Case Series of Intracranial Central Primitive Neuroectodermal Tumor in Two Adults Treated with Craniospinal Irradiation

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Abstract

Ewing sarcomas (ESs) and primitive neuroectodermal tumours (PNETs) exhibit identical genetic and histological characteristics, hence collectively denoted as ESs/PNETs, originating from the neuroectoderm and primarily consisting of primitive neuroectodermal cells. PNETs occur primarily in the cerebrum. They constitute 3-5% of all paediatric brain tumours. This case report describes two cases of intracranial central PNET with negative IHC and chromosomal markers in adult patients treated with craniospinal irradiation (CSI) and focal radiotherapy boost with concurrent and adjuvant chemotherapy.

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Key words : craniospinal radiotherapy, PNET, Intracranial cancers, Medulloblastoma.

Background

Ewing sarcomas (ESs) and primitive neuroectodermal tumours (PNETs) exhibit identical genetic and histological characteristics, hence collectively denoted as ESs/PNETs, originating from the neuroectoderm and primarily consisting of primitive neuroectodermal cells. Primary intracranial PNETs represent a rare, molecularly and clinically diverse group of brain tumours, which is more common in children than in adults. Though the appearance under microscope is similar to medulloblastoma (MB), PNETs occur primarily in the cerebrum. They constitute 3-5% of all paediatric brain tumours(1). The incidence of PNET in the United States are 0.15 per 1 lac children aged 0 to 4, 0.05 among 5 to 9 years old, 0.04 among 10 to 14 years old, and 0.03 among adolescents aged 15 to 19 years(2). They can be central PNET (cPNET) or peripheral PNET/ES (pPNET), indistinguishable based on morphology, but having different treatment and prognosis. Both of them can be differentiated based on immunohistochemistry (IHC) and chromosomal studies including Fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR). We describe two cases of intracranial central PNET with negative IHC and chromosomal markers

in adult patients treated with craniospinal irradiation (CSI) and focal radiotherapy boost with concurrent and adjuvant chemotherapy.

Case 1

A 22 years old male with no addictions or comorbidities, developed complaints of weakness in right sided upper limb and face, since January 2024. Magnetic resonance imaging (MRI) brain revealed a 5.3x4.5x4.1 cm well defined lesion with solid and cystic components in his left frontoparietal lobe, heterogenous enhancement of solid component and rim enhancement of cystic component, as shown in **Figure 1** . MR spectroscopy showed elevated Choline, creatinine and reduced NAA peak. The differentials as per the report included pleomorphic xanthoastrocytoma and ganglioglioma. He underwent left frontoparietal craniotomy with near total tumour decompression in the 3rd week of February 2024, at a local hospital. MRI brain was not repeated in postoperative setting. The post-operative histopathological report (HPR) indicated high-grade and poorly differentiated malignant neoplasm with possibility of high-grade glioma or high-grade embryonic neoplasm.

He presented to the Department of Radiation Oncology in the second week of March 2024, three weeks after his surgery. He had no specific complaints. On examination, he was conscious, cooperative and well oriented to time, place and person. Glasgow coma scale pupil score (GCS-P) and Karnofsky performance score (KPS) were normal, 15 and 100 respectively. The neurological examination was within normal limits and there was no focal neurological deficit; including higher mental functions (mini-mental state examination score 26), motor-sensory systems, cranial nerve examination and absence of cerebellar signs. The slide and block review done at our centre showed a markedly cellular neoplasm arranged in sheets, as illustrated in **Figure 2** . Small cells with hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm were evident, indicating malignant round cell tumour, favouring Ewing sarcoma / peripheral neuroectodermal tumour. NKX2.2, synaptophysin and FLI1 were positive while GFAP and CD99 were negative as per the IHC report. At the radiotherapy planning MRI brain, minimal solid residual lesion was identified, pointing towards a subtotal resection, as shown in **Figure 3** . Cerebrospinal fluid (CSF) was found to be negative for malignant cells, ruling out CSF dissemination. PET-CT confirmed the absence of any extracranial focus of hypermetabolism, ruling out extracranial primary with intracranial metastases, as shown in **Figure 4** . EWSR1 gene rearrangement testing using FISH showed split signals and/or loss of green signals only in 6% tumour cell nuclei, so in view of absence of EWSR1 gene rearrangement, it was classified as Embryonal tumour as per World health organization (WHO) Central nervous system (CNS) Tumour classification 2021 and treatment was decided upon as per High-risk MB protocol. The patient was started on craniospinal irradiation (CSI) to the entire craniospinal axis to a dose of 36 Gy in 20 fractions, 1.8 Gy per fraction by 3-dimensional conformal RT (3DCRT) technique, followed by radiotherapy boost to residual disease and tumour bed to a dose of 18 Gray (Gy) in 10 daily fractions, 1.8 Gy per fraction by volumetric arc radiotherapy (VMAT), overall treatment time being 7 weeks. The 95% target volume dose coverage for the CSI and boost plan have been illustrated in **Figure 5** . Blood counts were monitored weekly throughout CSI. He received concurrent vincristine during radiotherapy, however **only two cycles were received in view of depleting blood counts** . The adjuvant CTRT phase concluded in 1st week of June 2024. The patient was apparently alright at RT conclusion, with recovered blood counts. He has been planned for adjuvant chemotherapy as per six-weekly Packers A regimen, consisting of lomustine, cisplatin and vincristine.

Case 2

An 18 years old female, with no addictions or comorbidities, developed an episode of seizure in 2016. Without adequate workup, she was started on phenytoin. The seizures recurred in 2018, while she was on the same anti-epileptic drug. MRI brain done in August 2016 showed a well-defined solid cystic lesion measuring 48x37x46 mm in right parieto-occipital region, with heterogeneous post-contrast enhancement in solid component. Mass effect was seen in form of effacement of adjacent sulci and compression of ipsilateral lateral ventricle. She then underwent surgery with excision of right parieto-occipital lesion, with the post-operative HPR favoring a diagnosis of a peripheral PNET. She was advised to undergo RT, but she never received RT due to some personal reasons, nor did she receive any systemic therapy. She remained asymptomatic for the

next five years.

In April 2023, she developed pain in nape of neck, along with vomiting episodes, left sided upper and lower limb weakness. CT scan of brain revealed a heterogeneous space occupying lesion (SOL), measuring 68x49 mm in right parieto-occipital region, with areas of bleed and complex cystic component. Mass effect was seen in form of compression of third and right lateral ventricles and displacement of left lateral ventricle. She underwent surgical resection for the recurrence in September 2023. The HPR showed different diagnosis at three different centres, namely,

1. embryonal tumor with multilayered rosettes or CNS tumor with BCOR duplication,
2. WHO grade 2 ependymoma
3. high grade neoplasm with divergent differentiation.

