Current Practice in Neurosciences

Current Standards for Evaluation and Management of Brain Metastases

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Epidemiology

Brain metastases constitute a significant portion of clinical practice in Neuro-oncology. Yet the true incidence of brain metastases is difficult to determine as majority of patients are asymptomatic and we do not have a national level brain tumor registry. A report based on hospital-based cancer registries [HBCR] in India in 2021 consolidated data from 96 HBCR's across the country [1] but did not include brain metastases as a subtype in the assessment of cancers of brain and nervous system. Even in western countries with a centralised brain tumor registry it is not mandatory to report secondary brain tumors.

The estimated incidence in published literature in the United States is 2,00,000 new cases every year. Lung, breast, kidney, colorectal cancers, melanoma are the most common primary tumours which metastasize to the brain in adults while in children it is the sarcomas, neuroblastoma and germ cell tumours[2].

Indian studies have reported an incidence of 4.9% [3] but the actual incidence is likely to be much higher. In India, lung and breast cancers were the most common primaries in men and women respectively, while 52.7% of patients did not have a known primary and brain metastasis was the first manifestation of a malignancy which is higher than the figure of 15-20% that is typically reported in the literature [4]. Nearly 10-40 percent of all patients with cancer will eventually develop brain metastasis [4].

Clinical manifestations

Most patients with brain metastases present with symptoms like headache, seizure, neurological deficits and impaired cognition [4]

Infratentorial lesions tend to produce cerebellar signs and eventually lead to symptoms of raised intracranial pressure due to hydrocephalus. Supratentorial lesions are usually located in the frontal and parietal lobes and can cause seizures in upto 20% of patients [5]. These tumors can also cause symptoms of headache, altered mental status, gait abnormalities, speech and visual changes or focal neurological deficit if they are located close to the central sulcus [1].

Clinical evaluation begins with an appropriate neurological examination. Scoring systems such as neurologic assessment in neuro oncology [NANO] offer an objective, reproducible and comparable method of assessment of patient's condition at presentation and at follow up [6].

Imaging

The advent of highly sensitive imaging techniques has significantly improved the detection of smaller brain metastases (BMs) that might have been missed with less advanced methods. According to statistical data, approximately 75% of BMs are in the cerebral hemispheres, 21% in the cerebellum, and up to 3% in the brain stem.

Computed tomography (CT) - CT is the imaging method of choice in urgent situations. They are good at detecting haemorrhages, calcifications, and for evaluating bone structures, providing essential diagnostic and therapeutic information. The sensitivity of CT, even with contrast enhancement, is considerably lower than that of MRI. Furthermore, brain metastases typically do not calcify.

Magnetic resonance imaging (MRI) - MRI is the gold standard imaging modality. All patients of systemic cancers with suspected brain lesions must be evaluated with contrast MRI of the brain which should include thin slices (<1.5 mm) of T1 post-contrast sequences [7]. Using higher field strengths, such as 3 Tesla (T) scanners, significantly enhances sensitivity compared to 1.5T scanners. While double doses of gadolinium-based contrast agents (GBCAs) increase sensitivity, they also raise the risk of false-positive results.

3D Volumetric Fast Spin-Echo (FSE) Imaging techniques such as CUBE, SPACE, and VISTA offer high-resolution images with inherent suppression of background vascular signals which enhances lesion visibility, making it easier to deduct the enhancing parenchymal and leptomeningeal metastases.

3D T1 (FSE) contrast sequence particularly when combined with overlapping thick-section maximum intensity projection (MIP) reconstruction, provides high contrast-to-noise ratios for enhancing lesions within the brain, and enables quick and sensitive detection of brain metastases [Figure 1].

MRI imaging appearances

Brain metastases typically form at the junction between grey and white matter. Metastases in the cerebrum predominantly occur in the frontal and parietal lobes, whereas non-small cell lung carcinoma tends to prefer the parietal occipital lobes, and breast cancer metastases are more frequently observed in the cerebellum. Uterine, prostate, and gastrointestinal cancers tend to spread to the posterior fossa.

Brain metastasis are often associated with vasogenic edema, primarily affecting the white matter, and exhibit characteristic features such as a round shape, well-defined margin, and ring enhancement following contrast administration, suggesting central necrosis. Larger lesions often exhibit ring enhancement, which can be uniform or patchy, while smaller lesions typically demonstrate solid enhancement. Esophageal metastases may present with a cystic appearance whereas metastases from melanoma and renal cell carcinoma commonly hemorrhage [Figure 2].

It is noteworthy that fewer than half of all BMs present as a single lesion in the brain, and an even smaller proportion are solitary, meaning they are the only metastasis detected in the entire body.

MRI sequences and their specific advantages

Diffusion weighted images

Metastases typically demonstrate increased diffusion on diffusion imaging, but this is not consistently observed[8]. Approximately 20% of metastases may manifest overt hemorrhage, with about two-thirds of large metastases showing signs of hemorrhage on Susceptibility weighted images (SWI).

Magnetic Resonance Spectroscopy (MRS) helps distinguish brain metastases (BMs) from primary tumors based on metabolite ratios like (Cho)/Creatine (Cr)[9]. Elevated lipid signals in BMs indicate cellular necrosis. Sjobakk *et al* found higher baseline lipid signals correlate with increased 5-month survival in BMs [10]. MRS can also help differentiate radiation necrosis from tumor progression.

Perfusion MRI

Server *et al* observed significantly higher rCBV and rCBF in the peritumoral area of glioblastomas compared to metastases[11]. A peritumoral rCBV threshold of 0.8 displayed high sensitivity and specificity for differentiation. Perfusion imaging could assist in evaluating tumor vascularity, distinguishing between tumor types, and discerning tumor recurrence from treatment effects [Figure 3]. Both rCBV values from DSC and Ktrans from DCE have shown similar accuracy in distinguishing radiation necrosis from tumor progression [7].

Chemical Exchange Saturation Transfer (CEST)*:* *CEST* MRI assesses concentrations of molecules such as proteins and glucose. APT-CEST targets proteins, while gluco-CEST focuses on glucose. Brain metastases (BMs) usually have elevated protein concentrations and glucose metabolism rates. Desmond *et al* discovered changes in CEST signal within one week after treatment correlated with changes in tumor volume measured one month later[12]. Mehrabian *et al* demonstrated CEST's ability to differentiate between radiation necrosis and tumour progression in BMs [13].

Radiomics: Radiomics uses image features to reveal clinical links, aided by machine learning for BM detection and characterization. It predicts treatment response and differentiates between progression and radiation effects. Combining radiomics with AI improves BM diagnosis by analysing MRI texture patterns and automating lesion detection [14]. Validation with larger datasets is necessary for broader clinical use.

Follow up imaging: The RANO group's guidelines, RANO-BM and iRANO criteria, define progression as a 20% increase from baseline or a 30% reduction for treatment

response. Brain MRI should be done every 2-3 months or whenever neurological decline is suspected, maintaining consistency in protocol for accurate comparison. Following radiation therapy, brain metastases show changes such as perilesional edema, central T2 hyperintensity, blurred enhancement borders, reduced size and gliosis.

