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ONCOLOGY

# Renal cell carcinoma: predicting RUNX3 methylation level and its consequences on survival with CT features

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## Abstract

**Purpose** To investigate associations between CT imaging features, RUNX3 methylation level, and survival in clear cell renal cell carcinoma (ccRCC).

**Materials and methods** Patients were divided into high RUNX3 methylation and low RUNX3 methylation groups according to RUNX3 methylation levels (the threshold was identified by using X-tile). The CT scanning data from 106 ccRCC patients were retrospectively analyzed. The relationship between RUNX3 methylation level and overall survivals was evaluated using the Kaplan-Meyer analysis and Cox regression analysis (univariate and multivariate). The relationship between RUNX3 methylation level and CT features was evaluated using chi-square test and logistic regression analysis (univariate and multivariate).

**Results** $\beta$ value cutoff of 0.53 to distinguish high methylation ($N = 44$) from low methylation tumors ($N = 62$). Patients with lower levels of methylation had longer median overall survival (49.3 vs. 28.4) months (low vs. high, adjusted hazard ratio [HR] 4.933, 95% CI 2.054–11.852, $p < 0.001$). On univariate logistic regression analysis, four risk factors (margin, side, long diameter, and intratumoral vascularity) were associated with RUNX3 methylation level (all $p < 0.05$). Multivariate logistic regression analysis found that three risk factors (side: left vs. right, odds ratio [OR] 2.696; $p = 0.024$; 95% CI 1.138–6.386; margin: ill-defined vs. well-defined, OR 2.685; $p = 0.038$; 95% CI 1.057–6.820; and intratumoral vascularity: yes vs. no, OR 3.286; $p = 0.008$; 95% CI 1.367–7.898) were significant independent predictors of high methylation tumors. This model had an area under the receiver operating characteristic curve (AUC) of 0.725 (95% CI 0.623–0.827).

**Conclusions** Higher levels of RUNX3 methylation are associated with shorter survival in ccRCC patients. And presence of intratumoral vascularity, ill-defined margin, and left side tumor were significant independent predictors of high methylation level of RUNX3 gene.

**Key Points**

- *RUNX3 methylation level is negatively associated with overall survival in ccRCC patients.*
- *Presence of intratumoral vascularity, ill-defined margin, and left side tumor were significant independent predictors of high methylation level of RUNX3 gene.*

**Keywords** Clear cell renal cell carcinoma · Computed tomography · Radiogenomics

Dongzhi Cen and Li Xu contributed equally to this work.

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**Abbreviations**

| | |
|---|---|
| AUC | Area under the curve |
| ccRCC | Clear cell RCC |
| CI | Confidence interval |
| HR | Hazard ratio |
| NCI | National Cancer Institute |
| OR | Odds ratio |
| RCC | Renal cell carcinoma |
| RUNX3 | Runt-related transcription factor-3 |
| TCIA | The Cancer Imaging Archive |

Renal cell carcinoma (RCC) affects nearly 300,000 individuals worldwide annually, and its incidence is increasing. Clear cell RCC (ccRCC) is the most common histological subtype, accounting for 80–90% of all renal cortical tumors [1, 2]. Fuhrman grade and TNM stage remain the most commonly used predictors for survival in patients with ccRCC. However, patients with similar clinical features may have diverse outcomes. Consequently, there is a need to add prognostic value to the current staging system, which could be achieved with the use of validated biomarkers [3–5].

As DNA methylation is an important factor for cancer formation, it has attracted increasing attention as a biomarker for diagnosis and prognosis [3, 6–8]. The runt-related transcription factor-3 (RUNX3) gene belongs to the runt domain family of transcription factors that act as master regulators of gene expression in major developmental pathways [9]. RUNX3 gene is a known tumor suppressor gene which exhibits potent antitumor activity in several carcinomas [10–12]. RUNX3 gene contributes to tumorigenesis and metastasis at different levels, such as epithelial-mesenchymal transition, adhesion, migration, and invasion [12–14]. DNA methylation alters biological functions through regulating the stabilization of genomic sequences or the expressions of genes [15, 16]. There has been evidence that RUNX3 methylation level is negatively associated with survival [17–19].

In recent years, a new direction in cancer research has emerged that focuses on the relationship between imaging phenotypes and genomics. This direction is referred to as radiogenomics or imaging genomics [20–22]. Radiogenomics aims to correlate imaging characteristics (i.e., the imaging phenotype) with gene expression patterns, gene mutations, and other genome-related characteristics and is designed to facilitate a deeper understanding of tumor biology and capture the intrinsic tumor heterogeneity [23, 24]. RUNX3 methylation level is negatively associated with overall survival. And several CT features of ccRCC also correlate with overall survival [16, 25]. Radiogenomics analysis of ccRCC revealed associations between mRNA-based subtyping (m1-subtype and m3-subtype) and CT features [26]. Radiogenomics analysis of ccRCC also revealed associations between underlying mutations (VHL, PBRM1, SETD2, KDM5C, and BAP1) and CT features [26, 27]. However, so far, no study has investigated associations between RUNX3 methylation level, CT imaging features, and survival in ccRCC. Therefore, the aim of this hypothesis-generating radiogenomics study was to explore relationship between RUNX3 methylation level, CT imaging features of ccRCC, and OS.

