Abstract #550884

AI-driven risk stratification for distant recurrence in node-positive HR+/HER- early breast cancer: independent validation in the NSABP B-28 trial

American Society of Clinical Oncology
May 29 - June 2nd, 2026

P. Rastogi[1,2] G. Tang[3], J. Bennett[4], J. Shao[3], B. King[4], T. Freeman[1,5], G. Yu[3], R. Baehner[4], V. Gaury[6], V. Aubert[6], E. Hocquet[6], F. André[7,9], I. Garberis[7], C. Geyer[1,2], E.P. Mamounas[10], N. Wolmark[1,2], M. Lacroix-Triki[8]

[1] NSABP Foundation, Pittsburgh, PA, USA [2] Department of Medicine, University of Pittsburgh School of Medicine, UPMC Hillman Cancer, Pittsburgh, PA, USA [3] Department of Biostatistics and Health Data Science, University of Pittsburgh; NRG Oncology Statistical and Data Management Center, Pittsburgh, PA, USA [4] Exact Sciences, Redwood City, CA, USA [5] Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA [6] WAIV, Paris, France [7] INSERM U981, Gustave Roussy, Paris-Saclay University, Villejuif, France [9] Department of Cancer Medicine, Gustave Roussy, Paris-Saclay University, Villejuif, France [10] AdventHealth Cancer Institute, Department of Surgical Oncology, Orlando, FL, USA, 11 Department of Pathology, Gustave Roussy, Paris-Saclay University, Villejuif, France

Background

Accurate assessment of risk of distant recurrence (DR) in HR+, HER2-negative early-stage breast cancer (EBC) is important for optimizing adjuvant therapy decisions, including treatment escalation with CDK4/6 inhibitors (CDK4/6i)[1]. Current guidelines recommend consideration of CDK4/6i for node-positive, clinically high-risk EBC, including N1 patients. However, it is not well understood which patients will benefit, and guideline recommendations suggest that the risks may outweigh benefits for patients with low risk of distant recurrence. Identification of these patients may help prevent overtreatment.

RlapsRisk BC (RR) is a CE-marked AI-based digital pathology software that integrates deep learning–derived morphological features from standard H&E-stained whole-slide images (WSIs) with clinicopathologic variables (age, tumour size, number of invaded lymph nodes) to estimate the risk of distant recurrence in HR+/HER2− EBC. The model was developed and locked using >6,000 patients from 7 retrospective cohorts. Expert pathologist review confirmed that the model relies on established morphological tumor features(nuclear polymorphism, mitotic activity tumor architecture), RR requires no molecular testing, no additional tissue, and no pathologist annotations.

Objectives

Primary objective: To validate the prognostic utility of the RR score for DRFI in a cohort of node-positive, HR+/HER2− EBC patients from the phase III randomised NSABP B-28 trial.

Secondary objectives:

- Assess the independent prognostic value of the digital pathology-only calibrated image analysis score in multivariable Cox models
- Prognostic performance across clinically relevant subgroups (age, tumour size, grade, nodal burden, menopausal status, chemotherapy regimen)

References

1. Caswell-Jin J; Freedman R, Hassett MJ, et al. Optimal Adjuvant Chemotherapy and Targeted Therapy forEarly Breast Cancer—CDK4/6 Inhibitors: ASCO Rapid Guideline Update Clinical Insights. *JCO Oncol Pract.* 2024; 21:287-291
2. Bidard F.C, Gessain G, Bachelot T, et al. Identifying Patients With Low Relapse Rate Despite High-Risk Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer: Development and Validation of a Clinicopathologic Assay. *J Clin Oncol.* 2025 43:3090-3101
3. Garberis I, Gaury V, Saillard C, et al. Deep learning assessment of metastatic relapse risk from digitized breast cancer histological slides. *Nat Commun.* 2025;16:5876.

Conclusions

- The digital pathology-only score provides independent prognostic information beyond standard clinicopathologic variables and is consistently prognostic across all subgroups supporting the biological validity a of the AI-derived morphological features.
- Two-thirds of N1 patients were identified as low-risk by RR and exhibited a 10-year DR free of 90.6% (86.9 - 93.4) with standard chemoendocrine therapy.
- As the EBC clinical landscape shifts toward broader CDK4/6i use, RR could be developed to provide a biological threshold to identify N1 patients for whom benefit of treatment intensification may be limited.

