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BRAIN METASTASES: A REVIEW ARTICLE

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Abstract:

Cerebral metastases or brain metastases (brain mets) is the most common malignant intracranial cancer among all brain tumors. Brain mets are the secondary tumors migrated from the distinct organs to brain i.e. lung, breast, melanoma and kidney. Cerebral tumors have higher mortality rate among all cancers with poor prognosis. Main steps of brain metastatic cascade are: epethelial-to-mesenchymal transition of primary tumor cells, crossing the blood brain barrier (BBB) and colonization of metastatic cells in the brain. BBB plays important role in both protecting the CNS and also providing the support to metastatic tumor cells for angiogenenesis and propagation. Diagnosis of brain mets is done with imaging techniques and biopsy. Different therapeutics strategies are used to treat the brain metastases patient including surgery or stereotactic radiosurgery, whole brain radiation and targeted molecular and immunotherapies. The present review article will update the understanding of the reader by providing a comprehensive information related to brain metastases, how it is different from primary brain tumor and how the tumor cells cross the blood brain barrier and form the colonies in brain. Further, the present review article will describe the current studies on the molecular factors found to be associated with brain metastasis. At the end of the review article the available diagnosis and treatment options will be discussed.

Key Words : *Cancer, blood brain barrier, brain, tumor, metastasis.*

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INTRODUCTION:

Cancer is a multifactorial disease caused by genetic alteration through mutation or environmental factors [1]. Initiation and progression of tumor is triggered by any variation in chromosomal arrangement, DNA sequence and its copy number, and epigenetic markers [2,3]. Cancer cells exhibit some characteristics, called hallmarks of cancer which were explained by Hanahan and Weinberg as: sustaining proliferative signalling, growth suppressor signals insensitivity, tissue invasion activation and metastasis, uncontrolled replicative potential, inducing angiogenesis, and evading apoptosis [4] Moreover, cancer progression is also influenced by cellular metabolism deregulation, immune system dysfunctionality and tumor microenvironment [5]. All of above mentioned defects in cellular machinery is because of the three different factors i.e environment, epigenetics (for examples modifications on DNA and histone proteins) and genetics (for example aberrant DNA replication and DNA repair system [4,5].

Metastasis is one of the hallmarks of cancer which encompasses different steps like epithelial-to-messenchymal transformation (EMT), invasion, intravasation, circulation, extravasation, and colonization as shown in Figure 1. It is one of the leading causes of death among cancer patients globally [6,7], mainly because metastatic cancers are difficult or unable to treat because of their complexity. The mecahnsim of metastasis of primary tumor to different organs is controlled by number of genes and proteins depending upon the targeted organ [8,9]. Most common metastatic sites and their primary tumor sites are mentioned in Table 1 [10,11].

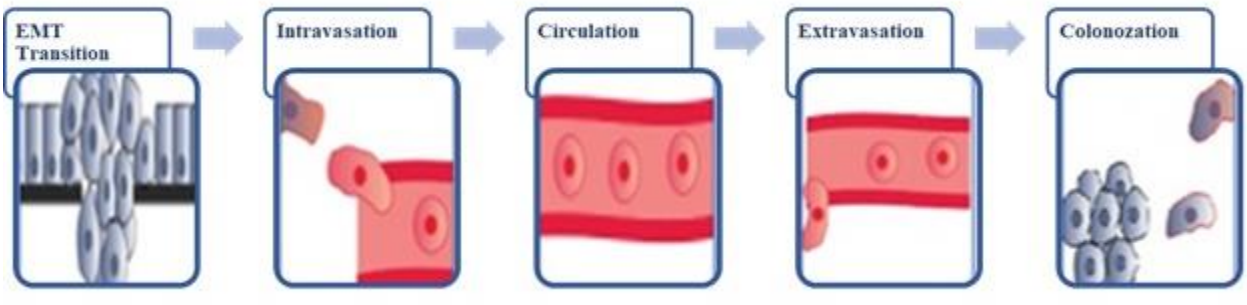

Figure 1 Metastasis Cascade (6,7): Mechanism of tumor spreading from its primary site to other distant organs (secondary site) comprised of various steps including; 1. epithelial to mesenchymal transition (EMT Trasnmition) of tumor cells from it's primary site, 2. Entering of tumor cells into the blood vessels (Intravasation), 3. Survival of tumor cells into blood stream, 4. Leackage of tumor cells from blood stream to secondary site (Extravasation), 5. Colonization of tumor cells to the secondary site

