NARRATIVE REVIEW

Consensus guidelines for the management of intracranial metastases for low- and middle-income countries

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Abstract

Metastatic tumours are among the most common types of brain tumours. However, in low- and middle-income countries (LMICs), the numbers are considerably lower. This does not necessarily indicate a decreased incidence but rather points to decreased survival rates or limited access to healthcare. The challenge of achieving better outcomes, along with associated costs and resource constraints, often hinders the effective management of brain metastasis. Even in cases where localised disease can potentially be managed to improve survival, these challenges persist. The purpose of these guidelines is to address these challenges and outline a management strategy within the context of LMICs.

Keywords: Incidence, survival rate, health care, brain neoplasms, metastases, tumours

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Introduction

Brain metastases (BM), are the most frequent type of brain tumours, that are found in 10–40% of individuals diagnosed with cancer. Several factors contribute to the increasing incidence, which include the aging population, improved facilities of neuro-imaging, and improved systemic treatment for the underlying disease. BM cause significant morbidity and mortality consequently.[1] Synchronous (diagnosed within 2 months of the primary tumour) or precocious (diagnosed before the primary tumour), brain metastasis constitutes up to 20% of the instances; the rest of the 80% of the cases present with an already known primary tumour.[1] According to data collected from neurosurgeons and published under the the Pakistan Brain Tumour Epidemiology study (PBTES), the incidence of brain metastasis was 3% This incidence is significantly less than rates reported from high-income countries, possibly due to limitations in collecting and reporting epidemiological data by the author. Another probable reason could be that more patients with metastasis are sent for palliative treatment in LMIC due to the high costs of surgical care.[2]

Brain metastasis is typically found at the interface of gray and white matter and the boundaries connecting the major territories of arterial vasculature. Around 80% of BM arise within the hemispheres of the cerebrum, 15% originate within the cerebellum, and 3% are found within the basal ganglia. Some cancers such as uterine cancers, prostate cancers, and primary gastrointestinal tumours may metastasise to the posterior fossa preferentially. Occasionally, these tumours may spread to the pituitary gland, leptomeninges, or choroid plexus. Infrequently, a few malignancies, such as lymphoma, may extend within or along the cerebral vessels.[3]

The majority of BM are solitary lesions (50%), two in 20%, and three in 30% of the cases. Some tumours, such as those of breast, colon, renal cell tumours, and thyroid tumours are typically solitary, whereas tumours like melanomas and lung cancers are usually multiple. Metastases from cancers like renal cell carcinoma, choriocarcinoma, melanoma, lungs, and thyroid classically cause haemorrhage.

Methodology

The literature search of the high-quality data on brain metastases was done on different databases including PubMed, Google Scholar, Scopus, and Embase in February, 2023. The most relevant and high-quality studies were analyzed to develop the evidence-based recommendations. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in diagnosis and management of brain metastases within Pakistan. This group was tasked with identifying best-practice recommendations and their application within the context of Pakistan as an LMIC. Recommendations were

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collated, reviewed and debated regarding utility and evidence-based practices, in a process that has been previously detailed.[4]

Initial evaluation

BM are asymptomatic up to 60-75% of the time. Symptoms may include seizure, headache loss of consciousness, papilloedema, or focal neurological deficit; which warrants further evaluation.[5] Screening is not routinely implemented. Patients suffering from advanced melanoma, small-cell lung carcinoma, and NSCLC, are currently recommended for screening brain MRI at diagnosis.[6]

The main factor in assessing the suitability of the treatment and prognosis is the performance status. Karnofsky performance status (KPS) is a part of the recursive partitioning analysis (RPA) classification system refer to table 1 and 2, together with age, status of primary tumour, and extent of disease outside the cranium. Graded prognostic assessment (GPA), a new prognostic index has been reported recently, which gives a score to each patient from 0 to 4 according to the number of metastases. More recently, for an accurate estimate of prognosis, Disease-specific graded prognostic assessment (DS-GPA) may be used.[1] Molecular profiles and tumour biology have also been integrated into the latest versions of the prognostic scoring systems. Changes in Anaplastic Lymphoma Kinase (ALK) and Epidermal growth factor receptor (EGFR) in non-small-cell lung cancer (NSCLC) (Lung-molGPA); estrogen/progesterone and human epidermal growth factor receptor 2 (HER2) status for breast cancer (Breast-GPA); and BRAF status in melanoma (Melanoma-molGPA), have been used more accurately to estimate the outcome of modern BM patient.[7]

