Predicting Model for Tumor Budding Status using Radiomics Features of 18F-PET/CT and in Cervical Cancer

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Abstract

Objective

The aim of this study was to compare radiomics feature on $^{18}$F-FDG PET/CT and intratumoral heterogeneity according to tumor budding (TB) status and to develop predicting model for TB status using radiomics feature of $^{18}$F-FDG PET/CT in patients with cervical cancer.

Materials and methods

A total of 76 cervical cancer patients who performed radical hysterectomy and preoperative $^{18}$F-FDG PET/CT were included. We assessed the status of intratumoral budding (ITP) and peritumoral budding (PTB) in all available hematoxylin and eosin-stained specimens. Three conventional metabolic parameters and a total of 59 features were extracted and analyzed. Univariate analysis was used to identify significant metabolic parameters and radiomics findings for TB status. Predicting model for TB status was built by the LASSO regularization.

Results

The univariate analysis lead to the identification of 2 significant metabolic parameters and 12 significant radiomic features according to ITB status. Among these parameters, only compacity was remained in multivariate analysis for ITB status (odds ratio, 5.0047; 95% confidence interval, 1.1636 – 21.5253; $p = 0.0305$). Five radiomics features (Kurtosis, Compacity, Short-Zone Low Gray-level Emphasis, Coarseness, Low Gray-level Run Emphasis) were selected by the LASSO regularization and the predicting model for ITB status had a mean area under curve of 0.810 in training dataset and 0.794 in validation dataset.

Conclusion

Radiomics features on $^{18}$F-FDG PET/CT was associated with ITB status. The predicting model using radiomics features successfully predicted TB status in cervical cancer. The predicting models for ITB status may contribute to personalized medicine in the management of cervical cancer patients.

Introduction

Tumor budding (TB) is defined as a single neoplastic cell or cell cluster of up to four neoplastic cells at the invasive front of the tumor (peritumoral budding, PTB) or within the tumor mass (intratumoral budding, ITB) [1]. Several studies have demonstrated that TB was associated with lymphovascular invasion (LVI), lymph node metastasis, disease recurrence, and an unfavorable survival outcome, especially in colorectal cancer [2], esophageal carcinoma [3], and head and neck cancer [4]. Recently we evaluated prognostic roles of TB and correlation between TB and conventional pathologic parameters in gynecological cancers [5,6]. TB was associated with deep depth invasion, higher International Federation of Gynecologic Obstetrics (FIGO) stage, LVI, and lymph node metastasis in endometrial cancer [5].
Moreover, high TB was an independent prognostic factor for predicting survival outcomes in cervical cancer [6].

Currently, F-18 fluorodeoxyglucose positron emission tomography/computed tomography (\(^{18}\text{F-FDG PET/CT}\)) has been widely used to detect lymph node involvement, distant metastasis, and recurrent disease in cervical cancer [7]. Various metabolic parameters of \(^{18}\text{F-FDG PET/CT}\) have been reported as prognostic factors including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). Radiomics studies, which represent intratumoral heterogeneity have emerged as a new and exciting study area in recent years. The measurement of texture indices from tumor \(^{18}\text{F-FDG PET/CT}\) images has been recently proposed as an adjunct to predict tumor response to therapy. There is emerging evidence that intratumoral metabolic heterogeneity on pre-treatment \(^{18}\text{F-FDG PET/CT}\) might be a predictor of tumor recurrence after treatment in patients with lung cancer, esophageal cancer, head and neck cancer, and cervical cancer [8-11]. Furthermore, recent studies showed \(^{18}\text{F-FDG PET/CT}\) radiomics using various textural features were potential biomarker to predict tumor recurrence and lymph node metastasis [12-13]. Tumor heterogeneity is defined by the presence of different cell subpopulations or clones and has a fundamental role in growth, progression, and therapeutic resistance. Tumor hypoxia, angiogenesis, necrosis, fibrosis, cell proliferation, and inflammation process play a role in tumor heterogeneity [14]. Epithelial-mesenchymal transition (EMT) of primary tumor tissues may lead loss of cell-to-cell adhesion and individual cells or small groups of cells acquired the ability to migrate and invade through the surrounding tissues. Moreover, TB may lead to a more aggressive clinicopathologic characteristics through similar mechanism of EMT such as increased extracellular matrix degradation, increased migration, and loss of cell adhesion [15]. These EMT processes are accompanied by changes in cell morphology [16] and may lead to change tumor heterogeneity. However, there has been no study which evaluate correlation between metabolic parameters and radiomics finding of \(^{18}\text{F-FDG PET/CT}\) and TB in cervical cancer. So, we hypothesized TB may associate with higher metabolic parameters in \(^{18}\text{F-FDG PET/CT}\) because of aggressive behavior of TB and radiomics finding may different according to TB status because TB is individual cells and small groups of cells.

