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Multimodal Machine Learning Enhances Risk Stratification And Prognostic Insights In High-Grade Serous Ovarian Cancer

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Abstract : Advances in biomarker development have enhanced cancer insights but often focus on single data modalities, missing the potential of integrated multimodal approaches. For high-grade serous ovarian cancer (HGSC), prognostic outcomes remain variable due to factors like homologous recombination deficiency, age, stage, and residual disease post-surgery. Emerging evidence highlights the prognostic importance of CT and histopathologic analysis, but integrated analysis of these diverse features is underexplored. This study developed a multimodal machine learning framework combining histopathologic, radiologic, and clinico-genomic data from 409 HGSC patients. It identified interpretable features-like necrosis in H&E slides and omental texture on CT-as poor prognostic indicators. The integration of imaging and clinico-genomic data enhanced risk stratification and better correlated with chemotherapy response scores than unimodal approaches, emphasizing the complementary value of multimodal analysis.

Index Terms - Multimodal strategies, Precision oncology, High-grade serous ovarian cancer (HGSC), Risk stratification, Homologous recombination deficiency, Clinico-genomic models, Histopathologic analysis, Radiologic imaging, Computed tomography (CT), Machine learning models, Prognostic variability, Pathological chemotherapy response scores, Omental textural complexity, Necrosis in H&E slides, Multimodal integration.

I. INTRODUCTION

Cancer management involves a complex interplay of diagnostics and therapeutic strategies as patients undergo various stages of diagnosis, treatment, and monitoring. Physicians frequently order an array of diagnostic tests from distinct modalities to direct patient care. This situation creates a significant opportunity to integrate and analyze these diverse digital data sources across large patient populations, unveiling multimodal prognostic features that can contribute to enhanced management of future patients. Genomic profiling of tumor tissue, for instance, has notably improved clinical decision-making, yielding a comprehensive molecular repository for ongoing research. Moreover, conventional imaging methods, such as positron emission tomography (PET) and computed tomography (CT), provide serial assessments of tumor burden during and after treatment, contributing to a wealth of data amenable to machine learning applications. As such, we assert that an integrated approach combining anatomical, histological, and molecular metrics can construct a more holistic “digital biobank” for each patient. Yet, despite the availability of massive datasets, integrating these data remains a challenge, and current advancements in computational methodologies rarely tap into the latent research potential embedded within multimodal data. This chapter aims to explore the integration of diverse diagnostic modalities and the development of innovative machine learning approaches to streamline cancer research and improve patient outcomes.

II. LITERATURE SURVEY

The majority of the discovery cohort was derived from a retrospective clinical database of patients who underwent diagnostic workup and neoadjuvant chemotherapy followed by delayed primary surgery (NACT-DPS) at our institution. We conducted a thorough review of electronic health records (EHR) to identify pathology cases linked to intraperitoneal soft tissue lesions, primarily focusing on the omentum, and expert pathologists selected high-quality specimens for digitization. To enhance the cohort, we examined the institutional data warehouse for patients who underwent MSK-IMPACT sequencing and had available contrast-enhanced CT studies, ensuring only those with clear mutational subtypes based on annotated variants were included. Following this, we reviewed CE-CT scans, excluding those of inadequate quality, and extracted critical variables such as cytoreductive status, chemotherapy cycles, pathologic stage, biopsy accession numbers, and patient age at diagnosis from the EHR. The internal test set was then curated, sampling patients receiving neoadjuvant chemotherapy with known HRD status, who also exhibited omental lesions on CT. In parallel, the TCGA test cohort was selected based on clinical data and pathologic grade from the TCGA-OV project, ensuring that only high-quality diagnostic slides were included. For HRD status inference, MSK-IMPACT sequencing was utilized along with variant and copy number analyses, alongside additional criteria for patient assignment to HRD subtypes. Expert radiologists manually segmented ovarian and omental lesions on pre-treatment CE-CT scans to facilitate imaging feature extraction, which was followed by standardized methods for extracting and selecting relevant radiomic and histopathologic features. The collected data underwent rigorous survival modeling, integrating various modalities to optimize prognostic stratification for patients.

