Molecular Therapy
Oncology
Review

Quantitative and qualitative metrics of tumor stroma in predicting ovarian cancer outcomes and expansion of its study with AI-based tools

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Epithelial ovarian cancer remains one of the deadliest gynecologic malignancies, with late-stage diagnosis, high recurrence rates, and resistance to platinum-based chemotherapy contributing to poor survival outcomes. Central to the effective management of ovarian cancer is the thorough evaluation of diagnostic and prognostic indicators. Critical determinants encompass the extent of the tumor; its stage and grade; and level of the circulating biomarker, CA-125. Additional tumor cell-centric factors such as BRCA1/2 mutation status, homologous recombination deficiency, and folate receptor-alpha (FRα) protein levels inform initial treatment and maintenance strategies. Unfortunately, these markers alone cannot fully predict outcomes or significantly improve survival rates. This review emphasizes the body of data suggesting that both quantitative and qualitative metrics of tumor stroma play a crucial role in the prognosis and outcomes of epithelial ovarian cancer. We examine quantitative and qualitative metrics such as stromal proportion, tumor density, stiffness, and texture. We explore how artificial intelligence (AI) tools advance the measurement of these parameters, offering unprecedented opportunities to integrate stromal biomarkers into clinical decision-making. By synthesizing emerging evidence, we propose a framework for leveraging stromal properties—individually and in combination—as novel prognostic indicators to improve outcomes for patients with ovarian cancer.

INTRODUCTION

At the core of managing epithelial ovarian cancer (EOC) is a comprehensive assessment of prognostic factors. EOC is the most common type of ovarian malignancy arising from epithelial cells. Depending on the cell of origin, the histologic subtypes include serous (high and low grade), mucinous, endometrioid, and clear cell.[1] EOC remains the second leading cause of death among gynecologic cancers.[1] Because EOC is typically asymptomatic in its earlier stages, about 75% cases remain undetected until reaching advanced-staged forms of the disease. Importantly, there remains no effective screening test to detect ovarian cancer at an early stage.[1,2] Key prognostic factors include histologic subtype, stage and grade, and concentration of the ovarian cancer circulating marker CA-125.[2] In addition, tumor cell-centric genetic and molecular markers of cancer cells, such as BRCA1/2 mutation status,[3–5] homologous recombination deficiency (HRD) status,[3–5] and folate receptor-alpha (FRα) protein levels,[6–8] play crucial roles in guiding initial treatment decisions, maintenance therapy, and long-term outcomes. The standard first-line treatment for advanced EOC involves a combination of cytoreductive surgery and chemotherapy with carboplatin and paclitaxel.[9–11] For patients with advanced disease or those who have undergone suboptimal debulking surgery, the angiogenesis inhibitor bevacizumab may be added to the treatment regimen.[12]

Treatment response is typically monitored using imaging and serial evaluations of CA-125 levels.[2] Metrics such as the rate constant of CA-125 elimination (KELIM score) provide valuable insights into patient responses to platinum-based therapies and inform subsequent treatment adjustments.[13–17] Patients with tumors that have BRCA1/2 mutations or high HRD scores may benefit from maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors, which have been shown to improve outcomes in this subset.[3–5,18] Conversely, patients whose tumors do not respond to multiple cycles of standard treatment and whose tumors express certain markers such as high levels of the FRα marker may be eligible for targeted therapies such as mirvetuximab soravtansine-gynx.[6–8] The tumor microenvironment

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has been a dominant research focus, and, although promising targets in the immune microenvironment have been identified,[19,20] the application of targeted immunotherapies into clinical trials for the treatment of EOC has unfortunately not demonstrated significant improvement in survival outcomes.[21–26]

Despite major advances in recognition of the molecular profiles of ovarian and other malignant tumor subtypes, therapeutic drugs targeting putative molecular biomarkers have overwhelmingly failed in producing cures or even clinically meaningful improvements in overall survival (OS), regardless of viable biologic mechanisms. Revising strategies for drug development begins with more holistic view of the ovarian tumor microenvironment, starting with its overall composition and biophysical characteristics. With that perspective in mind, this review emphasizes quantitative and qualitative metrics of tumor stroma, including tumor-stroma proportion (TSP), tumor stiffness, density, and texture in relation to their significance for ovarian cancer outcome. Even further, we also delve into how this perspective has strong potential to merge with the fast-emerging field of artificial intelligence (AI)-based tools used to measure these metrics, to aid in predicting ovarian cancer prognosis and outcomes. Advancements in AI provide researchers with innovative tools to analyze stromal features with unparalleled precision and efficiency. Taken together, the merging of a new school of thought to ovarian cancer drug development centered on incorporating assessable characteristics of tumors with their stroma, accelerated by emerging AI tools, provides a new paradigm that challenges current approaches to treatment of patients with ovarian cancer and similarly drug-refractory forms of malignancy.

