ORIGINAL ARTICLE

Open Access

Exploring a multiparameter MRI-based radiomics approach to predict tumor proliferation status of serous ovarian carcinoma

Li Liu^{1,2†}, Ling Zhao^{1†}, Yang Jing³, Dan Li⁴, Hua Linghu⁵, Haiyan Wang¹, Linyi Zhou⁶, Yuan Fang^{1*†} and Yonamei Li^{2*†}

Abstract

Objectives To develop a multiparameter magnetic resonance imaging (MRI)-based radiomics approach that can accurately predict the tumor cell proliferation status of serous ovarian carcinoma (SOC).

Materials and methods A total of 134 patients with SOC who met the inclusion and exclusion criteria were retrospectively screened from institution A, spanning from January 2016 to March 2022. Additionally, an external validation set comprising 42 SOC patients from institution B was also included. The region of interest was determined by drawing each ovarian mass boundaries manually slice-by-slice on T2-weighted imaging fat-suppressed fast spin-echo (T2FSE) and T1 with contrast enhancement (T1CE) images using ITK-SNAP software. The handcrafted radiomic features were extracted, and then were selected using variance threshold algorithm, SelectKBest algorithm, and least absolute shrinkage and selection operator. The optimal radiomic scores and the clinical/radiological independent predictors were integrated as a combined model.

Results Compared with the area under the curve (AUC) values of each radiomic signature of T2FSE and T1CE, respectively, the AUC value of the radiomic signature (T1CE-T2FSE) was the highest in the training set (0.999 vs. 0.965 and 0.860). The homogeneous solid component of the ovarian mass was considered the only independent predictor of tumor cell proliferation status among the clinical/radiological variables. The AUC of the radiomic-radiological model was 0.999.

Conclusions The radiomic–radiological model combining radiomic scores and the homogeneous solid component of the ovarian mass can accurately predict tumor cell proliferation status of SOC which has high repeatability and may enable more targeted and effective treatment strategies.

Critical relevance statement The proposed radiomic-radiological model combining radiomic scores and the homogeneous solid component of the ovarian mass can predict tumor cell proliferation status of SOC which has high repeatability and may guide individualized treatment programs.

[†]Li Liu and Ling Zhao contributed equally to this work and shared the first authorship.

[†]Yuan Fang and Yongmei Li contributed equally to this work and share the corresponding author responsibilities.

*Correspondence: Yuan Fang nmjyfy@sohu.com Yongmei Li lymzhang70@163.com Full list of author information is available at the end of the article



© The Author(s) 2024. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/



Key points

• The radiomic-radiological nomogram may guide individualized treatment programs of SOC.

- This radiomic-radiological nomogram showed a favorable prediction ability.
- Homogeneous slightly higher signal intensity on T2FSE is vital for Ki-67.

Keywords Serous ovarian carcinoma, Tumor proliferation status, Ki-67, Radiomics, MRI

Graphical Abstract



Introduction

Epithelial ovarian carcinoma accounts for more than 90% ovarian malignancies. Among them, serous ovarian carcinoma (SOC) has the highest incidence and is the most lethal gynecologic malignancy [1–4]. Currently, the standard treatment strategy for SOC is primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery. Regarding the aggressiveness and clinical behavior of SOC, tumor cell proliferation has important diagnostic and prognostic value. Hence, preoperative evaluation of the tumor proliferation status is important [5–7].

Ki-67 antigen is considered a tumor proliferation status index and has been extensively used both as a diagnostic and prognostic indicator of many malignancies, such as glioma, breast cancer, lung cancer, and liver cancer [8–11]. Ki-67 antigen is a DNA-binding protein that is expressed in all cells during the mitotic cycle. The higher its expression level, the more nuclear fission, indicating more active the cell proliferation. Excessive cell proliferation can easily contain physiological apoptotic DNA or replication error DNA endlessly entering the cell cycle, eventually leading to cell carcinogenesis [12]. Ki-67 antigen is usually overexpressed in malignant ovarian tumor compared with benign or borderline tumors. For ovarian carcinoma, the expression of Ki-67 antigen is widely used to guide clinical management, such as tumor aggression, vascular invasion, tumor metastasis, reserved prognosis, and poor response to chemotherapy [3, 13-16]. At present, Ki-67 expression status is mainly assessed by immunohistochemical (IHC) examination of biopsy or surgery specimens. However, with the IHC sampling method, the evaluation of Ki-67 expression is unrepresentative of its expression level in the entire tumor, which affects clinical decisionmaking. Therefore, the establishment of models that can predict Ki-67 expression levels of the entire tumor is crucial to guide individualized treatment decision-making and postoperative monitoring of patients with SOC.

SOC usually presents as ovarian cystic, cystic-solid, or solid masses on unilateral or bilateral ovaries on MRI, but how to determine the proliferative status of the masses by imaging methods? Wang et al. [17] used the parameters of apparent diffusion coefficient (ADC) histogram to distinguish the tumor stages of epithelial ovarian cancer and determine the lymph node status and correlations between ADC values and p53 and Ki-67 expressions. However, the histogram is only the extracted first-order features, which are used to describe the intensity distribution of voxels of images but cannot reflect tumor heterogeneity and complexity.

Radiomics, a recently developed technique, can help predict tumor phenotype and heterogeneity and provide information about tumor biological behaviors and pathophysiology based on a large amount of highthroughput data [18, 19]. At present, many researchers have applied radiomics to the diagnosis and differential diagnosis of diseases, efficacy evaluation, prediction, etc. [20–23]. However, too little work has focused on predicting the expression of Ki-67 in patients with SOC based on machine learning or radiomic features extracted from magnetic resonance imaging (MRI).

