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Incremental prognostic value of an AI-derived histology signature beyond the 21-gene recurrence score: A prospective-retrospective validation in TAILORx

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Magali Lacroix-Triki[1], Robert Gray[2], Valentin Gaury[3], Victor Aubert[3], Damien Jacobs[3], Estelle Hocquet[3], Ingrid Garberis[4], Glenn Broeckx[5], Amy Li[6], Gert Van den Eynden[7], Zuzana Kos[8], Balazs Acs[9], Trine Tramm[10], Elisabeth Ida Specht Stovgaard[11], Cornelia Focke[12], Laura Comerma Blesa[13], Akira Hida[14], Elena Provenzano[15], Fresia Pareja[16], Sai Maley[17], Nadia Villena[18], Elsa Li-Ning-Tapia, A[19], Christine Desmedt[20], Alexander Lazar[21], Sunil Badve[22], Fabrice André[4,23], Sherene Loi[24], Joseph Sparano[25], Roberto Salgado[26], on behalf of The International Immuno-Oncology Biomarker Working Group and the TAILORx Investigators

1. Department of Pathology, Gustave Roussy, Villejuif, France. 2. DFCI, Boston, MA, USA. 3. WAIV, Paris, France. 4. INSERM U981, Gustave Roussy, Paris-Saclay University, Villejuif, France, 5.Department of Pathology, ZAS Hospitals, Antwerp, Belgium. 6. Department of Pathology, Massachusetts General Hospital, Boston, MA, USA. 7. Department of Pathology and Cytology, Heilig Hartziekenhuis Lier, Lier, Belgium. 8. Department of Pathology and Laboratory Medicine, University of British Columbia & BC Cancer Vancouver Centre, British Columbia, Canada. 9. Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden.10. Dept. of Pathology, Aarhus University Hospital, Aarhus, Denmark and Dept. of Clinical Medicine, Aarhus University, Aarhus, Denmark. 11. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. 12. Department of Surgical Pathology, Dietrich Bonhoeffer Medical Centre, Allendestrasse 30, 17036 Neubrandenburg, Germany. 13. Pathology Department, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain. 14. Department of Pathology, Matsuyama City Hospital, Japan. 15.Department of Histopathology, Addenbrookes Hospital, and NIHR Cambridge Biomedical Research Centre, Cambridge, UK. 16. Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center. 17. NRG Oncology/NSABP Foundation, Pittsburgh, USA.18. Pathology department, Aalborg University hospital, Denmark. 19. Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. 20.Laboratory for Translational Breast Cancer Research; Department of Oncology; KU Leuven; Leuven; Belgium. 21.Departments of Pathology, Genomics Medicine, Dermatology, & Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. 22.Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia; Emory University Winship Cancer Institute, Atlanta, Georgia, USA. 23.Department of Cancer Medicine, Gustave Roussy, Paris-Saclay University, Villejuif, France.24.Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, Australia and The Sir Peter MacCallum Department of Medical Oncology, The University of Melbourne, Parkville, Australia.25.Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York USA.26. Department of Pathology, ZAS Hospitals, Antwerp, Belgium and Division of Research, Peter Mac Callum Cancer Centre, Melbourne, Australia.

Background

The 21-gene recurrence score (RS) is foundational for risk-stratifying HR+/HER2− early breast cancer (EBC) but predominantly captures early proliferation-driven recurrence; its discrimination for late distant recurrence (≥5 years) is known to diminished with time[1-2], and histologic subtypes such as invasive lobular carcinoma (ILC), where late recurrence biology dominates, are often classified into low-/intermediate-RS score despite worse long-term outcomes[3-4]. Even RSClin, integrating RS with clinicopathologic factors, leaves residual prognostic heterogeneity for late events[5]

RlapsRisk BC (RR) is an AI pathology-based pathology software which integrates features from H&E-stained whole-slide images with clinical data (age, tumor size, nodal status) and was developed and internally validated using 7 retrospective cohorts totaling 6,039 patients. We independently evaluated the clinical validity of RR and more specifically its histology-only component (RR-H) beyond RS and standard clinicopathologic factors in the landmark TAILORx trial

Objectives

1. Assess independent and incremental value of RR-H beyond the 21-gene RS and standard clinicopathologic factors for prognostic evaluation
2. Assess correlation of RR-H score with known histology features
3. Assess RR-H score distribution and prognostic performance depending on histology subtype

References and acknowledgment

[1] Sestak I; et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2018; 4:545-553
[2] Sgroi DC; Set al. Prediction of Late Distant Recurrence in Patients with Oestrogen-Receptor-Positive Breast Cancer: A Prospective Comparison of the Breast-Cancer Index (BCI) Assay, 21-Gene Recurrence Score, and IHC4 in the TransATAC Study Population. Lancet Oncol. 2013; 14:1067-1076
[3] Pestalozzi BC; et al. Distinct Clinical and Prognostic Features of Infiltrating Lobular Carcinoma of the Breast: Combined Results of 15 International Breast Cancer Study Group Clinical Trials. J Clin Oncol. 2008; 26:3006-3014
[4] Abel MK; et al. The 21-Gene Recurrence Score in Clinically High-Risk Lobular and Ductal Breast Cancer: A National Cancer Database Study. Ann Surg Oncol. 2022; 29:7739-7747
[5] Sparano JA; et al. Clinical and Genomic Risk for Late Breast Cancer Recurrence and Survival. NEJM Evid. 2024;