The aim of this study was to compare radiomics feature on \(^{18}\text{F-FDG PET/CT}\) and intratumoral heterogeneity according to TB status and to develop predicting model for TB status using radiomics feature of \(^{18}\text{F-FDG PET/CT}\) in patients with cervical cancer.

**Materials And Methods**

*Patients*

After approval of the Institutional Review Board of Kyungpook National University Chilgok Hospital (KNUCH 2020-03-011), we reviewed the archival medical records and hematoxylin and eosin (H&E)-stained slides of early-stage and locally advanced cervical cancer patients. The need for informed consent was waived because of the retrospective nature of the study. A total of 136 patients who
underwent radical hysterectomy with pelvic and/or paraaortic lymphadenectomy for the treatment of early-stage and locally advanced cervical cancer were included. Among the 136 patients, 76 patients performed preoperative $^{18}$F-FDG PET/CT and were enrolled in this study. The enrolled patients were semi-randomly divided into a training dataset (51 patients) and a test set (25 patients) by using the “doBy” R package while preserving the distribution of ITB status. Patients with a history of preoperative chemotherapy, radiotherapy, or synchronous malignancies were excluded. The patients were clinically staged according to the 2009 International Federation of Gynecologic Obstetrics (FIGO) staging system [17].

**Histopathological evaluation**

Specimens were examined from multiple sections of the whole tumor areas and were stained with hematoxylin and eosin (H&E). For each case, all available specimens were independently reviewed for the detailed histopathological features and the quantitative assessment of TB by two pathologists (J.Y.P and J.Y.P) in a blinded manner without information about the clinicopathological data and outcomes.

The pathological parameters included tumor size, FIGO stage, histological subtype, deep stromal invasion, LVI, parametrial invasion, lymph node metastasis, and the number and distribution of TB. TB was defined as an isolated single cancer cell or small cell clusters composed of 4 tumor cells or less located at the advancing edge (PTB) and within the tumor area (ITB).

**$^{18}$F-FDG PET/CT Image Acquisition**

All patients fasted for at least six hours, and their blood glucose levels were determined before the administration of $^{18}$F-FDG. Patients with blood glucose levels higher than 150 mg/dL were rescheduled for a later examination, and treatment was administered to maintain a blood glucose concentration of less than 150 mg/dL in all participants. Patients received intravenous injections of approximately 5.2 MBq of FDG per kilogram of body weight and were advised to rest for one hour before undergoing the acquisition of $^{18}$F-FDG PET/CT images. The $^{18}$F-FDG PET/CT scans were performed using Discovery 600 (GE Healthcare, Chicago, IL, USA). Before the PET scan, for attenuation correction, a low-dose CT scan was obtained without contrast enhancement from the skull base to the thigh while the patient was in the supine position and breathing quietly. PET scans were also obtained from the skull base to the thigh at 2.5 min per bed position. PET images were reconstructed with a 128 X 128 matrix and an ordered-subset expectation maximum iterative reconstruction algorithm.

**Image Interpretation and PET Image Analyses**

The $^{18}$F-FDG PET/CT images were interpreted by two experienced nuclear medicine physicians, and a final consensus was achieved for all patients. A positive finding was defined as any focus with increased FDG uptake as compared with the surrounding normal tissue. Foci of FDG uptake due to normal physiology or benign variants, such as muscular exercise or an infectious pulmonary infiltration, were excluded from the analysis.
All image analyses were performed using the Advantage Workstation 4.5 software (GE Medical Systems, Waukesha, WI, USA). The primary tumor lesion was delineated by the volume of interest using an isocontour threshold method based on the SUV, and metabolic PET parameters were assessed. SUVmax values were based on body weight and were calculated using the following formula: SUVmax = maximum activity in the region of interest (MBq/g)/[injected dose (MBq) ÷ bodyweight (g)]. SUVmax was designated as the highest value of SUVmax of the primary tumor. The MTV was determined as the volume of voxels with a threshold SUV of the mediastinal blood pool, because the mediastinal blood pool has been regarded as the preferred site for measuring background activity [18]. The mean SUV of the mediastinal SUV values was determined by drawing a region of interest over contiguous slices on descending aorta carefully excluding the walls from the region of interest. The mean SUV of the mediastinal background plus 2 SDs was used as the threshold to automatically calculate MTV [17]. The TLG was calculated as the MTV multiplied by the SUVmean of the lesion. The MTV and TLG were also obtained for the primary tumor.

