

ASCO Guideline Update: Management of Advanced HER2-Positive Breast Cancer and Brain Metastases

A Visual Clinical Decision-Making Reference

For Medical Oncologists, Radiation Oncologists,
Neurosurgeons, and Multidisciplinary Care Teams.

ASCO[®]
KNOWLEDGE

EXECUTIVE SUMMARY

The Bottom Line: 2022 Paradigm Shifts



Individualized Local Therapy

Moving away from broad use of standard WBRT. Strong emphasis on Stereotactic Radiosurgery (SRS) and the mandatory addition of Memantine + Hippocampal Avoidance (WB-M + HA) to WB-M + HA) to preserve cognition when whole-brain radiotherapy is required.



The Rise of Systemic Options

Highly CNS-penetrant systemic therapies (e.g., the HER2CLIMB tucatinib regimen) can now be used to safely defer local therapy in select asymptomatic patients.

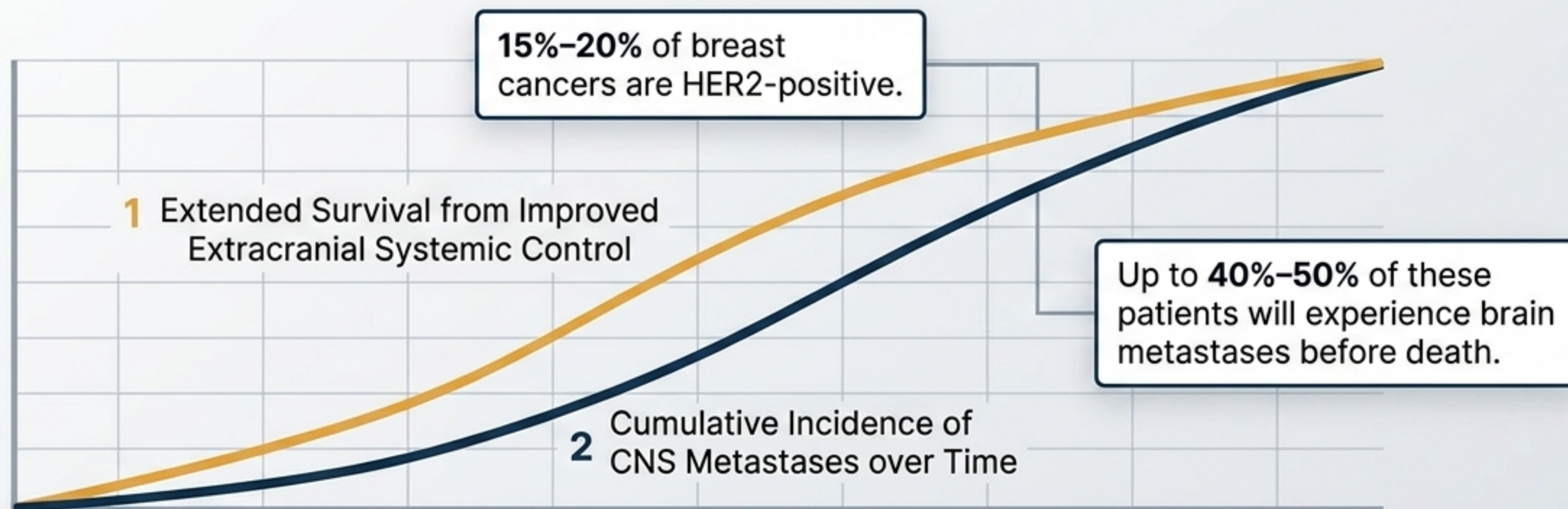


Multidisciplinary Mandate

Treatment is no longer sequential but highly integrated. Medical oncology, radiation oncology, and neurosurgery must collaborate at the precise point of diagnosis.

