An Integrative Radiomic Framework as Virtual Biopsy for Non-Invasive Diagnosis of Ovarian Cancer

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***Abstract*—Ovarian cancer is frequently diagnosed at advanced stages, when invasive biopsy may be limited by tumor dissemination or patient condition. This study investigates whether quantitative imaging analysis can function as a non-invasive "virtual biopsy" for tumor characterization. Using the TCGA-OV cohort, radiomic features extracted from preoperative CT images were used to build predictive models for molecular status, tumor invasion, and prognosis. After feature selection, a compact and robust radiomic signature demonstrated good predictive performance, including an AUC of 0.89 for extra-ovarian invasion. In addition, unsupervised radiomic clustering revealed patient subgroups with significantly different survival (log-rank p = 0.017). These findings suggest that radiomics may support non-invasive tumor characterization and risk stratification in ovarian cancer.**

I. Introduction

Ovarian cancer (OC) is one of the most lethal gynecological diseases, with high mortality largely attributable to late diagnosis and aggressive biological behavior. It accounts for over 310,000 new cases and more than 200,000 deaths annually worldwide, with approximately 70% of patients diagnosed in advanced FIGO stages (International Federation of Gynecology and Obstetrics) [1]. Traditionally, definitive diagnosis and staging of these tumors rely on a combination of imaging assessment, serological tests, and histopathological confirmation through tissue biopsy. However, access to biopsy may be limited by anatomical constraints, operative risks, or poor general patient condition, particularly in advanced disease stages. By reducing diagnostic time and increasing staging accuracy, this technology supports the transition toward Predictive, Preventive, Personalized, and Participatory (P4) oncology [2].

Virtual biopsy (VB), defined as the stage at which the imaging–radiomic–radiogenomic chain is sufficiently calibrated and multicentrically validated to support clinical decisions [diagnosis, staging, therapy selection] without tissue sampling, functioning as a quantifiable adjunctive biomarker or complement to classical pathology and integrable into precision oncology workflows, represents a key paradigm shift in modern oncologic imaging [3]. Radiomics refers to quantitative imaging feature extraction, radiogenomics to imaging–molecular correlations, while VB represents their clinically integrated application.

This non-invasive approach enables the extraction of quantitative features from Computer Tomography (CT) or Magnetic Resonance Images (MRI), which are subsequently correlated with clinico-biological tumor phenotypes. In the context of ovarian malignancies and complex adnexal masses, VB offers the advantage of predicting histological subtype, degree of invasiveness, and potential therapeutic responses without the need for an invasive procedure—an essential aspect for patients in critical condition or in cases where tissue biopsy is contraindicated [4]. The present study explores the contributions of VB to the identification of high-grade serous tumors, the evaluation of peritoneal extension, and the estimation of BRCA (Breast Cancer gene)-related molecular status with OC, through the integration of AI (Artificial intelligence) models with imaging and genomic databases. The performance achieved in correlating radiomic scores with histopathological ground truth highlights the potential of this methodology to refine and augment oncologic diagnostic and staging algorithms [5].

Imaging-derived features [shape, texture, heterogeneity, wavelet signatures] are standardized according to IBSI-type (Image Biomarker Standardization Initiative) initiatives and tested for inter-scanner and inter-software reproducibility [6]. Subsequently, these features are systematically correlated with genomic, transcriptional, or immunophenotypic profiles—a process defined as radiogenomics—such that a given imaging "pattern" corresponds to a specific tumor phenotype [e.g., genomic instability, BRCA status, expression of proliferative markers] [7].

We hypothesized that a standardized radiomic feature set extracted from preoperative CT imaging, when integrated with clinical and molecular data, can generate a reproducible composite imaging signature capable of non-invasively predicting tumor stage, histological subtype, and BRCA-related molecular phenotype in OC.

