

Research Article

A Prediction Model of Endometrial Cancer Lesion Metastasis under Region of Interest Target Detection Algorithm

Yuquan Xu  and Renfeng Zhao 

Department of Obstetrics and Gynecology, Guangxi Medical University, Guangxi Zhuang Autonomous Region, Nanning 530021, China

Correspondence should be addressed to Renfeng Zhao; xuyuquan@stu.gxmu.edu.cn

Received 15 March 2021; Revised 12 April 2021; Accepted 5 May 2021; Published 13 May 2021

Academic Editor: Gustavo Ramirez; drgustavophd@gmail.com

Copyright © 2021 Yuquan Xu and Renfeng Zhao. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The predictive values of region of interest (ROI) target detection algorithm-based radiomics for endometrial cancer (EC) lymph node metastasis was investigate in this work. 143 patients with EC admitted by hospital were selected as the research objects and divided randomly into a training group (group A) and a test group (group B). They received preoperative pelvic-enhanced magnetic resonance imaging (MRI) scanning. The ROI algorithm was applied to extract features to construct an EC lymph node radiomics model that was compared with a comprehensive prediction model of EC lymph node. The receiver operating characteristic (ROC) curve was employed to evaluate the diagnostic efficiency of the radiomic model and comprehensive predictive model. Results showed that both the radiomics model (area under the curve (AUC) of group A = 0.875 and AUC of group B = 0.882) and comprehensive prediction model (AUC of group A = 0.917 and AUC of group B = 0.893) had good predictive effects, and effect of the latter was markedly better than that of the former. It indicated that radiomics parameters of ROI target detection algorithm were effective markers for preoperative prediction of EC lymph node metastasis, and its comprehensive prediction model could play a guiding role in clinical decision-making.

1. Introduction

EC is a very common gynecological malignant tumor [1, 2]. In developed countries such as the United States, EC is the fourth largest cancer after breast, lung, and colorectal cancer [3]. The incidence of EC in China is also increasing year by year, and it is getting younger and younger. Although it is still more common in older women and its mortality is increasing, it is also being diagnosed among younger and younger women. Thus, EC has brought a great threat to the health of women in China [4]. EC is featured with high heterogeneity, and the prognosis of different risk stratifications is also different. Lymph node metastasis, myometrial infiltration, pathological grading, and age are the main factors affecting the prognosis, so the clinical treatment decisions are influenced by them to a certain extent [5]. Besides, low to moderate risk of EC can be treated non-surgically. Radiation and chemotherapy can also play a

therapeutic role. The main treatments for EC are total hysterectomy and bilateral salpingo-oophorectomy [6]. However, there are complications in surgical treatment, and not many people really suffer from lymph node metastasis. Most patients can be diagnosed early based on postmenopausal vaginal bleeding of EC, but it is not appropriate for all patients to take lymph node dissection. How to take an effective diagnosis method to accurately evaluate the lymph node metastasis of EC is of great significance to the treatment decision of patients with EC.

Clinically, imaging diagnosis technology is mainly used for preoperative evaluation of EC. Pelvic-enhanced MRI is a common diagnostic method [7, 8], but its sensitivity to the identification of lymph node metastasis needs to be improved. In recent years, the emergence of radiomics has become a new way to solve the prediction of lymph node metastasis. The important idea of radiomics is that medical images are not only pictures but also data [9]. At present,

radiomics is widely applied in the tumor research, such as tumor staging, efficacy evaluation, and prognostic analysis, and it is extensively used in diseases such as nonsmall cell lung cancer, cervical cancer, and pulmonary nodules [10, 11]. Existing studies have constructed preoperative prediction models of lymph node metastasis for colorectal cancer and bladder cancer based on radiomics, which suggests that radiomics technology has reliable clinical value for lymph node metastasis prediction. Radiomics technology involves image acquisition, identification, and segmentation of volumes of interest, extraction and analysis of quantitative features, and the development of classification or prediction models. Compared with traditional medical image vision, the in-depth mining of medical images by radiomics technology makes feature acquisition more effective, relatively objective, and rich in feature types. Moreover, image segmentation is to delineate ROI for subsequent feature extraction [12].