Imaging

Nonenhanced CT (NECT) due to its easy availability, low cost, and well tolerability is the best initial imaging technique for individuals with recent onset neurological impairments since it can diagnose life-threatening emergencies rapidly like significant mass effect, haemorrhage, or hydrocephalus. BM present as single or multiple lesions, with a variable density compared to the brain parenchyma and extensive surrounding vasogenic oedema. Acutely haemorrhagic metastases and melanoma appear hyperdense to brain parenchyma on CT. Iodinated contrast enhancement is needed for identifying metastases on CT. They may exhibit nodular, solid, or ring-like enhancement. If MRI is unavailable or contraindicated, Contrast-enhanced CT (CECT) can be used as a screening tool for metastases. In LMICs where accessibility and availability are the major limiting factors, CECT is a valuable diagnostic, screening, and surveillance tool.

On MRI images, metastases show isointense- or hypointense signals on T1-weighted images, and hyperintense signals on T2-weighted images, and display intense enhancement. Few metastases, like melanomas, show hyperintense signals on T1 due to melanin that has paramagnetic effects. Haemorrhagic metastases may also show hyperintensity on T1, varying based on the duration of haemorrhage. Usually, Diffusion Weighted Images demonstrate facilitated diffusion (i.e., bright on apparent diffusion coefficient (ADC) map), rather than diffusion restriction. Substantial vasogenic oedema is noted and is not associated with lesion size. Contrast enhancement with gadolinium is needed to identify compact metastases. Unlike cerebral abscesses, BM demonstrates elevated rather than reduced relative cerebral blood volume (rCBV). Furthermore, perfusion MRI helps differentiate lymphomas of CNS from high-grade glioma and metastasis; because compared to these two entities lymphoma demonstrates lower rCBV. One group suggested a minimum ADC threshold of non-enhancing T2-hyperintense lesion of $1.3X10^{-3}$ mm^2/s to differentiate metastasis from high-grade glioma: Values below this indicate high-grade glioma not metastasis, with a specificity of 79% and a sensitivity of 83%. Although FDG-PET is crucial in staging metastasis in other parts of the body, it is seen to be less sensitive than MRI in the assessment of brain metastases.

Some cancers are associated with the metastases of the dura, including lung, breast, lymphoma, and prostate cancers. Differentiating a meningioma from a metastasis originating from the dura is challenging. Both may appear as hyperdense lesions on non-contrast CT and may show avid enhancement. Any prior history of malignant tumour, the existence of both parenchymal lesions and dural-based lesions, and the emergence of a recent lesion of dura compared to previous imaging can provide useful indications to favour dural metastasis over meningioma.[4]

Surgical management

Surgery plays an important role in the multidisciplinary management of BM. Surgical resection reduces the need for corticosteroids, and helps in symptomatic improvement and local control of disease, particularly in patients having stable systemic disease. It helps establish a histopathological diagnosis and provides specimens for more extensive molecular and histological characterisation. Even in patients with known metastatic malignancy, an intra-axial mass can be a primary brain

tumour in 11% of cases.[3] Surgical resection is also needed to differentiate true progression from radionecrosis.[8]

Surgery together with radiotherapy is advised as the initial management strategy in patients with single brain metastasis with limited extracranial disease and favourable performance status. It enhances local control and improves survival. Compared to piecemeal resection, gross total tumour removal is recommended to reduce the risk of leptomeningeal disease postoperatively following resection of single brain metastasis. Complete tumour resection or gross total resection (GTR) is preferred over subtotal resection (STR) in recursive partitioning analysis Class I patients to prolong the time to recurrence and improve overall survival.[9] GTR with WBRT compared to STR with WBRT in 157 patients with BM found no statistically significant difference between the local recurrence rates, but overall survival was significantly increased in the GTR group (20.4 months versus 15.1 months). Even though it has less number of patients, this study suggests that total excision of the tumour showing contrast enhancement can prove to be beneficial, regardless of the subsequent adjuvant therapy.[10]

