HER2-positive intracranial metastases

- Stereotactic radiosurgery for HER2-positive breast cancer brain metastases: prognostic factors and the evolving role of anti-HER2 therapies
- Gene signatures associated with brain-topical proliferative activity in breast cancer
- 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

Epidemiology

Epidemiology of HER2-Positive Intracranial Metastases

HER2-positive intracranial metastases are a significant complication in **HER2-positive breast cancer (HER2+ BC)**, with increasing incidence due to **longer survival** and improved systemic treatments.

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1. Incidence & Prevalence - **Overall Risk**:

1. **30–50% of HER2+ breast cancer patients** will develop **brain metastases (BM)** at some point in their disease course.

- **Higher Risk in Advanced Disease**:

1. Among **metastatic HER2+ BC patients**, brain metastases occur in **up to 50%**.

- **Leptomeningeal Disease (LMD) Risk**:

1. **5–10% of HER2+ BC patients with CNS involvement** develop leptomeningeal metastases, a **poor prognostic factor**.

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2. Comparison to Other Breast Cancer Subtypes - **HER2+ BC has a higher rate of brain metastases** compared to hormone receptor-positive/HER2-negative and triple-negative breast cancer (TNBC). - **CNS metastases by subtype**:

1. HER2-positive: **30-50%**
2. Triple-negative: **40-50%** (similar risk but shorter survival)

3. Hormone receptor-positive/HER2-negative: **10-15%**

- HER2+ brain metastases **occur later** in the disease course compared to TNBC but **earlier** than in HR+/HER2-negative disease.

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3. Risk Factors for Developing Brain Metastases in HER2+ BC - **Young Age**:

1. Patients **<50 years old** have a higher risk of CNS involvement.

- **Visceral Metastases (Lung, Liver)**:

1. Higher burden of **extracranial disease** is associated with increased CNS spread.

- **Prolonged Survival with Systemic Therapy**:

1. Improved HER2-targeted treatments (**trastuzumab, pertuzumab, T-DXd, tucatinib**) have extended systemic disease control, allowing **brain metastases to emerge** as a common site of progression.

- **Blood-Brain Barrier (BBB) Challenge**:

1. Many HER2-targeted therapies have **limited CNS penetration**, allowing **brain metastases to develop despite systemic disease control**.

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4. Median Time to Brain Metastases Development - **Typically 2–3 years** after initial **HER2+ breast cancer diagnosis**. - **After systemic metastases**: Brain metastases may develop **within 12-24 months**.

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5. Survival Outcomes - **HER2+ Brain Metastases Median Survival**:

1. **9–24 months**, depending on treatment response.

- **Leptomeningeal Disease (LMD) Survival**:

1. **3–6 months**, significantly worse prognosis.

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Key Trends - **Increasing incidence** due to prolonged survival with HER2-targeted therapies. - **More effective CNS-active treatments** (tucatinib, trastuzumab-deruxtecan) are improving outcomes. - **Brain metastases often occur in controlled extracranial disease**, highlighting the need for **early CNS screening** in metastatic HER2+ patients.

Conclusion HER2-positive intracranial metastases remain a **major clinical challenge**, but advances in **targeted therapies and radiotherapy** have improved survival. Early detection and **CNS-specific treatment strategies** are essential for optimizing outcomes.

Classification

see HER2-positive brain metastases.

Classification of HER2-Positive Intracranial Metastases HER2-positive intracranial metastases can be classified based on **disease extent, response to treatment, and location within the central nervous system (CNS).** The classification helps guide treatment decisions and prognosis assessment.

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1. Based on Number and Extent of Metastases - **Oligometastatic Disease**:

1. **≤4 brain metastases** (typically ≤3 cm in size)
2. Better prognosis, suitable for **stereotactic radiosurgery (SRS)**

- **Multifocal Brain Metastases**:

1. **>4 brain metastases**
2. Often requires **systemic therapy + whole-brain radiotherapy (WBRT)** or **SRS if feasible**

- **Leptomeningeal Disease (LMD)**:

1. Tumor cells infiltrate the cerebrospinal fluid (CSF) and meninges
2. **Worst prognosis**, often requiring **intrathecal therapy (trastuzumab, chemotherapy), WBRT, or palliative care**

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2. Based on Response to HER2-Targeted Therapies - **Therapy-Responsive Metastases**:

1. Controlled with **trastuzumab, tucatinib, trastuzumab-deruxtecan (T-DXd), or neratinib**
2. Considered stable disease, manageable with maintenance therapy

- **Progressive CNS Metastases**:

1. Worsening disease despite targeted therapy
2. May require **radiotherapy, switching systemic therapy, or experimental options**

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3. Based on Radiological and Anatomical Features - **Parenchymal Brain Metastases**:

1. Located within brain tissue (most common, ~30-50% of HER2+ breast cancer patients develop these)

- **Leptomeningeal Metastases**:

1. Spread within the **meninges and cerebrospinal fluid**

- **Combined Parenchymal & Leptomeningeal Disease**:

1. Poor prognosis, often requiring a multimodal approach

- **Brainstem/Cerebellar Metastases**:

1. More challenging due to **critical location**
2. Requires **stereotactic approaches** to minimize neurological damage

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4. Based on Clinical Presentation - **Asymptomatic Metastases**:

1. Detected via screening MRI, common in HER2+ breast cancer

- **Symptomatic Metastases**:

1. Neurological deficits (headache, seizures, cognitive decline, ataxia, focal weakness)
2. Requires **urgent intervention (radiation, surgery, or systemic therapy adjustment)**

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Clinical Implications of Classification - **Oligometastatic and therapy-responsive disease → Better prognosis**, more aggressive interventions possible - **Multifocal or leptomeningeal disease** → Worse prognosis, often palliative treatment required - **Parenchymal vs. leptomeningeal involvement** → Different treatment approaches (WBRT/SRS vs. intrathecal therapy)

This classification helps in selecting **personalized treatment strategies** to optimize survival and quality of life in HER2-positive breast cancer patients with CNS involvement.

