Prediction of the Ki-67 marker index in hepatocellular carcinoma based on CT radiomics features

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Abstract
The noninvasive detection of tumor proliferation is of great value and the Ki-67 is a biomarker of tumor proliferation. We hypothesized that radiomics characteristics may be related to tumor proliferation. To evaluate whether computed tomography (CT) radiomics feature analyses could aid in assessing the Ki-67 marker index in hepatocellular carcinoma (HCC), we retrospectively analyzed preoperative CT findings of 74 patients with HCC. The texture feature calculations were computed from MaZda 4.6 software, and the sequential forward selection algorithm was used as the selection method. The correlation between radiomics features and the Ki-67 marker index, as well as the difference between low Ki-67 (<10%) and high Ki-67 (≥10%) groups were evaluated. A simple logistic regression model was used to evaluate the associations between texture features and high Ki-67, and receiver operating characteristic analysis was performed on important parameters to assess the ability of radiomics characteristics to distinguish the high Ki-67 group from the low Ki-67 group. Contrast, correlation, and inverse difference moment (IDM) were significantly different (P < 0.001) between the low and high Ki-67 groups. Contrast (odds ratio [OR] = 0.957; 95% confidence interval [CI]: 0.926-0.990, P = 0.01) and correlation (OR = 2.5∗10⁵; 95% CI: 7.560-8.9∗10⁹; P = 0.019) were considered independent risk factors for combined model building with logistic regression. Angular second moment (r = −0.285, P = 0.014), contrast (r = −0.449, P < 0.001), correlation (r = 0.552, P < 0.001), IDM (r = 0.458, P < 0.001), and entropy (r = 0.285, P = 0.014) strongly correlated with the Ki-67 scores. Contrast, correlation, and the combined predictor were predictive of Ki-67 status (P < 0.001), with areas under the curve ranging from 0.777 to 0.836. The radiomics characteristics of CT have potential as biomarkers for predicting Ki-67 status in patients with HCC. These findings suggest that the radiomics features of CT might be used as a noninvasive measure of cellular proliferation in HCC.

Abbreviations
HCC  hepatocellular carcinomas
IHC  immunohistochemistry
CT  computed tomography
EAP  early arterial phase
LAP  late arterial phase
PVP  portal venous phase
EP  equilibrium phase

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1. Investigate whether CT radiomics features analyses could aid in assessing Ki-67 marker index of hepatocellular carcinoma (HCC).

2. ASM, contrast, correlation, IDM, and entropy showed strong correlations with the Ki-67 scores. Contrast and correlation were considered independent risk factors for combined model building with logistic regression.

3. The radiomics characteristics of CT have potential as biomarkers for predicting Ki-67 status in patients with HCC.

1. Introduction

Hepatocellular carcinoma (HCC) has become the second most common cancer in the world and the sixth most common cause of cancer-related death (Zhang et al. 2019), causing a considerable global health burden (Ke et al. 2019). At present, pathological methods are often used to determine the state of tumor proliferation. However, pathological evaluation is limited to small nodules at the time of diagnosis, and these lesions are limited to patients with good liver function. Biopsies, an invasive and unpleasant procedure, are unnecessary for these patients. Hence, the noninvasive detection of tumor proliferation is of great value (Huang et al. 2015).

Ki-67 protein in the nucleus is associated with cell proliferation, which may indicate the aggressiveness of tumors and is expressed at all stages of the cell cycle except G0, with the highest expression levels in the G2/M phase (Gerdes et al. 1984). Paraffin-embedded section immunohistochemistry (IHC) is used to obtain the Ki-67 marker index, and the positive rate could be used as an indicator for the prognosis of patients. High Ki-67 expression is significantly associated with advanced HCC, including characteristics such as poor differentiation, large tumor size, multiple tumor nodules, metastasis, cirrhosis, and venous invasion, suggesting that Ki-67 may be an adverse prognostic factor for HCC patients (Perou et al. 1999, Luo et al. 2015).