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Conclusions

- ➔ These findings establish RR-H as an independent and strong prognostic biomarker incremental to the 21-gene RS for DRFI in HR+/HER2− EBC in the overall TAILORx population. Its incremental value in the combined model was sustained at 5 years (+1,13 AUC pts) and 10 years (+3.07 AUC pts).
- ➔ These data support a combined AI-pathology + genomic strategy for refining distant recurrence risk, especially for late-recurrence in HR+/HER2− EBC.
- ➔ A subanalysis per histology subtype confirmed the significant association of RR-H in the 3 groups (ILC, ductal carcinoma, other)

Method

- Design: Prospective-retrospective independent validation on TAILORx (NCT00310180);
- Cohort: n=7,584 patients from TAILORx trial with evaluable WSI (Whole slide Image), RS, central-read clinicopathologic data and adequate follow-up, including 532 distant recurrence events;
- Endpoint: Distant recurrence-free interval (DRFI) per STEEP 2.0 criteria was analyzed with cumulative Kaplan-Meier estimate
- Statistical analysis: Pre-specified Cox proportional hazards models compared Base (composed of age, tumor size, grade, histology and RS), with Base+RR-H. Discrimination assessed by Harrell's C-index;
- Pre-specified analytic framework: RR-H score were generated as a continuous score (HR per 1 SD), to preserve granular risk information;
- Concordance analyses: RR-H distributions was assessed against pathologist consensus grade, histologic subtype, and stromal TILs);

Results - Concordance of RR-H with histology criteria

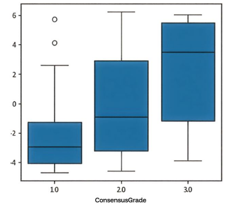

Fig 1 - RR-H by tumor grade (central read)
Median RR-H increases with grade but distributions overlap substantially desmontrating intra-grade prognostic granularity

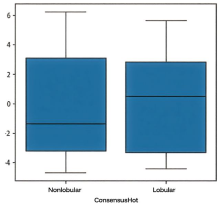

Fig 2 - RR-H by histologic subtype
RRBC distributes equivalently across invasive lobular and non-lobular carcinomas

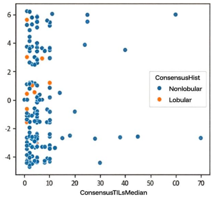

Fig 3 - RR-H *vs* TILs, by histology
Lobular cases distributed across the full RR-H range, without TILs driven clustering

Results - Independent and incremental prognostic value of RR-H

RR-H stratifies HR+/HER2− EBC into clinically meaningful risk groups, complementing the 21-gene RS in the overall TAILORx population

- Adding RR-H score to a base model (composed of age, tumor size, grade, histology and RS) improved discrimination both overall and at clinically meaningful time horizons: C-index increased from 0.673 to 0.701; 5-year time-dependent AUC increased from 77.5% to 78.6% and 10-year time-dependent AUC increased from 71.0% to 74.1%
- RR-H carries independent prognostic information for DRFI of magnitude comparable to RS itself: in the adjusted model, HR per 1 SD = 1.39 (95% CI 1.27–1.51) for RR-H vs 1.42 (95% CI 1.27–1.51) for RS.

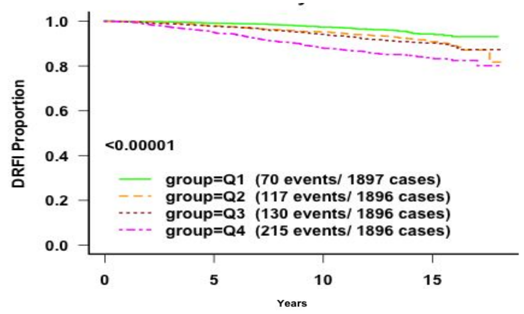

Fig 4 - Kaplan-Meier curve illustrating DR survival stratified by quartiles of RR-H
Compared with the lowest RR-H quartile (Q1), patients in Q4 had a 2.66 fold higher risk of DR (95% CI 2.00–3.52; p<0.0001), with intermediate quartiles showing graded effects: Q2 HR= 1.61 (1.19–2.17); Q3 HR=1.66 (1.23–2.23)

Application to invasive lobular carcinoma subgroup

- Consistent with prior evidence, ILC (n=953, 12.2%) showed worse outcomes in TAILORx: 15-year DRFI 87.0% vs 90.0% in ductal cases (and more specifically within RS≤25, 87.3% vs 91.1%), with an independent association for RFI in multivariable analysis within RS≤25 (HR=1.37, p=0.003), despite ILC concentration in lower RS bands (92.7% in RS≤25).
- In contrast, ILC distributed evenly across RR-H quartiles (10.2%/12.2%/13.0%/13.0% in Q1- Q4; p<0.05). In a histology-stratified Cox models, RR-H score shows significant association with DRFI in each subtype: HR per 1 SD = 1.41 (1.33–1.49) in ductal (n=6,057), HR = 1.26 (1.12–1.41) in lobular (n=918), and HR = 1.51 (1.24–1.83) in other (n=609), interaction p=0.55.