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Research Progress of 3D Ultrasonography and Radiomics in the Analysis of Tumor Heterogeneity in Cervical Cancer

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Abstract: *Cervical cancer is one of the most common malignant tumors among women worldwide, with particularly high incidence and mortality rates in developing countries. Early diagnosis and precise treatment of cervical cancer are critical for improving patient survival and quality of life. Current studies have identified tumor heterogeneity as a key factor influencing therapeutic outcomes in cervical cancer. Although conventional imaging modalities such as two-dimensional ultrasonography, CT, and MRI play important roles in tumor diagnosis and staging, they are limited in their ability to comprehensively reveal tumor heterogeneity. In recent years, the emergence of three-dimensional (3D) ultrasonography has provided a novel approach for precise tumor diagnosis and personalized treatment. Compared with traditional 2D ultrasonography, 3D ultrasonography can more accurately assess tumor morphology, volume, and boundaries, and can effectively distinguish between benign and malignant tumors through dynamic blood flow analysis. Thus, 3D ultrasonography offers clinicians more detailed spatial information about tumors and enables a more comprehensive evaluation of cervical cancer heterogeneity. Moreover, the integration of 3D ultrasonography with other imaging techniques, such as diffusion-weighted imaging (DWI), intravoxel incoherent motion (IVIM), and dynamic contrast-enhanced MRI (DCE-MRI), can further enhance the accuracy of early diagnosis, staging, and treatment response monitoring in cervical cancer.*

Keywords: *Cervical Cancer; 3D Ultrasonography; Radiomics; Tumor Heterogeneity*

1. Introduction

Cervical cancer is one of the most significant global health threats to women, ranking among the leading gynecologic malignancies due to its high incidence and mortality rates[1]. The establishment of an early, precise diagnostic and personalized treatment system is critical for improving patient outcomes and quality of life[2]. However, in clinical practice, tumor heterogeneity-a complex biological characteristic manifested in histomorphology, molecular phenotypes, metabolic profiles, and genomics-presents new challenges for treatment decision-making and efficacy evaluation. This biological diversity not only drives tumor evolution and metastasis but also directly contributes to inter-individual differences in treatment sensitivity and drug resistance[3]. Consequently, constructing precision diagnostic and therapeutic models based on tumor heterogeneity has emerged as a central focus in cervical cancer research.

In the field of imaging diagnostics, conventional modalities such as two-dimensional ultrasonography, CT, and MRI provide important morphological evidence for clinical decision-making; however, they are inherently limited in their ability to elucidate the microstructural heterogeneity of tumors. Notably, recent advances in three-dimensional (3D) ultrasonography have introduced new opportunities for precise tumor diagnosis and personalized therapy. Compared with two-dimensional ultrasound, 3D ultrasonography offers volumetric imaging that enables stereoscopic visualization of lesions, and when combined with radiomics, it can extract multidimensional quantitative indicators-including morphological parameters, gray-level texture features, and hemodynamic parameters-that effectively characterize tumor microenvironment heterogeneity[4]. These high-information features provide an objective imaging basis for constructing precise diagnostic and predictive models, thereby offering unique advantages in early screening, molecular subtyping, dynamic treatment response monitoring, and prognostic evaluation.

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2. Overview of Cervical Cancer

2.1 Anatomical Basis of the Female Pelvic Organs

The female pelvis comprises the pelvic cavity, uterus, ovaries, bladder, and other organs. In the context of cervical cancer, the cervix-located at the lower end of the uterus, between the uterine body and the vagina-plays a crucial physiological role. Its structure is divided into the endocervical canal and the exocervical os, with the epithelium primarily composed of a single layer of columnar cells and squamous cells[5]. Due to the propensity for cellular mutations in this region, cervical cancer often initially manifests as atypical cellular proliferation or precancerous lesions. The intricate and interconnected anatomy of the female pelvis means that the growth and spread of cervical cancer are influenced not only by the primary tumor site but also by infiltration into surrounding tissues and organs[6].