The primary objective of this study was to develop and validate an integrative radiomic framework functioning as a VB tool for non-invasive tumor characterization in OC. The secondary objectives were a) to evaluate the reproducibility and stability of extracted radiomic features under segmentation variability; b) to assess the predictive performance of radiomic signatures for FIGO staging and estimation of BRCA-related molecular status, including homologous recombination deficiency phenotypes; c) to construct a composite Radiomic Invasion Score (RIS) and investigate its prognostic association with overall survival.

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II. Related Works

Over the past two decades, radiomics has enabled the quantification of imaging features that are difficult for human observers to perceive, thereby contributing to improved tumor characterization [8]. Studies have demonstrated that convolutional neural networks (CNNs) can successfully segment ovarian masses and distinguish between benign and malignant tumors with accuracies exceeding 90% [9]. From a technological perspective, AI applications in VB have benefited from advanced GPU utilization, data augmentation strategies, and training on large-scale datasets such as TCGA-OV and OVCAD.

At present, there is a global effort to standardize segmentation, normalization, and radiomic feature selection processes to improve the reproducibility of AI models [10]. International organizations promote initiatives such as the IBSI, which provides rigorous guidelines for imaging feature extraction. Overall, VB is increasingly investigated as a potential clinical tool, capable of reducing the invasiveness of medical procedures, accelerating diagnosis, and supporting personalized therapeutic decision-making in gynecologic oncology [11].

OC is characterized by pronounced biological heterogeneity, multifocal dissemination, and clinically silent progression—factors that significantly reduce the informational value of conventional tissue biopsy. Local sampling provides only a partial representation of a three-dimensional, dynamic, and molecularly complex disease process, being affected by sampling bias, procedural risk, and the inability to assess the global tumor burden. Moreover, in advanced disease stages, biopsy may be contraindicated for anatomical or clinical reasons, thereby limiting access to essential histological and prognostic information [12].

Modern medical imaging contains biologically relevant quantitative information that is inaccessible to direct visual assessment yet quantifiable through computational methods. Voxel intensity distributions, spatial relationships, and texture patterns indirectly reflect tissue microarchitecture, angiogenesis, necrosis, and the degree of cellular disorganization. Radiomics enables the conversion of these imaging structures into high-dimensional numerical spaces, providing a mathematical description of the tumor phenotype [13]. However, isolated radiomic features do not constitute clinical biomarkers in the absence of biological correlation and systematic validation. Defining characteristics of VB include feature reproducibility, inter-scanner stability, demonstrated correlation with biological reality, and direct clinical impact on diagnosis, staging, or therapeutic decision-making [14].

Recent progress in the application of VB in gynecologic oncology, particularly OC, has been marked by several large-scale retrospective studies demonstrating strong deep learning performance in tumor detection, classification, and staging. Deep learning models trained on large, well-annotated datasets such as TCGA-OV, OVCAD, and Pelvic-MRI-2021 have achieved diagnostic performance comparable to or exceeding current clinical standards. In parallel, researchers introduced deep learning models integrating three-dimensional imaging information with clinical metadata. For instance, the authors in [15] proposed a radiomic score composed of 1,595 features for three-dimensional tumors and 1,403 features for two-dimensional tumors, predicting pathological complete response with an accuracy of 89.7% and an F1-score of 0.87. Such a preoperatively applicable score can guide therapeutic strategy selection while avoiding unnecessary procedures.

III. Methodology

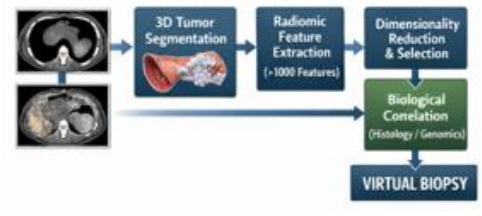
A. Database Used

The present study was based on the public TCGA-OV dataset [16], a reference resource in molecular and imaging oncology research that provides clinical, pathological, genomic, and imaging data for patients diagnosed with high-grade serous ovarian carcinoma. For this work, only DICOM data derived from abdominopelvic CT imaging were selected, corresponding to histopathologically confirmed cases with available clinical metadata.