Tumor proliferation leads to changes in tissue structures (Huang et al. 2015). Imaging can reflect the heterogeneity of the tumor’s internal structure and provide longitudinal information about disease status, such as disease evolution and treatment response (Tu et al. 2019). However, the identification of these computed tomography (CT) morphological features depends on the radiologist’s experience. Due to the strong subjectivity and the difference between the diagnostic doctors in reading the slices, the consistency of CT morphological feature analysis is not high enough (Tu et al. 2019). Radiomics has been used to predict diagnosis, survival, distant metastasis, and genetic mutations (Choi et al. 2018, Jiang et al. 2018, 2019, Lin et al. 2019, Tu et al. 2019, Wang et al. 2019, Yang et al. 2019, Zhang et al. 2019). Several studies have attempted to assess the relationship between texture characteristics and genetics or proteins (Aerts et al. 2014, Wan et al. 2016), and additional studies have analyzed the relationship between texture and histology (Khalvati et al. 2015). There have been several studies about the relations between Ki-67 and images or radiomics (Huang et al. 2015, Luo et al. 2015, Hu et al. 2017, Juan et al. 2018, Zhang et al. 2020). A nomogram composed of radiological features was established, and tumor size had the greatest accuracy in predicting the expression of Ki-67 in gastrointestinal stromal tumors (Zhang et al. 2020). Intratumoral subregions identified breast tumor subregions associated with an early time to peak, in which dynamic contrast-enhanced magnetic resonance imaging features were used as predictors of Ki-67 features in breast cancer (Fan et al. 2018). Apparent diffusion coefficient values on diffusion-weighted imaging may be used to measure cell proliferation in HCC (Huang et al. 2015, Meng et al. 2016), and the histogram parameters of the apparent diffusion coefficient and arterial phase were potentially helpful for predicting Ki-67 (Hu et al. 2017). Arterial heterogeneous enhancement was associated with high Ki-67 expression (Li et al. 2019); hence, it is possible to use noninvasive imaging to reflect the expression level of Ki-67.

Key points

1. Investigate whether CT radiomics features analyses could aid in assessing Ki-67 marker index of hepatocellular carcinoma (HCC).
2. ASM, contrast, correlation, IDM, and entropy showed strong correlations with the Ki-67 scores. Contrast and correlation were considered independent risk factors for combined model building with logistic regression.
3. The radiomics characteristics of CT have potential as biomarkers for predicting Ki-67 status in patients with HCC.
Table 1. Statistically significant clinical characteristics of patients with hepatocellular carcinoma (P < 0.050).

| Characteristics | Low Ki-67 (n = 20) | High Ki-67 (n = 54) | P   |
|-----------------|--------------------|--------------------|-----|
| Sex             | F                  | 5                  | 9   | 0.416 |
|                 | M                  | 15                 | 45  |       |
| Age (y)         | Average            | 59.15              | 58.07 | 0.865 |
|                 | Min                | 38                 | 26   |       |
|                 | Max                | 81                 | 82   |       |
| Child-pugh*     | A                  | 9                  | 18   | 0.617 |
|                 | B                  | 8                  | 28   |       |
|                 | C                  | 3                  | 8    |       |
| Size (cm)       | Average            | 6.38               | 6.1  | 0.855 |
|                 | Min                | 1.7                | 1.2  |       |
|                 | Max                | 16.3               | 15.1 |       |
| Pathogenesis    | Alcohol            | 1                  | 8    | 0.758 |
|                 | HBV                | 18                 | 44   |       |
|                 | HCV                | 1                  | 1    |       |
|                 | PBC                | 0                  | 1    |       |
| AFP (ng ml\(^{-1}\)) | 798.20** | 58.84** | 0.451 |
| STB (umol l\(^{-1}\)) | 63.09 ± 20.92 | 40.07 ± 24.14 | <0.001 |
| CT# (Slices)    | 16                 | 4                  | 2    | 0.073 |
|                 | 64                 | 5                  | 15   |       |
|                 | 320                | 11                 | 37   |       |

Statistically significant (P < 0.050)

*Liver function
PBC = Primary biliary cirrhosis
STB = Serum total bilirubin
#CT scanner
**median

In our study, we hypothesized that radiomics characteristics may be related to tumor proliferation and that Ki-67 is a biomarker of tumor proliferation. Therefore, the purpose of this study was to analyze the relationship between radiomics characteristics and Ki-67 molecular markers.

