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TREATMENT STRATEGIES AND PROGNOSTIC MODELING IN METASTATIC BRAIN TUMORS: CLINICAL AND TRANSLATIONAL PERSPECTIVES

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Abstract. Metastatic brain tumors represent a major challenge in contemporary neuro-oncology due to their high incidence, clinical heterogeneity, and poor prognosis. Advances in neurosurgical techniques, radiotherapy, stereotactic radiosurgery, and systemic chemotherapy have improved local tumor control and neurological outcomes; however, overall survival remains primarily dependent on extracranial disease progression. This review analyzes current therapeutic modalities and prognostic factors for metastatic brain tumors, with emphasis on multimodal treatment strategies and predictive modeling. Key prognostic determinants include patient age, performance status, number and localization of metastases, primary tumor histology, and systemic tumor burden. The development of integrated prognostic algorithms incorporating clinical, radiological, and molecular biomarkers is essential for personalized treatment planning and improved clinical outcomes.

Keywords: brain metastases, neuro-oncology, stereotactic radiosurgery, whole-brain radiotherapy, chemotherapy, prognostic factors, survival prediction.

СТРАТЕГИИ ЛЕЧЕНИЯ И ПРОГНОЗИРОВАНИЯ ИСХОДОВ ПРИ МЕТАСТАТИЧЕСКИХ ОПУХОЛЯХ ГОЛОВНОГО МОЗГА: КЛИНИКО-ТРАНСЛЯЦИОННЫЙ ПОДХОД

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Аннотация. Метастатические опухоли головного мозга представляют одну из наиболее сложных проблем современной нейроонкологии вследствие высокой распространенности, клинической гетерогенности и неблагоприятного прогноза. Современные методы хирургического лечения, лучевой терапии, стереотаксической радиохирургии и системной химиотерапии позволяют улучшить локальный контроль опухоли и неврологические исходы, однако общая выживаемость пациентов в значительной степени зависит от прогрессирования экстракраниального опухолевого процесса. В данном обзоре анализируются современные терапевтические подходы и прогностические факторы при метастатических опухолях головного мозга с акцентом на мультимодальные стратегии лечения и методы прогнозирования исходов. Основными прогностическими детерминантами являются возраст пациента, функциональный статус, количество и локализация метастазов, гистологический тип первичной опухоли и системная опухолевая нагрузка. Разработка интегрированных прогностических алгоритмов, основанных на клинических, радиологических и молекулярных биомаркерах, является ключевым направлением персонализированной нейроонкологии.

Ключевые слова: метастазы головного мозга, нейроонкология, стереотаксическая радиохирургия, тотальное облучение мозга, химиотерапия, прогностические факторы, прогноз выживаемости.

MIYADA METASTATIK O‘SMALARNI DAVOLASH VA NATIJALARNI PROGNOZLASH STRATEGIYALARI: KLINIK VA TRANSLATSION YONDASHUV

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Annotatsiya. Miyada metastatik o‘smalar zamonaviy neyroonkologiyada eng murakkab muammolardan biri bo‘lib, ularning yuqori uchrashi, klinik heterogenligi va yomon prognozi bilan tavsiflanadi. Zamonaviy jarrohlik, nurlanish terapiyasi, stereotaksik radioxirurgiya va tizimli kimyoterapiya usullari lokal o‘sma nazoratini va nevrologik holatni yaxshilaydi, biroq umumiy yashash ko‘rsatkichlari asosan ekstrakranial o‘sma jarayonining rivojlanishiga bog‘liq. Ushbu sharhda metastatik miya o‘smalarini davolashning zamonaviy usullari va prognozlovchi omillar tahlil qilinadi hamda multimodal terapiya strategiyalari va natijalarni bashoratlash modellari muhokama qilinadi. Asosiy prognostik determinantlar bemorning yoshi, funksional holati, metastazlar soni va joylashuvi, birlamchi o‘smaning gistologik turi hamda tizimli o‘sma yuklamasidir. Klinik, radiologik va molekulyar biomarkerlarga asoslangan integratsiyalashgan prognostik algoritmlarni ishlab chiqish shaxsiylashtirilgan neyroonkologiya uchun muhim ahamiyatga ega.

Kalit so‘zlar: miya metastazlari, neyroonkologiya, stereotaksik radioxirurgiya, umumiy miya nurlanishi, kimyoterapiya, prognostik omillar, yashash prognozi

