Joint prediction of breast cancer histological grade and Ki-67 expression level based on DCE-MRI and DWI radiomics

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Abstract— Objective: Histologic grade and Ki-67 proliferation status are important clinical indicators for breast cancer prognosis and treatment. The purpose of this study is to improve prediction accuracy of these clinical indicators based on tumor radiomic analysis. **Methods:** We jointly predicted Ki-67 and tumor grade with a multitask learning framework by separately utilizing radiomics from tumor MRI series. Additionally, we showed how multitask learning models (MTLs) could be extended to combined radiomics from the MRI series for a better prediction based on the assumption that features from different sources of images share common patterns while providing complementary information. Tumor radiomic analysis was performed with morphological, statistical and textural features extracted on the DWI and dynamic contrast-enhanced MRI (DCE-MRI) series of the precontrast and subtraction images, respectively. **Results:** Joint prediction of Ki-67 status and tumor grade on MR images using the MTL achieved performance improvements over that of single-task-based predictive models. Similarly, for the prediction tasks of Ki-67 and tumor grade, the MTL for combined precontrast and apparent diffusion coefficient (ADC) images achieved AUCs of 0.811 and 0.816, which were significantly better than that of the single-task-based model with p values of 0.005 and 0.017, respectively. **Conclusion:** Mapping MRI radiomics to two related clinical indicators improves prediction performance for both Ki-67 expression level and tumor grade. **Significance:** Joint prediction of indicators by multitask learning that combines correlations of MRI radiomics is important for optimal tumor therapy and treatment because clinical decisions are made by integrating multiple clinical indicators.

Index Terms— Breast cancer, Ki-67, histologic grade, radiomics, multitask learning

I. INTRODUCTION

BREAST cancer pathological grade and Ki-67 expression level are important clinical indicators for breast cancer diagnosis and treatment. Tumor histological grade, a well-established prognostic factor, is crucial for guiding the appropriate treatment in clinical practice [1]. The Ki-67 index is an indicator of tumor aggressiveness and proliferative activity [2], in which a higher expression level reliably indicates

more aggressive growth of breast cancer [3] and often a poorer pathological complete response (pCR) [3-7]. A large meta-analysis indicates that higher Ki-67 expression is associated with a greater risk of recurrence [8] and poorer prognosis [9].

At the time of diagnosis, imaging is primarily used to establish the clinical stage before treatment intervention to drive the decision making. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a highly sensitivity method for diagnosing invasive breast cancer, whereas the specificity is only moderate [10]. Diffusion-weighted imaging (DWI), on the other hand, is performed without the administration of contrast agents, and it measures the Brownian motion of free water in tissue that is affected by fluid viscosity, membrane permeability, fibers, and tissue cellularity by using a quantitative method to assess the apparent diffusion coefficient (ADC). This technology is increasingly used because it can add the specificity of breast tumor diagnosis and is complementary to DCE-MRI for tumor characterization [11, 12].

However, to predict tumor characteristics, only a single parametric MRI is usually used. For example, studies indicate that radiomic analysis of MRI may be helpful in predicting breast cancer subtypes [13-16], neoadjuvant chemotherapy responses [17-19], Ki-67 expression level [20-22], pathological stage [23], histological grade [24], tumor malignancy [25, 26], and breast cancer risk [27] based on either DCE-MRI or DWI. These studies were performed without considering complementary information that could be provided by different parametric images.

Great efforts have been devoted in utilizing MRI [28-32], including DCE-MRI, T2-weighted imaging or DWI for the diagnosis and treatment of breast cancer. For example, Partridge et al. improved the diagnostic accuracy of breast MRI through combined ADC and dynamic kinetics. Shin et al. extracted MRI and DWI features separately to predict the Ki-67 expression level. However, these studies were performed using separate images or by simply averaging the predictions without considering the common and complementary information of the image features.

On the other hand, although studies have shown the power of associating tumor radiomics and genomic or clinical features,

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most existing studies focus on separately estimating multiple clinical variables [24, 33, 34] and thus cannot utilize the intrinsically useful, correlated information among these variables. Different biomarkers provide complementary information for cancer treatment and diagnosis. Their measurements capture common histopathological information by jointly characterizing a patient's tumor status. For example, patients with breast cancer who show high Ki-67 expression levels are associated with high histological grade [35]. Importantly, while each clinical indicator gives limited and noisy information, considering them jointly provides a more complete and comprehensive diagnostic depiction, as diagnosis is usually based on a combination of these assessments. In the machine learning community, the joint estimations of Ki-67 expression level and tumor grade in breast cancer can be formulated as a multitask classification problem [36]. Multitask learning methods have been applied in brain images to jointly predict behavioral scores that make up the individual profiles [37], and the results of improved predictions justify the idea.

