

Advances in Ultrasonic Differential Diagnosis between Ovarian Clear Cell Carcinoma and Atypical Ovarian Endometrioma

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Abstract

Ovarian clear cell carcinoma (OCCC) is a distinct subtype of epithelial ovarian cancer, characterized by a propensity for early metastasis, resistance to platinum-based chemotherapy, and poor prognosis. It is closely associated with endometriosis, with more than 50% of cases concurrent with endometriosis. Ovarian endometrioma (OMA) is the most common manifestation of endometriosis; among OMAs, atypical ovarian endometrioma (AE) exhibits features such as thickened cyst walls, papillary projections, and irregular septations, which overlap with the ultrasound findings of some early-stage OCCC, posing considerable challenges in preoperative differential diagnosis. Transvaginal ultrasound, as the first-line imaging modality for ovarian lesions, plays an irreplaceable role in distinguishing benign from malignant lesions. However, conventional two-dimensional and color Doppler ultrasound relies heavily on the subjective judgment of the examiner, with limited capacity to differentiate atypical lesions. In recent years, emerging technologies including contrast-enhanced ultrasound, elastography, radiomics, and artificial intelligence have developed rapidly, extracting diagnostic information from multiple dimensions—such as microcirculatory perfusion, tissue stiffness, and quantitative texture features—that are difficult to discern by the naked eye. Moreover, multimodal combined diagnostic strategies have significantly improved the differential diagnostic performance for OCCC and AE. This article systematically reviews the research progress in the ultrasound differential diagnosis of OCCC and AE from the perspectives of clinicopathological features, conventional ultrasound findings, applications of new ultrasound technologies, and multimodal combined diagnosis, and summarizes the existing problems and future perspectives, aiming to provide a reference for accurate noninvasive preoperative differentiation and individualized patient management.

Keywords

Ovarian Clear Cell Carcinoma, Atypical Ovarian Endometrioma, Ultrasonography, Radiomics, Differential Diagnosis

1. Introduction

Ovarian cancer is one of the most common malignant tumors in women, and its mortality rate has long ranked first among gynecological malignancies, largely because most patients are diagnosed at an advanced stage and effective early screening methods are lacking. According to the 2026 American Cancer Statistics Report, there were approximately 20,000 new cases of ovarian cancer [1]; data from the National Cancer Center of China in 2022 also showed 61,100 new cases of ovarian cancer [2]. Ovarian clear cell carcinoma (OCCC) is a special subtype of epithelial ovarian cancer, with an incidence second only to high-grade serous carcinoma. Asia is a high-incidence region for OCCC, particularly Japan, where it accounts for as much as 25% of cases, with a trend of increasing incidence and younger onset [3]; the underlying cause remains unclear and may be related to the rising incidence of endometriosis. Compared with other subtypes of ovarian cancer, OCCC has unique clinicopathological features: relatively young age at onset, a high proportion of early-stage patients, a tendency to complicate with thromboembolism, susceptibility to platinum-based chemotherapy drug resistance in advanced-stage patients, high recurrence rate, and poor prognosis. The 5-year overall survival rate is approximately 80% - 89% for FIGO stage I-II patients, but drops to approximately 52% for stage III-IV patients [4]-[7]. Therefore, early and accurate identification of OCCC is crucial for improving patient prognosis.

Endometriosis is an estrogen-dependent chronic inflammatory disease, with a prevalence of 5% - 15% in women of reproductive age [8]. Ovarian endometrioma (OMA) is its most common manifestation; the typical ultrasound appearance is uniform ground-glass echogenicity within the cyst, a thin and smooth cyst wall, and no obvious solid components or blood flow. However, approximately 20% of OMAs may exhibit atypical features, including focal thickening of the cyst wall, irregular septations, inner wall papillary projections, and heterogeneous intracystic echogenicity, with the incidence significantly increasing in women over 45 years of age. Such endometriomas with atypical features are termed atypical ovarian endometriomas (AE). Their ultrasound findings overlap with those of some early-stage OCCC, creating certain difficulties in differential diagnosis. This may lead to OCCC being misdiagnosed as AE, thereby delaying the timing of radical surgery; conversely, if a benign AE is diagnosed as OCCC and subjected to surgery, the patient's fertility and quality of life may be impaired.