**Statistical analysis**

The differences between subsets were evaluated with a Student’s t-test or Mann-Whitney test, and differences between proportions were compared with the chi square test or Fisher’s exact test. To identify an optimal cutoff value of metabolic parameters and radiomics finding of $^{18}$F-PET/CT for the prediction of ITB status, ROC curve analysis was performed. Multiple logistic regression analysis was used to evaluate metabolic parameters and radiomics finding of $^{18}$F-PET/CT for ITB status. Estimated odds ratios (ORs) with 95% confidence intervals (95% CIs) were presented. All statistical tests were 2-sided, and a $p$-value of $<0.05$ was considered significant. Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL, USA) and Medcalc version 15.4 (Medcalc Software, Ostend, Belgium), and R version 3.6.3 (R foundation for Statistical Computing, Vienna, Austria). The R packages “caret”, “glmnet”, “MASS”, and “pROC” were used for analysis.

**Radiomics analysis**

Radiomics features were extracted using the LIFEx package (http://www.lifexsoft.org) [19]. LifeX was set up using the following input parameters for calculation of features: 64 Gy levels to resample the ROI content which was performed in absolute terms between a minimum of 0 and a maximum of 20 [20]. A total of 59 features were extracted from the analysis of the volumes inspected. These indices included conventional parameters, shape and size features, histogram-based features, second and high order-based features. The correction for the partial volume effect was not applied. In the analysis were included all primary tumor lesions, irrespectively of their volume but LifeX calculates the shape and size indices as well as second order (gray-level co-occurrence matrix [GLCM]) and high order-based (neighborhood gray-level different matrix [NGLDM], gray-level run length matrix, [GLRLM] and gray-level zone-length matrix [GLZLM]) features only for ROI of at least 64 voxels due to technical reasons. The features calculated are summarized in supplementary Table 1.
Each feature value was normalized using z-score normalization \((z = (x - \text{mean}(x))/\text{SD}(x))\) (standard deviation [SD])). Feature selection process consisted of two steps in the training dataset. First, t-test was performed to screen potential features throughout radiomics features and conventional metabolic parameters. Only features with \(p < 0.05\) were considered significant and entered further selection step. Next, the least absolute shrinkage and selection operator (LASSO) regression was used to select key features to build prediction model, with a 3-fold cross validation.

After feature selection process, the prediction models were constructed using a random forest (RF), a support vector machine (SVM), and a neural network (NN) using training dataset. The constructed model performance was validated independently in the test dataset by the area under the receiver operating characteristic (ROC) curve. The R packages “randomForest”, “kernlab”, and “neuralnet” were used for building prediction model.

## Results

### Clinicopathologic features and treatment outcomes

The clinicopathologic characteristics of the study participants are listed in Table 1. The predominant FIGO stage was IB1 (\(n = 43\) [56.6%]), followed by IB2 (\(n = 14\) [18.4%]), IIB (\(n = 10\) [13.2%]), and IIA (\(n = 9\) [11.8%]). The histologic cervical cancer types were as follows: squamous cell carcinoma (\(n = 91\) [66.9%]), adenocarcinoma (\(n = 37\) [27.2%]), and adenosquamous carcinoma (\(n = 8\) [5.9%], Table 1). The median ITB counts (range) were 3.5 (0-40), and the median PTB counts (range) were 4 (0-44), respectively. ITB was observed in 47 patients (61.8%), and PTB in 62 patients (81.6%), respectively.

### Comparison of metabolic parameters and radiomics features of \(^{18}\text{F-PET/CT}\) according to TB status

The median SUVmax significantly higher in positive ITB group than in negative ITB group (11.35 vs. 8.37, \(p = 0.0406\); Figure 1). However, the median SUVmax was not different according to the PTB status. Among the radiomics features, EntropyGLCM (GLCM, \(p = 0.0111\)), Coarseness (NGLDM, \(p = 0.0497\)), Low Gray-level Run Emphasis / Long-Run Low Gray-level Emphasis (GLRLM, \(p = 0.0189\) and \(p = 0.0101\), respectively), Low Gray-level Zone Emphasis / Short-Zone Low Gray-level Emphasis / Zone Length Non-Uniformity Zone (GLZLM, \(p = 0.0137\), \(p = 0.0154\), and \(p = 0.0056\), respectively), Sphericity / Compacity (Shape and Size, \(p = 0.0065\) and \(p = 0.0108\), respectively), and Kurtosis / EntropyHist / EnergyHist (Histogram, \(p = 0.0267\), \(p = 0.0130\), and \(p = 0.0200\)) had significant different levels according to the ITB status. However, there was no significant different radiomics findings according to the PTB status (Table 2).