QUANTIFYING TUMOR STROMA IN RELATION TO EOC OUTCOMES: TSP AS A NOVEL AND EASILY ASSESSED PROGNOSTIC BIOMARKER FOR EOC

Tumor stroma serves as a dynamic scaffold essential to sustain cancer growth and progression.[27] The individual cellular components that comprise the stroma have been extensively investigated in ovarian and many other epithelial forms of malignancy. Specifically, the TSP (also often referred to as tumor stroma ratio, or TSR), a basic histological measure of the stromal content within a tumor (Figure 1A), is based on tissue biopsy staining performed as part of routine clinical diagnosis. Leveraging assessment of TSP based on readily available specimens avoids any need for additional biopsies and additional testing and overall provides a simple and cost-effective prognostic tool that can be applied from the time of diagnosis.[28] In the era of increased recognition of financial toxicity of cancer care, the possibility that such a low-cost predictive assessment tool can exist and could be readily applicable worldwide, if validated appropriately, is an especially welcomed proposition.

TSP was initially investigated in the field of gynecologic oncology nearly two decades ago. The prognostic value of TSP in advanced-stage EOC was first identified in a 2010 French study of 194 patients.[29] The study identified a cutoff of greater than 50% stroma (stroma-rich tumors) as an independent predictor of OS, with a hazard ratio (HR) of 1.45 ($p = 0.011$).[29] The 50% threshold has been evaluated and linked to poorer prognosis in multiple cancer types.[30–34] Notably, TSP performed comparably to traditional prognostic factors such as disease stage and residual disease status in EOC.[29] Importantly, TSP was applicable across multiple histological subtypes,[29] highlighting its broad relevance in EOC (Figure 1B).

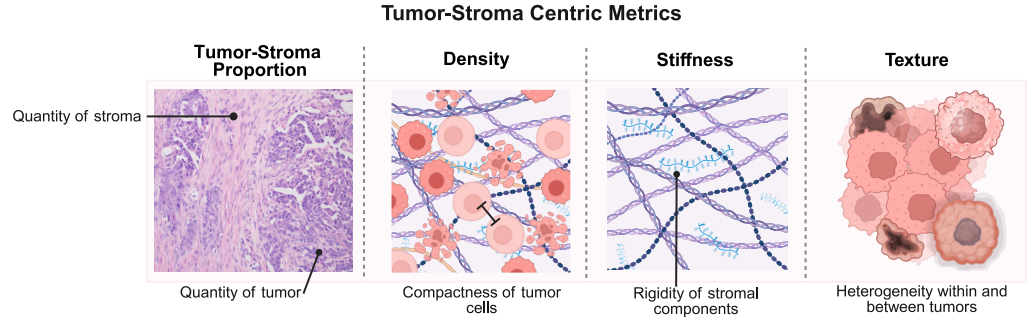
Subsequent studies have further reinforced these findings. A larger cohort of 838 patients with EOC demonstrated that stroma-rich tumors, as assessed in 10% increments by pathologists, correlated with advanced disease, higher recurrence rates, and increased lymph node metastases.[34] Using the same 50% cutoff, researchers observed that stroma-rich tumors were significantly associated with shorter progression-free survival (PFS) (39 vs. 29 months, HR 0.731, $p < 0.001$) and worse OS (58 vs. 50 months, HR 1.172, $p = 0.001$) (Figure 1B).[34]

TSP had been associated with worse survival outcomes, but our group explored the relationship specifically between TSP and platinum resistance. In an initial cohort of 24 ovarian cancer patients prospectively enrolled on study following diagnosis of a new pelvic mass, 80% of platinum-resistant tumors were stroma rich, compared to only 26.3% of platinum-sensitive tumors ($p = 0.047$).[35] These results were validated in a follow-up study by our group utilizing 192 patients with high-grade serous ovarian carcinoma (HGSOC) enrolled in a multi-institutional international clinical trial.[28] In this study, high TSP was linked to shorter OS (HR 1.867, $p = 0.002$) and PFS (HR 1.586, $p = 0.02$) (Figure 1B).[28]

A study combining pathologist evaluation with a deep learning computational pipeline to automate TSP scoring further confirmed its prognostic value in a cohort of 340 patients with advanced-stage HGSOC.[36] Among patients who underwent primary debulking surgery, stroma-rich tumors were significantly associated with worse OS (HR 1.64, $p < 0.001$) and shorter PFS (HR 1.57, $p < 0.001$) (Figure 1B).[36] While this association in OS was not observed in patients treated with neoadjuvant chemotherapy, stroma-rich tumors consistently predicted poor PFS in both treatment groups.[36] Additionally, there was a strong correlation between pathologist-determined TSP and automated TSP scoring, underscoring the reproducibility and reliability of this measure.