However, whether the prediction accuracy of correlating between combined MRI radiomics and multiple clinical variables is better than that of associating single parametric MR radiomics with one clinical indicator is still an open question.

Motivated by the above analysis, we aim to discriminate the histological grade and Ki-67 expression status jointly by multitask feature learning and classification to improve the prediction accuracy. We also aim to examine whether DCE-MRI and DWI can improve the prediction performance compared with that based on a single parametric image. Specifically, our contributions are threefold.

First, we established a multitask radiomic classification model for simultaneously discriminating Ki-67 and tumor grade in breast cancer. To the best of our knowledge, this is the first study to take advantage of tumor radiomics based on multitask feature selection (MTFS) and classification methods for the prediction of multiple clinical indicators. Our method can reduce possible noise in individual measurements of tumors and may be promising for improving the classifier performance of both targets. Second, our proposed model is flexible and extendible because more image series, such as T2-weighted images, and more clinical indicators, such as molecular subtypes (e.g., luminal A and luminal B), could be incorporated in the multitask learning-based radiomic analysis. Finally, the proposed model is important for optimal tumor therapy and treatment because clinical decisions are made by integrating multiple clinical indicators obtained from tumor biopsy.

II. MATERIALS AND METHODS

A. Dataset

We initially collected 203 biopsy samples indicating invasive breast cancer from the First Affiliated Hospital of Zhejiang Chinese Medical University between March 2013 and May 2017 (Fig. 1). The institutional review boards (IRB) approved this study (No. 2018001), and the requirement for informed consent was waived due to the retrospective nature of this study. Twenty-four of the patients who had incomplete MR sequence data and three for whom there was no pathological report available were excluded from the dataset. Thirty-two patients

were excluded because there was no histological grading information in their pathological reports. Thus, the final dataset included 144 women with a mean age of 52 years and an age range of 28-83 years. There were 68 low-grade (grade 2) and 76 high-grade (grade 3) tumors and 36 low Ki-67 and 108 high Ki-67 expression samples. There were no grade 1 tumors in our dataset because the number of this tumor grade is quite small in the initial collection of the data cohort (i.e., only 3 samples) and were excluded due to noncompliance with the selection criteria (i.e., incomplete MR sequence).

Fig. 1. Flowchart of patient selection.

All breast MR examinations were performed with a wide-bore Magnetom Verio 3.0T system (Siemens Medical Systems, Erlangen, Germany) fitted with a dedicated eight-channel breast array coil with the patient placed in the prone position. The DCE-MRI included one precontrast and five postcontrast bilateral sagittal image acquisitions performed with a fat-suppressed T1-weighted three-dimensional sequence. The following parameters were used: repetition time (TR) 4.51 ms, echo time (TE) 1.61 ms, matrix 448×448, flip angle 10°, field of view (FOV) 340×340 mm, slice thickness 1 mm, and in-plane resolution 0.759×0.759 mm. A bolus of 0.2 mmol/kg gadobutrol was intravenously injected at a rate of 2 mL/second using an MR imaging-compatible power injector. The first postcontrast acquisition was performed 60 seconds after the contrast material was injected. Five sequential contrast-enhanced images were then obtained with a temporal resolution of 60 seconds.

DWI was performed before the precontrast MR scan using the following parameters: TR = 8400 ms (or 7000 ms), TE = 84 ms (or 85 ms), flip angle = 90°, FOV = 147 mm × 359 mm (or 120 × 339), slice thickness = 4.0 mm, spacing between slices = 6.0 mm, and pixel bandwidth = 1263 Hz (or 1196 Hz). The acquisition matrix was 220 × 90 with a spatial resolution of 1.64 mm and b values = 50, 400 and 800 s/mm². The ADC maps were obtained from diffusion images with three b values.

Two pathologists with more than 15 years of experience who were blinded to the MRI results analyzed the breast tissue specimens. The histological type of breast cancer was defined according to the WHO classification [38]. Tumor histological grade was assessed using the Elston-Ellis System. For Ki-67, cases with more than 14% positive nuclei were determined as high Ki-67 expression, and other tumors were considered low-Ki-67 expression according to the St. Gallen consensus [39].

B. Image Processing

The location of the center of a suspicious breast tumor was first annotated in each case retrospectively via consensus between two radiologists (S.W. and M.X.) who have more than 10 years of experience. Image segmentation was performed on the third postcontrast series for all cases because this series is usually the most enhanced of all the time series and hence is usually useful for visual inspection. An initial “seed” was chosen using the location of the center of the labeled tumor. After that, a volumetric breast tumor boundary contour was automatically segmented by a spatial fuzzy C-means (FCM) algorithm and subsequently refined by a Markov random field (MRF)-based approach, the parameters of which were adaptively adjusted using the segmentation results of contiguous slices [40]. In less than 10% of all cases, the segmentation results were further examined by manual correction performed by our investigators. The breast MR images acquired from sequential MRI scans were registered as previously reported [40].