Distinguishing true progression from pseudo progression and radiation necrosis presents challenges. Pseudo progression initially elevates imaging abnormalities, often followed by reduction. Perfusion MRI helps differentiate between tumor progression and radiation necrosis/pseudo progression, with tumors typically showing higher cerebral blood volume due to increased vascularity. Similarly, diffusion imaging's ADC values are lower in tumor tissue and higher in radiation necrosis. Integrating changes in multiple imaging parameters enhances diagnostic accuracy, aiding effective brain metastases management during follow-up.

Imaging Guidelines

ASCO-SNO-ASTRO guidelines have no recommendations for imaging whereas the EANO-ESMO guidelines recommend MRI brain, plain and contrast of at least 1.5 T field strength. Recommended sequences include pre- and post-contrast T1 -weighted, T 2 - weighted and/or T2 -fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences.

Screening

There is no agreement on screening asymptomatic patients, even among those with cancer types that have a high risk of BMs**.** Screening imaging of brain by MRI in cases of lung, melanoma, sarcoma, and testicular primaries is often considered but not in breast, gastrointestinal, urogenital, gynaecological, renal, or thyroid primaries.

The National Comprehensive Cancer Network (NCCN) guidelines recommend brain MRI for staging in the initial evaluation of stages II–IV non-small cell lung cancer (NSCLC) and suggest it as an option for stage IB NSCLC. The diagnostic yield is higher in patients with adenocarcinoma compared to those with squamous cell carcinoma and in patients with epidermal growth factor receptor (EGFR) mutation–positive adenocarcinoma.

Screening at diagnosis may also be justified for metastatic human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer. Additionally, screening should be considered in stage IV melanoma because early detection of BMs can significantly influence clinical decision-making and improve outcomes.

Nuclear Medicine in Brain Metastases

Although contrast enhanced MRI is the investigation of choice for the evaluation of patients with brain metastases it can pose diagnostic challenges in some situations due to its low specificity. Especially in the post treatment setting where worsening reactive changes can be difficult to distinguish from true disease relapse. Nuclear medicine imaging i.e. Positron Emission Tomography with CT (PET/CT) is a whole-body imaging method which helps to assess the tumour physiology and characterise the lesion.

PET uses different compounds labelled with radioisotopes that specifically targets viable tumour cells. The use of PET with radiolabelled amino acids has been validated as an important diagnostic tool in brain cancer [15]. Various other radiopharmaceuticals have been investigated which target the pathophysiological processes in brain metastases; these are summarised in Table no 1.

Procedural Guidelines for Petct Imaging

FDG PET CT requires a fasting period of at least four hours before the scan. The scan is acquired 45 minutes post injection of recommended dose of FDG [16]. Whole body CT scan (Including Head) is acquired followed by PET imaging. Images are processed and co registered for image analysis. SUVmax is the most known quantitative parameter used for lesion interpretation. However, in Brain Imaging, it is highly variable due to high uptake of FDG in brain. Hence single system generated SUVmax value should not be considered for interpretation.

Table 1: Radiopharmaceuticals used in nuclear imaging

Radiopharmaceutical (RPs)	Mechanism of Localisation	Indication	Remarks
F18 Fluorodeoxyglucose (FDG)	Targets GLUT Receptors & enters glucose metabolism	Detection of primary tumour/extracranial disease in cases of suspected brain metastases	Limited sensitivity for detection of brain metastases due to high uptake in the brain
Amino Acid RPs 1. F18 Flurothymidine (FET) 2. F18 FDOPA 3. C11 Methionine (MET)	L amino acid transporters	Differentiation of recurrence from post treatment changes.	Better sensitivity compared to FDG
F18 Fluro thymidine (FLT)	Incorporation into membrane biosynthesis	Treatment response evaluation	Further prospective studies are required to establish the role.
Translocator protein (TSPO)	Targets mitochondrial translocator protein	Marker of neuroinflammation.	Further prospective studies are required to establish the role.

Amino acid PET CT does not require fasting and scans are acquired 20 mins post injection of recommended dose of FET/FDOPA Tumour to Background Ratio is the preferred quantitative parameter used for image interpretation.

Although guidelines do not mention contrast enhanced CT for PET CT, it can help characterise the lesion.

Role of PET CT in Brain metastases:

1. Identification of newly diagnosed brain metastases - FDG PETCT is not recommended for detection of brain metastases [17] because of physiological high uptake of FDG in normal brain parenchyma. Amino acid PETCT is more sensitive than FDG PET [18] but still inferior to MRI for smaller lesions.
2. Differential Diagnosis - FDG PETCT has limited ability to differentiate between brain metastases and primary glial tumour as both high grade pathologies show overlapping SUVmax values [19] It can help in differentiating brain metastases from Primary CNS lymphoma, as the latter is much more FDG avid [20]. The level of expression of L amino acid transporters is said to correlate with the aggressiveness of the brain metastases [21]. Initial data suggest that SUVs of the radiolabelled amino acid are lower in Brain Metastases than in glioma [22]. There is no robust data supporting the use of amino acid imaging for differential diagnosis of brain metastases from glioma [23].
3. Differentiation of Radiation necrosis from Recurrence
   Conventional MRI lacks the specificity to differentiate early recurrence from radiation necrosis, few studies have evaluated FDG PET CT for this purpose however, its diagnostic performance is inferior (sensitivity 40% & specificity 50%) to the advanced MRI techniques. Hence FDG PETCT is not recommended however amino acid PETCT [FET & FDOPA] has a diagnostic accuracy superior to advanced MRI sequences [24]. Moreover, FET PETCT appears to be more cost effective compared to advanced MRI. Hence Amino acid PETCT is recommended in post treatment settings [25].
4. Assessment of Treatment Response
   Flurothymidine (FLT) has been evaluated as a marker treatment response to systemic agents for brain metastases. Preliminary data has shown that FLT PETCT provide additional information in patients with equivocal MRI findings [26].

Current Recommendations for the use of PET imaging in evaluation of Brain Metastases:

1. NCCN, EANO-ESMO recommend doing FDG PET/CT in cases of Brain lesions under evaluation or occult primary for the detection of extracranial disease/ primary tumour. However, its sensitivity is low in characterising the brain lesions and differentiating them from other high-grade lesions.
2. At present, EANO-ESMO have documented the additional role of amino acid PETCT in initial evaluation of brain metastases and can be considered in cases where MRI findings are equivocal. However, there is not enough evidence for strong recommendation.

3. In post treatment settings, EANO-ESMO recommends doing an amino acid PETCT (category IIIC) to differentiate early recurrent disease from post treatment changes.

To summarize, MRI remains the investigation of choice at all time points in the management of brain metastases, amino acid PETCT & FDG PETCT helps in select indications as complimentary imaging modality. A proposed algorithms for imaging of brain metastases is shown in Figure 4.

Role of surgery

There is an increasing relevance for the role of surgery in brain metastases. Studies have shown that surgical excision followed by radiotherapy offers survival benefit over radiotherapy alone in lesions that can be excised [27]. The decision to offer surgery should be made carefully after through discussion with the patient about the risks and benefits of the planned surgical procedure. A discussion in the relevant site specific multi-disciplinary tumor board is mandatory to review other options such as targeted therapy or radiotherapy before finalising surgery. From a neurosurgical perspective surgical excision can be offered for large mass lesions that are causing midline shift, cortical or subcortical in location, single or multiple tumors that can be accessed through a single craniotomy and solitary brain metastases. After assessing the patient's fitness for surgery and finalising the decision in favour of surgery a detailed surgical plan must be made including inputs from the radiation oncologist regarding post operative radiotherapy.