2. Materials and methods

2.1. Clinical data

This retrospective study was approved by the institutional review board of the hospital and was conducted based on the principles of the Helsinki Declaration. The institutional review board waived the requirement for obtaining written informed consent from the participants.

HCC was diagnosed according to the World Health Organization (WHO) criteria of microscopic morphological assessments after surgical resection. A total of 98 patients with primary HCC who had undergone initial CT imaging between October 2009 and December 2019 were selected from the radiology report database. In this study, the inclusion criteria were as follows: (a) confirmation by pathology; (b) complete pathological data, including Ki-67; and (c) complete CT images. The exclusion criteria were as follows: (1) recurrent or metastatic tumors; (2) liver transplantation; (3) incomplete CT images or poor quality; and (4) lack of Ki-67 data. A review of clinical data from medical records found that no patients in this cohort received neoadjuvant therapy; 74 patients with HCC were enrolled in this study, as shown in Table 1.

2.2. CT protocols

CT examination was performed using a 16-(Aquilion 16, Toshiba Medical Systems Corporation; Tochigi ken, Japan), 64-(Brilliance 64, Philips, Netherlands) or 320-slice helical CT scanner (Aquilion ONETSX-301A, Toshiba Medical Systems Corporation; Tochigi ken, Japan). The technical parameters were as follows: tube voltage: 120 kVp; tube current: 200 mAs; beam collimation: 64 × 0.6 mm; pitch: 0.9; and rotation time: 0.5 s. The thickness of the reconstructed section was 5 or 7 mm for the picture archiving and communication system system, and 1 mm-thick images were saved for lesion segmentation. A non-ionic iodized contrast agent (iodipamide, 370 mg I ml\(^{-1}\) Bracco) was injected into a double-headed syringe at a rate of 3.5–4.0 ml s\(^{-1}\) and then rinsed with 20 ml of normal saline at a dose of 2.0 ml kg\(^{-1}\) of body weight. Images of the early arterial phase (EAP) (20–22 s), late arterial phase (LAP) (34–37 s), portal venous phase (PVP) (60 s) and equilibrium phase (EP) (300 s) were obtained.
2.3. Lesion segmentation and radiomics analysis

MaZda 4.6 software was used to calculate the texture features (Szczybinski et al. 2009) (URL: www.eletel.p.lodz.pl/programy/mazda/). This software was developed within the European Cooperation In The Field Of Scientific And Technical Research project B11 and has been used in several research areas for all texture calculations (Jiang et al. 2019). Lesions were evaluated on 1 mm thick images using the irregular shape of the region of interest (ROI). The size range of tumor ROIs was 11 mm$^2$–68 mm$^2$. Consistent quantitative measurements were performed by two abdominal radiologists with 12 and 8 years of experience. The primary radiologist selected the largest section of the lesion, manually drawing the ROI diagram (figure 1), and then the experienced senior radiologist confirmed the ROI setting, taking the lead when the two radiologists disagreed. We minimized the effects of contrast and brightness changes; otherwise, the true texture of the image would be blurred. To reduce the impact of contrast and brightness changes, we normalized the image gray intensity to $m - 3d$ and $m + 3d$ ($m$, mean gray value; $d$, mean standard deviation) (He et al. 2019).