In this study, we aimed integrated relevant clinical and radiological variables to establish a model based on MRI radiomics to predict tumor cell proliferation status, in which training, internal validation, and external validation sets were designed to test the robustness of the prediction model. If the model proves to be effective, our findings will play a pivotal role in clinical decision-making.

Materials and methods Patients

In total, 3276 patients were initially enrolled in this retrospective study from January 2016 to March 2022 (2779 and 497 patients from institutions A and B, respectively). The two institutional ethics committees approved this study, and the requirement for informed consent was waived owing to the retrospective design.

The inclusion criteria were as follows: (1) developed ovarian mass, (2) underwent PDS in the two institutions, and (3) had enhanced abdominal-pelvic MRI before surgery. The exclusion criteria were as follows: (1) absence of Ki-67 IHC in the two institutions, (2) poor image quality (e.g., artifact), (3) incomplete clinical data, (4) prior NACT, pharmacological treatment or other anticancer therapies before surgery, (5) an interval of > 1 month between MRI and subsequent pathological analysis, and (6) presence of other tumors in the same period. Finally, we screened 134 patients from institution A for the training and internal validation sets, and 42 patients from institution B for the external validation set. A total of 134 patients from institution A were randomly divided into training and internal validation sets, with a ratio of 7:3. The flow diagram of this study is summarized in Fig. 1a.

MRI acquisition and data collection

All patients from institution A and B underwent abdominal pelvic MRI using 3.0 T (GE) and 1.5 T (GE) MRI systems, respectively. The detailed parameters of the imaging sequences protocol we chose are shown in Table 1. Both T2-weighted imaging fat-suppressed fast spin-echo (T2FSE) and T1 with contrast enhancement (T1CE) are axial, and the contrast medium in both institutions A and B is gadopentetate dimeglumine (0.1 mmol/kg body weight, Magnevist; Bayer Schering).

Two radiologists with > 10 years of experience in gynecologic MRI were blinded to the clinicopathological information and independently evaluated preoperative MR images of each patient carefully for distribution (unilateral/bilateral), size of the ovarian mass (maximum diameter), shape of the ovarian mass (lobulated/non-lobulated), mass angiogenesis [24] (enlarged blood vessels supplying or draining the tumor observed around or in the center of the ovarian mass), homogeneous solid component of the ovarian mass (solid part containing homogeneous slightly higher signal intensity area on T2FSE), peritoneum/mesentery nodules, metastases of distant parenchymal organs, retroperitoneal lymphadenopathy, and amount of ascites. The spread of ascites in the abdomen and pelvis was quantified as no/small (ascites confined to the pelvic) and medium-to-large (ascites beyond the pelvis). If there was any disagreement, the MR image features were re-evaluated, and a consensus was reached.

The clinical and laboratory data associated with epithelial ovarian carcinoma of all patients were recorded [25], including age, serum carbohydrate antigen 125, human epididymis protein 4, neutrophil-to-lymphocyte ratio, and the International Federation of Gynecology and Obstetrics (FIGO) stage.

Ki-67 expression assessment

All specimens were fixed in 10% neutral formaldehyde solution, dehydrated conventionally, embedded in paraffin, and cut into sections of 4-µm thick. Hematoxylin and eosin (HE) staining and immunostaining was evaluated qualitatively by two pathologists. The proliferative index (PI) of the lesion was estimated by Ki-67 Mindbomb E3 ubiquitin protein ligase1 (MIB-1) of IHC and was quantitatively expressed as the Ki-67 MIB-1 labeling index when the number of positively stained cells per 100 epithelial



Fig. 1 The flow diagram of this study. **a** Workflow of this study. **b** Five steps of our predictive model building: MR image acquisition, ROI segmentation, features extraction, features selection and model building and evaluation. ROI, the region of interest

cells after counting was at least 1000 in each case by highpower objective of the microscope (× 400) [15, 16]. As there is no international consensus on the cutoff value for percentage of the Ki67 expression, the SOC lesions were divided into two groups according to several studies [15, 16, 26, 27]: the high expression group (PI \ge 50% immunoreactive cells are positive) and the low expression group (PI < 50% immunoreactive cells are positive).

Tumor segmentation and feature extraction

The overview of our modeling workflow is shown in Fig. 1b. The pathological changes of the tumor are reflected in T2FSE images, and the blood supply of the tumor is reflected in T1CE images. The region of interest (ROI) was determined by two radiologists (with \geq 10 years of experience in gynecological MRI) by drawing each ovarian mass boundaries manually slice-by-slice

MRI scans	T2FSE					T1CE (LAVA)					
	TR (ms)	TE (ms)	Slice thickness (mm)	Gap (mm)	FOV (cm)	TR (ms)	TE (ms)	Slice thickness (mm)	Gap (mm)	FOV (cm)	Scan time (s)
3.0 T (GE)	4260	108.6	5	5	40	4	2	4	2	40	30, 60, 90, 120
1.5 T (GE)	2700	68	5	5	40	4	2	4	0	40	30, 60, 90, 120

