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Backstory

Uncovering the molecular subtypes of triple-negative breast cancer with a noninvasive radiomic methodology

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In this Backstory, we illustrate how a recent work from our multidisciplinary collaborative group identifies molecular subtypes of triple-negative breast cancer with a noninvasive radiomic pipeline. These findings appeared in the July 2022 issue of *Cell Reports Medicine* (https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(22)00230-0).

The problem

Triple-negative breast cancers (TNBCs), the most aggressive subtype of breast cancer, are characterized by their tendency to recur at an early stage, urgent progression, and a lack of effective therapeutic targets. To gain deeper insight into the intertumor heterogeneity and potential treatment vulnerability of TNBC in the context of precision oncology, we profiled a comprehensive multi-omics landscape of TNBCs in East Asian populations to reveal their characterizations and therapeutic targets. Specifically, transcriptomic clustering classified TNBCs into four subtypes: luminal androgen receptor (LAR), basal-like immune suppressive (BLIS), immunomodulatory (IM), and mesenchymal like (MES).[1–3] We further conducted the Fudan University Shanghai Cancer Center TNBC umbrella (FUTURE) trial based on the therapeutic targets of the distinct subtypes. Subtyping-based precision medicine significantly improved the overall response rate from the previously reported 10% to 29%.[4] However, a convenient and noninvasive method is desperately needed to advance the subtyping of TNBC in clinical practice.

Technical hurdles

Artificial intelligence is an emerging and promising method in the realm of precision medicine. In recent decades, there has been a surge in machine learning research in the processing of medical images. For instance, radiomics recognized gray-level intensity and spatial disparity patterns by extracting high-throughput quantitative image features and correlated these radiomic features with clinical variables or genomic characteristics to predict crucial clinical events noninvasively, which paves the way for the convenient clinical application of some intriguing and crucial findings from the bench side.[5] On this premise, we considered that radiomics might be an appropriate option to achieve our goal. However, some pitfalls restrain the application of radiomics in the clinical context. The first is the redundancy. Tens of thousands of radiomic features are extracted with an acknowledged pipeline. The multicollinearity and redundancy of features cause dimension disasters and make it difficult to select the most informative features involved in specific prediction tasks. Second, there is poor interpretability. Due to the complexity of the calculation process of high-dimensional radiomic features, most of the features are transformed to unexplainable arithmetic formulas and thus lose their spatial and biological interpretability. The third is the irreproducibility. Radiomic features originating from multicenter or distinct scanning machines are usually incomparable because of different scanning protocols or imaging processes.

Our approach

Our research focused on revealing the intertumor and intratumor heterogeneity of TNBC with a radiomic method. In the first step, we established a radiomic model to identify the four distinct subtypes of TNBC. Subsequently, we found a peritumor-heterogeneity-related radiomics feature and interpreted its biological foundation.

We first extracted our radiomic features with the acknowledged "PyRadiomics" package. However, high-dimensional radiomics features might cause redundancy. To address this issue, we tried multistep feature selection. First, features with higher correlation in all feature pairs were removed. Second,

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Above image: Dr. Zhi-Ming Shao working with junior surgeons in the clinic

features with Wilcoxon test false discovery rate > 0.05 between binary groups were removed. Third, the least absolute shrinkage and selection operator (LASSO) was implemented on binary variables to select the most relevant features-predicting labels. LASSO and ridge regression are considered advanced forms of regression analysis that can handle multicollinearity. They use regularization to address overfitting and feature selection and have been widely applied to deal with large amounts of features. We considered LASSO to be suitable for the probably redundant features extracted by PyRadiomics.

In regard to the interpretability of radiomic features, we focused on a specific feature, variance among the MRI sequences of dependence nonuniformity extracted from peritumor region (Peri_V_DN), which was filtered from prognostic radiomic features and found to be correlated with peritumor heterogeneity. Given the important clinical and biological significance, we deeply analyzed the biological foundation of this unique radiomic feature. Intriguingly, we found that tumors with higher Peri_V_DN (i.e., higher peritumor heterogeneity) were immunosuppressive and metabolically dysregulated. In this case, we not only made efforts to improve the interpretability by establishing the relationship between biological characteristics and obscure radiomic features but also to correlate peritumor heterogeneity with immunometabolic alterations.