CONTEXT & RATIONALE

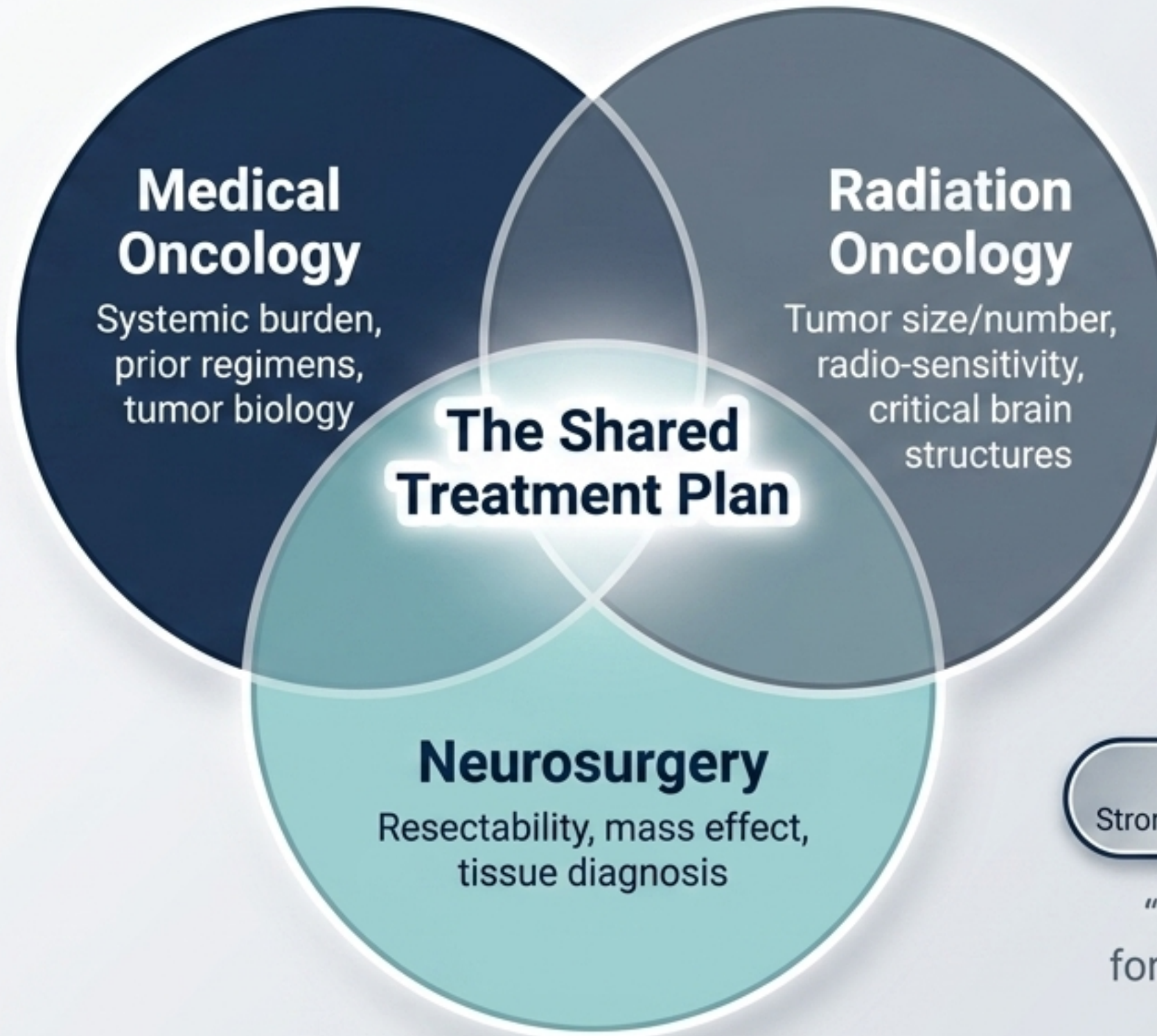
The Changing Landscape of HER2+ Brain Metastases



Core Insight

Brain metastases occur in a continuous fashion over many years. Optimal management is no longer just about acute tumor control; it is about long-term cognitive preservation and quality of life for a patient population now expected to survive years, not months.

The Multidisciplinary Triad: Recommendation 1.0



EVIDENCE Badge
Strong Recommendation | Intermediate Quality

“Multidisciplinary collaboration to formulate treatment and care plans should be the standard of care.”

Diagnostic Triggers for Brain MRI

Asymptomatic / No Known History



Action: Shared decision-making on surveillance.

Guideline Stance: Insufficient data to recommend for or against routine MRI screening.

Evidence: Weak | Low Quality

Neurologic Symptoms Present



New-onset headaches

Unexplained nausea/
Vertigo

Change in
motor/sensory function

Gait disturbance

Action: Immediate diagnostic brain MRI. Clinicians must have a “low threshold”.

Evidence: Strong | Low Quality

Defining Prognostic Pathways

Favorable Prognosis

- ✓ Karnofsky Performance Status (KPS) > 70
- ✓ Controlled extracranial disease
- ✓ Good additional systemic therapy options available



Gateway to Primary Localized Therapy Pathways

Poor Prognosis

- ✗ KPS ≤ 60
- ✗ Active, uncontrolled extracranial disease
- ✗ Exhausted systemic options

The Local Therapy Toolkit



Surgical Resection

Best for: Large lesions (>3-4cm), symptomatic mass effect, tissue diagnosis.

