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Advances in Preoperative Imaging-based Risk Stratification for Endometrial Carcinoma: A Comprehensive Review

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Abstract: Endometrial carcinoma (EC) risk stratification is important to guide individualized treatment and prognostic assessment. Accurate preoperative risk stratification can help optimize surgical plans and adjuvant treatment strategies. Conventional imaging plays an important role in risk assessment, including tumor size, myometrial infiltration depth, cervical stromal invasion, lymph node metastatic status, dynamic enhancement pattern, and signal characteristics of diffusion-weighted imaging. By extracting high-throughput features from medical images and combining them with artificial intelligence algorithms, radiomics is able to assess tumor heterogeneity in a more comprehensive way, providing a new method for noninvasive risk stratification. This article describes the research results of traditional imaging and imaging histology in EC risk stratification, discussing the technical advantages, challenges, and future development directions.

Keywords: Endometrial Carcinoma; Risk Stratification; Imaging; Radiomics; Presurgical Evaluation.

1. Introduction

Endometrial cancer is one of the common malignant tumors of the female reproductive system, and its incidence is increasing year by year, making it the fifth leading cause of cancer deaths in women [1].The 2022 European Society for Medical Oncology (ESMO) Guidelines categorize patients with EC into five risk classes: low-risk, intermediate-risk, high-intermediate-risk, high-risk, and advanced/metastatic[2]. Treatment options for endometrial cancer vary according to risk stratification: lymphadenectomy (LND) and postoperative adjuvant therapy are recommended for intermediate-risk, intermediate-high-risk, and high-risk patients, which can significantly improve the patient's prognosis, whereas low-risk patients require only total hysterectomy and double adnexa resection without LND, because systematic lymph node dissection may lead to complications, such as lymphedema and pelvic vascular and neurological injuries, thus reducing the quality of life of low-risk patients[3-5].Therefore, accurate risk stratification is crucial for prognostic assessment. However, traditional risk assessment methods mainly rely on postoperative pathological examinations and have limited preoperative assessment tools; therefore, the development of noninvasive preoperative risk stratification methods based on radiomics and artificial intelligence has become a hotspot of current research, which is of great significance for realizing precise diagnosis and treatment of EC.

Traditional imaging methods, such as transvaginal ultrasound (TVUS), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT), still have some limitations in the application of EC preoperative risk stratification, and individualized accurate diagnosis and treatment cannot be achieved yet. By extracting quantitative features from medical images and combining them with machine learning or deep learning algorithms, radiomics is able to deeply excavate the heterogeneous features of tumors and provide an objective basis for noninvasive risk assessment. In this article, we review the research progress of different imaging techniques and radiomics in EC risk stratification, with the aim of providing a basis for the selection of individualized clinical treatment plans, improving patient prognosis and reducing overtreatment.

2. Imaging Assessment for Preoperative Risk Stratification

Imaging enables noninvasive prediction of EC risk stratification by assessing parameters such as the depth of myometrial infiltration of the tumor, morphological features, density or signal of the tumor, and invasion of surrounding structures.

2.1. US

US plays a crucial role in preoperative detection and diagnosis of EC due to its advantages such as economy, convenience and wide application[4].Dynamic contrast-enhanced ultrasound (DCE-US) is performed by intravenously injecting microbubble ultrasound contrast agent, which is capable of clearly displaying the macrovascular and microvascular systems by taking advantage of its strong echoescattering properties within the vasculature, thus enabling the assessment of tissue perfusion characteristics. Green et al.[6]compared the effects of using two methods, conventional Two-dimensional transvaginal ultrasound/energy Doppler (2D-TVU/PD) and DCE-US methods for the diagnostic efficacy of myometrial infiltration depth (MI), cervical space invasion (CSI), and high-risk EC in patients with EC, and the diagnostic sensitivity of 2D-TVU/PD in combination with DCE-US was significantly better than that of 2D-TVU/PD alone: the MI (0.74 vs 0.62, $P=0.036$) and the CSI (0.75 vs 0.51, $P<0.001$), but the specificity was comparable in both groups (MI:0.87 vs 0.85; CSI:0.96 vs 0.95). Notably, the combined examination demonstrated higher specificity in the detection of high-risk EC (0.94 vs 0.85, P=0.024), whereas there was no significant difference in sensitivity(0.73 vs 0.71).DCE-US can improve the detection rate of MI and CSI and identify high-risk cases more accurately.