Table 1 The detailed parameters of the imaging sequences

T2FSE T2-weighted imaging fat-suppressed fast spin-echo, T1CE T1 with contrast enhancement, LAVA liver acquisition with volume acceleration 3D with fat saturation, TR time of repetition. TE time of echo: FOV. field of view

on T2FSE and T1CE images using ITK-SNAP software (version 3.8.0, http://openiconlibrary.sourceforge.net/), which is tumor segmentation. Any discrepancy was resolved by consensus. For patients with bilateral masses, the larger one was selected to delineate the ROI, which usually contained more comprehensive imaging features. Before feature extraction, each MR image was preprocessed as follows: (1) image standardization: a linear interpolation was used to resample the MR images to 1 mm $\times 1$ mm $\times 5$ mm voxel size to ensure image standardization. (2) Z-score normalization was conducted to ensure the repeatability of the results and reduce potential effects associated with different sequence parameters and scanner manufacturers [28]. Subsequently, 1688 handcrafted radiomic features from each sequence were extracted using the open-source Python package Pyradiomics (version 3.0.1; http://www.radiomics.io/pyrad iomics.html). The extracted radiomic features included four groups: morphologic features, intensity-based (firstorder), texture (second-order), and wavelet features formed based on these three feature categories. One month later, we repeatedly delineate the ROI in a subset of the training set with 31 data to assess the repeatability of feature extraction using intraclass correlation coefficients (ICC). In this study, an ICC value > 0.80 was considered robust, and 1686 and 1633 of the initial 1688 image features remained on T2FSE and T1CE sequences, respectively.

Feature selection, radiomic signature construction, and evaluation

After the repeatability test, three feature selection methods (variance threshold algorithm, SelectKBest algorithm, and least absolute shrinkage and selection operator [LASSO] regression) were used in turn for dimension reduction of each sequence (T2FSE and T1CE) and combined sequences (T1CE–T2FSE). Then, the radiomic scores (Radscores) of each sequence and combined sequences were calculated from the final radiomic features and their respective coefficients. Then, the radiomic features of each sequence (T2FSE and T1CE) and combined sequences (T1CE–T2FSE) were used to

establish models to predict Ki-67 expression levels. The receiver operating characteristic curve analysis was used to evaluate the predictive performance, and the DeLong test was performed to compare the differences between them. The optimal radiomic model was the radiomic model with the highest area under the curve (AUC).

Radiomic-clinical-radiological model construction and evaluation

The best cut-off values for age, CA-125, HE-4, and NLR were determined by univariate regression, respectively, and were converted into categorical variables. Univariate and multivariate analyses were used to obtain the independent predictors of the model among the clinical and radiological variables. Then, the radiomic–clinical–radiological model was obtained by integrating the optimal radiomic scores and the independent predictors using multivariable logistic regression. The predictive performance of the radiomic–clinical–radiological model was assessed using AUC, accuracy, sensitivity, and specificity and validated in the internal or external validation set.

Statistical analysis

Statistical analyses were performed with the Python package scipy (version 1.7.3, https://scipy.org/), and the radiomic–clinical–radiological model and nomogram were developed using the R software (version 3.5.1, http://www.r-project.org/). Student's *t*-test and Wilcoxon test were used to assess the differences of continuous variables. Chi-square test was used to assess the differences of categorical variables. The DeLong test was used to assess the differences in the AUC of the models. p < 0.05 was defined significant.

Results

Features of the study population

A total of 134 patients from institution A were screened based on the inclusion and exclusion criteria, and they were randomly allocated into training (n = 93) and internal validation (n = 41) sets, with a ratio of 7:3. From institution B, 42 patients were screened for the external validation set. The average age of 134 patients

Table 2	Equilibrium	comparison	between t	he training	and in	iternal	validation	sets,	and the	clinical	/radiological	characte	eristics	in the
external	validation													

Characteristics	Equilibrium comparison							
	Training set, <i>n</i> = 93	Internal validation set, $n = 41$	p value					
Clinical characteristics								
Age	53.05 ± 10.83	54.24 ± 10.40	0.554 ^a	54.31 ± 8.30				
FIGO			0.098 ^c					
I–II	16 (17.2)	15 (36.6)		7 (16.7)				
III–IV	77 (82.8)	26 (63.4)		35 (83.4)				
CA125	830.50 (307.70, 1856.10)	593.00 (239.50, 2036.70)	0.327 ^b	1000.50 (410.24, 2104.28)				
HE4	396.00 (153.00, 767.00)	224.00 (108.00, 597.00)	0.084 ^b	572.55 (201.58, 960.12)				
NLR	2.87 (1.89, 5.43)	3.26 (2.04, 4.58)	0.186 ^b	3.49 (2.57, 5.36)				
Radiological characteristics								
Distribution			0.106 ^c					
Unilateral	41 (44.1)	25 (61.0)		22 (52.4)				
Bilateral	52 (55.9)	16 (39.0)		20 (47.6)				
Lobulated ovarian mass			0.547 ^c					
No	3 (3.2)	3 (7.3)		3 (7.1)				
Yes	90 (96.8)	38 (92.7)		39(92.9)				
Angiogenesis of ovarian mass			0.741 ^c					
No	8 (8.6)	5 (12.2)		4 (9.5)				
Yes	85 (91.4)	36 (87.8)		38 (90.5)				
Size of ovarian mass (maximum diameter,	8.20 (6.00, 12.00)	8.60 (6.80, 11.00)	0.835 ^b	6.20 (4.82, 8.90)				
cm)			. (
Homogeneous solid in ovarian mass			14					
No	26 (28.0)	12 (29.3)		12 (28.6)				
Yes	67 (72.0)	29 (70.7)		30 (71.4)				
Peritoneum/mesentery nodules			0.837 ^c					
No	24 (25.8)	12 (29.3)		9 (21.4)				
Yes	69 (74.2)	29 (70.7)		33 (78.6)				
Metastases of distant parenchymal organs			1 ^c					
No	79 (84.9)	35 (85.4)		35 (83.3)				
Yes	14 (15.1)	6 (14.6)		7 (16.7)				
Retro-peritoneal lymphadenopathy			0.106 ^c					
No	73 (78.5)	26 (63.4)		35 (83.3)				
Yes	20 (21.5)	15 (36.6)		7 (16.7)				
Amount of ascites			0.013 ^c					
No/small	38 (40.9)	27 (65.9)		20 (47.6)				
Medium-to-large	55 (59.1)	14 (34.1)		22 (52.4)				