"Microscopic total resection", excision of the tumour and the infiltration of microscopic tumour cells within a seemingly normal-looking brain parenchyma within a 5 mm area using an ultrasonic aspirator, was evaluated and compared to radiological GTRs. The local control of tumour was better in the microscopic total resection group than the GTR group (The 1- and 2-year respective local recurrence rates were 29.1 & 29.1% in the microscopic total resection group and 58.6 & 63.2% in the gross total resection group).[11] Another step towards improving the degree of resection is by using fluorescent dye 5-aminolevulinic acid (5-ALA).[10]

In the context of multidisciplinary management of brain metastases, palliative surgical interventions can also provide benefits in select cases. Ommaya reservoir insertion and intrathecal/intraventricular delivery of the drug may be beneficial in patients suffering from leptomeningeal metastases or those diagnosed with large cystic growths in the eloquent region of the brain with impaired performance. Other surgical interventions with palliative intent are for patients experiencing acute hydrocephalus due to metastatic spread to the cerebral aqueduct, cerebellum, or brainstem and for those individuals diagnosed with carcinomatous meningitis causing obstruction to CSF absorption. These palliative interventions may improve the consciousness level and neurological condition of patients.[11]

Pathologic assessment

Histopathological analysis of the tumour is crucial in formulating a treatment plan for patients with BM as different histopathological tumour types offer different chemotherapeutic and radiation-based treatment options. The main etiology of BM is lung cancer (50–60%) in adults, which is followed by breast cancer (15–20%) and melanoma (5–10%) respectively, and rarely gastric and prostate cancer.[11]

Adjuvant therapy WBRT

In the past, Whole Brain Radiation Therapy (WBRT) was the mainstay for individuals suffering from BM due to its cost-effectiveness, speed, simplicity, and ability to maximise the control of total intracranial disease.[8] However due to recent deep insight into tumour molecular biology resulting in improved survival, the role of WBRT has significantly reduced because of its associated side effects like fatigue, headache, nausea, anorexia, alopecia, xerostomia, and particularly neurocognitive dysfunction. Currently, its role in clinical practice has been limited to patients with numerous brain metastases (> 4 lesions) those with leptomeningeal disease those having large-sized tumours or pathology with diffuse micrometastatic lesions such as small cell lung carcinoma or lymphoma, or those with the site of metastases not treatable with surgical resection or radiosurgery.

There isn't enough evidence to justify any specific dose or fractionation regimen for a patient with brain metastasis. A common dose/fractionation of the WBRT schedule is 30 Gy in 10 fractions however in patients having poor performance status short fractionation e.g., 20 Gy in 5 fractions can be considered without any significant differences in local control or median survival.

To reduce the neurocognitive decline in the patient getting WBRT different strategies have been proposed such as hippocampal sparing WBRT (HA-WBRT) and, the use of memantine alone or in combination with each other to potentially prevent, lessen, or delay the related neurocognitive toxicity.[12]

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS), pioneered by Lars Leksell in the 1950s,[13] involves the delivery of several radiations directed on a specific target lesion within a stereotactic setting providing treatment accuracy to submillimeters.[3] SRS is given either as one fraction of extremely precise, high-dose treatment (18–24 Gy generally) or as moderate-dose fractions termed as fractionated SRS (FSRS) given in 3 fractions ranging from 24 to 27 Gy, or 30

Gy in 5 fractions.[7] There is no randomised controlled trial that compares clinical outcomes concerning different SRS fractionation regimens. The Radiation Therapy Oncology Group (RTOG-90-05) a dose escalation phase 1 study according to tumour size has set the standard for single-fraction SRS for intact brain lesions.[14]

Stereotactic radiosurgery can be considered as an initial treatment because of its non-invasive nature, reduced out-patient visits, low morbidity, and provision of a high local control rate. SRS can be used alone in individuals with a known history of cancer and presented with a solitary or limited number of brain lesions without WBRT due to its protecting neurocognitive function ability or it can be utilized in adjunct to surgery for better local control particularly when surgery is indicated for tissue diagnosis or relieving mass effect or hydrocephalus.[6]