After surgery, the patient presented to us in February 2024, without having received any adjuvant therapy even this time. Our in-house slide and block review revealed PNET with PanCK, NKX2.2 and EMA positivity, while GFAP, OLIG 2, CK7 and CK20 were negative. MRI brain shown in**Figure 6** , revealed a heterogeneously enhancing solid cystic mass in the right parieto-occipital region, measuring 8.3 x 5 x 7.3 cm, underneath the craniotomy site, suggestive of disease recurrence for the second time. Also, a 9.2 x 9.2 mm well-defined enhancing lesion of similar morphology was seen in the right occipital lobe, likely a metastatic deposit. Mass effect was seen as a 6 mm midline shift to left. MR spectroscopy shows absolute choline peak with Choline to N-Acetyl Aspartate ratio 1.7. MR perfusion shows hyper perfusion with relative cerebral blood volume being 1.6. Whole body PET-CT was done to rule out any extracranial source of intracranial PNET, but there was no metabolically active disease noted elsewhere. CSF cytology was also negative.

She underwent Re-do right parieto-occipital craniotomy and near total tumor excision in last week of May 2024. The small occipital lesion could not be tracked with USG and was left behind. Post-operative MRI brain showed stable well-defined enhancing lesion involving the right occipital lobe, with expected postoperative changes in right parietal lobe, as shown in **Figure 7** . The postoperative HPR showed a tumor arranged in trabeculae, cords, nests, tubules and rosette pattern, with extensive sclerosis, as shown in **Figure 8** . It was composed of round to elongated cells with moderate nuclear pleomorphism and clear cytoplasm. A diagnosis of PNET was made again, with diffuse PanCK, focal EMA, strong complete membranous CD99, NKX2.2 and FLI-1 positivity, and negative staining for GFAP, INSM-1 and synaptophysin. EWSR1 gene rearrangement tested with FISH showed split signals and/or loss of green signals only in 8% tumour cell nuclei, and again it was classified as Embryonal tumour as per WHO CNS Tumour classification 2021 and treatment was decided upon as per High-risk MB protocol. She has been planned for CSI to a dose of 36 Gy in 20 fractions, 1.8 Gy per fraction, followed by radiotherapy boost to residual disease and tumour bed to a dose of 18 Gy in 10 daily fractions, 1.8 Gy per fraction by VMAT technique. The concurrent chemotherapy planned is daily vincristine, 1.5 mg/m^2, followed by adjuvant chemotherapy as per Packers A regimen.

Discussion

Historically, all embryonal tumours originating in the CNS were grouped under the umbrella term- PNET, irrespective of the site of tumour. They had similar appearance under microscope, consisting of small round blue, undifferentiated neuroepithelial cells, usually with high mitotic rate and had neuroectodermal origin. Even some tumours outside CNS, originating from the neural crest, were included and called pPNET, which resembled histomorphologically with Ewing sarcoma (ES) of bones and extra-osseous ES. Also, a reciprocal translocation t(11;22)(q24;q12) was found in more than 95% cases of both pPNETs and ESs, using cytogenetic analysis, so both were grouped together under Ewing sarcoma family of tumours (ESFT)(3). Intracranial ES/pPNET usually arise from meninges, while cPNETs have neuroparenchymal origin. While both cPNET and ES/pPNET have aggressive courses, the former rarely metastasises outside the CNS and the latter has higher metastatic potential, usually to bones and lungs. Treatment protocols also differ between the two types of PNET; CSI with focal boost RT and chemotherapy are needed for cPNET after its surgical debulking and for ES/pPNET, post-operative chemotherapy on the lines of ES followed by adjuvant local RT is sufficient. Hence, differentiation between the two entities is of utmost importance, especially in case

of overlapping areas of CNS and peripheral nervous system (PNS) like meninges and spinal canal. The survival rates, though, are similar if treated as per the standard protocols, ranging from 50-70% for localized diseases(4).

The differentiation, not feasible by morphology, is done using CD99 (MIC2 glycoprotein) IHC and FISH for EWSR1 gene rearrangement. The membranous expression of CD99 serves as a highly reliable and sensitive diagnostic indicator for primary intracranial ES/pPNETs, positive in almost all cases and negative in cPNET(5,6). It is not advised as a specific IHC marker for diagnosing ES/pPNETs due to its positivity in other small, blue round cell tumours like lymphoblastic lymphomas, ependymomas, and rhabdomyosarcomas, even though the staining pattern in these tumours often appears cytoplasmic rather than the characteristic membranous staining seen in ES/pPNETs. The membrane protein FLI-1 is typically present in ES/pPNETs and employing both CD99 and FLI-1 IHC proves beneficial in the diagnosis(7). The gold standard to diagnose ES/pPNET and rule out cPNET, however is molecular testing to depict EWSR1 gene rearrangement. ES/pPNET has a characteristic translocation between EWSR1 gene on chromosome 22 and one of the ETS family of genes, most commonly FLI1 (chromosome 11), i.e., t(11;22)(q24;q12), and also ETV1 on chromosome 7 and ERG on chromosome 21. FISH assays using EWS break-apart probes are around 91-100% sensitive and specific; RT-PCR is used particularly to identify the partner gene for EWSR1, with a 67% concordance with FISH assays(8,9). The bottom line is that all morphologically diagnosed intracranial (and spinal canal) ES/PNET must be subjected to CD99 IHC and EWSR1 gene rearrangement using FISH to get a clear picture of the diagnosis and accordingly, plan for the treatment.

The initial theories considered CNS PNETs and MBs to be the same disease, arising in different locations, former arising supratentorial and the latter, infratentorial(10). Slowly, both were accepted to be different biologically(11). The 2007 WHO classification of CNS tumors included CNS-PNET not otherwise specified (NOS) and four morphologically distinct CNS-PNET variants - Medulloepithelioma (ME), CNS ganglioneuroblastoma, CNS neuroblastoma, and ependymoblastoma (EB). CNS PNETs were then recognized as a molecularly heterogeneous group, with the need for better classification. Based on the expression of cell lineage markers, LIN28 and OLIG2, 3 molecular subgroups were identified - primitive neural, oligo-neural and mesenchymal(1). DNA methylation profiling identified four molecular entities under CNS-PNET-CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2), CNS Ewing sarcoma family tumor with CIC alteration (CNS EFT-CIC), CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1), and CNS HGNET with BCOR alteration (CNS HGNET-BCOR)(12). Top of Form

Bottom of Form

The term PNET has been scrapped by WHO ever since WHO classification of CNS tumours 2016 due to the advent of molecular classification(13). As per the latest WHO classification of CNS tumours 2021, these tumours are under the classification of embryonal tumours, which are broadly divided into MBs and other CNS embryonal tumours. The latter include a host of tumours with different molecular and histological hallmarks, and a subgroup called CNS embryonal tumour, which was devoid of any such hallmark, i.e., not otherwise specified (NOS) and not elsewhere classified (NEC)(14). So, the erstwhile intracranial central PNET (cPNET) would now come under CNS embryonal tumour. cPNET account for 3-5% of paediatric CNS tumours and are at least five times less common than MBs. cPNET occur mainly in the cerebral hemispheres, the most common region being frontoparietal(15). Though biologically different, pinealoblastomas (PB) are sometimes included under cPNET and account for 20% of cPNET(16). cPNETs are usually diagnosed in young children, mainly less than 5 years old(17,18). Staging investigations are usually the same as those for MBs, although the clinical significance and correlation with long term disease control, especially that of the extent of resection, is less clear than for MB(17,18). The survival is even poorer compared to MB. For average-risk, the five-year progression-free survival (PFS) is 50% and >80% respectively and for high-risk, <20% and 50-60% respectively(19). Despite differences in outcome, treatment is still done on the lines of high-risk MBs in children as well as adult patients, due to the rarity of these tumors(20,21).

