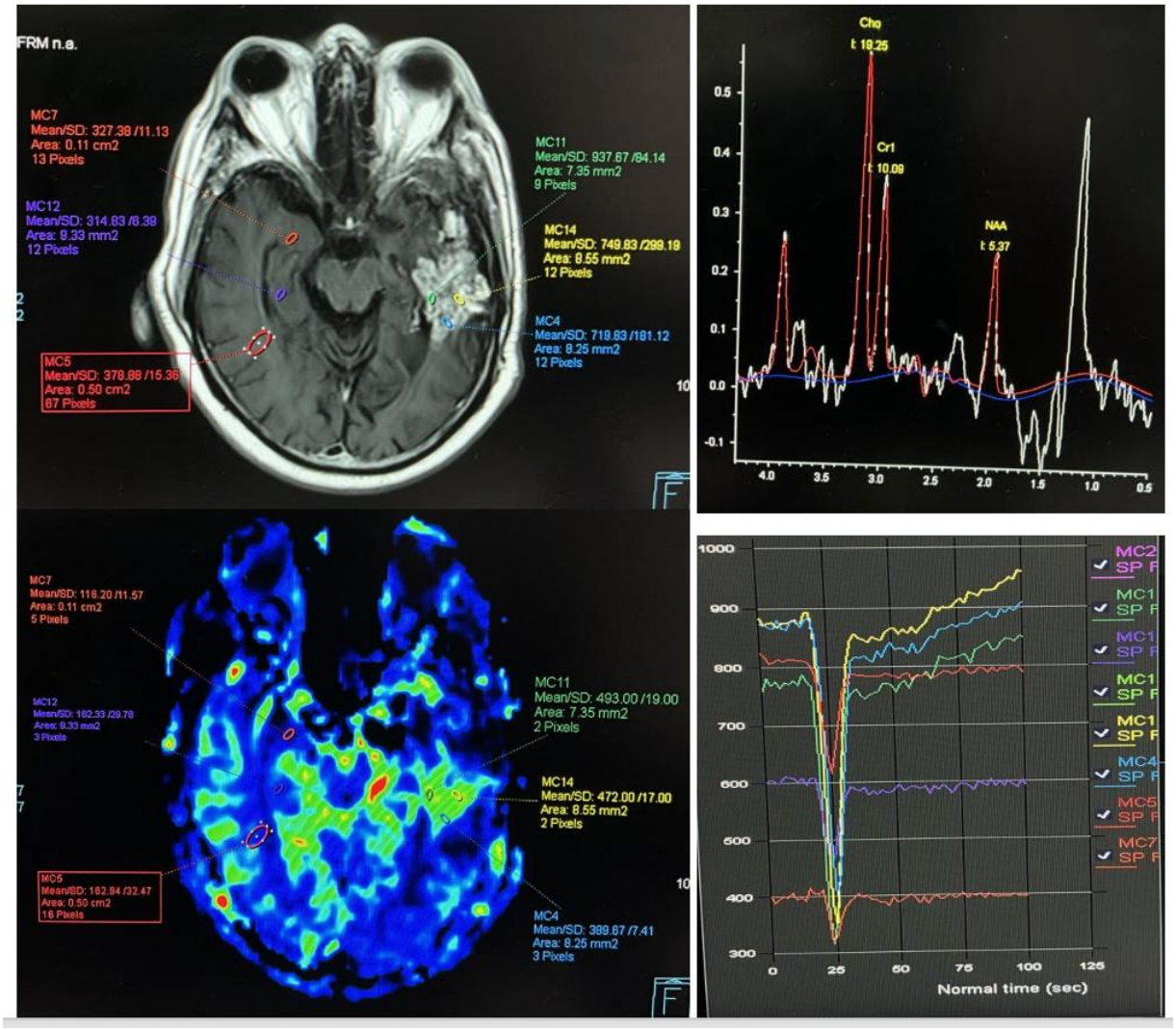
Case 1: 54 years/Male. GBM Post OP, CT, RT



