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Prediction of Genetic Alterations in Oncogenic Signaling Pathways in Squamous Cell Carcinoma of the Head and Neck: Radiogenomic Analysis Based on Computed Tomography Images

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Objective: This study investigated the role of radiomics in evaluating the alterations of oncogenic signaling pathways in head and neck cancer.

Methods: Radiomics features were extracted from 106 enhanced computed tomography images with head and neck squamous cell carcinoma. Support vector machine–recursive feature elimination was used for feature selection. Support vector machine algorithm was used to develop radiomics scores to predict genetic alterations in oncogenic signaling pathways. The performance was evaluated by the area under the curve (AUC) of the receiver operating characteristic curve.

Results: The alterations of the Cell Cycle, HIPPO, NOTCH, PI3K, RTK, RAS, and TP53 signaling pathways were predicted by radiomics scores. The AUC values of the training cohort were 0.94, 0.91, 0.94, 0.93, 0.87, and 0.93, respectively. The AUC values of the validation cohort were all greater than 0.7.

Conclusions: Radiogenomics is a new method for noninvasive acquisition of tumor molecular information at the genetic level.

Key Words: head and neck squamous cell carcinoma, radiogenomics, computed tomography, oncogenic signaling pathways

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Cancer is a global disease that accounts for millions of new cases each year; different cancer types are attributed to certain genetic information alterations that result in uncontrolled cell proliferation.¹ The development of different types of cancer is a complex process that involves the accumulation of multiple independent genetic alterations that may lead to the dysregulation of the cell signaling pathways.² Cell cycle progression, apoptosis, and cell growth are the most common regulatory genetic alterations in the oncogenic signaling pathways.^{3–5} However, the dysregulation of these genetic alterations may lead to the occurrence and progression of cancers.^{6,7} A literature search conducted by the researchers found an increasing number of studies on oncogenic

signaling pathways since 1979, especially in the last 5 years. Some high-quality studies have demonstrated that these genetic alterations in the signaling pathways can function as potential biomarkers that are related to specific targeted therapy and prognosis of tumors.^{8,9} Pathway dysregulation can be associated with sensitivity to targeted therapeutic agents in the pathway, and these oncogenic pathway characteristics can be used in the formulation of opportunities for targeted therapeutic agent use.² However, the degree of alterations, mechanisms, and coexisting mutually exclusive mode of the signaling pathways vary among different tumors or tumor types. Therefore, the effective monitoring of genetic alterations in oncogenic signaling pathways is of great importance to identify potential targeted therapy options.

Head and neck squamous cell carcinoma (HNSC) is the most common pathologic type of head and neck cancer,¹⁰ affecting approximately 550,000 people worldwide each year and causing approximately 300,000 deaths.¹¹ Head and neck squamous cell carcinoma is classified by location: oral cavity, oropharynx, nasal and paranasal sinus, nasopharynx, and larynx or hypopharynx, with the lower pharynx having the worst prognosis. It is the accumulation and development of a variety of epigenetic variations,¹² including genetic alterations in the signaling pathways. Patients who have undergone surgery, radiation, chemotherapy, and targeted therapies have had varying responses. The genetic alterations in the pathway of HNSC are associated with the prognosis.¹³ The acquisition of information on oncogenic pathway alterations is mainly dependent on high-throughput DNA sequencing technology. However, the high cost and high technical requirements hinder its clinical promotion. In addition, these alterations are mainly obtained after tumor resection, which may cause some more appropriate treatment options to be missed. Although preoperative biopsy can be obtained through postoperative puncture biopsy, the results may not be satisfactory because of the lack of tumor puncture tissue and tumor heterogeneity.¹⁴ Therefore, the exploration of a preoperatively effective monitoring system for oncogenic pathway alterations may provide more evidence for the selection of individualized treatment regimens.

Radiomics is an emerging artificial intelligence technology that realizes numerical quantitative characteristics of information contained in images through computer assistance and deeply evaluates the potential pathological alterations of tumors by analyzing the features related to the research objects, thus providing an objective basis for clinical decision making.^{15,16} At present, radiomics performs well in HNSC diagnosis, therapeutic effect, and biological behavior change, among others.^{17–19} The above-mentioned studies and others have mainly analyzed the correlation between radiomics features and potential molecular features. However, for HNSC, the association between radiomics features and genetic variation should be further studied by comprehensively

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analyzing the radiomics features in an information path-centric rather than in a gene-centric manner.

The objective of this study was to explore the relationship between radiomics features based on computed tomography (CT) images and alterations in the most common oncogenic signaling pathways in patients with HNSC. Predictive radiomics scores for preoperative noninvasive assessment of signaling pathway alterations were developed to effectively stratify patients with HNSC for individualized precision therapy.