Texture is a repeated pattern of the local variation in image intensity that is characterized by the spatial distribution of the intensity levels in adjacent regions. Texture features are derived from the gray-level histogram and the gray-level co-occurrence matrix (GLCM) (Chang et al., 2017, Ryu et al. 2014). The sequential forward selection algorithm was used as the selection method for logistic regression feature parameters. The purpose of feature selection is to find the optimal feature subset, eliminate irrelevant or redundant features, reduce the number of features, and improve the model accuracy. Suppose that given a feature set $F = (f_1, f_2, \ldots, f_n)$, the target function of the model is $J(\cdot)$, the subset $S$ is screened from the feature set $F$ by feature selection, and there is $J(S) > J(T)$ for any subset $T$. In the sequence forward selection algorithm, the feature subset $X$ starts from the empty set, and the first feature that makes the target function $J$ optimal is first found from all features through five-fold cross-validation. Thereafter, only one feature $x$ from the unselected feature set is selected each time to add to the feature subset $X$ to make $J$ optimal. This process is repeated until $J$ reaches the optimal result. Thirteen texture features with the highest discriminating ability were identified as follows: average brightness, variance, skewness, kurtosis, percentile (50% was selected), angular second moment (ASM), correlation, contrast, sum of squares (SumOfSqs), sum of variance, inverse difference moment (IDM), sum average, and entropy. After CT image preprocessing and intensity rescaling (0–255), 13 texture features were calculated from the PVP of all the patients.

2.4. Immunohistochemical staining and analysis

Histological evaluation was performed in all HCC patients after partial hepatectomy. After surgery, the specimens were fixed in a 10% formaldehyde solution and embedded in paraffin. Four-micron-thick serial sections were cut from the paraffin-embedded blocks and immunohistochemically analyzed for the expression of Ki-67 according to the manufacturer’s instructions. Ki-67 IHC was performed by using a commercially available mouse monoclonal antibody against human Ki-67. The results of Ki-67 IHC were
Immunohistochemical staining showed low expression of Ki-67 (<10%, (A)) and high expression of Ki-67 (>10%, (B)) (×100).

The specimens were retrospectively evaluated by a pathologist who was blinded to the clinicopathological features and CT data. Immunoreactive cells from 1000 malignant cells were used to determine the percentile of Ki-67-positive tumor cells and to score the region with the largest number of positive nuclei (hot spots) in the tumor.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 26.0 for Windows (SPSS, Armonk, NY, USA) and MedCalc software (www.medcalc.org). The differences between CT scan models were examined by independent sample Kruskal–Wallis tests. The Wilcoxon rank-sum test was used to compare the differences between the low Ki-67 and high Ki-67 groups (all P-values > 0.1; table 2). In contrast, correlation and IDM were significantly different between the low and high Ki-67 groups (all P-values < 0.001; figures 4(A), (B), and (C)). However, there were no significant differences in ASM, SumOfSqs, sum average, sum variance or entropy between the two groups (P > 0.05; table 2). Contrast, correlation, and IDM were entered into the multivariable logistic regression analysis. Finally, contrast (OR = 0.957; 95% CI: 0.926–0.990; P = 0.01) and correlation (OR = 2.5*10^5; 95% CI: 7.560–8.9*10^3; P = 0.019) were considered independent risk factors for combined model building with logistic regression (table 3).

3. Results

3.1. Ki-67 and CT features

The patients were divided into two groups according to their Ki-67 scores: patients with scores of 0 and 1 were classified as the low Ki-67 group (figure 2(A)) and those with scores of 2, 3, and 4 were classified as the high Ki-67 group (figure 2(B)). As indicators such as the mean and variance do not have a normal distribution, all results were expressed as the median and P25 ~ P75. The low Ki-67 group had a total of 20 lesions, and the high Ki-67 group had 54 lesions. The clinical characteristics of the patients are shown in table 1. An overview of the case selection process is shown in figure 3.
Figure 3. Flowchart illustrating subject selection.

