Multimodal machine learning model prediction of pathological complete response to neoadjuvant chemotherapy in triple-negative breast cancer

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Poster #372

1 Highlights

- The aggregation of **multiple data modalities** (clinical, biological, imaging) could help improve **prediction of pathological complete response** (pCR) status after neoadjuvant chemotherapy in **non-metastatic triple-negative breast cancer** (TNBC) patients.
- **SOPHiA DDM™ for Radiomics Platform** (Research Use Only; SOPHiA GENETICS SA; Switzerland) enabled **tumor segmentation** and **radiomics features** extraction.
- Predicted probability of non-pCR status was generated for each patient through a full **machine learning (ML) pipeline** integrating **real-life multimodal data.**
- Interpretability tools were proposed to bridge the gap towards a clinical adoption of a ML-based predictive signature of non-pCR status.

2 Background

- TNBC is a biologically and clinically heterogenous disease, associated with poorer outcomes when compared with other BC subtypes.
- In non-metastatic TNBC, neoadjuvant chemotherapy (NAC) is often given prior to surgery and achieving pathological complete response (pCR) has been associated with improved clinical outcomes (Figure 1).
- There is thus high clinical interest in the ability to accurately predict pCR status using data collected before NAC initiation.

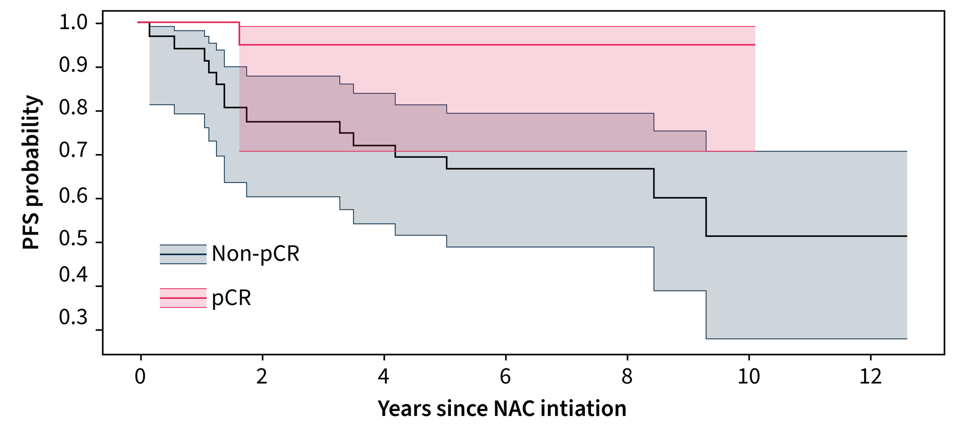

Figure 1. Observed progression-free survival (PFS) according to pCR status in our study cohort (n=57; p=0.015).

3 Methods & Materials

- 57 patients with stage 2 or 3 TNBC treated with NAC[1]. TNBC cohort from NCT02600442 (ClinicalTrial. gov).
- 36 non-pCR (63%), 21 pCR (37%).
- Multimodal baseline data were collected including clinical, biological, and imaging data in the form of baseline PET/CT scan and the radiology report, as well as pathological-clinical data (pCR, PFS, OS).

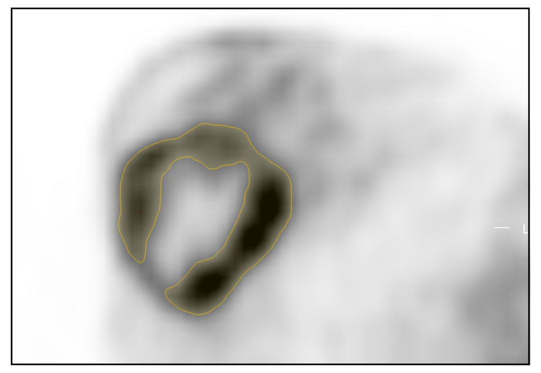

Figure 2. Illustrative PET/CT segmentation of a necrotic tumor, axial section.