FIGO the International Federation of Gynecology and Obstetrics, CA125 carbohydrate antigen 125, HE4 human epididymis protein 4, NLR neutrophil-to-lymphocyte ratio; Age is presented as means ± standard deviations; CA-125, HE-4, NLR and Size of ovarian mass are expressed as medians (interquartile ranges); other characteristics are expressed as absolute numbers and percentages

^a Student's *t* test

^b Wilcoxon test

^c Chi-square test

with SOC eligible from institution A was 54 years (range 27–80 years), and that of 42 patients with SOC eligible from institution B was 54 years (range 30–74 years). As shown in Table 2, a significant difference was found only in the amount of ascites among the five

clinical and nine radiological variables (p < 0.05), indicating that the two data sets were from the same population. After univariate logistic regression, the optimal cutoff values of the continuous variables were as follows: age (cutoff = 55, C-index = 0.652), CA-125 (cutoff

= 1231, C-index = 0.559), HE-4 (cutoff = 418, C-index = 0.561), NLR (cutoff = 3.73, C-index = 0.614), and maximum diameter of the ovarian neoplasm (cutoff = 7.4, C-index = 0.646).

Among 134 cases of SOC from hospital A, there were 89 cases of high Ki-67 expression (PI \geq 50%), accounting for 66.4%, whereas there were 45 cases of low Ki-67 expression (PI < 50%), accounting for 33.6%. And among 42 cases of SOC from hospital B, there were 31 cases of high Ki-67 expression, accounting for 73.8%, whereas there were 11 cases of low expression, accounting for 26.2%.

In the training set, significant differences in variables of the homogeneous solid component of the ovarian mass and FIGO stage were found between the high and low Ki-67 expression groups on the univariate regression analysis (p < 0.05), whereas there was no significant difference in clinical variables between the high and low Ki-67 expression groups. On the multivariate regression analysis, only the homogeneous solid component of the ovarian mass was considered the independent predictor of the expression level of Ki-67 (Tables 3 and 4).

Construction and internal and external validation of the radiomic signature

Extracted from T2FSE and T1CE sequences, we included 1688 radiomic features, both. After the elimination of redundancy using the variance threshold algorithm, SelectKBest algorithm, and LASSO, 20, 15, and 35 features were left from the T2FSE, T1CE, and T1CE–T2FSE,

respectively (Fig. 2). Subsequently, the radiomic signature of T2FSE, T1CE, and T1CE–T2FSE was constructed respectively. Compared with the AUC values of each radiomic signature, the AUC value of the radiomic signature (T1CE–T2FSE) was the highest in the training set (0.999 vs. 0.965 and 0.860). The DeLong test showed that the AUC value of the radiomic signature (T1CE–T2FSE) was significantly different from those of the other two radiomic signatures (p < 0.05). As a result, the radiomic signature (T1CE–T2FSE) was considered the optimal radiomic signature.

Establishment and internal and external validations of the radiomic-radiological model

By univariate and multivariate analyses, only the homogeneous solid component of the ovarian mass was considered the independent predictor (Fig. 3) among the five clinical and nine radiological variables. Thus, we developed a radiological model instead of a clinical-radiological model using the only independent predictor. Likewise, we integrated the optimal radiomic scores and the only independent predictor to establish a radiomic-radiological model instead of radiomic-clinical-radiological model (Fig. 4). Compared with the AUC values of the radiomic signature, radiological model, and radiomicradiological model, the radiomic-radiological model had the best AUC of the training set of 0.999, internal validation set of 0.974, and external validation set of 0.894. The DeLong test showed a significant difference between the

 Table 3
 Univariate and multivariate regression analysis of the clinical features

Characteristics	Univariate r	egression analysis	Multivariate regression analysis			
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age						
≤ 55	1					
> 55	0.987	0.962-1.044	0.924	N/A	N/A	N/A
FIGO						
–	1			1		
III-IV	2.08	1.061-4.395	0.040	1.64	0.68-3.99	0.27
CA-125						
≤ 1231	1					
> 1231	0.497	0.19-1.22	0.137	N/A	N/A	N/A
HE4						
≤ 418	1					
> 418	0.483	0.194-1.116	0.109	N/A	N/A	N/A
NLR						
≤ 3.73	1					
>3.73	0.513	0.968-1.643	0.111	N/A	N/A	N/A

Chi-square test *FIGO* the International Federation of Gynecology and Obstetrics, *CA-125* carbohydrate antigen 125, *HE4* human epididymis protein 4, *NLR* neutrophil-to-lymphocyte ratio, *OR* odds ratio, *95% CI* 95% confidence interval