The publication process

We initially submitted our manuscript to *Cell Reports*. Editor Dr. Kyle Legate told us that our study was a clinical research study and suggested that *Cell Reports Medicine* might have been more suitable for publishing this paper. We sent a presubmission inquiry to *Cell Reports Medicine* and learned from the editors that our manuscript fit into the scope of the journal very well. We submitted our manuscript on January 5, 2022, and the article was sent for review in a week. On February 8, the reviewers' comments were sent back. The major concerns reviewers proposed were the main theme of the article and the performance of external validation as well as the redundancy and irreproducibility of radiomic features. To solve these problems, we reorganized our manuscript, supplemented the results of new external validation cohorts, demonstrated the nonredundancy, and illustrated the reproducibility of our radiomic models. In the consequent minor revision stage, we addressed the reviewers' concern about the moderate performance of the external validation of the TNBC identification model. On June 23, we received an e-mail from the editorial office and were informed that our manuscript was accepted by *Cell Reports Medicine*.

The people behind the science

Three investigation teams specializing in different research directions collaborated to fulfill this work. The work was initiated and led by Professor Zhi-Ming Shao, who is the leader of the multidisciplinary

Members of the Gu lab from the Department of Radiology, Fudan University Shanghai Cancer Center

group of breast cancer research in Fudan University Shanghai Cancer Center. Team members in the Shao lab established a comprehensive dataset from Chinese TNBC patients containing multiomics data and clinical follow-up, conducted radiogenomic analysis, and connected the radiomic features with clinical outcomes and genomic alterations. Team members led by Professor Ya-Jia Gu, the director of radiology at Fudan University Shanghai Cancer Center, curated the original MRI and delineated the tumor area as regions of interest (ROIs). The team led by Professor He Wang from the Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, extracted quantitative radiomic features from these ROIs. Without the intense collaboration from the three teams, our work would not be successfully completed and, ultimately, published. The success of this work is an excellent beginning and provides a template for multidisciplinary cooperation. In the future, we will seek to deepen the series of breast cancer research and conduct more high-quality studies in the field of translational oncology.

Future directions

Although we have made efforts to avoid the redundancy and poor interpretability of radiomic features, we have not fully addressed the irreproducibility of these features and the models we built. On the one hand, we are not sure if our subtyping model would perform well in another dataset. We found no appropriate external validation cohort because it needed matched transcriptomic data and features from magnetic resonance images. On the other hand, we found that the radiomic machine learning model distinguishing TNBC from non-TNBC only achieved a moderate performance in the external

Members of the Wang lab from the Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University

validation cohort, which proves that further efforts are needed to improve the reproducibility of radiomic features and models in multiple centers.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Jiang, Y.Z., Ma, D., Suo, C., Shi, J., Xue, M., Hu, X., Xiao, Y., Yu, K.D., Liu, Y.R., Yu, Y., et al. (2019). Genomic and transcriptomic landscape of triple-negative breast cancers: Subtypes and treatment strategies. Cancer Cell *35*, 428–440.e5. https://doi.org/10.1016/j.ccell.2019.02.001.
2. Gong, Y., Ji, P., Yang, Y.S., Xie, S., Yu, T.J., Xiao, Y., Jin, M.L., Ma, D., Guo, L.W., Pei, Y.C., et al. (2021). Metabolic-pathway-based subtyping of triple-negative breast cancer reveals potential therapeutic targets. Cell Metab. *33*, 51–64.e9. https://doi.org/10.1016/j.cmet.2020.10.012.
3. Xiao, Y., Ma, D., Yang, Y.S., Yang, F., Ding, J.H., Gong, Y., Jiang, L., Ge, L.P., Wu, S.Y., Yu, Q., et al. (2022). Comprehensive metabolomics expands precision medicine for triple-negative breast cancer. Cell Res. *32*, 477–490. https://doi.org/10.1038/s41422-022-00614-0.
4. Jiang, Y.Z., Liu, Y., Xiao, Y., Hu, X., Jiang, L., Zuo, W.J., Ma, D., Ding, J., Zhu, X., Zou, J., et al. (2021). Molecular subtyping and genomic profiling expand precision medicine in refractory metastatic triple-negative breast cancer: The FUTURE trial. Cell Res. *31*, 178–186. https://doi.org/10.1038/s41422-020-0375-9.
5. Pinker, K., Chin, J., Melsaether, A.N., Morris, E.A., and Moy, L. (2018). Precision medicine and radiogenomics in breast cancer: New approaches toward diagnosis and treatment. Radiology *287*, 732–747. https://doi.org/10.1148/radiol.2018172171.