METHODS

Image Cohort

The CT imaging data of 211 HNSC tumors were obtained from The Cancer Imaging Archives.²⁰ The images were obtained from 7 medical units: Ontario Cancer Institute, University of Pittsburgh, University of North Carolina, MD Anderson Cancer Center, Vanderbilt University Medical Center, Johns Hopkins University, University of Miami, and Barretos Cancer Hospital, which further excluded the following images: (1) nonenhanced images, (2) images without the target part, (3) postoperative images, (4) images whose target lesions were affected by artifacts more than 50%, (4) controversial images of target lesions, and (5) images that were more than 3 mm thick. Finally, 113 cases were included for image analysis. In addition, from the previous analysis of the comprehensive oncogenic signaling pathway status of The Cancer Genome Atlas pan-cancer project, a binary change matrix of the oncogenic signaling pathway status was obtained. This matrix plotted the alterations spectrum of 10 common oncogenic signaling pathways across 33 cancer types.²¹ Genetic alterations included the definition of gene duplication, the location of repetitive mutations, known functional gene fusion/rearrangement, and epigenetic silencing. If one or more genetic information in the tumor sample was changed, it was considered that the tumor sample was considered to have changed in the specific oncogenic signaling pathway.²² In this study, a total of 106 patients with HNSC with both CT images and alterations in the oncogenic signaling pathways were included (Fig. 1). Six of the most common oncogenic signaling pathway

alterations were predicted and evaluated, namely, Cell Cycle, HIPPO, NOTCH, PI3K, RTK RAS, and TP53. Figures 2A and B summarized the alterations in the 6 oncogenic signaling pathways.

Image Preprocessing and Feature Extraction

In the ITK-SNAP software (Version 3.8.0),²³ 2 radiologists with 5 years of CT diagnosis experience delineated the region of interest of the HNSC layer by layer. All discrepancies were resolved by consensus, and the regions of interest were saved for subsequent analysis. Feature extraction was carried out using the Intelligence Foundry software (Version 1.3, GE Healthcare) by mainly extracting 1022 features and generating a data set: 122 original (first-order statistics, shape descriptors, texture classes, gray-level co-occurrence matrix, gray-level run length matrix, and gray-level size zone matrix), 468 co-occurrence of local anisotropic gradient orientations (CoLIAGe), and 432 wavelets + local binary pattern (WLBP), (Figs. 2C, D). The software was based on the Python environment to develop according to the algorithms provided by the Pyradiomics software package.²⁴ The features were defined according to the imaging biomarker standardization initiative.²⁵ Each data set of the oncogenic signaling pathways was randomly split into 2 cohorts, namely, training cohorts and validation cohorts, according to the alterations and nonalterations of the oncogenic signaling pathways in a ratio of 7:3. The training cohort was intended for the development of the radiomics scores, whereas the validation cohort was applied to verify the robustness and reliability of the radiomics scores. To improve the comparability of data between images, the min-max normalization method was applied to normalize the 2 cohorts.²⁶ The formula was $X = (X - X_{min}) / (X_{max} - X_{min})$.

Support Vector Machine Radiomics Scores Development

To avoid overfitting and redundancy problems, the Spearman correlation coefficient was used to remove the high correlation features of the training cohort with a threshold of 0.75. Afterward, the remaining radiomics features were further submitted to the support vector machine-recursive feature elimination (SVM-RFE) for analysis, and the features for the development

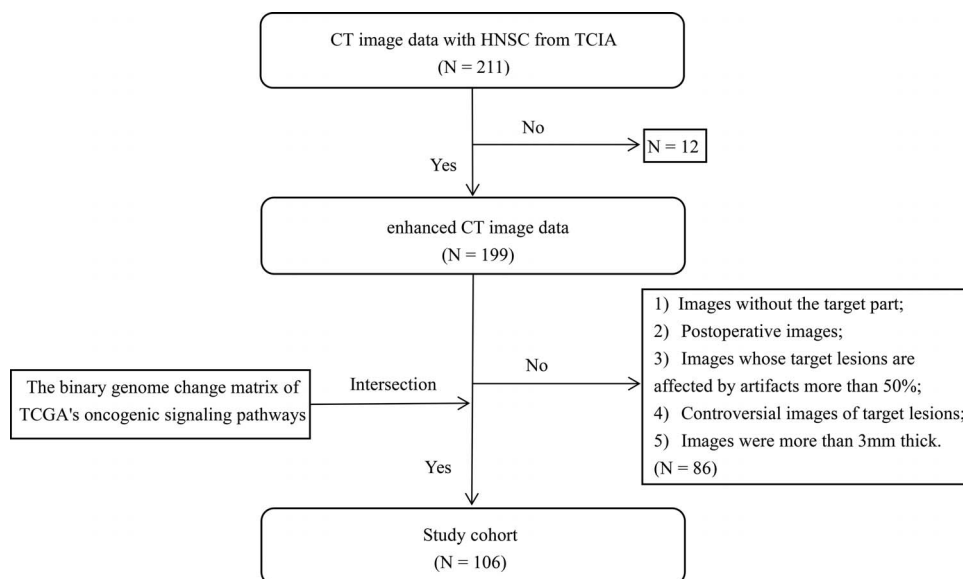


FIGURE 1. Flowchart of image cohort.