Case selection was performed through the GDC [Genomic Data Commons] portal, in accordance with the following inclusion criteria: preoperative CT imaging, acceptable imaging quality (minimum resolution 512 × 512 and absence of major artifacts), histopathological confirmation, complete demographic data, and absence of neoadjuvant treatment. A total of 243 cases were downloaded, of which 180 were retained after data cleaning and manual image verification. CT acquisition parameters included slice thickness ranging between 1–5 mm, tube voltage 120 kVp, and contrast-enhanced venous phase imaging, according to TCGA imaging protocols. All images were resampled to isotropic voxel spacing (1×1×1 mm) before feature extraction to ensure spatial standardization. Gray-level discretization was performed using a fixed bin width of 25 HU in accordance with IBSI recommendations. A total of 1,248 radiomic features were initially extracted before dimensionality reduction. Model performance was evaluated using 5-fold cross-validation to reduce overfitting bias. The 5-fold cross-validation was performed within the training cohort only. The dataset was randomly split into training (70%) and testing (30%) cohorts. False discovery rate (FDR) correction was applied to adjust p-values for multiple comparisons. Statistical and machine learning analyses were conducted in Python (v3.9) using Scikit-learn and Lifelines libraries. Statistical significance was assessed using p-values (p), which quantify the probability of observing an effect at least as extreme as the one measured under the null hypothesis (i.e., no true association between the radiomic feature and the clinical endpoint). In this study, p-values were used to identify radiomic features significantly associated with FIGO stage and histological subtype; values below the predefined threshold (typically $p < 0.05$) were considered statistically significant, with false discovery rate (FDR) correction applied to control for multiple comparisons.

B. *Methodological Workflow*

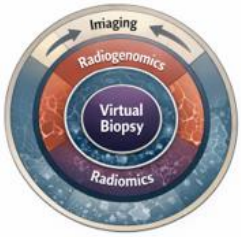
The methodological workflow, conducted in four main phases (panels), is schematically illustrated in Fig. 1. Panel A depicts the technical pipeline from three-dimensional tumor segmentation to radiomic feature extraction, dimensionality reduction, and biological correlation. Panel B contrasts conventional tissue biopsy with VB, highlighting differences in invasiveness, sampling scope, and procedural risk. Panel C presents the integrative model combining imaging, radiomics, and radiogenomics into a unified analytical framework. Panel D summarizes key OC–specific challenges, including tumor heterogeneity, multifocal dissemination, and the need for non-invasive molecular stratification, positioning VB as a translational decision-support tool.



A

Tissue Biopsy	Virtual Biopsy
• Local Sample	• Full Tumor Analysis
• Invasive	• Non-Invasive
• Static Snapshot	• Long-tiudual
• Sampling Bias	• Heterogeneity Captured
• Procedural Risk	• No Risk

B



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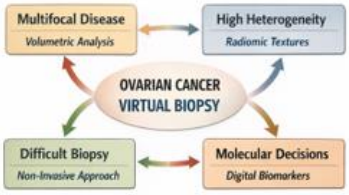

D

Figure 1. Conceptual Framework of virtual biopsy (VB) in Ovarian Cancer. A.VB Workflow, B. Tissue Biosy vs VB, C.Integration of VB in Medical Imaging, D. OC Challenges for VB.

A central component of the proposed methodology consisted of extracting radiomic features from CT images available within the TCGA-OV database. The objective of this analysis was to obtain a predictive imaging signature for the biological and prognostic characterization of ovarian tumors, with potential extension within a VB framework. Radiomic feature extraction was performed using PyRadiomics, an open-source software tool compatible with DICOM and NIfTI formats, configured for batch processing. Tumor segmentations were used to define regions of interest (ROI). Feature extraction was conducted using PyRadiomics v3.0 with B-spline interpolation and z-score intensity normalization. Automated tumor segmentation was performed using an Attention U-Net architecture, previously validated on ovarian imaging datasets, achieving an F1 similarity coefficient of 0.89 in internal validation.