Since most brain metastases are in the cerebral cortex and not in the skull base, a planned or Neuronavigation guided tailored craniotomy is usually sufficient to excise these tumors. Most brain metastases are well defined and have a good plane of differentiation unlike gliomas which aids in surgical excision. In appropriate situations intraoperative neuromonitoring may be used. Intraoperative ultrasound is very useful to identify the site of corticectomy in subcortical tumors. Since most metastatic tumors are contrast

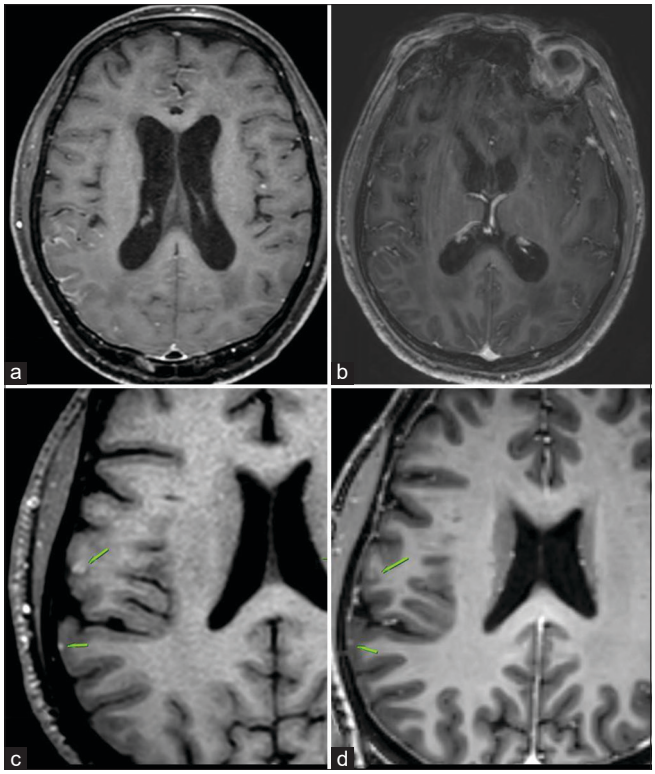

Figure 1: A case of carcinoma lung with leptomeningeal metastasis, better appreciated in black blood imaging, post contrast 3D T1 spin echo sequence (a), compared to post contrast gradient SPGR T1 sequence(b). Vessels are suppressed in 3D T1 SE and hence leptomeningeal lesions are well seen. In another of carcinoma lung with small cortical metastasis. Lesions are seen well in post contrast 3D T1 spin echo sequence (c), which could be missed in post contrast gradient SPGR T1 sequence (d). Tiny metastasis and leptomeningeal metastasis relatively common in lung carcinoma

enhancing, sodium fluorescence and blue light filter is very useful in identifying tumor and ensuring completeness of excision especially in small or deep tumors. Most brain metastases do not bleed too much, but metastases from thyroid, renal cell carcinomas can bleed profusely. In cases where there is calvarial destruction, a craniectomy can be performed and followed by a titanium mesh cranioplasty in the same setting.

The ASCO-SNO-ASTRO guidelines do not note any difference in outcome in complete en mass excision versus piecemeal excision, although some studies have demonstrated a difference. For small tumors en-mass excision can be planned whereas for larger tumors, piecemeal excision is equally effective. Gross total excision has shown to be more effective than subtotal excision and should be the aim of surgery [28]. Meticulous attention must be paid to the closure of dura, galea and skin to ensure timely wound healing and avoiding delays in adjuvant radiotherapy.

Immediate imaging following surgery, preferably with MRI, is critical for assessing the completeness of surgical resection and identifying any residual tumor or surgery-related changes. This imaging should be conducted within 48 to 72 hours post-surgery to minimize the impact of surgery-related enhancement, which could obscure accurate interpretation.

International Guidelines for Surgery

The ASCO-SNO-ASTRO guidelines recommend surgery in patients with suspected brain metastases without a primary cancer diagnosis for diagnosis. Patients with large tumors and mass effect are more likely to benefit from surgery. Whereas those with multiple metastases and/or uncontrolled systemic disease are less likely to benefit. No method of resection (piece-meal or en bloc) has been recommended. The EANO-ESMO guidelines additionally recommend surgery when changes in molecular profile compared with the primary tumour may impact clinical decision making, in single BMs and in patients with symptoms of raised intracranial pressure. A post operative MRI is recommended within 48 hours.

Pathological aspects of brain metastases

Just as tumors and their molecular subtypes exhibit differences in their likelihood to spread to the brain, recently variations in potential biomarkers between primary tumors and metastatic brain deposits and the analysis of actionable biomarkers for targeted therapy in brain metastasis has gained considerable importance [29].

The gross histological features are relatively preserved and similar to primary tumor with distinct demarcation from adjacent brain parenchyma, however, microinvasion and spread via Robin Virchow spaces is commonly present. Tumor necrosis is usually evident with viable tumor cells restricted to periphery or around blood vessels. Other common accompanying features include reactive gliosis, microvascular proliferation, and inflammatory cell infiltrate. Meningeal carcinomatosis leads to diffuse infiltration of arachnoid space by tumor cells.

Immunohistochemistry plays a pivotal role in BM both in the diagnosis of unknown primary as well as correlation with the primary tumor. Advanced techniques such as next generation sequencing (NGS), reverse transcriptase polymerase chain reaction (qRT-PCR), gene microarray, microRNA profiles and methylation profiling help in diagnosing metastatic brain tumors of unknown primaries and reveal actionable therapeutic or prognostic markers. A proposed flowchart for pathological evaluation of unknown brain primary is shown in Figure 5.

Furthermore, several additional oncogenic alterations in BM evolve with time which can be picked up the molecular testing [30]. In the era of targeted therapy, it is even more relevant to perform molecular analysis in BM cases, wherever, it is feasible before starting high-cost targeted therapy.

Discrepancies between primary tumor vis-à-vis brain metastasis

The continuous evolution of newer subclones, spatial and temporal heterogeneity, impact of radiotherapy and chemotherapy treatment leads to variation in both histological as well as molecular profile of tumors. These changes are mainly determined by acquisition and deletions of newer mutations and cytogenetic changes.