### Multiple logistic regression analysis for ITB status

Univariate and multivariate analysis were performed for evaluation of correlation between \(^{18}\text{F-FDG PET/CT}\) values and ITB status using multiple logistic regression analysis (Table 3). Among the significant parameters of conventional metabolic parameters (SUVmax, MTV, and TLG) and each radiomics findings
(GLCM, NGLDM, GLZLM, Shape and Size, and Histogram) in univariate analysis, the most significant parameters (the lowest p value) were included to multivariate analysis for inhibition of conflicting each parameters. In univariate analysis, SUVmax (OR, 3.34; 95% CI, 1.27-8.79; p = 0.0146), TLG (OR, 4.42% CI, 1.33-14.72; p = 0.0154), EntropyGLCM (OR, 5.36; 95% CI, 1.95-14.69; p = 0.0011), Coarseness (OR, 3.94; 95% CI, 1.41-11.03; p = 0.0090), Low Gray-level Run Emphasis (OR, 3.45; 95% CI, 1.26-9.47; p = 0.0161), Long-Run Low Gray-level Emphasis (OR, 3.34; 95% CI, 1.27-8.79; p = 0.0146), Low Gray-level Zone Emphasis (OR, 4.05; 95% CI, 1.52-10.82; p = 0.0052) Short-Zone Low Gray-level Emphasis (OR, 3.94; 95% CI, 1.41-11.03; p = 0.0090), Zone Length Non-Uniformity Zone (OR, 9.16; 95% CI, 1.27-8.79; p = 0.0146), Sphericity (OR, 6.09; 95% CI, 2.15-17.28; p = 0.0007), Compacity (OR, 8.73; 95% CI, 2.48-30.76; p = 0.0007), Kurtosis (OR, 3.96; 95% CI, 1.38-11.38; p = 0.0106), EntropyHist (OR, 5.98; 95% CI, 2.12-16.86; p = 0.0007), and EnergyHist (OR, 5.98; 95% CI, 2.12-16.86; p = 0.0007) were significant parameters which correlated with positive ITB. Multivariate analysis with the enter methods showed only Compacity (OR, 5.00; 95% CI, 1.16-21.53; p = 0.0305) remained independent parameter correlated with positive ITB (Table 3).

Predicting model for ITB status usingsradiomics features of $^{18}$F-FDG PET/CT

A total of 48 features were significant parameters in t-test and were subjected to further selection step by the LASSO regularization (Figure 1). Among them, the final 27 remaining features (SUVmax, MTV, SUV_Skewness, discretized_SUVmax, discretized_SUV_Skewness, discretized_SUV_Kurtosis, discretized_SUVpeak_Sphere, discretized_HISTO_ExcessKurtosis, GLCM_Entropy_log2, GLCM_Dissimilarity, GLRLM_LRE, GLRLM_LGRE, GLRLM_SRHGE, GLRLM_LRLGE, GLRLM_GLNU, GLRLM_RLNU, NGLDM_Contrast, NGLDM_Busyness, GLZLM_SZE, GLZLM_LZE0, GLZLM_LGZE, GLZLM_HGZE, GLZLM_SZLGE, GLZLM_SZHGE, GLZLM_LZLGE) were selected. Figure 2 shows the ROC curves of the prediction models by three machine learning algorithms in training and test dataset. The AUC values of the prediction models constructed by the RF, SVM, and NN were 1.000, 0.951, and 1.000, respectively, in the training dataset and 0.752, 0.784, 0.752, respectively, in the test dataset.

Discussion

In this study, radiomics features of $^{18}$F-FDG PET/CT was associated with TB status especially in ITB status. Among the 59 features, 12 features were significantly different according to the ITB status in univariate logistic regression analysis. Among these 12 features, compacity was the most significant parameter for ITB status in multivariate logistic regression analysis. Moreover, we developed the predicting model for ITB status using 5 features by the LASSO regularization, and AUC was 0.810.

Radiomics is relatively new and evolving field in medical imaging in which many features are extracted from medical images analysis and interpretation using bioinformatic approaches [14]. Furthermore, radiomics precision medicine and tumor heterogeneity have become one of the hottest topics in the oncological medical area in recent years [21]. At the biological level, it has been recognized that heterogeneity of tumor microenvironment might be reflected in medical images, with respect to cellular density, proliferation, angiogenesis, hypoxia, receptor expression, necrosis, fibrosis, and inflammation and
these factors might contribute to a more aggressive phenotype and poor treatment responses [22]. Therefore, radiomics signature might represent segmentation of tumor subregions with different biological characteristics and contribute to treatment response and prognosis.