C. Radiomic Features

The radiomic features were derived from the precontrast images (S0), and from the subtraction images between the second postcontrast or the fifth postcontrast images and the precontrast images; these subtraction images were termed S20, and S50, respectively. Additionally, the tumor region of interest (ROI) on the DCE-MRI was aligned to that of the ADC map using the Statistical Parametric Modeling toolbox version 12 (SPM12) platform (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>). Imaging Features, including textural, statistical and morphological features were extracted from the DCE-MRI and ADC maps. To quantify spatial heterogeneity within each tumor, we extracted 19 volumetric textual features that was calculated from gray-level cooccurrence matrices (GLCM) [41–43]. To reduce the feature space dimension, texture features are extracted from the nondirectional GLCMs by summing up the 13 directional GLCMs, which is a common practice reported in the literature [44].

Although the gray-level quantization could affect the calculated texture features, different groups tend to use arbitrarily chosen quantization methods when constructing the GLCM [44]. A previous study analyzed quantization parameters of texture, and recommend the same number of gray levels in all quantized images for texture features [45]. Following the previous studies, we used a fixed number of 32 bits for texture feature analysis [46].

We obtained 10 statistical features for evaluating the histogram distributions of image pixels inside the tumor. Additionally, we calculated 10 morphological features to measure the shape of the tumor. The detailed image features are listed in TABLE I. The textural and statistical features were extracted from all the image series, whereas the morphological features were computed only from the S0 image and ADC map. Therefore, 97 features were calculated for each tumor.

D. Multitask Learning Methods

We wanted to simultaneously improve the prediction of pathological grading and Ki-67 proliferation status from the DCE-MRI and ADC images. Fig. 2 depicts the workflow of the proposed model, which is a multitask learning model built with

a two-layer architecture. The first step performs a supervised MTFS on each image series separately and yields a feature set that is correlated to both the Ki-67 level and the tumor grade for each image series. The second level learns a common multioutput model using the generated feature sets in MTFS and returns the final prediction of the clinical indicators based on a combination of all the image series.

Feature selection is used for dimensionality reduction, as well as for removal of irrelevant features derived from MR images.

TABLE I
FEATURE DESCRIPTION

Feature	Description
Texture feature	
Autocorrelation	Detect repetitive patterns of texture elements
Cluster prominence	Asymmetry
Cluster shade	Asymmetry or uniformity
Contrast	Local variations presented in an image
Correlation	Image complexity
Difference entropy	Randomness of the difference in neighboring voxel gray levels
Difference variance	Variations of difference in gray level pairs
Dissimilarity	Local contrasts
Energy	Uniformity of the image gray distribution
Entropy	Randomness of the intensity distribution
Homogeneity	Uniformness of pixel pair
Information correlation	Nonlinear gray level dependence
Information correlation	Nonlinear gray level dependence
Inverse difference	Local similarity
Maximum probability	Highest frequency of pixel pair
Sum average	Overall brightness
Sum entropy	Randomness of the sum of gray levels of neighboring voxels
Sum of squares variance	Spread in the gray level distribution
Sum variance	Spread in the sum of the gray levels of voxel-pairs distribution
Statistical feature	
Entropy	Randomness of the intensity distribution
Interquartile range	A robust estimate of the spread of the data
Kurtosis	Distribution apart from the variance
Maximum	The maximum pixel gray value of the lesion
Mean	The average pixel gray value of the lesion
Median	The median pixel gray value of the lesion
Minimum	The minimum pixel gray value of the lesion
Range	An indication of statistical dispersion
Skewness	Asymmetry of the histogram
Standard deviation	Variation in or dispersion of pixel value of the lesion
Morphological feature	
Compactness	The degree to which the lesion is compact
Compactness 1	The degree to which the lesion is compact
Compactness 2	The degree to which the lesion is compact
Eccentricity	Covariance between morphological shape elements
Equivalent radius	Radius of a sphere with the same volume as the lesion
Max radius	The maximum radius of the lesion sections
Mean radius	The mean radius of the lesion sections
Surface area	Surface area of the lesion
Surface area/volume	Ratio of the surface area to volume
Volume	Volume of the lesion

Fig. 2. Overview of the proposed method. Multitask learning for radiomic analysis of DCE-MRI and ADC map.