Given the fact that up to 33-35% of cPNETs have CSF spread at diagnosis, lumbar puncture and CSF cytology is a very crucial step in staging and evaluation of CNS-PNETs(22,23). Another point worth mentioning

is the 3.3% chance of brain metastases and 9% chances of skull bone metastases in ESs(24,25). Hence, PET-CT has some role in ruling out occult extracranial primary ES with intracranial metastases. F-18 FDG PET-CT has been shown to localise the primary disease in carcinoma of unknown primary (CUP) in 40% cases, with the detection rate being 77% in case of CUP with brain lesions(26,27).

The surgical approach has been maximum safe resection with the aim of gross total resection (GTR). The improvement in outcomes in patients with minimal residual disease has been well demonstrated in non-disseminated MBs, though similar evidence is lacking for cPNETs(28). It should also be the aim of surgery to maintain neurologic function. Surgery is conventionally followed by radiotherapy and chemotherapy. RT guidelines are similar to high-risk MB, though the need of CSI in non-disseminated cPNET has never been proven and focal RT has been tried in well-localised lesions post GTR(19). Chemotherapy is also planned on similar lines as high-risk MB, with concurrent and adjuvant chemotherapy. Multiple attempts have been done to further intensify the treatment in view of poor outcomes with the conventional treatment. A report from the ANCS0332 randomized trial focussed on the molecular heterogeneity within the umbrella term cPNET and showed that the outcomes of these patients were considerably better when histologically cPNET, but molecularly high-grade gliomas (HGGs) were excluded from the analysis using DNA methylation profiling(29). This trial also showed that unlike high-risk MB patients, cPNET patients did not derive any event-free survival (EFS) benefit with the use of carboplatin concurrently with radiotherapy, so vincristine is sufficient for cPNET patients.

Non-PB cPNET was found to be resistant to Packer's chemotherapy regimen(30). Intensive chemotherapy without radiotherapy was found to jeopardize the survival, and so was the omission of CSI(31). A report of the Head Start I and II trials experience, however, showed that postoperative intensified induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell transplant, without irradiation was associated with better outcomes and avoidance of CSI-associated adverse effects. RT was reserved for salvage setting; local recurrences were much higher than local and distal recurrences and 60% patients alive at 5 years had no RT exposure. However, long-term data are not available(32). Massimino et al., after debulking surgery, used high-dose chemotherapy (methotrexate, etoposide, cyclophosphamide and carboplatin ± vincristine), followed by hyperfractionated accelerated RT, two daily 1.3 Gy fractions, to a dose of 31.2Gy and 39Gy in less than 10 and more than 10 years old patients respectively. Local boost was delivered in two daily 1.5 Gy fractions, up to 59.7-60 Gy. RT was followed by myeloablative dose of thiotepa and autologous stem cell rescue. Upon the observation that local failure was seen even after CSI and that no isolated distal relapse occurred in first 15 patients treated, local conventionally fractionated RT to a dose of 54 Gy was attempted in rest of the patients with localized disease and with no progression during induction chemotherapy. The results of focal RT, analysed separately were better than the entire series(33). Chintagumpala et al. classified cPNET patients into average-risk (M_0 and residual tumor < 1.5 cm^2) and high-risk (neuraxial dissemination or residual > 1.5 cm2) and planned adjuvant RT as per MB guidelines for each risk group, i.e., lower CSI dose for average risk. RT was followed by 4 cycles of nonmyeloablative high-dose chemotherapy (high-dose cyclophosphamide, cisplatin, and vincristine), each cycle with stem cell support. Average-risk cPNET treated with lower CSI dose and high-dose chemotherapy with stem cell rescue had excellent 5-year EFS of 75%, thereby highlighting the advantage of risk-adapted approach(34). Timmerman et al analysed the results of two trials, done on less than 3 years old children with supratentorial PNET to compare intensive postoperative chemotherapy alone and adjuvant induction chemotherapy followed by delayed RT. They concluded that RT should not be omitted despite intensive chemotherapy and even in less than 3 years old, RT should not be delayed for more than 6 months(31).

Our first patient had a residual tumour more than $1.5cm^2$ post-surgery without any evidence of CSF dissemination, and was treated as per high-risk MB protocol, though vincristine, and not carboplatin was used concurrently with RT(29). The adjuvant chemotherapy planned was Packer's A regimen. However, the second patient had a smaller residual (0.8 cm^2) post-surgery, without any CSF dissemination. She was also treated as per high-risk MB protocol with vincristine concurrent with RT and adjuvant chemotherapy as per Packers A regimen.

Conclusion

Patients with intracranial PNET should be managed as per EWSR1 gene rearrangement report. If rearrangement is detected, the treatment will be planned on the lines of peripheral PNET / Ewing's sarcoma, including focal RT and chemotherapy as per EFT protocol. If rearrangement is not detected, the line of management will be as per embryonal tumor, i.e., like high-risk medulloblastoma, necessitating CSI with tumor bed boost, with concurrent chemotherapy, followed by adjuvant chemotherapy. Vincristine can be used in concurrent setting instead of carboplatin.