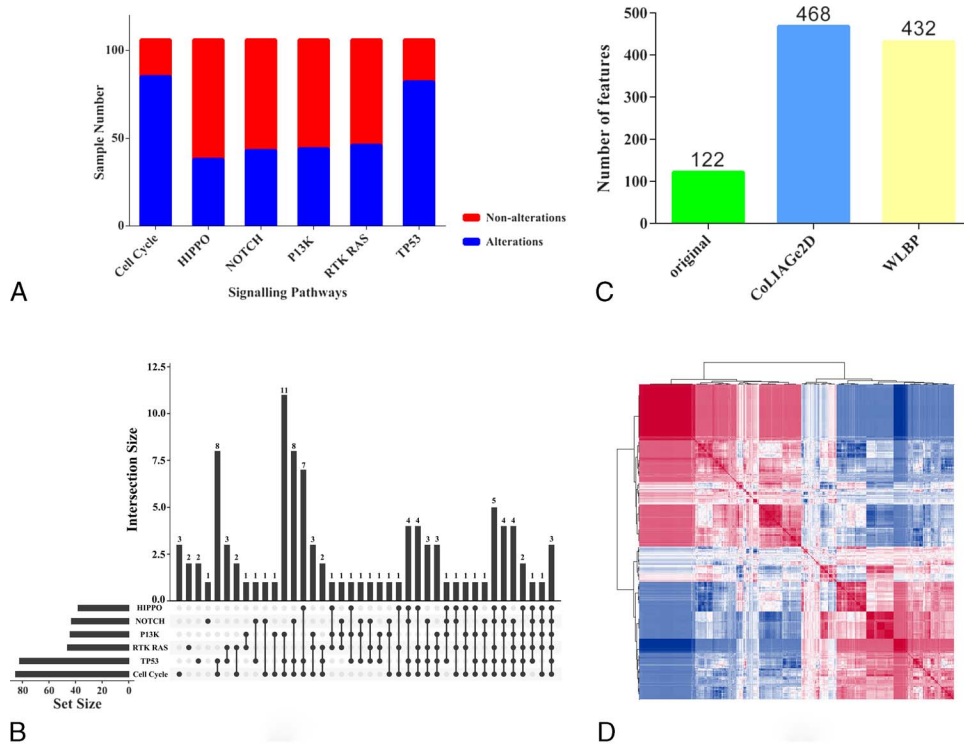


FIGURE 2. Alteration information of the oncogenic signaling pathways and radiomics features in HNSC. A, Histogram analysis of the status of 6 oncogenic signaling pathways. B, Up-set plot of the coexpression of oncogenic signaling pathways in 106 samples. C, Classification of 1022 radiomics features. D, Correlation clustering heatmap of 1022 features (Spearman test). Figure 2 can be viewed online in color at www.jcat.org.

of the radiomics scores were selected.^{27,28} Finally, the SVM classifier developed the radiomics scores based on the above selected features to distinguish the altered state of the oncogenic signaling pathways.^{29,30} To address the problem of small sample size, 5-fold cross validation was used to screen for the best performance of the radiomics scores. The radiomics score for each patient was calculated. An independent validation cohort developed radiomics scores through the SVM classifier with the same features to verify the applicability and reliability of the predicted scores. There were synergistic and mutually exclusive modes of action between the oncogenic signaling pathways.³¹ Therefore, the correlations between the radiomics scores of each oncogenic signaling pathways were analyzed. To evaluate the performance of the radiomics scores in classifying the alterations of the oncogenic signaling pathways, the receiver operating characteristic curve (ROC), area under the curve (AUC), and accuracy were applied. Figure 3 summarized the radiogenomics analysis development processes.

Statistical Analysis

SPSS23.0 and R language were used for statistical analysis. The age and radiomics scores were expressed as median [interquartile range (IQR)]. Sex, histologic type, alcohol history, pathological grading, stage, Cell Cycle, HIPPO, NOTCH, PI3K, RTK RAS, and TP53 were expressed as cases (percentage). Mann-Whitney *U* test was used to compare the differences in the radiomics scores of the training cohort or validation cohort between alterations and nonalterations in the oncogenic signaling pathways. Chi-square test was used to evaluate the difference between alterations and nonalterations in the oncogenic signaling pathways at different clinical stages. The Pearson correlation coefficient was used to analyze the relationship between the radiomics scores of each

carcinogenic signaling pathway. *P* < 0.05 for the difference was statistically significant.

RESULT

Baseline Data and Oncogenic Pathway Alterations of Patients

This study included 106 patients with HNSC, aged 24 to 87 years; the mean age was 60 (53–68) years; there were 79 males (74.53%); and 73 patients had alcohol history (68.87%). In terms of pathological types, there were 8 mouth floor cancers, 38 laryngeal cancers, 17 oral cavity cancers, 26 oral tongue cancers, 8 tonsil cancers, and 9 other types of cancers. In terms of pathological grading, there were 12 cases of G1, 64 cases of G2, 29 cases of G3, and 1 unknown case. In terms of clinical stages, 5 cases were stage I, 16 cases stage II, 23 cases stage III, and 62 cases stage IV.