In contrast to conventional single-task feature selection, MTFS simultaneously selects a common feature subset relevant to all tasks. This point is especially important for breast cancers because the clinical indicators are determined by the same underlying cancer pathology of the tumor. In addition, simultaneously performing the feature selection for clinical variables such as Ki-67 and histological grade can be very helpful for suppressing noise in the individual variables. We used multitask elastic-net regression, which can enforce sparse restrictions for a given regularization, assuming that different tasks share the same parameter that control sparsity. Assuming there are T tasks and M image series, the i^{th} images with an input matrix $X_i \in R^{N \times V}$ denote the input matrix for N subjects and V features, and the output matrix $Y \in R^{N \times T}$ denotes the labels of N subjects for T tasks. The coefficient matrix $W_i \in R^{V \times T}$ for the i^{th} image is estimated as follows:

$$\hat{W}_i = \underset{W_i \in R^{V \times T}}{\operatorname{argmin}} \|Y - X_i W_i\|_F^2 + \alpha \|W_i\|_1 + \beta \|W_i\|_F^2 \quad (1)$$

where the regularization parameter $\alpha > 0$ controls the sparsity of the estimate, and the parameter β controls the ℓ_2 -norm penalty. $\|W_i\|_F^2$ is the Frobenius norm of matrix W_i , which can be computed by a trace of $W_i^T W_i$, and β is the regularization parameter that controls the amount of shrinkage, i.e., the larger the value of β is, the greater the amount of shrinkage. In this elastic-net, both the ℓ_1 -norm and ℓ_2 -norm are used. If a feature is not relevant across all tasks, the corresponding row in the estimated matrix $\hat{W}_i$ is zero. After the MTFS procedure, the estimated weight matrix W is used to define the selected features for its nonzero entries to perform multitask prediction optimally. At present, many algorithms have been developed to solve MTFS; in this paper, we adopt the MALSAR-toolbox [47].

In this study, we developed a multiple images-based classifier with features selected by the above MTFS method. After obtaining the common feature subset for all different tasks by MTFS as described above, we used a multitask learning method to train the final classification models. We utilized a multitask classifier (MTC) in which the matrix that models the relations between tasks is learned using a convex optimization problem that can be approached by means of alternating minimization [48]. Prediction from each image was integrated by an average method weighted by the accuracy of the trained model in a cross-validation procedure.

E. Statistical Analysis

At the preprocessing stage, we performed a common feature normalization step, i.e., subtracting the mean and then dividing

the standard deviation (of all training subjects) for each feature value. Univariate logistic regression analysis was performed to assess the predictive power of individual predictors. We used a nested leave-one-out cross-validation (LOOCV) strategy in the training and classification tasks. Specifically, in each LOOCV loop, one subject sample was selected as the testing sample, and the remaining subjects were used for training the predictive models, in which the elastic-net parameters (i.e., α and β) were re-optimized by the grid search method. This process was repeated N times, each of which generated a predictive variable to produce a prediction performance, i.e., an area under the receiver operating characteristic (ROC) curve (AUC) value. The significance of the comparison between the AUC values was assessed using a bootstrapping test (pROC package in R program). Sensitivity and specificity were obtained at maximum Youden's index derived from ROC curves. All p values were corrected for false discovery (FDR) correction using the Benjamini-Hochberg method. Statistical analysis was performed using MATLAB (R2015) and R (version 3.4.1).

III. RESULTS

A. Patients

Table II shows the histopathological characteristics of the 144 patients. The statistical tests showed a significant association between histological grade and Ki-67 expression level ($p=0.001$). No significant differences in histological information, including progesterone receptor (PR) status, menopausal status, age, and Ki-67 status, were observed between the low and high Ki-67 expression breast tumors. We observed significant differences in the maximum tumor diameter between the low and high Ki-67 expression tumors.

TABLE II
TUMOR CHARACTERISTICS

	All	Low-Ki-67	High-Ki-67	P value*
	144	(n=36) (%)	(n=108) (%)	
PR [†]				0.078
Positive	90	27(18.75)	63(43.75)	
Negative	54	9(6.25)	45(31.25)	
Histological grade [‡]				0.001
2	68	26(18.1)	42(29.2)	
3	76	10(6.9)	66(45.8)	
Menopausal status [‡]				0.440
Premenopausal	78	22(15.3)	56(38.9)	
Postmenopausal	66	14(9.7)	52(36.1)	
Age (y) [‡]	52.1 (28–83)	51.3(28–83)	52.4(31–82)	0.605
Maximum tumor diameter (mm) [‡]	23.44(6–100)	17.61(6–50)	25.4(7–100)	<0.001

*P value for low Ki-67 versus high Ki-67 comparison.

[†]The data were tested using Fisher's exact test.

[‡]The data were tested using a t-test.

