Quantitative analysis of fiber-level collagen features in H&E whole-slide images predicts neoadjuvant therapy response in patients with HER2+ BC

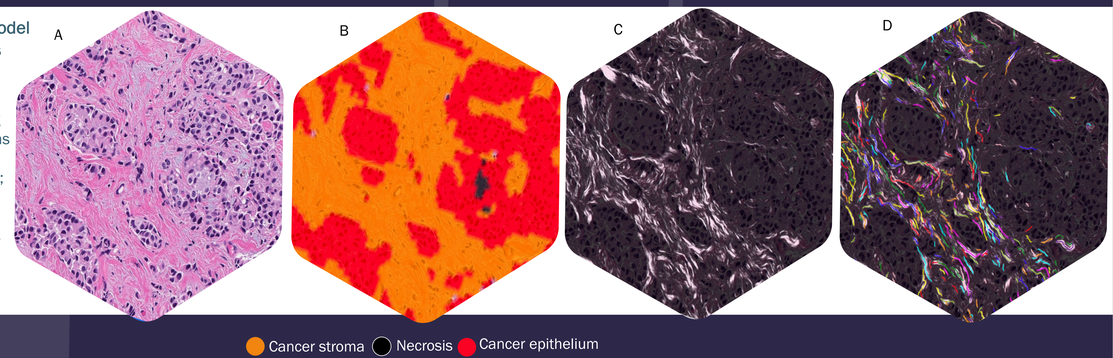
Poster #P5-02-09

BACKGROUND

Neoadjuvant treatment (NAT) combining chemotherapy and HER2-targeted agents is frequently administered to HER2-positive (HER2+) breast cancer (BC) patients, with some experiencing a pathological complete response (pCR) and others having residual disease measured by the residual cancer burden (RCB) score. Here, we investigate associations between treatment response in this patient population and properties of collagen fibers and the tumor microenvironment. Detailed visualizations of collagen were generated by inferred quantitative multimodal anisotropy imaging (iQMAI), a machine learning (ML)-based model that infers fiber-level collagen features from hematoxylin and eosin (H&E)-stained whole slide images (WSIs). iQMAI models were trained on fiber-level collagen images using QMAI, a polarization-based imaging technique that highlights structured substances like collagen in breast tissue[1] or liver tissue.[2]

Figure 3. Tissue Model and iQMAI Overlays

H&E-stained image of BC tissue (A); Tissue model overlay showing predicted tissue regions (B); collagen fibers visualized by iQMAI (C); and colorized collagen fibers showing individual fiber shapes and trajectories in the TME



METHODS

Diagnostic core needle biopsies (N=89) from stage II-III HER2+ BC patients enrolled on the De-escalation to Adjuvant Antibodies Post-pCR to Neoadjuvant THP (DAPHNe; NCT03716180) clinical trial and treated with neoadjuvant paclitaxel/trastuzumab/pertuzumab were digitized into whole slide images (WSI) and analyzed by a ML-based model and iQMAI (Figure 1).

A previously-trained ML model identified regions of BC tissue as invasive carcinoma, ductal carcinoma in situ (DCIS), diffuse inflammatory infiltrate, stroma, necrosis, or normal tissue and generated tissue overlays (Figure 2, Figure 3). Using a transformation of model tissue predictions, additional areas were identified including tumor nests (continuous regions predicted as invasive cancer epithelium), tumor nest borders (stromal region boundaries 10 µm from tumor nests), and bulk tumor borders (stromal region boundaries 300 µm from aggregated tumor nests).

iQMAI identified fiber-level collagen features and fiber feature extraction pipeline characterized properties of all identified collagen fibers in the WSI (on the order of hundreds of thousands per slide), including length, width, tortuosity, and angle (Figure 2). Fiber features were then assessed based on their position within the tumor (*e.g.,* relative to the tumor nest border). Logistic regression univariate analyses explored combinatorial features (*e.g.,* angle of fibers with respect to bulk tumor borders; N=609) for associations with treatment response (Figure 2), where patients with pCR (RCB=0; N=53) were considered responders, while all other cases (RCBI-III; N=36) were designated non-responders (NR). Due to the small size of the cohort analyzed here, raw p-values are reported.

Figure 1. iQMAI H&E Model Training

Paired images of H&E-stained breast cancer tissue scanned on a standard scanner and QMAI are used to train the iQMAI model. Deployed iQMAI can visualize collagen fibers in tissue like QMAI imaging.