Based on the feature location of the MRI target image, the ROI area of image was established in this study to achieve the purpose of target detection. Therefore, ROI target detection algorithm imageomics was proposed and applied to the prediction and analysis of EC lymph node metastasis, so as to provide theoretical basis for clinical imaging diagnosis of EC and preoperative evaluation.

2. Materials and Methods

2.1. Research Objects. 143 patients with EC were selected as the research objects received, who were admitted to hospital from October 2016 to October 2019. The age of the patients ranged from 51.24 years to 57.93 years, with an average age of 53.82 ± 3.76 years. This experiment had been approved by the Ethics Committee of the hospital, and the patients included in the study had known and agreed.

The criteria for inclusion were defined to include patients who were diagnosed as EC, underwent MRI examination (sequence parameters of T1 weighted imaging + contrast enhanced imaging (T1WI + C), T2 weighted imaging (T2WI), and diffusion weighted imaging (DWI) are shown in Table 1), had the lymph node dissection results, and had complete clinical data.

The criteria for exclusion were defined to include patients who suffered from cervical cancer, had a history of nonsurgical treatment, had negative lymph node metastasis, had poor quality of MRI image, possessed the unstandardized MRI sequence, and had incomplete clinical data.

2.2. MRI Imaging Based on ROI Target Detection Algorithm.

The ratio of positive and negative lymph node patients included in the study was generally 1 : 3–1 : 4, which was the best. The research objects in this study were retrieved from the Department of Medical Records and Pathology. A total of 153 patients were retrieved from positive patient database, and 50 cases of them could retrieve pelvic-enhanced MRI images through picture archiving and communication system (PACS). Then, 33 cases of them were obtained through the inclusion criteria limited machine scanning. In

addition, a total of 1,065 patients were retrieved from negative patient database, and the pelvic-enhanced MRI images of 496 cases could be retrieved through PACS. Finally, 383 cases were selected after the scanning of inclusion criteria limited machine.

All relevant data of the selected patients were collected, and manual reading was adopted during the collection process. Those that did not meet the inclusion criteria would be excluded. The collected information was as follows. First one was the MRI images and related reports of patients, and the report should have the artificial evaluation of the patient's lymph node metastasis state and myometrial infiltration. Second one was the clinically basic information, mainly including the age of patients, carbohydrate antigen 125 (CA125), and biopsy pathological types. Third one was macropathological lymph node metastasis. Then, a database was established after information was collected, and the standards of inputting data included the following. First one was that the exact age of patients should be recorded. Second one was the values of CA125. If there was an increase before the surgery, it was recorded as "1;" if the value was within the normal range, namely, $CA125 \leq 35$ U/mL, it was recorded as "0." Third one was the preoperative biopsy results. It was recorded as "1" if the patient was at high risk, and "0" should be given if the patient was at low risk. Fourth one was the MRI imaging results. If the image presented possible lymph node metastasis, it was recorded as "1;" if the patient's lymph node state was normal, it was recorded as "0;" if the lymph node state was not mentioned in the MRI examination result, it was also recorded as "0;" "1" would be given if it indicated that the myometrium was infiltrated; in addition, "0" would be recorded if this phenomenon did not occur. Fifth one was the outcome of macropathological lymph nodes. If metastasis occurred, it was recorded as "1," and "0" would be given if there was no metastasis. The above five aspects of data needed to be complete, and the information of a patient would not be input if any item was omitted. In the end, 26 patients were selected from the positive patient database and 302 patients were chosen from the negative patient database. A simple random sampling was used for the negative patient database, and finally, 142 patients were selected.

The pelvic MRI images of all patients were downloaded from PASC, ITK Snap 3.8.0 software was employed to delineate ROI, and the primary lesion of EC was used as ROI. The MRI scanning sequence included axial view (T1WI, T2WI, T1WI + C, and DWI), coronal view (T1WI + C), and sagittal view (T2WI and T1WI + C). In this study, the MRI images were selected to delineate the lesion area and then transferred to the postprocessing workstation to obtain the analog-to-digital converter (ADC) images. Because of the full-layer delineation method applied in this study, the results obtained from different orientations of the same sequence were almost the same. Therefore, each sequence only needed to choose one orientation and the final lesion delineation selected sagittal T2WI and sagittal T1WI + C in this study. Based on the above, the EC lesions were delineated by sagittal T2WI, sagittal T1WI + C, and axial ADC. The patients should be excluded if their images had poor image

TABLE 1: MRI detection sequence information.