Characteristics	Univariate	regression analysis	Multivariate regression analysis			
	OR	95% CI	p Value	OR	95% CI	<i>p</i> Value
Distribution						
Unilateral	1					
Bilateral	0.719	0.293-1.717	0.461	N/A	N/A	N/A
Lobulated ovarian mas	S					
NO	1					
Yes	0.967	0.045-10.845	1	N/A	N/A	N/A
Angiogenesis of ovaria	n mass					
No	1					
Yes	1.22	0.237-5.344	0.794	N/A	N/A	N/A
Size of ovarian mass (cr	m)					
≤ 7.4	1					
> 7.4	0.906	0.802-1.019	0.104	N/A	N/A	N/A
Homogeneous solid in	ovarian mass					
No	1			1		
Yes	23.94	7.859-86.448	< 0.01	22.15	6.7-73.21	< 0.01
Peritoneum/mesentery	/ nodules					
No	1					
Yes	2.07	0.790-5.430	0.135	N/A	N/A	N/A
Metastases of distant p	arenchymal organs					
No	1					
Yes	2.01	0.572-9.443	0.312	N/A	N/A	N/A
Retro-peritoneal lymph	nadenopathy					
No	1					
Yes	1.66	0.570-5.569	0.375	N/A	N/A	N/A
Amount of ascites						
None/ small	1					
Middle/large	1.30	0.541-3.129	0.551	N/A	N/A	N/A

Table 4 Univariate and multivariate regression and	nalysis of the radiological features
--	--------------------------------------

Chi-square test *FIGO* the International Federation of Gynecology and Obstetrics, *CA-125* carbohydrate antigen 125, *HE4* human epididymis protein 4, *NLR* neutrophil-to-lymphocyte ratio, *OR* odds ratio, *95% CI* 95% confidence interval

radiological model and the radiomic–radiological model and between the radiomic signature and the radiological model (p < 0.05). Moreover, no significant difference was found between the radiomic signature and the radiomic– radiological model (p = 0.480) in the training set, whereas the difference was significant in the external validation set (p < 0.05). Figure 5 shows the calibration curves of the radiomic–radiological model in the three sets.

Discussion

In this study, we developed a radiomic–radiological model to predict the Ki-67 expression level of the tumor by extracting features from preoperative or pretreatment MRI of patients with SOC, integrating clinical and radiological variables probably related to tumor proliferation, which was verified in the external validation set. This model demonstrated excellent performance in predicting Ki-67 expression. To our knowledge, this is the first study

to establish a radiomic–radiological model to predict the Ki-67 expression levels of SOC using MRI data. The robustness and generalizability of the model were further verified by external validation of the calibration curve.

Before feature extraction, we conducted standardized preprocessing of image data (including voxel size resampling and Z-score normalization) according to previous research methods [28] to significantly reduce the differences among scanners and imaging parameters. Wang et al. [17] used the ADC histogram parameters to distinguish different tumor stages of epithelial ovarian cancer and determine lymph node status and correlations between ADC values and Ki-67 expression. Li et al. [29] used ADC histogram parameters to differentiate highgrade SOC from low-grade SOC and correlate those parameters with the Ki-67 proliferation index. These studies indicate that we can use first-order statistics to study the correlation between tumors and IHC indicators



Fig. 2 Features retained after radiomics high-throughput feature dimension reduction. **a** MSE PATH, the dotted line represents the *a* value (1.9) with the smallest mean square error. **b** LASSO PATH, the radiomic features are determined according to the *a* value with the smallest mean square error. **c** Lasso coefficient of the features after radiomics high-throughput feature dimension reduction

of SOC. However, first-order statistics usually describe the voxel intensity distribution of images. Relative to the first- and second-order statistics (texture analysis), radiomics is a high-order statistic using image filter feature transform to reduce noise and enhance edge detection. It can help reveal tumor characteristics that cannot be observed in the original image by naked eyes [30] and play an important role in predicting pathological status [31, 32]. In this study, the radiomic model was established using the 35 most discriminative features extracted (including 3 morphologic, 15 intensity-based [firstorder], and 17 texture [second-order] features), on the basis of which 12 wavelet features were formed (Fig. 2).

In our study, the radiomic signature of T1CE–T2FSE had the highest AUC value among the three radiomic signatures (0.999 vs. 0.965 and 0.860). It indicated that



Fig. 3 The radiological features on MR images and corresponding HE and Ki-67 of IHC. The radiological features on MR images and corresponding HE (hematoxylin-eosin staining, × 400) and Ki-67 of IHC (Immunohistochemistry], × 400). **a**–**c** A 70-year-old woman with high-grade serous papillary cystadenocarcinoma. **a** An axial T2FSE (T2-weighted imaging fat-suppressed fast spin-echo) image shows a cystic mass with solid nodules in the left ovary (red line) which contains homogeneous slightly higher signal intensity area (red arrow). **b** HE of high-grade serous papillary cystadenocarcinoma. **c** IHC of high-grade serous papillary cystadenocarcinoma displaying high Ki-67 PI (proliferative index) (80%). **d**–**f** A 64-year-old woman with high-grade serous cystadenocarcinoma. **d** An axial T2FSE image shows a fused cystic-solid mass (red line) from bilateral ovaries which looks like sponge and contains no homogeneous slightly higher signal intensity area. **e** HE of high-grade serous cystadenocarcinoma. **f** IHC of high-grade serous cystadenocarcinoma displaying low Ki-67 PI (40%). **g**–**i** A 32-year-old woman with non-invasive micropapillary serous carcinoma. **i** IHC of non-invasive micropapillary serous carcinoma. **i** IHC of non-invasive micropapillary serous carcinoma low Ki-67 PI (10%)

multiple sequences can provide more important information than a single sequence, and the performance of the combined model of multiple sequences is higher [33–36]. Although no literature focused on predicting Ki-67 expression of SOC based on radiomics, the result of our study was consistent with that of using radiomics to predict Ki67 of hepatocellular carcinoma [37] and lung cancer [38].

