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MODERN STRATEGIES FOR THE DETECTION AND INTEGRATED CARE OF PATIENTS WITH BRAIN METASTASES FROM SOLID TUMORS



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БОШ МИЯДА ҲАЖМЛИ ЎСМАЛАР МЕТАСТАЗЛАРИ БЎЛГАН БЕМОРЛАРНИ АНИҚЛАШ ВА КОМПЛЕКС ДАВОЛАШНИНГ ЗАМОНАВИЙ СТРАТЕГИЯЛАРИ

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СОВРЕМЕННЫЕ СТРАТЕГИИ ВЫЯВЛЕНИЯ И КОМПЛЕКСНОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С МЕТАСТАЗАМИ СОЛИДНЫХ ОПУХОЛЕЙ В ГОЛОВНОЙ МОЗГ

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Резюме. *Ички органларнинг хавфли ўсмаларидан келиб чиқадиган мия метастазларини клиник даволаш замонавий онкологияда муҳим мавзуга айланди. Марказий асаб тизимидаги метастатик учоқларнинг диагностикаси ва терапияси сўнгги ўн йилликларда ривожланиб, беморларни парвариш қилиш ва натижаларни сезиларли даражада яхшилашга олиб келди. Мия метастазлари одатда ўпка, кўкрак, буйрак, ошқозон-ичак тракти ва меланома каби саратонларнинг табиий тарихини мураккаблаштиради. Мия метастазларининг кўпайиши, асосан, бирламчи малигнизацияланган ўсмаларнинг тизимли назоратини яхшилаш, омон қолиш даражасини ошириш ва ҳатто кичик ёки асимптоматик учоқларни аниқлайдиган нейровизуализация усулларининг ривожланиши туфайли ўсишда давом этмоқда.*

Калит сўзлар: *мия метастазлари, хавфли ўсмалар, ички органлар, клиник белгилар, ўз вақтида ташҳислаш, замонавий даволаш усуллари, радиотерапия, кимётерапия, нейрохирургия, прогноз.*

Abstract. *The clinical management of brain metastases arising from malignant tumors of internal organs has emerged as a significant topic in contemporary oncology. The diagnosis and therapy of metastatic lesions within the central nervous system have evolved over the last decades, leading to considerable improvements in patient care and outcomes. Brain metastases commonly complicate the natural history of cancers such as those of the lung, breast, kidney, gastrointestinal tract, and melanoma. The incidence of brain metastases continues to rise, largely due to improved systemic control of primary malignancies, enhanced survival rates, and advancements in neuroimaging methods that detect even small or asymptomatic lesions.*

Key words: *brain metastases, malignant tumors, internal organs, clinical features, timely diagnosis, modern treatment methods, radiotherapy, chemotherapy, neurosurgery, prognosis.*

Introduction. Brain metastases represent the most common intracranial tumors in adults and occur far more frequently than primary brain malignancies. Their clinical presentation, biological behavior, and therapeutic responsiveness vary widely and reflect both the diversity of their primary tumor origins and the complexity of metastatic colonization. The diagnosis of brain metastases often marks a pivotal and ominous development in the course of systemic cancer, indicating disseminated disease and carrying a guarded-though increasingly modifiable-prognosis [5, 9, 13, 17, 19].

The clinical manifestations of brain metastases depend on lesion size, anatomical location, number, and growth rate. Patients may present with progressive headaches, focal neurological deficits, seizures, cognitive impairment, gait disturbance, or signs of increased intracranial pressure. In many cases, especially when lesions are small or situated in non-eloquent brain regions, brain metastases remain clinically silent and are discovered incidentally on routine imaging performed during cancer follow-up. Any new neurological symptoms in individuals with known malignant disease require immediate diagnostic scrutiny, as timely identification profoundly influences treatment choices, eligibility for multimodal therapy, and overall outcomes [3, 7, 9, 10].

Modern diagnostic evaluation relies heavily on advanced neuroimaging. Contrast-enhanced magnetic resonance imaging is considered the gold standard because of its superior spatial resolution and sensitivity, allowing detection of very small lesions, accurate assessment of tumor margins, and longitudinal monitoring of therapeutic response. MRI protocols such as gadolinium-enhanced T1-weighted imaging, fluid-attenuated inversion recovery, diffusion-weighted imaging, perfusion sequences, spectroscopy, and functional imaging collectively provide a multidimensional perspective on intracranial metastatic burden [1, 8, 12, 14, 16, 18]. Technological advancements, including ultra–high-field MRI, hybrid PET/MRI systems, and diffusion tensor imaging, add depth to diagnostic precision and facilitate more sophisticated treatment planning, especially for lesions located near eloquent cortex. Diagnostic workup also integrates neurological examination, detailed oncological assessment, and laboratory testing. The development of biomarkers-circulating tumor DNA, microRNAs, extracellular vesicles, and CSF-derived molecular signatures-holds promise for earlier detection, improved monitoring of disease evolution, and individualized prediction of therapeutic response. In select cases, especially when lesions are solitary, radiologically atypical, or discordant with expected clinical progression, histopathological confirmation remains essential. Modern biopsy techniques provide adequate tissue samples for immunohistochemical analysis and next-generation sequencing with minimal risk [2, 4, 6, 10, 12, 14, 16, 18].