Sequence	Orientation	Thickness of layer (mm)	Time of repetition (TR)/time of echo (TE) (msec)	B value (sec/mm ²)	Matrix
DWI	Axial view	5	4800/96	600	192 × 128
T2WI	Sagittal view	5	3120/88	—	192 × 320
T1WI + C	Sagittal view	5	130/1.2	—	192 × 288

quality and could not be delineated during this process. Finally, 25 positive cases and 118 negative cases were selected, with a total of 143 patients.

2.3. Radiomics Analysis. The obtained 143 patients were grouped randomly into group A and B. Furthermore, there were 95 patients in group A and 48 patients in group B. After imaging analysis, the process was shown in Figure 1.

First, there was image feature extraction, and T2WI, T1WI + C, and ADC sequences were extracted to all obtain 524 3-dimensional (3D) features in turn. A total amount of 3D features was 1572 (=524 × 3), of which 16 were first-order statistical features, 456 were wavelet features, 6 were morphological features, and 46 were texture features. After feature screening, the screening process was shown in Figure 2.

Finally, the model was constructed and evaluated. Through the construction and analysis of the logistic regression model, the patient's Radiomic score was obtained and could represent the prediction probability value of the radiomics model of lymph node metastasis. In addition, it could be expressed as

$$\text{Radiomic signature} = \frac{1}{1 + e^{-\text{radiomic_score}}} \quad (1)$$

Then, the basic information of patients in group A was for the clinical information screening that was adopted by the forward stepwise regression method. The marked difference of pathological features obtained after screening included CA125 and preoperative biopsy pathology ($P < 0.05$), as shown in Table 2.

On the basis of the radiomics model constructed above, the new comprehensive prediction model for lymph node metastasis was established by combining with the clinical information screening. The ROC curve was applied to assess the diagnostic performance of the EC radiomics model and comprehensive predictive model, including AUC, sensitivity, specificity, and accuracy.

2.4. Statistical Analysis. SPSS20.0 statistical software was used for analysis, measurement data were expressed as the mean ± standard deviation ($\bar{x} \pm s$), and Mann-Whitney U test was used for comparative analysis. Besides, the count data was represented by percentage (%) and compared and analyzed between groups by χ^2 test. If $P < 0.05$, the difference was statistically substantial.

3. Results

3.1. Basic Information of Patients in the Two Groups. The 143 patients with EC were selected and divided randomly into

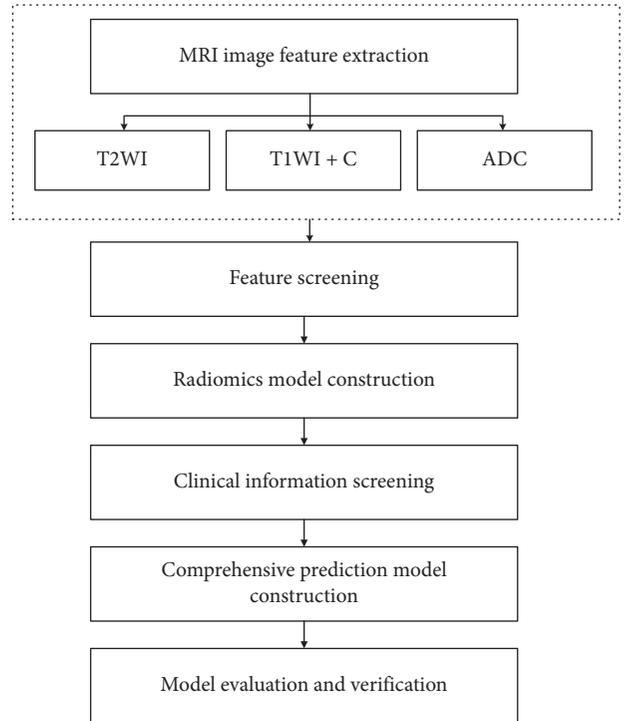


FIGURE 1: Radiomics analysis process.