The patient was stable since 3 years, then he developed an episode of seizure, MR images showing: There is "Swiss Cheese" pattern of Post contrast enhancement is noted in left high parietal region.
1.The area Marked by Yellow arrow shows following MR spectroscopy findings(Superior image): Cho/NAA(0.33), Cho/Creat(1.01), Naa/Creat(4.26), also shows lipid- lactate peak, it does not show increased rCBV (197) and rCBV ratio is 0.52 compared to normal white matter.
The above findings suggests area of **Radiation injury.**
2.The area marked by Red arrow shows following MR Spectroscopy findings (Inferior image): high Cho/NAA (8.02), Cho/Creat(3.5), NAA/creat (0.45), it shows significant increased rCBV(1215) and rCBV ratio is 3.9 compared to normal white matter

The above findings suggest: **Residual lesion**
So, There is mixed area of radiation necrosis and residual lesion.

Case 2: 58 years/Male. GBM Post OP, CT, RT



There is intense post contrast enhancement is noted in left temporal region which shows following findings

MR spectroscopy findings:

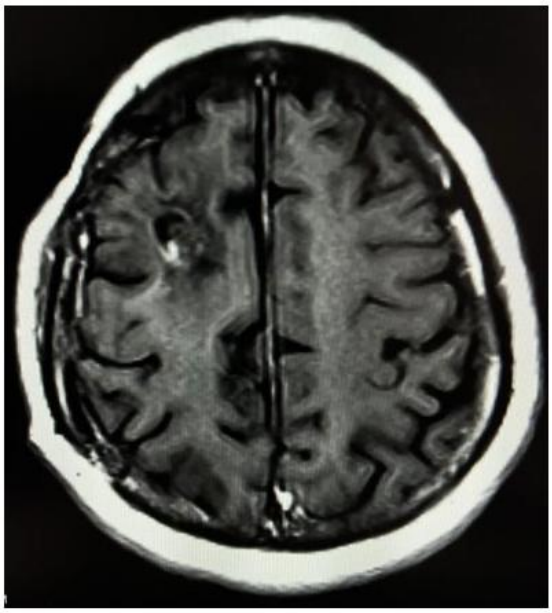
Cho/NAA	Cho/Creat	Naa/Creat
2.9	2.58	0.88

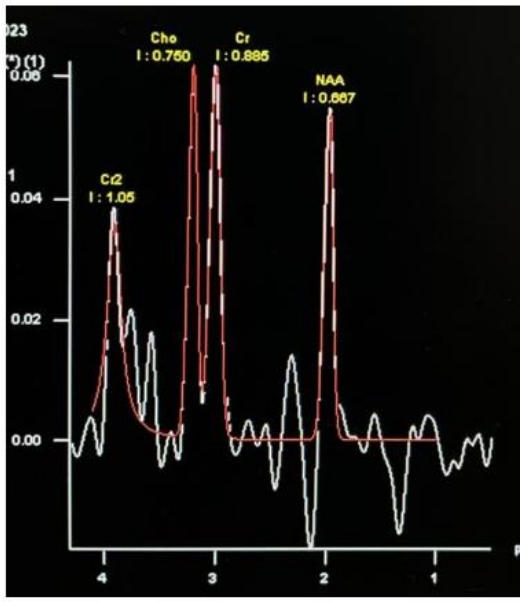
MR Perfusion findings:

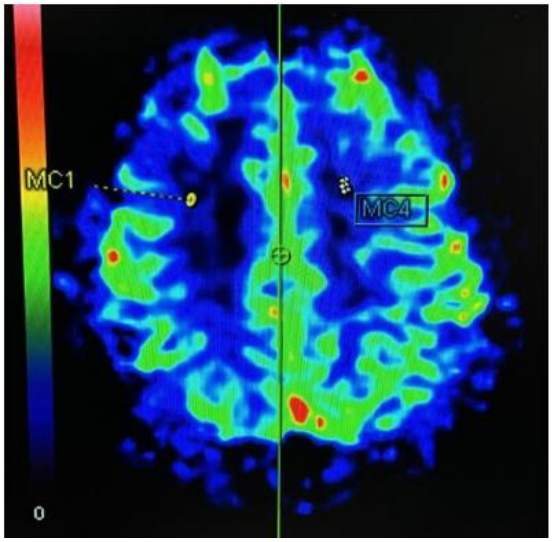
rCBV Lesion	rCBV control	rCBV(l)/rCBV(c)
498	126.7	3.9