Multiple studies have shown that endometriosis is associated with an increased risk of ovarian cancer, with a malignant transformation risk of approximately 0.5% - 1.0% [9]. This increased risk may stem from the impact of endometriosis

on the reproductive system, as patients with endometriosis often suffer from infertility, which is a recognized risk factor for ovarian cancer. Moreover, the risk of ovarian cancer in patients with endometriosis increases with longer follow-up duration; among study subjects followed for ≥ 10 years, the risk of ovarian cancer increased to 2.5 times the baseline level. In addition, patients with ovarian endometriosis have a higher incidence of ovarian cancer; for women with OMA followed for more than 10 years, the risk of ovarian cancer is increased 4.2-fold [10]. Currently, commonly used differential methods in clinical practice include serum tumor markers, conventional ultrasound, contrast-enhanced ultrasound, and MRI. Serum markers such as CA125 and HE4 show overlapping elevations in both conditions, with low specificity when used alone; MRI offers high soft-tissue resolution but is costly and time-consuming. Transvaginal ultrasound has the advantages of being noninvasive, convenient, repeatable, and low-cost, making it the first-line method for preoperative evaluation of ovarian lesions. However, conventional ultrasound relies on the subjective judgment of the examiner, with limited ability to differentiate atypical lesions.

In recent years, domestic and international scholars have conducted extensive research on the ultrasound differential diagnosis of OCCC and AE. New technologies such as contrast-enhanced ultrasound, elastography, radiomics, and artificial intelligence have been gradually applied in clinical practice, and multimodal combined diagnostic strategies have shown promising prospects. However, a standardized and unified diagnostic workflow has not yet been established, and research specifically targeting the differential diagnosis of OCCC and AE remains very limited. This article reviews the research progress in the ultrasound differential diagnosis of OCCC and AE, analyzing the current applications of conventional ultrasound, new ultrasound technologies, and multimodal combined diagnosis based on the clinicopathological foundation, to provide a theoretical basis for precise clinical diagnosis and scientific research.

This review was primarily based on literature searches in the PubMed and CNKI (China National Knowledge Infrastructure) databases. Search terms included “endometriosis,” “atypical endometriosis,” “ovarian cancer,” “ovarian clear cell carcinoma,” “endometriosis-associated ovarian cancer,” “ultrasonography,” and “radiomics.” Studies were selected based on their relevance to the ultrasound differential diagnosis of ovarian clear cell carcinoma and atypical ovarian endometrioma. Articles published within the past 15 years were prioritized, and early classic literature was also included when necessary. The reference lists of retrieved articles were additionally screened to identify other relevant studies.

2. Pathological and Clinical Features of Ovarian Clear Cell Carcinoma and Atypical Ovarian Endometrioma

2.1. Pathogenetic Association and Histological Differences

Endometriosis is characterized by ectopic implantation or metaplastic proliferation of endometrial cells, coupled with persistent ectopic growth and inflamma-

tion resulting from impaired immune function. Histopathological examination requires the presence of at least two of the following features: endometrioid glands, endometrioid stroma, or evidence of chronic hemorrhage [11]. Histologically, atypical endometriosis was first proposed by Czernobilsky and Morris in 1979 [12], defined as the presence of cytological and structural abnormalities in the epithelium of endometriotic cysts without stromal invasion, characterized by cytological atypia (nuclear stratification, hyperchromasia, and pleomorphism) and architectural atypia (simple or complex hyperplasia). Approximately 0.7% - 2.5% of atypical endometriosis may undergo malignant transformation [13]; among these, architectural atypia is primarily associated with ovarian cancer, and its Ki-67 expression is significantly higher than that of cytological atypia [14]. However, the pathological diagnostic criteria for AE have not yet been standardized, and clinical detection rates vary widely (0.8% - 8.8%) [13] [15], with clinicians having insufficient awareness of its malignant transformation risk.

Among all subtypes of ovarian cancer, clear cell carcinoma has the closest association with endometriosis [16]. The WHO defines OCCC as a malignant ovarian tumor composed of clear, eosinophilic, and hobnail cells arranged in tubulocystic, papillary, and solid patterns. Grossly, it typically presents as a unilateral, large (3 - 30 cm in diameter, most commonly 13 - 15 cm) cystic-solid mass, with white, yellow, or brown polypoid nodules visible on the inner cyst wall; the cyst wall shows a typical chocolate-brown color and is often associated with endometriotic lesions [17]. Microscopically, the histopathology mainly manifests as three cell types: the clear cell type, rich in glycogen with clear cytoplasm, which constitutes the main body of solid nodules and is the typical cell of OCCC; the hobnail cell type, with nuclei protruding toward the glandular lumen and scant cytoplasm, showing characteristic hobnail morphology, which is the hallmark pathological cell of OCCC and the key morphological feature for pathological diagnosis; and the eosinophilic cell type, with eosinophilic and red-stained cytoplasm, abundant mitochondria, and often intermingled with clear cells [18].