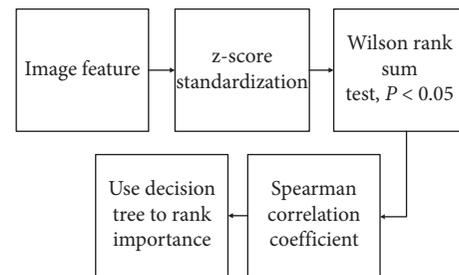


FIGURE 2: Image feature screening process.

group A and B, and there were 95 patients in group A and 48 patients in group B. Table 3 shows the basic conditions of patients with EC in group A and B. It was found that the age of EC patients in group A was 51.24–57.89 years, with an average age of 53.27 ± 4.65 years. There were 22 cases with elevated values of CA125 and 73 cases with normal values of CA125. Besides, 31 cases had high-risk preoperative biopsy results and 64 cases had low-risk preoperative biopsy results. The macropathological results of 18 cases showed positive and those of 77 cases displayed negative. 4 patients might suffer from lymph node metastasis, 32 patients had multiple small lymph nodes, and 59 patients were normal or not

TABLE 2: Screening of clinical information for EC patients.

Item	Age	CA125	MRI		Biopsy pathological type
			Lymph node metastasis	Myometrial infiltration	
<i>P</i>	0.1254	0.0032	0.8721	0.1432	0.010

TABLE 3: Basic information of patients with EC in the two groups.

		Group A (<i>n</i> = 95)	Group B (<i>n</i> = 48)	<i>P</i>
		Age (years old)	Range	
	Average	53.27 ± 4.65	54.01 ± 3.98	
CA125	Elevated	22	9	0.209
	Normal	73	39	
Preoperative biopsy results (number of cases)	High risk	31	10	0.072
	Low risk	64	38	
Macropathological results (number of cases)	Positive	18	10	0.306
	Negative	77	38	
State of lymph node (number of cases)	Metastasis perhaps	4	3	0.423
	Multiple small lymph nodes	32	18	
	Normal/not mentioned	59	27	
Myometrial infiltration (number of cases)	Deep	8	2	0.213
	Shallow or none	87	46	

mentioned. In addition, there were 8 cases with deep myometrial infiltration and 87 cases with shallow or no myometrial infiltration.

In group B, patients were 52.48–57.93 years old, with an average of 54.01 ± 3.98 years. The CA125 values of 9 cases were increased and 39 cases had normal values of CA125. The macropathological results of 10 cases reflected positive and those of 38 cases displayed negative. There were 3 cases with lymph node metastasis perhaps, 18 cases with multiple small lymph nodes, and 27 cases with normal or unmentioned. Moreover, 2 patients were for deep myometrial infiltration and 46 were for shallow or no myometrial infiltration. Compared with the distribution of the above six features of EC patients in group A and B, the difference was not statistically obvious ($P > 0.05$).

3.2. MRI Imaging Features of Patients with Endometrial Cancer. Figure 3 indicated the MRI imaging features of patients with EC. It revealed that the imaging features were mainly as follows. The image of T1WI examination showed iso-signal, the image of T2WI examination displayed endometrial signal slightly lower than the normal, the image of DWI presented that the tumor signal was risen and its ADC value was reduced, and the image of T1WI + C reflected that the degree of enhancement in the delayed stage was sharply lower than that of the endometrium.

3.3. Comparison of Model Prediction Efficiency. The ROC curve method was applied to assess the diagnostic efficacy of the radiomics model and the comprehensive prediction model of EC lymph node metastasis, and the detailed results are shown in Figures 4–9. Figures 4 and 5 indicate that the AUC values of the radiomics model in group A and B were 73.4 and 89.2 in sequence, while the AUC values of the