The alterations of the 6 oncogenic signaling pathways in the image cohort were as follows: 85 Cell Cycle alteration patients (80.19%) and 21 Cell Cycle nonalteration patients (19.81%); 38 HIPPO alteration patients (35.85%) and 68 HIPPO nonalteration patients (64.15%); 43 NOTCH alteration patients (40.57%) and 63 NOTCH nonalteration patients (59.43%); 44 PI3K alteration patients (41.51%) and 62 PI3K nonalteration patients (58.49%); 46 RTK RAS alteration patients (43.40%) and 60 RTK RAS nonalteration patients (56.60%); and 82 TP53 alteration patients (77.36%) and 24 TP53 nonalteration patients (22.64%). The detailed baseline information is summarized in Table 1. Because of the different stages of tumor progression, the relationships between alterations in the oncogenic signaling pathways and clinical stages are shown in Table 2. Except for the training cohort, the

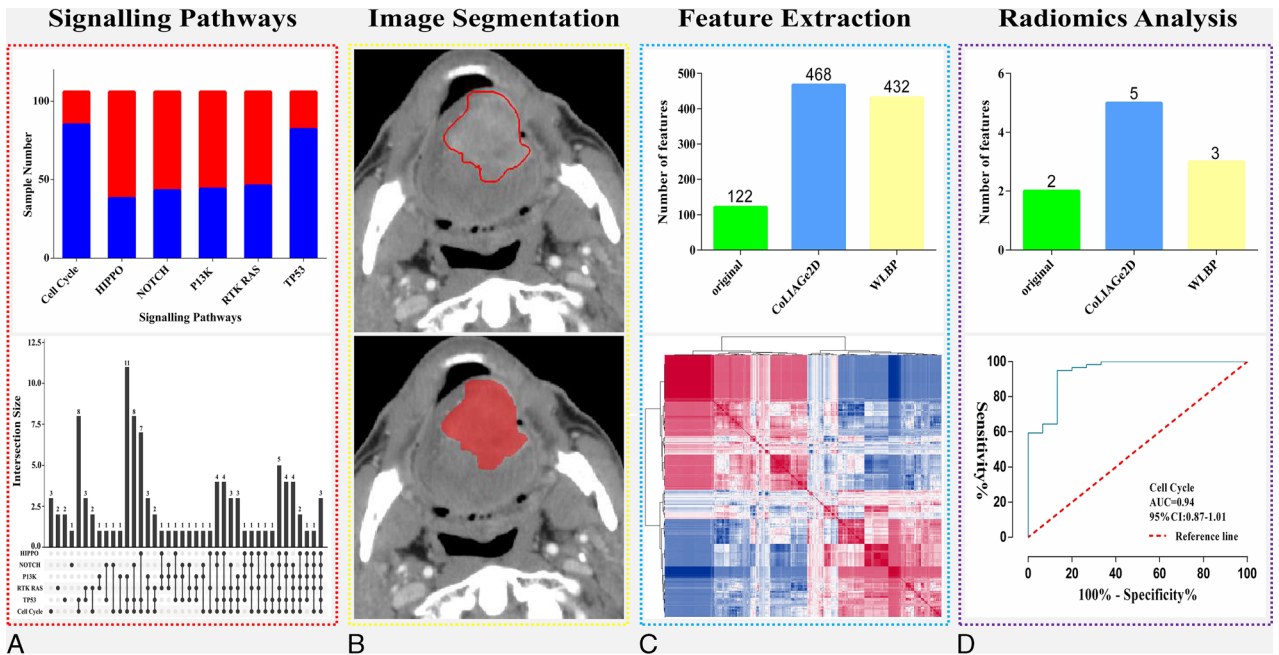


FIGURE 3. Flowchart of radiogenomics analysis. Figure 3 can be viewed online in color at www.jcat.org.

TABLE 1. Baseline Data and Oncogenic Pathway Alterations of Patients

Characteristics	Total (N = 106), n (%)	Characteristics	Total (N = 106), n (%)
Median age (IQR), y	60 (53–68)	Cell Cycle	
Sex		Alterations	85 (80.19)
Male	79 (74.53)	Nonalterations	21 (19.81)
Female	27 (25.47)	HIPPO	
Histologic type		Alterations	38 (35.85)
Mouth floor	8 (7.55)	Nonalterations	68 (64.15)
Larynx	38 (35.85)	NOTCH	
Oral cavity	17 (16.04)	Alterations	43 (40.57)
Oral tongue	26 (24.53)	Nonalterations	63 (59.43)
Tonsil	8 (7.55)	P13K	
Other	9 (8.49)	Alterations	44 (41.51)
Alcohol history		Nonalterations	62 (58.49)
Yes	73 (68.87)	RTK RAS	
No	33 (31.13)	Alterations	46 (43.40)
Pathological grading		Nonalterations	60 (56.60)
G1	12 (11.32)	TP53	
G2	64 (60.38)	Alterations	82 (77.36)
G3	29 (27.36)	Nonalterations	24 (22.64)
GX	1 (0.94)		
Stage			
I	5 (4.72)		
II	16 (15.09)		
III	23 (21.70)		
IV	64 (60.38)		

TABLE 2. Relationship Between Alterations in the Oncogenic Signaling Pathways and Clinical Stages

Pathways		Training Cohort			Validation Cohort		
		Stage I/II	Stage III/IV	P	Stage I/II	Stage III/IV	P
Cell Cycle	Alterations	14	45	1.00	2	24	1.00
	Nonalterations	4	11		1	5	
HIPPO	Alterations	3	24	0.14	1	10	0.59
	Nonalterations	12	35		5	16	
NOTCH	Alterations	9	21	0.35	1	12	1.00
	Nonalterations	9	35		2	17	
P13K	Alterations	1	30	0.01	4	9	0.84
	Nonalterations	12	31		4	15	
RTK RAS	Alterations	5	27	0.19	2	12	1.00
	Nonalterations	12	30		2	16	
TP53	Alterations	11	46	1.00	6	19	0.97
	Nonalterations	3	14		1	6	

alterations of the P13K pathway varied in different stages, and there were no differences in other pathways in different stages.