While there is a growing body of data that higher TSP using the 50% cutoff is associated with a worse prognosis for patients with EOC, what is not known is which cell populations (or populations taken together) constituting the stroma are driving more aggressive tumor phenotypes at the cellular level. Is it cancer-associated fibroblasts, or vascular endothelial composition, or any one of or a series of immune-infiltrative cell subtypes or all of the above? While ongoing investigations may unravel this mystery at a deeper level for scientific understanding, it remains clear that the consistent association of high tumor-stroma content with poor outcomes across diverse studies and methodologies underscores the importance of stromal quantity as a prognostic factor in EOC.[30–34] Quality of the stroma

A



B

Study	Metric	Sample Size (N=)	Study type	Summary	Significant Statistics
Labiche et al. (2010)	TSP	194	Retrospective	Stroma rich tumors (greater than 50%) had poorer OS in OC	HR 1.45, p=0.011
Lou et al. (2024)	TSP	295	Retrospective	Stroma rich tumors had poorer PFS and OS, and twice as likely to be chemoresistant	PFS HR 1.586, p=0.02; OS HR 1.867, p=0.002
Chen et al. (2015)	TSP	838	Retrospective	Stroma rich tumors had significantly shorter PFS and reinforced 50% threshold for stroma contents in EOC	Median PFS 29 mo in stroma rich vs. 39 mo in stroma poor, p<0.001
van Wagensveld et al. (2023)[a]	TSP	340	Retrospective	Utilized automated deep learning model to score TSP, and demonstrated significant association with survival outcomes for manual and deep learning	PFS HR 1.54, p=0.003; OS HR 1.37, p=0.024
Tothill et al. (2008) and Leong et al. (2016)	Stiffness	285	Retrospective	Identification of molecular subtype of high grade OC Mesenchymal- characterized by extensive desmoplasia within stroma demonstrate poor survival outcomes	PFS, p=0.012; OS, p=0.034
Sharma et al. (2014)	Stiffness	9 human cell lines	In vitro	Cisplatin-resistant OC cells were significantly stiffer than cisplatin-sensitive cells via Atomic Force Microscopy	Correlation between Stiffness and platinum sensitivity, R^2= 0.76, p=0.002
Wei et al. (2021)	Stiffness	132	In vivo/in vitro	Identified TAGLN as stiffness-responsive gene that may contribute to increased stiffness in OC, high expression correlated with poor prognosis	PFS HR 1.27, p=0.00035; OS HR 1.22, p=0.0034
Lei et al. (2015)	Stiffness	50	In vitro	OC cell cultures grown on 3D collagen matrix (stiffer) exhibited higher rates of EMT gene expression and increased chemoresistance	3D matrix IC_{50} 154±5.9 μmol/L^{-1}[b] vs. 2D matrix 41±1.8 μmol/L^{-1}[b]
Danala et al. (2018)[a]	Density / Texture	91	Retrospective	Identified new imaging characteristics of tumor density and texture to develop model to predict PFS	PFS AUROC (4 tumor characteristics model)- 0.810±0.045[b], p<0.05
Qiu et al. (2016)[a]	Density	30	Retrospective	CT image feature analysis of tumor density, volume, and heterogeneity can predict 6 month PFS with higher accuracy than RECIST guidelines	PFS AUC 0.831±0.078[b]; 76.5% accuracy vs. 60% (RECIST)
Veeraraghaven et al. (2020)**	Density / Texture	75	Retrospective	CT image analysis of tumor density and heterogeneity between the primary tumor and metastatic lesions more accurately predicts platinum resistance and PFS	PFS HR 1.38, p=0.009, AUROC platinum resistance: 0.78, p<0.001
Zhang et al. (2024)[a]	Density	286	Retrospective	Integration of texture characteristics from PET images to conventional methods more accurately predicts platinum resistance	AUC 0.928 (95% CI: 0.872-0.984)

Figure 1. Characterization of tumor-stroma-centric metrics and summary of their relevant studies in epithelial ovarian cancer

(A) Depicts the tumor-stroma metrics discussed throughout the review. (B) Summary of pertinent studies discussed in the review. Abbreviations: AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; CT, computed topography; EMT, epithelial-mesenchymal transition; HR, hazard ratio; IC_{50}, concentration of carboplatin to inhibit 50% of cell growth; PFS, progression-free survival; OS, overall survival; PET, positron emission tomography; TSP, tumor stroma proportion; 2D, two-dimensional; 3D, three-dimensional. [a]Study used artificial intelligence techniques. [b]Data expressed as mean ± standard deviation. Created in BioRender, Madill, M. (2025); https://BioRender.com/dqcrkdj.

notwithstanding, its sheer abundance confers unfavorable clinical outcomes, potentially by serving as a barrier to drug penetration and facilitating tumor progression, because of underlying resistant mechanisms,[37] or is representative of a resistant stromal phenotype.[38–41] Assessment of TSP provides a potentially novel, widely applicable, and practical prognostic marker for patients with EOC as it can be ascertained from tumor specimens at the time of first diagnosis, which is comparatively advantageous to the established or putative biomarkers in this space. It is implicitly cost efficient in comparison to genomic and transcriptomic data, because no additional resources are required (only H&E-stained tissue slides and microscopy needed for diagnosis) other than pathologist time to perform simple analysis.[42,43] TSP has even been validated using multiple methods of quantification from manual pathologist review to computer-automated or assisted technology.[36,44–47]