Large growths (usually those >3 cm in diameter) are usually not suitable for single fraction radiosurgery and should require a short fractionation approach because it increases the peritumoral oedema and risk of Radiation necrosis (RN) that may occur in a minimum of 10% of patients post-treatment who receive SRS, typically between 6 and 18 months. Based on conventional MRI it is often difficult to differentiate recurrent/progressive BM from radiation necrosis because of the resembling appearance of both oedema and contrast enhancement. The standard treatment is surgical resection for the diagnosis of the lesion which is not always desirable or feasible and may show a mixture of tumour and radiation necrosis. A lot of recent studies have explored the potential of different noninvasive neuroimaging techniques to help differentiate between tumour recurrence from radiation necrosis. These noninvasive neuroimaging modalities include dual-phase PET and MR perfusion. While adjunctive information can be provided by these two tests, no modality has shown adequate specificity and sensitivity to effectively distinguish between these 2 phenomena noninvasively, as recognized in the recently published Response Assessment in Neuro-Oncology–Brain Metastases (RANO-BM) guidelines.[6]

Chemotherapy/ immunotherapy

Systemic treatment of brain metastasis depends upon primary malignancy. Previously, conventional platinum-based chemotherapy regimens had a role in brain metastases from NSCLC, in the upfront setting particularly. Cisplatin alone has a positive response of 30%, with response rates ranging from 28% to 45% when combined with 1st, 2nd, and 3rd generation EGFR TKI seto¬poside, teniposide, fotemustine, paclitaxel, and vinorelbine/gemcitabine (carboplatin instead of cispla¬tin). With the advancement in treatment, various targetted therapies enter brain tumours and can target specific genetic alterations in cancer that reach the brain metastatic disease that began elsewhere.

• For metastatic non-small cell lung cancer (NSCLC) with a genetic change in the EGFR gene, osimertinib can be used.

• Alectinib, brigatinib, or ceritinib for metastatic NSCLC that has a genetic change on the ALK gene

• For HER2-positive metastatic breast cancer, tucatinib, trastuzumab, and capecitabine can be used

•For metastatic melanoma, dabrafenib with trametinib can be used.

Immunotherapy

Certain immunotherapy types have shown promising results in managing BM from melanoma and lung cancer which include ipilimumab (Yervoy), pembrolizumab (Keytruda), and nivolumab (Opdivo).

In a heavily pretreated setting, temozolomide has shown modest activity. Bevacizumab (vascular endothelial growth factor inhibitor) has proved to be safe and has some role in treating non-haemorrhagic brain metastases from NSCLC.[8] Pembrolizumab and nivolumab (Anti-PD1 agents) especially in PD-L1 positive individuals or those who have other immunogenicity biomarkers, or anti-folate chemotherapeutic agent, pemetrexed in individuals suffering from adenocarcinomas may help in managing intracranial disease in certain patients, although outcomes may be limited.[7]

For breast cancer, cytotoxic regimens have a role. Rosner et al in their study reported a 52% response rate in individuals managed with prednisone (P), cyclo-phosphamide (C), and fluorouracil (F) and a 54% of response rate in those treated with CFP-methotrexate.[14] Similarly, another study reported the efficacy of high-dose metho¬trexate in parenchymal or leptomeningeal metastases, which should be investigated further.[14] Bevacizumab's role is currently under investigation. In a case series involving 4 patients suffering from CNS metastases from breast cancer, all patients responded to bevacizumab and paclitaxel. Many reports describe the response to Intrathecal trastuzumab, which is a humanized monoclonal antibody against HER2, in LM from HER2-positive "breast cancer."[17]

In Melanoma BM, the response has been seen with BRAF inhibitor dabrafenib, vemurafenib, and Ipilimumab, an

Table 1 – Components of recursive partitioning analysis (RPA) classification use to determine prognosis in cerebral metastasis[16].

Class	Clinical parameters	Median overall survival (OS) (months)
I	<65 years; Karnofsky performance status (KPS) ⩾ 70; controlled primary; no extracranial spread	7.1
II	⩾65 years; KPS ⩾ 70; uncontrolled primary; extracranial spread	4.2
III	KPS < 70	2.3

Table-2: Eastern Cooperative Oncology Group Score.

