Development of a Predictive Model for Lymph Node Metastasis in Epithelial Ovarian Cancer Patients Based on 18F-FDG PET-CT Radiomics: Postprint

Authors: Yuan Xiaorui, Tan Yanlin, Fu Chun, Fu Chun

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Abstract

Background Accurate preoperative assessment of lymph node metastasis in patients with epithelial ovarian cancer is of great significance for treatment planning and prognosis evaluation. Radiomics technology has been used as a non-invasive method for preoperative prediction of lymph node metastasis in various cancers, but there are few research reports on its application effect in the field of gynecological cancers. Objective To construct a predictive model for lymph node metastasis in patients with epithelial ovarian cancer using radiomics technology based on 18F-fluorodeoxyglucose positron emission tomography-CT (18F-FDG PET/CT). Methods A total of 98 patients with epithelial ovarian cancer who were hospitalized in the Department of Gynecology of the Second Xiangya Hospital of Central South University from September 2020 to December 2022 were selected. According to their lymph node metastasis status, they were divided into a lymph node metastasis group (65 cases) and a non-lymph node metastasis group (33 cases), and simultaneously randomly sampled at a 7:3 ratio into a training set (68 cases) and a validation set (30 cases). The clinical characteristics of all patients were analyzed, and models were constructed with lymph node metastasis status as the outcome label. Results The lymph node metastasis rate of epithelial ovarian cancer patients in this study was 66.3% (65/98). There were statistically significant differences in human epididymis protein 4 (HE4) levels and primary tumor location between the lymph node metastasis group and the non-lymph node metastasis group ($P<0.05$). Multivariate Logistic regression analysis showed that HE4 level, primary tumor location, and radiomics score (Radscore) were predictive factors for lymph node metastasis in epithelial ovarian cancer patients ($P<0.05$). A clinical prediction model was constructed using HE4 level and primary tumor location, and a combined prediction model was constructed using HE4 level, primary tumor location, and

Radscore. Delong' s test results showed that the area under the receiver operating characteristic curve (AUC) of the combined prediction model for predicting lymph node metastasis in epithelial ovarian cancer patients in the training set was 0.80 [95%CI (0.70~0.90)], which was higher than that of the clinical prediction model (0.73 [95%CI (0.61~0.85)]) (P=0.042). The calibration curve showed that the combined prediction model passed the calibration test (P=0.990) and had good discriminative ability. Decision curve analysis (DCA) results showed that both the clinical prediction model and the combined prediction model had good predictive efficacy, but the combined prediction model had higher net benefit. Conclusion The combined prediction model for lymph node metastasis in epithelial ovarian cancer patients was successfully constructed using radiomics technology based on 18F-FDG PET/CT, with high robustness, good discriminative ability, and high net benefit, which can provide reference for clinicians in formulating individualized treatment plans and evaluating patient prognosis.

Full Text

Construction of a Predictive Model for Lymph Node Metastasis in Patients with Epithelial Ovarian Cancer: Based on 18F-FDG PET/CT Radiomics Technology

YUAN Xiaorui[1], TAN Yanlin[2], FU Chun[1]*

[1]Department of Gynecology, the Second Xiangya Hospital of Central South University, Hunan 410010, China
[2]Department of PET/CT, the Second Xiangya Hospital of Central South University, Hunan 410010, China

Corresponding author: FU Chun, Chief Physician/Professor; E-mail: fuchun0814@csu.edu.cn

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Abstract

Background Accurate preoperative assessment of lymph node metastasis in patients with epithelial ovarian cancer is crucial for treatment planning and prognosis evaluation. Radiomics technology has been employed as a non-invasive approach to predict lymph node metastasis across various cancers, though few studies have reported its application in gynecological malignancies. **Objective** To construct a predictive model for lymph node metastasis in epithelial ovarian cancer patients using radiomics technology based on 18F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (18F-FDG PET/CT). **Methods** A total of 98 epithelial ovarian cancer patients admitted to the Department of Gynecology at the Second Xiangya Hospital of Central South University between September 2020 and December 2022 were enrolled. Based on lymph node metastasis