Table 2. Parameters with significant differences in the Wilcoxon rank–sum test and independent sample Kruskal–Wallis test.

| Parameters   | Low Ki-67 | High Ki-67 | Z    | P   | P(CT)* |
|--------------|-----------|------------|------|-----|--------|
| Mean         | 127.633   | 125.852    | −0.451 | 0.652 | 0.346  |
| Variance     | 365.555   | 423.448    | −0.201 | 0.84  | 0.777  |
| Skewness     | −0.153    | −0.182     | 0.472 | 0.353 | 0.291  |
| Kurtosis     | −0.231    | −0.255     | 1.8   | 0.75  | 0.453  |
| Perc.50%     | 132.25    | 127.92     | −0.196 | 0.845 | 0.546  |
| ASM          | 0.002     | 0.001      | 0.196 | 0.845 | 0.546  |
| Contrast     | 221.439   | 128.888    | −4.245 | <0.001 | 0.772  |
| Correlation  | 0.678     | 0.832      | 3.642 | <0.001 | 0.338  |
| SumOfSqs     | 352.967   | 374.485    | −0.621 | 0.535 | 0.891  |
| SumAverg     | 296.828   | 252.121    | 445.903 | −0.877 | 0.381  |
| SumVarnc     | 1203.667  | 1328.878   | 0.146 | 0.884 | 0.891  |
| IDM          | 0.081     | 0.107      | 4.067 | <0.001 | 0.477  |
| Entropy      | 3.223     | 3.226      | 0.798 | 0.425 | 0.906  |

Perc.50% = percentage 50%
ASM = angular second moment
SumOfSqs = sum of squares
SumAverg = sum average
SumVarnc = sum variance
IDM = inverse difference moment
Statistically significant (P < 0.050)
* Differences between CT scan models

(r = −0.285, P = 0.014), contrast (r = −0.449, P < 0.001), correlation (r = 0.552, P < 0.001), IDM (r = 0.458, P < 0.001), and entropy (r = 0.285, P = 0.014) strongly correlated with the Ki-67 scores (table 4). Overall, higher ASM and contrast were associated with low Ki-67 scores, while correlation, IDM and entropy increased with high Ki-67 scores.
Table 3. Multivariable odds ratios for the associations between CT texture parameters and high Ki-67.

|                | B    | S.E  | Wald | P     | OR   | 95% C.I. for OR |
|----------------|------|------|------|-------|------|----------------|
|                |      |      |      |       | Lower| Upper          |
| Contrast       | -0.044 | 0.017 | 6.572 | 0.01  | 0.957 | 0.926 - 0.997  |
| Correlation    | 12.467 | 5.329 | 5.474 | 0.019 | 259  | 646.7 - 7.56   |
| IDM            | -89.966 | 48.593 | 3.428 | 0.064 | 0    | 0 - 195.42     |
| Constant       | 7.582  | 6.991 | 1.176 | 0.278 | 1962.772 |                |

Figure 4. Violin plot of the contrast (A), correlation (B), and inverse difference moment (IDM) (C) features.

3.3. Prediction of Ki-67 status

The diagnostic efficacy of these important parameters (contrast, correlation, and combined predictor) was further evaluated by ROC analyses to identify the high Ki-67 group (table 5, figure 5). These three texture
parameters were predictive of Ki-67 status ($P < 0.001$), with AUCs ranging from 0.777 to 0.836. The combined predictor had the highest AUC for discriminating low Ki-67 from high Ki-67, with the cut-off at −31.16, a sensitivity of 96.30%, and a specificity of 75.00%. We also compared the ROC curves in pairs and observed no statistically significant differences between them.

4. Discussion

The thickness of image acquisition and reconstruction will affect the stability of the results of radiomics (Incoronato et al 2017). In this study, there were no significant differences between different CT models after a 1 mm layer thickness was adopted, and the images were standardized ($P > 0.1$). Previous studies have shown that there is a certain correlation between the expression of Ki-67 and image performance (Huang et al 2015, Luo et al 2015, Hu et al 2017, Juan et al 2018, Zhang et al 2020). At present, there is no unified standard for the high and low expression groups of Ki-67. In some studies, 10% was used as the cut-off value of Ki-67 expression (Meng et al 2016, Hu et al 2017, Li et al 2019, Zhang et al 2020), but in others, 14% (Fan et al 2018, Juan et al 2018) or 20% (Holli-Helenius et al 2017) was used, and we used 10% as the cut-off value.