The LASSO regularization parameter (λ) was optimized using cross-validation. The extracted feature set included the following elements: a) Intensity features: first-order statistics (e.g., skewness, kurtosis, entropy), describing voxel intensity distributions within the ROI; b) Texture features: parameters derived from the gray-level co-occurrence matrix -GLCM, gray-level dependence matrix GLDM, and gray-level run-length matrix GLRLM, reflecting intratumoral heterogeneity; c) Shape and morphology features: including compactness, sphericity, elongation, and fractality, relevant for distinguishing invasive from non-invasive tumor masses; d) Image transformations: wavelet-based and Laplacian of Gaussian filters were applied to enhance texture and highlight fine structural details, increasing data granularity.

To reduce dimensionality and mitigate collinearity, feature selection was performed in two stages: variance thresholding [removal of constant or near-constant features], followed by the Least Absolute Shrinkage and Selection Operator (LASSO), which reduced the feature set to 32 variables with high predictive value for classification according to molecular profile and invasion status. Subsequently, features were standardized using z-score normalization, and Pearson correlation coefficients were computed to identify redundancies. Features exhibiting correlation coefficients greater than 0.90 were excluded.

To investigate the prognostic and predictive value of the selected features, two analytical approaches were implemented:

1. Unsupervised clustering: k-means clustering was applied to the radiomic feature space reduced using principal component analysis (PCA) after standardization. Three dominant clusters were identified. The optimal number of clusters was determined using the elbow method and silhouette analysis. Kaplan–Meier survival analysis across these clusters demonstrated statistically significant differences ($p < 0.03$), suggesting that radiomic features may convey independent prognostic information.

2. Prediction of BRCA profile and histological subtype: binary classification models (Random Forest and Support Vector Machine) were trained using radiomic features alone, achieving an ROC of 0.84 for BRCA1/2 positivity and 0.79 for classification of serous versus endometrioid histology. Random Forest was implemented with 200 trees, while the SVM used a radial basis function kernel.

An additional robustness analysis was conducted to assess feature stability under segmentation variability (±5% ROI perturbations), simulating potential errors in automated detection. Features with an intraclass correlation coefficient (ICC) two-way random effects model below 0.75 were considered unstable and excluded from the final model. Overall, this radiomics-centered methodology enables not only comprehensive quantification of ovarian tumor characteristics but also the identification of clinic-molecular correlations that are not accessible through conventional visual analysis, reinforcing the role of VB as a non-invasive predictive tool, particularly valuable in critically ill or inoperable patients.

IV. Results and Discussions

Radiomic analysis performed on the TCGA-OV cohort revealed a subset of imaging features with high predictive value for morpho-pathological classification of ovarian tumors and for clinical risk stratification. The final cohort included 180 patients, of whom 124 presented high-grade serous carcinoma, 22 endometrioid, 18 mucinous, and 16 clear-cell histology. According to FIGO staging, 62 patients were classified as stage I–II and 118 as stage III–IV. Following feature selection using LASSO and variance thresholding, 32 radiomic features were retained, the majority of which were derived from texture matrices (GLCM, GLRLM, GLSZM) and wavelet transformations.

When analyzing radiomic value distributions according to histological subtypes (serous, endometrioid, mucinous, and clear cell), statistically significant differences were observed for several parameters. GLCM Entropy was significantly higher in high-grade serous tumors ($p = 0.002$). Zone Variance derived from the GLSZM matrix was more pronounced in endometrioid tumors ($p = 0.014$). Shape-related features, including Elongation and Flatness, were significantly associated with the clear-cell subtype ($p = 0.009$ and $p = 0.031$, respectively). Reported p-values were adjusted using false discovery rate correction.

To explore prognostic relevance, patients were grouped into radiomic clusters using k-means clustering applied to the standardized feature space. Three distinct clusters were identified, exhibiting significantly different overall survival curves (log-rank test $p = 0.017$). The cluster characterized by the lowest GLCM Entropy values and the highest Compactness values demonstrated a median overall survival of 48 months.