2.2 Etiology and Histopathological Characteristics of Cervical Cancer

Persistent high-risk HPV infection is the primary etiological factor for cervical cancer. The virus invades the squamous epithelial cells of the cervix, leading to genetic alterations and ultimately malignant transformation. Viral infection generally develops into cervical tumor through the process of cervical intraepithelial neoplasia. The cervical cancer virus will persistently infect, disrupt the normal regulation of cell cycle, lead to gene mutation, cell proliferation and apoptosis, and form malignant tumor[7].In addition to HPV infection, other known risk factors include immunosuppression, smoking, early marriage and childbearing, and multiple sexual partners.Cervical cancer is generally classified into squamous cell carcinoma and adenocarcinoma, with squamous cell carcinoma accounting for approximately 90% of cases, with rare variants like adenosquamous or neuroendocrine carcinoma[8].

2.3 Clinical Staging

Clinical staging of cervical cancer is crucial for evaluating the extent of tumor spread, selecting appropriate treatment modalities, and predicting patient prognosis. The staging is primarily based on the International Federation of Gynecology and Obstetrics (FIGO) system, which classifies cervical cancer according to tumor size, depth of invasion, lymph node involvement, and distant metastasis[9]. Cervical cancer stages include: stage 0 (carcinoma in situ), stage I (cancer confined to the cervix), stage II (cancer extending beyond the cervix but not involving the pelvic wall or lower third of the vagina), stage III (cancer involving the pelvic wall or lower third of the vagina), and stage IV (cancer with distant organ involvement, such as the bladder, rectum, or other distant sites).

Imaging examinations not only provide information on tumor size and location but also assess local infiltration. Both CT and MRI play crucial roles in evaluating local and distant metastases in cervical cancer, especially in terms of local extension, lymph node metastasis, and distant spread[10]. Ultrasonography also plays an important role in cervical cancer screening, preoperative evaluation, and post-treatment monitoring.

3. Overview of Three-Dimensional Ultrasound

Three-dimensional (3D) ultrasound is an imaging modality derived from conventional two-dimensional ultrasound. By acquiring multiple 2D images from different probe angles and performing real-time or offline volumetric reconstruction, it generates stereoscopic images of cardiac and vascular structures, thereby providing a more intuitive and comprehensive depiction of the morphology and function of cardiac chambers, valves, and large vessels[11].

As a rapidly advancing imaging technique, 3D ultrasound supplements traditional 2D imaging by offering richer spatial information and has been widely adopted in clinical practice. In cardiovascular medicine, it permits precise quantification of chamber volumes and ejection fraction, evaluation of valvular pathology, and image guidance for structural cardiac interventions[12]. In obstetrics and gynecology, it is employed for fetal malformation screening, assessment of placental and uterine anatomy, and morphological and hemodynamic appraisal of tumors[13]. In abdominal and superficial organ imaging, 3D ultrasound more clearly delineates lesion extent and spatial relationships[14]. Its key advantages—noninvasiveness, cost-effectiveness, and reproducibility—enhance diagnostic accuracy and facilitate therapy follow-up and prognostic evaluation, making 3D ultrasound a valuable adjunct in

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clinical imaging.

4. Three-Dimensional Ultrasound Assessment of Cervical Cancer

Three-dimensional (3D) ultrasound also holds significant value in the evaluation of cervical cancer. Its strengths include the ability to intuitively display tumor morphology and spatial relationships with adjacent structures, to accurately measure tumor volume, and—via 3D power Doppler analysis—to quantify hemodynamic characteristics. These capabilities provide objective information that supports clinical staging, prognostic assessment, and therapeutic monitoring[15].

4.1 Differentiation of Benign and Malignant Tumors

Early diagnosis of cervical cancer relies primarily on effective imaging screening, particularly diagnostic methods capable of distinguishing between benign and malignant lesions. Traditional two-dimensional (2D) ultrasonography estimates tumor nature by assessing morphology and size; however, it cannot fully capture the internal heterogeneity of tumors and is easily influenced by local tissue characteristics[16]. In contrast, 3D ultrasonography provides a comprehensive spatial representation of the tumor and, when combined with hemodynamic data, significantly enhances the accuracy of differentiating benign from malignant tumors[17].