- Always followed by postoperative radiotherapy to the resection bed.



Stereotactic Radiosurgery (SRS)

Best for: Limited lesions (<3-4cm), surgically inaccessible tumors, preserving healthy brain tissue.



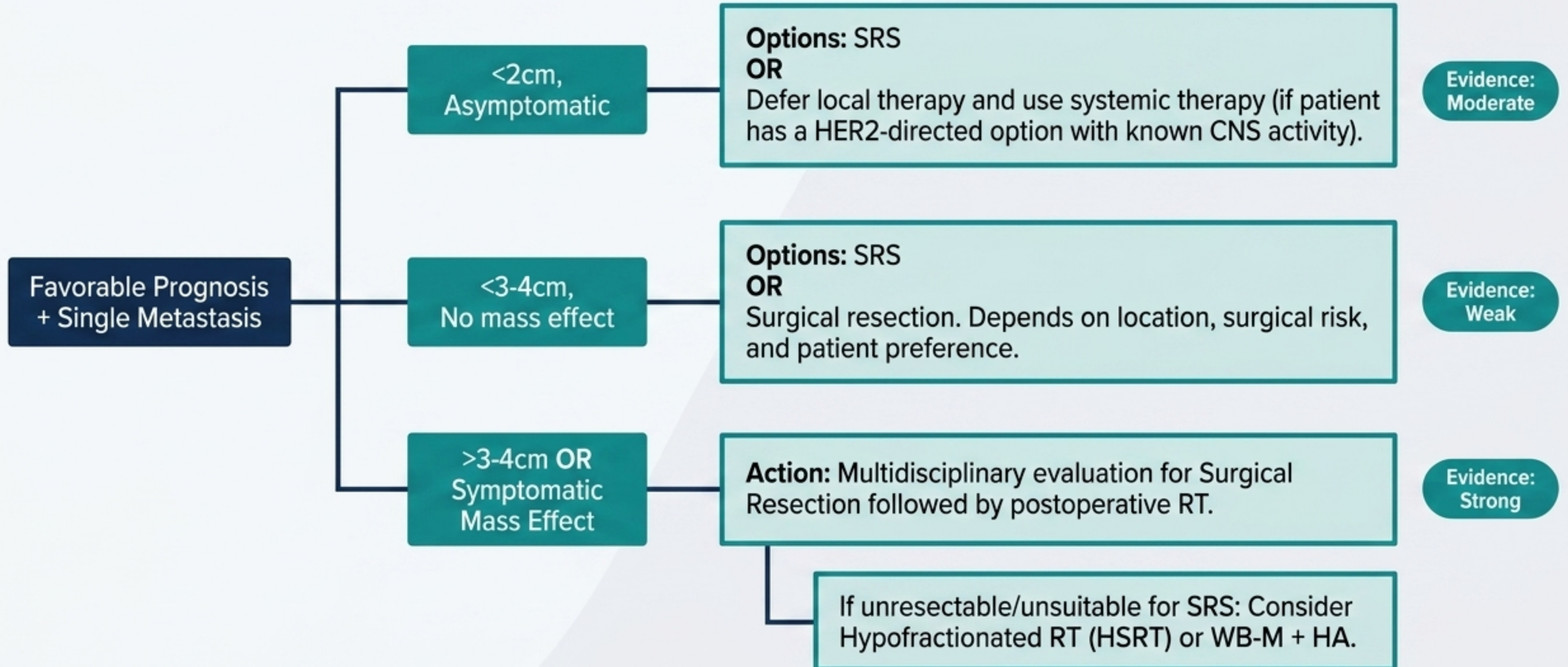
WB-M + HA

Whole-Brain Radiotherapy +
Memantine + Hippocampal
Avoidance

Key Concept: The 2022 mandate is to preserve cognitive function. Memantine delays cognitive decline; HA preserves memory formatting if no metastases are within 5mm of the hippocampus.