Although the above studies have demonstrated the potential value of US, most of the existing studies are limited to conventional two-dimensional ultrasound images, whereas Shear wave elastography (SWE) provides more discriminative mechanical parameters by quantifying myometrial and lesion stiffness characteristics, and future studies should further refine the content of US imaging.

2.2. MRI

Currently, preoperative biopsy and MRI are the main means of obtaining risk stratification information[7]. Some studies have shown[8]that as the risk grade increases, tumors tend to exhibit more aggressive characteristics, including significant cell proliferation activity, abundant microvessel density (MVD), and higher histological grades, and that these malignant biological characteristics cause tumors in the high-risk group to usually present lower apparent diffusion coefficient (ADC) values in high-risk groups, accompanied by significantly elevated dynamic contrast-enhanced MRI (DCE-MRI) parameters.

Huang et al.[9]performed a comparative analysis of ADC values and semiquantitative DCE-MRI parameters in patients with stage IA or IB, and constructed single-parameter, single-modality and multimodal MRI classifiers. The results showed that the ADCmin, ADCmean, and rADC were significantly higher in the early-stage EC low-risk group than in the non-low-risk group, whereas the positive enhancement integral (PEI) and maximum slope of ascent (MSI) were lower than in the non-low-risk group. In the single-parameter assessment, the diagnostic efficacy of the MSI classifier was optimal, with an AUC, specificity and sensitivity of 0.887, 87.5% and 92.0%. Further analysis showed that the AUC of the combined semi-quantitative DCE-MRI parameters PEI and MSI was elevated to 0.908, while the multimodal classifier combining ADC values with semi-quantitative DCE-MRI parameters performed optimally, with an AUC of up to 0.966 and specificity and sensitivity of 90.6% and 100%. This study suggests that multimodal MRI combined analysis can significantly improve the accuracy of early EC risk stratification and provide a more reliable imaging basis for clinical decision-making. Wang et al.[10]evaluated the value of DCE-MRI and intravoxel incoherent motion (IVIM) in the differential diagnosis of low-risk and non-low-risk groups of early EC by using DCE-MRI and IVIM, and the results showed that volume transfer constant (Ktrans), the volume of extravascular extracellular space per unit volume of tissue (Ve), and microvascular volume fraction (f) were all independent predictors, and their combination had the best diagnostic efficacy (AUC=0.947), in which Ktrans was the most important perfusion-related parameter, and demonstrated significant value in risk stratification. In addition, this study also found that this method has equally high clinical value in identifying TP53 mutants from wild type, further expanding the prospect of functional MRI in EC molecular typing.

The above studies show that functional MRI imaging is capable of noninvasively assessing early EC risk stratification, but it is dependent on differences in signal intensity, contrast dose, and scanning technique, and its widespread application still needs to address issues such as technology standardization, diagnostic threshold definition, and clinical applicability.

2.3. PET/CT

^{18}F-Fluorodeoxyglucose positron emission tomography/ computed tomography (^{18}F-FDG PET/CT), with its morphological and functional imaging capabilities, is more reliable than conventional imaging in detecting distant metastases of cancer and is not only widely used for preoperative evaluation of patients with high-risk EC[11,12], but also has significant predictive value in its metabolic and volume parameters standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) have important predictive value in risk stratification of multiple malignancies[13-15]. Liu et al.[16]examined lymph node metastasis (LNM) by ^{18}F-FDG PET/CT with a sensitivity, specificity and accuracy of 83.3% , 99.7% and 99.2%, respectively. It was found that MTV and TLG of primary foci in LNM and high-risk patients were significantly higher than those of patients in the no-metastasis and low-risk groups ($p<0.010$), and that MTV and TLG were superior to the maximum standardized uptake value (SUVmax) in predicting deep myeloid infiltration, LNM and high-risk stratification ($p<0.005$). These results suggest that MTV and TLG of primary foci can be important indicators for EC risk stratification, and that preoperative PET/CT can provide a basis for clinical decision-making and help avoid unnecessary lymph node dissection in low-risk patients.

