Key findings of glioblastoma metastasis

Here is a summary of the **key findings and insights** from *"Unraveling the Molecular Basis of Extracranial Glioblastoma Metastasis: A Case Report and Literature Review"* (Manzano-Benito et al., 2025) PubMed +2 Wiley Online Library +2

Context & Rationale

- Glioblastoma (GB), IDH-wildtype, is the most frequent primary malignant brain tumor in adults, and despite aggressive therapies, the prognosis remains poor (median survival ~15–18 months) PubMed +1 .
- Extracranial (i.e. beyond the central nervous system) metastases from GB are exceedingly rare, but reports are becoming more frequent — likely because patients are living longer, being followed more carefully, and molecular/genomic tools are improving PubMed +2 Wiley Online Library +2 .
- The molecular mechanisms that allow GB to escape the CNS and metastasize remain poorly understood; it is unclear whether metastatic GBs carry distinct molecular signatures or follow particular clinical patterns. The authors aim to shed light on this via a detailed case + review. Wiley Online Library +1

Case Report: Clinical and Molecular Findings

Clinical Course & Metastatic Sites

- The index case is a woman in her early 40s diagnosed with an IDH-wt glioblastoma. PubMed +1
- After initial therapy, she developed extracranial metastases to the **liver** and **spine** (i.e. bone/vertebral) sites. Wiley Online Library +2 PubMed +2
- The authors document the timing, imaging, pathology, and molecular evolution through diagnosis, recurrence, and metastasis stages. Wiley Online Library +1

Molecular & Genomic Observations

- At initial diagnosis and in subsequent metastatic sites, **TP53 mutations** were recurrent, suggesting that TP53 alterations may play a role in the metastatic dissemination. PubMed +1
- The authors observed **molecular heterogeneity** among clones: i.e. subclonal diversification as the tumor evolves from primary brain tumor to recurrence and metastasis. PubMed +1

- They note that a subgroup of younger female GB patients who harbor **PTEN alterations** at diagnosis seem to later acquire additional TP53 clonal changes at recurrence/metastasis. This suggests a pattern in which PTEN loss may predispose to further clonal evolution contributing to extracranial spread. PubMed +1

Broader Insights from Literature Review & Synthesis

From their review and analysis, the authors make several broader observations and hypotheses about extracranial GB metastasis:

1. **Frequent TP53 alterations in metastatic cases**
   Multiple reported GBs with extracranial spread show TP53 mutations, underscoring that TP53 alteration may be a recurring feature in metastasizing glioblastomas. PubMed +1

2. **Clonal heterogeneity and evolution**
   Metastatic lesions may derive from subclones present in the primary tumor. The metastatic clones often reflect genetic divergence (i.e. new mutations) acquired during tumor progression, rather than being exact copies of the original tumor. PubMed +1

3. **PTEN alteration as a potential predisposition**
   Some cases (especially younger females) present with PTEN alterations in the primary tumor, which may predispose to later acquisition of TP53 mutations and metastatic evolution. PubMed +1

4. **Mechanistic pathways of metastasis (hypotheses)**
   The authors overview possible routes and mechanisms by which GB cells might escape the CNS and seed extracranially, including:

   - **Hematogenous dissemination** (via blood vessels) after breach of blood–brain barrier or invasion into venous structures
   - **Surgical disruption**: The idea that surgery, biopsy, or craniotomy may provide "escape routes" (e.g. via emissary veins or breakdown of physical barriers)
   - **Glymphatic / lymphatic pathways**: The possible role of lymphatic/glymphatic channels connecting CNS drainage and extracranial lymph nodes
   - **Circulating tumor cells (CTCs)** and immune evasion: The capacity of GB cells to circulate and evade immune detection may facilitate metastasis
   - **Genetic susceptibility / adaptation**: Specific mutations may confer properties (invasion, motility, survival in circulation) enabling extracranial seeding
   - **Anatomical or mechanical factors**: For example, connections through emissary veins, surgical tracts, or shunts might act as "shortcuts"
     Wiley Online Library +2 PubMed +2

5. **Clinical phenotypes & patterns**

   - Many reported extracranial GB metastases occur in **bones**, **lymph nodes**, **lungs**, **liver**, etc. The vertebral column is a common site for osseous metastases. PubMed +1
   - In many cases, extracranial metastasis co-occurs with intracranial recurrence; but in some reports extracranial metastases appear even without CNS relapse, suggesting independent dissemination potential. Wiley Online Library +1
   - Because extracranial metastases are rare, the median time from initial diagnosis to detectable metastasis is usually short; the survival after metastasis is generally very poor. PubMed +1
   - Some clinical "signals" may predict risk: younger age, female sex (in a few reported cases), presence of PTEN and TP53 mutations, aggressive tumor biology, etc.

Key Contributions / Novelty

- This is one of the more complete case studies combining **deep molecular profiling** with longitudinal disease progression (diagnosis → recurrence → metastasis).

- It highlights **clonal evolution** and **heterogeneity** as critical in extracranial dissemination, rather than thinking of metastasis as a linear “escape” of the initial dominant clone.
- The association between **PTEN alteration in primary tumor** and later acquisition of **TP53 mutations** suggests a possible molecular pathway (or “cascade”) that supports metastasis in a subset of GB patients.
- By comparing with the literature, it frames a hypothesis-driven roadmap for future studies: e.g. tracking CTCs, studying the genomic evolution of metastatic lesions, imaging surveillance, and exploring therapeutic strategies targeting metastatic-prone clones.

Limitations & Open Questions

- Being a single-case report, the observations cannot prove causality, only suggest associations or hypotheses.
- The rarity of extracranial GB metastasis means that statistical power is low, and many reported cases are heterogeneous.
- Whether the molecular features seen (PTEN, TP53, etc.) are causative or merely associated remains uncertain.
- The actual pathways of dissemination (e.g. which route the tumor cells traveled) are inferred rather than directly demonstrated.
- The potential for therapeutic interventions targeting metastasis-prone clones will require further work, validation, and probably prospective cohorts.

Implications & Future Directions

- For patients with GB, particularly those with certain molecular profiles (e.g. PTEN alterations), more careful **surveillance** or consideration of metastatic risk might be warranted.
- Deep molecular profiling of recurrence and metastasis (not just primary tumors) is important to detect emerging subclones.
- Investigating **circulating tumor cells (CTCs)** in GB patients may help detect early dissemination or stratify risk.
- Experimental and translational work should explore **mechanisms of immune evasion, invasion, motility**, and factors that allow tumor cells to survive in non-CNS environments.
- Therapeutic approaches may need to target not only local intracranial disease, but also potential disseminating clones, perhaps via systemic strategies.

[19 oct 2025]