status, patients were divided into a lymph node metastasis group (n=65) and a non-metastasis group (n=33), and randomly assigned to a training set (n=68) and validation set (n=30) at a 7:3 ratio. Clinical characteristics were analyzed, with lymph node metastasis status serving as the outcome label for model construction. **Results** The lymph node metastasis rate was 66.3% (65/98). Significant differences were observed between the metastasis and non-metastasis groups in human epididymal protein 4 (HE4) levels and primary lesion location (P<0.05). Multivariate logistic regression analysis identified HE4 level, primary lesion location, and radiomics score (Radscore) as predictive factors for lymph node metastasis (P<0.05). A clinical prediction model was constructed using HE4 level and primary lesion location, while a combined prediction model incorporated HE4 level, primary lesion location, and Radscore. Delong' s test revealed that the combined model achieved an AUC of 0.80 [95%CI (0.70~0.90)] in the training set, significantly higher than the clinical model' s 0.73 [95%CI (0.61~0.85)] (P=0.042). The calibration curve demonstrated good discrimination ability with successful calibration (P=0.990). Decision curve analysis (DCA) indicated that both models exhibited good predictive performance, though the combined model yielded higher net benefit. **Conclusion** The combined prediction model for lymph node metastasis in epithelial ovarian cancer patients, constructed using 18F-FDG PET/CT-based radiomics technology, demonstrates high robustness, good discrimination ability, and substantial net benefit, providing a valuable tool for clinicians to formulate individualized treatment plans and assess patient prognosis.

Keywords Ovarian Neoplasms; Carcinoma, Ovarian Epithelial; Epithelial Ovarian Cancer; Lymph Nodes; Fluorodeoxyglucose F18; Positron Emission Tomography Computed Tomography; Imaging Genomics

1. Subjects and Methods

Ovarian cancer represents one of the most lethal gynecological malignancies, with approximately 230,000 new cases and 150,000 deaths annually worldwide, and a five-year survival rate of only 46% following diagnosis. Pelvic and para-aortic lymphadenectomy constitutes a standard component of staging surgery for early-stage ovarian cancer; however, the lymph node positivity rate in early-stage disease is merely 13%~20%, and randomized controlled trials have confirmed that systemic lymph node dissection (SLND) does not significantly improve survival outcomes. Consequently, accurate preoperative assessment of lymph node metastasis is essential. Current clinical evaluation relies heavily on radiologists' visual interpretation of medical images, which carries inherent subjectivity and uncertainty. Radiomics technology, which extracts and quantifies features from medical images, has emerged as a non-invasive tool for preoperative prediction of lymph node metastasis across multiple cancer types, though its application in gynecological oncology remains underexplored. This study employs 18F-FDG PET/CT-based radiomics to develop a predictive model for

lymph node metastasis in epithelial ovarian cancer patients, aiming to support clinical decision-making and prognostic assessment.

1.1 Study Population

We retrospectively enrolled 98 epithelial ovarian cancer patients admitted to the Department of Gynecology at the Second Xiangya Hospital of Central South University between September 2020 and December 2022. The cohort comprised 89 cases of serous cystadenocarcinoma, 5 endometrioid carcinomas, 2 mucinous cystadenocarcinomas, and 2 clear cell carcinomas. Inclusion criteria were: (1) pathologically confirmed epithelial ovarian cancer; (2) history of lymph node sampling or dissection; (3) availability of preoperative PET/CT images in DICOM format within 14 days before surgery; and (4) complete medical records with accessible clinical data. Exclusion criteria included: (1) non-epithelial ovarian cancer; (2) concurrent malignancies or recurrent epithelial ovarian cancer; and (3) severe cardiac, hepatic, or renal insufficiency. This retrospective study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, with waiver of informed consent. The patient screening flowchart is presented in [Figure 1: see original paper], and the radiomics workflow is illustrated in [Figure 2: see original paper].

1.2 Grouping Method

Clinical characteristics were reviewed from medical records, including demographic data, laboratory findings, pathological results, and imaging data. Patients were stratified into a lymph node metastasis group (n=65) and a non-metastasis group (n=33) based on pathological confirmation. Subsequently, the cohort was randomly divided into a training set (n=68) and a validation set (n=30) at a 7:3 ratio.

