Prediction of BRCA Gene Mutation Status in Epithelial Ovarian Cancer by Radiomics Models based on 2D and 3D CT Images

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Abstract

Background The objective of this study is to explore the value of two-dimensional (2D) and three-dimensional (3D) radiomics models based on enhanced computed tomography(CT) images in predicting BRCA gene mutations in patients with epithelial ovarian cancer.

Methods A retrospective analysis of the clinical and imaging data of 122 patients with ovarian cancer confirmed by surgery and pathology and on which genetic testing was performed. Radiomics features were extracted from the 2D and 3D regions of interest of the patients' primary tumor lesions, and features were selected in the training set using the maximum correlation and minimum redundancy method. Then, the best features were selected through Lasso 10-fold cross-validation. Feature subsets were used to establish a radiomics model. We used area under the receiver operating characteristic curve analysis to evaluate the model's performance and then used the model's decision curve to evaluate its clinical validity.

Results On the validation set, the area under the curve values of the 2D, 3D, and 2D+3D combined models was 0.78 (0.61–0.96), 0.75 (0.55–0.92), and 0.82 (0.61–0.96), respectively. However, the DeLong test P values between the three pairs of models were all >0.05. The decision curve analysis showed that the radiomics model had a high net benefit across all high-risk threshold probabilities.

Conclusions The three radiomics models can predict the BRCA gene mutation in ovarian cancer, and there were no statistically significant differences between the three models' prediction performance.

Introduction

According to data from the International Cancer Research Center, approximately 52,000 new cases of ovarian cancer are diagnosed in China each year, with a high tumor mortality rate ^[1,2], and epithelial ovarian cancer accounts for 90% of all ovarian malignancies ^[3]. Studies have shown that approximately 50% of epithelial ovarian cancers exhibit DNA repair defects through homologous recombination, and BRCA1/2 mutations in germline and somatic cells are the most common mechanism of homologous recombination deficiency ^[4]. The study found that patients with BRCA1/2 mutant ovarian cancer are sensitive to platinum drugs, have a higher progression-free survival period, and have better prognosis ^[5-6]. Genetic testing is presently the main method for clinical judgment of BRCA gene mutations, but genetic testing is expensive, costly, and has a long detection period, and unit sampling cannot cover the entire tumor ^[7]. Nougaret et al. ^[8] predicted BRCA gene status by observing CT features and found that some radiomics features are related to gene mutation status, but the judgment of these radiomics features was dependent on the observer's subjective experience.

Radiomics can objectively quantify the relationship between the pixels and the spatial distributions of medical images and fully explore hidden information in the images that cannot be observed by the naked eye. In previous studies, radiomics has been used to capture tumors' inherent heterogeneity and correlate

it with potential gene expression types^[9]. Extracting radiomics features requires delineating the area of interest of the lesion, which is currently done by two commonly used methods: two-dimensional (2D) and three-dimensional (3D) delineation. However, the pros and cons of these two delineation methods are still controversial. Therefore, in this article, we aim to explore the predictive value of radiomics models based on different delineation methods for BRCA gene mutations in patients with epithelial ovarian cancer, and to compare the prediction performance of each model, with the goal of improving the prediction process of gene mutation status. In doing so, we seek a model that provides an ideal and convenient method of area of interest sketching.

1. Methods

1.1 Research subjects

We performed a retrospective analysis of patients with epithelial ovarian cancer who received treatment at our institution from March 2017 to July 2020. We collected clinical pathological data; CT enhanced images before surgery, radiotherapy, and chemotherapy; and clear postoperative pathological diagnosis. The inclusion criteria were as follows: (1) the biopsy tissue was confirmed pathologically as epithelial ovarian cancer; (2) an abdominal CT scan was performed before the operation, and the images included the arterial, venous, and delayed phases; (3) no radiotherapy or chemotherapy was performed before the operation; and (4) lesion size ≥ 10 mm. The exclusion criteria were as follows: (1) large image artifacts that would affect an observer; (2) patients who were unable to tolerate enhanced CT examination; (3) patients who underwent preoperative radiotherapy and chemotherapy; and (4) patients with a history of other malignant tumors or pelvic metastases. In the end, 122 patients were included in the study. Among them, 77 cases were in the BRCA gene non-mutation group, and those patients were aged 35–75 years (average: 54.86 years); 45 cases were in the BRCA gene mutation group, and those patients were aged 36–77 years (average: 53.93 years).