TUMOR STIFFNESS AND ITS MEDIATORS PREDICT OUTCOMES IN EOC

Biophysical properties of malignant tumors are heterogeneous, well recognized, and established in the basic sciences; at the same time, no

aspect of the biophysical properties of ovarian cancer is included in the clinical decision-making equation when it comes to treatment selection or sequence.[1] Tumor stiffness is one example of a biophysical property that has gained interest in and of itself as a potential therapeutic target, and it plays a role in development of TSP. Tumor stiffness is a term that reflects the rigidity of environment produced by the extracellular matrix (ECM) particularly during cell growth (Figure 1A).[48] The stiffening of tumors appears to occur because of a desmoplastic reaction and metabolic changes in stromal cells in response to their environment.[49] The exact causes of this desmoplastic reaction are complex and multifactorial (changes in environment—substrate, pressure, or inflammatory response) but result in increased deposition and reorganization of the ECM and its components.[49] Variations in both tumor stiffness and stiffness of tumor environment (or substrate) have corresponded in ovarian and other cancers to promote or hinder tumor progression.[50–53]

Mesenchymal HGSOC is a subtype of EOC with extensive myofibroblast proliferation, poorer survival outcomes, and increased platinum resistance, which could be related to increased tumor stiffness.[54,55] In comparison to non-mesenchymal EOC tumors, mesenchymal tumors have increasing stiffness with increasing tumor growth.[56] Stromal stiffness correlates with platinum resistance[41] and cellular changes that further lead to increasing stiffness (Figure 1B).[56] The development of stromal stiffness may be the underlying etiology for the poorer prognosis seen with stroma-rich ovarian malignancies.

Genetic pathways that appear to be regulated by the ECM and its stiffness have been found to be independent prognostic predictors in ovarian cancer, further supporting the importance of stiffness to the progression of ovarian malignancies. STAT3 is a transcription factor that responds to the ECM stiffness, and its role in tumorigenesis has been established in various cancers including ovarian carcinomas.[48,57–60] *In vitro* studies of STAT3 transcription demonstrated upregulation in ovarian cancer cells exposed to a stiff substrate (mimicking the stiffness of ECM), which promotes malignant cell proliferation.[48] Overexpression of FBP1, a regulator of STAT3, increases sensitivity to cisplatin *in vitro*, and significantly lower levels of FBP1 have been found in ovarian cancer cells compared to normal ovarian cells.[61] Similarly, *in vitro* studies of actin cytoskeleton regulation (via Rho GTPase activation) in human ovarian cancer cell lines demonstrated that activation of Rho GTPase, increase cell stiffness, and increased cellular resistance to cisplatin.[41] The interplay of STAT3/Rho GTPase with tumor stiffness underscores the possible pathologic mechanisms from increased tumor stiffness that promote platinum resistance and tumorigenesis in ovarian cancer[41,61]

Tissue stiffness not only varies between normal and malignant cells but also varies among primary and metastatic ovarian cancer sites, supporting inter-tumor heterogeneity within patients and its role in disease progression. When compared to primary tumors, omental nodules were found to be stiffer, largely due to increased collagen deposition and desmoplasia.[62] To investigate if modulation of stiffness of the environment around cells could impact the progression of ovarian cancer cells, metastatic cancer cells were cultured on soft and stiff substrates.[62] *In vitro*, metastatic disease grown on varying substrate stiffnesses demonstrated changes to ECM assembly, increased proliferative and invasive properties, and increased resistance to platinum-based chemotherapy.[56,62] This indicates the regulatory interplay of tumor stiffness in response to mechanical environmental cues.

The regulation of transgelin (TAGLN), an actin crosslinking protein, is a key component in this biomechanical difference in metastatic ovarian cancer cells *in vivo*, so the genomic profiles of ovarian cancer tumors were evaluated for TAGLN expression. Among 132 patients with EOC, overexpression of TALGN was associated with shorter OS (1.22, 95% confidence interval [CI] 1.07–1.40) and PFS (HR = 1.27, 95% CI 1.11–1.44) (Figure 1B).[62] Though the genomic profiles do not delineate expression from tumor or stromal cells, this underscores the impact tumor stiffness, and its regulation, may play in the progression of ovarian cancer.

A major component of stroma and tumor stiffness is the orientation and composition of collagen within the ECM. The role of collagen alignment in cancer progression and prognosis was originally illustrated in breast cancer following the development of second harmonic generation (SHG) microscopy.[38,63] Best categorizations of ovarian cancer collagen architecture have required three-dimensional models of similar SHG images and identified distinctive patterns among high-grade serous, endometrioid, and benign ovarian cells. Distinctive collagen patterns of patients with a genetic predisposition to HGSOC were also identified, and further study could help predict and depict the progression of ovarian malignancy.[64] Application of AI to digital pathology provides the ability to quantify tumor-stromal features such as collagen organization.[65] In breast cancer, more stiffly aligned collagen fibers were associated with shorter disease-free survival.[66,67] Though ovarian cancer does have a more complex collagen architecture than breast cancer,[64] less disordered collagen architecture was similarly associated with higher risk of death.[68,69] Interestingly, chemotherapy treatment and density of immune-infiltrated cells within stroma are associated with changes in collagen architecture and organization in EOC.[68,69]