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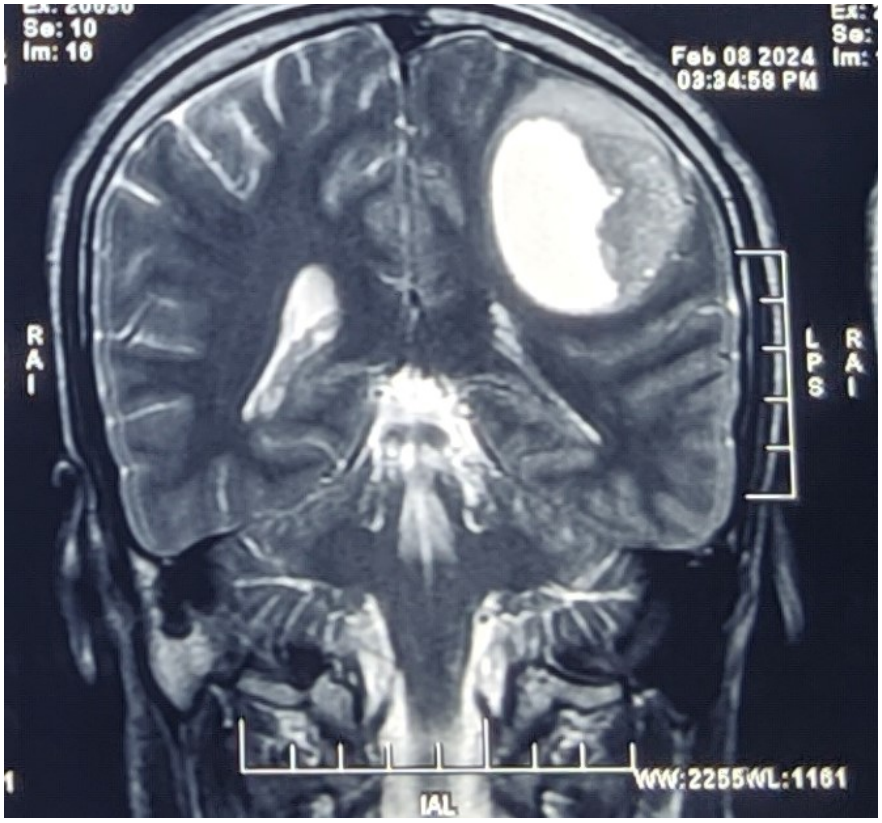
Figures :



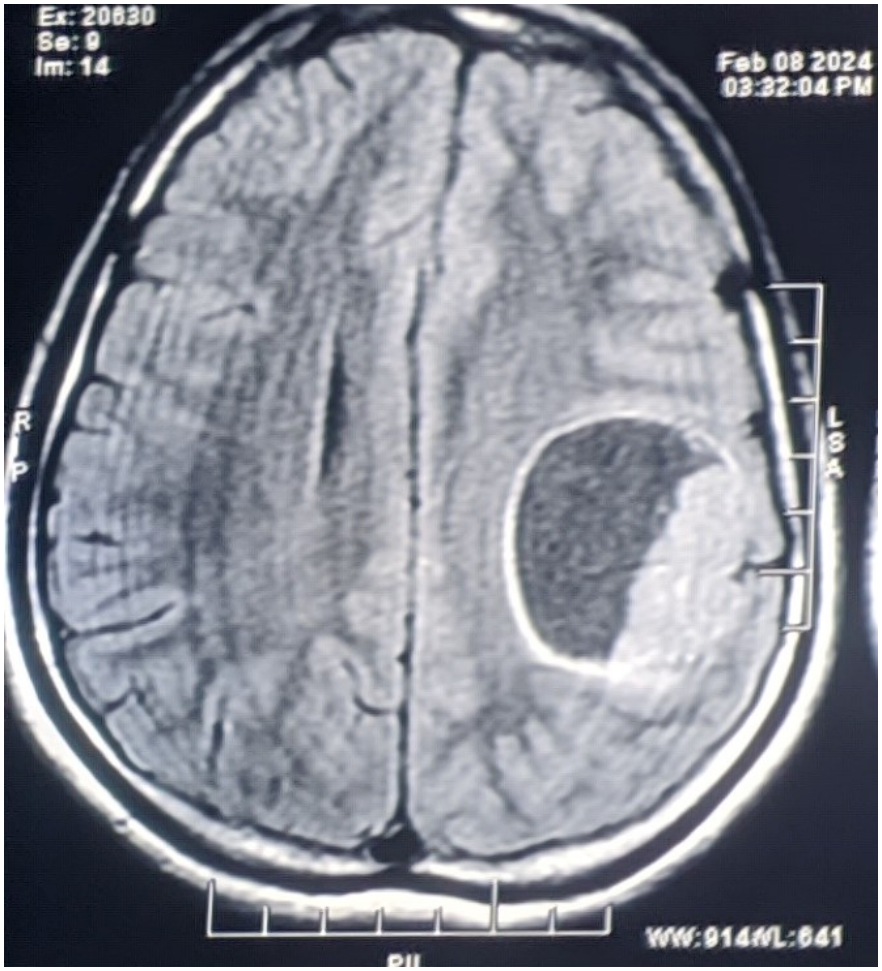


Figure 1 - Preoperative MRI scans of first patient- (a) T2w and (b) T2 FLAIR images respectively showing the well-defined lesion with solid and cystic components in left fronto-parietal lobe.

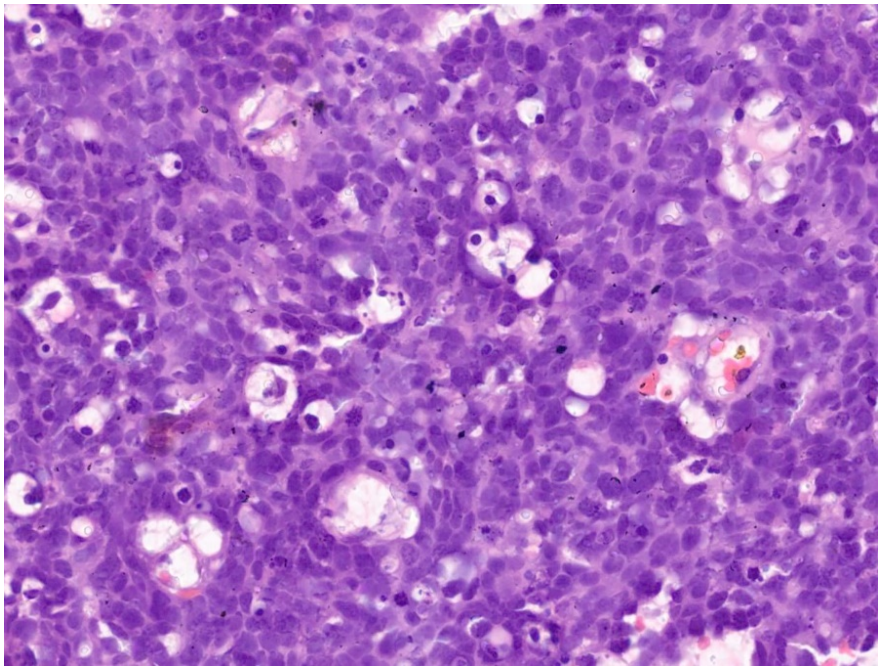


Figure 2 - Microscopic and IHC images of specimen of first patient - (A) Microsection shows tumor cells arranged predominantly in sheets. The tumor cells are medium-sized, with hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm. Interspersed numerous apoptotic bodies are seen [H&E, 40X]. (B) On immunohistochemistry, tumor cells are positive for FLI-1 (moderate nuclear staining). (C) Diffuse strong nuclear positivity is noted for NKX2.2 (D) Tumor cells are weakly positive for synaptophysin.