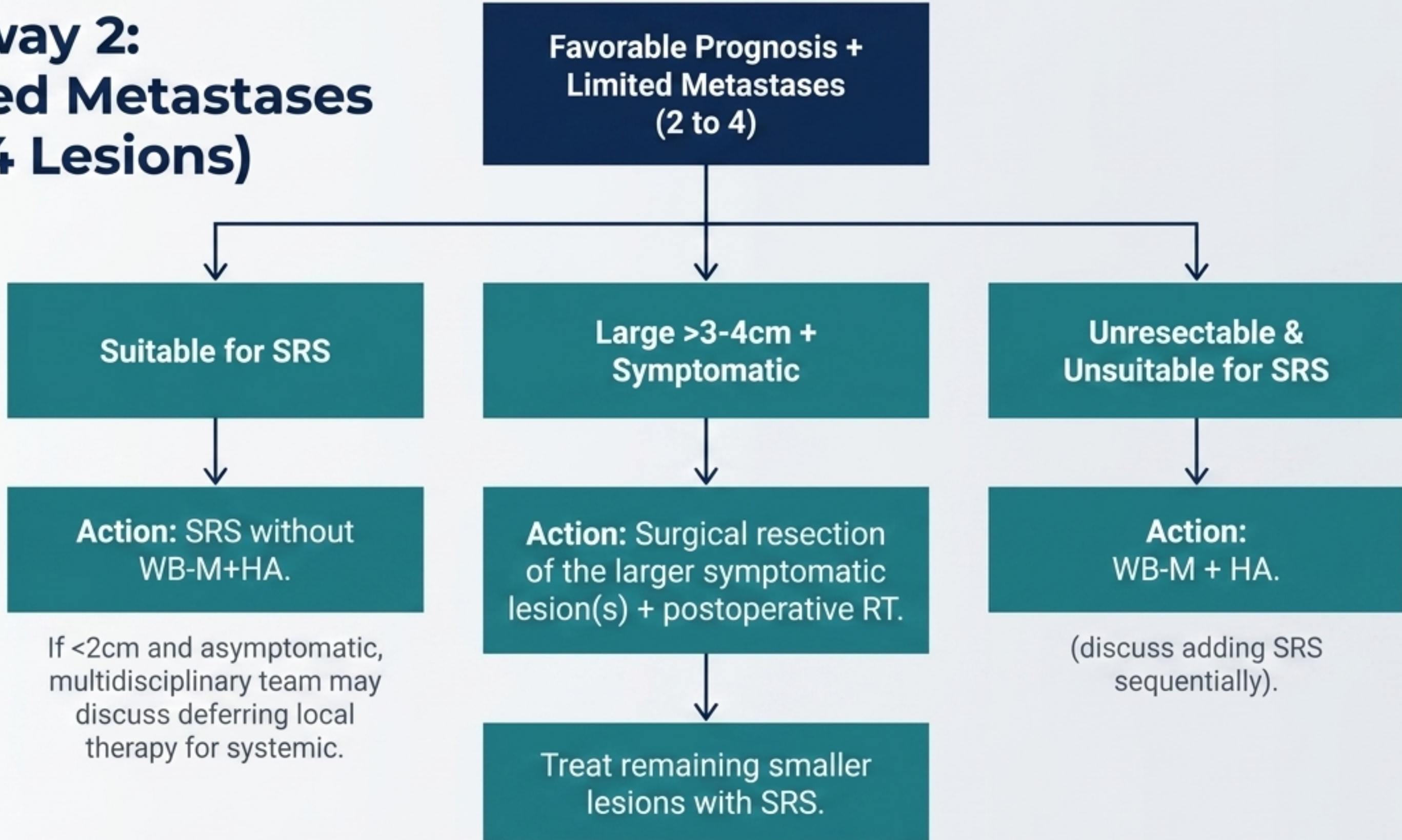
LOCAL THERAPY

Pathway 1: Single Metastasis



LOCAL THERAPY

Pathway 2: Limited Metastases (2 to 4 Lesions)



Pathway 3: Diffuse Disease & Leptomeningeal Involvement

Diffuse / Extensive Disease (≥5 Metastases)

Condition: Favorable prognosis, no leptomeningeal disease.

Action: SRS or WB-M + HA.

Nuance: If lesions are <2cm and asymptomatic, systemic therapy deferral remains an option after MDT discussion.

Leptomeningeal Metastases

Condition: Symptomatic leptomeningeal brain metastases (present in ~5% of patients).

Action: WBRT + Memantine.

Note: Intrathecal/systemic management of leptomeningeal disease is complex and outside this specific guideline scope.

Evidence: Moderate

The Poor Prognosis Pathway

Poor Prognosis
(KPS \leq 60, progressive systemic disease, exhausted options)



Core Recommendation
Best Supportive Care and/or Palliative Care
(which may or may not include radiation).