The composition of various collagen types has proven to correspond to platinum resistance and disease progression in ovarian cancer.[70,71] Type 1 collagen is the most common structural collagen within tumor stroma, and its accumulation is associated with poor prognosis.[72] *In vitro*, type 1 collagen has been associated with epithelial-mesenchymal transition, a process associated with the proliferation and invasion of cancer cell, in several malignancies.[73–75] In EOC, cells rich in type 1 collagen-induced upregulation of the pathways related with mesenchymal changes and chemoresistance to carboplatin and paclitaxel.[70] Type 1 collagen is theorized to serve as a structural barrier promoting chemoresistance, but newer studies demonstrate its role in regulating pathways for cancer invasion and progression.[38,70–72] Type II and IV collagen contribute to the strength of connective tissue and the basement membrane, respectively, and are associated with EOC

invasion and tumor growth.[76–79] EOC cells express lower type IV collagen, preventing basement membrane remodeling and promoting invasive disease.[77,80] Tumor stroma is impacted by the composition of collagens and plays a role in chemoresistance and poor prognosis in EOC.

The stiffness of normal and cancer cells is a dynamic feature of both cell-intrinsic and cell-extrinsic factors that respond to and are regulated by their environment. Tumor cells react to mechanical changes in their environments that promote stiffness of tumor through changes in alignment and composition of the ECM. Increasing stiffness confers poor prognosis, increased progression/growth, and facilitate chemoresistance in EOC (Figure 1B). Tumor stiffness is a potential novel target to mediate or prevent to improve outcomes in EOC.[41,49,50,61]

TUMOR DENSITY AND TEXTURE ARE NOVEL AND TESTABLE PROGNOSTIC FACTORS FOR EOC: CALL FOR BROADER INVESTIGATION OF THESE FACTORS USING RADIOMICS

Over the past decade, technology in the field of radiologic research has transitioned in numerous ways from theoretical to more practical with advancements in diagnostic imaging spurred by improving nuclear medicine therapies for solid tumors.[81] Hand in hand with this relatively rapid clinical advancement has been the emergence of radiomics that has refined the ability to identify specific components of tumors and surrounding organs more systemically and beyond the traditional confines of two-dimensional imaging. Although not stroma-specific, radiomic-based assessment of tumors can be leveraged to assess tumor components individually for association with clinical outcomes. Tumor density and texture are essential radiological features identifiable through imaging techniques such as computed tomography (CT) scans, positron emission tomography/computed tomography (FDG PET/CT), and magnetic resonance imaging (MRI).[82–84] Due to the incongruous terms throughout the radiomic literature to categorize novel tumor characteristics, for the purpose of this review, "tumor density" specifically refers to how "solid" or "compact" a tumor or a region of a tumor is from a biophysical perspective. In contrast, the term "tumor texture" refers to the variations in patterns observed within a tumor of its regions as assessed by examining the intricate details of radiological images and can be considered a property that falls under the broader category of "tumor heterogeneity" from a physical microenvironmental perspective (Figure 1A).[85] Interestingly, measurement or other assessment of tumor density and texture can be obtained from routine CT scans, thus providing a highly unique and non-invasive method for assessing biophysical properties of tumors. However, the current application of imaging still concentrates on basic radiologic assessments of tumor size in two dimensions (length and width), as well as shape, and anatomic site of origin or of metastatic spread.

Assessment of tumor texture and density provides a fertile field for creating a new category of testable correlative biomarkers of prognosis and of treatment response in epithelial ovarian carcinomas, and beyond. The supposition rests on the premise that these factors can be associated with survival outcomes in various solid tumors, including ovarian cancer, and assessed for reliability of prediction of treatment efficacy. For example, a computer-aided detection (CAD) framework was developed to predict PFS in patients with high-grade ovarian carcinoma undergoing neoadjuvant chemotherapy.[86] The approach utilized preoperative CT scans and evaluated imaging changes 4–6 weeks post-therapy. Specifically, the CAD schema analyzed 159 imaging features grouped into four categories: density, shape, wavelet, and texture, to forecast 6-month PFS.[86] Two quantitative imaging markers derived from these features were compared against the Response Evaluation Criteria in Solid Tumors (RECIST) scoring which is clinically used to assess treatment response in ovarian cancer patients.[87,88] The results revealed that pre-treatment imaging identified tumor density-related features—skewness, contrast, and uniformity—as the strongest predictors of PFS with areas under the receiver operating characteristic curve (AUROCs) of 0.684 ± 0.056, 0.652 ± 0.059, and 0.643 ± 0.058, respectively. In contrast, features reflecting tumor shape, such as volume and compactness, showed the greatest predictive power when assessing changes between pre- and post-treatment imaging (AUROCs of 0.771 ± 0.050 and 0.755 ± 0.051, respectively).[86] Overall, the newly identified cluster of image markers outperformed RECIST scoring, achieving a higher predictive accuracy for 6-month PFS (80.2% vs. 74.7%) (Figure 1B).[86]

These results were corroborated in a separate, albeit smaller, study involving thirty patients.[89] This study utilized a similar schema, though less complex than discussed earlier, for assessing changes in three image features related to tumor volume, density, and density variance. The findings from this second study indicated that the AUROCs were 0.773 ± 0.086, 0.680 ± 0.109, and 0.668 ± 0.101 for each of the three features, respectively.[89] When these features were combined, the AUROC value improved to 0.831 ± 0.078. Additionally, the decision-tree classifier demonstrated a higher predictive accuracy (76.7%) compared to the RECIST guideline, which had an accuracy of 60.0% (Figure 1B).[89]

