

HER2-positive intracranial metastases treatment

- Stereotactic radiosurgery for HER2-positive breast cancer brain metastases: prognostic factors and the evolving role of anti-HER2 therapies
- Advances in Targeted Therapy for Brain Metastases in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer: A Focus on ADCs and TKIs
- Efficacy and safety of trastuzumab deruxtecan in HER2-positive breast cancer patients with brain metastases after failure of pyrotinib-based therapy
- Breast Cancer Brain Metastases: A Neurosurgical Point of View From a Single-Center Experience
- Excellent Response to Trastuzumab Deruxtecan of a Large Medullary Metastasis from Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: A Case Report
- Factors associated with local failure after stereotactic radiation to the surgical bed of patients with a single breast cancer metastasis
- Treatment Outcome of Brain Metastases from Breast Cancer Following Gamma Knife Radiosurgery: A Retrospective Study in Vietnam
- Efficacy of disitamab vedotin (RC48) for previously treated human epidermal growth factor receptor 2-positive breast cancer with symptomatic brain metastases: a case report and review of the literature

1. Localized Therapy

Surgery

- Indicated for large, symptomatic, or surgically accessible metastases.
- Improves neurological symptoms and reduces tumor burden.

Stereotactic Radiosurgery (SRS)

- Preferred for patients with ≤ 4 **metastases** or selected cases with more.
- Delivers high-dose radiation precisely, sparing normal tissue.
- Can be combined with systemic therapy.

Whole-Brain Radiation Therapy (WBRT)

- Used for multiple metastases but less favored due to neurotoxicity.
- Consider **hippocampal-sparing WBRT with memantine** to reduce cognitive decline.

2. Systemic Therapy

HER2-Targeted Therapy Options

- **Tucatinib + Trastuzumab + Capecitabine (HER2CLIMB Trial)**
 - Tucatinib is a selective HER2 TKI with CNS penetration.
 - Improves **progression-free survival (PFS) and overall survival (OS)**.
 - **Trastuzumab Deruxtecan (T-DXd, Enhertu)**
 - Antibody-drug conjugate with high intracranial activity.
 - Effective even in progressive brain metastases.
 - **Lapatinib + Capecitabine**
 - Historically used, but less effective than tucatinib.
 - Option for patients who cannot access newer agents.
 - **Pyrotinib + Capecitabine** (China-based studies)
 - Pan-HER TKI with intracranial efficacy.
 - Limited global availability.
 - **Neratinib + Capecitabine**
 - TKI with CNS penetration.
 - Consider in **progressive brain metastases** after other TKIs.
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3. Combination Approaches

- **Radiation + HER2-targeted therapy** (e.g., **SRS + tucatinib-based regimen**).
 - **Immunotherapy** (e.g., **pembrolizumab**) under investigation for synergy with HER2-directed agents.
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4. Novel and Emerging Strategies

- **Intrathecal HER2-directed therapy** (experimental, for leptomeningeal disease).
 - **Chimeric antigen receptor (CAR) T-cell therapy targeting HER2** (preclinical/early trials).
 - **Blood-brain barrier modulation strategies** to improve drug delivery.
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Conclusion

A **multimodal approach** combining systemic therapy (**especially tucatinib-based regimens**), **SRS**, and **possibly surgery** provides the best outcomes. **Trastuzumab deruxtecan** is a promising option for progressive disease. Clinical trials continue to refine treatment strategies.

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