ECOG/WHO score

0 Fully active, able to carry on all predisease performance without restriction
1 Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light and sedentary nature (e.g. light house work, office work)
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5 Dead

anti-CTLA4 monoclonal antibody.[8]

Routine use of chemotherapy alone or after WBRT or SRS for brain metastases is not advised.[18]

Single brain metastasis

In individuals with solitary BM with favourable performance status and controlled extracranial disease, WBRT after surgery is advised as the first-line treatment option to extend the overall survival and local control based on randomised trials.[9] Patchell et al. carried out a randomised controlled trial under which 48 patients diagnosed with a solitary BM were randomised to undergo WBRT with or without an initial attempt at complete tumour resection. The addition of surgical removal showed benefits in the duration of functional independence (median duration, 38 vs. 8 weeks; P<.005) and overall median survival (mean duration, 40 vs. 15 weeks; P<.01). [19]

Recently studies have shown similar clinical outcomes with stereotactic radiation therapy alone for small brain lesions without mass effect or even the preferred approach for deep-seated lesions. In the case of surgical excision of solitary brain lesion, post-operative radiation to the operative bed by stereotactic radiation is the common clinical practice instead of WBRT because of largely spares the grossly uninvolved brain tissue thus improving or preserving neuro-cognitive function. However, it requires close surveillance with an MRI brain every 2-3 months due to the frequent risk of distant brain failure.[9]

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology and the American Society for Radiation Oncology, both published their consensus statements supporting the use of SRS alone or after surgical removal of a solitary metastasis, instead of using WBRT, in individuals with a solitary lesion and good control of systemic disease.[20]

Multiple (2-4) brain metastases

Stereotactic radiation treatment whether single or fractionated is preferred to manage tumours locally, rather than whole brain radiation therapy, when there is a limited number of brain metastasis (<4) with cumulative tumour volume not exceeding 10 CC. However, patients with significant mass effect or hydrocephalus and < 4 lesions brain lesions require surgical excision before proceeding with stereotactic radiation treatment.[20] Collectively, trials demonstrate high rates of local disease control with better preservation of neuro-cognitive function without compromising overall survival by omitting WBRT though with the understanding that higher rates of new distant BM may be observed, necessitating more frequent salvage treatment.[6,22]

Multiple (> 4) brain metastases

Whole brain radiation therapy is still considered to be the standard of treatment in the majority of patients with a life expectancy > 3 months based on their performance status and systemic disease. According to recent evidence, SRS may prove to be successful in up to 10 brain metastases; if they are small in size and not exceeding a collective tumour volume of 10-15cc. and favourable tumour velocity. Since there is no consensus about stereotactic RT clinical application in multiple brain metastases (> 4) hence can be considered carefully in highly selected patients after thorough discussion in neuro-oncology MDT.[12]

Management of recurrent brain metastasis:

Management of recurrent brain metastasis is highly controversial. Since no consensus guideline is available for guidance hence requires MDT input based upon histopathology, patient performance status, details of