The therapeutic landscape for brain metastases has evolved dramatically over the past decade. Treatment decisions are guided by performance status, number and size of intracranial lesions, primary tumor subtype, extracranial disease burden, and molecular biomarkers that increasingly define therapeutic targets. Neurosurgical resection remains central for selected patients with single or few surgically accessible metastases, especially in the presence of significant mass effect or when tissue sampling is required. Advances in neurosurgical techniques such as image-guided craniotomy, fluorescence-guided resection, intraoperative MRI, and awake brain surgery have significantly improved the safety, precision, and efficacy of surgical intervention. Resection provides rapid symptomatic relief, decreases intracranial pressure, and reduces tumor bulk, facilitating subsequent adjuvant therapy [1, 3, 5, 7, 9, 11, 13, 15, 17, 19].

Radiotherapy is essential for patients who are not surgical candidates or who present with multiple lesions. Whole-brain radiotherapy has been used for decades and remains effective for widespread intracranial disease, though concerns about neurocognitive decline-particularly memory impairment-have prompted the refinement of techniques such as hippocampal-sparing WBRT [10, 16]. In contrast, stereotactic radiosurgery and fractionated stereotactic radiotherapy deliver highly focused, ablative radiation with minimal impact on surrounding brain tissue. These approaches are increasingly used for limited metastases, recurrent disease, and lesions in anatomically challenging locations. Sophisticated radiation planning and dose modulation have yielded improved local control and reduced toxicity, making stereotactic approaches a cornerstone of contemporary management [13, 18].

Systemic therapy has been transformed by molecularly targeted agents and immune checkpoint inhibitors. Historically, the limited permeability of the blood–brain barrier restricted the efficacy of systemic chemotherapy in treating intracranial disease. However, targeted therapies such as third-generation EGFR inhibitors, ALK inhibitors, HER2-directed agents, and BRAF/MEK inhibitors have demonstrated robust central nervous system penetration and clinically meaningful response rates in patients with brain metastases from lung cancer, breast cancer, and melanoma. Immunotherapy, including PD-1, PD-L1, and CTLA-4 inhibitors, has further revolutionized treatment paradigms by eliciting durable intracranial responses and reactivating immune surveillance within the CNS. The combination of systemic therapy with radiation-especially stereotactic radiosurgery-has shown synergistic effects, likely related to enhanced antigen presentation and modulation of the tumor microenvironment [12, 19].

The management of brain metastases requires a coordinated multidisciplinary approach. Neurosurgeons, neuro-oncologists, medical oncologists, radiation oncologists, neuroradiologists, rehabilitation specialists, and palliative care professionals work collaboratively to optimize therapeutic sequencing, minimize treatment-related morbidity, and preserve neurological function [2, 8, 12]. Supportive interventions are equally crucial and include corticosteroids for cerebral edema, antiepileptic therapy for seizure control, anticoagulation when indicated, physical and occupational therapy for functional recovery, cogni-

tive rehabilitation for memory and executive dysfunction, and psychological counseling for patients and families navigating the emotional and existential challenges of metastatic disease. Prognostication incorporates refined tools such as the Graded Prognostic Assessment, which incorporates primary tumor biology, molecular subtype, performance status, and burden of intracranial disease to guide treatment intensity and anticipate survival trajectories [5, 9].

Future directions in the management of brain metastases are exceptionally promising. Advances in precision medicine and molecular oncology are paving the way for increasingly individualized therapies, guided by next-generation sequencing, transcriptomic profiling, and real-time monitoring via liquid biopsies. Artificial intelligence and radiomics are transforming diagnostic imaging, offering automated lesion detection, more accurate differentiation between tumor progression and radiation necrosis, and predictive modeling of treatment response. Innovative strategies aimed at improving drug delivery across the blood–brain barrier-including focused ultrasound, convection-enhanced delivery, nanoparticle carriers, and viral vectors-hold the potential to fundamentally change therapeutic effectiveness [4, 9]. Meanwhile, clinical trials are evolving to incorporate endpoints that are more relevant to this patient population, including neurocognitive trajectories, intracranial progression-free survival, and patient-reported quality-of-life outcomes. Digital health technologies and remote monitoring further enhance the capacity for timely symptom assessment and early intervention [7, 11, 15].