Support Vector Machine Radiomics Scores: Predicting Alterations in Oncogenic Signaling Pathway States

Based on the SVM-RFE, to decrease the redundancy feature set and formulate the best child set to predict the pathway alterations, among the 1022 radiomics features of the training cohort, the top 26, 24, 21, 61, 15, and 12 features for developing the radiomics scores were finally chosen for the Cell Cycle, HIPPO, NOTCH, P13K, RTK RAS, and TP53 pathways, respectively. Figure 4 summarizes the specific conditions of the features. Two original, 5 CoLIAGe, and 3 WLBP features were found to play a role in the development of radiomics scores with more than 2 oncogenic signaling pathways.

Table 3 shows the distribution of the radiomics scores in the training and validation cohorts. Surprisingly, there were significantly different radiomics scores across all training cohorts ($P < 0.0001$). Unfortunately, in the validation cohort, there were no differences in the radiomics scores of Cell Cycle and TP53. The performance

of the radiomics scores in predicting the status of the oncogenic signaling pathways is summarized in Figures 5 and 6. The AUC values of the training cohort of Cell Cycle, HIPPO, NOTCH, P13K, RTK RAS, and TP53 were 0.94 [95% confidence interval (CI), 0.87–1.01], 0.91 (95% CI, 0.84–0.98), 0.94 (95% CI, 0.87–1.00), 0.93 (95% CI, 0.86–0.99), 0.87 (95% CI, 0.79–0.95), and 0.93 (95% CI, 0.85–1.02), respectively, whereas the accuracy was 0.93, 0.88, 0.95, 0.89, 0.77, and 0.95, respectively. The AUC values of the validation cohort were 0.74 (95% CI, 0.54–0.95), 0.77 (95% CI, 0.61–0.93), 0.81 (95% CI, 0.63–0.98), 0.76 (95% CI, 0.57–0.95), 0.71 (95% CI, 0.51–0.92), and 0.72 (95% CI, 0.49–0.95), respectively, whereas the accuracy was 0.75, 0.72, 0.75, 0.69, 0.69, and 0.81, respectively. Through the analysis of the correlation between the radiomics scores of the 6 oncogenic signaling pathways, it was found that the Cell Cycle and RTK RAS ($r = -0.20$, $P = 0.04$) and the NOTCH and TP53 ($r = 0.26$, $P < 0.01$) pathways had significant correlation (Fig. 7).

DISCUSSION

In this study, the relationship between the HNSC radiomics features and the alterations in the oncogenic pathway states was

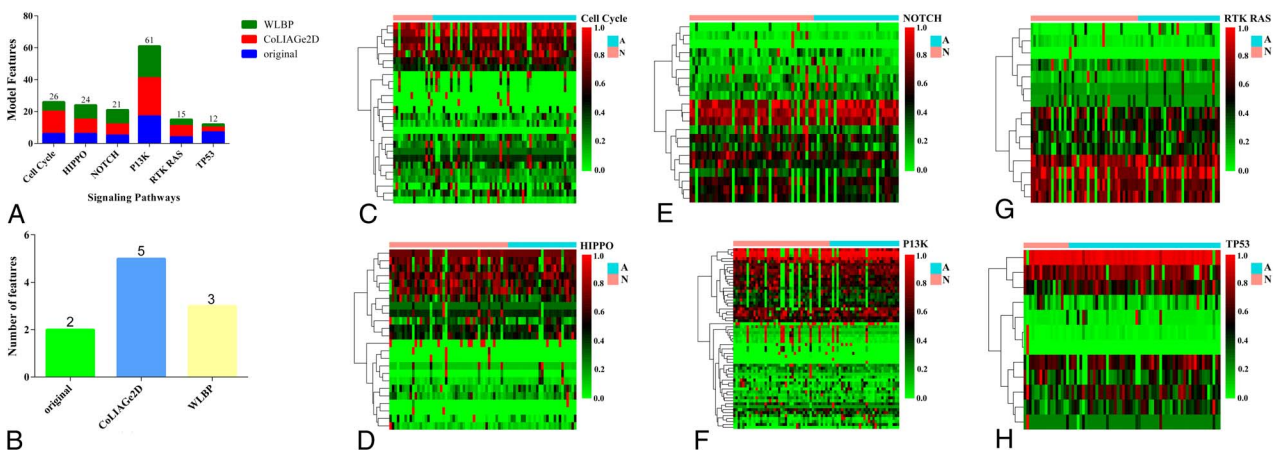


FIGURE 4. Features in developing the radiomics scores. A, Classification features in the development of radiomics scores. B, Two original, 5 CoLIAGe, and 3 WLBP features played a role in developing the radiomics scores with more than 2 oncogenic signaling pathways. C–H, Heatmaps for developing the features: Cell Cycle (C), HIPPO (D), NOTCH (E), P13K (F), RTK RAS (G), and TP53 (H). The ruler on the right of the heatmaps represents the range of normalized feature expression values [0, 1]. Status of oncogenic signaling pathways: the alterations are represented by “A,” and nonalterations are represented by “N.” Figure 4 can be viewed online in color at www.jcat.org.