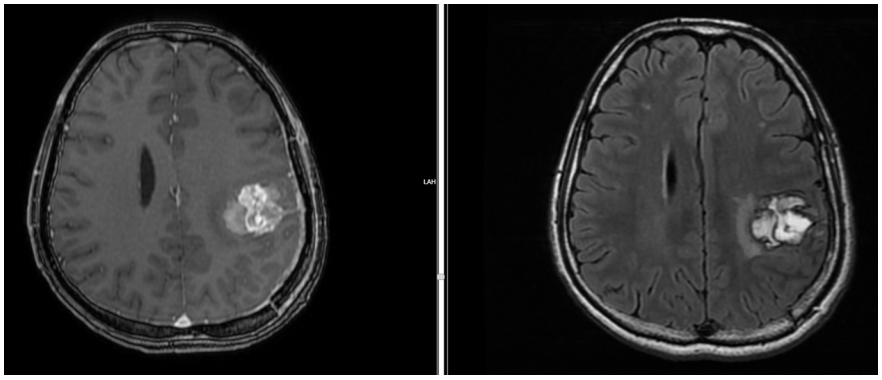


Figure 3 - Postoperative residual tumor in left frontoparietal region of first patient (a) contrast enhanced T1w (b) T2 FLAIR MRI images in the first case.

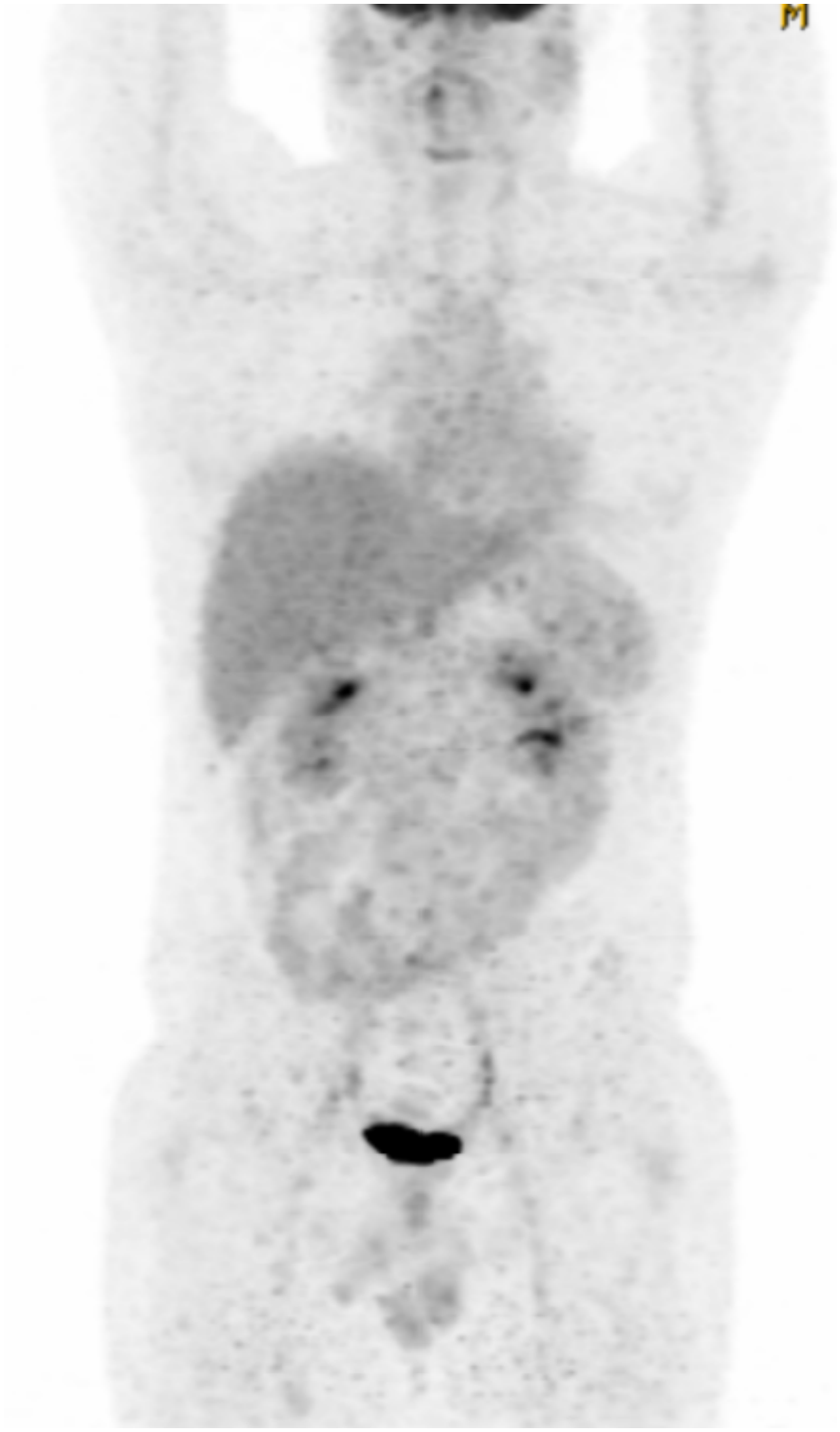
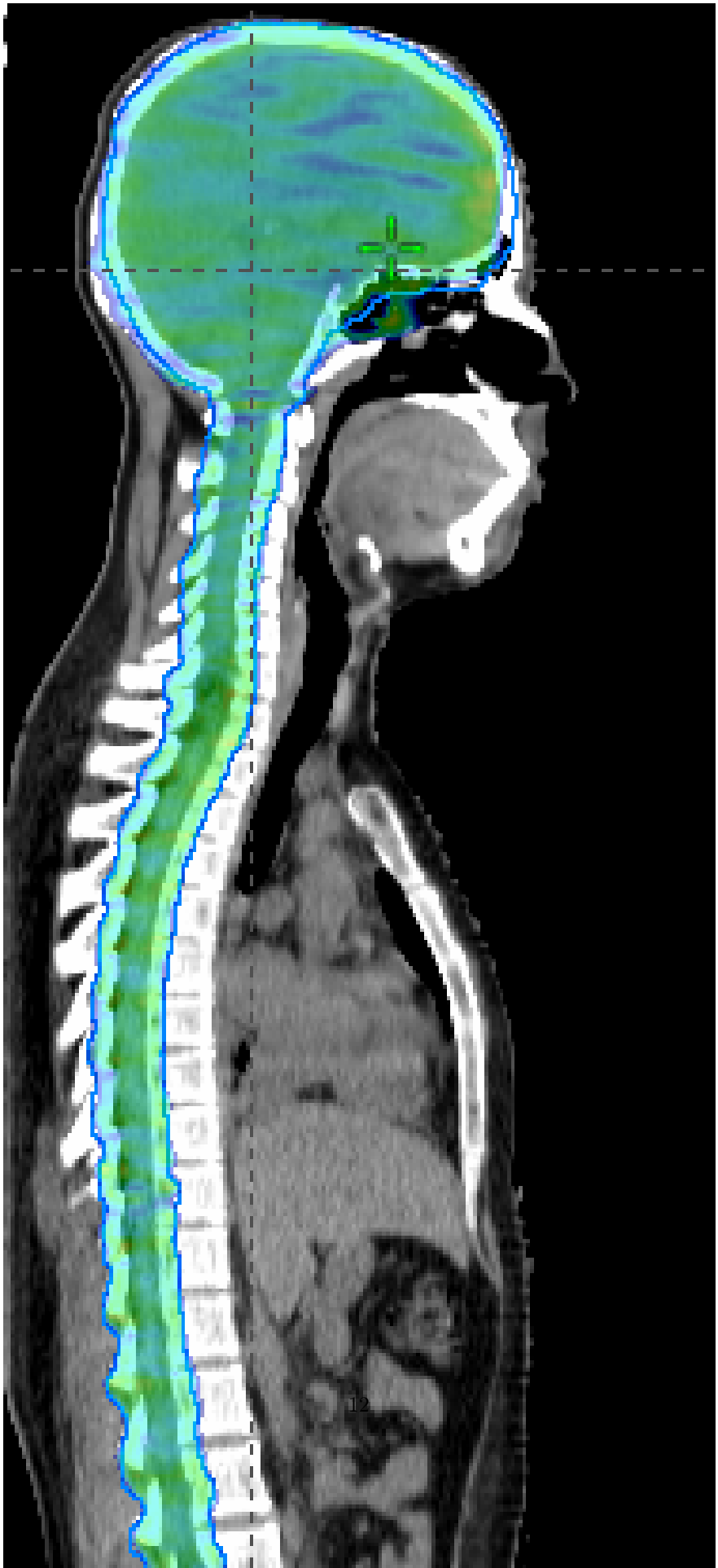