In this study, we analyzed the relationships between radiomics features and Ki-67 expression, used radiomics features to identify the expression of Ki-67 in HCC, and characterized five grayscale histograms and eight texture features for each lesion. The result shows that correlation, contrast, and IDM values were significantly different between the low Ki-67 group and the high Ki-67 group ($P < 0.001$). Contrast and correlation were considered independent risk factors for combined model building with logistic regression. Spearman correlation analysis found that ASM and contrast were negatively correlated with the Ki-67 scores, while correlation, IDM, and entropy were positively correlated with the Ki-67 scores ($P < 0.05$). In the ROC analyses, correlation, contrast, and the combined predictor also had a high ability to identify Ki-67 expression, but no significant differences were found between them. Correlation is a measure of the linear grayscale correlation between adjacent pixels Yang et al (2012), and it reflects the relevance of grayscale in the image texture Herlidou-Mème et al (2003, Yang et al 2012, Zhao et al 2014). The correlation of the low Ki-67 group was lower than that of the high Ki-67 group. Because Ki-67 is used as a marker for cellular proliferation, the high Ki-67 group tended to have a higher cell density and less necrosis than the low Ki-67 group. This finding may suggest that the density difference between the lesion and the surrounding liver tissue is small in the low Ki-67 group. Contrast is a texture feature that is related to the image sharpness and groove depth (Juan et al 2018). The contrast of the low Ki-67 group was higher than that of the high Ki-67 group. This indicates that the low Ki-67 group has deeper grooves and clearer images, which could be attributed to the relatively loose cell structure and reduced invasion of the surrounding structure found in the low Ki-67 group.

This work demonstrates that Ki-67 status can be predicted through radiomics analysis features. Although some important findings have been revealed, there are also some limitations. First, this study was a single-center retrospective analysis with a small sample size; multicenter prospective studies are needed to validate the results in a larger population in the future. Second, the use of contrast agents may affect radiological properties, and standardization may not be sufficient to overcome this effect. Third, the CT models in this study were different, which may affect the results, but we standardized the image processing to minimize the impact. In the future, we will design prospective studies and adopt unified CT models and scanning parameters to minimize the error. In addition, other predictive biomarkers can be added to improve the accuracy of the model.

In summary, our study suggests that the radiomics characteristics of CT have potential as biomarkers for predicting Ki-67 status in patients with HCC. These findings suggest that the radiomics features of CT might be used as a noninvasive measure of cellular proliferation in HCC. We hope that in the future, these features will be an ideal noninvasive tool to obtain information about tumor progression and the response to anticancer therapies.

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Competing interests

The authors declare that they have no competing interests.
Table 4. Correlations of Ki-67 scores and CT texture parameters.

| Ki-67 level | Correlation coefficient | P       |
|-------------|-------------------------|---------|
| Mean        | -0.094                  | 0.425   |
| Variance    | -0.072                  | 0.54    |
| Skewness    | -0.028                  | 0.815   |
| Kurtosis    | 0.142                   | 0.228   |
| Perc.50%    | -0.071                  | 0.549   |
| ASM         | -0.285                  | 0.014   |
| Contrast    | -0.449                  | <0.001  |
| Correlation | 0.552                   | <0.001  |
| SumOfSqs    | 0.076                   | 0.518   |
| SumAverg    | -0.046                  | 0.695   |
| SumVarnc    | 0.189                   | 0.107   |
| IDM         | 0.458                   | <0.001  |
| Entropy     | 0.285                   | 0.014   |

Perc.50% = percentage 50%
ASM = angular second moment
IDM = inverse difference moment
Statistically significant (p < 0.05)

Figure 5. ROC curves of the texture features of HCC using the high Ki-67 or low Ki-67 groups.
Table 5. Differentiation performance of texture parameters assessed by receiver operating characteristic analysis.