This study and others represent a growing trend of investigation at the intersection of radiomics and the tumor microenvironment as novel prognostic and predictive biomarkers for EOC that would exceed capabilities of the currently limited, principally blood and tissue assessment-based, biomarkers in common clinical use. In a separate study, Veeraraghavan et al. analyzed the differences in imaging between primary tumors and their metastatic sites in patients diagnosed with high-grade ovarian carcinoma and developed a cluster dissimilarity (cluDiss) model that integrates both inter-site (differences between metastatic sites) and intra-site (variations within a single site) radiomic tumor heterogeneity.[90] The study involved 75 patients and synthesized not only imaging data but also clinical variables such as age, disease stage, and surgical resection status. Additionally, genomic sequencing data, specifically copy-number burden, were analyzed to examine the correlation between genomic changes

and imaging characteristics. The results of this study showed that the cluDiss model was more effective than traditional radiomic or clinical-genomic measures alone in predicting PFS and platinum sensitivity in ovarian cancer patients.[90] Specifically, when combined with clinical and genomic data, the model's predictive power significantly improved, yielding an HR of 1.03 (95% CI: 1.01 to 1.05, $p = 0.002$) and an AUC of 0.78 (95% CI: 0.77 to 0.80).[90] These results highlight the potential of integrating features related to tumor texture with clinical and genomic data as diagnostic and prognostic tools in ovarian cancer.[90]

Use of nuclear imaging such as PET/CT provides an additional layer of promising data that is also being explored. Zhang et al. reports the acquisition of tumor texture information from FDG PET/CT imaging to evaluate its effectiveness in predicting resistance to platinum-based treatments in 286 patients diagnosed with high-grade serous carcinoma.[91] The study extracted conventional quantitative indicators from the PET/CT scans such as tumor size, shape, and location and Haralick texture features,[92] an advanced method that analyzes the spatial arrangement of pixels in the images to capture subtle variations in tumor texture.[91] Using these indicators, the researchers developed three sets of predictive models to assess platinum resistance, a conventional model based on standard features from the CT and PET images, a model based solely on the Haralick texture features, and a model that integrated both.[91] The results of this study showed that the texture model performed particularly well, achieving an area under the curve (AUC) of 0.904, while the conventional model reached an AUC of 0.790.[91] They also showed that the best-performing model was the integrated model, which combined both conventional and heterogeneity features, resulting in an impressive AUC of 0.928.[91] In addition to evaluating predictive accuracy to platinum resistance, this study also looked at the relationship between the tumor texture features as measured by PET/CT scans and key biomarkers associated with ovarian cancer prognosis and outcome—Ki-67 and p53.[93–96] The results by Zhang et al. showed a strong correlation between some of the extracted features of tumor texture and these markers. Specifically, there was a correlation between the feature Hounsfield unit kurtosis, which measure the uniformity of texture and density of a tumor[97] and the immunohistochemical score for p53, with a correlation coefficient (ρ) of 0.718 ($p < 0.01$) in the 86 patients for which p53 immunohistochemical staining was available.[91] Similarly, among 84 patients who had Ki-67 immunohistochemical staining, the contrast-specific entropy feature, a measure of heterogeneity of a tumor.[98] demonstrated the strongest positive correlation with the Ki-67 immunohistochemical score, with a correlation coefficient (ρ) of 0.759 ($p < 0.01$).

In summary, the literature discussed earlier highlights the significance and potential of tumor density and texture features as reliable biomarkers. These features can be used alone or in combination with clinically established markers for the diagnosis and prognosis of ovarian cancer. Thus, this and other potential forthcoming studies like this provide important angles toward integrating existing knowledge in the field with radiomic features, an approach that conceivably would have far-ranging influence through application to other forms of relevant cancers as well if proven successful.[99,100]

APPLICATION OF AI EXPANDS THE LANDSCAPE OF OVARIAN CANCER RESEARCH

The field of AI has experienced remarkable progress over the past two decades, driven by advances in computational technology and the development of deep learning techniques.[101] AI comprises algorithms and neural networks capable of self-learning, with applications spanning diverse domains.[101] In the medical field, as shown in Figure 2, AI addresses the challenge of analyzing vast datasets, enabling automated learning, pattern recognition, and continuous refinement. This capability has been harnessed for various clinical applications, including developing treatment algorithms, diagnostic tools, and risk stratification models across multiple diseases.[101] Specifically in ovarian cancer and other solid tumors, AI research has predominantly focused on histologic and radiologic characterization and diagnostic accuracy, but the application of AI to pathology has expanded the knowledge and ability to quantify elements of tumor stroma.