Common tumours associated with discrepancies

1. Breast cancer

Discordances between the hormonal profile (oestrogen receptor (ER), progesterone receptor (PR), and (HER2)) between primary breast tumors and subsequent BM is a

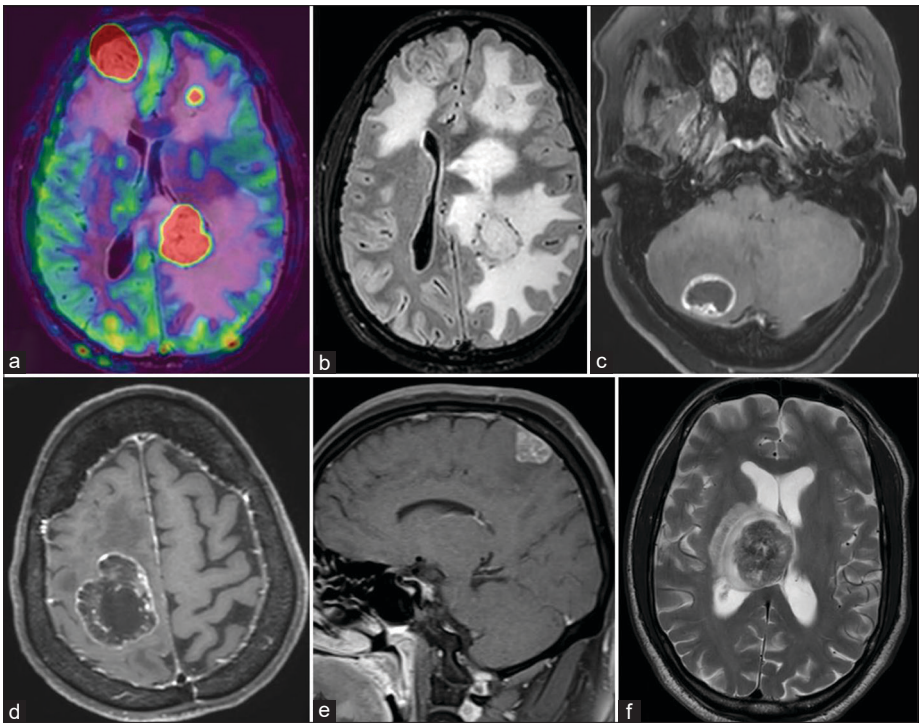

Figure 2: a-A case of renal cell carcinoma with multiple intra cerebral metastasis, with hyper perfusion in Arterial spin labelling (ASL). b-Usually in metastasis, significant perilesional white matter edema will be seen. c- A case of carcinoma breast with cystic metastasis at the cerebellum. d- case of carcinoma cervix with cystic/ necrotic metastasis at right perirolandic region. e-A case of parotid carcinoma with cerebral metastasis. f- A case of colonic mucinous carcinoma with T2 hypointense right thalamic metastasis

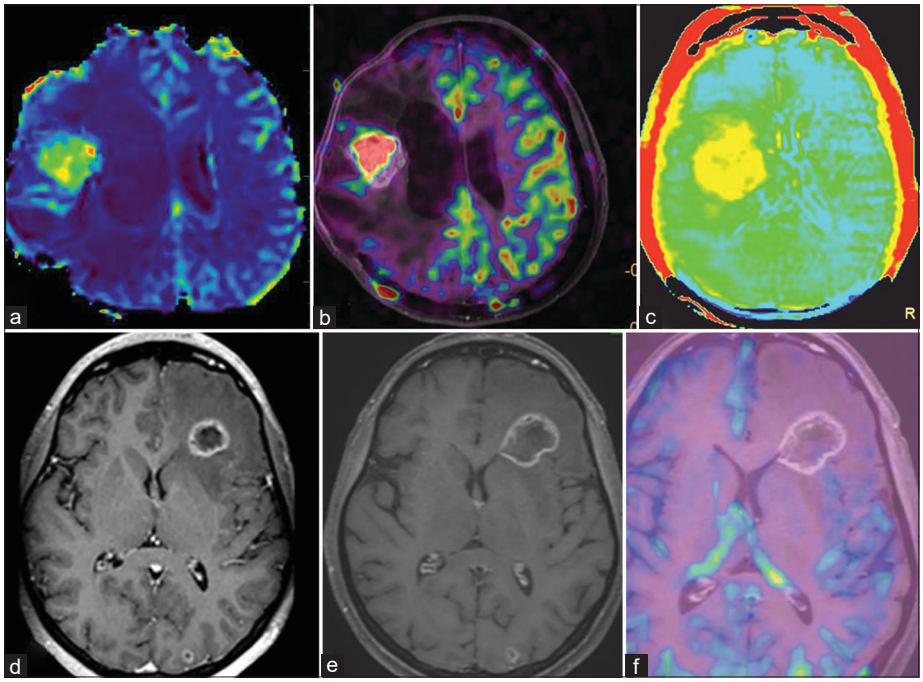

Figure 3: Tumor progression (a,b,c) A case of carcinoma breast right frontal lobe. Recurrent mass lesion after surgery, chemotherapy and radiotherapy. Lesion showed raised perfusion, cerebral blood flow in ASL (a), Cerebral blood volume (b) in DSC perfusion, raised values at amide proton transfer (c). Pseudoprogression (d,e,f). A case of carcinoma lung with left frontal lobe metastasis (d). Post radiotherapy, lesion has increased in size (e). Lesion appears completely hypoperfused in ASL, suggesting pseudoprogression (f)