Method

Blinded independent validation study: The RlapsRisk BC model was locked prior to analysis; no parameter tuning was performed on NSABP B-28 data. Image analysis, score computation, and risk classification were performed by Waiv; Statistical analyses were conducted independently.

Parent trial: NSABP B-28 Phase III RCT (N=3,060) comparing doxorubicin/cyclophosphamide (AC) vs AC followed by paclitaxel (AC→P) in node-positive breast cancer. Addition of paclitaxel improved DFS but not OS (HR=0.87; 95% CI 0.72–1.05; P=0.14).

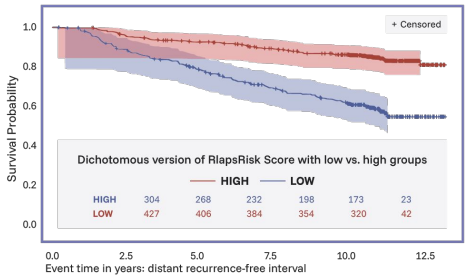
Evaluable population N=731 HR+/HER2− patients with available WSIs meeting quality control criteria. Exclusions: missing tissue blocks or ER-negative; WSI QC failure; HER2 positive/equivocal by RT-PCR; ER-negative by IHC; missing clinical data; WSIs reserved for calibration.

Endpoint & statistical methods: Primary endpoint: DRFI (time from surgery to first distant recurrence or breast cancer death). Median follow-up: 11.1 years (max 13.3 years; 170 DR events).

Results - Prognosis performance

- → Across the entire cohort, RR classified 58% of patients as low-risk and 42% as high-risk.
- → RR (high vs low) was significantly associated with DRFI: HR= 3.1 (95% CI: 2.3-4.3; p < .001) in an analyzable population of 731 patients with 170 events (Fig 1).
- → In a multivariable Cox model, the continuous digital pathology-only score remained significant after adjusting for clinicopathologic factors: HR=1.6 (95% CI: 1.4-1.9; p < .001)
- → Digital pathology-only score was significantly associated with tumour grade (p<.001), tumour size (p<.001), nodal burden (p<.001), and ER/PR status (p=0.007), but was not associated with age, race, menopausal status, or surgery type, supporting its use as an objective, unbiased risk assessment tool.

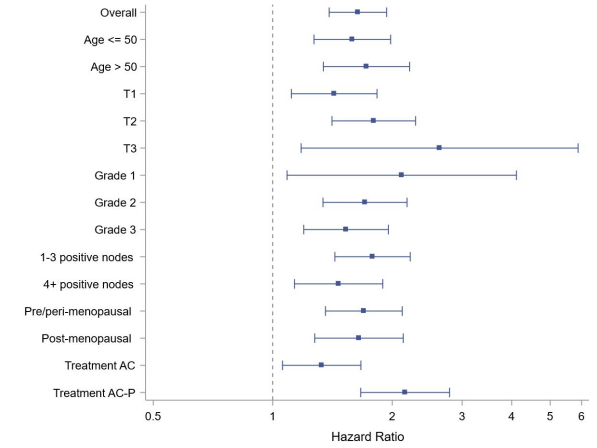
Fig 1: Risk of DR across RR risk groups (N=731)



Results - Subgroup analysis

Histology-only score of RR provides significant risk stratification across all patients subgroups in a multivariate analysis

Fig 1: Hazard ratios for digital pathology-only score on distant recurrence in clinically-relevant subgroups



In the N1 group including n=504, 91 DR events, RR (high *vs* low) was significantly associated with DRFI: HR = 3.6 (95% CI: 2.3–5.5; p < .001)

	RR Low (65.7%)	RR High (34.3%)
5-yr DR free (95% CI)	**94.8% (91.8–96.7)**	82.3% (75.7–87.3)
10-yr DR free (95% CI)	**90.6% (86.9–93.4)**	69.8% (62.2–76.2)