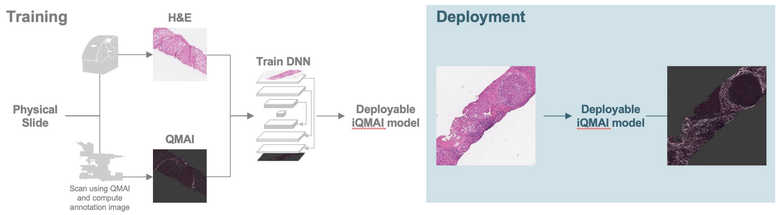
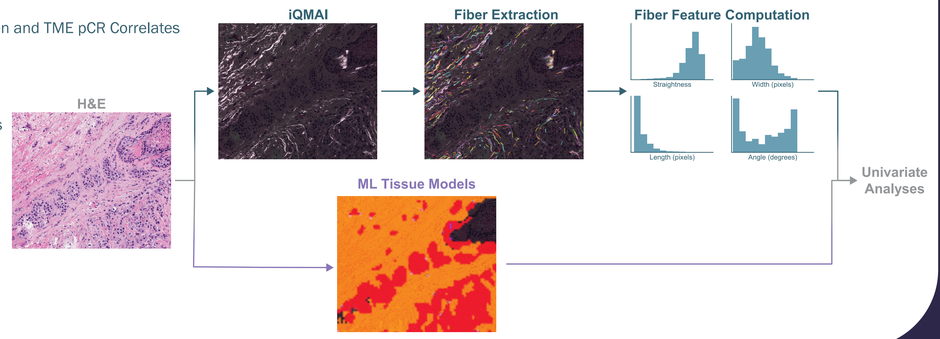


Figure 2. Pipeline for Generating Collagen and TME pCR Correlates

Features are generated from a H&E-stained WSI on two ML-based models – a TME tissue model and iQMAI model. Associations between extracted features and pCR are determined in univariate analyses.



RESULTS

Using estrogen receptor status as a clinical covariate, a logistic regression-based univariate analysis of 609 collagen-associated features revealed six features negatively associated with pCR ($p<0.05$, AUC≥0.75; Table 1). Notable feature themes were identified: 1) fiber tortuosity in tumor nest borders and tumor borders, 2) angle of fibers with respect to tumor boundary, and 3) distribution patterns of fiber widths (Table 1). The presence of fibers perpendicular to tumor boundary tangents was negatively associated with pCR, as was higher fiber tortuosity and thickness in tumor nest borders (data not shown).

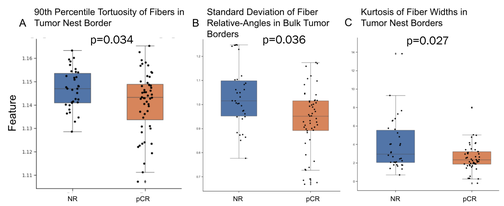
Figure 4 shows three features significantly predictive of pCR. Greater tortuosity or "curviness" of collagen fibers (Figure 4A), the angle (Figure 4B), and distribution (Figure 4C), of the width of fibers are more prevalent in NR.

Table 1. Predictive Value of Combined Collagen Fiber and TME features for NAT NR

Theme	Feature	P-value	AUC
Tortuosity	90th percentile tortuosity of fibers in tumor nest border	0.034	0.79
Tortuosity	Standard deviation of fiber tortuosity in tumor nest borders	0.042	0.80
Tortuosity	Mean tortuosity of fibers in tumor nest borders	0.043	0.77
Angle	Standard deviation of fiber relative-angles in bulk tumor borders	0.036	0.79
Angle	Proportion of fibers with high relative-angle in bulk tumor borders	0.053	0.77
Width	Kurtosis of fiber widths in tumor nest borders	0.027	0.78
Width	Skewness of fiber widths in tumor nest borders	0.038	0.78

Figure 4. Features Predictive of pCR/R

Example features that are predictive of pRC (A) max tortuosity and (B) angel of fibers in tumor borders, and (C) distribution of fiber widths in tumor ne borders



CONCLUSIONS

We have shown that ML-predicted collagen-associated features, measured directly from WSIs of H&E-stained diagnostic BC biopsies, negatively correlate with pCR in this proof-of-concept study. Additional development of this strategy, including the addition of cell identification models and known clinical information, is underway to further refine this novel predictive model.

AUTHORS

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