1.3 Radiomics Technique

All patients underwent preoperative 18F-FDG PET/CT imaging within 14 days before surgery. Imaging acquisition involved 6-7 bed positions using a Siemens Biography mCTx PET/CT scanner (serial number: 11057, 128-slice CT/52-ring PET). 18F-FDG tracer was produced in-house with radiochemical purity >95%. CT parameters were set at 120 kV voltage and 3.75 mm slice thickness. PET 3D imaging was acquired at 2 minutes per bed position. The imaging protocol included attenuation correction of PET images based on CT data, followed by iterative reconstruction to obtain coronal, sagittal, and transverse CT, PET, and PET-CT images, which were then transferred to an MMWP workstation and saved in DICOM format.

Two radiologists performed image segmentation using 3DSlicer software (version 4.11.20210226, https://www.slicer.org). The process involved semi-automatic tumor boundary delineation using the PET-IndiC module to obtain the maximum standardized uptake value (SUVmax), followed by automatic region of in-

terest (ROI) segmentation using a 40% SUVmax threshold. Radiomics features were extracted using the Radiomics module with wavelet transformation, generating eight decomposed images (LLL, LLH, LHL, LHH, HLL, HLH, HHL, HHH) through high-pass (H) and low-pass (L) filtering along x, y, and z axes. To ensure feature reliability, 30 PET images were randomly selected for inter-observer consistency assessment, and 20 images were re-segmented by the same radiologist after a 2-week interval for intra-observer consistency assessment. Features with intraclass correlation coefficient (ICC) >0.75 were retained for analysis.

1.4 Construction of the Epithelial Ovarian Cancer Lymph Node Metastasis Prediction Model

The modeling process comprised four steps. First, redundancy analysis was performed on features with ICC>0.75: normally distributed features underwent Pearson correlation analysis, while non-normally distributed features were assessed using Spearman rank correlation. Features with correlation coefficients (r or rs) <0.9 were retained. Second, LASSO regression (α=1.00) was applied for dimensionality reduction, selecting predictive features with non-zero coefficients through 5-fold cross-validation based on minimum criteria. The optimal tuning parameter (λ) was determined, and selected features were linearly combined with their non-zero coefficients to construct the radiomics signature and calculate each patient' s Radscore. Third, clinical variables including CA125, HE4, age, primary lesion location, lymphocyte count, lymphocyte fraction, and SUVmax were dichotomized based on ROC AUC optimal cutoffs and subjected to univariate and multivariate logistic regression analysis to develop a clinical prediction model. Finally, a combined prediction model was constructed by incorporating both clinical characteristics and Radscore into multivariate logistic regression analysis, with results visualized using a nomogram.

1.5 Statistical Analysis

Statistical analysis was performed using R software (version 4.0.2, https://www.r-project.org) and WPS software. Levene' s test assessed variance homogeneity. Normally distributed continuous variables were expressed as mean±standard deviation and compared using Student' s t-test, while non-normally distributed variables were presented as median (interquartile range) and analyzed using Mann-Whitney U test. Categorical data were expressed as frequencies and percentages, compared using ^{2} test or Fisher' s exact test. R packages included: "irr" for ICC calculation, "glmnet" for LASSO regression, "pROC" and "ROCR" for ROC analysis and Delong' s test, "rms" for nomogram, Hosmer-Lemeshow test, and calibration curves, and "rmda" for decision curve analysis (DCA). Two-sided P<0.05 was considered statistically significant.

2. Results

2.1 Comparison of Clinical Characteristics

The lymph node metastasis rate in this cohort was 66.3% (65/98). No significant differences were observed between groups in age, blood type, FIGO stage, CA125 level, pathological type, pathological grade, ascites cytology, lymphocyte count, lymphocyte fraction, or SUVmax (P>0.05). However, HE4 levels and primary lesion location differed significantly between the metastasis and non-metastasis groups (P<0.05) .

2.2 Radiomics Features

A total of 1,023 radiomics features were extracted, comprising 279 original features and 744 wavelet features. In the training set, LASSO regression identified λ=0.132 based on the minimum criterion, selecting three predictive features with non-zero coefficients [Figure 3: see original paper]A-B: (1) wavelet.HHH glszm Small Area Low Gray Level Emphasis (X1), (2) wavelet.LLL gldm Gray Level Variance (X2), and (3) wavelet.LLL ngtdm Contrast (X3). The Radscore was calculated as: Radscore = -2.0987121×X1 + 0.7531706×X2 + 0.7010890×X3 + 0.7928437. The Radscore achieved AUCs of 0.77 and 0.68 in the training and validation sets, respectively [Figure 3C: see original paper], demonstrating good performance. The mean Radscore was significantly higher in the metastasis group (0.3$±0.3)$thaninthenon - metastasisgroup$(0.2±$0.2) (t=3.0715, P=0.003) [Figure 4: see original paper].