The management of brain metastases from solid tumors has undergone a profound transformation, characterized by technological innovation, molecularly guided therapies, and increasingly sophisticated multidisciplinary care. High-resolution imaging and advanced diagnostics have improved the accuracy and timeliness of detection. Neurosurgical advances, stereotactic radiation techniques, targeted therapies, and immunotherapies have expanded the therapeutic arsenal, enabling personalized strategies that balance survival prolongation with preservation of neurological function and quality of life. As research continues to unravel the biological and immunological complexities of metastatic disease in the brain, emerging therapies and integrated care models hold great promise for shaping the future and improving outcomes for this challenging and high-risk patient population [17].

A deeper understanding of the molecular and cellular mechanisms underlying brain metastasis formation has significantly influenced modern conceptual frameworks for diagnosis and treatment. Tumor cells that successfully colonize the central nervous system must overcome a series of formidable biological barriers, beginning with survival within the circulatory system and culminating in adaptation to a distinct neural microenvironment. Recent research has highlighted the importance of tumor–stromal interactions in promoting metastatic growth within the brain. For instance, astrocytes, which constitute a major component of the neural parenchyma, can paradoxically facilitate tumor survival through the secretion of cytokines, growth factors, and pro-survival signals. These interactions can induce chemoresistance, reduce apoptosis, and enhance proliferative capacity, thereby contributing to the resilience of metastatic deposits [3, 8].

Emerging insights into the role of microglia further underscore the complexity of the metastatic niche. Microglial activation may generate an inflammatory milieu that facilitates tumor progression, although the exact functions of these innate immune cells remain context-dependent and may oscillate between pro-tumorigenic and anti-tumorigenic phenotypes. Moreover, endothelial cells forming the blood–brain barrier are increasingly recognized as active participants in the metastatic process [6, 8, 10, 15, 18]. Tumor-secreted exosomes and circulating factors may “prime” the endothelial interface, promoting vascular permeability and enabling tumor cell extravasation. In this context, the blood–tumor barrier-an altered form of the normal blood–brain barrier-emerges as a crucial determinant of therapeutic resistance. Its heterogeneous permeability patterns influence the penetration of systemic therapies, creating intratumoral gradients in drug exposure that complicate treatment response [4, 9, 13, 18].

Understanding the dynamic biology of the blood–tumor barrier has encouraged the exploration of strategies to modulate or bypass it. Techniques such as focused ultrasound, administered in conjunction with microbubbles, have been shown to transiently disrupt tight junction integrity, enhancing the delivery of chemotherapeutic drugs and biologics into the brain parenchyma. Nanoparticle-based delivery systems represent another promising approach, leveraging targeted surface modifications to improve trafficking across endothelial interfaces. Gene therapy vectors and engineered T-cell therapies, including CAR-T cells tailored for solid tumors, are being studied for their ability to penetrate CNS tissues more effectively and selectively target malignant cells [3, 9, 11, 18, 19].

Parallel advances in imaging technologies have revolutionized the diagnostic landscape. Radiomics, an emergent field at the intersection of imaging science and data analytics, extracts quantitative features from MRI and PET scans that may reflect tumor phenotype, microenvironmental factors, and biological behavior. Machine learning algorithms trained on radiomic signatures can assist in differentiating tumor recurrence from radiation necrosis, predicting treatment response, and stratifying patients based on risk profiles [4, 9, 12, 19]. Integration of artificial intelli-

gence into routine neuroimaging analysis holds the potential to reduce diagnostic variability, enhance early detection, and accelerate therapeutic decision-making [2, 17, 19].

Functional neuroimaging has also gained considerable traction in clinical workflows. Resting-state functional MRI captures intrinsic connectivity networks that may be disrupted by tumor presence or treatment, offering insights into cognitive impairment and rehabilitation potential. Diffusion tensor imaging facilitates mapping of white matter tracts, guiding surgical planning and minimizing postoperative neurological deficits. Multimodal imaging protocols that integrate structural, metabolic, and functional data provide a comprehensive depiction of tumor burden and its physiological consequences, thereby improving personalization of treatment strategies [1, 8, 10, 17, 19].