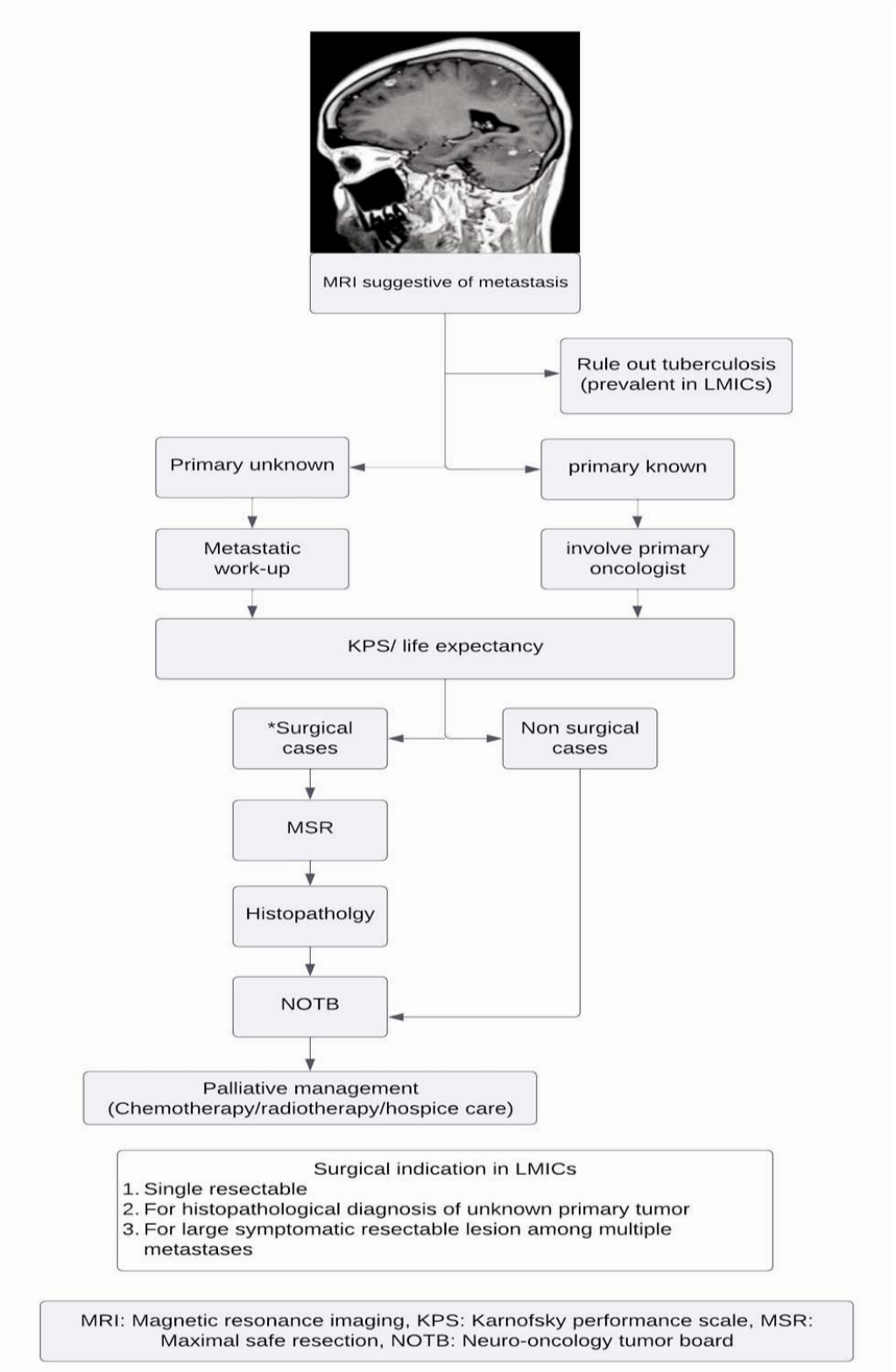

Figure-1: Management of Intra cranial Metastases algorithm.

Table-3: Summary of recommendations for Metastasis.