n=57	non-pCR (*n*=36)	pCR (*n*=21)	*p*-value
Age	53.7 (13.6)	55 (9.5)	0.734
Familiy history of BC			0.078
No/Yes	27/9	19/1	
Missing	0	1	
Clinical T-stage			0.032
T1-T2/T3-T4	13/23	14/7	
p53			0.346
Mutated/Wild type	34/2	18/3	
Ki67	36.7 (27.2)	46.9 (26.3)	0.186
Missing	8	2	
rGGI*	0.3 (0.2)	0.5 (0.3)	0.007
Tumour SUVmax	10.7 (6)	14.1 (7.1)	0.07
Tumour volume (cm³)	20.2 (34.7)	32.1 (76.2)	0.691

Continuous data: Mean (standard deviation)
Categorical data: Amount
p-value obtained from Wilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data
*rGGI: reduced Genomic Grade Index

Table 1. Univariate analyses of selected multimodal features with pCR status in the study cohort.

Image processing

- For each patient, breast tumors were segmented in 3D through a semi-automatic segmentation method using 42% of SUVmax (Figure 2).
- The segmentation was performed by an experimented nuclear physician using the SOPHiA DDM™ for Radiomics Platform (Research Use Only; SOPHiA GENETICS SA; Switzerland).
- Radiomics features were then extracted following the IBSI standards and combined with other data modalities.

Data mining, model building and evaluation

- Batch-effect correction for genomic expression data.
- Filter-based variable selection method to deal with data dimensionality.
- Multiple imputation (MICE algorithm) to deal with missing data.
- ML algorithms optimized & evaluated using a nested cross-validation[2].
- Optimization metric: Area under the ROC Curve (AUC).

Interpretability tools

- Permutation feature importance and partial dependence plots (PDP) to understand, validate and justify the prediction model.
- Shapley Additive exPlanations (SHAP) values to explain each patient-specific predicted probability of non-pCR.

4 Results

Predictive performances

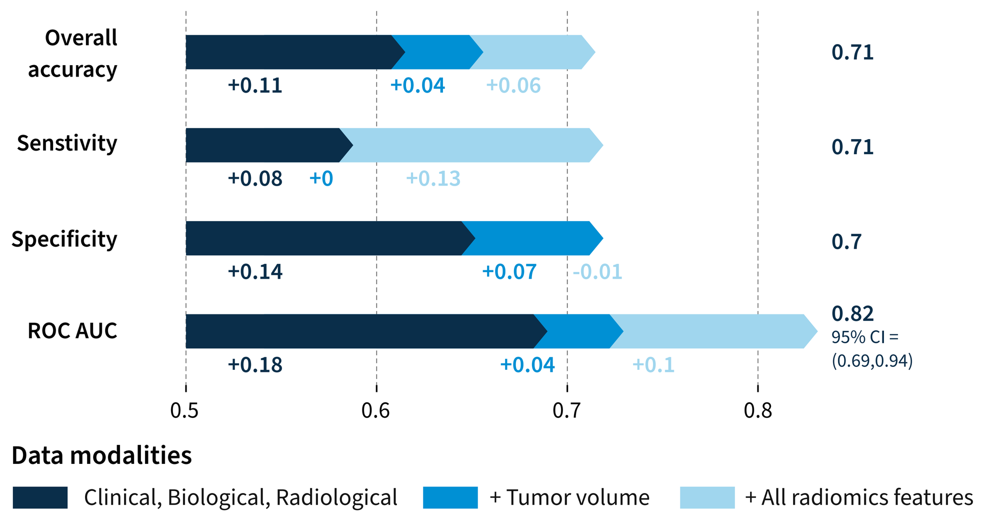

Figure 3. Cross-validated predictive performances using various data modalities.

- 235 features collected (5 clinical, 24 biological, 11 radiological, 195 radiomics).
- 19 features selected for the final analysis (2 clinical, 5 biological, 3 radiological, 8 radiomics).
- Best results obtained using the aggregation of clinical, biological, radiological and radiomics features, highlighting the importance of a truly multimodal analysis.
- The selected predictive model was a Support Vector Machine algorithm with a linear kernel.

Long-term outcomes

Baseline multimodal data could help predict long-term outcomes.