Table 1: Common Sites for Metastasis (10, 11)

Primary Tumor Site	Metastases Sites
Lung	Liver, Brain, Bone, Adrenal Gland
Breast	Bones, Lung, Brain, Liver
Skin	Brain, Liver, Muscle
Kidney	Lung, Brain, Bones, Liver
Colon	Lung, Liver, Peritoneum
Stomach	Lung, Liver, Peritoneum
Pancreas	Lung, Liver, Peritoneum
Thyroid	Bones, Lung, Liver
Rectum	Liver, adrenal gland, Peritoneum
Ovary	Lung, Liver, Peritoneum
Uterus	Lung, Liver, Peritoneum
Prostrate	Lung, Bones, Liver

Primary Brain Tumor:
Lesions formed in cranial regions like brain, nerves and glands are reffered to as brain tumor. Intracranial tumors are divided into two categories based on the origin of tumor i.e. primary or localized tumor and secondary or metastatic tumor. Futhermore, depending on the nature of tumor, these are either benign or malignant [12,13]. Brain tumor has higher mortality rate than other cancers because of the treatment hindrance and has lethal effects on mental impairment. According to WHO, grading of brain tumor depends on its malignancy i.e. from least aggressive (grade I) to most aggressive form (grade IV) . Brain tumors is categorized on the basis of its position and cell type i.e. like glial cell, cranial nerves, skull, meninges, pituitary glands and pineal glands etc [14-16]. According to the position and initiation central nervous system (CNS) tumors are divided into different categories including glioma (glial cell's tumors), meningioma (meninges cell's tumor), craniopharyngioma and pituitary adenoma (sellar region tumors), pineal tumor, medulloblastoma (embryonal tumors) and schwannoma (cranial nerve tumors of PNS) etc [17].

Brain Metastases (BM):
Among all other cranial tumors, brain metastases (brain mets) are the most common and lethargic CNS tumors also reffered to as secondary brain tumors or cerebral metastases. Most common symptoms of brain metastases include seizure, headache, mental status change, numbness and focal weakness [18-20]. BM comprises of almost 80% of all cerebral tumors and has poor prognosis. Metastatic brain tumors spread from extracranial primary cancers towards brain, like breast, skin, colon or lungs etc [21-25]. Because of the brain physiology and anatomy treatment of brain tumour is very challenging. The main hinderance in therapeutics of brain malignancies is blood brain barrier and its permeability due to which there are difficulties in targeting specific region and drug administration [26-30]. Management and treatment of metastatic brain tumors is complex and dependent on several factors, including age, performance status, number of metastases at presentation, and status of systemic disease [31,32].

The adults of both genders are affected equally by brain metastasis. Majority of cancer patients (about 80%) have more than one metastatic tumors, while 10-20% patients have only one secondary tumor in brain. Of all primary tumor patients, about 20-40% patient's tumor metastatize to brain [33,34]. Among them lung cancer (40-50%) [35,36] is most common primary tumour which is metastasized to brain followed by breast cancer (15-20%) [37,38], skin cancer (5-10%) [39,40], kidney cancer (7%) and colon cancer (4-7%) [41,42] etc as summarized in Table 2. Pimary tumors which are left untreated or poorly treated have higher frequency of secondary brain tumor development. This can leads to poor diagnosis and treatment difficulty of brain metastases [43,44].