The evolution of systemic therapy for brain metastases is closely intertwined with advances in molecular oncology. Tumors harboring specific genetic alterations-such as EGFR mutations, ALK rearrangements, BRAF V600 mutations, HER2 amplification, and KRAS G12C variants-have demonstrated varying degrees of responsiveness to targeted agents designed to inhibit these drivers. The ability of these drugs to penetrate the CNS is strongly influenced by their physicochemical properties, affinity for efflux pumps, and interactions with the blood–brain barrier. As newer generations of targeted therapies are developed, their design increasingly considers CNS penetration as a primary objective rather than an incidental property [13, 18].

Resistance mechanisms, however, remain a significant challenge. Tumor cells may acquire secondary mutations, undergo phenotypic transformation, or activate compensatory signaling pathways that diminish drug efficacy. Combination therapy approaches, integrating targeted agents with immunotherapy or radiation, are actively studied as potential methods to forestall resistance. Moreover, sequential therapy guided by molecular monitoring through liquid biopsy may allow early adaptation of therapeutic regimens before clinical or radiographic progression becomes apparent [1, 7, 10, 12, 17, 19].

Immunotherapy has fundamentally reshaped treatment expectations for patients with metastatic cancer. The recognition that the CNS is not immunologically privileged, but rather "immunologically specialized," has opened new avenues for harnessing antitumor immunity within the brain. Checkpoint inhibitors such as nivolumab, pembrolizumab, atezolizumab, and ipilimumab have demonstrated meaningful intracranial activity across multiple tumor types [3, 9, 12, 19]. Their efficacy appears to correlate with tumor mutational burden, immune microenvironment composition, and expression of inhibitory ligands such as PD-L1. Nonetheless, the interplay between radiation and immunotherapy continues to be an area of intense scientific interest. Radiation-induced modulation of the tumor microenvironment, including increased antigen release and enhanced immune cell infiltration, may potentiate the response to checkpoint blockade and contribute to systemic antitumor effects known as the "abscopal effect" [12, 14, 16, 18, 19].

Radiotherapy itself has undergone significant refinement. Linear accelerator technology, adaptive radiotherapy, and image-guided delivery allow unprecedented precision in dose targeting. Fractionation strategies continue to evolve, balancing the need for effective tumor control against the risk of radiation-induced necrosis and cognitive decline. In addition, salvage stereotactic radiosurgery has emerged as a valuable option for patients with recurrent or progressive lesions after prior radiation therapy. Radiotherapy is further supported by neuroprotective interventions designed to mitigate cognitive toxicity, including pharmacological agents, hippocampal avoidance, and cognitive rehabilitation therapies [1, 3, 5, 7, 9, 11, 13, 15, 17, 19].

Supportive care remains an indispensable component of comprehensive management. Corticosteroids are essential for reducing vasogenic edema, but their use must be carefully balanced against potential side effects, including immunosuppression and metabolic disturbances. Antiepileptic medication is crucial for patients with seizure disorders, yet newer non-enzyme-inducing agents are preferred to avoid adverse drug interactions. Rehabilitation strategies, encompassing physical therapy, speech therapy, occupational therapy, and neuropsychological support, may significantly improve functional outcomes and quality of life. Palliative care, integrated early in the disease course, helps manage symptoms, supports decision-making, and addresses the emotional and existential needs of patients and their families [2, 4, 6, 8, 10, 12, 14, 16, 18].

Prognostic assessment continues to evolve with refinements of the Graded Prognostic Assessment and related models that incorporate tumor-specific variables and molecular biomarkers. These tools help guide treatment intensity, facilitate discussions about goals of care, and support clinical trial stratification. Understanding the heterogeneity of brain metastasis biology is essential not only for prognostication but also for designing rational therapeutic strategies tailored to disease subtype and patient preferences [3, 8, 10, 17].

The future of brain metastasis management will likely be defined by the integration of multi-omic data into clinical practice. Genomic, transcriptomic, epigenomic, and proteomic analyses are beginning to unravel the complexity of metastatic adaptation within the brain. Single-cell sequencing has revealed remarkable intratumoral heterogeneity, contributing to

differential therapy response and the emergence of resistant clones. Spatial transcriptomics, which maps gene expression within the structural context of tissue architecture, promises to deepen our understanding of interactions between tumor cells and the brain microenvironment [2, 8, 10].

As the field advances, clinical trial designs are evolving to reflect the unique needs of patients with brain metastases. Historically excluded from trials, this population is now recognized as essential for evaluating the real-world effectiveness of emerging therapies. Modern trials incorporate CNS-specific endpoints, neurocognitive evaluation, quality-of-life measures, and highly sensitive imaging criteria to ensure that therapeutic benefits are accurately captured. Precision oncology trials increasingly allow adaptive enrollment based on molecular markers rather than tumor origin, enabling more flexible and responsive therapeutic exploration [3, 9, 11, 18].