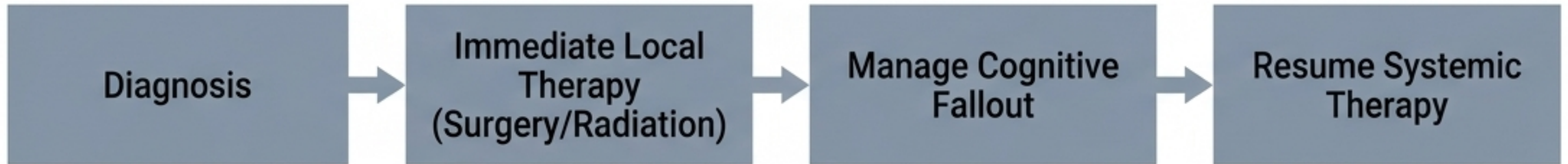
! **The WBRT Caveat**
For symptomatic patients, WB-M + HA may be offered ONLY IF there is a reasonable expectation of symptomatic improvement that outweighs the acute toxicities (fatigue, neurocognitive decline). Case-by-case evaluation.

Evidence: Weak

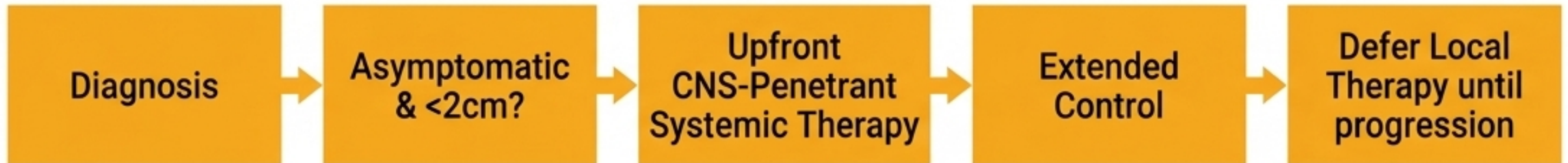
SYSTEMIC THERAPY

The Paradigm Shift: Deferring Local Therapy

The Old Paradigm



The 2022 Paradigm



Key Takeaway

Highly active HER2-targeted agents now offer the unprecedented ability to treat the brain systematically upfront, delaying the neurocognitive risks of radiation.

SYSTEMIC THERAPY

Upfront Systemic Therapy: The HER2CLIMB Regimen

The Regimen: Tucatinib + Trastuzumab + Capecitabine

Strict Eligibility Criteria for Upfront Use:

- 1. HER2-positive metastatic breast cancer.
- 2. Brain metastases without symptomatic mass effect.
- 3. Disease progressed on ≥ 1 prior HER2-directed therapy for metastatic disease (trastuzumab, pertuzumab, T-DM1).

The Clinical Action: If criteria are met, local therapy may be delayed until evidence of intracranial progression.

Efficacy Badge

CNS-PFS HR: 0.48

Tucatinib combination increases CNS-PFS outcomes.