III. RESEARCH METHODOLOGY

Patients with high-grade serous ovarian cancer demonstrate poor prognosis and variable response to treatment. Homologous recombination deficiency status, patient age, pathologic stage, and residual disease status after cytoreductive surgery are important prognostic factors, with recent work also highlighting prognostic information captured in computed tomography and histopathologic specimens. However, little is known about the capacity of combined features to discriminate between patients and explain clinical outcomes. In this work, we developed and integrated histopathologic, radiologic, and clinico-genomic machine learning models to determine their combined impact on risk stratification. We assembled a multimodal dataset of 409 high-grade serous ovarian cancer patients and showed that human-interpretable features, such as necrosis on H&E and omental textural complexity on CT, are associated with worse prognosis. We then integrated these models and demonstrated that the imaging models contain complementary-rather than purely mutual-prognostic information to clinico-genomic prognostic factors, as evidenced by improved risk stratification and stronger association with pathological chemotherapy response score than unimodal models. This work empirically supports multimodal machine learning approaches as a promising path toward improved risk stratification of cancer patients.

3.1 COHORT CHARACTERISTICS

In this study, we analyzed a total of 409 patients, comprising 262 high-grade serous ovarian carcinoma (HGSOC) cases from Memorial Sloan Kettering Cancer Center (MSKCC) for discovery purposes of which, 222 were used for training and 40 for internal testing. Additionally, 147 cases from The Cancer Genome Atlas (TCGA) were included for external validation. The internal test cohort consisted of 40 cases randomly selected from the discovery group prior to analysis. The discovery cohort included 143 patients with Stage IV, 115 with Stage III, along with 3 Stage II and 1 Stage I. In contrast, the external cohort exhibited 31 Stage IV, 103 Stage III, 7 Stage II, and 6 Stage I cases. Median ages at diagnosis were 65 years for the discovery cohort and 60 years for the external cohort. Notably, 72% of discovery patients underwent neoadjuvant chemotherapy followed by surgery, while the external cohort did not have treatment regimens annotated. We also assessed progression-free survival (PFS), reporting medians of 15.9 months for discovery patients and 14.9 months for TCGA testing patients, with significant numbers of censored outcomes. Furthermore, we utilized clinical sequencing to infer homologous recombination deficiency (HRD) status, leveraging various genomic factors across both cohorts.

3.2 CT IMAGING FEATURE SELECTION AND STRATIFICATION

We initiated our investigation by evaluating the prognostic significance of features extracted from pre-treatment contrast-enhanced computed tomography (CE-CT) scans. Fellowship-trained radiologists segmented these scans, specifically analyzing omental implants and adnexal lesions. Employing the training cohort, we identified key radiomic features linked to progression-free survival through univariate Cox

proportional hazards models, leading to the development of a five-feature radiomic signature aimed at minimizing multicollinearity. This signature, derived from various imaging matrices, notably outperformed ovarian lesion features in stratifying patients. The analysis revealed that denser omental zones correlated with higher risks, while larger lower-density zones indicated reduced risks. Overall, unimodal radiomics yielded c-index values of 0.55 and 0.61 in the training and TCGA test cohorts, respectively. By integrating this radiomic model with homologous recombination deficiency (HRD) status via a late fusion strategy, we achieved better stratification within the internal test set, resulting in improved prognostic accuracy for patient outcomes. Here, the highest-risk group exhibited significantly shorter median progression-free survival compared to their lower-risk counterparts, demonstrating the potential of a multimodal approach to enhance patient risk evaluation.

3.3 HISTOPATHOLOGIC TISSUE TYPE CLASSIFIER FOR INTERPRETABLE FEATURES

We proceeded to develop a tissue type classifier utilizing histology images through a weakly supervised learning framework. By annotating tissue types on 65 hematoxylin and eosin (H&E) whole slide images (WSIs), we generated over 1.4 million partially overlapping tiles, each containing 4096 μm^2 of tissue. A ResNet-18 convolutional neural network, pretrained on the ImageNet dataset, was then trained using this extensive dataset. We assessed the model's performance through four-fold slide-wise cross-validation, achieving a balanced classification accuracy of 0.81 ± 0.05 for areas classified by pathologists as fat, stroma, necrosis, and tumor. Notably, the model demonstrated proficiency in identifying small stromal regions at the edges of fat and necrotic areas within tumors, thereby underscoring the effectiveness of weakly supervised deep learning for refining tissue annotations into more detailed categories. The cross-validation results revealed a robust overall performance, although there was some confusion between necrotic and tumor regions. Despite the inherent limitations of weakly supervised learning due to imprecise labeling, the qualitative analysis of the predictions illustrated the model's ability to effectively capture histological structures, suggesting its potential for improving tissue classification accuracy in HGSOC assessments.