comprehensive prediction model in group A was 79.2 and that of group B was 66.9. Therefore, the training results and test results were similar to the prediction performance results of the two models. Both the radiomics model and the comprehensive prediction model had good predictive effects, and the comprehensive prediction model had better prediction performance in contrast to the radiomics model. Figures 6–9 showed that the radiomics model in group A had an accuracy of 82.1%, a specificity of 84.7%, and a sensitivity of 73.4% for predicting lymphatic metastasis of endometrial cancer, while the accuracy, specificity, and sensitivity of the comprehensive prediction model were 87.9%, 90.2%, and 79.2% in turn. Furthermore, the accuracy, specificity, and sensitivity of the radiomics model in group B were 83.8%, 82.3%, and 89.2% in turn for EC lymphatic metastasis prediction. Moreover, the comprehensive prediction model had an accuracy of 83.5% for endometrial cancer lymphatic metastasis prediction, a specificity of 86.8%, and a sensitivity of 66.9%.

4. Discussion

EC is the most common malignant tumor of the female reproductive tract in Western countries [13]. EC patients are classified into different risk categories based on histopathological tumor type and grading and depth of myometrial infiltration. The International Federation of Obstetrics and Gynecology (FIGO) system is used for EC to have surgical staging. Since FIGO (2009) staging is related to prognosis, preoperative staging is essential for tailored treatment. MRI plays a crucial role in the evaluation of EC and cervical cancer, from detection to evaluation of recurrent disease. MRI shows the depth of myometrial infiltration, which is correlated to tumor grading and lymph node metastasis, so it is associated with prognosis [14]. Radiomics is very

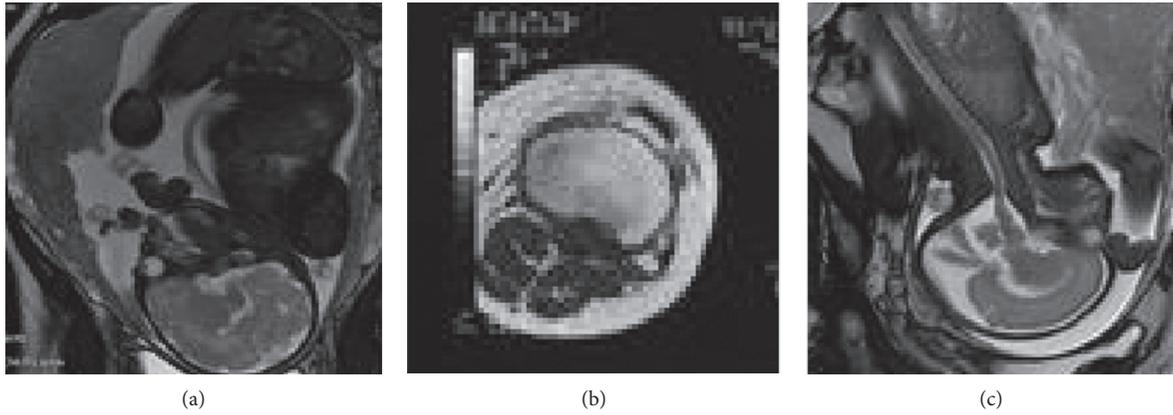


FIGURE 3: MRI images of patients with EC: (a) the image after DWI examination; (b) the image after T2WI examination; and (c) the image after T1WI+C examination.

promising in tumor screening, early diagnosis, accurate grading and staging, and treatment and prognosis. It is helpful for tumor diagnosis and prediction [15]. The radiomics based on the ROI target detection algorithm was employed in this study to predict and analyze the focal metastasis of EC, and the radiomics model and comprehensive prediction model were constructed, suggesting that the radiomics model (AUC of group A = 0.875 and AUC of group B = 0.882) and the comprehensive prediction model (AUC of group A = 0.917 and AUC of group B = 0.893) could have great predictive effects.