Table 2: Primary Cancers Contribute to Brain Metastases

Primary Cancers	Percentage (%)	References
Lung Cancer	40-50%	35, 36
Breat Cancer	15-20%	37, 38
Melanoma	5-10%	39, 40
Renal Cancer	07%	41, 42
Colon Cancer	4-7%	41, 42

Epidemiology:

Brain tumor has relatively higher mortality rate with poor prognosis among all cancers in children and teenager and has very poor survival rate i.e. under 15 months if primary tumor metastatisize to 20-40% [45,46]. Globocan 2018 cancer registry data reported that cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths worldwide. Among which, Asia accounts for nearly half of new cancer cases and more than half of cancer deaths because of the poor prognosis, limited access to timely diagnosis and treatment. According to the report, breast and lung cancers have highest incidence rate in Pakistan, which are the main contributors of secondary brain metastases. Primary brain tumor is at 13th rank based on incidence rate while at 8th rank based on mortality rate in Pakistan (Globocan 2018) [47].

Aetiology:

Metastatic progression of tumors from its origin towards secondary site is explaind by the Paget's hypothesis of seed and soil theory. According to this theory, cerebral metastatsis progression and colonization depend upon the characteristics of primary tumor cells (seed) and microenvironment of brain parenchyma (soil) [48]. As mentioned above metastasis is triggered by a cascade called metastatic cascade involving several steps like; escaping of tumor cells from primary site, entering and surviving in blood stream, seeking and colonizing into a new site [49,50]. The spread of brain metastases depends on some key factors including, tissue volume and blood flow. The pattern of tumor detection in brain metastases are: 80% in cereberal hemisphere, 15% in cerebellum and 5% in brain stem [51,52].

Brain Metastatic Mechanism:

Mechanism of metastasis depends on the tissue's microenvironment. It is known that brain has unique microenvironment different from extracranial tumor's microenvironment because of its anatomy, cell type, immune environment and metabolic constraints [53,54]. Brain metastatic cascade involves following steps: first, epithelial-to-messenchymal transformation (EMT) of primary tumor cells by the loss of adhesion molecules (E-cadherin). Second critical step is to pass the blood brain barrier, cell adhesion molecules (like selectins, integrins, chemokines, heparanases and matrix metallopropeases) are the main mediator for adhesion and migration [55-59]. Once the barrier is crossed, tumor cells forms a niche in perivascular region, then either spread along this plane or induce angiogenesis for proliferation. Neo-angiogenesis induction initiates through the activation of vascular endotheial growth factor (VEGF)/hypoxia-inducible factor 1 alpha (HIF 1 alpha). Further, proliferation and invasion depends on the interaction with the brain microenvironment including astrocytes, microglia and immune system. Several genes are involved in metastatic process, specifically HBEGF, COX2 and ST6GALNAC5 genes mediate the transfer of tumor cells from blood brain barrier [60-64]. In case of brain metastases main hindrance is to cross the blood brain barrier and survive in the unique microenvironment of the central nervous system [65-68]. Molecular factors which are involved in the realm of metastatsis in cranial region are enlisted in Table 3 [51, 59, 60, 69].