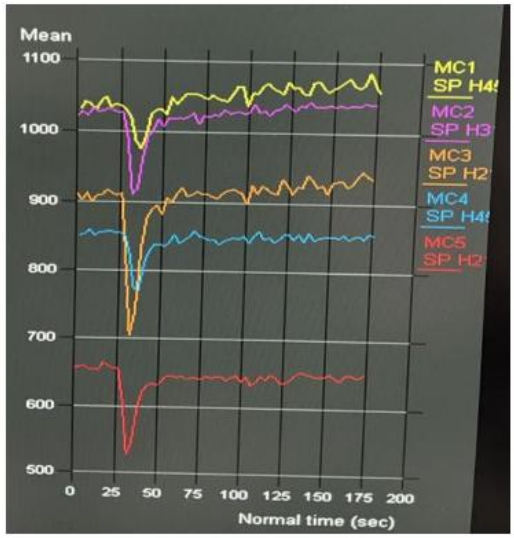
The above findings suggest: **Recurrent tumor**

Case 3:52 years/Female.Astrocytoma, Grade II. Post OP CT RT.







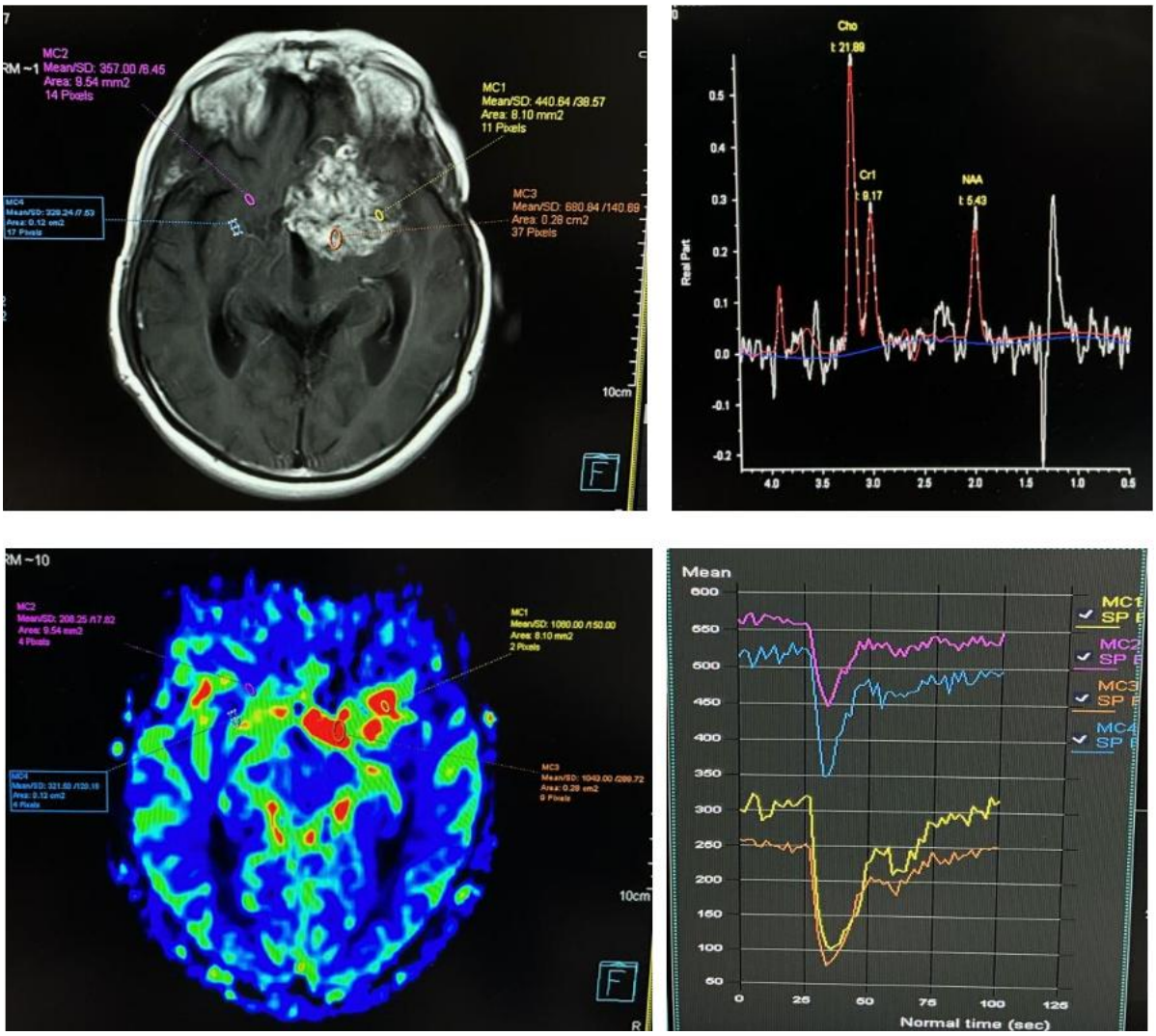


There is area of peripheral enhancement is noted in right Frontal region.

MR spectroscopy show no significant increased Cho/NAA , Cho/Creat ratio.
On Perfusion images: There is no increased rCBV.