TABLE 3. Radiomics Scores for the Training Cohort and the Validation Cohort

Pathways	Training Cohort			Validation Cohort		
	Nonalterations	Alterations	P	Nonalterations	Alterations	P
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
Cell Cycle	-1.00 (-1.00 to 0.48)	1.84 (1.00 to 3.10)	<0.0001	0.88 (-7.83 to 2.10)	2.03 (1.24 to 2.03)	0.07
HIPPO	-1.00 (-1.20 to -0.82)	0.40 (-0.33 to 1.00)	<0.0001	-0.88 (-1.31 to -0.52)	-0.31 (-0.74 to 0.27)	0.01
NOTCH	-1.18 (-2.15 to -1.00)	1.00 (0.96 to 1.57)	<0.0001	-0.75 (-2.40 to 0.01)	1.59 (0.24 to 1.94)	0.00
PI3K	-1.00 (-1.33 to -0.88)	0.86 (0.38 to 1.00)	<0.0001	-0.48 (-1.07 to 0.13)	0.35 (-0.70 to 0.87)	0.01
RTK RAS	-0.93 (-1.07 to -0.40)	0.16 (-0.42 to 0.79)	<0.0001	-0.82 (-1.22 to -0.41)	-0.20 (-0.69 to -0.03)	0.04
TP53	-0.10 (-2.42 to 0.34)	2.54 (1.30 to 4.97)	<0.0001	0.80 (-1.16 to 2.53)	2.32 (1.37 to 3.08)	0.08

systematically analyzed, which could be used as a noninvasive preoperative evaluation method. In addition, the radiomics scores developed were verified by an independent validation cohort, which showed moderate evaluation performance. This study constitutes an exploratory study of radiogenomics in predicting the molecular level of HNSC.

Carcinogenic signaling pathways are widespread in cells. They are important for cell division, growth, and apoptosis. Sanchez-Vega et al²¹ used TCGA data to analyze the mechanisms and patterns of somatic alterations in 10 typical pathways in 9125 tumors, moving away from the traditional use of the gene-centric approach and opting for the pathway-centric technique. The above study results further explored the relationship between the status of oncogenic signaling pathways and the radiomics features in this study. To the authors' knowledge, this study was the first comprehensive analysis of the association between the radiomics features and the oncogenic pathway phenotypes of HNSC. The radiomics scores were used to evaluate the 6 oncogenic signaling pathways of HNSC that changed most frequently: Cell Cycle, HIPPO,

NOTCH, PI3K, RTK RAS, and TP53. The disorders in these pathways have been confirmed to be closely related to the occurrence and development of cancers. For example, Poma et al³² suggested that the HIPPO pathway affects the overall survival of head and neck cancers and could be a candidate for the development and testing of YAP1 inhibitors. Meanwhile, Grilli et al³³ found that the activation of the NOTCH pathway was more related to the prognosis of patients with HNSC, revealing that the NOTCH pathway in HNSC had an inhibitory effect rather than a carcinogenic effect. Marquard et al³⁴ demonstrated that the PI3K signaling pathway was significantly upregulated in HNSC to enhance radiotherapy resistance and cytostatic resistance. Therefore, this study was mainly based on the radiomics features of CT images to unveil the imaging markers related to the genetic information of HNSC.

Radiomics is a computer-aided technology that quantifies the features of medical images, further builds predictive models that are related to research purposes based on machine learning algorithms, and provides information for clinical decision