During the study, if the SOC masses were classified according to the traditional method (cystic, cystic-solid, and solid components), the Ki-67 expression of cystic masses might be high (Fig. 3a–c), whereas that of solid masses might be low (Fig. 3d–i). We hypothesized that the expression level of Ki-67 might not significantly correlate with the proportion of the cystic/solid component of the mass. After repeated careful observations, we found that some of the solid masses with low Ki-67 expression were either polycystic or spongiform

(Fig. 3d-f), and they did not contain areas of slightly hyperintense T2FSE homogeneity. In our study cohort, we found that the expression level of Ki-67 was mostly higher if the solid part of the ovarian mass contained a homogeneous slightly hyperintense T2FSE area, and lower if not. As a result, we tried to divide the characteristics of the ovarian masses into a new category according to the degree of signal uniformity in the solid component: including homogeneous slightly higher signal intensity area or not on T2FSE. This is a new classification of the ovarian mass, which is independent of the presence or absence of a cystic component of the mass or the percentage of cystic/solid component of the mass. In our study, the ovarian mass has higher expression levels of Ki-67 if the solid part contains homogeneous slightly higher signal intensity area on T2FSE. By univariate and multivariate analyses, a significant difference in this mass feature was found between the high and







Fig. 4 The radiomic-radiological model and its performance. **a** The radiomic-radiological model for the training set. **b**–**d** The confusion matrix of the training, internal validation, and external validation sets, respectively. **e** The ROC curves of the radiomic, radiological, and radiomic-radiological models for the internal validation set. **f** The ROC curves of radiomic-clinical-radiological model for the three sets. ROC, receiver operating characteristic





Fig. 5 Calibration curves of the radiomic-radiological model in the training, internal validation, and external validation sets. **a** Training set. **b** Internal validation set. **c** External validation set

low Ki-67 expression groups compared with other variables. In other words, homogeneous slightly higher signal intensity area on T2FSE indicates the presence of densely packed cells in the mass, which may be related to the higher degree of tumor proliferation.

In addition to radiomic signature, we included a total of five clinical and nine radiological factors that may have significance for tumor proliferation status, including FIGO stage, serum tumor markers, tumor maximum diameter, homogeneous solid component of the ovarian mass, lobulation, tumor angiogenesis, and peritoneal metastases. However, by univariate and multivariate analyses, only the homogeneous solid component of the ovarian mass was confirmed to be the independent predictor. According to our analysis, because SOC is highly malignant and often has a large volume when it is found, there is a large amount of ascites with peritoneal metastasis. The lobulation sign and tumor angiogenesis are also malignant characteristics of ovarian tumors. However, the cases in our study were all SOC. Therefore, this may be the reason why there were no significant differences between the high and low expression groups of Ki-67 among other clinical and radiological characteristics in this study.

Wang et al. [17] demonstrated there was a negative correlation between apparent diffusion coefficient parameters and Ki-67 labeling index values using ADC histogram analysis. To develop a nomogram predicting the expression of Ki-67, which is more intuitive compared to the result of Wang et al. [17], we integrated the optimal radiomic scores and the radiological independent predictor determined by univariate and multivariate analyses. The AUC of the radiomic-radiological model is significantly higher than that of the optimal radiomic signature or the radiological model in the internal validation set (0.974 vs. 0.937 and 0.897) and external validation set (0.894 vs. 0.725 and 0.867). The AUC of our radiomic-radiological model was significantly higher than that of ADC histogram analysis by Li et al. [29] (0.717–0.807).

This study has several limitations. First, a potential selection bias exists in terms of the inclusion of patients owing to the retrospective design. Second, the sample size can still be considered relatively small for the development of prognostic models. Third, although some studies support the use of 50% as the cut-off value [15, 16, 26, 27], there is no clear consensus on the Ki-67 expression level in SOC. Fourth, through the DeLong test, we found no significant difference between the performance of the radiomic–radiological and the radiomic models in the training set, whereas a significant difference was found in the external validation set. According to our analysis, the AUC of both models in the training

set was 0.999; thus, the lack of a significant statistical difference between them was reasonable. Such a result may be related to the selection of our samples (all of them SOC) or sample size; however, it at least indicates that the radiomic model and radiomic-radiological model both have an excellent ability to identify the high and low expressions of ki-67 in SOC. In addition, the difference between the two models was significant in the external validation set, which also suggests a certain generalizability of the model. Fifth, clinical variables were relatively few, such as patient comorbidities, family history, or other molecular biomarkers. Hence, in future studies, we will include multiple pathological subtypes of ovarian carcinoma, expand the sample size, and include more relevant variables for prospective studies and prospectively develop objective assessment criteria for the percentage determination of Ki-67.

Conclusion

We established a radiomic–radiological model to accurately predict the expression level of Ki-67, which also demonstrated perfect performance in the external validation set. This method has high repeatability and may enable more targeted, effective treatment strategies and clinical monitoring of patients with SOC.

Abbreviations

- AUC The area under the receiver operating characteristic curve
- CA-125 Carbohydrate antigen 125
- FIGO International Federation of Gynecology and Obstetrics
- HE-4 Human epididymis protein 4
- NLR Neutrophil-to-lymphocyte ratio
- PDS Primary debulking surgery
- ROC Receiver operating characteristic
- SOC Serous ovarian carcinoma

Acknowledgements

The author would like to thank Ling Zhao for her contribution to the collection of patients.

Authors' contributions

Conceptualization and designation: LL, LZ, YF, YL. Curation, analysis, and interpretation of the data: LL, YJ, DL, HL, HW, LZ. Methodology: LL, YJ, HW, LZ. Writing-original draft: LL, LZ. Supervision and writing-review: YF, YL.