The assessment of lymph node metastasis is very vital for the treatment decision and prognosis prediction of EC. De et al. [16] adopted radiomics technology for the construction of positron emission tomography (PET) EC lymph node metastasis prediction model, and the results showed that this method could improve the sensitivity of lymph node staging detection and better provide stratified treatment options for patients. However, PET is not a routine examination for EC, and the sensitivity of routine MRI is low. Xu et al. [17] explored the role of prediction models based on magnetic resonance images and clinical parameters in the prediction of EC lymph node metastasis, extracted 4,179 radiological features to establish the clinical models, radiomics models, and two combined models. The results suggested that these four models had the ability to predict lymph node metastasis. The combined models were in the training group (AUC was 0.892 and 95% CI was 0.834–0.951) and in the test group (AUC was 0.883 and 95% CI was 0.786–0.980) showed the best recognition ability. In the analysis of the ROI target detection algorithm-based radiomics, 1,572 3D features were extracted in this study, of which 16 were first-order statistical features, 456 were wavelet features, 6 were morphological features, and 46 were texture features. Moreover, the models could meet both the specificity and sensitivity at the same time. In group A, the radiomics model had an accuracy of 82.1%, a specificity of 84.7%, and a sensitivity of 73.4% for predicting lymphatic metastasis of EC; the accuracy, specificity, and sensitivity of the comprehensive prediction model for predicting lymphatic metastasis of EC were 87.9%, 90.2%, and 79.2%, respectively. The accuracy of the radiomic

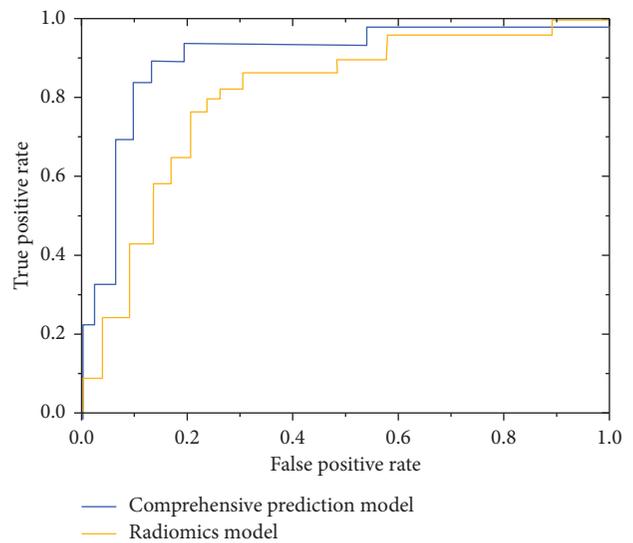


FIGURE 4: ROC curve analysis results of group A.

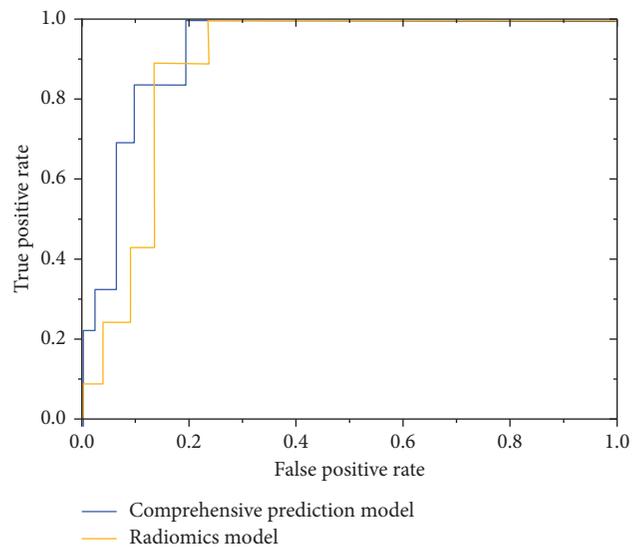


FIGURE 5: ROC curve analysis results of group B.

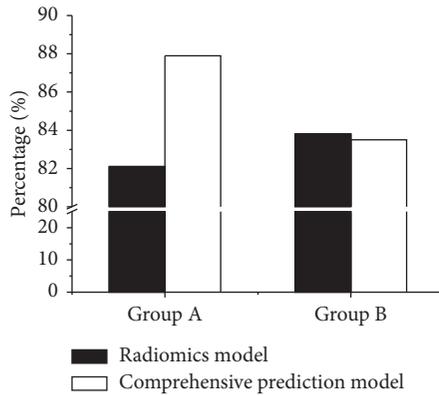


FIGURE 6: Comparison on accuracy of different prediction models.