3.4 HISTOPATHOLOGIC STRATIFICATION

In our study, we applied a tissue type classifier to a set of 141 hematoxylin and eosin (H&E) whole slide images (WSIs) of soft tissue lesions sourced from pretreatment biopsies. By integrating the resulting tissue type maps with detected cellular nuclei, we generated labeled nuclei (Figure 3.1a). We extracted both cell-type features from these nuclei and tissue-type features from the maps, following the methodologies of Diao et al. We then utilized univariate Cox models on features derived from the training cohort slides to select significant prognostic features (Figure 3.2). Among these, specific tissue-type features, including the overall necrotic area, required adjustments based on specimen sizes during the selection process. Through cross-validation (Figure 3.3), we identified the top four features significantly associated with progression-free survival (PFS): the ratio of necrotic area to stromal area, the perimeter-to-area ratio of the largest tumor component, the skew of maximal hematoxylin of tumor nuclei, and the kurtosis of median eosin of tumor nuclei (Table 3.1). Integrating genomic and histopathologic models improved stratification accuracy, yielding c-indices of 0.65, 0.64, and 0.56 for the training, internal test, and TCGA test sets, respectively. Ultimately, our multimodal approach not only enhanced prognostic differentiation but also correctly adjusted the estimated risk profiles for patients, demonstrating the value of combining histopathologic features with genomic data.

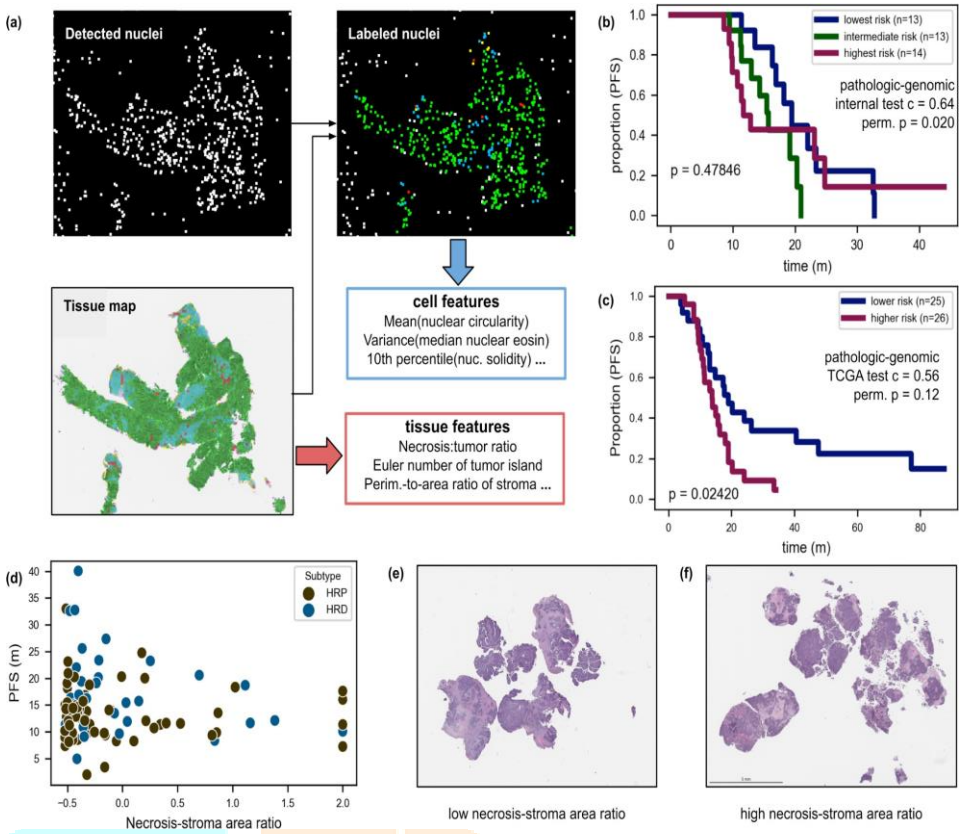

Figure 3.1: Interpretable histopathologic features stratify HGSOC patients by PFS.