Funding

No funding was received to assist with this study.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

Our institutional review board approved this retrospective study, so the requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

YJ is an employee of Huiying Medical Technology Co., Ltd. The remaining authors declare that they have no competing interests.

Author details

¹Department of Radiology, The People's Hospital of Yubei District of Chongqing City, No. 23 ZhongyangGongyuanBei Road, Yubei District, Chongqing 401120, China. ²Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, Yuanjiagang, China. ³Huiying Medical Technology Co., Ltd, Dongsheng Science and Technology Park, Room A206, B2Haidian District, Beijing 100192, China. ⁴Department of Pathology, Chongqing Medical University, No.1 Medical College Road, Yuzhong District, Chongqing Medical University, No.1 Medical College Road, Yuzhong District, Chongqing 400016, China. ⁵Department of Obstetrics and Gynecology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road Yuzhong District, Chongqing 400016, Yuanjiagang, China. ⁶Department of Radiology, Army Medical Center, Daping Hospital, Army Medical University, 10# Changjiangzhilu, Chonqqing 40024, China.

Received: 23 June 2023 Accepted: 27 January 2024 Published online: 18 March 2024

References

- 1. Fagotti A, Vizzielli G, Fanfani F et al (2013) Introduction of staging laparoscopy in the management of advanced epithelial ovarian, tubal and peritoneal cancer: impact on prognosis in a single institution experience. Gynecol Oncol 131:341–346. https://doi.org/10.1016/j.ygyno.2013.08.005
- Rutten MJ, Sonke GS, Westermann AM et al (2015) Prognostic value of residual disease after interval debulking surgery for FIGO stage IIIC and IV epithelial ovarian cancer. Obstet Gynecol Int 2015:464123. https://doi. org/10.1155/2015/464123
- Khandakar B, Mathur SR, Kumar L et al (2014) Tissue biomarkers in prognostication of serous ovarian cancer following neoadjuvant chemotherapy. Biomed Res Int 2014;401245. https://doi.org/10.1155/2014/401245
- Prat J (2012) New insights into ovarian cancer pathology. Ann Oncol 23(Suppl 10):x111-117. https://doi.org/10.1093/annonc/mds300
- Heeran MC, Høgdall CK, Kjaer SK et al (2013) Prognostic value of tissue protein expression levels of MIB-1 (Ki-67) in Danish ovarian cancer patients. From the "MALOVA" ovarian cancer study. APMIS 121:1177–1186. https://doi.org/10.1111/apm.12071
- Ezzati M, Abdullah A, Shariftabrizi A et al (2014) Recent advancements in prognostic factors of epithelial ovarian carcinoma. Int Sch Res Notices 2014;953509. https://doi.org/10.1155/2014/953509
- Gursan N, Sipal S, Calik M, Gundogdu C (2009) P53, bcl-2, ki-67 li (labeling index) status in benign, proliferative, and malignant ovarian surface epithelial neoplasms. Eur J Med 41:10
- Gates E, Lin JS, Weinberg JS et al (2019) Guiding the first biopsy in glioma patients using estimated Ki-67 maps derived from MRI: conventional versus advanced imaging. Neuro Oncol 21:527–536. https://doi.org/10. 1093/neuonc/noz004
- Harbeck N, Rastogi P, Martin M et al (2021) Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 32:1571–1581. https://doi.org/10.1016/j.annonc.2021.09.015
- Li Z, Li F, Pan C et al (2021) Tumor cell proliferation (Ki-67) expression and its prognostic significance in histological subtypes of lung adenocarcinoma. Lung Cancer 154:69–75. https://doi.org/10.1016/j.lungcan.2021.02. 009
- 11. Wu H, Han X, Wang Z et al (2020) Prediction of the Ki-67 marker index in hepatocellular carcinoma based on CT radiomics features. Phys Med Biol 65:235048. https://doi.org/10.1088/1361-6560/abac9c
- Wang X, Xu C, Grzegorzek M, Sun H (2022) Habitat radiomics analysis of pet/ct imaging in high-grade serous ovarian cancer: application to Ki-67 status and progression-free survival. Front Physiol 13:948767. https://doi. org/10.3389/fphys.2022.948767
- Mita S, Nakai A, Maeda S, Takeshita T (2004) Prognostic significance of Ki-67 antigen immunostaining (MIB-1 monoclonal antibody) in ovarian cancer. J Nippon Med Sch. https://doi.org/10.1272/jnms.71.384