Molecular pathological studies have further revealed the association between the two conditions. Inactivation of the ARID1A tumor suppressor gene is the initiating core event in the malignant transformation of endometriosis, and its mutation rate in atypical endometriosis and OCCC is significantly higher than that in typical endometriosis. Wiegand *et al.* [19] found that 46% of OCCC cases harbored ARID1A mutations, and that this mutation and loss of BAF250a protein expression were present in both the tumor and the surrounding atypical endometrial tissue, but not in distant normal endometrium, suggesting that ARID1A mutation is a key event in the early transformation of endometrial lesions to ovarian cancer; studies by Ayhan and Xiao *et al.* [20] [21] have also confirmed this conclusion.

Meanwhile, the “retrograde menstruation—iron overload—oxidative stress—proliferative signal activation” axis also constitutes a core driver of malignant transformation in endometriosis. Retrograde menstruation causes repeated bleeding from ectopic endometrium; macrophages in the peritoneal cavity phagocytose

and degrade large numbers of red blood cells, releasing excessive free iron that leads to peritoneal iron overload. Iron overload generates large amounts of reactive oxygen species (ROS) through pathways such as the Fenton reaction, causing persistent oxidative stress, which in turn leads to cellular damage and an increased risk of DNA mutations, and activates the NF- κ B and ERK/MAPK pathways, conferring a proliferative advantage on ectopic cells [22]. In addition, activating mutations of PIK3CA, MET gene amplification, RASSF methylation, and loss of PTEN and KRAS collectively drive abnormal cellular proliferation and malignant transformation [23]-[27].

2.2. Differences in Clinical Features and Their Value in Differential Diagnosis

OCCC is a special subtype of ovarian cancer, and its clinical features also differ from those of other subtypes. The mean age at onset of OCCC is 53.5 - 56 years; most cases are unilateral; approximately 60% - 70% are diagnosed at FIGO stage I-II; the mean tumor diameter is 10 - 15 cm; and OCCC is often associated with endometriosis [5] [28]-[31]. In addition, patients with OCCC have a higher incidence of venous thromboembolism (VTE), twice that of other ovarian cancer subtypes; approximately 10% are accompanied by paraneoplastic syndromes; and serum CA125 is mostly mildly to moderately elevated [32]. Clinical stage is the most important prognostic factor; the 5-year overall survival rates for stages I, II, III, and IV are 88%, 70%, 33%, and 0%, respectively, and platinum resistance in advanced disease is the main cause of poor prognosis [33]. Liver metastasis is a unique high-risk prognostic factor for OCCC, distinct from high-grade serous carcinoma [34].

In contrast, in the study by So KA *et al.* [15], patients with AE had a mean age of 34.8 years, a mean cyst diameter of 7.2 cm, and were mostly unilateral. Risk factors for malignant transformation of endometriosis include advanced age (40 - 60 years), cyst diameter > 9 cm, postmenopausal status, and long-term estrogen exposure [35] [36]. The following clinical situations should raise suspicion of malignant transformation: age $\geq$ 45 years, postmenopausal status, disease duration of endometriosis $\geq$ 10 years, change in pain rhythm (dysmenorrhea transitioning to chronic pelvic pain), cyst diameter $\geq$ 8 cm, imaging findings suggesting solid or papillary structures with abundant low-resistance blood flow, and concurrent endometrial lesions [37]. These clinical features themselves serve as important clues for differential diagnosis and should be incorporated into a comprehensive assessment system.

Differences in Serum Tumor Markers

Serum tumor markers are also among the important features for the differential diagnosis of the two conditions. CA125 has high sensitivity but low specificity, and may be elevated in endometriosis, pelvic inflammatory disease, and even during menstruation [38]. HE4 has superior specificity to CA125 (93% vs. 78%), is not affected by the menstrual cycle, and is elevated in approximately 69% of pa-

tients with clear cell carcinoma [39]-[41]; urinary HE4 can serve as a supplement to serum testing and may help identify patients with primary platinum resistance [42]. The combined detection of CA125 and HE4 constitutes the ROMA (Risk of Ovarian Malignancy Algorithm) index; a study by Suri *et al.* [43] showed that ROMA is the best diagnostic marker for epithelial ovarian cancer in postmenopausal women, whereas HE4 is the best predictive indicator in premenopausal women.

Smac is a pro-apoptotic protein. Dobrzycka *et al.* [44] first detected its levels in the serum of patients with ovarian cancer in 2015, and its levels were negatively correlated with tumor stage and pathological grade. A study by Xu XR *et al.* [45] showed that serum Smac in OCCC was significantly lower than in benign endometriosis; the sensitivity of Smac alone reached 91.67%, and the specificity of HE4 reached 98.75%. The three-marker combination (Smac + HE4 + CA125) had the highest sensitivity (98.33%) but lower specificity (75%), while the combination of Smac and HE4 offered a relatively better balance of sensitivity and specificity. A study by Xu T *et al.* [46] demonstrated that HE4 > 59.7 pmol/L and CA19-9 > 8.5 U/mL are independent risk factors for malignant transformation of endometriosis, with the combined detection achieving a sensitivity of 72.73% and specificity of 78.41%. In addition, an elevated neutrophil-to-lymphocyte ratio (NLR) is an independent predictor of poor prognosis in OCCC [47].