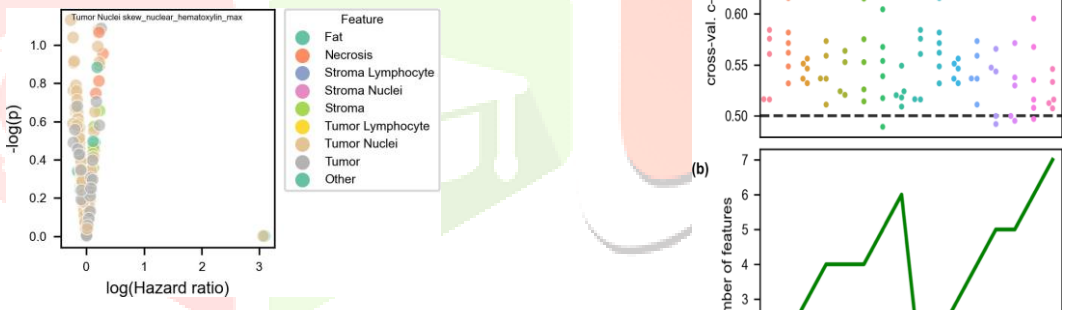

Figure 3.2: Histopathologic feature discovery.

Figure 3.3: Histopathologic feature selection hyperparameters and resultant cross-validation performance.

Table 3.1: Histopathologic Cox model parameters.

Variable	Coefficient
ratio_necrosis_to_stroma	0.17
Tumor_largest_component_PA_ratio	0.21
Tumor_Other_skew_nuclear_hematoxylin_max	-0.23
Tumor_Other_kurtosis_nuclear_eosin_median	0.14

IV. Results And Discussion

The integration of histopathologic, radiologic, genomic, and clinical data into a multimodal prognostic model demonstrated significant improvement in performance over traditional models. In the internal test set, this model exhibited a concordance index of 0.66, outperforming various unimodal models and highlighting its potential for effective risk stratification. Kaplan-Meier analysis indicated that while the HRD status-based model distinguished between two risk groups with median progression-free survival (PFS) of 14.3 and 19.1 months, the multimodal approach enhanced stratification to 12.8, 15.7, and 19.4 months. The observed low Kendall rank correlation coefficients among individual modalities (<0.25) reinforced that distinct information is provided by each modality. Notably, despite similar unimodal c-indices, individual imaging modalities revealed unique patient subgroups, emphasizing complementary strengths in patient risk assessment. Additionally, GHR model findings indicated that poor chemotherapy response scores correlated with higher inferred multimodal risk, further validating the model's clinical utility in optimizing treatment strategies.