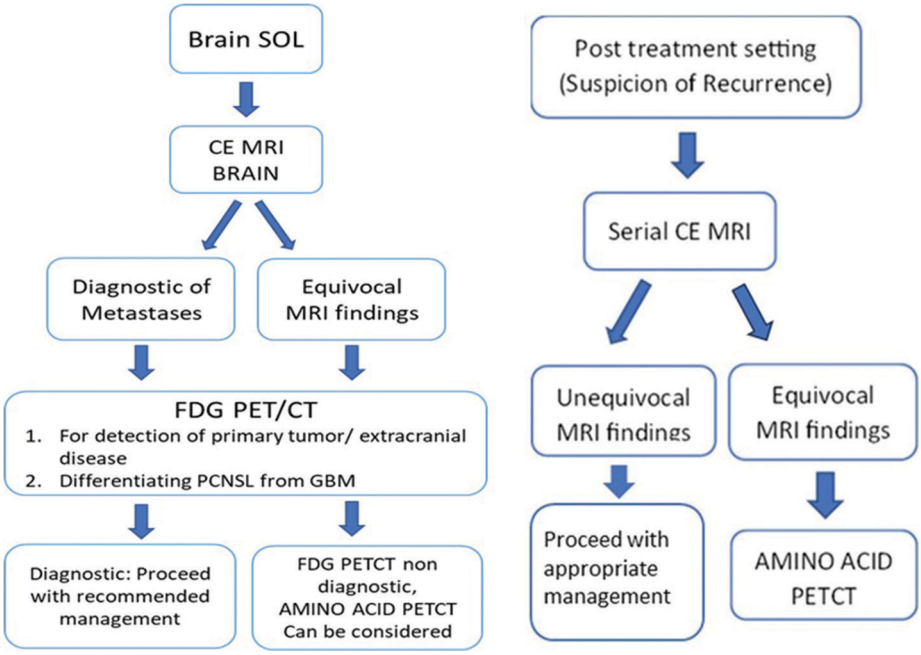

Figure 4: Algorithm for imaging

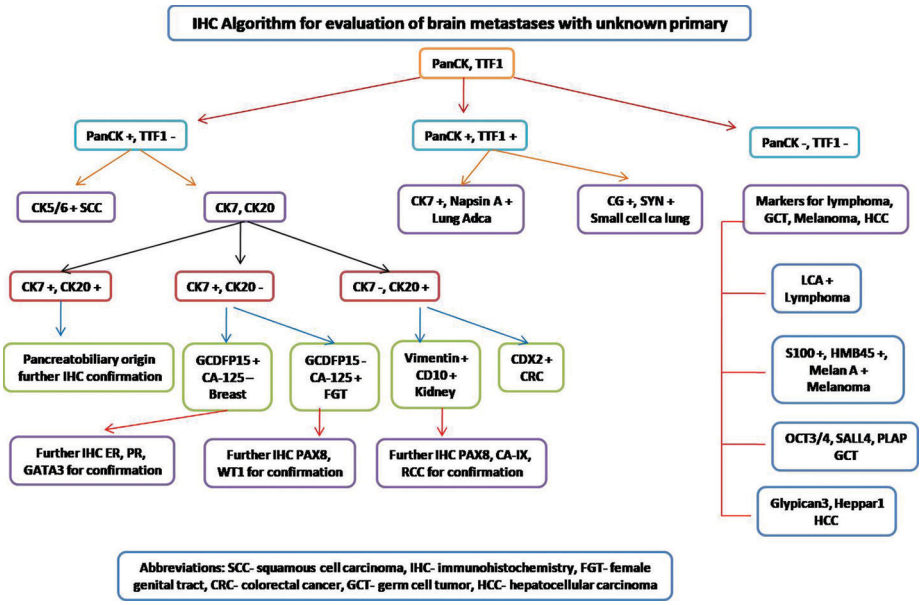

Figure 5: Algorithm for pathological evaluation of unknown brain primary

well-known phenomenon. These alterations in the hormonal expression directly impact both therapeutic decisions as well as outcomes in breast cancer patients with BM. Person *et al* [31] concluded that about 20% of breast cancer patients show receptor discrepancy between the primary tumor and BM.

2. Lung cancer

Patients of lung cancer with BM can have alteration in the expression of various molecular markers and immune check points such as programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) expression.

Brain metastases in lung cancer often respond poorly to immune check point inhibitors (ICI) in comparison to primary tumors, possibly because of a decreased infiltration of PD-1+ tumor infiltrating lymphocytes (TILs) [32].

3. Malignant Melanoma

Targeted therapy and immunotherapy has shown better outcomes in patients with BM from malignant melanoma. BRAF mutations are seen in about 40%-60% of patients, 90% of which are V600E variant. BRAF inhibitors like vemurafenib and dabrafenib have demonstrated significant improvement in both progression free survival and overall survival in such patients[33]. BRAF mutation and PD-L1 expression bear a direct implication in therapeutic decision making and should be evaluated in BM from malignant melanoma.

4. Others

Sarcomas rarely cause BM with an incidence of about 4-6%. Most common sarcomas which metastasise to brain are osteosarcoma, alveolar soft part sarcoma and synovial sarcoma. Metastases from bone sarcomas usually occur within 3 years of diagnosis, while soft tissue sarcomas can occur up to 10 years from diagnosis [34].

Brain accounts for <1% of metastases from colorectal cancer with an average interval of 20–40 months from the time of primary diagnosis. The cases with RAS mutations have a significantly high tendency for BM in comparison to RAS wild type [35]. Hence, paired mutation analysis in both primary and metastatic lesions is very important to determine the targeted therapy.

The prevalence of BM in malignant mesothelioma is about 2.7%. Roughly 11% of cases with BM show variation in histological features including dedifferentiation to a more aggressive histologic subtype [36]. They also frequently show expression of PD-L1 and PD-1 in brain lesions.

Radiation therapy in brain metastasis

The common radiation therapy treatment modalities in brain metastasis are whole brain radiation therapy (WBRT), hippocampal avoidance whole brain radiation therapy (HA-WBRT) and stereotactic radiosurgery [SRS].

Whole brain radiotherapy [WBRT]

WBRT is practiced uniformly across different parts of India [37-39] and studies have shown that WBRT is the most common practice in majority of the centres.

A dose of 30 Gy in 10 daily fractions or 20 Gy in five fractions or 8 Gy single fraction is usually the standard protocol depending upon the facilities available, performance status of the patients and extra-cranial disease status. There has been no benefit with hyperfractionation or dose escalation. A summary of multi-centric randomized studies with different radiation schedule in brain metastasis is shown in Table 2.

Hippocampal avoidance WBRT (HA-WBRT) HA-WBRT protects the hippocampal neural stem cells from injury in WBRT thus helping in memory preservation. HA WBRT plus Memantine has lower risk of deterioration in executive functions, learning and memory without any significant difference in OS, toxicity or intracranial PFS [40]. HA-WBRT is indicated in more than 4 brain lesions, oligo brain metastasis with extra-cranial progression and good PS and oligo brain metastasis with poor performance score (PS). HA-WBRT in randomized study have shown to preserve some of the cognitive function domains (memory, reading) compared with WBRT.

Stereotactic radiosurgery [SRS]

SRS indication is driven by the number of brain metastases, total tumor volume, tumor location, age and the extracranial disease status. Dose schedules in SRS/SRT is dependent on size of the lesion and location. Dose schedules vary from 15-30Gy in 1-5 fractions. Level I evidence exists for SRS in 1-4 brain metastasis and for post-operative SRS.

Cognitive function preservation is one of the major end-point of SRS and hippocampal sparing RT treatment. With increased availability of radiosurgery facilities and mature published data on radiosurgery in brain metastasis, radiosurgery as treatment option in brain metastasis now has increased acceptance in Indian medical community.

In summary HA WBRT and SRS have significantly better outcomes in terms of memory and cognitive performance. A summary of cognitive performance after radiotherapy is shown in Table 3.

Table 2: Multi-centric randomized studies with different radiation schedule in brain metastasis

Author	Study	Design	Results
Patchell *et al* NEJM 1990 (Ref)	Phase III RCT 54 patients	Surgery plus WBRT vs WBRT alone in solitary brain met	Surgery reduced local recurrence (52% vs 20%) and improved median survival (40 vs 15wks)
EORTC 22952-26001 Kocher *et al* JCO 2011 (Ref)	Phase III study 359 patients	Adjuvant WBRT vs Observation after Surgery/SRS in 1-3 brain mets	WBRT decreased 2 yr distant brain failure (27% vs 59%) No difference in OS (WBRT vs Obs) 10.7 vs 10.9 mon Median time to PS >2 9.5 vs 10 mon
Patchell *et al* JAMA,1998 (Ref)	Phase III RCT 95 patients	Surgery followed by WBRT vs Surgery alone in single brain mets	WBRT reduced in brain failure (anywhere 18% vs 70%; local 10% vs 46%); likelihood of neurological death (14% vs 44%) No effect on OS (48 vs 43 weeks)
QUARTZ study Mulvenna *et al* Lancet 2016 (Ref)	Phase III non inferiority study 538 patients NSCLC with brain mets unsuitable for resection or SRS	Optimal supportive care vs WBRT (20Gy/5fr)	No difference in MS (8.5 vs 9.2 wks) OS(48 vs 43 wks)
Brown *et al* Lancet, 2017 (Ref)	Phase III RCT 194 patients with 1-4 mets and resection of one brain lesion	Post op SRS vs WBRT	No difference in OS (MS 11.8 m vs 11.5m) Less neurocognitive decline with SRS (54% vs 86%) and better QOL . Less time to intracranial failure with SRS (6.4 m vs 27.5 m)
Aoyama *et al* JAMA,2006 (Ref)	Phase III RCT 132 patients with 1-4 brain mets	SRS+WBRT vs SRS alone	No difference in OS(SRS alone 8m vs 7.5 in SRS + WBRT) Distant brain control(24% in SRS alone and 53% in SRS + WBRT)
Mahajan *et al* Lancet, 2017 (Ref)	Phase III RCT 132 patients with complete resection of 1-3 brain mets	Post op SRS vs Observation	One year local control (72% in SRS group vs 43% in Observation group) Similar median OS