- Scholzen T, Gerdes J (2000) The Ki-67 protein: from the known and the unknown. J Cell Physiol 182:311–322. https://doi.org/10.1002/(SICI)1097-4652(200003)182:3%3c311::AID-JCP1%3e3.0.CO;2-9
- Kritpracha K, Hanprasertpong J, Chandeying V, Dechsukhum C, Geater A (2005) Survival analysis in advanced epithelial ovarian carcinoma in relation to proliferative index of MIB-1 immunostaining. J Obstet Gynaecol Res 31:268–276. https://doi.org/10.1111/j.1447-0756.2005.00270.x
- Aune G, Stunes AK, Tingulstad S, Salvesen O, Syversen U, Torp SH (2011) The proliferation markers Ki-67/MIB-1, phosphohistone H3, and survivin may contribute in the identification of aggressive ovarian carcinomas. Int J Clin Exp Pathol 4:444–453
- Wang F, Wang Y, Zhou Y et al (2019) Apparent diffusion coefficient histogram analysis for assessing tumor staging and detection of lymph node metastasis in epithelial ovarian cancer: correlation with p53 and Ki-67 expression. Mol Imaging Biol 21:731–739. https://doi.org/10.1007/ s11307-018-1295-7
- Lambin P, Leijenaar RTH, Deist TM et al (2017) Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol. https://doi.org/10.1038/nrclinonc.2017.141
- Segal E, Sirlin CB, Ooi C et al (2007) Decoding global gene expression programs in liver cancer by noninvasive imaging. Nat Biotechnol 25:675–680. https://doi.org/10.1038/nbt1306
- Huang YQ, Liang CH, He L et al (2016) Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer. J Clin Oncol 34:2157–2164. https://doi.org/10. 1200/JCO.2015.65.9128
- Li H, Zhu Y, Burnside ES et al (2016) MR imaging radiomics signatures for predicting the risk of breast cancer recurrence as given by research versions of MammaPrint, Oncotype DX, and PAM50 gene assays. Radiology 281:382–391. https://doi.org/10.1148/radiol.2016152110
- 22. Ji GW, Zhu FP, Xu Q et al (2019) Machine-learning analysis of contrastenhanced CT radiomics predicts recurrence of hepatocellular carcinoma after resection: a multi-institutional study. EBioMedicine 50:156–165. https://doi.org/10.1016/j.ebiom.2019.10.057
- Lucia F, Visvikis D, Desseroit MC et al (2018) Prediction of outcome using pretreatment 18F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging 45:768–786. https://doi.org/10.1007/s00259-017-3898-7
- Brancatelli G, Federle MP, Grazioli L, Blachar A, Peterson MS, Thaete L (2001) Focal nodular hyperplasia: CT findings with emphasis on multiphasic helical CT in 78 patients. Radiology 219:61–68. https://doi.org/10. 1148/radiology.219.1.r01ap0361
- Li H, Zhang R, Li R et al (2021) Noninvasive prediction of residual disease for advanced high-grade serous ovarian carcinoma by MRI-based radiomic-clinical nomogram. Eur Radiol 31:7855–7864. https://doi.org/10. 1007/s00330-021-07902-0
- Marinaş MC, Mogoş G, Ciurea R, Mogoş DG (2012) EGFR, HER2÷neu and Ki67 immunoexpression in serous ovarian tumors. Rom J Morphol Embryol 53:563–567
- Sylvia MT, Kumar S, Dasari P (2012) The expression of immunohistochemical markers estrogen receptor, progesterone receptor, Her-2-neu, p53 and Ki-67 in epithelial ovarian tumors and its correlation with clinicopathologic variables. Indian J Pathol Microbiol 55:33–37. https://doi.org/ 10.4103/0377-4929.94852
- Shafiq-Ul-Hassan M, Zhang GG, Latifi K et al (2017) Intrinsic dependencies of CT radiomic features on voxel size and number of gray levels. Med Phys 44:1050–1062. https://doi.org/10.1002/mp.12123
- Li HM, Zhang R, Gu WY et al (2019) Whole solid tumour volume histogram analysis of the apparent diffusion coefficient for differentiating high-grade from low-grade serous ovarian carcinoma: correlation with Ki-67 proliferation status. Clin Radiol 74:918–925. https://doi.org/10. 1016/j.crad.2019.07.019
- Zwanenburg A, Vallières M, Abdalah MA et al (2020) The image biomarker standardization initiative: standardized quantitative radiomics for highthroughput image-based phenotyping. Radiology 295:328–338. https:// doi.org/10.1148/radiol.2020191145
- Gillies RJ, Kinahan PE, Hricak H (2016) Radiomics: images are more than pictures, they are data. Radiology 278:563–577. https://doi.org/10.1148/ radiol.2015151169
- 32. Xu L, Yang P, Hu K et al (2021) Prediction of neoadjuvant chemotherapy response in high-grade osteosarcoma: added value of non-tumorous

bone radiomics using CT images. Quant Imaging Med Surg 11:1184–1195. https://doi.org/10.21037/gims-20-681

- Zhang Y, Shu Z, Ye Q et al (2021) Preoperative prediction of microvascular invasion in hepatocellular carcinoma via multi-parametric MRI radiomics. Front Oncol 11:633596. https://doi.org/10.3389/fonc.2021.633596
- 34. Zhao Y, Wu J, Zhang Q et al (2021) Radiomics analysis based on multiparametric MRI for predicting early recurrence in hepatocellular carcinoma after partial hepatectomy. J Magn Reson Imaging 53:1066–1079. https:// doi.org/10.1002/jmri.27424
- Zhao L, Ma X, Liang M et al (2019) Prediction for early recurrence of intrahepatic mass-forming cholangiocarcinoma: quantitative magnetic resonance imaging combined with prognostic immunohistochemical markers. Cancer Imaging 19:49. https://doi.org/10.1186/s40644-019-0234-4
- Lisson CS, Lisson CG, Flosdorf K et al (2018) Diagnostic value of MRI-based 3D texture analysis for tissue characterisation and discrimination of low-grade chondrosarcoma from enchondroma: a pilot study. Eur Radiol 28:468–477. https://doi.org/10.1007/s00330-017-5014-6
- Fan Y, Yu Y, Wang X, Hu M, Hu C (2021) Radiomic analysis of Gd-EOB-DTPAenhanced MRI predicts Ki-67 expression in hepatocellular carcinoma. BMC Med Imaging 21:100. https://doi.org/10.1186/s12880-021-00633-0
- Fu Q, Liu SL, Hao DP et al (2021) CT radiomics model for predicting the Ki-67 index of lung cancer: an exploratory study. Front Oncol 11:743490. https://doi.org/10.3389/fonc.2021.743490

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.