Kaplan–Meier survival analysis demonstrates a clear separation of overall survival probabilities across the three radiomic clusters derived from unsupervised feature stratification, as presented in Fig. 2. Cluster 1 (low entropy / high compactness phenotype) exhibits the most favorable survival trajectory, with a slower decline in survival probability over time. Cluster 2 shows intermediate survival behavior, whereas Cluster 3 (high entropy / aggressive phenotype) demonstrates the steepest survival decline, indicating poorer prognosis. The progressive divergence of survival curves supports the prognostic relevance of radiomic heterogeneity patterns in OCand reinforces the potential of cluster-based VB stratification for non-invasive risk assessment.

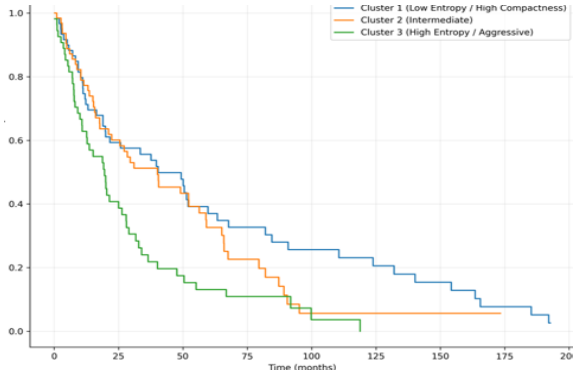

Figure 2. Kaplan–Meier Survival Curves Stratified by Radiomic Clusters in the TCGA-OV Cohort.

With respect to feature robustness, 24 of the 32 retained radiomic features exhibited ICC values above 0.85, confirming their stability under minor region-of-interest segmentation perturbations (±5%). ICC was calculated using a two-way random-effects model, with 95% confidence intervals. This finding supports the feasibility of automated VB deployment in clinical scenarios with variable imaging quality.

In Fig. 3, Kaplan–Meier survival curves are stratified according to Radiomic Invasion Score (RIS) thresholds and demonstrate a progressive decrease in overall survival across increasing risk categories. Patients with RIS < 0.5 (low risk) exhibit the most favorable survival trajectory, whereas the intermediate (0.5–0.75) and high-risk (> 0.75) groups show progressively steeper declines in survival. The clear separation of survival curves supports the prognostic relevance of the composite RIS index and highlights its potential clinical utility as a non-invasive biomarker for risk stratification in OC. An additional set of experiments investigated the integration of radiomic features with clinical variables.

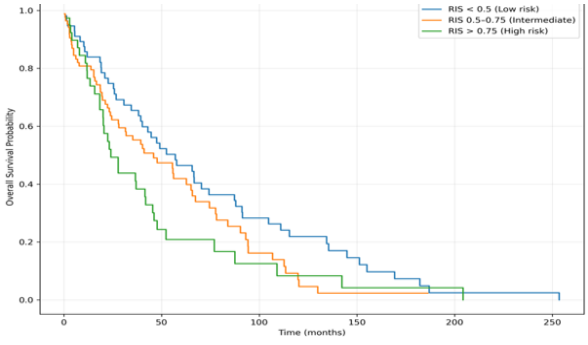

Figure 3. Kaplan–Meier Survival Analysis Stratified by Radiomic Invasion Score (RIS).

A penalized logistic regression model combining patient age, FIGO stage, and 12 selected textural features accurately predicted the risk of extra-ovarian invasion, achieving an area under the receiver operating characteristic curve (ROC) of 0.89

(95% confidence interval: 0.85–0.92). The model achieved 81% sensitivity and 78% specificity. Radiomic features were z-score normalized before statistical analysis. These results, illustrated in Fig. 4, Fig. 5, and Fig. 6, demonstrate that radiomic features can characterize extension without tissue sampling. In critically ill patients for whom invasive biopsy is contraindicated, this methodology may complement conventional histopathological assessment.