| Parameters | Contrast | Correlation | Combined predictor |
|------------|----------|-------------|-------------------|
| AUC        | 0.823    | 0.777       | 0.836             |
| Standard Error | 0.063    | 0.061       | 0.0688            |
| 95% Confidence | 0.716,0.902 | 0.665,0.865 | 0.732,0.912      |
| z statistic | 5.086    | 4.522       | 4.885             |
| P (Area = 0.5) | <0.001   | <0.001      | <0.001            |
| Youden index J | 0.639    | 0.652       | 0.713             |
| Sensitivity (%) | 88.890   | 85.190      | 96.30             |
| Specificity (%) | 75.000   | 80.00       | 75.00             |
| Cutoff value  | 186.026  | 0.688       | –31.16           |

IDM = inverse difference moment
AUC = area under the curve
Statistically significant (P < 0.05)

References

Aerts H J et al 2014 Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach Nat. Commun. 5 4006
Chang C C, Chen H H, Chang Y C, Yang M Y, Lo C M, Ko W C, Lee Y F, Liu K I and Chang R F 2017 Computer-aided diagnosis of liver tumors on computed tomography images Comput. Methods Programs Biomed. 145 45–51
Choi W, Rihayi S, Kligerman S J, Liu C J, Mechalakos J G and Lu W 2018 Technical note: identification of CT texture features robust to tumor size variations for normal lung texture analysis Int. J. Med. Clin. Eng. Radiat. Oncol. 07 330–38
Fan M, Cheng H, Zhang P, Gao X, Zhang J, Shao G and Li L 2018 DCE-MRI texture analysis with tumor subregion partitioning for predicting Ki-67 status of estrogen receptor-positive breast cancers J. Magn. Reson. Imaging 48 237–47
Gerdes J, Lemke H, Baisch H, Wacker H H, Schwab U and Stein H 1984 Cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67 J. Immunol. 133 1710–15
He X, Wei Y, Zhang H, Zhang T, Yuan F, Huang Z, Han F and Song B 2020 Grading of clear cell renal cell carcinomas by using machine learning based on artificial neural networks and radiomic signatures extracted from multidetector computed tomography images Acad. Radiol. 27 157–68
Herlidou-Merre S, Constans J M, Carsin B, Olivie D, Eiat P A, Nadal-Desbarats L, Gondry C, Le Rumeur E, Idy-Pereiti I and de Certaines J D 2003 MRI texture analysis on texture test objects, normal brain and intracranial tumors Magn. Reson. Imaging 21 889–93
Holli-Helenius K, Salminen A, Rinta-Kiikka I, Koskiiva I, Bruck N, Bostrom P and Parkkola R 2017 MRI texture analysis in differentiating luminal A and luminal B breast cancer molecular subtypes - a feasibility study BMC Med. Imaging 17 69
Hu X et al 2017 Whole-tumor MRI histogram analyses of hepatocellular carcinoma: correlations with Ki-67 labeling index J. Magn. Reson. Imaging 46 383–92
Huang Z, Xu X, Meng X, Hou Z, Liu F, Hua Q, Liu Q and Xiu J 2015 Correlations between ADC values and molecular markers of Ki-67 and HIF-1alpha in hepatocellular carcinoma Eur. J. Radiol. 84 2464–9
Incoronato M, Aiello M, Infante T, Cavaliere C, Grimaldi A, Mirabelli P, Monti S and Salvatore M 2017 Radiogenomic analysis of oncological data: a technical survey Int. J. Med. Sci. 18 805
Jiang Y et al 2018 Radiomics signature of computed tomography imaging for prediction of survival and chemotherapeutic benefits in gastric cancer E BioMedicine 16 74–81
Jiang Y et al 2019 Radiomics signature on computed tomography imaging: association with lymph node metastasis in patients with gastric cancer Frontiers Oncol. 9 340
Juan M W, Yu J, Peng G X, Jun L J, Feng S P and Fang L J 2018 Correlation between DCE-MRI radiomics features and Ki-67 expression in invasive breast cancer Oncol. Lett. 16 5084–90