Table 3: Molecular Factors Invovled in Brain Metastases

Molecular Factors Involved in Brain Metastases	
Genes	EGFR, ALK, PI3K, FGFR1, PTEN, HER2, ER, GALNT9, CCDC8, BNC1, AKT, mTOR, Cyclin D, CDK (4/6), BRAF, MAPK, RAS, PIK3CA, BRCA (1/2), TP53, ATM, CHEK2, PARP, VEGF, PTEN, PIK3CA, CDKN2A (56) TWIST1, GABA-R, GLUT-R, BCL2L1, PTEN, GSTA5, VEGFS, EGF, PD-L1, IL1, IL6, TNF, MMP1, ST6GALNAC5, HB-EGF, COX2, PIK3CA, HER2, CDK, CDH2, KIF1C, FALZ, LEF1, HOXB9, BMP4, BRAF, RAS, PLEKHA5, CPTIC (51) ST6GALNAC5, VEGF, COX2, EGFR, HK2, $Her2^{+}$, ER, αvβ3, GSTA5, BCL2L1, TWIST, TGFβ1, HGF, EGF, IL (-1, -3, -6), Myc, ATAD2, DERL1, FOXM1 (59) ST6GALNAC5, VEGF, IL-1 , GLUT-1, HK2, LAT1, GABA (69)
Proteins	Caspase 8, Stromal Cell-derived Factor 1α (SDF1/CXCL12), G-protein Coupled Receptor (CXCR4); Transmembrane Proteins i.e. occluding, caudin, junctional adhesion molecules (JAMs); Molecules releases fron astrocytes i.e. P-glycoprotein, aquaporin 4 (AQP4), Glucose-transporter (GLUT1), Connexin; Transmigration mediators i.e. Cathepsin S (CTSS), cyclooxygenase (COX2), Angiopoitin-like 4 (ANGPTL4), EGFR Ligand, Heparin-binding EGF (HB-EGF); Adhesion facilitator i.e. αN-acetylgalactosaminide α2,6 sialytransferase 5 (ST6GALNAC5); Protein Kinase B, Phosphatidylinositol-3-Kinase, Focal Adhesion Kinase; heat-shock protein i.e. α-crystallin; neuroserpin, serpin B2 (51) Cadherins (E/N), Integrins, Matrix Metalloproteeases (MMPs), Cytokines, Catenin (α/β), Neurotrophins (heparinase), Growth Factors, Enzymes, Reactive Oxygen Species (ROS), Exosomes, Interleukins (IL), Colony Stimulating Factors (CSF1), Singaling Mediator, Surface Receptors (CD95), Focal adhesion kinase (FAK) (59) Claudins, Occludins, Zona occludens, Glucose Transporters, P-glycoprotein, Chemokines, Cytokines, Inflammatory Mediators, Basic Fibroblast Growth Factor, Transforming Growth Factor-β, Interleukin-1β, TNF-α, Interferon-ɣ, CCL2, CXCL8, Prostaglandin-endoperoxide synthase 2 (COX2), MMPs, Proteases, Amyloid Precursor Protein (APP), Death Receptor 6 (DR6), Serpins,Nitricoxide Synthase (iNOS), Amino acid Transporters (EAATs), Neurotransmitters, Hexokinase, Glucose Transporter (69)
Cells	Endothelial Cells, Pericytes, Cancer-associated Fibroblasts (CAFs), Leukocytes, Macrophages, Neutrophils, Microglia, Astrocytes, Immune Cells, Mast Cells (59)
MicroRNAs	Small non-coding RNAs (59)
Epigenetic Factor	Generalized Hypomethylation of DNA and E-Cadherin Promoter (59) Methylation of GALNT9, CCDC8, BNC1 promotors (51, 60)

Blood Brain Barrier:

Neo-vascularization - formation of new blood vessels, is the salient feature of the metatstatic tumor cells to colonize into secondary site. Brain has a unique property of microvasculature i.e. smallest blood vessels arranged in a specific way to protect the cranial region and restrict the movement of macromolecules across brain. Blood brain barrier (BBB) plays an important role in brain metastasis i.e. to protect the CNS through tight junctions. But BBB also provides the shelter to metastatic cells and helps in proliferating the metastatic cells in brain. BBB is semipermeable and does not allow free movement of cellular components and solute across the brain from circulation. BBB consists of astrocytes, endothelial cells and pericytes, collectively called neurovascular unit [70-71]. Blood brain barrier is made up of microvascular endothelial cells contributing to extremely selective permeability of brain through intercellular tight junctions formation. Defects in the BBB leads to the development and spreading of many diseases of CNS including brain metastases [63,72-76]. Integrity of blood brain barrier is being compromised during the progression of tumor across brain through angiogenesis resulting a vasculature is formed called blood-tumor barrier (BTB). However, blood-tumor barrier has erratic permeablity and vigorous diffusion of molecules as compared to BBB as shown in Figure 2 [77]. Structure and functionality of BBB and BTB is heterogenous within the same tumor microenvironment and across different cancer subtypes [78-80]. BBB/BTB presence restrict the administration of chemotherapeutics to malignant lesions resulting treatment failure [81-83].