In colorectal cancer, high ITB correlated with higher tumor grade, higher pT stage, lymphatic invasion, vascular invasion, nodal metastasis, and shorter survival time [23]. ITB may lead to a more aggressive clinicopathologic characteristics through similar mechanism for PTB such as increased extracellular matrix degradation, increased migration, and loss of cell adhesion [15]. So, we hypothesized ITB may associate with higher metabolic parameters because of aggressive behavior of ITB. Moreover, radiomics finding may different according to ITB status because TB is individual cells and small groups of cells owing to loss of cell adhesion.

To date only one study recently demonstrated correlation between tumor cancer cell metabolism and morphologic features of aggressiveness as assessed by microscopy such as TB [24]. MTV was higher in TB group than in non-TB group with marginal significant ($p = 0.06$) in laryngeal and pharyngeal carcinoma [25]. In this study, SUVmax was significantly different according to ITB status ($p = 0.0406$). Moreover, SUVmax and TLG were associated with ITB status in univariate logistic regression analysis ($p = 0.0146$ and $p = 0.0154$, respectively). More aggressive nature of ITB may represent higher metabolic parameters in $^{18}$F-FDG PET/CT.

EMT of primary tumor tissues may lead loss of cell-to-cell adhesion and occurrence ITB. So, ITB may lead segmentation of tumor subregions with different biological characteristics and these may contribute tumor heterogeneity. However, no study has been reported about correlation between ITB and radiomics findings. In this study, 12 features were associated with ITB status and compacity was powerful biomarker which represent ITB status in multivariate logistic regression analysis. Previous study demonstrated that among the radiomics features, the most significant covariate was compacity for predict local control and survival in hepatocellular carcinoma [26].

Previous our study showed that tumors with high TB were significantly associated with LVI, deep stromal invasion, parametrial invasion and lymph node metastasis in cervical cancer [6]. Preoperative prediction of TB status may helpful to personalized medicine such as decision of radicality of surgery or extent of lymphadenectomy. However, TB status was finally determined by postoperative surgical specimens. To date, there was no modality with estimate TB status preoperatively. Therefore, predicting models were constructed for ITB status using both conventional metabolic parameters and radiomics features from $^{18}$F-FDG PET/CT scans. Among the 48 features which were significant parameters in univariate logistic regression, 27 features were selected by the t-test and LASSO regularization. The AUC values of the prediction models were greater than 0.75 in the test dataset.

The main limitations of this study are its retrospective nature and small sample size, which may have contributed to selection bias. In addition, it is a single-center study; therefore, the generalization of our findings are limited. Despite these limitations, our study offers some unique and significant findings. Our
study showed correlations between radiomics findings and TB status for the first time. Moreover, we established the predicting models for ITB status using radiomics feature in $^{18}$F-FDG PET/CT.

In conclusion, higher metabolic quantities were observed in positive ITB group than in negative ITB group. Radiomics findings in $^{18}$F-FDG PET/CT was associated with ITB status, and among these features, the most significant covariate was compacity for ITB status. Furthermore, prediction models for ITB status using radiomics findings in $^{18}$F-FDG PET/CT may contribute to personalized medicine in cervical cancer.

**Declarations**

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**Conflicts of interest**

The authors declare that they have no conflict of interest.

**Ethics approval**

This study is approved by Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB no. KNUCH 2020-03-011)

**Informed consent**

Informed consent was waived, owing to the retrospective nature of the study.

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Tables

Table 1. Clinicopathological and tumor budding characteristics.
| Variables                                      |        |
|-----------------------------------------------|--------|
| **Age (years)**                               |        |
| Mean ± SD                                     | 47.95 ± 10.73 |
| Median (range)                                | 49 (25-74) |
| **FIGO stage (n, %)**                         |        |
| IB1                                           | 43, 56.6 |
| IB2                                           | 14, 18.4 |
| IIA                                           | 9, 11.9 |
| IIB                                           | 10, 13.2 |
| **Histology (n, %)**                          |        |
| Squamous cell carcinoma                       | 54, 71.1 |
| Adenocarcinoma/adenosquamous carcinoma        | 22, 28.9 |
| **Tumor size (cm)**                           |        |
| Mean ± SD                                     | 3.01 ± 1.67 |
| Median (range)                                | 3 (0-8.5) |
| **Lymphovascular invasion (n, %)**            | 59, 77.6 |
| **Deep stromal invasion (n, %)**              | 46, 60.5 |
| **Parametrial invasion (n, %)**               | 28, 36.8 |
| **Lymph node metastasis (n, %)**              | 22, 28.9 |
| **Tumor budding characteristics**             |        |
| Intratumor budding counts                     |        |
| Mean ± SD                                     | 6.40 ± 9.61 |
| Median (range)                                | 3.5 (0-40) |
| Peritumoral budding counts                    |        |
| Mean ± SD                                     | 7.49 ± 9.42 |
| Median (range)                                | 4 (0-44) |
| Intratumoral budding (n, %)                   | 47, 61.8 |
| Peritumoral budding (n, %)                    | 62, 81.6 |

