Organ specific metastasis and survival across molecular subtypes in de novo stage IV breast cancer: A population based retrospective cohort study, 2010-2022.

P. Jain[1], R. Patel[1], N. Ganatra[1], S. Patel[1], M. Patel[2], A. Jamal[1], S. Modi[3], T. Naqvi[4]

[1]Internal medicine, Baptist Hospital of Southeast Texas, Beaumont, TX, [2]Surgical Oncology, University of Miami Miller School of Medicine, Miami, FL, [3]Medicine, Smt. NHL Municipal Medical College, Ahmedabad, INDIA, [4]Hematology-Oncology, Baptist Hospital of Southeast Texas, Beaumont, TX.

Background

- De novo stage IV breast cancer (dnMBC) prognosis is driven by *where* the cancer first metastasizes and by *molecular subtype*, but most population-level analyses don't evaluate both together.
- Organotropism matters: bone is the commonest first site and tends to have the most indolent course, whereas visceral (liver), pulmonary, and particularly brain or multi-organ involvement are consistently linked with early breast cancer–specific mortality.
- Since 2010, SEER captures ER/PR/HER2, allowing contemporary, U.S. representative analysis of how **site of metastasis** and **molecular subtype** jointly shape outcomes in dnMBC.

Introduction

- **Aim:** To determine, in a recent nationwide SEER cohort, how the **first metastatic organ** and the **tumor molecular subtype** jointly influence breast cancer–specific survival (BCSS) among women diagnosed with de novo stage IV breast cancer, 2010–2022.
- **Rationale:** Organ of first spread and biology are often reported separately, but treatment decisions, prognostication, and clinical-trial eligibility actually depend on both.
- **Hypothesis:** Brain and multi-organ metastasis, and TNBC biology, would show the poorest BCSS even after adjustment, whereas lung-only disease may resemble bone-only once covariates are considered.

Methods

- Data source: **SEER-17 Research database**, diagnosis years **2010-2022**.
- Population: Women presenting with **de novo metastatic breast cancer** (N = **38,078**).
- Molecular subtype (from ER, PR, HER2):
  - HR+/HER2−
  - HR+/HER2+
  - HR−/HER2+ (reference)
  - Triple-negative breast cancer (TNBC)
- First metastatic organ (SEER "Combined Mets at Diagnosis"): **bone, liver, lung, brain, multiple sites, other/unspecified**; **bone-only** used as site reference.
- Outcomes: **Breast cancer–specific survival (BCSS)** estimated by Kaplan–Meier; **multivariable Cox** models adjusted for age, race/ethnicity, and grade → adjusted HRs (aHRs) with 95% CIs.
- Sensitivity: repeat analyses **excluding unknown organ codes** (<5% change in aHRs).

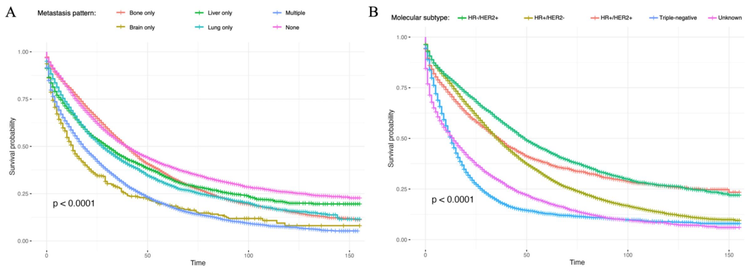


Figure 1 : Kaplan-Meier analysis of BCSS among patients diagnosed with dnMBC, stratified by first metastatic organ (A) and molecular subtype (B).

Characteristic	Hazard Ratio	Lower CI	Upper CI	p-value
Molecular subtype:				
HR-/HER2+	Reference	—	—	—
HR+/HER2-	0.88	0.83	0.92	< 0.001
HR+/HER2+	0.75	0.71	0.79	< 0.001
Triple negative	2.27	2.14	2.40	< 0.001
Unknown	1.27	1.20	1.35	< 0.001
Metastasis pattern:				
Bone only	Reference	—	—	—
Brain only	1.78	1.60	1.98	< 0.001
Liver only	1.33	1.26	1.41	< 0.001
Lung only	1.03	0.98	1.07	0.30
Multiple	1.81	1.76	1.87	< 0.001
None	0.90	0.87	0.94	< 0.001

Table 1 : Multivariate Cox regression analyses of BCSS in patients diagnosed with dnMBC.

Results

Pattern of spread:
- Bone-only was most common: **59% overall**, **73% in HR+/HER2−**.
- Liver-only: **20%**; Lung-only: **14%**; Brain-only: **7%**.
- **28%** had **≥2 metastatic organs** at diagnosis.
- TNBC showed the **highest lung or multi-site involvement (≥35%)**.

Unadjusted 5-year BCSS by first site (log-rank p < 0.001):
- Bone: **31%**
- Liver: **12%**
- Lung: **14%**
- Brain: **5%**
- Multiple sites: **8%**

Adjusted prognosis by subtype (vs HR−/HER2+):
- HR+/HER2+: **aHR 0.75 (0.71–0.79)** → best survival
- HR+/HER2−: **aHR 0.88 (0.83–0.92)** → modest benefit
- TNBC: **aHR 2.27 (2.14–2.40)** → worst survival
- Sensitivity analyses changed all aHRs by **<5%**.

Discussion

- **Site of first metastasis** and **molecular subtype** both remained **independent prognostic factors**, confirming dnMBC is not a single-risk group.
- **Brain** and **multi-organ** presentation carried the **worst survival**, even after adjustment.
- **Lung-only ≈ bone-only** after covariate adjustment → **not all visceral-first disease is equally poor**.
- Subtype modified risk: **HR+/HER2+ and HR+/HER2− did better**, while **TNBC had the highest mortality**, supporting **site + subtype**–based counselling and trial stratification.

Conclusion

- **Both first metastatic organ and tumor subtype determine outcome** in de novo stage IV breast cancer.
- **Highest-risk:** brain and multi-organ; **lower-risk:** bone-only and lung-only (after adjustment).
- These data support **subtype-guided imaging**, **site-specific risk stratification**, and **more granular prognostic discussions** at diagnosis.

References

1.Wu SG, Li H, Tang LY, et al. The effect of distant metastases sites on survival in de novo stage IV breast cancer: a SEER database analysis. *Tumour Biol.* 2017;39(6):1010428317705082. doi:10.1177/1010428317705082.
2.Wang R, Zhu Y, Liu X, Liao X, He J, Niu L. The clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. *BMC Cancer.* 2019;19:1091. doi:10.1186/s12885-019-6311-z.
3.Tao L, Chu L, Wang LI, et al. Occurrence and outcome of de novo metastatic breast cancer by subtype in a large, diverse population. *Cancer Causes Control.* 2016;27(9):1127-1138. doi:10.1007/s10552-016-0791-9.
4.He Y, Shao Y, Chen Q, Liu C, Zhu F, Liu H. Brain metastasis in de novo stage IV breast cancer. *Breast.* 2023;71:54-59. doi:10.1016/j.breast.2023.07.005.
5.Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence – SEER Research Data, 18 Registries. National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program. Available at: *seer.cancer.gov*. Accessed November 4, 2025.

Contact
Pragya Jain
Email: pragyajainmd@gmail.com Phone: +19452173586