Recent studies have demonstrated that 3D ultrasonography, through quantitative analysis of tumor blood flow and three-dimensional vascular modeling, can clearly reveal intratumoral microvascular distribution and hemodynamic parameters. Malignant tumors typically display irregular vascular walls, heterogeneous blood flow velocities, and markedly increased vascular density[18]. Measurement of parameters such as blood flow velocity, volume, and vascular density allows for more accurate differentiation of cervical cancer from benign lesions, which is critical for effective diagnosis[19].

4.2 Clinical Advantages of 3D Ultrasonography

While 2D ultrasonography has long been the conventional tool for cervical cancer diagnosis-providing information on tumor size and morphology via planar imaging-it is inherently limited by its lack of spatial resolution. Cervical tumors often exhibit complex and irregular architectures that 2D imaging fails to fully depict, particularly in terms of the complete tumor structure and its spatial relationship with adjacent tissues. In contrast, 3D ultrasonography can acquire data from multiple planes and perform three-dimensional reconstruction, enabling a comprehensive evaluation of tumor morphology, volume, and location. This facilitates more accurate delineation of tumor boundaries, especially for irregularly shaped tumors, thereby enhancing diagnostic accuracy[20].

Moreover, 3D ultrasonography can yield additional vascular-related data, assisting clinicians in identifying tumors with a rich blood supply-a key indicator of tumor aggressiveness and an important factor in determining treatment strategies[21].

4.3 Treatment Efficacy Evaluation

3D ultrasound is an important modality for assessing therapeutic response in cervical cancer. Using volumetric imaging, it enables dynamic and precise measurement of changes in tumor volume, objectively reflecting tumor shrinkage after radiotherapy, chemotherapy, or surgery. When combined with 3D power Doppler, quantitative vascular metrics (e.g., vascularity and flow indices) can be derived to monitor alterations in tumor perfusion, thereby aiding prediction of treatment response and prognosis. Moreover, the technique's noninvasive nature, reproducibility, and real-time capability make it well suited for repeated follow-up during the course of therapy[22]. Although 3D ultrasound is less sensitive than MRI for evaluating deep stromal invasion or distant metastases, it serves as a valuable adjunct for treatment monitoring in clinical practice and can inform the tailoring of individualized therapeutic strategies.

5. Analysis of Tumor Heterogeneity in Cervical Cancer Using 3D Ultrasound Radiomics

With the rapid advancement of medical imaging technologies, the application of three-dimensional (3D) ultrasound imaging in tumor diagnosis, monitoring, and treatment has become increasingly widespread. Compared with traditional two-dimensional ultrasound, 3D ultrasound imaging provides

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more intuitive and comprehensive tumor information. In the radiologic evaluation of cervical cancer, 3D ultrasound not only clearly delineates the three-dimensional structure of tumors but also, when integrated with radiomics analysis, reveals the inherent heterogeneity of cervical cancer[23]. Radiomics extracts high-dimensional quantitative features from images, thereby offering novel approaches for early diagnosis, prognostic prediction, and personalized treatment.

5.1 Combination of Diffusion-Weighted Imaging and 3D Ultrasound

Diffusion-weighted imaging (DWI) is an MRI-based functional imaging technique that characterizes tissue microstructure and pathological alterations by probing the degree of restriction of random water-molecule diffusion within biological tissues[24]. Under normal conditions, water molecules diffuse relatively freely through interstitial spaces; however, diffusion becomes restricted when cellularity increases, cell-membrane integrity is altered, or interstitial water content is abnormal, producing characteristic signal changes on DWI. The technique is noninvasive, highly sensitive, and does not require exogenous contrast agents, and it has been widely applied for early diagnosis of central nervous system disorders (e.g., acute cerebral infarction), differentiation of benign and malignant tumors, treatment response assessment, and detection of multifocal systemic lesions. DWI thus constitutes an essential component of MRI functional imaging[25].

In cervical cancer imaging, DWI is commonly used to assess tumor malignancy. However, when used in isolation, DWI may struggle to accurately distinguish different regions within cervical cancer, especially in smaller lesions or when tumor margins are ambiguous[26]. The incorporation of 3D ultrasound technology provides higher-resolution visualization of tumor morphology, aiding in more precise tumor localization and complementing DWI findings. By jointly analyzing 3D ultrasound and DWI images, one can integrate macroscopic morphological features with microscopic diffusion characteristics to establish a comprehensive tumor assessment framework, ultimately enhancing early diagnostic accuracy and guiding personalized treatment.