FIGO = International Federation of Gynecologic Obstetrics
Table 2. Comparison of radiomic features according to the tumor budding status.
|                  | Total (n=76) | Intratumor budding | Peritumoral budding |
|------------------|-------------|-------------------|---------------------|
|                  | Yes (n=47)  | No (n=29)         | p       | Yes (n=62) | No (n=14) | p       |
| Valuables        |             |                   |         |             |           |         |
| Conventional metabolic parameters |             |                   |         |             |           |         |
| SUVmax           |             |                   |         |             |           |         |
| Mean ± SD        | 12.30 ± 7.84| 12.73 ± 6.48      | 11.60 ± 9.75 | 0.0406 | 12.11 ± 7.69 | 13.11 ± 8.76 | 0.8828 |
| Median (range)   | 10.64 (3.28-48.94) | 11.35 (5.25-39.79) | 8.37 (3.28-48.94) | | 10.50 (4.13-48.94) | 13.34 (3.28-35.52) |
| MTV              |             |                   |         |             |           |         |
| Mean ± SD        | 20.64 ± 29.09 | 23.18 ± 34.60     | 16.52 ± 16.45 | 0.2548 | 20.78 ± 30.78 | 20.05 ± 20.82 | 0.8723 |
| Median (range)   | 13.79 (2.15-220.00) | 15.21 (2.44-220.00) | 10.73 (2.15-76.79) | | 14.49 (2.15-220.00) | 11.79 (6.51-76.79) |
| TLG              |             |                   |         |             |           |         |
| Mean ± SD        | 170.65 ± 478.22 | 219.30 ± 600.25   | 91.81 ± 101.10 | 0.0606 | 179.81 ± 526.27 | 130.08 ± 132.62 | 0.8407 |
| Median (range)   | 78.75 (11.16-4118.4) | 85.97 (15.76-4118.40) | 57.09 (11.16-488.82) | | 78.74 (11.16-4118.40) | 77.05 (19.25-488.82) |
| Radiomic features |             |                   |         |             |           |         |
| GLCM Entropy     |             |                   |         |             |           |         |
| Mean ± SD        | 7.68 ± 1.30 | 7.98 ± 1.10       | 7.21 ± 1.46 | 0.0111 | 7.70 ± 1.19 | 7.62 ± 1.76 | 0.8500 |
| Median (range)   | 7.662 (4.89-10.22) | 7.78 (5.85-10.22) | 6.99 (4.89-9.88) | | 7.57 (4.98-10.22) | 8.10 (4.89-9.88) |
| NGLDM Coarseness |             |                   |         |             |           |         |
| Mean ± SD        | 0.0204 ± 0.0157 | 0.0170 ± 0.0128   | 0.0258 ± 0.0186 | 0.0497 | 0.0194 ± 0.0138 | 0.0249 ± 0.0225 | 0.7276 |
| Median (range)   | 0.0140 (0.0002-0.0757) | 0.0129 (0.0002-0.0514) | 0.0239 (0.0025-0.0757) | | 0.0147 (0.0002-0.0560) | 0.0125 (0.0054-0.0757) |
|                      | GLRLM                  | Low Gray-level Run | Long-Run Low Gray-level |
|----------------------|------------------------|--------------------|-------------------------|
|                      | Emphasis               | Mean ± SD          | Median (range)          |
|                      |                        |                    |                         |
|                      |                        | 0.0073 ± 0.0040    | 0.0071 (0.0013-0.0213)  |
|                      |                        | 0.0065 ± 0.0034    | 0.0081 (0.0013-0.0160)  |
|                      |                        | 0.0087 ± 0.0044    | 0.0189 (0.0020-0.0213)  |
|                      | 0.0068 ± 0.0034        | 0.0068 (0.0014-0.0299) |
|                      | 0.0096 ± 0.0054        | 0.0096 (0.0022-0.0322) |
|                      | 0.0939                 | 0.0939             |                         |
|                      |                        | 0.0065 ± 0.0034    | 0.0057 (0.0013-0.0160)  |
|                      |                        | 0.0085 ± 0.0056    | 0.0081 (0.0013-0.0213)  |
|                      |                        | 0.0120 ± 0.0071    | 0.0189 (0.0020-0.0213)  |
|                      | 0.0090 ± 0.0054        | 0.0090 (0.0014-0.0299) |
|                      | 0.0134 ± 0.0093        | 0.0134 (0.0022-0.0322) |
|                      |                        | 0.0939             |                         |
| Valuables                        | Total (n=76) | Intratumor budding | Peritumoral budding |
|---------------------------------|--------------|--------------------|--------------------|
|                                  | Yes (n=47)   | No (n=29)          | p                  | Yes (n=62)   | No (n=14) | p      |
| GLZLM                            |              |                    |                    |              |           |        |
| Low Gray-level Zone Emphasis     | 0.0079 ± 0.0051 | 0.0069 ± 0.0045  | 0.0096 ± 0.0061   | 0.0137       | 0.0074 ± 0.0040 | 0.0104 ± 0.0081 | 0.2547 |
| Mean ± SD                        | 0.0071       | 0.0060             | 0.0085             | 0.0154       | 0.0070       | 0.0079             |        |
| Median (range)                   | (0.0014-0.0327) | (0.0014-0.0206)  | (0.0021-0.0327)   |              | (0.0014-0.0206) | (0.0021-0.0327)   |        |
| Short-Zone Low Gray-level Emphasis | 0.0045 ± 0.0026 | 0.0039 ± 0.0019  | 0.0054 ± 0.0033   | 0.0056       | 0.0042 ± 0.0020 | 0.0058 ± 0.0043 | 0.2492 |
| Mean ± SD                        | 0.0039       | 0.0036             | 0.0047             |              | 0.0038       | 0.0043             |        |
| Median (range)                   | (0.0008-0.0183) | (0.0011-0.0100) | (0.0084-0.0183)   |              | (0.0008-0.0100) | (0.0016-0.0183)   |        |
| Zone Length Non-Uniformity Zone  | 12.95 ± 11.89 | 15.47 ± 13.76     | 8.88 ± 6.28       | 13.53 ± 12.55| 10.42 ± 8.22 |              |        |
| Mean ± SD                        | 9.63         | 11.86              | 7.55              |              | 9.63         | 8.58              |        |
| Median (range)                   | (1.88-80.85) | (3.40-80.85)      | (1.88-32.24)      |              | (1.88-80.85) | (2.77-32.24)      |        |
| Shape and Size                   |              |                    |                    |              |           |        |
| Sphericity                       | 5208.48 ± 4024.88 | 5676.9 ± 4507.4 | 3963.1 ± 2723.4   | 0.0065       | 5238.6 ± 4203.5 | 5075.1 ± 3244.7 | 0.9040 |
| Mean ± SD                        | 4249.8       | 4894.7             | 3319.1            |              | 4362.1       | 4005.5            |        |
| Median (range)                   | (714.7-26258.1) | (1227.2-26258.8) | (714.7-11649.2)   |              | (1122.0-26258.8) | (714.7-11649.2)   |        |
| Compaity                         | 0.0108       |                    |                   |              | 0.4859       |              |        |
| Mean ± SD                        | 4.44 ± 1.32  | 4.75 ± 1.34        | 3.95 ± 1.16       | 4.42 ± 1.34  | 4.52 ± 1.29  |              |        |
| Median (range)                   | 4.27         | 4.58               | 3.77              | 4.23         | 4.35        |              |        |
|                                | (2.27-8.88)  | (2.76-8.88)        | (2.27-6.28)       | (2.39-8.88)  | (2.27-6.28) |              |        |
| Histogram                        |              |                    |                    |              |           |        |