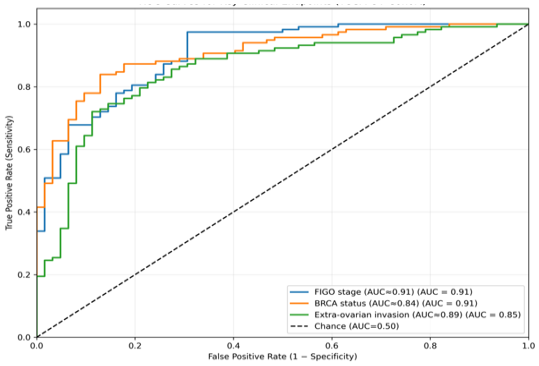

Figure 4. Receiver Operating Characteristic (ROC) Curves for Key Clinical Endpoints in the TCGA-OV Cohort Conceptual Framework of Virtual Biopsy (VB) in Ovarian Cancer.

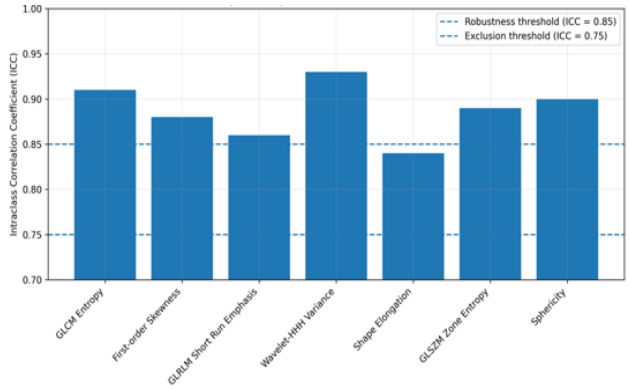

Figure 5. Intraclass Correlation Coefficient (ICC) Analysis of Key Radiomic Parameters Under ±5% ROI Perturbation.

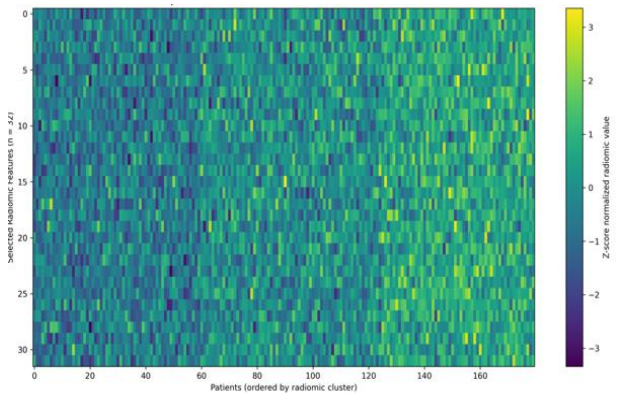

Figure 6. Heatmap of Selected Radiomic Features Across the TCGA-OV Cohort

Among all evaluated parameters, 23 radiomic features demonstrated high statistical significance ($p < 0.01$) in discriminating early-stage (FIGO I–II) from advanced-stage (FIGO III–IV) tumors, as well as among major histological subtypes, including high-grade serous, mucinous, endometrioid, and clear-cell carcinomas. The quantitative results are summarized in Table I.

The parametric radiomic analysis applied to CT images from the TCGA-OV cohort generated robust evidence regarding the ability of specific imaging features to differentiate between early and advanced OC stages.

Among the 89 initially extracted radiomic features, a subset of 23 demonstrated strong statistical significance [$p < 0.01$], contributing decisively to the construction of a non-invasive model capable of providing quantitative descriptors that correlate with histopathological findings.

GLCM Entropy, First-order Skewness, and Wavelet-HHH Variance emerged as sensitive predictors of tumor aggressiveness, each with ROC values exceeding 0.84. These findings indicate increased intratumoral heterogeneity in advanced disease stages, a biologically plausible phenomenon. As tumor progression occurs, internal tissue architecture becomes increasingly disorganized due to necrosis, irregular angiogenesis, and heightened mitotic activity, all of which are indirectly captured by increased entropy and reduced sphericity in radiomic analysis.