5.2 Complementarity of Intravoxel Incoherent Motion and 3D Ultrasound

Intravoxel incoherent motion (IVIM) imaging, a recent advancement built on diffusion-weighted MRI, noninvasively captures both true molecular diffusion and microvascular perfusion information[27]. The approach acquires data using multiple b-value diffusion sequences and fits the signals to a biexponential model to yield parameters such as the pure molecular diffusion coefficient (D), the perfusion-related pseudo-diffusion coefficient (D*), and the perfusion fraction (f)[28]. Compared with conventional DWI, IVIM more accurately evaluates tissue cellularity and microstructure while enabling quantitative analysis of microcirculatory perfusion characteristics. Consequently, IVIM offers distinct advantages and broad applicability in tumor diagnosis and grading, monitoring radiotherapy and chemotherapy response, assessment of liver and renal diseases, and neuroimaging research[29]. IVIM has emerged as a focal point in contemporary imaging research and is increasingly regarded as a pivotal tool linking tissue microstructure with functional status.

In cervical cancer studies, IVIM provides critical insights into tumor perfusion and cellular diffusion, which are essential for understanding angiogenesis and tumor biology. However, IVIM requires high-resolution imaging to optimally capture these vascular and diffusion features[30]. Here, 3D ultrasound technology plays a unique role by offering real-time visualization of the spatial distribution and volumetric attributes of cervical tumors. By integrating IVIM-derived perfusion data with 3D ultrasound-derived morphological and volumetric measurements, clinicians can significantly enhance diagnostic precision and tailor treatment strategies more effectively. Therefore, it can be concluded that the complementarity of IVIM and 3D ultrasound lies in their ability to synergistically decode both microvascular dynamics and macrostructural anatomy, offering a dual perspective for tissue characterization.

5.3 Combination of Dynamic Contrast-Enhanced MRI and 3D Ultrasound

Dynamic contrast-enhanced MRI (DCE-MRI) is a technique that evaluates the dynamic changes in tumor blood flow following the administration of contrast agents, thereby assessing vascular permeability and perfusion-parameters crucial for analyzing tumor angiogenesis[31]. In the clinical management of cervical cancer, DCE-MRI can elucidate the vascular characteristics of tumors, aiding clinicians in evaluating tumor invasiveness and treatment response. Although DCE-MRI is invaluable in angiogenesis assessment, its use in cervical cancer imaging is limited by the potential risks

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associated with contrast agents and high costs. In contrast, 3D ultrasound offers precise three-dimensional tumor morphology and real-time monitoring of tumor size and position changes, providing a more cost-effective and user-friendly alternative to MRI. The integration of 3D ultrasound data with DCE-MRI findings allows for a more comprehensive evaluation of cervical cancer vascularity, thereby enhancing both diagnostic accuracy and the guidance of personalized treatment.

However, integrating DCE-MRI with 3D ultrasound necessitates overcoming challenges related to spatiotemporal alignment and data harmonization. Specifically, DCE-MRI relies on precise temporal resolution to track contrast agent kinetics, while 3D ultrasound captures physiological changes in real time—a discrepancy that may lead to temporal mismatches in dynamic data acquisition[32]. To address this, advanced co-registration algorithms leveraging artificial intelligence (AI) are under development; these tools aim to synchronize DCE-MRI-derived parametric maps with 3D ultrasound volumetric datasets through deformable image fusion techniques.

6. Conclusion

3D ultrasound imaging technology, by providing detailed tumor morphology and hemodynamic analysis, effectively elucidates the microstructural heterogeneity of cervical cancer. When combined with other imaging modalities, such as DWI, IVIM, and DCE-MRI, it offers multidimensional data support that further enhances the precision of cervical cancer diagnosis and treatment planning. In the future, the integration of 3D ultrasound imaging with radiomics will become an essential tool in precision medicine for cervical cancer, offering clinicians a comprehensive basis for decision-making.

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