PR, progesterone receptor; numbers in parentheses are percentages

Tumors with Ki-67 >14% were considered high-Ki-67; others were considered low-Ki-67

B. Univariate Analysis of Image Features

The ability of individual features to predict tumor grade and Ki-67 expression status is illustrated in Fig. 3 and Supplementary Fig. 1, respectively. The results show that textural and morphological features have relatively greater AUC values that are significantly (corrected p values < 0.05) higher than random

Fig. 3. Individual AUC values of texture, statistic, and shape features from the images for prediction of histological grade. The predictive power is reported as directly or inversely proportional to the tumor grade as the feature value increased, which is represented on the right and left sides of the bar diagram, respectively. Features reported with an asterisk are significant from a random guess (Bootstrap test, $p < 0.05$, false discovery rate-corrected).

values (i.e., $AUC = 0.5$). However, no statistical features in the MR images (i.e., S0, S20, S50 and ADC) showed high predictive power (corrected p values > 0.05). As illustrated in Fig. 4, the texture feature of difference entropy showed a significantly higher (p value < 0.001) value in the low Ki-67 expression tumors for image S0, S20 and S50. This significant, high trend was also observed for low histological grade tumors compared with that for high-grade tumors (p values < 0.001). On the other hand, we observed a different trend in this feature for comparing between the two groups in ADCs, in which a significantly higher value of this feature was found in high Ki-67 or grade 3 tumors than in low Ki-67 or grade 2 tumors.

Fig. 4. Distribution of DCE-MRI and ADC texture features of difference entropy for prediction of a) Ki-67 status and b) histological grade in breast cancer patients.

Fig. 5. Distribution of DCE-MRI and ADC texture features of entropy for prediction of a) Ki-67 status and b) histological grade in breast cancer patients.

We also observed that entropy features based on ADC had high discriminative power in the histological prediction task ($AUC = 0.763$ and p value < 0.001) and moderate predictive ability for predicting Ki-67 status ($AUC = 0.681$ and p value < 0.001), which were among the best individual performance features (Fig. 5). However, for the DCE-MRI series (i.e., S0, S20, and S50), entropy features showed a less significant association with either Ki-67 or histological grade in breast cancer. More specifically, a higher value of this feature was observed in low Ki-67 and low histological grade tumors than in high Ki-67 or high-grade tumors for the DCE-MRI series, a result that was opposite to that based on the ADC images.

Fig. 6. Examples of image feature values of difference entropy for a) tumor with low Ki-67 expression level and histological grade 2 and b) tumor with high Ki-67 expression level and histological grade 3. Feature values are derived from images of S0, S20, S50 and ADC, respectively. FV=feature value.

Fig. 6 illustrates an example of a difference entropy feature in a low Ki-67 and low-grade patient compared with that in a patient with a high Ki-67 and high-grade tumor from the images of S0, S20, S50 and ADC. Patients with low Ki-67 and low-grade tumors showed higher values of difference entropy than did those with high Ki-67 and high-grade tumors. On the other hand, for ADC, this feature showed an inverse trend between the two groups.

C. Single-Task Prediction Using Features from ADC and DCE-MRI Series Separately

We separately examined the performance of single-task methods for predicting Ki-67 expression or histological grade

TABLE III
CLASSIFIER PERFORMANCES FOR TUMOR KI-67 STATUS AND HISTOLOGICAL GRADE

Predictive model	Feature selection	Images	Ki-67			Histological grade		
			AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
Logistic regression	Lasso	S0	0.756±0.086	0.731	0.722	0.780±0.078	0.947	0.574
		S20	0.737±0.101	0.713	0.722	0.766±0.081	0.947	0.529
		S50	0.733±0.093	0.676	0.694	0.765±0.082	0.934	0.544
		ADC	0.738±0.089	0.501	0.917	0.757±0.082	0.737	0.721
Logistic regression	RFE	S0	0.778±0.084	0.648	0.806	0.796±0.074	0.803	0.691
		S20	0.766±0.097	0.759	0.750	0.774±0.081	0.961	0.618
		S50	0.757±0.093	0.787	0.667	0.743±0.084	0.816	0.618
		ADC	0.750±0.089	0.593	0.889	0.742±0.085	0.895	0.559
SVM	RFE	S0	0.664±0.113	0.852	0.556	0.741±0.089	0.908	0.588
		S20	0.660±0.121	0.815	0.556	0.754±0.085	0.842	0.662
		S50	0.584±0.118	0.602	0.639	0.756±0.081	0.697	0.735
		ADC	0.573±0.117	0.796	0.444	0.757±0.085	0.789	0.691
MTC	Lasso	S0	0.761±0.087	0.574	0.889	0.786±0.078	0.961	0.559
		S20	0.738±0.098	0.731	0.694	0.768±0.079	0.987	0.471
		S50	0.775±0.086	0.787	0.667	0.788±0.077	0.776	0.721
		ADC	0.771±0.083	0.537	0.917	0.785±0.076	0.895	0.588

RFE = recursive feature elimination, LASSO = least absolute shrinkage and selection operator, SVM = support vector machine.

based on features from the ADC and DCE-MRI series. We tested the classifiers of least absolute shrinkage and selection operator (lasso), logistic regression, support vector machine (SVM), and MTC [48] for prediction. The performance of AUC values is listed in Table III.