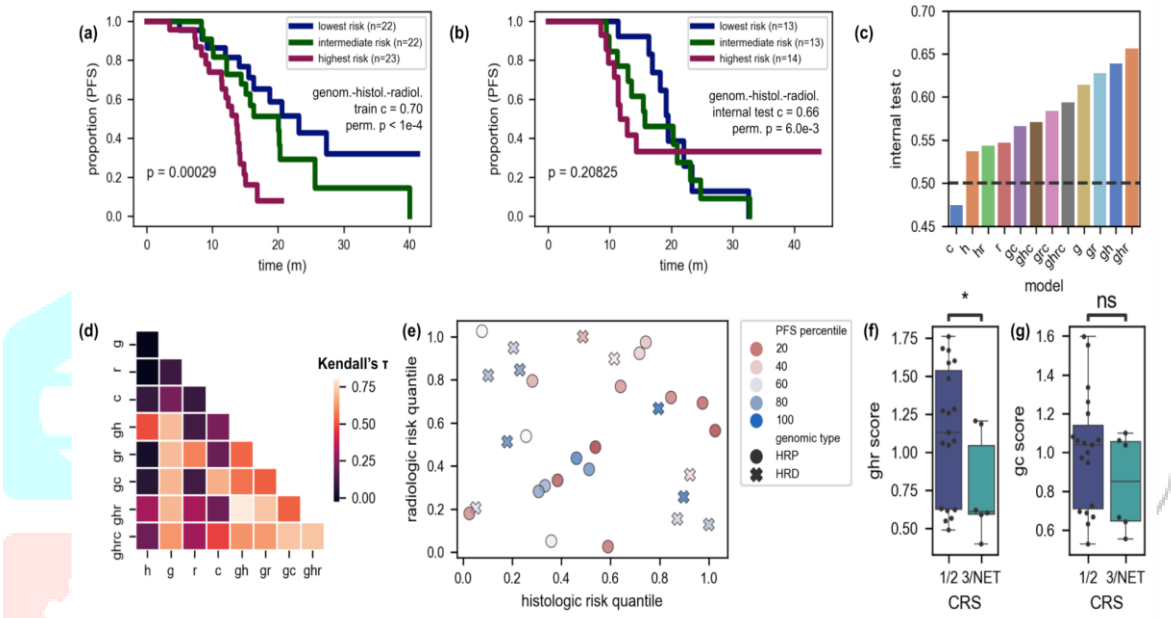

Figure 4.1 : Multimodal integration identifies clinically significant subgroups and improves stratification by response to therapy in the internal test cohort.

The application of machine learning in cancer prognostics is a rapidly evolving area that holds significant promise; however, the potential contributions of multimodal integration across standard diagnostic modalities to risk stratification remain inadequately explored. In this study, we introduced two novel unimodal models aimed at stratifying patients with high-grade serous ovarian cancer (HGSOC) using routine clinical imaging, which we validated on two distinct test sets. Our radiologic model focused on omental implants, revealing that increased heterogeneity-indicated by higher-density zones in Hounsfield Units on contrast-enhanced CT-correlates with poorer patient outcomes. This focus on the omentum is justified, given its prevalent role in HGSOC progression and the relative ease of identifying and delineating these lesions.

Table 4.1: Clinical cox model parameters.

Variable	Coefficient
dps_cgr [1=True]	-0.36
parp_nact [1=True]	-0.31
patient_age	0.39
pathologic_stage [0=III; 1=IV]	-0.09
cycles_nact	0.06

For the histopathologic model, we identified significant prognostic features related to progression-free survival, including ratios of necrotic areas to stroma and tumor morphological characteristics. Notably, our multimodal approach, which integrated clinical imaging data with homologous recombination deficiency (HRD) status, demonstrated an enhanced ability to stratify patients compared to unimodal or clinico-genomic models. While our findings indicate the complementary nature of these modalities, as they illuminate tumor architecture at distinct scales, they suggest that multimodal integration does not universally ensure improved performance. Our results emphasize the ongoing challenge of data limitations, as the dataset of 409 HGSOC patients, while substantial, remains inadequate for more complex machine learning methodologies due to the risk of overfitting. As we advance toward larger, multi-institutional datasets and refined methodologies, the potential for multimodal machine learning in oncology appears promising. Ultimately, our findings advocate for expanded studies utilizing integrated multimodal data to enhance cancer patient stratification across various cancer types.

V. CONCLUSION

This project successfully highlights the potential of multimodal machine learning (ML) in addressing the critical challenges of risk stratification and prognostic assessment in high-grade serous ovarian cancer (HGSC). By integrating histopathologic, radiologic, and clinico-genomic data, the study demonstrates the enhanced accuracy and interpretability achieved through complementary data modalities. Key findings include the identification of novel prognostic features, such as necrosis in H&E slides and omental textural complexity in CT scans, which contribute to a deeper understanding of patient outcomes. The integration of these diverse data types improved predictive capabilities and demonstrated stronger correlations with chemotherapy response scores than unimodal models. These results underline the importance of multimodal approaches in overcoming the limitations of single-modality analyses, offering a more holistic perspective for personalized treatment strategies. This project serves as a proof of concept for the application of multimodal ML in oncology, setting the stage for future research and implementation in clinical settings. The findings not only validate the feasibility of such approaches but also contribute to advancing the field of precision medicine in HGSC and beyond.

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