Current serum marker assays offer some assistance in the differential diagnosis of OCCC and AE, but they also have limitations. CA125 may be elevated in both conditions, with limited discriminatory capacity; HE4 has relatively high specificity but insufficient sensitivity; Smac, as an emerging marker, has high sensitivity, but related studies have small sample sizes and lack multicenter validation. In real clinical scenarios, one should not rely solely on serum markers, but rather integrate them with ultrasound findings and clinical features into a combined model, which is also one of the multimodal diagnostic strategies. A comparison of the clinical and pathological features of OCCC and is atypical ovarian endometrioma presented in **Table 1**.

Table 1. Comparison of clinicopathological features between OCCC and atypical ovarian endometrioma.

Feature Dimension	Atypical Ovarian Endometrioma (AE)	Ovarian Clear Cell Carcinoma (OCCC)
Age at onset	Mean 34.8 years, predominantly reproductive age	Mean 53.5 - 56 years, predominantly perimenopausal
Cyst/mass diameter	Mean 7.2 cm, mostly < 8 cm	Mean 10 - 15 cm, frequently > 10 cm
Laterality	Predominantly unilateral (55.1% right-sided)	Predominantly unilateral (84% - >90%)
Serum CA125	Mild-to-moderate elevation, menstruation-related	Mild-to-moderate elevation
Serum HE4	Mostly normal or mildly elevated	Elevated in ~69%, relatively high specificity
Serum Smac	Near normal levels	Significantly decreased, inversely correlated with stage
VTE incidence	No significant elevation	11% - 42%, twice that of other subtypes
FIGO stage	Benign lesion, no staging	60% - 70% at stages I-II

3. Current Status of Conventional Ultrasound Differential Diagnosis

3.1. Conventional Ultrasound Features

Transvaginal ultrasound (TVU) is the first-line imaging modality for ovarian lesions, with diagnostic sensitivity and specificity both approaching 90% [48]. The typical ultrasound features of OMA include a unilocular cyst, ground-glass echogenicity within the cyst, positive tenderness on probe compression, and rare papillary projections or solid components [49] [50]. In contrast, AE presents with atypical features such as multilocular cysts, thickened cyst walls, papillary projections on the cyst wall, and cystic-solid lesions [49] [50].

An analysis of ultrasound features in 152 cases of OCCC by Pozzati *et al.* [31] showed: 84.2% were unilateral; the median maximum tumor diameter was 117 mm; solid components were visible in all lesions (median solid nodule diameter 69 mm); 34.9% were unilocular cystic-solid, 41.4% multilocular cystic-solid, and 23.7% solid masses; papillary projections were visible in 38.2% (of which 51.7% had >3 projections and 91.1% showed detectable blood flow); and cyst fluid was most commonly hypoechoic (43.5%). Among these, patients with OCCC pathologically confirmed to have arisen from malignant transformation of endometriosis were younger (median 47.5 years vs. 55.0 years) and more frequently showed ground-glass echogenicity (50.0% vs. 16.5%).

A comparative study of 63 cases of AE and 57 cases of OCCC by Huang KJ *et al.* [51] showed that patients with OCCC were older (53.11 ± 9.28 years vs. 39.33 ± 7.04 years), had larger cyst diameters (12.68 ± 4.60 cm vs. 7.81 ± 2.81 cm), larger solid components (4.82 ± 3.53 cm vs. 0.93 ± 1.74 cm), and more frequent disappearance of ground-glass echogenicity (68.4% vs. 6.3%). Multivariate analysis showed that age > 47.5 years, cyst diameter > 11.55 cm, solid component > 1.37 cm, and disappearance of ground-glass echogenicity were independent factors suggestive of malignancy.

Among the above ultrasound features, the disappearance of ground-glass echogenicity is a noteworthy sign. Some studies have speculated that locally expressed degradative enzymes within endometriotic cysts gradually break down the cyst fluid, while periodic bleeding replenishes the cyst contents, maintaining the typical ground-glass echogenicity; after perimenopause, fresh bleeding decreases, and the typical ground-glass echogenicity may disappear [52] [53]. After adjusting for age, the disappearance of ground-glass echogenicity in individuals under 45 years of age may be an important indicator for differentiating AE from OCCC [51]. From a pathological perspective, the cystic-solid structure of OCCC corresponds to solid echogenic areas within a cystic mass on ultrasound; the cyst fluid appears chocolate-like due to old hemorrhage, explaining the fine punctate or mixed echogenicity on ultrasound; tumor cells rich in glycogen arranged in solid sheets constitute the main body of solid nodules, and abundant eosinophilic hyaline material in the stroma may form sclerotic hyaline nodules, which may appear as hyperechoic spots or calcification-like echoes within solid areas on ultrasound; papillary

projections and hobnail cells protruding into the lumen form intracystic wall nodules visible on ultrasound [18]. The main conventional ultrasonographic features differentiating OCCC from atypical ovarian endometrioma are shown in **Table 2**.