The result shows that the S20-based predictive model had lower performance than did the models based on the other images. For Ki-67 status, the predictive model used features derived from S0, S20, S50 and ADC images with recursive feature elimination (RFE) as the feature selection and logistic regression as the classifier [48] and had AUCs of 0.778, 0.766, 0.757 and 0.750, respectively. For tumor grade prediction, the images of S0, S20, S50 and ADC showed relatively high prediction performance in terms of AUCs (0.796, 0.774, 0.743 and 0.742, respectively). Although different classifiers were utilized, the performance for the prediction tasks was similar.

D. Multitask Learning Improves Single Parametric Image-based Prediction Performance

We applied multitask learning for single-model prediction on the DCE (S0, S20, and S50) and ADC images separately. MTFS was conducted using the least squares loss. The ROC curves of S20 in single and multitask learning for predicting Ki-67 and tumor grade are shown in Fig. 7. The selected features that commonly target the two indicators were then used in the multitask learning classifier. The prediction of the two tasks was performed using a multitask classifier [48]. The results showed that prediction performance was increased for all image series, while MTFS and classification methods were utilized (Table IV and Fig. 8). The performance of the S20-based predictive model was significantly improved by using multitask learning both for the Ki-67 task and tumor grade in breast cancer, with p values of 0.032 and 0.024, respectively.

We tested the proposed framework by comparing the prediction performance of multitask learning to those of single-task for the MR images. For the Ki-67 prediction, multitask learning using images of S20, S50 and ADC significantly ($p < 0.05$) improved the single-task based prediction performance

Fig. 7. ROC of the single-task and multitask learning on the S20 and the combination with ADC series.

Fig. 8. Multitask learning improves classifier performance for both the a) Ki-67 and b) histological grade prediction tasks.

(in terms of AUCs). For histological grade prediction, multitask learning using images of S0 and S20 significantly ($p < 0.05$) improved predictive model performance.

TABLE IV
MULTITASK LEARNING PERFORMANCES USING DCE-MRI AND ADC IMAGES

Ki-67							
Images	Single-task			Multitask			
	AUC	Sens	Spec	AUC	Sens	Spec	P value
S0	0.761	0.574	0.889	0.795	0.769	0.750	0.105
S20	0.738	0.731	0.694	0.768	0.796	0.694	0.032
S50	0.775	0.787	0.667	0.810	0.843	0.667	0.011
ADC	0.771	0.537	0.917	0.805	0.676	0.917	0.028
Histological Grade							
S0	0.786	0.574	0.889	0.810	0.769	0.750	0.007
S20	0.766	0.731	0.694	0.797	0.796	0.694	0.024
S50	0.788	0.787	0.667	0.792	0.843	0.667	0.739
ADC	0.785	0.537	0.917	0.796	0.676	0.917	0.312

Sens= Sensitivity; Spec= Specificity.

E. Multitask Learning Improves MRI-radiomics-based Prediction Performance

We combined radiomics from the MRI series to improve the performance of a single parametric image-based model for both single-task-based Ki-67 expression and tumor grade prediction. Classifiers that incorporated image features from S0, S20, S50 and ADC were evaluated, and the results showed that the performance of combined images was improved while the ADC features were introduced to the model (Table V). Additionally, compared with that for a single image, the prediction accuracy was moderately improved by combining features from the DCE-MRI scans (i.e., S0, S20 and S50).

We further performed multitask learning to improve the model performance using image features from the DCE-MRI

and ADC. Table V shows the multitask performance of the classifiers based on combined predictions from S0, S20, S50 and ADC. The prediction performance of MR images based on a single-task was improved by multitask learning (Table V). Additionally, while the MTFs and classification methods were utilized, most of the MR-image-based prediction performance (in terms of AUC values) was significantly improved ($p < 0.05$) for Ki-67 status except for the classifier using the combined S0 and S20 images. While multitask learning was performed, the predictive model by integrating the S0 series with ADC was significantly improved for the Ki-67 and tumor grade prediction tasks ($p = 0.005$ and 0.017 , respectively).

F. Comparison of the Prediction Performance of Image Series Within Single-Task and Multitask Learning

We compared the AUCs of a subset of MR series (i.e., DCE-MRI and ADC images) within single-task and multitask learning (Fig. 9). The predictive model for S50 has significantly better prediction performance than that for S20 for both the single-task and multitask Ki-67 prediction (p values of 0.044 and 0.011 , respectively). Moreover, the model performance based on the combination of the S0, S20 and S50 series has a significantly higher AUC value than that based on S20 for both the single-task and multitask learning models (p values of 0.016 and 0.011 , respectively). For tumor histological grade prediction, the combined radiomics from the three DCE-MRI series showed the best prediction performance in single-task learning and was significantly ($p = 0.018$) higher than that of the S20-based predictive model. However, we did not observe significantly different AUC values within multitask learning for these imaging series.