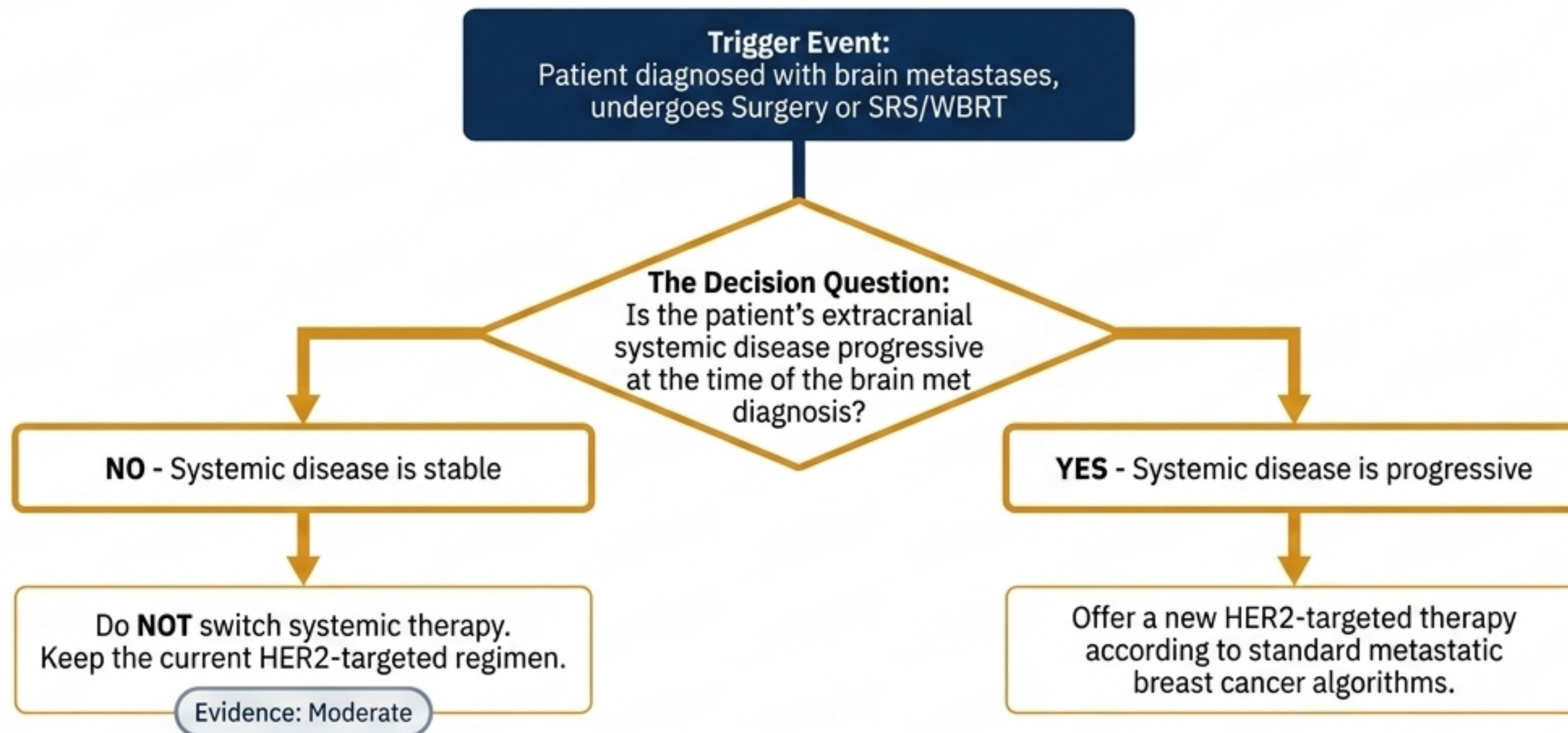
Efficacy Badge

CNS-OS HR: 0.58

OS: 18.1 months vs 12.0 months

SYSTEMIC THERAPY

Systemic Therapy After Local Therapy



Special Exception Callout

The HER2CLIMB regimen (tucatinib combo) or Trastuzumab deruxtecan can be offered in the second-line setting even to patients with stable brain metastases after local therapy.