Current studies on PET/CT metabolic parameters and EC risk stratification are mostly limited to descriptive statistical analysis, and reliable quantitative prediction models have not yet been established. Although the application of PET/CT in endometrial cancer is far less popular than MRI, its unique whole-body metabolic imaging advantages and high sensitivity properties provide a new perspective for in-depth analysis of tumor biological behaviors. Future studies should explore the value of other specific imaging agents such as 18F-fluoroestradiol (18F-FES) in estrogen receptor-positive EC.

3. Advances in Radiomics for Preoperative Prediction of EC Risk Stratification

As a medical image analysis method based on artificial intelligence, imageomics transforms traditional medical images into quantifiable high-dimensional feature data through a systematic processing flow (including standardized data acquisition, accurate tumor segmentation, high-throughput feature extraction and machine learning modeling)[17]. Currently, imaging histology has a wide application potential in gynecological diseases[18].

3.1. US Radiomics

Characterization based on US radiomics is able to extract potential quantitative information beyond conventional 2D morphology, hemodynamics, and other conventional assessment metrics, providing more comprehensive imaging information for disease diagnosis. Moro et al.[19]provided a more comprehensive imaging information for the diagnosis of diseases by constructing three predictive models (a random forest-based radiomics model, a logistic regression model based on clinic-ultrasound features, and a hybrid integrating the two models) to risk stratify endometrial cancer. The results of the study showed that the AUC of the radiomics model, the clinical-ultrasound model, and the hybrid model were 0.80, 0.90, and 0.88, for the high-risk group, and 0.71, 0.85, and 0.85, for the low-risk group. The study demonstrated that, although the radiomics features were better than the low-risk group in the discrimination of the high-risk group, the integration of the radiomics features with the clinical-ultrasound features did not result in a significant improvement in the predictive efficacy. did not lead to a significant improvement in predictive efficacy, and more studies are still needed to validate the clinical application value of these models in the future. A multicenter retrospective study on the prediction of LNM by Liu et al.[20]extracted the radiomics features on US 2D grayscale and color images, and used logistic regression (LR), random forest (RF), decision tree (DT), K-nearest neighbor (KNN), and extreme Gradient Enhancement (XGBoost) machine learning (ML) algorithms were used for modeling and analysis, in which the XGBoost model performed the best (AUC=0.900 for the training set, AUC=0.865 for the test set), while the nomogram model integrating clinical and radiomics features showed the best diagnostic efficacy (AUC=0.919 for the training set, AUC=0.884 for the test set) and concluded that US radiomics nomogram are beneficial for individualized preoperative prediction of LNM.

The above studies show that US radiomics demonstrates good potential for preoperative prediction of EC risk stratification. In the future, we should also combine genomics features such as molecular typing (POLE, p53 mutations), enhance the biological interpretability of the model while ensuring clinical utility, and apply deep learning algorithms to mine higher-order image features, so as to ultimately realize the routine clinical application of US radiomics in the precision diagnosis and treatment of endometrial cancer.

3.2. MRI Radiomics

MRI-based radiomics characterization achieves precise quantification of anatomical and functional abnormalities, and this quantitative assessment method not only improves the accuracy of tumor risk classification, but also provides a key objective basis for in-depth investigation of the phenotypic characteristics of tumors and their microenvironmental properties[21,22]. It has been widely studied in the diagnosis, preoperative prediction and prognostic assessment of EC[23-25].