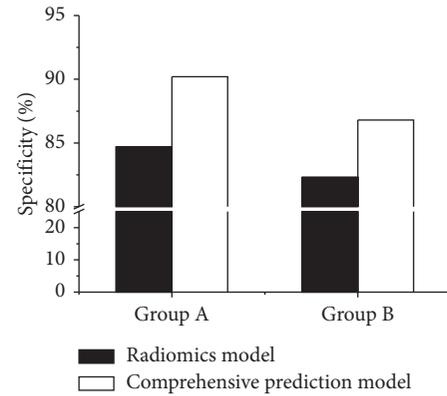


FIGURE 9: Comparison on specificity of different prediction models.

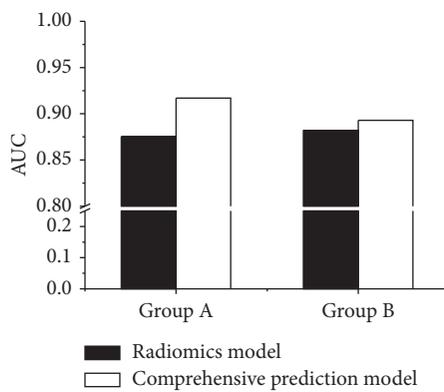


FIGURE 7: Comparison on AUC values of different prediction models.

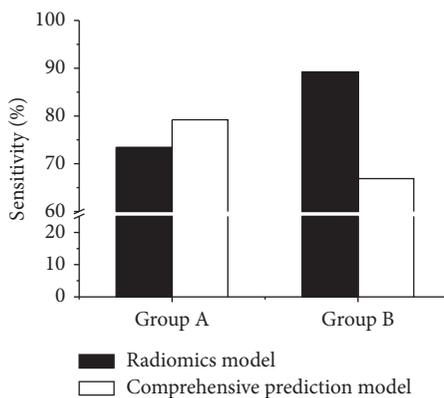


FIGURE 8: Comparison on sensitivity of different prediction models.

model for predicting lymphatic metastasis of EC was 83.8% in group B, its specificity was 82.3%, and its sensitivity was 89.2%; the comprehensive prediction model for EC lymphatic metastasis prediction had an accuracy of 83.5%, a specificity of 86.8%, and a sensitivity of 66.9%. The comprehensive prediction model had better diagnostic performance in group A and B in contrast to the radiomics model, which was consistent with the research

results of Xu et al. (2019). It revealed that the evaluation of the disease required a combination of clinical, imaging, and pathological information. Among the five clinical pathological information evaluated in this study, CA125 and preoperative biopsy pathological results were obviously different ($P < 0.05$) and were included in the comprehensive prediction model. This suggested that CA125 and preoperative biopsy pathological results were important risk factors for lymph node metastasis in EC, which was in accord with the findings of previous studies by Ünsal et al. [18] and Li et al. [19]. The insignificant differences in the other four clinical pathological information might also be caused by the limited number of this study or other factors, which still should be further confirmed by subsequent research.