rCBV Lesion	rCBV control	rCBV(l)/rCBV(c)
47	69	0.68

The above findings suggest: **Radiation injury**
Case 4: 42 years /Male. Astrocytoma Grade II. Post OP CT RT



There is another case of intense post contrast enhancement is noted involving left insular cortex extending into left frontal and temporal region.

MR spectroscopy findings:

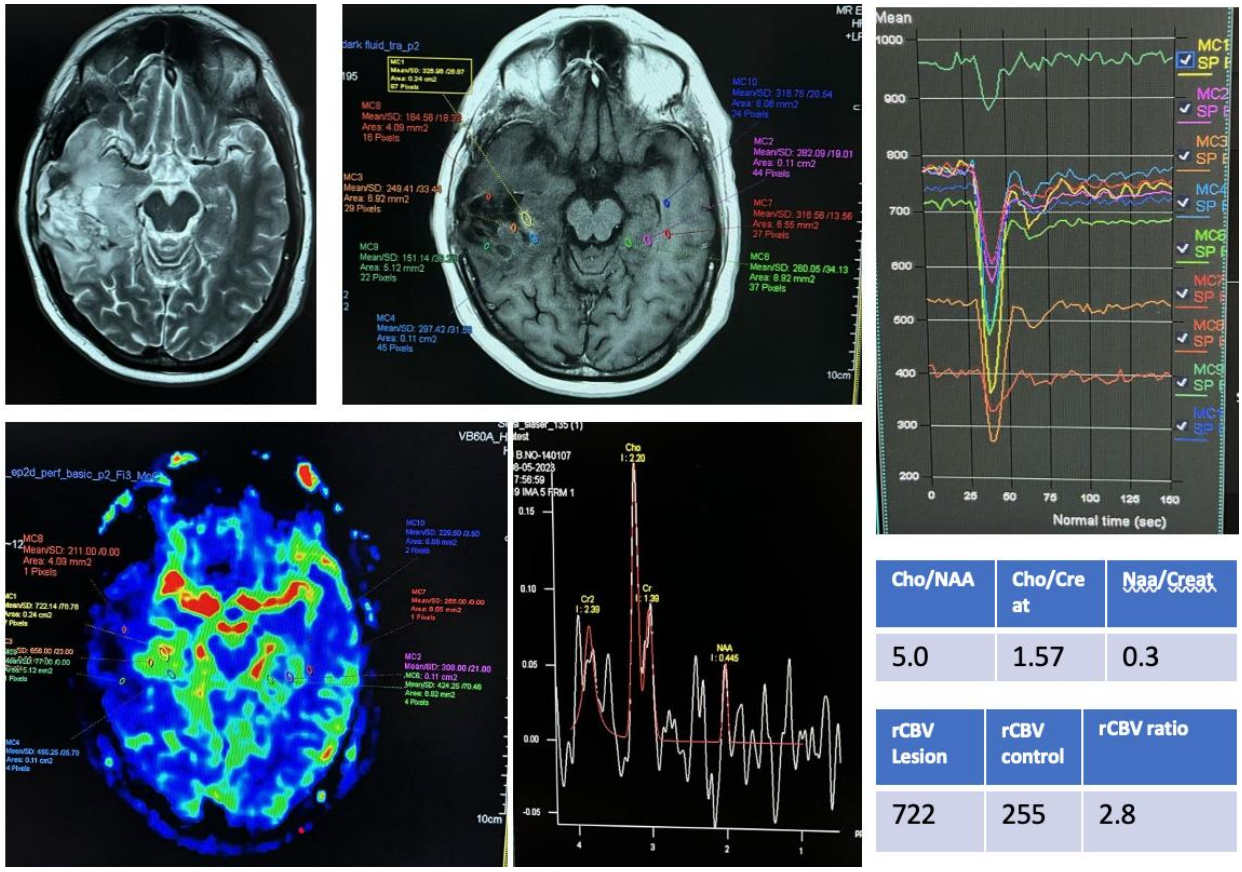
Cho/NAA	Cho/Creat	Naa/Creat
4.03	2.39	0.59