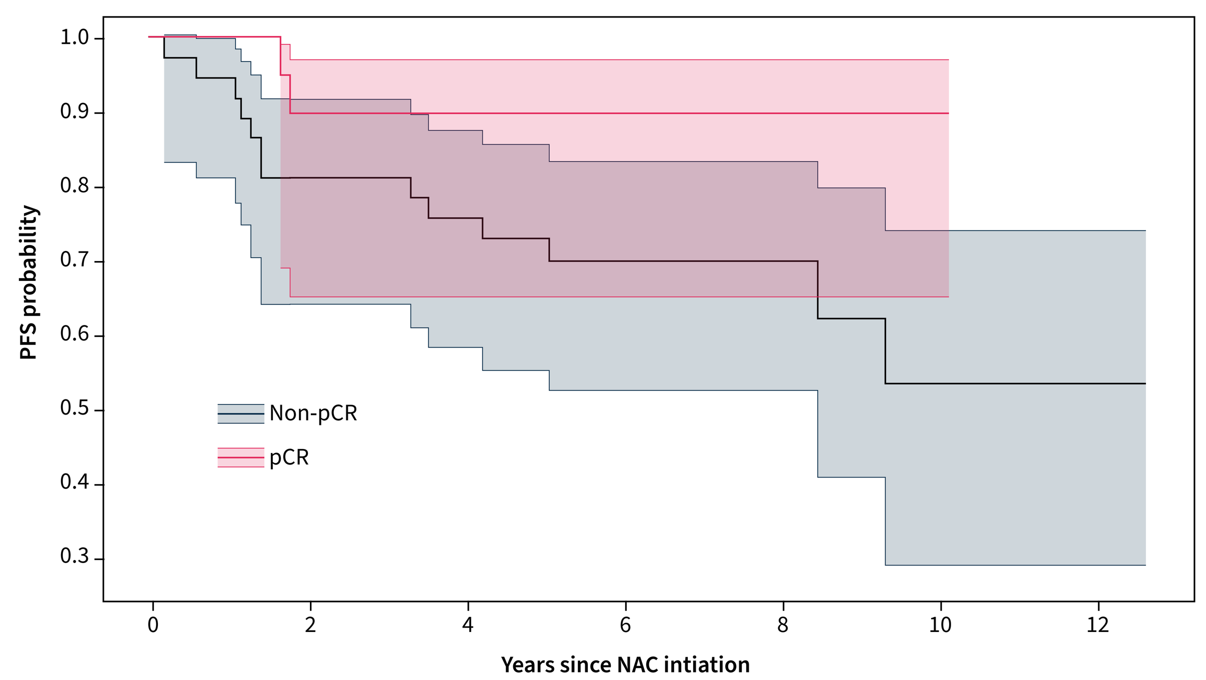

Figure 4. Observed PFS according to cross-validated predictions of pCR status (p=0.077).

Global interpretability

Permutation feature importance measures the decrease in the AUC of the model when a single feature value is randomly shuffled.