Figure 4 - Extracranial primary with intracranial metastases ruled out with absence of significant hypermetabolism in PET-CT apart from the primary in first patient.



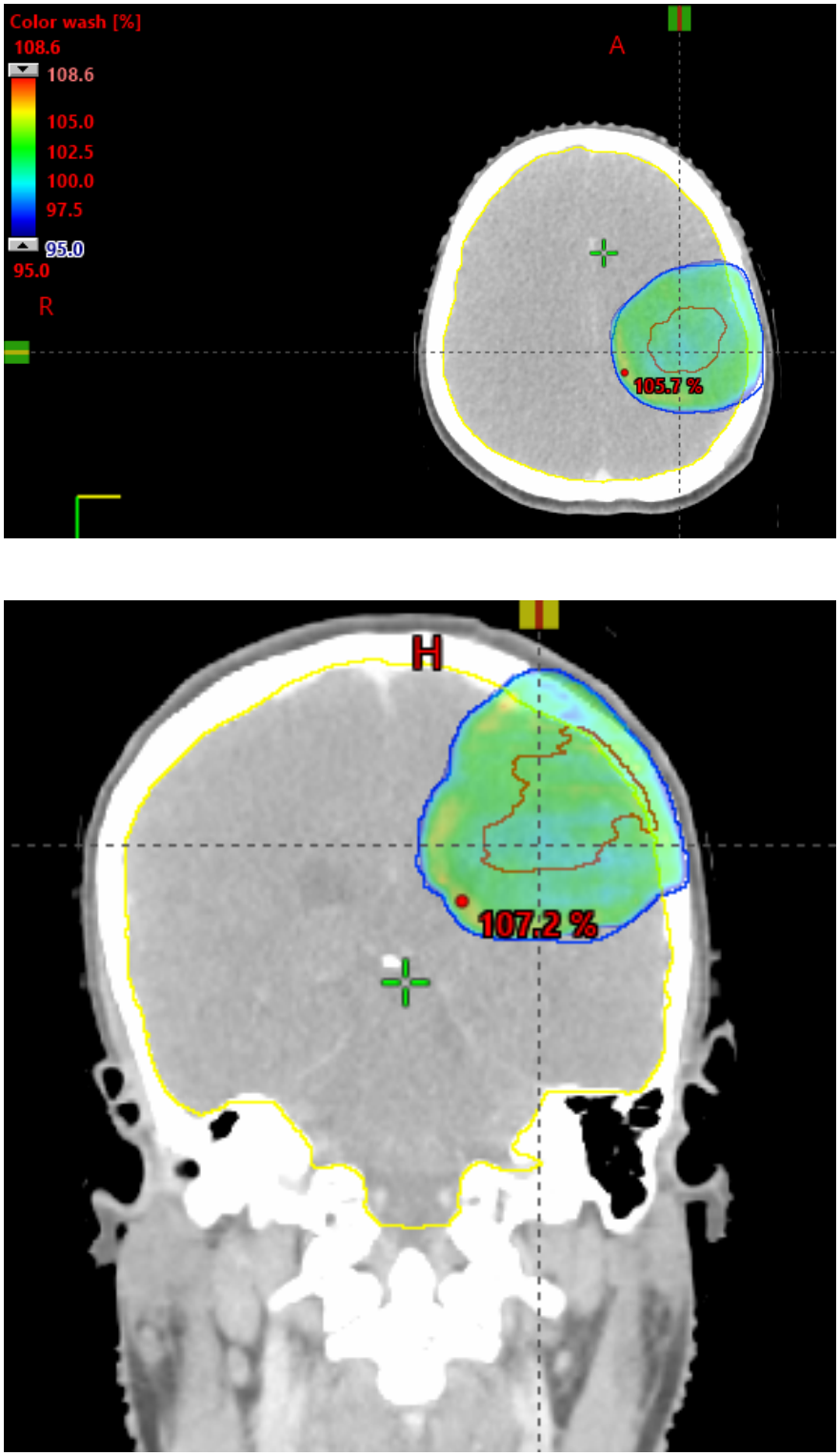
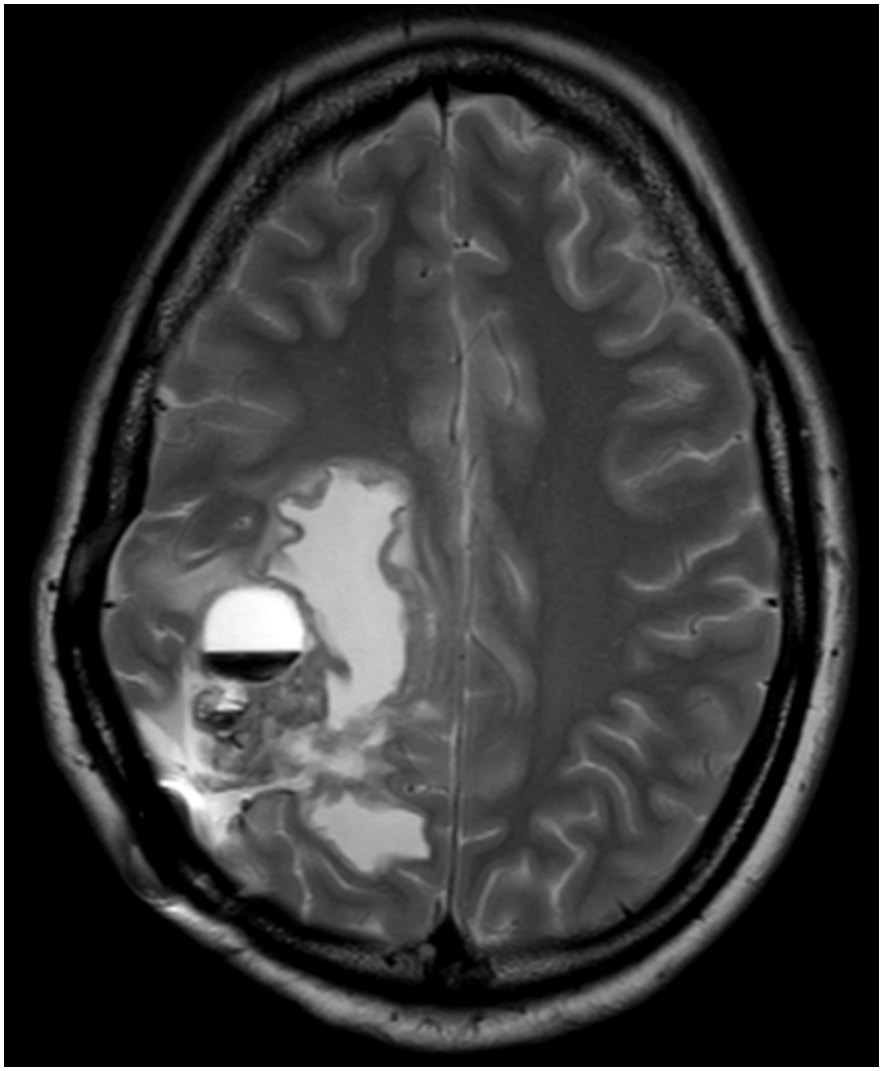