Ultrasound is an important modality for the differential diagnosis of OCCC and AE, with cyst size, solid component diameter, and changes in ground-glass echogenicity being the main differentiating features. However, these signs are not absolute and may overlap between patients with OCCC and AE, particularly in perimenopausal women, where the disappearance of ground-glass echogenicity may merely reflect changes in cyst fluid composition rather than malignant transformation. Therefore, ultrasound should serve as a screening tool, and atypical cases require further evaluation in combination with new ultrasound technologies and MRI.

Table 2. Key conventional ultrasonic features for differentiating OCCC from atypical ovarian endometrioma.

Ultrasonic Feature	Atypical Ovarian Endometrioma (AE)	Ovarian Clear Cell Carcinoma (OCCC)	Diagnostic Value
Cyst diameter	Mostly < 8 cm, mean 7.2 cm	Mostly > 10 cm, median 11.7 cm	High, threshold 11.55 cm
Solid component	Rare, mean 0.93 cm	Invariably present, mean 4.82 cm	High, threshold 1.37 cm
Ground-glass echogenicity	Mostly present	Mostly absent	Moderate-high, age-adjusted
Papillary projections	Rare, mostly avascular	Visible in 38.2%, vascular in 91.1%	High
Cyst fluid echogenicity	Homogeneous hypoechoic/ground-glass	Predominantly hypoechoic, may be heterogeneous	Moderate
Number of locules	Mostly ≤ 4	Unilocular or multilocular cystic-solid	Low
Ascites	Rare	Complicated in 21.1%	Moderate
Probe tenderness	Common	Not prominent	Moderate

3.2. Color Doppler Ultrasound Features

Color Doppler ultrasound can further improve the differential diagnostic performance for the two conditions by assessing the microcirculatory perfusion and hemodynamic features of lesions. Blood flow signals in AE lesions are mostly confined to the cyst wall or septations, presenting as scant punctate or linear signals, and solid components are mostly avascular; in contrast, blood flow in OCCC lesions is predominantly distributed within solid components and wall nodules, manifesting as relatively abundant linear blood flow signals, consistent with tumor neovascularization.

Regarding hemodynamic parameters, OCCC lesions are mostly low-resistance, with a resistive index (RI) mostly < 0.4, whereas AE lesions mostly have an RI > 0.6. However, RI may be influenced by factors such as tumor size, lesion location, and measurement technique, limiting its differential diagnostic value. In addition, power Doppler ultrasound is more sensitive in detecting low-velocity blood flow and can identify neovascularization within small solid components, offering sup-

plementary value. Overall, the septations and intracystic solid components of AE cysts are mostly avascular or show only scant blood flow signals; the presence of vascularized solid papillary structures is highly suggestive of malignancy. Furthermore, Doppler interpretation is substantially influenced by operator experience, equipment performance, and parameter settings. In clinical differential diagnosis, caution should also be exercised with benign lesions such as decidualized endometriomas during pregnancy, which may also show hypervascular solid projections internally and can be easily confused with malignant lesions [50].

4. Applications of New Ultrasound Technologies in Differential Diagnosis

4.1. Ultrasound Radiomics and Artificial Intelligence

4.1.1. Technical Principles and Basic Workflow

In recent years, with the rapid development of the integration of artificial intelligence technology and medical imaging, radiomics has emerged as a new field and research hotspot in quantitative assessment techniques for precision medical imaging. The concept of radiomics was first proposed by the American scholar Gillies [54] in 2010, and Lambin [55] further refined its definition in 2012. It refers to a technology that uses computers to extract a large number of quantitative features carried in medical images through high-throughput processing and obtains information reflecting the underlying pathophysiology of lesions through machine learning analysis [54] [55]. Ultrasound radiomics applies radiomics methods to ultrasound images, extracting quantitative features such as morphology, texture, and wavelet transform from grayscale ultrasound, and capturing subtle image structures and intrinsic relationships that are difficult to observe with the naked eye [56] [57]. Its basic workflow comprises five main steps: medical image acquisition, region of interest (ROI) segmentation, feature extraction, feature selection, and model construction and validation. Under the supervised learning framework, commonly used feature selection methods include LASSO regression and mRMR, and classifiers include support vector machines (SVM), random forests, logistic regression, and convolutional neural networks (CNN) [58] [59].