MR Perfusion findings:

rCBV Lesion	rCBV control	rCBV(l)/rCBV(c)
1080	208	5.2

The above findings suggests: **Residual tumor**

Case 5: 50 years/Male. Diffuse Glioma Grade II. Post OP CT RT



Cho/NAA	Cho/Creat	Naa/Creat
5.0	1.57	0.3

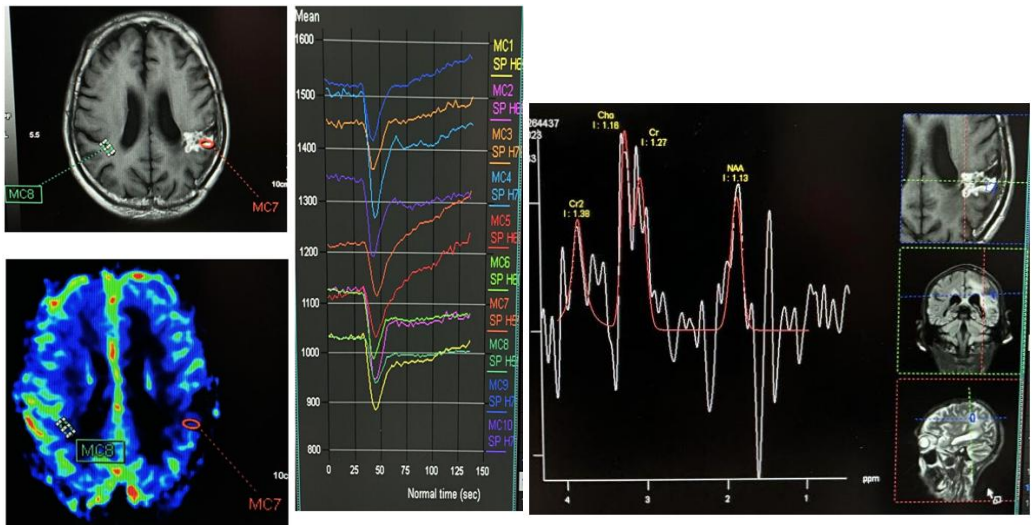
rCBV Lesion	rCBV control	rCBV ratio
722	255	2.8

This is a case of diffuse glioma, WHO grade II. Post OP CT and RT.

On follow up MRI scan, there is T2 hyperintense lesion is noted in right parieto-temporal region with no significant post contrast enhancement.
MR spectroscopy favors residual lesion, while MR perfusion images show area of high rCBV. Which may be region with high grade glioma.
So, MR perfusion image also helps to guide the biopsy site.