Table 3: Cognitive performance after radiotherapy

Author	Study	Design	Results
Eric Chang *et al* Lancet, 2009	Phase III RCT 58 patients 1-3 brain mets	SRS + WBRT vs SRS alone	Memory decline at 4 months (24% in SRS vs 52% in SRS + WBRT)
Brown *et al* JAMA, 2016	RCT 213 patients 1-3 brain mets	SRS vs SRS + WBRT	Cognitive deterioration at 3 months (63.5% in SRS vs 91.7% in SRS + WBRT)
Gondi *et al* JCO 2014	RTOG 0933 Phase II trial 100 patients	HA-WBRT for brain mets 5 mm away from hippocampus	Mean relative decline of HVLT-R from baseline to 4 months was 7% for HA WBRT vs 30% for WBRT.

Response to the treatment (SRS) and complication probability (radiation necrosis) after SRS treatment depends upon the dose delivered, volume of disease and fractionation schedule. Higher biological equivalent dose schedules have higher response to treatment, however have higher radiation necrosis probability. The details of different dosage schedule and their response to treatment explained in Tables 4 and 5.

ASTRO 2022 guidelines

The American Society for Radiation Oncology (ASTRO) has updated its 2012 guideline on the use of radiation therapy to treat patients with brain metastases as follows [41].

Table 4: Local control & toxicity with marginal dose to the brain metastasis

Volume	Dose	LC	Toxicity - RN
<2 cm	24 Gy	85%	<5%
2.1-3 cm	18 Gy	49%	<5%
3.1-4 cm	15 Gy	45%	<5%
<3 cc	24 Gy	90%	<5%
>3 cc	24 Gy	78%	<5%

Table 5: Common toxicities after brain RT

Time period	Clinical manifestations
Acute Toxicities (Within 6 weeks of RT)	Fatigue, radiation-induced alopecia, dermatitis, nausea and vomiting, decreased appetite, cerebral oedema
Early Delayed Toxicities (6 weeks to 3 months)	Fatigue, somnolence, neurocognitive deficits such as decline in memory, and other general or focal neurologic symptoms.
Late Toxicity (>3 months)	Neurocognitive dysfunction, Leukoencephalopathy, Radiation Necrosis.

Intact/Unresected Brain Metastases

- In 1-4 brain metastases and good performance status (ECOG 0-2), stereotactic radiosurgery (SRS) is recommended.
- 5-10 brain metastases and good performance status, SRS is conditionally recommended.
- For patients with tumors exerting mass effect and/or larger size, surgical resection is suggested.
- Symptomatic brain metastases: upfront local therapy (radiation and/or surgery) is strongly recommended.
- Asymptomatic brain metastases eligible for CNS-directed systemic therapy, local therapy may be deferred in only definitive conditions after multi-disciplinary decision.
- Brain metastasis with favorable prognosis: ineligible for surgery and/or SRS (multiple lesions, leptomeningeal involvement), whole brain radiation therapy (WBRT) is recommended as a primary treatment. Hippocampal avoidance is recommended when appropriate to preserve memory function, (along with memantine).
- Routine adjuvant WBRT added to SRS is not recommended.
- WBRT may not improve outcomes compared to supportive care alone in patients with Poor prognosis. Hence palliative / supportive care / hospice, or short-course WBRT is recommended.

Resected Brain Metastases

- Radiation therapy is recommended for all patients following resection of brain metastases to improve intracranial control. For patients with limited brain metastases after resection, post-operative SRS is recommended over WBRT to preserve the patient's neurocognitive function and quality of life [42].
- SRS prior to brain metastasis resection is conditionally recommended.

Leptomeningeal Disease (LMD)

Although leptomeningeal involvement is considered as a poor prognostic parameter, patients with good performance status and normal CSF levels have a relatively more favourable prognosis.

In an National Cancer Database (NCDB) analysis of 519 patients treated for LMD from any histology from 2005 to 2014 by Hyun *et al*, 52 patients were treated with RT alone, 88 patients were treated with RT+C, 232 patients were treated with C alone, and 147 patients were treated with BSC [43]. Of the patient's that received RT, 85% were treated with WBRT, Median OS was highest for patients treated with C+RT [5 months] compared to all treated patients [3 months].

Re-radiation in brain metastasis

Although reirradiation in brain metastases after prior WBRT has its own limitations, it is reasonably well tolerated and can give an additional median survival of 2.8 months. Good performance status at the start of the re-irradiation is a key indicator for longer survival.

Complications of RT in brain metastasis and their management

In brain radiotherapy, local control depends upon the peripheral dose while dose delivered, and tumour volume determines the toxicities.

Post radiation oedema and radiation necrosis are the most common complications of SRS in brain metastasis [Table 6]. Higher marginal dose delivered have higher possibility of radiation necrosis. In marginal dose less than 15Gy, there is minimal radiation necrosis and local control of almost 60%. Whereas, when marginal dose is higher than 24Gy, radiation necrosis possibility is 10% and local control probability is 93% [Table 5].

Single fraction SRS have higher radiation necrosis compared with fractionated SRS. Radiation necrosis probability with 24Gy in single fraction schedule is about 10%, whereas in 27Gy in three fraction schedules is about 5%.

Patients with slow growing tumours and those with previous WBRT have poorer response and higher radiation necrosis while immunotherapy along with SRS reduce radiation necrosis.

Normal brain dose is considered as predictor for radiation necrosis. Usually in single fraction regimen, 14Gy whole brain dose and in multiple fraction regimen 18Gy whole brain dose predicts radiation necrosis

Radiation necrosis occurs in approximately 10-15% of patients. In brain metastasis less than 3cm size with biological equivalent dose [BED] of 90-127 (dose 24-35Gy/3-5fr) possibility of radiation necrosis ranges from 2-15%. In fractionation schedule of 25Gy in 5 fractions, local control is only 56% and radiation necrosis probability is 4% [44]. A summary of Local control & toxicity with marginal dose to the brain metastasis is shown in Table 5.

Majority of the clinical outcome data of radiation necrosis after radiation therapy is from retrospective series. Radiation necrosis is diagnosed in 24% of cases after SRS by radiology, majority of the patients (14%) are asymptomatic. Only 10% of cases have new neurological deficit. The median time to symptomatic necrosis is 11 months (range, 2-32 months). Volume and dose were independent risk factors for necrosis. Risk of necrosis is more than 10% when more than 8.5cc normal brain vol receives >12 Gy. Majority (20%) of radiation necrosis are diagnosed radiologically and need only conservative management. Only 5% of the patients need intervention.