4.1.2. Diagnostic Performance of Radiomics Based on Grayscale Ultrasound

In a large-sample study of 6809 pathologically confirmed cases of endometriosis by Chao *et al.* [60], a gradient boosting decision tree was used to construct a prediction model, achieving an AUC of 0.942 in the test set, with a sensitivity of 86.8% and specificity of 86.7%, significantly outperforming the traditional logistic regression model (AUC = 0.891); moreover, the AUC remained at 0.876 in a prospective dataset. In a benign-malignant prediction model for adnexal masses developed by Moro *et al.* [61] based on 2428 patients, the clinical-radiomics combined model constructed using the XGBoost algorithm achieved the best diagnostic performance, with a validation set AUC of 0.89, sensitivity of 0.83, and specificity of 0.81.

Miao *et al.* [62] used the ConvNeXt deep learning algorithm to differentiate OMA from benign mucinous cystadenoma, enrolling 184 patients; the test set AUC reached 0.90, with sensitivity and specificity both at 90%, and decision curve analysis (DCA) confirmed its clinical utility. Liu *et al.* [63] developed a machine learning model to differentiate OMA from benign teratoma; the logistic regression model achieved an AUC of 0.981, accuracy of 94.8%, and sensitivity of 95.5%; a nomogram model integrating clinical and radiomics features achieved an AUC of 0.987. The diagnostic performance of this radiomics model was comparable to that of senior physicians and superior to that of junior physicians; moreover, after using it for assisted diagnosis, the performance of junior physicians significantly improved. The above studies have all confirmed the excellent performance of ultrasound radiomics in the differential diagnosis of gynecological diseases.

4.1.3. Prediction Models Combining Radiomics with Clinical Features

Prediction models combining radiomics with clinical features have also demonstrated certain value in the early identification of OCCC. The study by Moro *et al.* [61] showed that the clinical-radiomics combined model (AUC 0.89) outperformed the radiomics-only model, confirming the value of multimodal information fusion. The nomogram model by Liu *et al.* [63] (AUC 0.987) also outperformed the radiomics-only model. When imaging data are combined with clinical, genomic, and pathological information, the predictive performance of these models is significantly enhanced. This also applies to the differentiation of OCCC and AE; integrating clinical features such as age, cyst size, and serum markers with ultrasound radiomics features holds promise for constructing more accurate early malignant transformation risk prediction models.

Existing research on ultrasound radiomics in gynecological diseases has established a certain foundation, but studies directly targeting the specific differential diagnosis of OCCC and AE remain very limited. Most studies simply include OCCC within the broad category of ovarian malignant tumors, failing to capture its unique radiomics features. As a special subtype of ovarian cancer, OCCC has certain unique clinical features, and its radiomics features may also differ from those of other types of ovarian cancer. Future studies specifically focusing on the radiomics of OCCC and AE are needed.

4.2. Ultrasound Elastography and Contrast-Enhanced Ultrasound

4.2.1. Elastography

The concept of ultrasound elastography was first proposed by Ophir *et al.* [64] in 1991, inspired by clinical palpation. It utilizes differences in stiffness among biological tissues for coded imaging and elasticity measurement. Common modalities include strain elastography (SE), acoustic radiation force impulse imaging (ARFI), and shear wave elastography (SWE) [65]. Among these, SWE is the most widely used. It generates transverse shear waves by transmitting excitation acoustic beams from the probe; utilizing the Mach cone effect, shear waves propagate faster in stiffer tissues and slower in softer tissues, allowing color coding based on tissue

stiffness. Young's modulus values can also be directly calculated using the Young's modulus formula to reflect tissue stiffness [66] [67].

Herek *et al.* [68] investigated the diagnostic value of transabdominal ultrasound elastography for ovarian lesions, showing that ovarian endometriomas and complex cystic lesions tend to be stiff with high strain ratios; malignant lesions are mostly soft with very low strain ratios; and benign tumors have moderate stiffness, overall stiffer than malignant lesions. A transvaginal elastography study by Ciledag *et al.* [69] also showed that OMA overall presents as stiff due to old intracystic hemorrhage and fibrous deposition; simple physiological cysts are extremely soft; and complex cystic malignant lesions, due to intracystic solid papillary and infiltrative components, mostly have elastic stiffness between that of simple cysts and OMA.

The combination of elastography and conventional ultrasound can improve differential diagnostic performance, particularly offering supplementary value in determining the benign or malignant nature of solid components. Within the solid components of OCCC, tumor cells are loosely arranged with stromal edema, resulting in soft texture; in contrast, the cyst walls and septations of AE show increased stiffness due to long-term hemorrhagic organization and fibrous tissue proliferation. This difference in stiffness endows ultrasound elastography with certain value in the differential diagnosis of OCCC and AE.