Figure 5 - 95% target volume dose coverage in CSI and boost plans of first patient



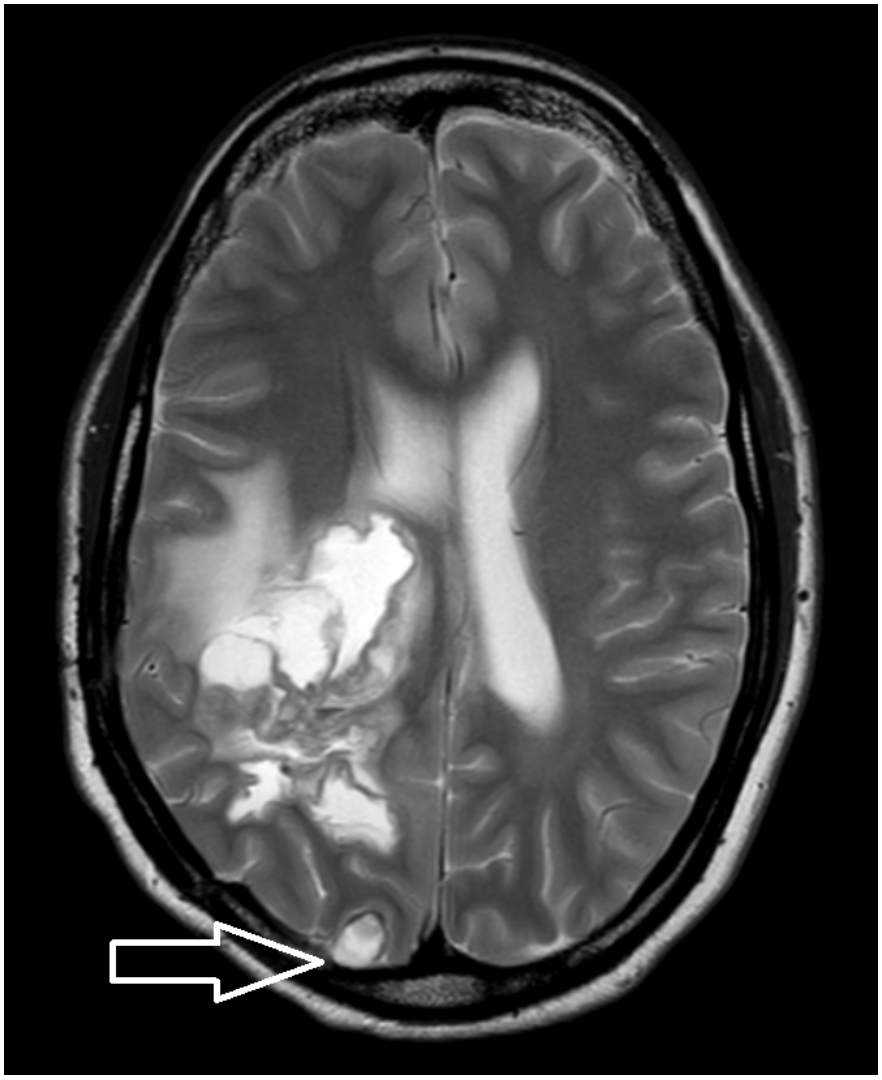
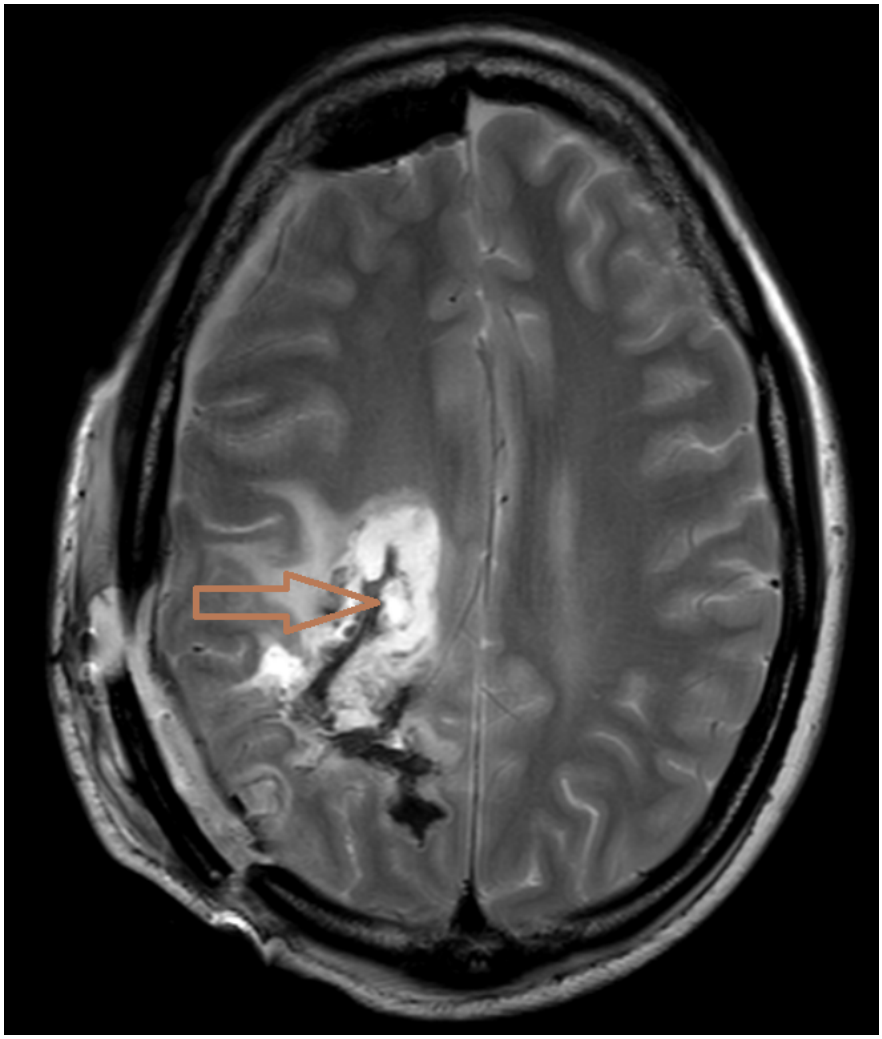