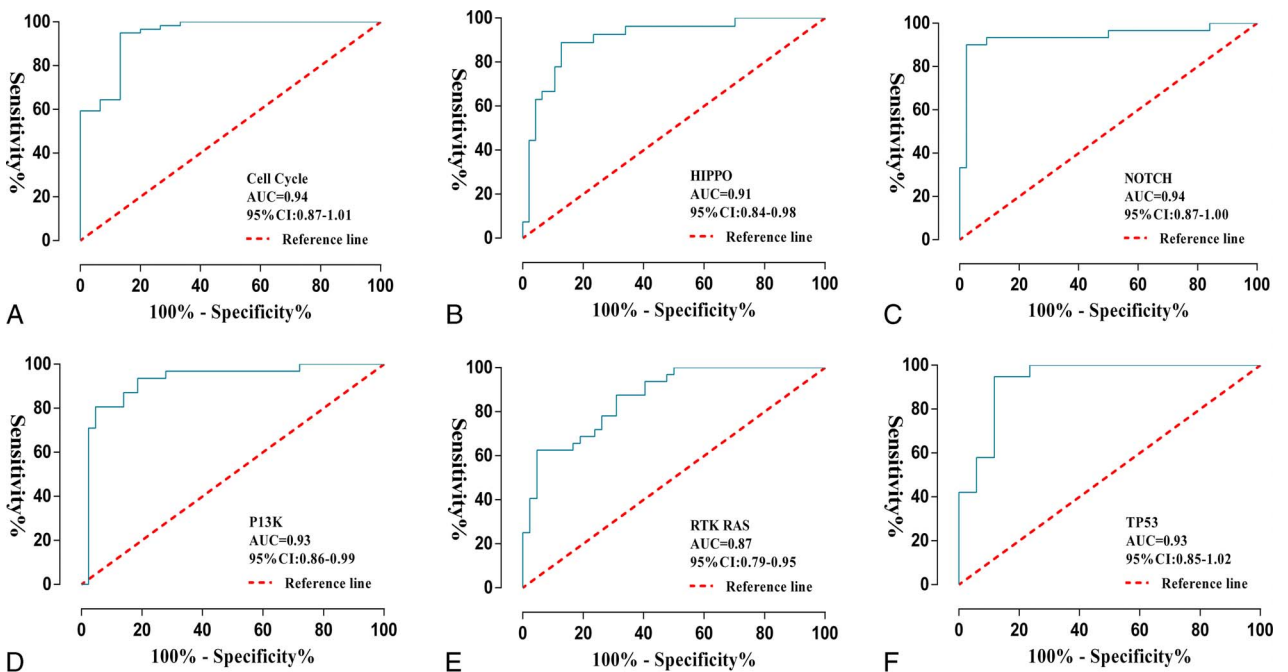


FIGURE 5. Prediction performance of SVM radiomics scores in the training cohort. The ROC showed that the 6 radiomics scores had moderate potential for predicting alterations in the Cell Cycle (A), HIPPO (B), NOTCH (C), PI3K (D), RTK RAS (E), and TP53 (F) signaling pathways. Figure 5 can be viewed online in color at www.jcat.org.

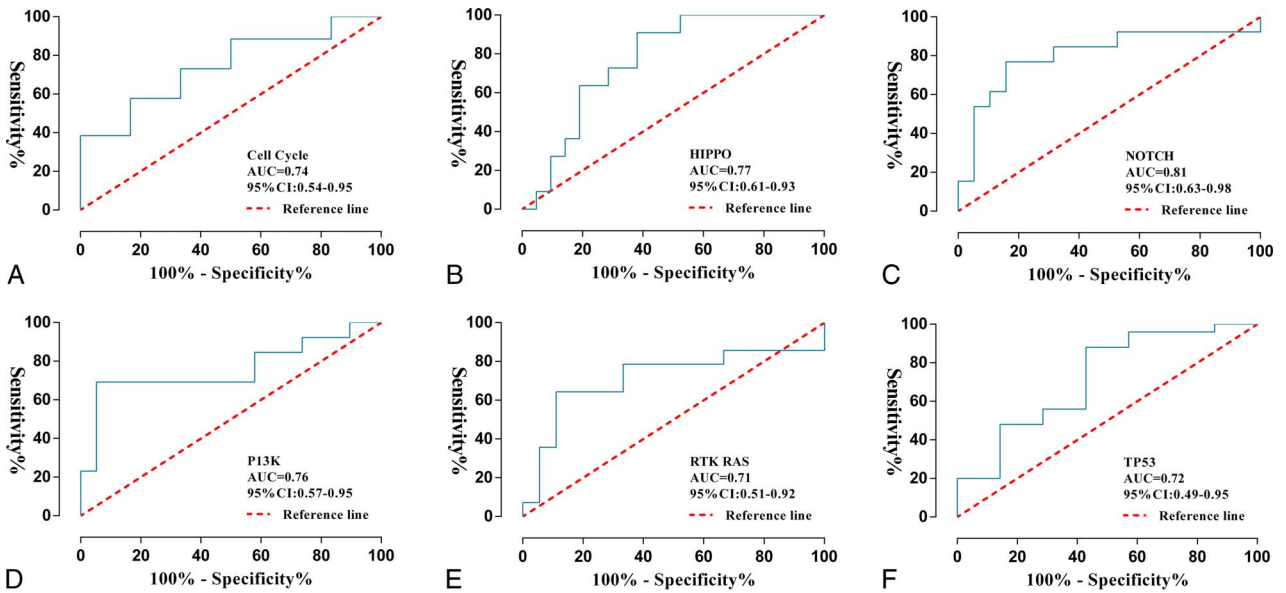


FIGURE 6. Prediction performance of SVM radiomics scores in the validation cohort. The ROC showed that the SVM scores had good stability and reliability, as verified by the independent validation cohort. Cell Cycle (A), HIPPO (B), NOTCH (C), PI3K (D), RTK RAS (E), and TP53 (F). Figure 6 can be viewed online in color at www.jcat.org.

making.^{35,36} Radiomics technology has been applied in HNSC diagnosis, efficacy judgment, and molecular-level correlation; it can also be used as a noninvasive method to predict the potential molecular phenotypes of tumors. For example, Katsoulakis et al²⁰ analyzed imaging markers that identified the tumor human papillomavirus status and biological characteristics of T cell infiltration, contributing to patient risk stratification. Based on the radiomics features of CT images, Bagher-Ebadian et al³⁷ identified the features and carried out characterization and prediction of human papillomavirus status, with the differentiated AUC value reaching 0.878. These previous studies suggested that radiogenomics could identify reliable radiobiomarkers with distinct molecular properties that could be used to predict patient prognosis and, thus, identify patients who are sensitive to targeted drugs.