Case 6: 62/Male, Diffuse glioma, Grade II . Post OP CT RT

z	rCBV control	rCBV(l)/rCBV(c)
132	120	1.1
Cho/NAA	**Cho/Creat**	**Naa/Creat**
1.04	0.86	0.89



There is area of contrast enhancement is noted in left parietal region,
On MR spectroscopy no significant increased Cho/NAA ration
On MR Perfusion images, There is no significant increased rCBV is noted.
The above findings suggests,

Radiation injury over residual/recurrent lesion.

Discussion:

- General approach for treating solitary or limited brain tumor is surgical resection followed by radiotherapy with or without chemotherapy.
- Goal of Radiotherapy is to halt the progression of tumor, although injury to adjacent normal tissue is an inevitable complication of radiotherapy.
- In tumor, there is neo angiogenesis which are structurally weak vessels which have leaky membranes which leads to extravasation of contrast resulting in post contrast enhancement.
- So even if primary tumor is non enhancing like low grade glioma, recurrent tumor can show post contrast enhancement.
- Radiation impairs vascular integrity which leads to extravasation of contrast which leads to post contrast enhancement.
- The most common MR finding in radiation necrosis is Swiss cheese like enhancement with feathery margin and central necrosis.

Radiation injury and tumor recurrence both share common findings:

- Both occur close to the tumor site
- Both shows post contrast enhancement
- Both can show growth over time
- Both shows perilesional edema
- Both produces mass effect

So, occurrence of a new lesion after radiation treatment can be:

- Recurrence of tumor
- Radiation induced demyelination
- Radiation necrosis
- Ischemic stroke, secondary to radiation induced vasculopathy
- Secondary tumor
- SMART syndrome (Stroke like migrain attacks after radiation therapy)

Radiation injury:

1. **Acute** (Days to weeks) :

• Clinical symptoms: Headache and drowsiness

• Imaging findings: Often Normal, occasionally transient white matter edema in T2/FLAIR, may shows changes in MRS, DTI and fMR

2. **Early delayed** (1 to 6 months):

• Transient interruption of myelin synthesis

• Clinical symptoms: Somnolence, attention deficit, short term memory loss.

• Imaging: Periventricular white matter hyperintensities in T2/FLAIR

3. **Late delayed** (9 months to 2 years):

• Irreversible and progressive and leads to radiation necrosis (Necrotising leukoencephalopathy).

• Vasculopathy, mineralizing microangiopathy

• Vascular malformations

• Radiation induced neoplasms.

MR Spectroscopy:

• MR Spectroscopy is a means of non invasive physiological imaging of the brain that measures absolute and relative levels of various brain tissue metabolites.

• **Principle**: Chemical shift phenomenon forms the basis of MR spectroscopy.

• Changes in NAA/Cho, NAA/Cr & Cho/Cr are most reliable 4 months after RT, because dueto radiation induced inflammation or gliosis, initially there is increase in the Choline.