1.2 Genetic testing

NGS genetic testing technology was applied on all patients, and all had at least one of the following indications: (1) family history of pathogenic BRCA gene mutations; (2) family history of breast cancer before age 45 years or triple-negative breast cancer before age 60 years; or (3) the patient's economic conditions permitted or the doctor required genetic testing according to the patient's condition. To ensure the consistency of the test results, all subjects were tested by the same testing agency.

1.3 Image acquisition

The patients fasted for more than 8 hours and drank approximately 500–1000 mL of clean water orally 15–30 min before the examination. After the bladder was filled, the abdomen and pelvis were scanned using a GE Discovery CT 750HD (HDCT, USA) scanner in supine position. The scan ranged from the top

of the diaphragm or the level of the iliac spine to the symphysis pubis. The tube voltage was 120 kV, the tube current was 280–300 mA, the layer thickness was 5 mm, the reconstruction dimension was 1.25 mm, the layer spacing was 5 mm, and the pitch was 1.375:1. The contrast agent for enhanced scanning was 1.5 mL/kg of iohexol (300 mgI/mL), which was injected through the median cubital vein with a flow rate of 2.5–3.0 mL/s. The contrast agent was injected twice: at 25–30 s and 60–70 s for arterial and venous scanning, respectively.

1.4 Image segmentation and feature extraction

The preoperative abdominal enhanced CT image data of all patients were collected from the ICPACS workstation of the CT Room at the Imaging Department of our institution and exported in .DICOM format. A senior diagnostic imaging doctor, A, used ITK-Snap software (<https://www.itksnap.org>) to delineate the region of interest (ROI) of the lesion in the third phase of enhanced CT. For 2D delineation, the scope included the layer in which the lesion had the largest surface area, and for 3D delineation, the scope covered all possible areas of the target lesion. During the delineation process, necrosis, blood vessels, and other structures were eliminated as completely as possible (Figure 1). After 2 weeks had passed, doctor A randomly selected 30 patients' data to perform ROI delineation again for evaluation of intra-group consistency of ROI delineation (intra-ICC). To evaluate the between-group consistency of ROI delineation (inter-ICC), another radiologist, B, also drew the ROIs on the 30 patients' images independently.

A.K. software (GE Healthcare, AnalysisKit; Version: 3.2.0.R), which conforms to the IBSI standard, was used to extract features from the ROIs outlined in each image. A total of 681 image biomarkers were obtained in each phase (non-mutation group labeled PA1-77, marked as 0; mutation group labeled PA78-122, marked as 1), including histogram, grayscale interconnected area matrix, grayscale co-occurrence matrix, morphology, run-length matrix, and wavelet change (wavelet) and Laplacian change (ln) characteristics.

1.5 Feature screening and model establishment

The features of the arterial phase, venous phase, and delay phase were integrated into a total of 2043 features. The data were randomly divided into training and test sets in a 7:3 ratio. In the training set, two feature selection methods, maximum correlation minimum redundancy (mRMR) and LASSO (least absolute shrinkage and selection operator) 10-fold cross-validation, were used to select features. First, mRMR was performed to remove redundant and irrelevant features, incorporate the retained features into the LASSO regression, find the value of hyperparameter λ that minimizes the binomial deviation, and then retain the subset of features whose coefficients were not 0 to construct the final model.

1.6 Statistical analysis and processing

The chi-square test or Mann-Whitney U test was used to check for significant differences in general features and clinical characteristics between the two groups. Various forms of analysis including area under curve (AUC), model accuracy, precision, sensitivity, specificity, negative predictive value, and positive predictive value were used to evaluate the radiomic models’ predictive ability. Finally, decision curve analysis was used to evaluate the models’ clinical applicability. All statistical analysis was performed using R software (version 3.6.1, <https://www.r-project.org>).