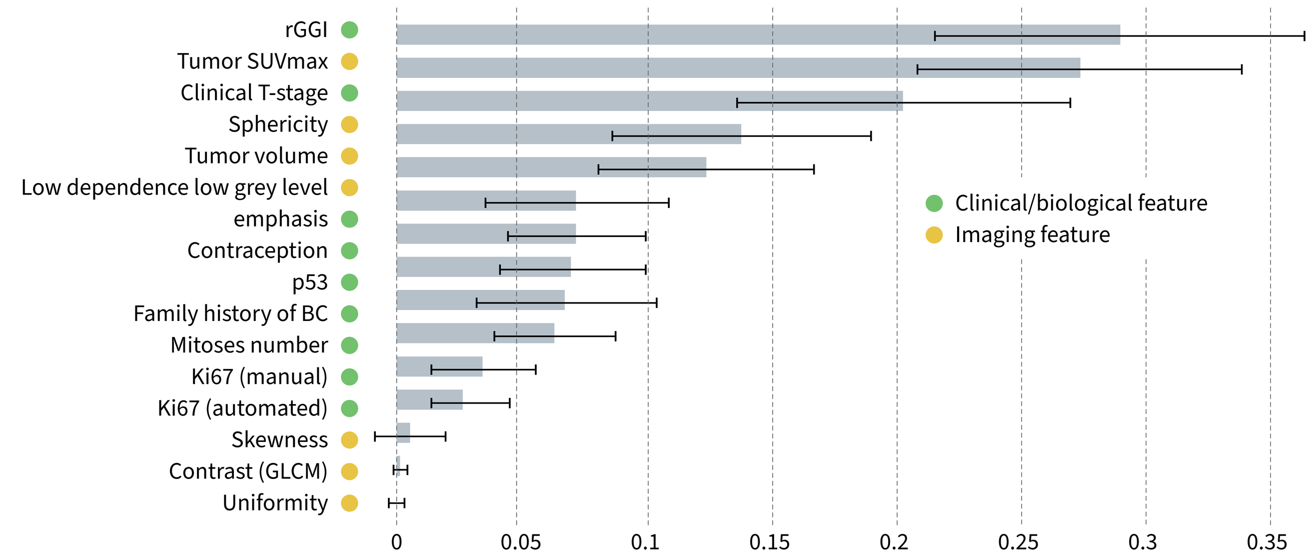

Figure 5. Permutation-based feature importance.

- 4 of the 6 most important features were imaging descriptors
- 3 most important features in the prediction model were *rGGI*, *Tumor SUVmax* and *Clinical T-stage*

Local (patient-specific) interpretability

Patient *PMOL222* had a predicted probability of non-pCR at 22% *(output value)* whereas the averaged prediction in the dataset was 63.1% *(base value)*. Features decreasing the risk level were notably *sphericity* (low value) and *rGGI* (high value) while *clinical T-stage (high value)* was the main feature causing increased risk level.

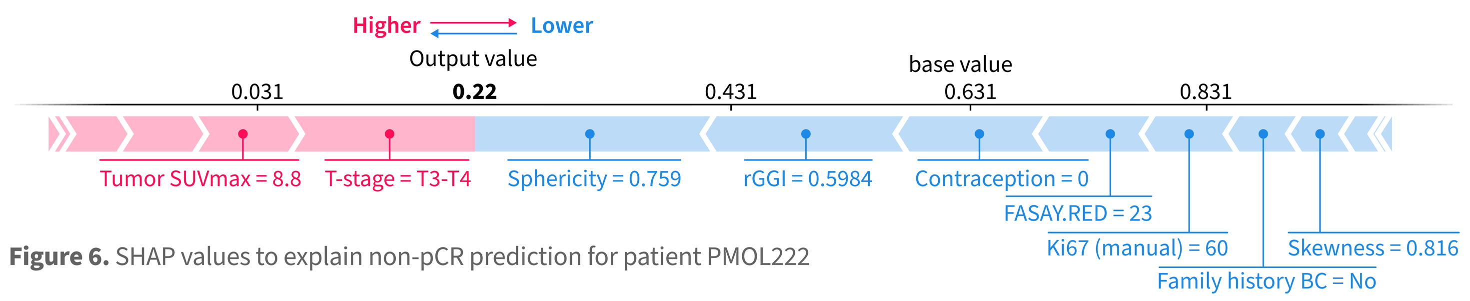

Figure 6. SHAP values to explain non-pCR prediction for patient PMOL222

5 Conclusion and perspectives

Knowledges gain

Proof of concept study suggesting that machine learning applied to baseline multi-modal data can help predicting pCR status after neoadjuvant chemotherapy for TNBC at the individual patient level, as well as stratifying patients to inform long-term outcomes.

Clinical applications

Patients that would be predicted as non-pCR could benefit from concomitant treatment with immunotherapy, or dose intensification.

Global democratization

This algorithm will be further validated in a larger, multicentric cohort.

[1] Inclusion criteria: > 18 years old, non-metastatic TNBC, NAC treatment received before surgery, baseline (before NAC initiation) F-FDG PET/CT imaging available; Exclusion criteria: bilateral cancer, pre-treatment follow-up in an external hospital, missing imaging at baseline, missing pCR status.
[2] A double leave-pair-out cross validation (LPOCV; for outer and inner loops) was applied.

GL-MM-2300002-r1

References: Groheux et al, Eur J Nucl Med Mol Imaging. 2018

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