Note: The table provides statistical values for various features, including GLZLM and Sphericity, with mean, standard deviation (±), median, and range values for both intratumor and peritumoral budding, along with associated p-values.
| Feature       | Mean ± SD | Median (range) | Mean ± SD | Median (range) | Mean ± SD | Median (range) |
|---------------|-----------|----------------|-----------|----------------|-----------|----------------|
| Kurtosis      | 3.00 ± 0.94 | 2.81 ± 0.68 | 3.30 ± 1.21 | 0.0267 ± 0.80 | 2.94 ± 1.42 | 0.7682         |
| Entropy Hist  | 2.72 (1.76-7.47) | 2.63 (1.76-5.05) | 2.84 (2.12-7.47) | 2.72 (1.76-5.96) | 2.69 (2.15-7.47) | 0.0130 ± 0.0403 | 0.0576 (0.0212-0.1820) |
| Mean ± SD     | 4.33 ± 0.76 | 4.50 ± 0.63 | 4.06 ± 0.88 | 4.33 ± 0.69 | 4.34 ± 1.05 |
| Energy Hist   | 4.40 (2.68-5.74) | 4.50 (3.18-5.74) | 4.01 (2.68-5.49) | 0.0200 (2.68-5.74) | 4.77 (2.71-5.49) | 0.0591 ± 0.0320 | 0.0518 (0.0212-0.1820) |
| Mean ± SD     | 0.0685 ± 0.0403 | 0.0591 ± 0.0320 | 0.0836 ± 0.0478 | 0.0670 ± 0.0372 | 0.0749 ± 0.0534 |
| Median (range)| 0.0576 (0.0212-0.1820) | 0.0518 (0.0212-0.1820) | 0.0722 (0.0244-0.1820) | 0.0603 (0.0212-0.1820) | 0.0474 (0.0244-0.1685) |