• These changes tend to resolve over time

• mI/Cr ratio serves as one of the first indicators of local irradiation injury

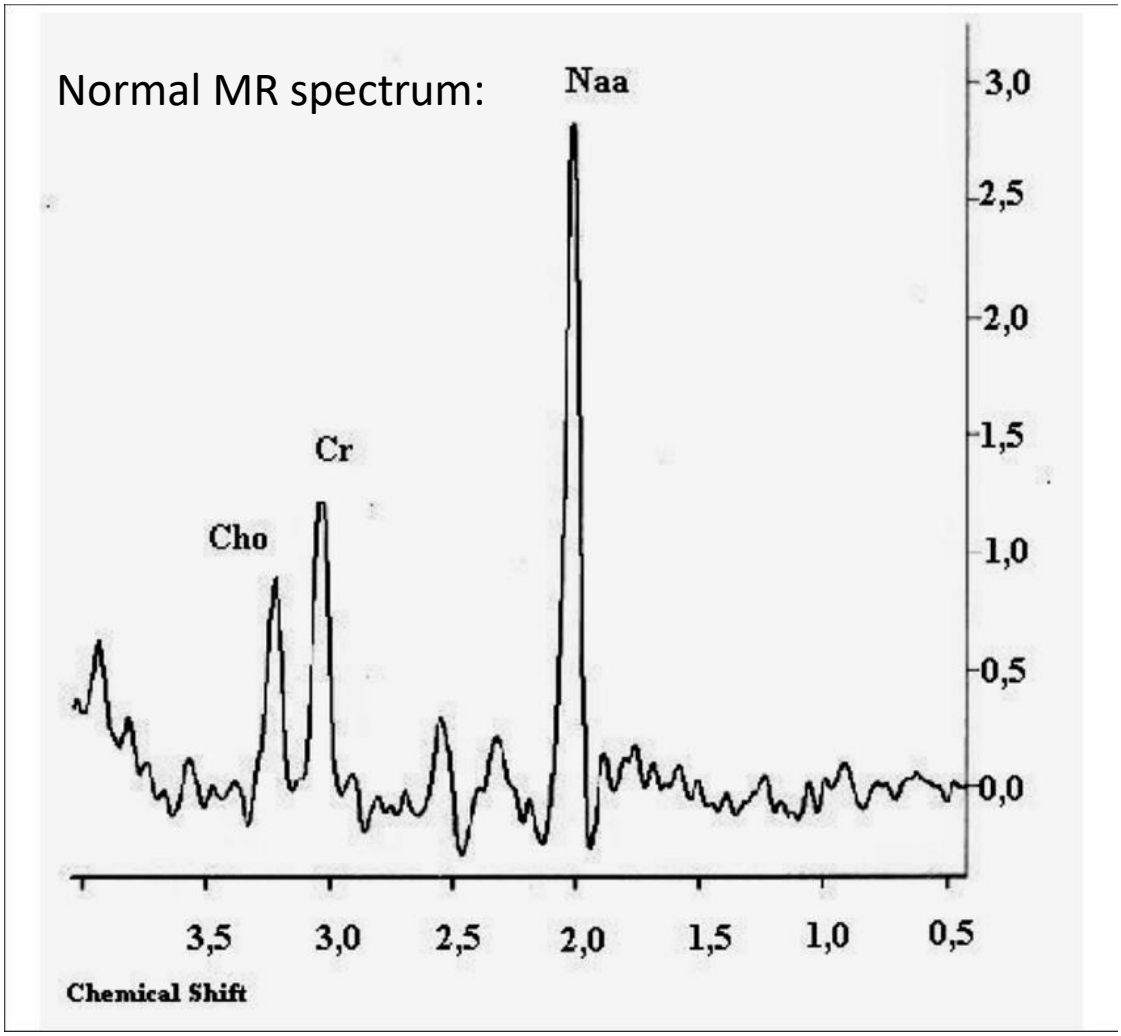
• Mobile lipids & lactate represent necrosis

Short TE is required for reliable assessment of lipids

• **Choline is the most reliable indicator of a regrowing glioma**

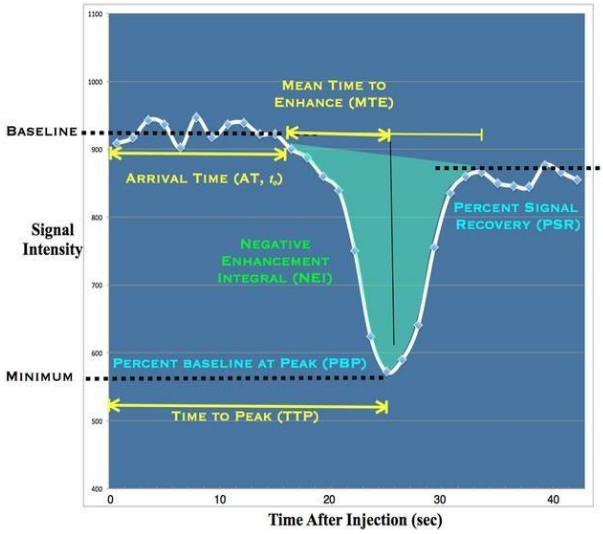
• A high Cho/Cr ratio , or Substantial elevation in the Cho/Cr ratio between serial studies increases the likelihood of tumor regrowth