In this study, there were 6 radiomics scores developed to predict signaling pathway alterations based on 1022 imaging markers of CT images. The discriminant performance of these scores suggested a broad prospect for the preoperative noninvasive search

for effective molecular pathways for radiotherapy drugs. The radiomics features can not only quantify the visual image features but also quantify the features that are at a subtle level that cannot be detected by the naked eye, thus revealing the heterogeneity of the tumor. In this study, the SVM-RFE feature selection algorithm was used. Support vector machine-RFE is a widely used dimension-reduction method for ranking independent variables that are related to research. Support vector machine-RFE was used to perform feature selection to develop the radiomics scores. Unfortunately, the selected features failed to reach single digits. The method of feature selection is not confined to SVM-RFE only, as we can also explore other methods, such as random forest. The SVM machine learning algorithm is a powerful classifier whose purpose is to create a decision boundary between 2 categories that can predict labels based on one or more feature vectors. The training cohort all showed high predictive performance, whereas the validation cohort had AUC values of more than 0.7 in small case of sample size. The NOTCH validation cohort even

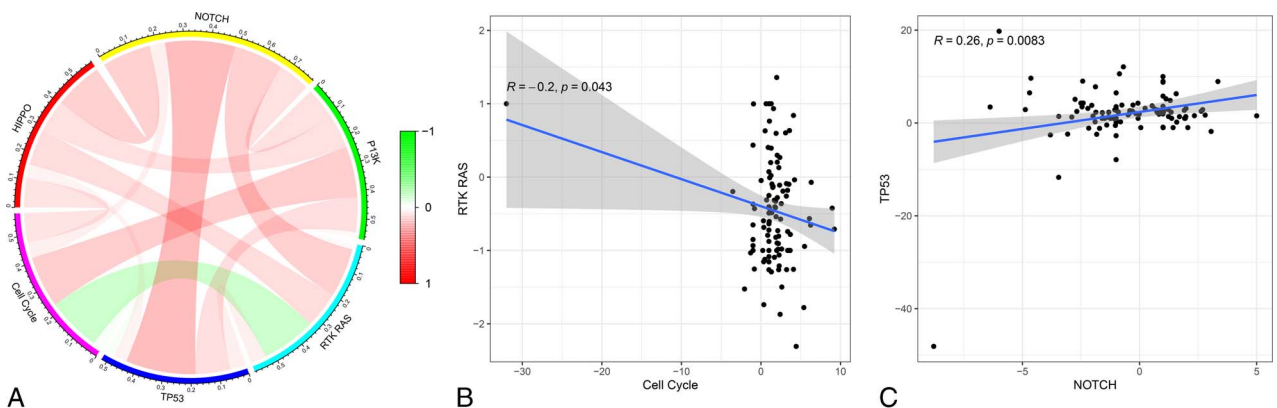


FIGURE 7. Correlation between the radiomics scores of the oncogenic signaling pathways. A, Correlation analysis of the radiomics scores of 6 oncogenic signaling pathways. Only the Cell Cycle and RTK RAS ($r = -0.20$, $P = 0.04$) (B) and the NOTCH and TP53 ($r = 0.26$, $P < 0.01$) (C) pathways had a significant correlation. Figure 7 can be viewed online in color at www.jcat.org.

reached 0.81. We think these results were acceptable. Concurrently, the correlation analysis found a correlation between the Cell Cycle and RTK RAS and between the NOTCH and TP53 pathways, suggesting existence of a mutual cooperation between the oncogenic signaling pathways. The results also provided an explanation for the combined targeted therapy. The evaluation of signaling pathways in cancer genetic alterations and the use of imaging markers and correlation studies to determine the changes in the oncogenic signaling pathways may comprise a new and efficacious method for the further exploration of targeted therapy.

The limitations of this study were as follows. First, this was a retrospective study, and the image cohort was limited. The sample size of the validation cohort was small, so it needs to be prospectively explored in a multicenter research. However, there are currently no conditions for further verification. Second, the manual mapping of lesions was subjective and could be further developed by a fully automatic algorithm. Finally, the significance of the radiomics scores in the performance evaluation of targeted therapy could be further explored.

In summary, this study revealed the correlation between the alterations in the HNSC signaling pathways and the radiomics features. In addition, the radiomics scores developed in this study demonstrated higher-than-moderate performance in predicting pathway alterations, which can constitute a new method for the noninvasive acquisition of tumor molecular information at the genetic level. Future studies are warranted to determine the efficacy of radiogenomics in predicting cancer treatment by acting on the oncogenic signaling pathways.

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