Radiology	• MRI brain with and without contrast. • 'Minimum required' MRI protocol: o Imaging on at least 0.5T. o Sequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast enhanced T1. • Tumor location, tumour margins, enhancement pattern, tumour size, oedema, number of lesions, volume and presence of haemorrhage/mineralisation must be included. • DWI and ADC: Helpful to rule out differential diagnoses such as abscess, if needed. • CT with contrast (chest, abdomen, and pelvis) with bone scan/ PET Scan: to see the status of the primary lesion. * • Considering the high prevalence of breast cancer, clinical examination of the breast is advised. • Postoperative MRI is recommended within 72 hours of surgery. If delayed, then an MRI should be performed after 6 weeks. o To identify the extent of resection. o To have a baseline to compare successive imaging. o Not required after biopsy.
Neurosurgery	• GTR: Excision of all contrast-enhancing parts. • STR: In eloquent areas where GTR is not possible. • Biopsy: Extensive disease or locations with high surgical risks. • Palliative surgical interventions: Ventriculoperitoneal shunt or Endoscopic third ventriculostomy, Ommaya reservoir insertion and Intraventricular/Intrathecal delivery of the drug, procedures for patients with CSF obstruction or the ones with metastasis to the mesencephalic aqueduct, cerebellum or brainstem resulting in acute hydrocephalus.
Neuropathology	• Haematoxylin and eosin (H&E) preparation for histological typing. • Intraoperative consultation to rule out gliomas and metastatic tumours is crucial. • Immunohistochemical stain panel including GFAP, Olig-2, pan-cytokeratins and site-specific immunostains are required for definite characterisation.
Radiation Oncology	• Patients suffering from leptomeningeal disease, a high brain metastasis velocity or multiple brain metastases (> 4 lesions), WBRT is considered as a preferred treatment approach. • The common dose fractionation schedule of WBRT is 30 Gy delivered in 10 fractions or 20 Gy in 5 fractions. • Stereotactic radiation is considered a preferred approach in patients with a limited number of brain metastases < 4 and small volume. • It can be used as a single fraction SRS or hypofractionated SRS depending upon the size and volume of brain metastasis or resection cavity. • For SRS common radiation dose is 18–24 Gy. For fractionated SRS 27-30 Gy in 3-5 fractions can be considered. • Peer review of radiation treatment plans by site-specific specialists is an integral and essential component of quality assurance and should be a part of stereotactic radiation therapy services to improve patient care.
Medical Oncology	• Tailored approach for each pathology after discussing in NOTB.
Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology, and NOTB recommendations. • Clinical follow-up with MRI brain and systemic imaging at 3 monthly intervals or earlier if indicated.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient, CT: Computed tomography, PET: Positron Emission Tomography, GTR: Gross total resection, STR: Subtotal resection, CSF: Cerebrospinal fluid, GFAP: Glial fibrillary acidic protein, WBRT: Whole brain radiation therapy, Gy: Gray, SRS: Stereotactic radiosurgery, NOTB: Neuro-Oncology tumor board.

*In case of financial constraints, chest X-ray and ultrasound abdomen can be used as an alternative option to screen before surgery.

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previous treatment received, disease-free interval, number of lesions, and possible re-treatment options available such as surgery, chemotherapy, or radiation.[9,23]

Role of Steroids

Steroids are not indicated for asymptomatic patients without mass effect but are recommended for providing temporary symptomatic relief due to raised intracranial pressure and oedema. For such patients, it is recommended to start a dose of 4–8 mg of dexamethasone per day. If patients have serious symptoms consistent with raised ICP, higher doses i.e.[17] mg/day or more should be given. According to the available evidence, the best drug choice is dexamethasone. Corticosteroids, if given, should be tapered off rapidly but not faster than the patient's clinical tolerance, based upon a personalised treatment plan and a thorough understanding of the long-term harmful effects of corticosteroid therapy.[24]

Role of AEDs

For individuals with brain metastasis who didn't undergo surgery and are seizure free, prophylactic antiepileptic drugs (AEDs) are not recommended. Routine usage of anti-epileptic drugs post-craniotomy in patients with BM who are seizure-free is also not advised.[25]

Emerging and investigational therapies

There is not enough proof to advise regarding the usage of high-intensity focused ultrasound (HIFU), laser interstitial thermal therapy (LITT), interstitial chemotherapy, immune therapy, brachytherapy, the daily usage of radiation sensitizers, such as temozolomide, motexafin-gadolinium, chloroquine or sodium nitrite in other clinical settings for patients suffering from BM.

There is inadequate data to recommend epidermal growth factor receptor inhibitors like gefitinib and erlotinib in individuals with BM due to NSCLC; the role of BRAF inhibitors like vemurafenib and dabrafenib in the management of patients with BM due to metastatic melanoma; the role of HER2 agents like lapatinib and trastuzumab to manage patients with BM due to metastatic breast carcinoma; the role of vascular endothelial growth factor agents like bevacizumab, sorafenib and sunitinib, in the management of patients with solid tumour BM.[26]

Prognosis

The mean survival is approximately 7 months.[1] If left untreated, death occurs from progressive neurologic worsening in about 4 to 6 weeks.16 Despite progress in its management, the prognosis remains poor for patients with BM. Specialist palliative care involvement has a role in the treatment of rapidly progressive and highly aggressive brain neoplasm.[27]

Conclusion

These guidelines provide a practical roadmap informed by valuable expertise (as indicated in Table 3 and Figure 1) and are intended for use by physicians working in areas with limited resources. By following these guidelines, there is a substantial opportunity to enhance specific outcomes and promote a greater focus on multidisciplinary healthcare in low- and middle-income countries like Pakistan.

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