In larger volume metastasis, if we need to treat with SRS & keep toxicity same (<5%), then there is a need for dose reduction. However, reduced dose will increase the recurrence possibility. We need to accept higher radiation necrosis probability in larger brain metastasis to have acceptable local control. Common toxicities after brain RT are summarized in Table 6.

Management of symptomatic radiation necrosis

Serial MRI scans done at 3 months to assess disease response and rule out interim new metastases. A probable necrotic lesion in an asymptomatic patient warrants only observation [41], if patient is symptomatic, then steroids (dexamethasone 2-4mg) can

Table 6: Radiation necrosis with normal brain volume

18Gy normal brain vol in 3 fr SRS schedule	
Normal brain vol	**RN (%)**
<30cc	5%
>30cc	14%
<22.8cc	0%
22.8-30.2cc	6%
30.3-41.2cc	13%
>41.2cc	24%
14Gy normal brain vol in single fr SRS schedule	
>7cc	>14%
<7cc	<5%

be started [44]. In case of persistent symptoms, surgery, hyperbaric oxygen therapy [HBOT] or immunotherapy is considered. In cases where radiology is inconclusive, biopsy is recommended to distinguish from recurrence. If the patient is not fit for surgery bevacizumab or HBOT may be considered [45].

There are only a few prospective studies evaluating radiation therapy outcome in Indian patients with brain metastasis. Dutta *et al* [46] have published prospective assessment of outcome data in 138 patients with 251 lesions treated with radiosurgery alone. Patients with up to four lesions with good PS and relatively small volume or controlled primary disease were accrued in the study. 52% of patients were treated with single fraction (20-24Gy), 15% with three fractions (27Gy) and 33% with five fractions (25-30Gy) schedule. At mean follow up of 15 months, 78% of patients were alive at 6 months, 47% at 12 months and 19% were alive at more than 24 months follow up. 9% of patients had radiological diagnosis of radiation necrosis and only 2 patients required surgical intervention. Survival outcome was similar with breast or lung primary. However, patients with solitary brain metastasis had significantly better survival compared with multiple metastasis (p=0.019). Indian brain metastasis patients are younger with targetable mutations (lung cancer with less EGFR/ALK mutation; Breast cancer with lesser ER/PR positive), however the outcome after radiosurgery alone is similar with western patient population. A summary of the relationship of Radiation necrosis with normal brain volume is shown in Table 6.

International Guidelines for Radiotherapy

The ASCO-SNO-ASTRO guidelines recommend that patients with symptomatic brain metastases should be offered radiosurgery and/or radiation therapy and /or surgery regardless of the systemic therapy used. For patients with asymptomatic brain metastases, local therapy should not be deferred except where appropriate targeted therapy can be given. They also recommend SRS alone (as opposed to WBRT or combination of WBRT and SRS) to patients with one to four unresected brain metastases, excluding small-cell carcinoma while SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status. In cases where WBRT is planned memantine and hippocampal avoidance should be offered while radiation-sensitizing agents are not recommended.

The EANO-ESMO guidelines additionally recommend SRS for patients with a higher number of BMs (5-10) with a cumulative tumour volume <15 ml and to the resection cavity after complete or incomplete resection of BMs [47]. Post-operative WBRT after neurosurgical resection or after SRS is discouraged. WBRT is recommended for treatment of multiple BMs not amenable to SRS while supportive care with omission of WBRT is recommended in patients with multiple BMs not eligible for SRS and poor PS. Prophylactic cranial irradiation [PCI] is still recommended for patients with limited and extensive-stage SCLC with complete response to chemoradiotherapy.

Systemic therapy in Brain Metastases

Systemic therapy in brain metastases has been revolutionised with introduction of targeted therapy based on characteristic genetic alterations. The identification of such genetic 'driver' mutations/rearrangements using next generation sequencing has thus become an essential pre-requisite towards better response rates and overall survival in patients with brain metastases. Newer targeted therapy molecules like Osimertinib and alectinib cross the blood brain barrier and have better response rates. Immunotherapy is another newer systemic therapy modality which has influenced the outcomes of brain metastases in a positive way.

Molecular tests and special immunohistochemistry tests are essential for deciding systemic therapy in brain metastases from lung, breast, colon, melanoma etc whereas they are often not needed for cancers like renal cell carcinoma and ovarian cancers.

Brain metastases from primaries in lung, breast, melanoma etc often have the same genomic profile as that in the primary though there are reports of newer mutations [48].

The following tests are recommended for defining the molecular or immunotherapy treatments

1) Programmed Death Ligand -1 (PDL1) -: Lung/Upper GI/ Head and Neck/ etc. Platforms like 22C2 Pharm Dx, SP263 etc are useful in the PDL1 testing
2) Special Immunohistochemistry tests:
   A) Her2Neu- Breast/GI/Lung
   B) Microsatellite Instability (MSI) – loss of any of the four MMR proteins (MSH2, MSH6, MLH1, PMS2) implicates the occurrence of MSI -High status which suggests that drugs like Pembrolizumab can be effective irrespective of the primary tumor [49]. This is known as tumor agnostic therapy.
   C) BRAF V600E mutation- Melanoma
   D) ALK mutations by IHC- Lung.
3) Limited Cancer Gene panel: In resource limited settings, dedicated cancer gene panels are useful in cancers like lung/ colorectal cancers.
   Lung cancer- EGFR/ALK/ROS-1/BRAF/Her2/NTRK/MET etc
   Colon cancer- KRAS/NRAS/BRAF/Her2.
3) Next Generation Sequencing (NGS):
   When there are no resource constraints or in cases when there is metachronous brain metastases, next generation sequencing is preferred for molecular analysis. It offers the advantage of detection of rare mutations and higher chances of detecting common mutations due to the depth of analysis.
4) Tumor Mutational Burden(TMB) is the approximate amount of gene mutation that occurs in the genome of a cancer cell. In cancers with high TMB defined as >10 mutations/Mb, there is benefit of immunotherapy [50]. Drugs like combination immunotherapy (Nivolumab/Ipilimumab), Pembrolizumab are approved in solid tumors with high TMB.

Approach to Systemic therapy in Brain metastases

1) Sequencing of local therapy (Surgery/Radiation) with Systemic therapy

Different clinical, radiological, pathological parameters are taken into consideration for deciding the optimal sequencing of multimodality treatment.

Clinical parameters include the general condition of patients, symptomatic burden due to brain metastases and extracranial disease and age. The physical fitness for systemic therapy is assessed by performance scores like ECOG and KPS.

Radiological parameters: Single metastases vs 2-5 metastases vs Multiple metastases (Asymptomatic vs Symptomatic)

In single or limited metastases systemic therapy is started after 2 weeks of completion of radiation therapy or surgery. In multiple brain metastases the systemic therapy is started post radiation.

In asymptomatic brain metastases especially when multiple and in molecular driven cancers like EGFR mutation positive lung cancer or ALK rearrangement positive, the option of surveillance of brain metastases without any radiation can be considered as drugs like Osimertinib (anti EGFR), Lorlatinib (anti ALK) have excellent intracranial efficacy. Immunotherapy like Ipilimumab, Nivolumab can also be considered as first line therapy in asymptomatic brain metastases in melanoma to delay local therapy when feasible.