2.3 Model Construction

Multivariate logistic regression incorporating HE4 level (coded: <343 pmol/L=0, $ $343 pmol/L=1) and primary lesion location (coded: unilateral=1, bilateral=2) identified both as independent predictors of lymph node metastasis (P<0.05) , forming the clinical prediction model. The combined model, which additionally included Radscore as a continuous variable, also identified HE4 level, primary lesion location, and Radscore as significant predictors (P<0.05) .

2.4 Model Validation

Delong' s test showed that the combined model achieved an AUC of 0.80 [95%CI (0.70~0.90)] in the training set, significantly higher than the clinical model' s 0.73 [95%CI (0.61~0.85)] (Z=-2.025, P=0.042). In the validation set, the combined model and clinical model achieved AUCs of 0.80 [95%CI (0.57~0.99)] and 0.76 [95%CI (0.54~0.98)], respectively, without significant difference (Z=-0.873, P=0.383) [Figure 5: see original paper]. The calibration curve confirmed good discrimination ability with successful calibration (P=0.990) [Figure 6: see original paper]A. DCA demonstrated that both models had good predictive performance, but the combined model yielded higher net benefit [Figure 6: see original paper]B.

2.5 Nomogram

The nomogram for the combined prediction model is presented in [Figure 7: see original paper].

3. Discussion

Systemic lymph node dissection, including pelvic and para-aortic lymphadenectomy, has been integral to ovarian cancer staging since 1988. For early-stage epithelial ovarian cancer, SLND aims to identify occult lymph node metastasis and guide surgical and pathological staging. However, only 20%-30% of early-stage patients harbor lymph node metastasis, subjecting at least 70% to unnecessary dissection. Furthermore, SLND is technically complex and associated with high complication rates, including increased blood loss and lymphocyst formation in 26.9% and 54.7% of patients, respectively. Population-based studies have shown that while SLND improves disease-free survival, it does not enhance overall survival, suggesting its primary value lies in pathological staging rather than therapeutic benefit.

Recent investigations have explored imaging techniques such as sentinel lymph node mapping to improve metastasis detection, though these remain invasive. Our study successfully developed a combined prediction model incorporating three radiomics features and two clinical characteristics, demonstrating robust performance with AUCs of 0.80 in both training and validation sets. The inclusion of HE4 level and bilateral primary lesion location aligns with previous research identifying these as risk factors for lymph node metastasis. Notably, we excluded pathological grade from the combined model as it is typically obtained postoperatively, contradicting our preoperative prediction objective, and CA125 level showed no significant difference in univariate analysis, likely due to our small sample size and variable specimen collection timing.

While the mechanistic basis of radiomics in predicting lymph node metastasis remains under investigation, radiomics features primarily reflect tumor heterogeneity, with high-dimensional data capturing cellular-level variations that correlate with genomic heterogeneity, treatment resistance, and metastatic potential. Our approach offers several advantages over previous studies: (1) incorporation of HE4 and primary location enhances clinical relevance; (2) semi-automatic ROI segmentation using 40% SUVmax threshold improves reproducibility; (3) applicability to early-stage disease; and (4) wavelet transformation provides additional heterogeneity information. Limitations include small sample size with predominance of advanced-stage disease, lack of stratified analysis by pathological subtype, and absence of external validation due to the retrospective design.

In conclusion, our 18F-FDG PET/CT-based radiomics model for predicting lymph node metastasis in epithelial ovarian cancer demonstrates high robustness, good discrimination, and substantial net benefit, offering a valuable reference for clinical decision-making and prognostic assessment.

Author Contributions: YUAN Xiaorui was responsible for manuscript writing, radiomics feature extraction, and data analysis. TAN Yanlin performed PET-CT image evaluation and tumor segmentation.

Conflict of Interest Statement: The authors declare no conflicts of interest among investigators, ethics committee members, or relevant parties involved in the publication of this research.

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ORCID: YUAN Xiaorui: https://orcid.org/0000-0002-7647-4777

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