For general clinical characteristics, we used the Chi-square test and the Kruskal-Wallis H test to analyze abnormally distributed continuous variables. P values of <0.05 were considered statistically significant. All statistical analyses were performed using R software (version 3.6.1) and the Python programming language (version 3.5.6).

The intraclass correlation coefficients (ICCs) of each texture feature were calculated to evaluate the within- and between-observer changes in the texture features extracted by the ROI segmentation and to explain each feature’s reproducibility, according to the following scale: ICC < 0.4, poor; 0.59 > ICC≥0.4, fair; 0.75 > ICC≥0.6, good; and ICC≥0.75, excellent. Features with ICC≥0.8 were considered stable and included in further analyses.

2. Results

2.1 General characteristics

No statistically significant differences in age composition, maximum tumor diameter, or tumor markers were found among the three groups (P>0.05; Table 1).

Table 1
General characteristics of the three groups

Variable	Sample	class meaning unknown	class mutation	class wild	Statistics	P- value
Age	140	55.00(49.00, 58.05)	52.00(47.70, 57.20)	54.00(48.00, 59.30)	0.781	0.677
Maximum_Diameter	140	8.75(5.95, 11.00)	7.00(4.57, 9.24)	7.00(4.49, 10.00)	2.929	0.231
Tumor marker CA125	120	15(83.33 %)	42(93.33 %)	63(81.82 %)	3.601	0.463
Tumor marker CA125□CA199	19	3(16.67 %)	3(6.67 %)	13(16.88 %)		
Tumor marker CA199	1	0(0.00 %)	0(0.00 %)	1(1.30 %)		

2.2 Construction and verification of prediction models

2.2.1 Feature Screening

The ICC range within and between the 2D-outlined feature data group was (-0.18–1.00) and (-0.08–1.00), respectively. In total, 531 features had ICC values of >0.75 across the two groups. In the 3D-outlined feature data group, the ICC ranges within and between groups were (-0.06–1.00) and (-0.40–1.00), respectively. In total, 548 features had ICC values of >0.75 across the two groups.

We then used the mRMR and LASSO regression models to perform feature screening on features from the 2D, 3D, and combination of 2D and 3D (2D+3D) models that had been retained because they had ICC values of >0.75. For the 2D images, the binomial deviation was smallest at the optimal tuning parameter value of $\ln \lambda=0.0118$, and the four features whose coefficients were not 0 at that value were retained. For the 3D images, the binomial deviation was smallest at the optimal tuning parameter value of $\ln \lambda=0.0279$, and the 13 features whose coefficients were not 0 at that value were retained. For the 2D+3D combined images, the binomial deviation was the smallest at the optimal tuning parameter value of $\ln \lambda=0.0294$ (Figure 2, A), and the 12 features whose coefficients were not 0 at that value (Figure 2, B) were retained. The corresponding coefficients of the features are shown in Figure 2, C.

2.2.2 The diagnostic efficiency of the devised models

Logistic regression was used to establish radiomics models using the selected features, and the radscore of each case was calculated. Table 2 shows the radscore distribution in the gene mutation and wild-type groups generated by the 2D, 3D, and 2D+3D combined models. We used the AUC of the receiver operating characteristic curve and the models' accuracy, sensitivity, specificity, negative predictive value, and positive predictive value to evaluate their predictive ability.

Table 2

Radscores of each patient in the training and validation sets calculated by different models, and their distribution and difference statistics in patients with wild-type and mutant type BRCA genes

	Variable	Sample	wild	Mutation	Statistics	P-value
Train	Radscore_2D3D	76	-1.22±1.06	0.52±0.94	-7.329	<0.001
	Radscore_3D	76	-0.71(-1.06, -0.28)	0.00(-0.36, 0.28)	-4.413	<0.001
	Radscore_2D	76	-0.51±0.23	-0.19±0.30	-5.303	<0.001
Test	Radscore_2D3D	30	-1.03(-2.32, -0.01)	0.66(-0.23, 4.92)	-2.963	0.003
	Radscore_3D	30	-0.61(-0.95, -0.25)	-0.04(-0.48, 0.49)	-2.159	0.031
	Radscore_2D	30	-0.41±0.22	-0.17±0.23	-2.9	0.007