SYSTEMIC THERAPY

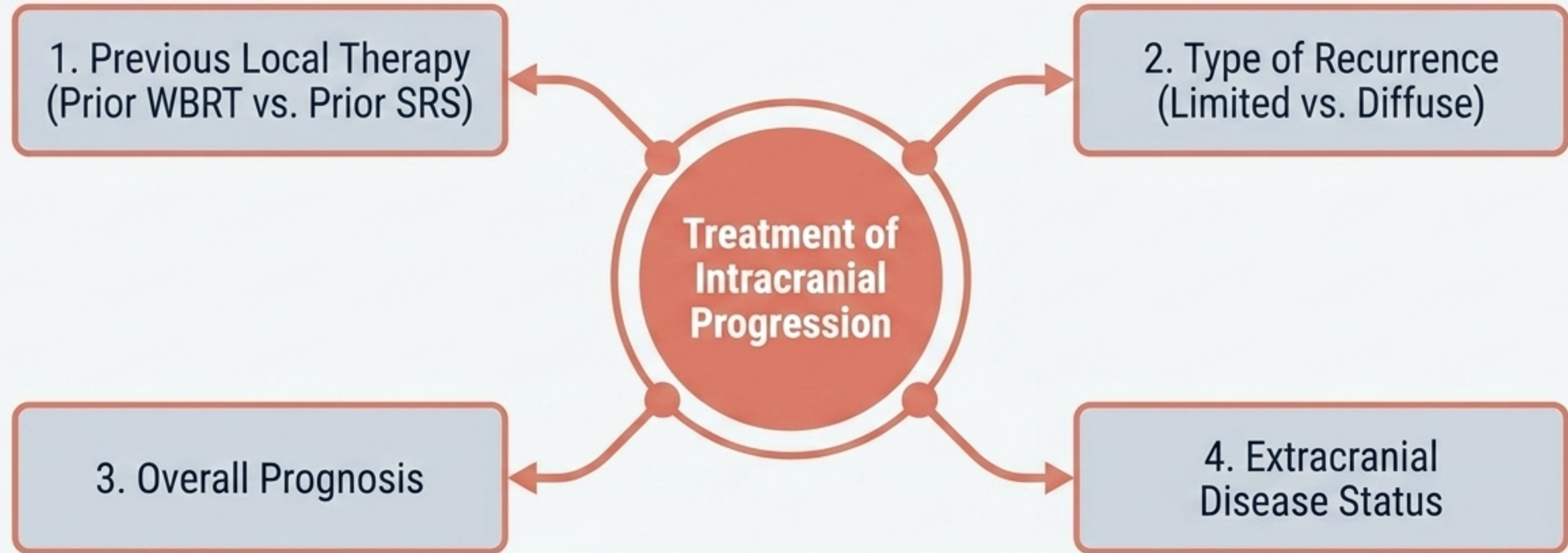
Systemic Therapy Evidence Matrix

HER2CLIMB (Tucatinib Combo)	NALA (Neratinib + Capecitabine)	KAMILLA (T-DM1)
<p>Focuses on definitive PFS and OS improvements in patients with active and stable brain mets.</p> <p>HR 0.32 for CNS-PFS</p>	<p>Highlights the delayed time to CNS disease intervention.</p> <p>Cumulative incidence 22.8% vs 29.2%</p> <p>Evidence: Moderate</p>	<p>Exploratory data showing a 30% reduction in lesion diameter in 42.9% of patients with measurable BMs.</p>

Disclaimer/Context: Note that comparative randomized data specific to HER2+ brain mets is still evolving; clinical trial enrollment is strongly encouraged.

RECURRENCE

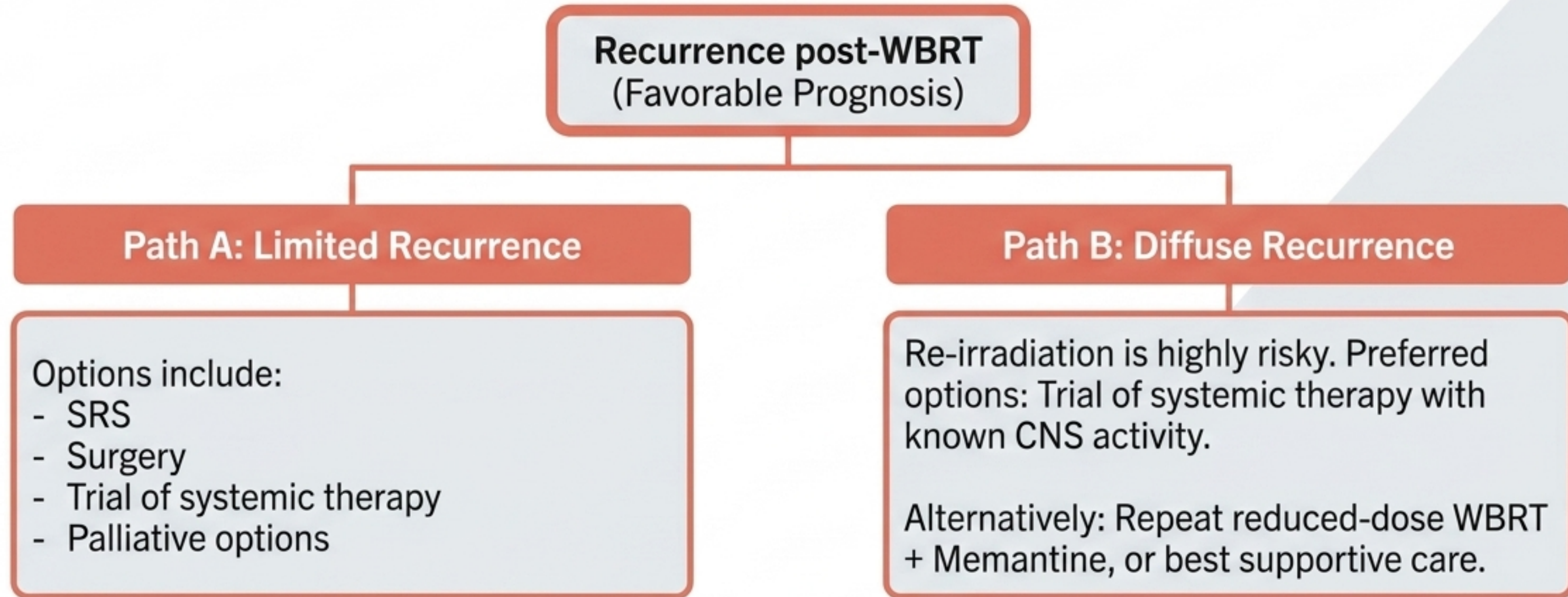
Intracranial Progression Architecture



Because the brain has previously been irradiated, the margin for error is smaller, and the risk of radiation necrosis and cognitive decline is higher.