Introduction. Metastatic brain tumors represent one of the most complex and clinically challenging entities in modern neuro-oncology. The increasing incidence of systemic malignancies and improvements in oncological survival have led to a rising prevalence of secondary intracranial metastatic lesions, which now exceed primary brain tumors in many epidemiological cohorts. Metastatic brain tumors are diagnosed in approximately 15–35% of patients with systemic cancer during life, while an additional significant proportion remains clinically silent and is detected only postmortem. Lung carcinoma, breast cancer, melanoma, and malignancies of the gastrointestinal and genitourinary tracts are among the most frequent primary sources of cerebral metastases [1-3]. The biological mechanisms underlying cerebral metastasis involve hematogenous dissemination, disruption of the blood–brain barrier, tumor cell extravasation, and adaptation to the neural microenvironment, which collectively contribute to tumor heterogeneity and therapeutic resistance. Advances in neuroimaging, including magnetic resonance imaging and computed tomography, have substantially improved early detection rates and contributed to the apparent epidemiological increase in metastatic brain lesions [4,5]. Despite significant progress in neurosurgical techniques, radiation oncology, and systemic therapy, the prognosis for patients with metastatic brain tumors remains poor, with untreated survival ranging from one to two months, highlighting the urgent need for optimized therapeutic strategies and predictive models. Modern neuro-oncology increasingly focuses on personalized therapeutic decision-making based on prognostic factors such as patient age, functional status, tumor burden, extracranial disease control, and molecular tumor characteristics [6,7]. This article aims to provide an updated scientific synthesis of therapeutic modalities for metastatic brain tumors, structured according to the IMRAD framework, and to discuss prognostic modeling approaches that may improve clinical outcomes and individualized treatment strategies.

Materials and Methods. This work represents an analytical narrative review based on previously published randomized controlled trials, retrospective clinical studies, and neuro-oncological literature addressing the management of metastatic brain tumors. The primary source material includes historical and contemporary studies on neurosurgical resection, whole-brain radiotherapy, stereotactic radiosurgery, interstitial brachytherapy, and systemic chemotherapy. Prognostic factors and survival outcomes were extracted from multicenter trials and large clinical cohorts to construct a conceptual framework for treatment stratification. Clinical endpoints

evaluated across the literature include overall survival, progression-free survival, neurological functional status, local tumor control, recurrence rates, and treatment-related morbidity. Prognostic determinants were assessed using multivariate statistical analyses reported in prior studies, including performance indices such as the Karnofsky Performance Status and systemic disease burden. The methodological approach integrates translational oncology perspectives, emphasizing biological and clinical heterogeneity in metastatic brain disease.

Results. Surgical resection remains a cornerstone in the management of solitary brain metastases, particularly in patients with controlled systemic disease and favorable functional status. Randomized clinical trials have demonstrated that surgical excision combined with adjuvant radiotherapy significantly improves survival and quality of life compared with radiotherapy alone [8]. Surgical intervention provides rapid relief from intracranial hypertension, neurological deficits, and mass effect while enabling histopathological verification and molecular characterization of the metastatic lesion. Multicenter randomized studies have reported median survival times ranging from 10 to 12 months following combined surgery and radiotherapy, compared with approximately 6 months with radiotherapy alone. Favorable prognostic factors include younger age, absence of extracranial tumor progression, long disease-free intervals, and complete resection of the metastatic lesion. Advanced microsurgical techniques, neuronavigation, intraoperative imaging, and laser thermodestruction have further improved surgical radicality while minimizing neurological morbidity [9-11].

The role of surgery in patients with multiple brain metastases remains controversial. Traditionally, surgical intervention was reserved for solitary lesions; however, recent evidence suggests that aggressive surgical resection of all accessible metastases may yield survival outcomes comparable to those observed in solitary metastasis cohorts. Complete resection of multiple lesions has been associated with median survival times of up to 14 months, whereas incomplete resection results in significantly shorter survival [12,13]. The selection of surgical candidates requires careful assessment of lesion accessibility, functional brain mapping, patient performance status, and systemic disease control. Advances in minimally invasive neurosurgery and endoscopic techniques have expanded the indications for surgical intervention in multifocal metastatic disease.

Recurrent metastatic brain tumors pose a major therapeutic challenge, with recurrence rates after surgical resection ranging from 31% to 48%. Repeat craniotomy has been shown to improve neurological outcomes and extend survival in selected patients. Median survival after reoperation ranges from 9 to 11.5 months, with neurological improvement reported in up to 75% of patients [14,15]. Negative prognostic factors for reoperation include low Karnofsky Performance Status, early recurrence within four months, progressive systemic disease, melanoma or breast cancer histology, and older age [16]. Reoperative neurosurgery requires careful risk-benefit assessment due to increased perioperative morbidity and the cumulative burden of systemic cancer therapy.

Whole-brain radiotherapy (WBRT) has been a standard therapeutic modality for metastatic brain tumors for several decades. WBRT improves median survival from approximately 3 months to 6 months and achieves neurological symptom improvement in up to 85% of patients. Radiotherapy is particularly effective for radiosensitive tumors such as small-cell lung carcinoma and germ cell tumors [17,18]. Clinical trials conducted by the Radiation Therapy Oncology Group have demonstrated comparable survival outcomes across different fractionation schedules, suggesting that treatment regimens should be individualized based on patient condition and prognosis rather than standardized dose escalation [19]. Hyperfractionated and accelerated hyperfractionated radiotherapy protocols have shown modest survival benefits but have not consistently demonstrated superiority over conventional regimens [20]. Postoperative radiotherapy significantly reduces local and regional recurrence rates but does not consistently improve overall survival, indicating that systemic disease progression remains the dominant determinant of mortality [21].