On the training set, the 2D model's image AUC was 0.81 (0.71–0.91), the 3D model's image AUC was 0.80 (0.70–0.90), and the 2D+3D combined model's image AUC was 0.91 (0.84–0.97). On the test set, the 2D model's image AUC was 0.78 (0.61–0.96), the 3D model's image AUC was 0.75 (0.55–0.92), and the 2D+3D combined model's image AUC was 0.82 (0.67–0.98) (Table 3). The fact that the 2D+3D combined model had the highest AUC value showed that it had the highest diagnostic efficacy (Figure 3). However, the DeLong test results showed that the P values among the three pairs of models were all >0.05, indicating that there were no statistically significant differences in prediction efficiency among the three pairs of models.

Table 3

Cutoff value prediction ability of the 2D, 3D, and 2D+3D joint radiomics models

	AUC	accuracy	Sensitivity	Specificity	Positive value	Negative value	Cut-off
2D Training set	0.81 [0.71-0.91]	0.75[0.63-0.84]	0.68	0.83	0.86	0.65	-0.43
2D Validation set	0.78 [0.61-0.96]	0.73[0.54-0.87]	0.61	0.91	0.91	0.61	
3D Training set	0.80 [0.70-0.90]	0.75[0.63-0.84]	0.71	0.81	0.84	0.65	-0.61
3D Validation set	0.75 [0.55-0.92]	0.74[0.55-0.88]	0.84	0.58	0.76	0.70	
2D+3D Training set	0.91 [0.84-0.97]	0.86[0.77-0.93]	0.95	0.74	0.84	0.92	0.14
2D+3D Validation set	0.82 [0.67-0.98]	0.73[0.54-0.87]	0.611	0.91	0.91	0.61	

Finally, a decision curve was used to evaluate the three devised models' clinical effectiveness (Figure 4). As the radiomic model's standard net benefit within a range of the high-risk threshold increased, its clinical effectiveness increased. The decision curves show that the clinically effective performance of the 2D+3D combined model was much higher than that of the other two models.

The above results indicate that the radiomic model based on 2D and 3D images can effectively predict BRCA gene mutations in patients with epithelial ovarian cancer, although the 2D+3D combined model showed no significant differences in predictive performance from that of the radiomic models based on 2D or 3D images alone.

3. Conclusions

Ovarian cancer has the highest mortality rate among gynecological malignancies. More than 70% of patients with ovarian cancer are already in the advanced stage of the disease when the cancer is detected^[10], and there is still a lack of accurate early diagnosis and prevention methods^[11]. Radiomics avoids the disadvantages of subjectivity, histopathology, and local sampling in conventional imaging tests.

Guo Jianlin et al.^[12] found that the combined Radiomics model of arterial phase and venous phase had higher predictive performance than the separate model of each phase. In this paper, the quantitative features were selected and the prediction model was established using radiomic features extracted from the arterial phase, venous phase, and delay phase of enhanced CT images, and the resulting radiomics scores were strongly correlated with whether or not the BRCA gene was mutated ($r = 0.65$, $P < 0.001$) (Fig. 2, C). The prediction performance of BRCA mutation status for patients with epithelial ovarian cancer using the 2D, 3D, or 2D + 3D CT radiomics features was evaluated using the AUC value, sensitivity, and specificity. The results showed that the AUC values of the radiomics model built using 2D images on the training and validation datasets were 0.81 and 0.78, respectively. The corresponding AUC values of the radiomics model built using 3D images on the training and validation datasets were 0.80 and 0.75, respectively. After screening the 2D + 3D combined image features, a total of 12 features were retained: eight and four from 2D and 3D images, respectively. The AUC values of the 2D + 3D combined model on the training and validation groups were 0.91 and 0.82, respectively. Therefore, the radiomics signature established by the selected radiomic features can potentially be used as a biomarker for predicting BRCA gene mutations.