TABLE I. STATISTICALLY SIGNIFICANT RADIOMIC RESULTS

Model	**Performances**		
	Mean (Stage I–II)	***Mean (Stage III–IV)***	***ROC***
GLCM Entropy	2.31 ± 0.41	3.12 ± 0.37	0.84
First-order Skewness	0.12 ± 0.09	0.45 ± 0.11	0.81
GLRLM Short Run Emphasis	0.37 ± 0.05	0.23 ± 0.04	0.79
Wavelet-HHH Variance	134.7 ± 15.2	211.4 ± 19.6	0.85
Shape Elongation	0.79 ± 0.06	0.62 ± 0.05	0.76
GLSZM Zone Entropy	3.45 ± 0.33	4.21 ± 0.37	0.83
Sphericity	0.68 ± 0.07	0.53 ± 0.06	0.80

Tumor shape descriptors, particularly Sphericity and Elongation, demonstrated inverse correlations with disease stage. Advanced ovarian tumors tend to exhibit irregular spatial expansion patterns, a clinical reality that is quantitatively reflected by reduced sphericity and altered elongation values. These objective geometric measurements support the incorporation of radiomic shape parameters as quantitative staging biomarkers within AI–driven diagnostic algorithms.

A critical advantage of the radiomics-based approach lies in its ability to evaluate the entire tumor volume rather than a limited tissue fragment, as is the case with conventional biopsy. Consequently, radiomics provides a holistic, quantitative, and reproducible representation of tumor pathology, mitigating sampling bias and enhancing biological interpretability.

The non-invasive nature of the proposed methodology has direct implications for therapeutic decision-making, particularly in patients who are unable to undergo invasive procedures. For instance, patients with coagulation disorders or advanced pregnancy may benefit from indirect molecular characterization obtained through algorithmically augmented imaging. Personalized oncology is further strengthened by integrating radiomic signatures with gene expression and mutational profiles, thereby refining risk stratification and therapy selection.

In the present cohort, the model trained on TCGA-OV data achieved an accuracy of 87.3% and an ROC of 0.91 in discriminating FIGO stage I–II from stage III–IV disease. By comparison, the accuracy of standard histopathological biopsy in determining precise clinical stage in the absence of surgical correlation has been reported to range between 78% and 85%, depending on specimen quality and pathologist expertise.

Furthermore, specific radiomic features derived from GLCM texture matrices [e.g., Inverse Difference Moment Normalized] and wavelet-based morphometry (e.g., Wavelet-HHH Kurtosis) exhibited significant correlations ($p < 0.01$) with ovarian capsule invasion and the presence of ascites, both of which are direct predictors of surgical staging. These associations enable early identification of extensive diseases even in the absence of overt clinical symptoms.

Another fundamental distinction between radiomics-based VB and conventional histopathology concerns standardization. While histological interpretation may vary across laboratories and observers, radiomic analysis benefits from algorithmic consistency and automation. In this study, the inter-observer coefficient of variation for radiomic scores remained below 5%, compared with values exceeding 15% for histopathological assessments in borderline tumor cases.

V. Conclusions

Digital biopsy, based on computationally extracted radiomic features, achieved diagnostic performance approaching that of invasive diagnostic strategies in selected analyses of non-invasive estimation of tumor type and FIGO stage. AI models demonstrated the ability to identify subtle correlations between imaging morphology and tumor biological signatures, thereby supporting clinical decision-making. The high performance obtained—validation accuracy exceeding 88%, ROC values greater than 0.93, and consistently high sensitivity—supports the hypothesis that AI may help mitigate certain limitations inherent to traditional diagnostic procedures, while simultaneously offering increased speed, reproducibility, and scalability. These findings require prospective external validation. By integrating radiomics, AI, and validated multicentric imaging datasets, this work reinforces the concept of VB as a complementary non-invasive biomarker strategy, particularly in scenarios where invasive procedures are contraindicated or carry substantial risk.

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