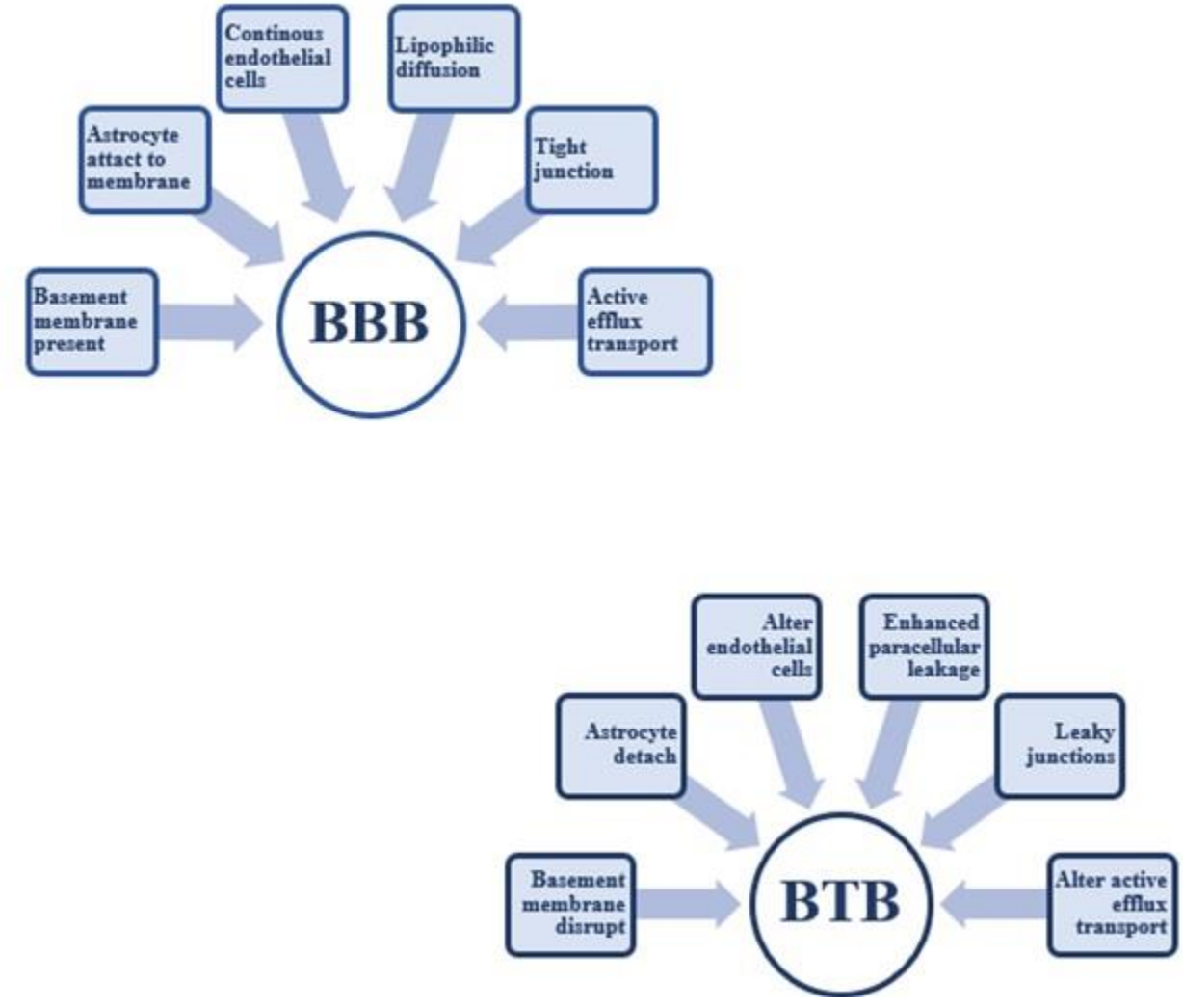

Figure 2 Blood Brain Barrier in Normal Brain and Blood Tumor Barrier in Brain Tumor (77): Tumor cells in brain alter the composition of BBB by disturbing the basement membrane, epithelial cells arrangement, astrocytes attachment, junction leakage and transport of molecules across brain

Diagnosis:

Recent advances in medical diagnostics contribute to accurate and early diagnosis of brain metastases . Moreover, controlling primary tumors through effective therapeutics increases the life span and resulting chances of primary tumor metastasis to brain is elevated. To minimize the mortality rate of brain metastases and increase the treatment efficiency only solution is the early detection. Poor prognosis of brain metastases, negligence of clinical monitoring, no precautionary measures and inefficacy of treatment increases the malignancy of tumor and thus maximizes the intracranial injury [84]. Brain lesions detects thorugh imaging techniques including magnetic resonance imaging (MRI) and computed tomography scan (CT scan). Further confirmation of brain metastases is being done by using histopathological protocols, biopsy and molecular level investigation of tumor specimen. Advancement in MRI imaging technique including magnetic resonance spectroscopy (MRS) and perfusion-weighted imaging (PWI) helps to distinguish between primary/benign tumors and secondary/metastatic tumors [85-88]. Besides these imaging technologies, investigation at molecular level i.e. genetic and epigenetic markers of brain metastases is required to ensure the correct diagnosis. For molecular diagnostics, expression of brain specific organotropism genes, DNA methylation pattern and protein biomarkers for brain metastases can be the indicators [84,89].

Therapeutic Strategies:

Now a days, different therapeutic approaches are used to increase the survival rate of brain metastases patients and their quality of life. Prevention of brain metastases is possible thorugh different strategies like shrinkage of macroscopic lesions through radiations, chemotherapeutics and targeted therapy using molecular biomarkers [90]. Treatment of brain mets is divided into two groups i.e. palliative and definitive. Palliative therapy aims to reduce the symptoms of brain mets while definitive therapy targets the tumor cells. Basic treatment of brain mets patients treatment are surgical resection, radiotherapy and chemotherapy which depend on the progression of tumor and its malignancy. These remedies comprises the definitive therapy approach which are mostly non-curative, although through palliative therapy approach chances of survival and good life of brain metastases patients will improve [91]. However, treatment approaches which will used to treat brain metastases depend on number of primary tumors and cerebral metastases, patient's physiological condition and treatment response and related factors [92].

Patients diagnosed with localized brain metastases early will be treated with surgery or sterotactic radiosurgery (SRS). Radiotherapy used for treating brain tumor is whole brain radiation therapy (WBRT). Due to the position and size of the lesions, surgical resectioning is not an option for majority of brain tumor patients. Whereas WBRT, may cause the toxicity and neurological diorders. Therefore, SRS is the most accepted and preferable option for treating intracranial tumors and oligometastases [53]. Patients with only one brain metastase will either be treated with surgery resection if possible or through SRS. However, sterotactic radiosurgery and whole brain radiations will be used to treat the patients with more than 2 brain mets. Promising results in case of increase survival rate and good neurological outcome has been obtained by combining these treatment options i.e. surgery or SRS with WBRT [93].

Treatment of brain metastases through chemotherapeutics has shown non significant results because of the BBB which does not allow the drugs to enter the brain. Also, several drugs used in chemotherapy have worsen the effect on the integrity of BBB resulting tumor cells can migrate from blood stream into the cranial region [94]. Thus, figuring out the solution to target the BBB only to pass the therapeutic agents through temporaray passage and delaying the formation of blood tumor barrier (BTB) which facilitates the tumor cells to propagate is required to overcome this problem [18, 81].

Recent studies showed that targeted therapies at molecular level and immune system are designed to treat the malignant cancers as shown in Figure 3 [95]. Molecules present on the cell surface help metastatic tumor cells to invade brain microenvironment through BBB epithelail cells are being targeted to prevent the spreading of tumor [96]. Furthermore, targeting proteases activity to degrade the extracellular matrix of tumor microenvironment will be useful to kill micro-metastatic cells and ultimately metastatic tumor proliferation is blocked [44]. Limitted options of surgeries because of brain anatomy, harmful effects of radiations and inefficacy of chemotherapy drugs on brain hamper the cerebral metastases control and management [78].