TABLE V
mpMRI-BASED PREDICTION PERFORMANCE USING SINGLE-TASK AND MULTITASK LEARNING SEPARATELY

mpMRI	Ki-67						
	Single task			Multitask			
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	p value
S0+S20	0.761±0.088	0.778	0.694	0.788±0.083	0.796	0.694	0.068
S0+S50	0.780±0.083	0.713	0.750	0.809±0.077	0.713	0.806	0.026
S0+S20+S50	0.772±0.087	0.778	0.694	0.798±0.081	0.806	0.694	0.023
S0+ADC	0.776±0.082	0.556	0.944	0.811±0.076	0.676	0.917	0.005
S20+ADC	0.771±0.087	0.704	0.778	0.805±0.078	0.676	0.889	0.013
S50+ADC	0.796±0.080	0.778	0.722	0.821±0.074	0.741	0.833	0.017
S0+S20+ADC	0.777±0.084	0.713	0.778	0.805±0.078	0.694	0.889	0.040
S0+S50+ADC	0.794±0.080	0.787	0.722	0.820±0.074	0.722	0.833	0.015
S0+S20+S50+ADC	0.782±0.084	0.741	0.750	0.810±0.077	0.704	0.833	0.019
mpMRI	Histological Grade						
	Single task			Multitask			
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	p value
S0+S20	0.790±0.077	0.842	0.691	0.815±0.074	0.947	0.647	0.014
S0+S50	0.780±0.076	0.921	0.618	0.812±0.075	0.921	0.647	0.124
S0+S20+S50	0.794±0.077	0.868	0.662	0.810±0.075	0.908	0.662	0.071
S0+ADC	0.798±0.075	0.934	0.588	0.816±0.072	0.803	0.750	0.017
S20+ADC	0.790±0.077	0.947	0.618	0.803±0.075	0.934	0.632	0.141
S50+ADC	0.799±0.076	0.789	0.735	0.802±0.076	0.921	0.618	0.709
S0+S20+ADC	0.799±0.075	0.882	0.676	0.816±0.073	0.947	0.647	0.040
S0+S50+ADC	0.808±0.074	0.855	0.691	0.813±0.074	0.961	0.618	0.506
S0+S20+S50+ADC	0.802±0.076	0.816	0.721	0.814±0.074	0.947	0.662	0.119

Fig. 9. Comparisons of AUCs within single-task and multitask learning for the MRI series. The prediction of Ki-67 in a) single-task and b) multitask learning and that of tumor histological grade in c) single-task and d) multitask learning are shown.

G. Case Study for Feature Selection in Single-task and Multitask Learning

To evaluate and compare the feature selection frequency in single-task and multitask learning, we performed a case study for a S20-based predictive model targeting Ki-67 and tumor grade classification. The frequencies of selected features in the nested LOOCV method for these methods are shown in Table VI. Two morphological features (i.e., the ratio between surface area and volume and compactness 2) and one texture feature (i.e., information correlation 2) were mostly frequently selected in the cross-validation both for the Ki-67 and histological grade prediction tasks. The features of energy, homogeneity and volume were not included in the Ki-67 prediction task but were selected with a frequency of more than 50% in multitask learning. Although the feature of mean radius has a relatively high AUC in the single-task (i.e., AUC value of 0.78 and 0.80 for the prediction of Ki-67 and tumor grade, respectively), it was less selected (41%) in the multivariate model for the single-task prediction of histological grade, whereas it was most frequently selected (100%) in multitask prediction. On the other hand, the feature of information correlation 1 was selected at

approximately 50% in both the single-task of Ki-67 and the histological grade, whereas was **seldomly** selected in multitask learning. This feature showed low prediction power in both the Ki-67 (AUC=0.588) and tumor grade prediction tasks (AUC=0.555) and was almost never selected (i.e., 1.4% and 0% for the Ki-67 and histological grade tasks, respectively) in multitask learning.

IV. DISCUSSION

In this study, multitask learning was performed for the first time to predict Ki-67 status and tumor grade in breast cancer specimens. Our study provides a promising attempt to predict multiple clinical **indicators** simultaneously following a normal diagnostic procedure. Multitask prediction models using tumor radiomics were designed, and the results suggested enhanced prediction accuracies for both tasks. Moreover, radiomics from DCE-MRI and DWI were combined and showed higher performance than that of the single parametric image.