4.2.2. Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) is a noninvasive imaging technique that applies acoustic contrast agents on the basis of conventional ultrasound and identifies masses by observing microvascular perfusion patterns. CEUS examination includes the assessment of parameters such as tumor enhancement pattern (homogeneous/heterogeneous), degree of enhancement (hypo-/iso-/hyperenhancement), vascular morphology (presence of coarse, disorganized, and irregular vessels within the lesion), and contrast agent washout time.

Generally, there are marked differences in CEUS enhancement patterns between benign and malignant lesions: malignant lesions show fast-in and fast-out enhancement, heterogeneous enhancement, and visible disorganized neovascular features, whereas benign lesions mostly show homogeneous enhancement without abnormal perfusion. Benign ovarian tumors typically show ring enhancement at the cyst wall and papillary projections, whereas ovarian cancer manifests as rapid and heterogeneous enhancement. The solid portions of OCCC are rich in vessels, but abundant hyaline material deposition in the stroma may form hypovascular fibrotic areas, which on contrast imaging may manifest as heterogeneous hypoenhancement or a differential pattern of fast-in and slow-out [18].

A CEUS study of benign, borderline, and malignant ovarian epithelial tumors by Wang *et al.* [70] showed that the benign group was characterized by late enhancement, low enhancement, and synchronous washout, with overall homogeneous mild enhancement; the borderline group was characterized by late enhancement, low enhancement, and early washout, with relatively intact capsules; the

malignant group manifested as early enhancement, high enhancement, and early washout, with overall heterogeneous high enhancement, abundant coarse and disorganized vessels visible within solid areas, and radial enhancement of contrast agent extending outward from the interior of the lesion. A study by Tian Cai *et al.* [71] found that the combination of IOTA (International Ovarian Tumor Analysis) simple rules with CEUS significantly improved the diagnostic value for adnexal masses compared with IOTA rules alone.

CEUS has important supplementary value in the identification of small solid components and early malignant transformation lesions. For small nodules that cannot be clearly identified by two-dimensional and color Doppler ultrasound, CEUS can detect low-velocity blood flow and display the microvascular perfusion pattern within solid components, providing key information for the identification of early malignant transformation.

5. Research Progress in Multimodal Combined Diagnosis

Currently, multimodal approaches represent a trend in clinical diagnosis and have also demonstrated good differential diagnostic capacity in gynecological diseases, particularly when imaging features are combined with clinical, genomic, and pathological information, significantly enhancing disease prediction performance.

For example, the combination of ultrasound with serum tumor markers such as CA125, HE4, and Smac is currently the most commonly used multimodal diagnostic mode in clinical practice. The ROMA index is a risk assessment model combining CA125 and HE4; a study by Suri *et al.*⁴³ showed that ROMA is the best diagnostic marker for epithelial ovarian cancer in postmenopausal women. The combination of ultrasound and serum markers can compensate for the limitations of single modalities and improve the ability to differentiate atypical lesions. However, there is currently a lack of an ultrasound-serum combined scoring system specifically designed for the differentiation of OCCC and AE.

Integrating clinical features such as age, duration of endometriosis, changes in cyst size, and changes in pain rhythm with ultrasound findings to construct malignant transformation risk prediction models is also an important direction for multimodal diagnosis. In a large-sample study by Chao *et al.* [60] enrolling 6809 patients with endometriosis, a machine learning model integrating clinical features and ultrasound parameters achieved an AUC of 0.942, significantly outperforming the traditional ultrasound logistic regression model. This approach fully leverages the supplementary value of clinical information and is particularly suitable for risk stratification in populations at higher surgical risk, such as women of reproductive age.

The combination of ultrasound radiomics with clinical features is currently the core research direction. The clinical-radiomics combined model constructed by Moro *et al.* [61] (AUC 0.89) outperformed the radiomics-only model; the nomogram model by Liu *et al.* [63] (AUC 0.987) also confirmed the value of fusing clin-

ical features with radiomics. When imaging data are combined with clinical, genomic, and pathological information, the predictive performance of these models is significantly enhanced. For the differentiation of OCCC and AE, integrating grayscale ultrasound radiomics features, CEUS perfusion parameters, and elastography stiffness values with clinical features such as age and serum markers to construct a multidimensional combined model holds promise for achieving optimal differential diagnostic performance.

Multimodal combined diagnosis with radiomics is an inevitable trend in current development, but it still faces several challenges. First, there is substantial data heterogeneity across modalities; different equipment, parameters, and contrast agent dosages can all affect feature extraction, and there is currently a lack of standardized data preprocessing and normalization workflows. Second, high feature dimensionality and small sample sizes easily lead to overfitting, necessitating the introduction of strategies such as feature selection, dimensionality reduction, and cross-validation. Third, model validation is insufficient; most studies have only performed internal validation, lacking multicenter external validation and prospective clinical validation. Therefore, establishing standardized multimodal data acquisition protocols, conducting large-sample multicenter studies, and developing interpretable AI models are key to promoting the clinical translation of multimodal diagnosis.