Ke R S, Zhang K, Lv L Z, Dong Y P, Pan F, Yang F, Cai Q C and Jiang Y 2019 Prognostic value and oncogene function of heterogeneous nuclear ribonucleoprotein A1 overexpression in HBV-related hepatocellular carcinoma Int. J. Biol. Macromol. 129 140–51
Khalvati F, Wong A and Haider M A 2015 Automated prostate cancer detection via comprehensive multi-parametric magnetic resonance imaging texture feature models BMC Med. Imaging 15 27
Li Y, Chen J, Wang S, Sun H, Yan C, Xu X, Ye R and Hong J 2019 Small hepatocellular carcinoma: using MRI to predict histological grade and Ki-67 expression Clin. Radiol. 74 653–e1
Lin Q, Ji Y F, Chen Y, Sun H, Yang D D, Chen A L, Chen T W and Zhang X M 2019 Radiomics model of contrast-enhanced MRI for early prediction of acute pancreatitis severity J. Magn. Reson. Imaging 51 397–406
Luo Y, Ren F, Liu Y, Shi Z, Tan Z, Xiong H, Dang Y and Chen G 2015 Clinicopathological and prognostic significance of high Ki-67 labeling index in hepatocellular carcinoma patients: a meta-analysis Int. J. Clin. Exp. Med. 8 10235–47
Meng X, Li H, Kong L, Zhao X, Huang Z, Zhao H, Zhu W, Li X, Yu J and Xing L 2016 MRI in rectal cancer: correlations between MRI features and molecular markers Ki-67, HIF-1alpha, and VEGF J. Magn. Reson. Imaging 44 594–600
Perou C M et al 1999 Distinctive gene expression patterns in human mammary epithelial cells and breast cancers Proc. Natl Acad. Sci. USA 96 9212–7
Ryu Y, J, Choi S H, Park S J, Yun T J, Kim J H and Sohn C H 2014 Glioma: application of whole-tumor texture analysis of diffusion-weighted imaging for the evaluation of tumor heterogeneity PLoS One 9 e108335
Szczypinski P M, Strzelecki M, Materka A and Klepaczko A 2009 MaZda—a software package for image texture analysis Comput. Methods Programs Biomed. 94 66–76
Tu W, Sun G, Fan L, Wang Y, Xia Y, Guan Y, Li Q, Zhang D, Liu S and Li Z 2019 Radiomics signature: A potential and incremental predictor for EGFR mutation status in NSCLC patients, comparison with CT morphology Lung Cancer 132 28–35
Wan T, Bloch B N, Plecha D, Thompson C L, Gilmore H, Jaffe C, Harris L and Madabhushi A 2016 A radio-genomics approach for identifying high risk estrogen receptor-positive breast cancers on DCE-MRI: preliminary results in predicting oncotypeDX risk scores Sci. Rep. 6 21394
Wang H Y C et al 2019 The stability of imaging biomarkers in radiomics: a framework for evaluation Phys. Med. Biol. 64 165012
Yang X, Tridandapani S, Beiter J J, Yu D S, Yoshida E J, Curran W J and Liu T 2012 Ultrasound GLCM texture analysis of radiation-induced parotid-gland injury in head-and-neck cancer radiotherapy: an in vivo study of late toxicity Med. Phys. 39 5732–9
Yang Z, He B, Zhuang X, Gao X, Wang D, Li M, Lin Z and Luo R 2019 CT-based radiomic signatures for prediction of pathologic complete response in esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy J. Radiat. Res. 60 538–45
Zhang Q W, Gao Y J, Zhang R Y, Zhou X X, Chen S L, Zhang Y, Liu Q, Xu J R and Ge Z Z 2020 Personalized CT-based radiomics nomogram preoperative predicting Ki-67 expression in gastrointestinal stromal tumors: a multicenter development and validation cohort Clin. Transl. Med. 9 12
Zhang Z, Jiang H, Chen J, Wei Y, Cao L, Ye Z, Li X, Ma L and Song B 2019 Hepatocellular carcinoma: radiomics nomogram on gadoxetic acid-enhanced MR imaging for early postoperative recurrence prediction Cancer Imaging 19 22
Zhao Q, Shi C Z and Luo L P 2014 Role of the texture features of images in the diagnosis of solitary pulmonary nodules in different sizes Chin. J. Cancer Res. 26 451–8