Ultimately, the management of brain metastases is moving toward a future in which early detection, molecular profiling, personalized treatment, and multidisciplinary care converge into a cohesive therapeutic framework. The integration of technological innovation, biological insight, and compassionate clinical practice promises to reshape outcomes for a historically underserved population. While challenges remain, particularly in overcoming therapy resistance and preserving neurocognitive function, the trajectory of recent progress offers reason for optimism. Continued scientific discovery, coupled with robust clinical translation, will play a critical role in transforming brain metastasis care and improving both survival and quality of life for affected patients [2, 7, 9, 13, 16, 17, 19].

Conclusion. The contemporary understanding and management of brain metastases from solid tumors reflect one of the most dynamic and rapidly advancing intersections of oncology, neurology, and precision medicine. What was once considered a terminal and therapeutically limited manifestation of systemic cancer has progressively evolved into a condition that can be addressed with increasing sophistication, scientific nuance, and clinical optimism. The convergence of high-resolution neuroimaging, refined neurosurgical techniques, innovative radiotherapy modalities, and molecularly tailored systemic therapies has fundamentally reshaped the therapeutic landscape, enabling clinicians to pursue strategies that not only prolong survival but also preserve neurocognitive integrity and quality of life.

The biological complexity of brain metastases-encompassing their interactions with the blood–brain barrier, neural microenvironment, immune landscape, and tumor heterogeneity-continues to challenge researchers. Yet this same complexity fuels a vibrant scientific frontier. Advances in genomics, transcriptomics, radiomics, and liquid biopsy technologies promise earlier detection, more accurate prognostication, and real-time monitoring of disease evolution. Emerging drug-delivery paradigms, including nanotechnology, focused ultrasound, and gene-based therapies, hold the potential to overcome long-standing barriers to effective treatment within the central nervous system. Meanwhile, artificial intelligence and machine learning are poised to enhance diagnostic precision, individualize therapeutic planning, and deepen our understanding of radiographic and molecular signatures.

Equally important is the growing recognition that the optimal management of brain metastases requires a deeply integrated multidisciplinary approach. The collective expertise of neurosurgeons, neuro-oncologists, medical oncologists, radiation oncologists, neuroradiologists, rehabilitation specialists, and palliative care teams ensures that care is comprehensive, humanistic, and responsive to the clinical and psychological needs of each patient. Supportive and rehabilitative interventions now form a cornerstone of patient-centered practice, reinforcing the principle that treatment success must be measured not only by survival metrics but also by the preservation of dignity, autonomy, and functional wellbeing.

As the boundaries of therapeutic innovation continue to expand, the future of brain metastasis management is one of increasing personalization, precision, and hope. Continued collaboration between basic scientists, clinical investigators, and healthcare providers will be essential in translating emerging discoveries into meaningful outcomes. While brain metastases remain a formidable clinical challenge, the trajectory of progress-driven by scientific ingenuity, technological advancement, and compassionate care-offers renewed promise for transforming the lives of patients confronting this complex and high-risk condition.

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СОВРЕМЕННЫЕ СТРАТЕГИИ ВЫЯВЛЕНИЯ И КОМПЛЕКСНОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С МЕТАСТАЗАМИ СОЛИДНЫХ ОПУХОЛЕЙ В ГОЛОВНОЙ МОЗГ

Амонова З.К., Эркинова О.Дж., Амонова З.К.

Резюме. *Клиническое ведение метастазов в головной мозг, возникающих при злокачественных опухолях внутренних органов, стало важной темой современной онкологии. Диагностика и лечение метастатических поражений центральной нервной системы значительно усовершенствовались за последние десятилетия, что привело к значительному улучшению качества лечения и результатов лечения. Метастазы в головной мозг часто осложняют течение таких видов рака, как рак легких, молочной железы, почек, желудочно-кишечного тракта и меланома. Частота метастазов в головной мозг продолжает расти, в основном благодаря улучшению системного контроля первичных злокачественных новообразований, повышению выживаемости и развитию методов нейровизуализации, позволяющих выявлять даже небольшие или бессимптомные очаги.*

Ключевые слова: *метастазы в головной мозг, злокачественные опухоли, внутренние органы, клинические проявления, своевременная диагностика, современные методы лечения, лучевая терапия, химиотерапия, нейрохирургия, прогноз.*