6. Existing Problems and Challenges

In the differential diagnosis of AE and OCCC, the two conditions may overlap in aspects such as thickened cyst walls, papillary projections, and increased blood flow signals, posing certain difficulties for conventional ultrasound differentiation. Moreover, conventional ultrasound diagnosis is highly dependent on the experience and technical proficiency of the examiner, and some primary hospitals have insufficient ability to recognize atypical features, leading to high rates of missed diagnosis and misdiagnosis. For patients of reproductive age with fertility desires, balancing malignant transformation risk screening with fertility preservation also imposes higher demands on precise preoperative diagnosis.

Second, in the application of new ultrasound technologies, radiomics research has not yet established unified standards in image preprocessing, ROI segmentation, feature extraction, and algorithm selection, making it difficult to directly compare results across different studies. Different ultrasound equipment, probe frequencies, and gain settings can all affect image quality and feature extraction, limiting the generalizability of models across different centers. Furthermore, due to the relatively low incidence of OCCC, clinical studies are mostly single-center and small-sample in design, and there is a marked imbalance in the number of OCCC and AE cases, which easily leads to model overfitting and low generalizability. Most studies are retrospective in design, subject to selection bias, and lack validation from large-sample prospective multicenter studies. The data imbalance problem may also lead to insufficient model recognition capacity for the minority

class (OCCC), affecting the safety of clinical application.

Currently, most radiomics and artificial intelligence research remains at the laboratory stage, lacking multicenter, prospective, and external validation studies, making it difficult for diagnostic models to be directly applied in routine clinical work. The insufficient interpretability of models makes it difficult for clinicians to understand the diagnostic basis, affecting trust and acceptance. In addition, radiomics analysis requires dedicated software and computational resources, which are difficult to implement in primary hospitals, limiting the popularization and promotion of the technology.

Finally, radiomics features are mostly mathematical quantitative parameters, and research on their association with tumor pathological molecular mechanisms and biological behavior is insufficient, making it difficult to explain the diagnostic basis of models and limiting clinical acceptance. Which texture features correspond to chromatin remodeling caused by ARID1A mutations, and which gray-scale features reflect the degree of stromal hyalinization, remain to be elucidated. Establishing the correspondence among imaging features, pathological morphology, and molecular alterations is the key to moving radiomics from a “black box” toward interpretability.

7. Conclusion and Perspectives

Due to the overlap in ultrasound features between OCCC and AE, accurate pre-operative differentiation remains a clinically urgent problem. Based on the clinicopathological foundation, this article systematically reviews the application progress of conventional ultrasound, color Doppler ultrasound, ultrasound radiomics and artificial intelligence, elastography, contrast-enhanced ultrasound, and multimodal combined diagnosis in the differentiation of the two conditions. Conventional two-dimensional and color Doppler ultrasound is the first-line method for the differential diagnosis of OCCC and AE; features centered on cyst diameter, solid component size, ground-glass echogenicity, and blood flow characteristics have key differential value. Contrast-enhanced ultrasound and elastography also provide supplementary information from the perspectives of perfusion and stiffness, respectively, while new technologies such as ultrasound radiomics and artificial intelligence quantitatively extract tumor heterogeneity features. Finally, multimodal combined diagnostic strategies have shown excellent application prospects, providing new avenues for noninvasive and accurate preoperative differentiation of OCCC and AE.

In the future, it is necessary to further establish a standardized AE ultrasound feature assessment system and risk stratification criteria for malignant transformation of endometriosis, conduct multicenter, large-sample prospective studies, promote the clinical translation of AI models, develop integrated prediction models incorporating multidimensional indicators, and simultaneously establish standardized follow-up protocols for patients of reproductive age, ultimately achieving early screening, precise diagnosis, and individualized treatment of ma-

lignament transformation of endometriosis. The biological basis of radiomics features should be explored. By integrating pathological, molecular biological, and genomic data, the associations between radiomics features and the tumor micro-environment, molecular subtypes, and prognosis should be analyzed, establishing the correspondence among imaging features, pathological morphology, and molecular alterations, and realizing the transition from imaging diagnosis to imaging-based precise subtyping.

Author Contributions

Conceptualization, Liping Liu and Jiaxin Wang; methodology, Jiaxin Wang; formal analysis, Jiaxin Wang; investigation, Jiaxin Wang; resources, Liping Liu; data curation, Jiaxin Wang; writing—original draft preparation, Jiaxin Wang; writing—review and editing, Liping Liu; visualization, Jiaxin Wang; supervision, Liping Liu; project administration, Liping Liu and Jiaxin Wang; funding acquisition, Liping Liu.

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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