The image features in this study have been reported by previous studies. For example, the feature of difference entropy, which measures heterogeneous textural appearance, i.e., randomness of the difference in neighboring voxel gray levels, was high in low Ki-67 expression tumors [49]. Moreover, a related study found that luminal A tumors had a higher value of this feature than luminal B tumors did [20]. Our results are partly consistent with those of the previous study because the Ki-67 index has also been used as a proliferation marker to distinguish between the luminal A and luminal B molecular subtypes of ER-positive breast cancer [50]. The feature of homogeneity, which showed the most discriminative power in a similar study [23], also had relatively high prediction performance in either the Ki-67 or tumor grade prediction task in breast cancer. Additionally, Burnside et al. provided effective greatest dimensions and surface areas as important features for prediction [23]. Our findings show that morphological features such as maximum tumor diameter, tumor volume, tumor diameter derived from image slices, mean radius, and diameter from tumor volume have high individual performance (AUC larger than 0.70). Therefore, our results are consistent with previous findings.

The results of this study showed that our multitask learning models improve the prediction of Ki-67 status and tumor grade. This outcome may be explained by the fact that these models

TABLE VI
FEATURE SELECTION FREQUENCY OF MORE THAN 50% FOR MULTITASK LEARNING USING S20 IMAGES

Feature	Ki-67		Histological grade	
	Single task	Multitask	Single task	Multitask
Surface area/volume	144 (100%)	144 (100%)	144 (100%)	144 (100%)
Compactness 2	144 (100%)	144 (100%)	144 (100%)	132 (91.7%)
Information correlation 2	144 (100%)	125 (86.8%)	115 (79.9%)	129 (89.6%)
Mean radius	132 (91.7%)	144 (100%)	59 (41.0%)	144 (100%)
Information correlation 1	78 (54.2%)	2 (1.4%)	59 (41.0%)	0 (0%)
Minimum	2 (1.4%)	0 (0%)	144 (100%)	144 (100%)
Difference variance	0 (0%)	0 (0%)	144 (100%)	144 (100%)
Autocorrelation	0 (0%)	0 (0%)	144 (100%)	119 (82.6%)
Energy	0 (0%)	107 (74.3%)	1 (0.7%)	25 (17.4%)
Homogeneity	0 (0%)	116 (80.1%)	0 (0%)	2 (1.4%)
Volume	0 (0%)	96 (66.7%)	0 (0%)	0 (0%)

exploit similar and complementary evaluation of tumor characteristics, hence overcoming the limitations of pathological assessment with noisy data. In both the evaluation tasks we studied, Ki-67 expression and tumor grade, the pathological assessment is important for prognosis and treatment management. Notably, high Ki-67 proliferation status is associated with aggressive growth of breast cancers and hence larger tumor size or higher tumor grade. This measurement is inevitably accompanied by noise; furthermore, tumor proliferation is often spatially heterogeneous [51]. Moreover, in our study, Ki-67 expression status was significantly correlated with tumor grade. These results show that jointly capturing related clinical targets has a crucial impact on the correlated and complementary data. Our experiments show that a multitask prediction approach not only improves the prediction of these indicators but also enhance patient classification for prognostic analysis.

The proposed framework includes combined information from S0, S20, S50 and ADC images, which reflect both morphological and functional tumor biology and could contribute to a net increase in classification performance. Moreover, MRI radiomics analyzed in a multitask way can improve the classifier accuracy for both tasks. The results suggested that the presence of noisy features extracted from heterogeneous tumor images could be partly reduced by the multitask learning method.

Despite some significant findings, the limitations in this study should be addressed. First, the statistical power of this study is limited due to the relatively small number of samples. Further studies with larger sample sizes should be conducted to generalize the findings of this study. Second, we aligned the tumor ROI on the DCE-MRI to that on the ADC images, but the morphological feature values are not identical, hence generating different prediction performances. This limitation is because the ADC map has a relatively low resolution compared with that of DCE-MRI. Third, we collected samples with small tumor sizes (i.e., less than 10 mm) for a comprehensive analysis; however, the small size may affect the feature calculation procedure and hence the classification accuracy. Fourth, although we extracted radiomics on subtraction images that may reflect tumor vascularity and angiogenic information, more contrast enhancement features should be included to assess the patterns of kinetic curves, such as the maximum contrast enhancement, time to peak (s) and time at which the maximum enhancement occurs.

V. CONCLUSION

In this paper, we proposed a multitask learning framework for the prediction of breast tumor Ki-67 proliferation status and histological grade. We first analyzed MR series of S0, S20 and S50 and ADC images to evaluate their predictive power. An MTFS and prediction framework was then developed to classify the Ki-67 and tumor grade tasks simultaneously. Multitask learning was conducted using the MR series and DWI along with the proposed multitask framework. The experimental results of breast tumor Ki-67 expression level and grade classification demonstrate the effectiveness of our method. The results are promising for clinical use because patient management decisions are made by simultaneously

considering several different biomarkers. Our proposed model could be extended by including additional clinical indicators, such as molecular subtypes, as well as more parametric images, such as T2-weighted imaging, to perform multiple predictions.

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