Recently, Lin et al.[26]extracted sequential features of first-order and three-dimensional shapes based on diffusion-weighted imaging (DWI)and constructed a radiomics model (Rad-Score) using LASSO regression, which demonstrated an accuracy of 71% in both the training and test sets. The Rad-Signature model, which further incorporates clinical parameters, increased the accuracy to 73.2% and 75.4% in the training and test cohorts, and the study showed that the predictive efficacy of the radiomics model was comparable to the ESMO clinical criteria, and that the radiomics features were significantly correlated with the increase in the total choline level detected by magnetic resonance spectroscopy (MRS). However, LVSI, DMI and lymph node status were not included in the clinical model because they required postoperative pathological confirmation. Celli et al.[27]showed moderate to high diagnostic performance in predicting low-risk EC and LVSI based on radiomics models with T2WI and ADC texture features. Lefebvre et al.[28]extracted three-dimensional radiogenomic features based on multiparametric MRI features and screened predictive features using a random forest (RF) algorithm, and the model was externally validated with predictive AUC values of 0.81 (95% CI:0.68-0.88), 0.80 (95% CI:0.67-0.93), 0.74 (95% CI:0.61-0.86) and 0.84 (95% CI:0.72-0.92). The results suggest that radiomic characterization may enable risk stratification of endometrial cancer for high-risk pathologic factors based on preoperative MRI, and its efficacy in identifying advanced lesions and deep myometrial infiltration is comparable or superior to that of radiologists.

3.3. Deep Learning Radiomics

Deep learning (DL), as an important development direction of radiomics, adopts an end-to-end learning method based on deep neural networks (convolutional neural network, Transformer, etc.), which is able to segment images automatically, avoiding the errors caused by manual segmentation of images[29]. The deep learning-based radiomics (DLR) model can directly process complete medical image data and automatically learn valuable information from images through its multilevel feature extraction network, which can dig deeper into the complex features of tumors and show great potential in clinical applications[30,31]. In a multicenter study of US DLR model for endometrial cancer risk prediction, super-resolution (SR) technology was applied to improve image quality before feature extraction, Pyradiomics was used to extract radiomics features to construct R model, convolutional neural network (CNN) to extract deep learning features to construct CNN model, and DLR model combining radiomics and deep learning features, the DLR model showed comparable diagnostic performance among the three models (AUC = 0.893 in the internal test set and AUC = 0.871 in the external test set), and has strong predictive value in early and accurate identification of EC[32].Yang et al.[33]used a deep learning method to extract image features based on Densenet121 convolutional neural network and organically combined them with traditional radiomics features, while integrating a number of clinical indicators, including key parameters such as patient's age, preoperative CA125 level, tumor imaging features, pathology grading, and family history, to construct a predictive risk-stratified radiomics nomogram model obtains AUC values of 0.923 and 0.842 in the training and validation sets, and its predictive efficacy is significantly better than that of a single traditional radiomics or deep learning model.

The above study provides a reliable quantitative prediction tool for tumor risk assessment through the organic integration of traditional radiomics and deep learning features. However, the current application of DLR in EC has not been fully validated by large-scale prospective clinical studies, and the field of DL can be further expanded and more techniques can be explored in the future. Secondly, since the data of existing studies mainly come from a single region, the prediction models they establish may be affected by population-specific bias, and representative samples from different races and geographic regions need to be included in the future to validate the generalizability of the existing models.

4. Summary and Prospects

In summary, risk stratification of EC is a key link to guide clinical treatment decisions, and its precise preoperative prediction is important for surgical scope determination and adjuvant treatment selection. Existing imaging technologies and radiomics have demonstrated potential value in risk assessment, especially big data-based radiomics models have shown better predictive efficacy, but there are still limitations: current studies are generally limited by insufficient sample size, multicenter data heterogeneity, poor feature stability, and the lack of external validation, which makes it difficult to apply the research results directly to clinical practice. Although imaging genomics has improved the accuracy of traditional imaging assessment, its clinical application still faces many challenges, including differences in image acquisition parameters (MRI field strength, sequence parameters), redundancy in feature selection, and inconsistency in ROI outlining. Multicenter prospective cohort studies are needed to establish uniform image acquisition specifications and develop a standardized feature extraction process in future studies. In recent years, habitat analysis, as an emerging method to analyze the spatial heterogeneity of tumor microenvironment, provides a new perspective to reveal the invasive metastasis pattern of EC. Future studies should integrate multimodal images, combine habitat features with genomics data, and apply deep learning technology to establish robust prediction models with clinical utility, and ultimately realize the transformation from scientific research exploration to clinical routine application.

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