5. Conclusion

In order to investigate the application values of the ROI target detection algorithm in the prediction of EC lymph node metastasis, the EC radiomics model and comprehensive prediction model were constructed in this study. It was found that the diagnosis efficacy of the comprehensive prediction model was superior to the radiomics model, indicating that the parameters of the ROI target detection algorithm-based radiomics were effective preoperative prediction markers for EC lymph node metastasis, and its comprehensive prediction model could play a guiding role in clinical decision-making. However, there were still some shortcomings in this study. For example, the number of samples was limited and geographical factors were not considered, and other factors were not included, such as cervical involvement, human epididymis protein 4 (HE4), and genetic markers. In the future, the number of samples should be increased, the scope of the experiment should be expanded, and the discussions of influence on factors, such as cervical involvement, HE4, and genetic markers. To sum up, the results of this study could provide a reference for the prediction of lymph node metastasis of EC before surgery.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- [1] M. Habiba, N. Pluchino, P. Petignat, P. Bianchi, I. A. Brosens, and G. Benagiano, "Adenomyosis and endometrial cancer: literature review," *Gynecologic and Obstetric Investigation*, vol. 83, no. 4, pp. 313–328, 2018.
- [2] M. E. Urlick and D. W. Bell, "Clinical actionability of molecular targets in endometrial cancer," *Nature Reviews Cancer*, vol. 19, no. 9, pp. 510–521, 2019.
- [3] M. M. Braun, E. A. Overbeek-Wager, and R. J. Grumbo, "Diagnosis and management of endometrial cancer," *American Family Physician*, vol. 93, no. 6, pp. 468–474, 2016.
- [4] K. Moore and M. A. Brewer, "Endometrial cancer: is this a new disease?" *American Society of Clinical Oncology Educational Book*, vol. 37, pp. 435–442, 2017.
- [5] R. A. Brooks, G. F. Fleming, R. R. Lastra et al., "Current recommendations and recent progress in endometrial cancer," *CA: A Cancer Journal for Clinicians*, vol. 69, no. 4, pp. 258–279, 2019.
- [6] M. Janda, V. Gebiski, L. C. Davies et al., "Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer," *Journal of the American Medical Association*, vol. 317, no. 12, pp. 1224–1233, 2017.
- [7] S. Nougaret, M. Horta, E. Sala et al., "Endometrial cancer MRI staging: updated guidelines of the european society of urogenital radiology," *European Radiology*, vol. 29, no. 2, pp. 792–805, 2019.
- [8] M. M. Otero-García, A. Mesa-Álvarez, O. Nikolic et al., "Role of MRI in staging and follow-up of endometrial and cervical cancer: pitfalls and mimickers," *Insights Imaging*, vol. 10, no. 1, p. 19, 2019.
- [9] R. J. Gillies, P. E. Kinahan, and H. Hricak, "Radiomics: images are more than pictures, they are data," *Radiology*, vol. 278, no. 2, pp. 563–577, 2016.
- [10] S. Sanduleanu, H. C. Woodruff, E. E. C. De Jong et al., "Tracking tumor biology with radiomics: a systematic review utilizing a radiomics quality score," *Radiotherapy and Oncology*, vol. 127, no. 3, pp. 349–360, 2018.
- [11] Y.-q. Huang, C.-H. Liang, L. He et al., "Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer," *Journal of Clinical Oncology*, vol. 34, no. 18, pp. 2157–2164, 2016.
- [12] Q. Li and Z. X. Ye, "Radiomics: the process and applications in tumor research," *Zhonghua Zhong Liu Za Zhi*, vol. 40, no. 11, pp. 801–804, 2018.
- [13] K. Passarello, S. Kurian, and V. Villanueva, "Endometrial cancer: an overview of pathophysiology, management, and care," *Seminars in Oncology Nursing*, vol. 35, no. 2, pp. 157–165, 2019.
- [14] B. B. Rafael, V. Macchi, A. Porzionato, and R. De Caro, "Editorial for "preoperative assessment for high-risk endometrial cancer by developing a MRI- and clinical- based radiomics nomogram: a multicenter study"" *Journal of Magnetic Resonance Imaging*, vol. 52, no. 6, 2020.
- [15] H. C. Kniep, F. Madesta, T. Schneider et al., "Radiomics of brain MRI: utility in prediction of metastatic tumor type," *Radiology*, vol. 290, no. 2, pp. 479–487, 2019.
- [16] E. De Bernardi, A. Buda, L. Guerra et al., "Radiomics of the primary tumour as a tool to improve ^{18}F -FDG-PET sensitivity in detecting nodal metastases in endometrial cancer," *EJNMMI Research*, vol. 8, no. 1, p. 86, 2018.
- [17] X. Xu, H. Li, S. Wang et al., "Multiplanar MRI-based predictive model for preoperative assessment of lymph node metastasis in endometrial cancer," *Frontiers in Oncology*, vol. 9, p. 1007, 2019.
- [18] M. Ünsal, G. Kimyon Comert, A. Karalok et al., "The preoperative serum CA125 can predict the lymph node metastasis in endometrioid-type endometrial cancer," *Ginekologia Polska*, vol. 89, no. 11, pp. 599–606, 2018.
- [19] J. Li, X. Wang, W. Qu, J. Wang, and S.-W. Jiang, "Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: a meta-analysis," *Clinica Chimica Acta*, vol. 488, pp. 215–220, 2019.