Treatment

HER2-positive intracranial metastases treatment

Prognosis

The prognosis for **HER2-positive intracranial metastases** varies depending on several factors, including the number and size of metastases, treatment response, and extracranial disease. However, compared to **HER2-negative** cases, patients with HER2-positive breast cancer brain metastases (BCBM) tend to have **a better prognosis** due to advances in targeted therapies.

Key Prognostic Factors

1. **Systemic Disease Control**: Patients with well-controlled extracranial disease tend to survive better.

2. **Number of Brain Metastases**: Fewer metastases (<4) generally correlate with better prognosis.

3. **Performance Status**: Higher Karnofsky Performance Status (KPS) is associated with improved survival.

4. **Treatment Response**: Sensitivity to **HER2-targeted therapies** (trastuzumab, tucatinib, and neratinib) significantly improves outcomes.

5. **Radiotherapy Approach**: Stereotactic radiosurgery (SRS) is associated with longer survival compared to whole-brain radiotherapy (WBRT).

6. **Presence of Leptomeningeal Disease**: This worsens prognosis significantly.

Survival Outcomes

- **Median overall survival (OS)**: Ranges between **9 to 24 months**, with some long-term survivors in the era of modern HER2-targeted therapies. - **Better prognosis with**:

1. **Tucatinib-based regimens (HER2CLIMB trial)**: OS ~ 18 months for patients with active brain metastases.
2. **SRS + systemic therapy**: OS > 15 months in some studies.
3. **Combination of trastuzumab-deruxtecan (T-DXd) and SRS**: Promising results in recent trials.

While HER2-positive intracranial metastases remain a serious complication, targeted therapies and advanced radiation techniques have **significantly improved survival** and quality of life in recent years. Prognosis is **better than HER2-negative cases**, especially in patients with limited brain metastases and controlled extracranial disease.

Case report

A 64-year-old female patient was diagnosed with HER2-positive invasive ductal carcinoma of the right breast. She achieved a complete pathological response following neoadjuvant chemotherapy, mastectomy, and adjuvant trastuzumab. However, two years after treatment completion, she developed axillary lymphadenopathy and a solitary cerebellar metastasis. This case highlights the importance of long-term follow-up and the role of targeted therapies in HER2-positive breast cancer with central nervous system involvement.

- **Medical History:** Chronic bronchitis, former smoker, previous mammoplasty, inguinal hernia repair, and urinary incontinence surgery.

- **Family History:** Mother had ovarian cancer; father had laryngeal and lung cancer.

2.2 Initial Diagnosis and Treatment

- **Primary Tumor:** Right breast, 9 cm lesion with microcalcifications extending to the nipple. - **Biopsy (Core Needle Biopsy, 14G):**

1. Invasive ductal carcinoma, Grade II (2,3,2).
2. **Immunohistochemistry:**
    1. ER: 0% (negative)

2. PR: 0% (negative)
3. HER2: 3+ (positive)
4. Ki-67: 25% (high proliferation index)

- **Neoadjuvant Chemotherapy:** CTHP (Carboplatin, Docetaxel, Trastuzumab, Pertuzumab) for 6 cycles, achieving a complete pathological response (pCR, RCB 0).

- **Surgery (12/2022):** Right mastectomy with sentinel lymph node biopsy (negative for malignancy, ypT0 snN0).

- **Adjuvant Therapy:** Trastuzumab SC, completed.

- **Reconstructive Surgery:** Expander placement (May 2024), final implant replacement (October 2024).

2.3 Follow-Up and Recurrence - **11/2023:** Mammogram of the left breast (BIRADS 2, no evidence of malignancy). - **02/2025:** The CT scan showed suspicious left axillary lymphadenopathy (1.4 cm) but no distant metastases. - **03/2025:** Brain MRI revealed a solitary **3.8 x 3.1 x 3.6 cm cerebellar lesion** with perilesional edema and partial compression of the 4th ventricle, suggesting metastasis.

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3. Discussion This case illustrates the natural course of HER2-positive breast cancer with an initial favorable response to neoadjuvant chemotherapy but late recurrence in the CNS.

- **CNS Metastases in HER2-Positive Disease:** The brain is a common metastatic site due to the inability of trastuzumab to penetrate the blood-brain barrier effectively. - **Management Considerations:**

1. The axillary lymphadenopathy requires biopsy confirmation and, if positive, consideration of additional systemic or local therapy.
2. The cerebellar metastasis may be amenable to **stereotactic radiosurgery (SRS) or surgical resection**, depending on symptoms and tumor accessibility.
3. **Tucatinib-based therapy** (Tucatinib + Trastuzumab + Capecitabine) should be considered, given its proven CNS efficacy in HER2-positive patients.

This case underscores the importance of long-term surveillance in HER2-positive breast cancer patients and highlights the need for personalized treatment approaches for CNS metastases. The patient’s management will require a multidisciplinary approach, including oncology, neurosurgery, and radiation oncology teams.

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5. Future Directions - **Further Imaging:** Serial MRI scans to monitor disease progression. - **Biopsy of Axillary Adenopathy:** To confirm metastatic involvement. - **CNS-Directed Therapy:** Consider SRS, surgery, or targeted systemic treatment. - **Clinical Trial Enrollment:** Evaluation for novel HER2-directed CNS therapies.