Stereotactic radiosurgery (SRS) represents a highly precise noninvasive therapeutic modality that delivers high-dose focal radiation to metastatic lesions while sparing surrounding brain tissue. Techniques include Gamma Knife radiosurgery and linear accelerator-based systems. Local tumor control rates range from 73% to 94%, with radiation necrosis occurring in approximately 5–10% of

cases [22]. Large retrospective cohorts have reported median survival times of approximately 9.4 months following SRS, with improved survival associated with younger age and absence of systemic disease progression. SRS offers several advantages over surgery, including outpatient treatment, reduced morbidity, and cost-effectiveness. However, limitations include tumor size greater than 3 cm, cystic lesions, hydrocephalus, and severe intracranial hypertension [23,24]. Combination therapy with WBRT and SRS improves local control but does not consistently increase survival, reinforcing the importance of systemic disease management in determining patient outcomes.

Interstitial brachytherapy involves stereotactic implantation of radioactive isotopes directly into tumor tissue. Median survival times reported in uncontrolled studies range from 9 to 18.3 months, suggesting a potential role for brachytherapy in selected cases with recurrent or deep-seated lesions [25]. However, this modality remains limited due to technical complexity and lack of large randomized trials.

Systemic chemotherapy plays a critical role in managing metastatic brain tumors, particularly for chemosensitive malignancies such as breast cancer, small-cell lung cancer, ovarian cancer, and germ cell tumors [26]. Chemotherapy stabilizes systemic disease and indirectly improves survival by preventing further metastatic dissemination. Studies have demonstrated objective response rates of up to 50% in breast cancer brain metastases treated with combination chemotherapy regimens, with median survival ranging from 7 to 10 months depending on response. Small-cell lung cancer metastases show response rates up to 76% with platinum-based chemotherapy, reflecting the systemic chemosensitivity of this tumor type [27,28]. Temozolomide has emerged as a promising agent for brain metastases due to its ability to penetrate the blood–brain barrier. Combined chemoradiotherapy regimens have demonstrated higher response rates compared to radiotherapy alone, with complete remission achieved in up to 38% of patients [29].

The prognosis of metastatic brain tumors depends on multiple clinical and biological factors. Key prognostic variables include patient age, Karnofsky Performance Status, primary tumor histology, number and location of brain metastases, extracranial disease control, and interval between primary cancer diagnosis and brain metastasis detection [30]. Multivariate analyses have identified systemic tumor burden and functional status as the most significant predictors of survival. Younger patients with controlled systemic disease and solitary metastases have significantly better outcomes compared with older patients with disseminated systemic malignancy and multiple intracranial lesions [31]. Despite extensive research, no universally accepted prognostic scoring system has been established that integrates clinical, radiological, and molecular biomarkers into a unified predictive algorithm. The development of such models remains a critical unmet need in neuro-oncology.

Discussion. The management of metastatic brain tumors requires a multidisciplinary approach integrating neurosurgery, radiation oncology, medical oncology, neuroimaging, and supportive care. The evolution of neuro-oncological therapeutics has transformed metastatic brain disease from a purely palliative condition to a potentially controllable chronic disease in selected patient populations. Surgical resection remains the gold standard for solitary metastases with mass effect and neurological deficits, while stereotactic radiosurgery provides a minimally invasive alternative for small and deep-seated lesions. Whole-brain radiotherapy continues to play a role in patients with multiple metastases, although concerns regarding neurocognitive toxicity have stimulated interest in hippocampal-sparing techniques and targeted radiotherapy strategies. Systemic therapy has undergone a paradigm shift with the introduction of targeted therapies and immunotherapy, although traditional cytotoxic chemotherapy remains relevant for chemosensitive tumors. The blood–brain barrier continues to represent a significant pharmacological challenge, limiting the efficacy of many systemic agents. From a prognostic perspective, the heterogeneity of metastatic brain disease underscores the necessity for individualized treatment planning. Traditional prognostic indices based on clinical parameters should be complemented by molecular profiling, radiomic biomarkers, and artificial intelligence-based predictive models. Future research should focus on integrating genomic, transcriptomic, and imaging data to develop precision neuro-oncology frameworks. The persistence of high recurrence rates and limited survival highlights the

need for novel therapeutic strategies, including immunotherapy, gene therapy, nanomedicine-based drug delivery, and personalized surgical planning using 3D modeling and neuro-navigation technologies.

Conclusion. Metastatic brain tumors remain one of the most challenging problems in contemporary neuro-oncology, characterized by high morbidity, limited survival, and complex therapeutic decision-making. Surgical resection, radiotherapy, stereotactic radiosurgery, brachytherapy, and systemic chemotherapy each play complementary roles in multidisciplinary treatment strategies. Prognostic outcomes depend primarily on systemic disease control, patient functional status, and tumor burden, while local intracranial therapies mainly improve neurological outcomes and quality of life. Despite significant advances in therapeutic modalities, the absence of integrated prognostic algorithms and personalized treatment frameworks represents a critical gap in clinical neuro-oncology. Future research should prioritize the development of predictive models incorporating clinical, molecular, and radiomic data to optimize therapeutic strategies and improve survival outcomes in patients with metastatic brain tumors.

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