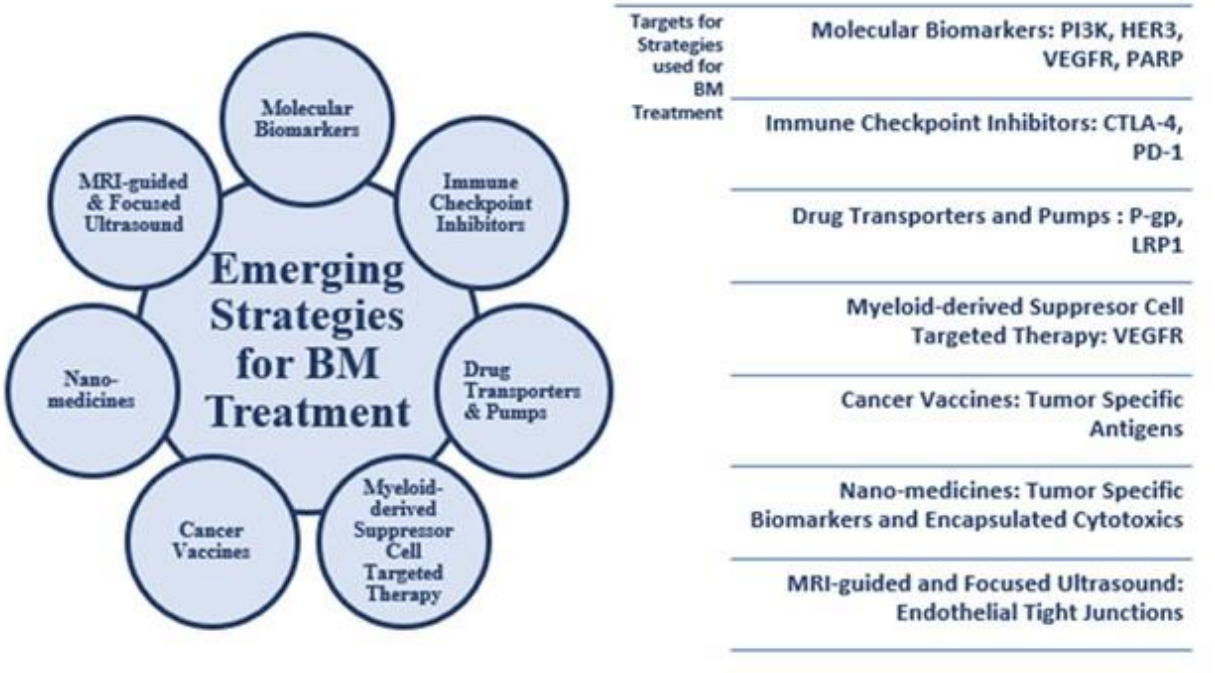

Figure 3 Emerging Strategies used for Brain Metastases Treatment **(**95): Molecular targets for treating the BM are based on the used strategy i.e. in case of molecular biomarkers the targets are Phosphoinositide 3 Kinase (PI3K), Human Epidermal Growth Factor Receptor 3 (HER3), Vascular Endothelial Growth Factor Receptor (VEGFR) & Poly(ADP-Ribose) Polymerase (PARP); targets of immune checkpoint inhibitors are Cytotoxic T-Lymphocyte-associated Protein 4 (CTLA-4) & Programmed Cell Deathe-1 (PD-1); targets of drug transporters and pumps are P-glycoprotein (P-gp) & Low-density Lipoprotein-related Protei 1 (LRP1); target of myeloid-derived suppressor cell targeted therapy is Vascular Endothelial Growth Factor Receptor (VEGFR); targets of cancer vaccines are Tumor specific Antigens; targets of nanomedicnies are Tumor specific Biomarkers & Encapsulated Cytotoxics; targets of MRI-guided & focused Ultrasound are Endothelial Tight Juntions

Concluding Remarks:

Brain metastases is the most lethal and deadly cancer among all malignant cancers with poor prognosis. Brain anataomy and blood brain barrier structure are the main hurdles in the treatment of intracranial malignanacies. In order to lower the statistics of brain metastases, improving life span and quality and reduce mortality rate new therapeutics strategies and measures will have to be developed. Additionaly, more deep understanding of brain metastatic cascade at molecular level is needed to identify the novel targets that will helpful in formulating new drugs and therapeutics strategies.

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