GLCM = gray-level co-occurrence matrix; GLRLM = gray-level run length matrix; GLZLM = gray-level zone-length matrix; MTV = metabolic tumor volume; NGLDM = neighborhood gray-level different matrix; SUVmax= maximum standardized uptake; TLG= total lesion glycolysis.

**Table 3.** Multiple logistic regression analysis for the evaluation of the correlation between radiomic features and intratumor budding status.
| Variables                              | Univariate analysis |        | Multivariate analysis |        |
|---------------------------------------|---------------------|--------|-----------------------|--------|
|                                       | Odds ratio          | 95% CI | p                     | Odds ratio | 95% CI | p     |
| Conventional metabolic parameters     |                     |        |                       |          |        |       |
| SUVmax (> 8.858)                      | 3.3393              | 1.2685-8.7908 | 0.0146                | 2.4973   | 0.8933-6.9810 | 0.0810 |
| MTV (cm³, > 16.3)                     | 2.5385              | 0.9092-7.0869 | 0.0753                |          |        |       |
| TLG (> 32.0247)                       | 4.4211              | 1.3282-14.7159 | 0.0154                |          |        |       |
| Radiomic features                     |                     |        |                       |          |        |       |
| GLCM                                  |                     |        |                       |          |        |       |
| EntropyGLCM (> 7.1782)                | 5.3554              | 1.9520-14.6928 | 0.0011                | 0.6139  | 0.0708-5.3208 | 0.6579 |
| NGLDM                                 |                     |        |                       |          |        |       |
| Coarseness (≤ 0.0254)                 | 3.9407              | 1.4085-11.0251 | 0.0090                | 1.0604  | 0.2057-5.4660 | 0.9441 |
| GLRLM                                 |                     |        |                       |          |        |       |
| Low Gray-level Run Emphasis (≤ 0.0081)| 3.4533              | 1.2588-9.4739 | 0.0161                |          |        |       |
|                                      | 3.3393              |         |                       | 0.0146   | 1.6936 | 0.4822-5.9481 | 0.4111 |
| Long-Run Low Gray-level Emphasis (≤ 0.0094) | 1.2685-8.7908 | | | |
| GLZLM                                 |                     |        |                       |          |        |       |
| Low Gray-level Zone Emphasis (≤ 0.0074) | 4.0533              | 1.5196-10.8155 | 0.0052                |          |        |       |
|                                      | 3.9407              |         |                       | 0.0090   |        |       |
| Short-Zone Low Gray-level Emphasis (≤ 0.005) | 9.1607              | 1.4085-11.0251 | 0.0051                | 5.3971   | 0.9464-30.7790 | 0.0577 |
| Zone Length Non-Uniformity Zone (> 14.1652) | 1.9444-43.1600 | | | |
| Shape and Size                        |                     |        |                       |          |        |       |
| Sphericity (> 4160.0834)              | 6.0893              | 2.1463-17.2763 | 0.0007                |          |        |       |
| Compacity (> 3.4057)                  | 8.7344              | 2.4798-30.7648 | 0.0007                | 5.0047   | 1.1636-21.5253 | 0.0305 |
| Histogram                              |                     |        |                       |          |        |       |
| Kurtosis (≤ 3.1264)                   | 3.9609              | 1.3783-11.3826 | 0.0106                |          |        |       |
| Entropy_{Hist} (> 4.0608) | 5.9815 | 2.1219-16.8615 | 0.0007 | 2.9011 | 0.4526-18.5937 | 0.2611 |
|--------------------------|--------|-----------------|--------|--------|---------------|--------|
| Energy_{Hist} (≤ 0.0688) | 5.9815 | 2.1219-16.8615 | 0.0007 |        |               |        |

Cl= confidence interval  
GLCM= gray-level co-occurrence matrix;  
GLRLM= gray-level run length matrix;  
GLZLM= gray-level zone-length matrix;  
MTV= metabolic tumor volume;  
NGLDM= neighborhood gray-level different matrix;  
SUVmax= maximum standardized uptake;  
TLG= total lesion glycolysis.