In oncogene driven cancers, the treatment of choice is targeted therapy, mostly tyrosine kinase inhibitors (TKI). Most of these molecules have intracranial penetration which along with their toxicity profile and safety with concurrent radiation makes them the preferred agents to start once diagnosis is established.

Her2 positive breast cancers are treated with monoclonal antibodies like trastuzumab, trastuzumab deruxetecan (TDM1), Trastuzumab Deruxetecan (TDXD) and with TKIs like Lapatinib, Tucatinib.

In non-oncogene driven cancers, the main modality of treatment is chemotherapy which has limited penetration into the brain and overall low efficacy. Commonly used drugs include Ifosfamide, Cisplatin, Carboplatin, Etoposide and Pemetrexed. Methotrexate is often used in high doses in hematological cancers with intracranial involvement. In

patients with leptomeningeal disease (LMD), intrathecal methotrexate is commonly used for palliation.

The other options in non-oncogene driven cancers are immunotherapy and monoclonal antibodies which are specifically directed against cancer cells. Rituximab is a monoclonal antibody against CD20 and has good intracranial efficacy in CD20 positive lymphomas with intracranial metastases. Immunotherapy is useful in brain metastases from melanoma and in those cancers with high TMB or MSI-H status. Combination immunotherapy with Ipilimumab- Nivolumab has high intracranial efficacy and is used upfront without any local radiation if they are asymptomatic brain metastases.

International guidelines for Systemic therapy

The EANO-ESMO guidelines recommend systemic pharmacotherapy based on histological and molecular characteristics of the primary tumour and previous treatment for most patients. Wherever feasible, molecular genetic work-up of BMs rather than primary tumour should be considered for selecting targeted therapy and immunotherapy.

In HER2-positive breast cancer patients with a preserved general status systemic treatment of asymptomatic or oligosymptomatic BMs is recommended to delay WBRT whereas HER2-negative breast cancer patients with progressive BMs after local treatment should be considered for standard chemotherapy, such as capecitabine, eribulin or carboplatin and bevacizumab.

Patients with NSCLC without actionable oncogenic driver alterations with asymptomatic or oligosymptomatic BMs are recommended to be treated by upfront immune checkpoint inhibition alone (PD-L1 50%) or systemic chemotherapy combined with immune checkpoint inhibition (PD-L1 <50%) whereas patients with NSCLC with actionable oncogenic driver alterations such as EGFR or ALK or ROS1 rearrangement and asymptomatic or oligosymptomatic BM should be treated by upfront systemic targeted therapy.

Patients with SCLC should be treated by platinum-based chemotherapy without or with immune checkpoint inhibition.

The combination of ipilimumab and nivolumab is recommended as the preferred first-line treatment option not only in BRAF wild-type, but also in BRAF-mutated asymptomatic patients whereas patients with multiple symptomatic BRAF-mutated BMs are recommended dabrafenib plus trametinib.

The ASCO-SNO-ASTRO guidelines suggest targeted therapy in asymptomatic brain metastases where they might help delay local treatment until there is radiological or clinical progression. The suggested targeted therapies are

- Osimertinib or icotinib to patients with asymptomatic brain metastases from EGFR-mutant non–small-cell lung cancer (NSCLC).
- Alectinib, brigatinib, or ceritinib in patients with asymptomatic brain metastases from ALK-rearranged NSCLC.
- Pembrolizumab in patients with asymptomatic brain metastases from immunotherapy naive, programmed death-ligand 1–NSCLC.
- Ipilimumab plus nivolumab (for all patients regardless of BRAF status) or dabrafenib plus trametinib (for patients with BRAF-V600E mutation) in patients with asymptomatic brain metastases from melanoma.
- The combination of tucatinib, trastuzumab, and capecitabine may be offered to patients with human epidermal growth factor receptor 2–positive metastatic breast cancer who have asymptomatic brain metastases.

Prognosticating brain metastases

The prognosis for patients with brain metastases has traditionally considered to be poor, which is not always true. One of the early attempts to scientifically identify prognostic factors in patients with brain metastases was a recursive partitioning analysis (RPA) of 1200 patients from three RTOG [radiation therapy oncology group] trials [51]. The best outcomes were seen in < 65 years of age with a Karnofsky Performance Status (KPS) of at least 70, and a controlled primary tumor with the brain the only site of metastases. The

worst survival was seen in patients with a KPS less than 70. A significant disadvantage of this study was that it considered all brain metastases as one disease, still it remains one of the most used classifications for prognosticating brain metastases. Patients with RPA class I and II were recommended to be considered for brain metastases directed treatment while RPA class III were suggested best supportive care.

Over time the field of oncology developed many other scores were for prognostication of patients with brain metastases such as Rotterdam score, score index for radiosurgery [SIR] and basic score for brain metastases [BSBM]. A graded prognostic assessment [GPA] was developed in 2008 [52] based on the age, Karnofsky Performance score, number of brain metastases, and the presence/absence of extracranial metastases but it still considered all sources of brain metastases as one disease. In 2010 a diagnosis specific version of the graded prognostic assessment was developed to account for the differences in outcomes for brain metastases for different primaries [53] which was then updated in 2020 [54]. This ds-GPA [diagnosis specific graded prognostic assessment] calculates a score from 0 to 2.0 in increments of 0.5 and predicts prognosis based on the score. It is calculated differently for different source of primaries and is available for cancers of lung, breast, renal cell carcinoma, melanoma and gastrointestinal cancers and includes molecular markers relevant to the primary. The tool is available for free online at brainmetgpa.com.

Summary

The management of brain metastases is undergoing a paradigm shift around the globe. Longer lifespans of patients with systemic cancer, better and more widely available imaging modalities, refined microneurosurgical techniques, advancements in planning of radiotherapy and individualised targeted therapy [precision oncology] have all come together to prolong survival and ensure quality of life to patients with BMs.

The authors recommendations may be summarised as follows

Clinical examination

Basic clinical examination to establish baseline has relevance for further treatment

Neurological assessment in neuro oncology [NANO] can be quickly performed as a standard assessment.

Prognostication

Karnofsky performance score [KPS] and eastern co operative group [ECOG] scores are widely used but DS GPA is more accurate and can be readily applied at brainmetgpa.com.

Imaging

All patients of systemic cancers with suspected brain lesions must be evaluated with contrast MRI of the brain which should include thin slices (<1.5 mm) of T1 post-contrast sequences.

Specialised sequences can add more information as described.

Amino acid PET CT can help in suspected recurrence with doubtful MRI findings.

Surgery

Gross total excision should be the aim by either piece meal or en-masse excision.

Appropriate surgical adjuncts – IONM, intra op USG and sodium fluorescence may be used.

Multidisciplinary tumor board decision advised for considering other options and for planning adjuvant treatment after surgery.

Radiotherapy

WBRT in 5 or 10 fractions is most widely practiced.

Hippocampal avoidance and stereotactic radiosurgery can preserve cognitive function better.

The balance between tumor volume, local control and toxicity needs meticulous planning.

Systemic therapy

Important molecular differences in brain metastases from their primary tumors that can lead to actionable targets are increasingly being recognised for common BMs.

Wherever possible tissue from BMs should be checked for such alterations and appropriate systemic therapy chosen

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Conflicts of interest

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