Chemical compound	Chemical shift (ppm)	Comments
NAA	2.0	Neuronal marker
Creatine/Phosphocreatine	3.0 , 3.94	Energy metabolism
Choline	3.22	Cell membrane marker
Myo-inositol	3.56, 4.0	Glial cell marker, osmolyte hormone receptor mechanism
Glutamate/Glutamine	2.1-2.5	Excitatory neurotransmitter and regulator
Lipid	0.9-1.4	Cell breakdown/ brain destruction indicator
Lactate	1.33, 4.1	End product of anaerobic glycolysis



MR Perfusion:
• Contrast enhancement suggests areas of disruption of Blood brain barrier, it doesn't neccessarily correlate with tumor activity.
• Whereas, Perfusion images measures degree of tumor angiogenesis and capillary permeability.
• Increased blood flow and blood volume predicts tumor activity.
• Increasing rCBV is associated with recurrent/residual lesion.
• Corrected CBV values > 2.6 suggests tumor recurrence, <0.6 suggests therapy related.
(Radiology: 2002: 225: 871-879)

MR Perfusion technique:
• There are various techniques available, in our study DSC (Dynamic Susceptibility Contrast) Perfusion technique was used.
• Rapid IV injection of Gadollinium : 15 ml at 5 ml/sec is done
• Time series of GRE EPI T2* weighted images obtained.
• We can calculate Arrival time(AT), Time to peak (TTP), Mean Transit time(MTT), Cerebral blood Volume (CBV), and Cerebral blood flow (CBF). **CBV is used to evaluate brain tumor images.**



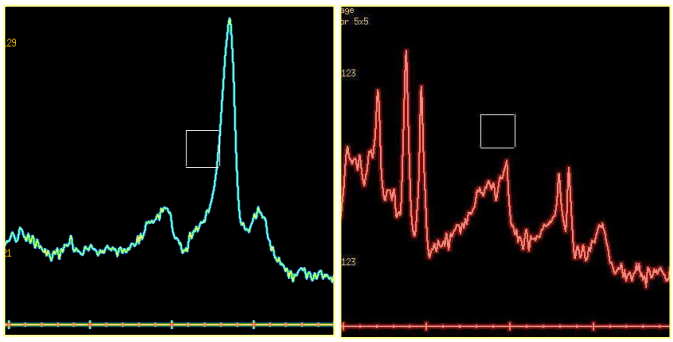
Application of Perfusion in tumor images:

- Tumor vs Non tumor
- Tumor recurrence vs Radiation necrosis
- Type (Glioma vs Lymphoma vs Metastasis)
- Grading of glioma
- Biopsy guidance
- Pseudoprogession and Pseudo response
- Response to therapy

Conclusion:

- The majority of the cases had residual/recurrent lesion than radiation injury.
- Mean value of Cho/NAA were significantly higher in residual/recurrent lesion (5.4), compared to radiation injury(0.33).
- Mean value of Cho/creat were significantly higher in residual/recurrent lesion(2.9), compared to radiation injury(1.01).
- Mean value of NAA/Creat were significantly lower in residual/recurrent lesion(0.45) compared to in radiation injury(4.2).
- Mean value of rCBV in a contrast enhancing lesion were significantly higher in residual/recurrent lesion(713), compared to in radiation injury(129).
- Mean value of rCBV ratio in lesion compared to contralateral normal white matter were significantly higher in residual/recurrent lesion(3.4), compared to in radiation injury(0.49).
- MR Spectroscopy and MR Perfusion may increase the accuracy of differentiating recurrent/residual tumor from radiation injury in radiotherapy treated cases of brain tumors and can help avoid unnecessary invasive procedures like biopsy.

RADIATION NECROSIS	TUMOUR RECURRENCE
Decrease Choline	Raised Choline, reduced NAA
Decreased Creatinine	Easily identifiable creatinine
Decreased rCBV	Increased rCBV



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