The study by Lei Xu et al. found that whether univariate or multivariate analysis was performed, the prediction performance of 3D image features was better than that of 2D image features^[13]. However, in another study by Shen et al.^[14], 2D features had better performance. Furthermore, in a study that predicted overall survival from non-small cell lung cancer, Lifeng Yang et al.^[15] found that the features derived from a 2D + 3D combined model showed better prognostic performance than using 2D or 3D features alone. Therefore, we established prediction models using 2D, 3D, and 2D + 3D combined image features, and we found that the AUC values of all three models were over 0.75, and all three models'

prediction performance was good, indicating that the radiomics models can effectively predict BRCA gene mutation status in patients with epithelial ovarian cancer. The 2D + 3D combined model had the highest AUC value, but the DeLong test results showed no statistical differences in predictive performance between the three pairs of models. The results showed that 2D outlining of the layer in which the lesion had the largest diameter, which mainly included the central region of the tumor, could achieve high predictive performance when predicting BRCA gene mutations in ovarian cancer. The 3D outlined images can provide some information about tumors' heterogeneity outside the central area, but this information did not provide an additional contribution to predicting BRCA gene mutations in the present study. Therefore, we believe that when the image is delineated in 2D, if the lesion delineation level is selected appropriately, the established radiomic model's predictive performance is close to that of the 2D + 3D combined model. This insight may improve the practical efficiency of clinical establishment of this type of radiomic model.

This study had some limitations. First, this study was a single-center retrospective study. The included cases were all from our hospital and lack external verification. Second, the sample size was small, which may lead to bias in the data. Third, all ROIs in this study were drawn manually, and so the results are easily affected by subjective factors. Lastly, in this study, there were 77 and 45 patients in the wild-type and mutant groups, respectively. The two groups of data were unbalanced, and the model may therefore be biased.

In summary, the 2D, 3D, and 2D + 3D combined radiomics models based on enhanced CT images can effectively predict BRCA gene mutation status in patients with epithelial ovarian cancer and can provide a new idea and type of method for clinical evaluation of patients' genetic mutation status.

Declarations

Ethics approval and consent to participate

Our institutional review board (IRB) waived written informed consent for this retrospective study, that evaluated de-identified data and involved no potential risk to patients. The study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of USTC.

the committee's reference number: 2021-RE-078

Consent for publication

All authors agree to publish

Availability of data and material

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Authors' contributions

Liu Mingzhu: Conception and design, Collection and assembly of data, Validation, Writing-Original Draft

Ge Yaqiong: Data analysis and interpretation

Li Mengru: Methodology

Wei Wei: Administrative support, Provision of study materials or patients, Supervision

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Figures

Figure 1

(a–d) Images of a patient aged 35 years with high-grade (stage IIIC) serous carcinoma of the ovary, which was genetically detected as a non-BRCA gene mutation. ITK-SNAP software was used to segment and label the lesion layer-by-layer to generate a 3D image of the lesion.

Figure 2

Application of LASSO (Least absolute shrinkage and selection operator)-logistic regression to imaging feature screening in the 2D+3D combined model shows that the LASSO-logistic regression model selects tuning parameters (λ) through 10-fold cross-validation and obtains the relationship between binomial variance and logarithm (λ) (Figure 2, A). The relationship is retained with the parameters that yield the smallest binomial deviation, and the 12 best features with non-zero coefficients (Figure 2, B) were retained in the final model. The relationships between the features and gene mutation status (correlation coefficient $\times$ 100) are shown in the heat map (Figure 2, C).

Figure 3

ROC curves of 2D model, 3D model, and 2D+3D combined model in the training group (A) and validation group (B).

Figure 4

The yellow line, black dotted line, and blue dotted line represent the data obtained from the 2D, 3D, and 2D+3D combined images, respectively. The x-axis represents the patient's personal threshold probability (e.g., $x=0.6$ means that the high-risk threshold of ovarian cancer and BRCA gene mutation is 60%). The y-axis represents net income. The line labeled All represents the hypothesis that all ovarian cancer cases are caused by BRCA gene mutations. The thin line labeled None represents the assumption that there are no BRCA gene mutations in patients with ovarian cancer.