AI has shown promise in mitigating inter-observer variability in histopathological diagnoses of ovarian malignancies. A machine learning model trained on a dataset of 948 cases, validated externally, achieved a diagnostic concordance of 80.97% ± 0.03%.[102] While this model did not outperform expert gynecologic pathologists, it surpassed the performance of general pathologists, underscoring its potential as an adjunct diagnostic tool.[102] Further, deep learning models have been employed for histopathological subtyping of HGSOC, a task prone to significant variability.[103] A model trained on H&E-stained slides subtyped HGSOC into categories such as papillioglandular, immune reactive, solid and proliferative, and mesenchymal transition, achieving mean accuracies of 0.897 and 0.910 across two cohorts.[103] While subtyping is not yet standard clinical practice, AI offers the scalability and generalizability necessary to facilitate such advancements within resource-constrained settings.

AI has also been employed to identify histologic subtypes of ovarian malignancies using preoperative imaging, aiding in treatment decision-making. For instance, a deep learning-based radiomic nomogram (DLRN) was developed to differentiate between type I and type II EOCs.[104] Type I EOCs are characterized by slower progression and chromosomal stability, while type II EOCs, including HGSOC and carcinosarcoma, exhibit rapid progression and chromosomal instability.[104] Utilizing radiomic features from MRI images of 427 patients, alongside clinical variables such as parity, human epididymis protein 4 (HE4) levels, and menopausal status, the DLRN achieved an accuracy of 84% in discriminating between the two subtypes, with an AUC of 0.866 in external validation.[104] Distinctive imaging features, such as irregular tumor shape, were linked to the invasiveness of type II EOCs, underscoring the potential of AI to extract clinically relevant imaging features beyond human interpretation.[104]

Cytoreductive surgery is a cornerstone in ovarian cancer management, with AI models aiding in the assessment of surgical feasibility

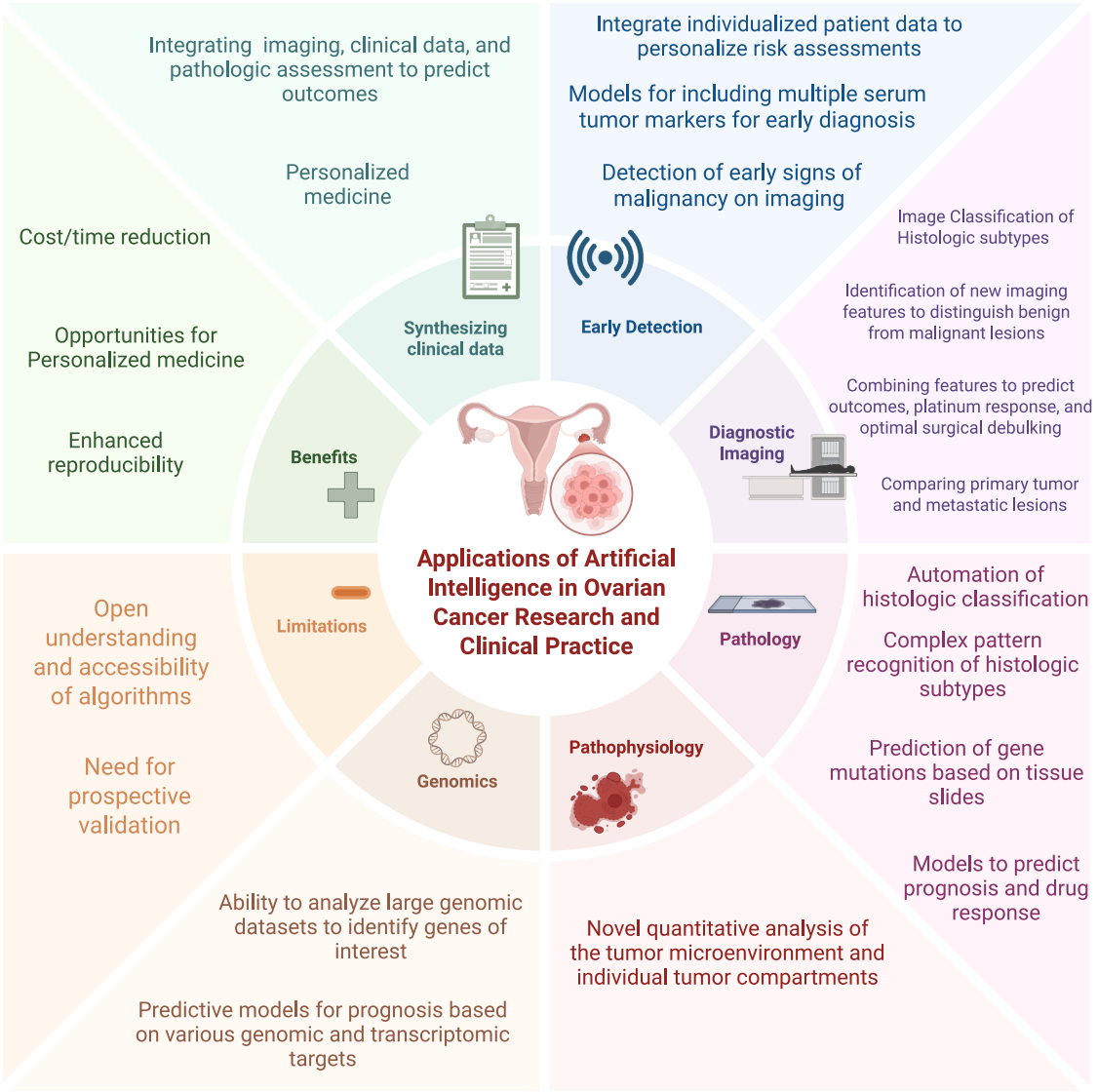


Figure 2. Application of artificial intelligence in ovarian cancer research and clinical practice