Figure 6 - MRI scans before the last surgery of second patient- T2w images with white arrows showing (a) well-defined lesion with solid and cystic components in right parieto-occipital region and (b) another lesion in right occipital region.



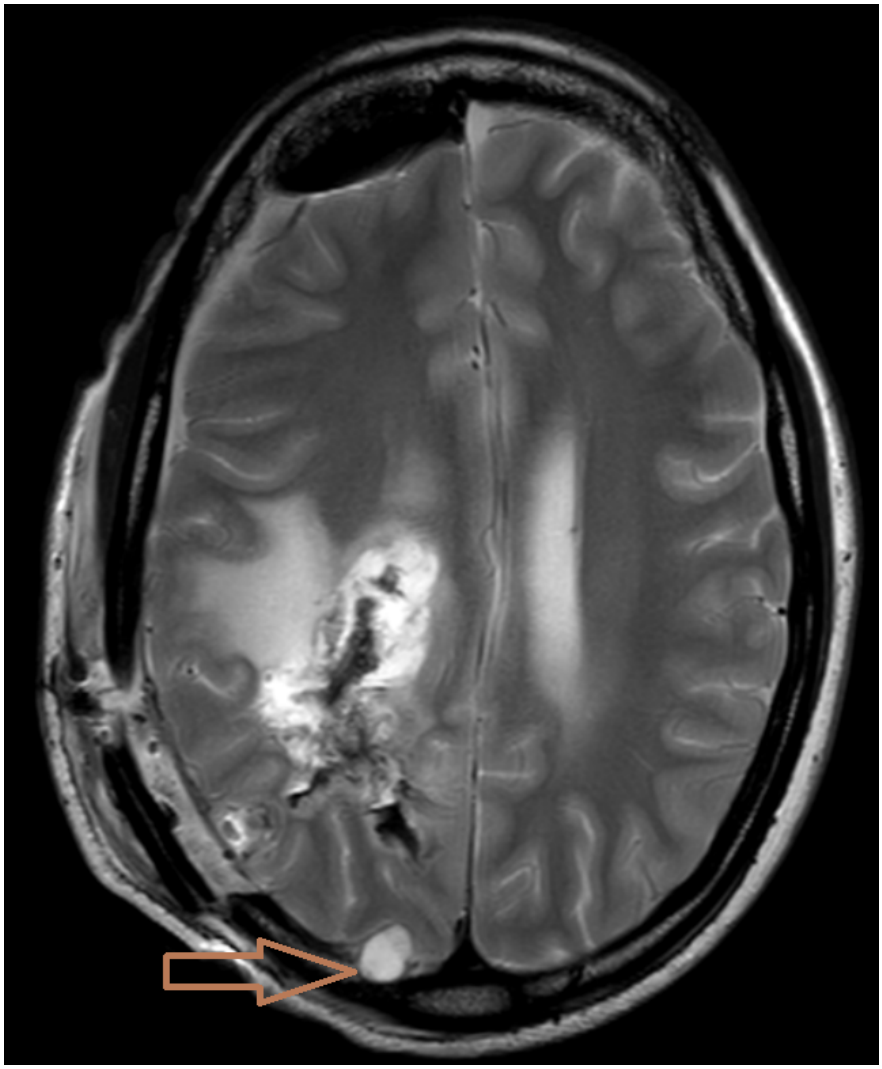


Figure 7 - Postoperative T2w MRI scan of second patient (a) irregular resection cavity noted in right parietal lobe (b) Stable well-defined enhancing lesion involving the right occipital lobe.

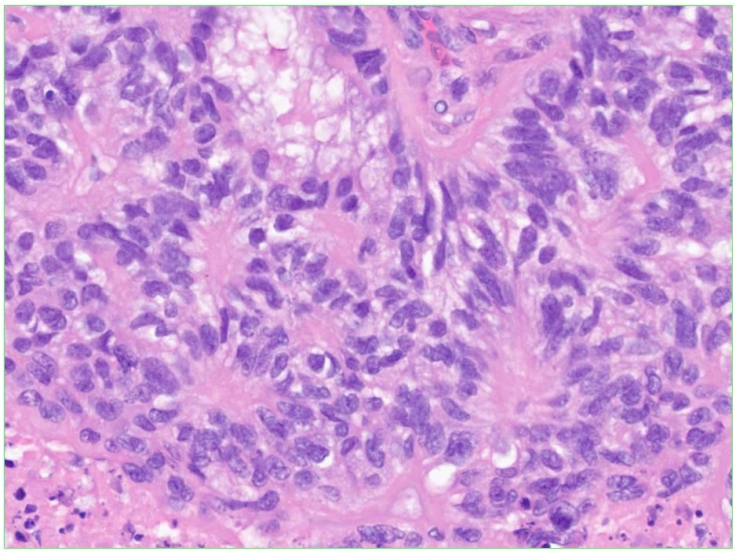


Figure 8 - Microscopic and IHC images of specimen of second patient (A) Microsection shows tumor cells arranged in cords, nests, trabeculae and rosette (arrows) pattern. The tumor is composed of round to elongated cells with moderate nuclear pleomorphism and brisk mitosis, [H&E, 40X]. (B) Stroma is predominantly sclerotic. Focal tumor cells show moderate to abundant clear cytoplasm, [H&E, 40X]. (C) On immunohistochemistry, Pan-CK is diffusely positive in the tumor cells. (D) Tumor cells show patchy positivity for EMA. (E) Diffuse membranous positivity is seen for CD99. (F) NKX2.2 is positive. (G) FLI-1 show strong nuclear positivity. (H) Tumor cells show patchy positivity for CK7.