RECURRENCE

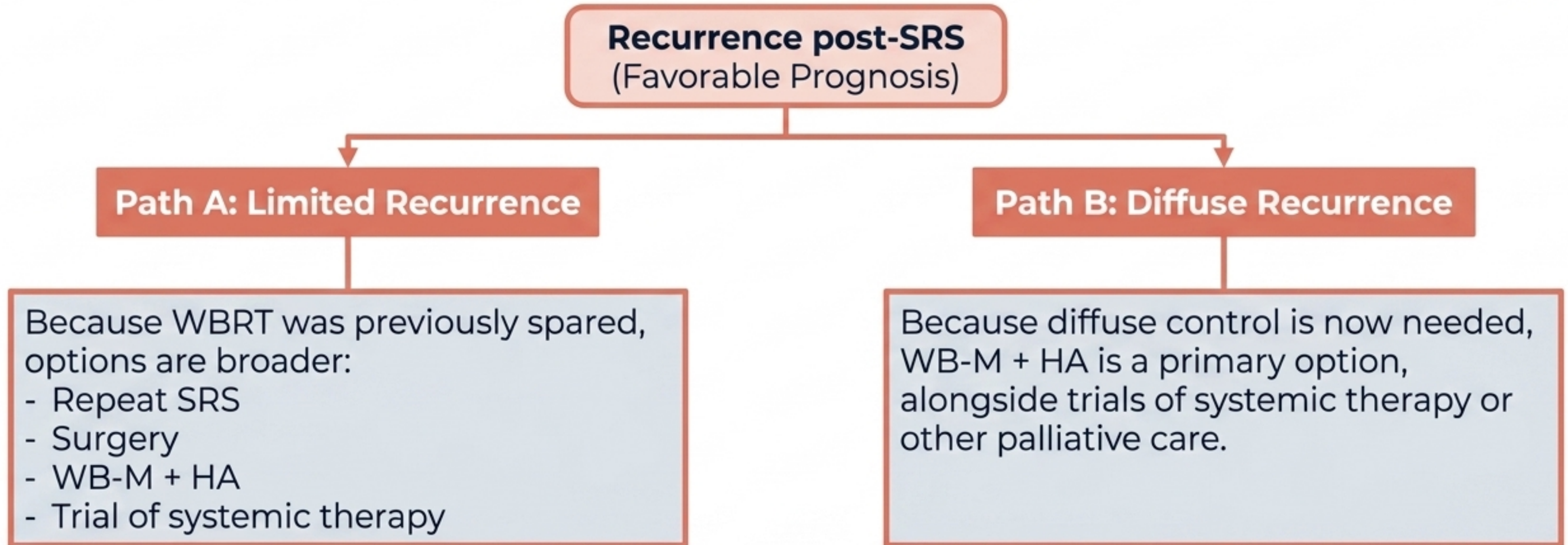
Prior WBRT Recurrence Pathway



Evidence: Weak to Moderate (reflecting the lack of high-level randomized data in the salvage setting).

RECURRENCE

Prior SRS Recurrence Pathway



Systemic Salvage Callout

Regimens with CNS activity (tucatinib, neratinib-based) are vital considerations here to spare further radiation toxicity.

Patient & Clinician Communication

Best Practices



Tailored Communication

Acknowledge the difference between a patient newly diagnosed with metastatic disease vs. a patient facing multi-line treatment failure.



Shared Decision Making

Explicitly required when discussing the deferral of local therapy for upfront systemic therapy, or when debating the neurocognitive risks of WB-M+HA vs. best supportive care.



Palliative Integration

Introduce concepts of concurrent palliative and antitumor therapies early. Do not wait for poor prognosis to initiate supportive care discussions.

SYNTHESIS

Addressing Complexities in Care

Health Equity Mandate

Insight: Race, socioeconomic status, and geographic location severely impact access to specialized SRS equipment, multidisciplinary tumor boards, and premium systemic agents.

Action: Providers must actively work to ensure equitable access to high-quality care and clinical trials for minority and vulnerable populations.

Multiple Chronic Conditions (MCC)

Insight: Clinical trials often exclude patients with MCCs, limiting the reliability of data for complex real-world patients.

Action: Guideline applications must be modified based on the patient's full comorbidity profile; do not blindly apply algorithms if intersecting chronic conditions raise toxicity risks.

SYNTHESIS

The 2022 Blueprint



The 2022 ASCO update shifts the treatment of HER2+ brain metastases from acute palliative control to long-term, brain-sparing disease management.