Categorization of various areas of practice and research where artificial intelligence has been applied and benefits and limitations of its application. Created in BioRender, Madill, M. (2025); https://BioRender.com/9cvsfq2.

and survival outcomes.[105] Laios et al. applied an eXtreme gradient boosting (XGBoost) algorithm to predefined clinical and operative predictors, achieving an AUC of 0.866 in predicting optimal cytoreduction.[106] Similarly, another XGBoost model predicted survival outcomes with high accuracy (88.72%; AUC 82.38%), highlighting key factors such as histology, stage, age, and grade.[107] These models demonstrate the utility of explainable AI in aligning with established clinical knowledge while offering personalized insights tailored to individual patient characteristics.

In EOC, computational pathology entails the application of AI to analyze digital pathology images (often H&E whole-slide images) to extract data beyond human capability to identify and quantify novel tumor features.[65,108,109] The spatial relationships between immune and non-immune cells within individual tumor compartments (stroma, epithelium, and invasive tumor front) were explored with AI, and subsequent model was predictive of OS in ovarian cancer (HR 1.96, $p = 0.04$, CI = 1.06–3.76).[110] One of the stromal prognostic features included in the model was the ratio of stromal clusters in close proximity to other stromal clusters (HR 1.34),[110] and it accentuates the importance of stromal quantity and density in predicting EOC outcomes. As discussed earlier, collagen architecture plays a role in tumor growth and invasion in EOC, but the effect of immune mediators on collagen disruption was unclear, so a computational

pathology model was developed that helped delineate this relationship by quantifying stromal immune cells and collagen entropy (disorganization).[68] EOC patients at higher risk for disease progression demonstrated lower density of immune cells and lower entropy (i.e., more organized collagen architecture), and the inverse was seen in the low-risk population,[68] which suggests that immune cells mediate collagen disorganization and confer improved outcomes.[68,69] Computational pathology has both broadened our knowledge of tumor stroma and reinforced its prognostic value in EOC and other cancers.[30,66,108,111]

AI has demonstrated unparalleled capabilities in identifying risk factors and disease progression patterns in ovarian cancer, often exceeding human performance. Moreover, when integrated with expert input, AI enhances diagnostic and prognostic accuracy, paving the way for personalized medicine. However, most AI applications in ovarian cancer remain retrospective and susceptible to sampling bias, limiting their clinical impact (Figure 2). Prospective validation and integration into clinical workflows are critical next steps to fully realize AI's transformative potential in ovarian cancer management.

CONCLUSION

In the era of deep focus on molecular oncology and isolated cellular subsets, examining the stroma in its full context in relation to tumoral components may provide an equally if not more efficient approach to uncovering tissue-based biomarkers of prognosis and therapeutic response. This review emphasizes the evolution and dynamic interplay between the tumor and its stromatous elements in growth and metastases of ovarian carcinomas over time.

As shown in Figure 1B, tumor-stroma-centric metrics in EOC lack prospective investigation in larger, more diverse cohorts to establish their scope and clinical utility. Prospective clinical studies to validate these markers, such as TSP, are feasible, with or without the use of AI, and may aid in prediction of drug response[112] and prognosis. Future research should focus on prospectively validating radiomic models that integrate novel features like tumor density and texture, with genomic or other clinical data, to alter clinical practice and improve outcomes. For example, these models can quantify the feasibility of optimal debulking (to appropriately time cytoreductive surgeries), improve detection of early-stage disease, and differentiate between benign or malignant tumors prior to biopsy (Figure 2).[100,104,113]

These translational applications may prove beneficial, but understanding the causal relationship between these tumor-stroma metrics may prove invaluable to identifying therapeutic targets and optimal drug sequences.[39,114] To date, such anti-tumor-stromal agents have not been designed for use in clinical trials in EOC.[39,114] The application of AI-driven stroma-centric models (both H&E- and radiomic-based) has limitations that required their refinements. These limitations lie in data quality and standardization which are inherent to the use of multi-institutional datasets. In this respect, developing standardized protocols for sample collection and processing would be paramount. While some publicly available sources like The Cancer Genome Atlas program exist, the scarcity of well-annotated H&E images represents a challenge. Lastly, validation and clinical implementation that translates AI-based models from research to the clinical setting will require conducting extensive validation across diverse patient cohorts and establishing regulatory guidelines for clinical deployment.[109]

The landscape of ovarian cancer has been vastly expanded by the application of AI, because it not only enhances the measurement of stromal attributes but also enables the discovery of new targets within the stroma. This dual approach—targeting both tumor cells and their supportive microenvironment—offers a promising pathway to advance precision medicine and improve outcomes for ovarian cancer patients.[65,68,108,111]

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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