## Materials and methods

### Study population

All patient data was acquired from the published TCGA Kidney Renal Clear Cell Carcinoma (TCGA-KIRC) project (http://cancergenome.nih.gov/), and within this publication, it is stated "Specimens were obtained from patients, with appropriate consent from institutional review boards." TCGA level 3 data were downloaded from the TCGA FTP site: methylation $\beta$ value (Illumina HumanMethylation450 BeadChip) and clinical data. Methylation $\beta$ value were normalized by the $Z$-score method as described previously [28, 29]. The Infinium HumanMethylation450 BeadChip Kit uses the Infinium HD Methylation Assay and is compatible with the iScan and HiScan systems. Details of $\beta$ value used in this study are described in the Data Supplement (Table E1). For the subset of the KIRC patients from TCGA, the CT exams were made available by The Cancer Imaging Archive (TCIA) through a collaborative effort between the National Cancer Institute (NCI) and multiple clinical institutions in the USA (http://cancerimagingarchive.net/).

The inclusion criteria for the study were as follows: (1) available CT images from TCIA, (2) data were available to evaluate the CT features mentioned below ("Radiologist review of CT images" features i–ix), (3) RUNX3 methylation levels were available (lower levels of methylation or higher levels of methylation). A total of 106 patients met the selection criteria.

### Radiologist review of CT images

The detailed assessment criteria for the CT features used in this study have been previously described [16, 27]. Two experienced radiologists, blinded to the RUNX3 methylation level and clinical information, independently reviewed the CT imaging. Discrepancies between the two radiologists were settled by consensus. All CT imaging features were evaluated: (i) tumor architecture (solid or multicystic), (ii) margin (ill-defined or well-defined), (iii) intratumoral calcifications (presence or absence), (iv) collecting system invasion (presence or absence), (v) necrosis (presence or absence), (vi) renal vein invasion (presence or absence), (vii) enhancement (homogeneous or nodular), (viii) gross evidence of intratumoral vascularity (yes vs. no), (ix) long diameter (< 70 mm vs. ≧ 70 mm).

## Statistical analysis

To evaluate interreader agreements regarding qualitative CT feature analyses between the two readers, Fleiss' kappa was calculated separately for each feature. Patients were divided into two groups according to RUNX3 methylation levels (the threshold was identified by using X-tile [30]): (1) lower levels of methylation ($\beta <$ threshold); (2) higher levels of methylation ($\beta \geq$ threshold). The relationship between RUNX3 methylation level and overall survivals was evaluated using the Kaplan-Meyer analysis and Cox regression analysis (univariate and multivariate) [31]. Adjusted hazard ratio (HR) was obtained. The relationship between RUNX3 methylation level and CT features (features i–ix) was evaluated using chi-square test and logistic regression analysis (univariate and multivariate). Heat map was drawn to show a visual representation of RUNX3 methylation level (low methylation and high methylation). A univariate analysis of variables was carried out using a chi-square test with a $p$ value of $< 0.05$ as the limit of statistical significance. The variables that obtained a $p$ value $< 0.05$ with univariate analysis were subjected to multistep multivariate binary logistic regression (version 21.0; SPSS Company, Chicago, IL). The discrimination of the models was assessed [32–34]. It is measured using the receiver operating characteristic curve and summarized by the area under the curve (AUC). Statistical significance was set at $p < 0.05$.

## Results

Patients with lower levels ($\beta$ 0.46 ± 0.05) of methylation, compared with patients with higher levels ($\beta$ 0.61 ± 0.06), had longer median overall survival (49.3 vs. 28.4) months (low vs. high, adjusted HR 4.933, 95% CI 2.054–11.852, $p < 0.001$). OS was assessed using the Kaplan-Meyer analysis (log rank = 23.723, $p < 0.001$; Fig. 1). Univariate Cox regression analysis of prognostic factors for overall survival is summarized in Fig. 2. On multivariable Cox regression analysis, predictors of mortality in ccRCC were the lower levels of RUNX3 methylation (HR, 4.933; 95% CI, 2.054–11.852; $p < 0.001$), advanced stage (HR, 10.821; 95% CI, 4.819–24.303; $p < 0.001$), and age (HR, 1.051; 95% CI, 1.014–1.090; $p =$ 0.007; Table E2). Demographic and tumor characteristics of all 106 patients are summarized in Table 1. Interreader agreements for the assessment of qualitative tumor features on CT images were excellent ($\kappa = 0.854$–1; Table E3).

Frequencies of all qualitative CT features per RUNX3 methylation level are illustrated in Fig. 3 and Table 2. Low methylation subtype rates were significantly higher (a) in right side (41 of 62 [66.1%]) lesions than in left side lesions (21 of 62 [33.9%]) ($p = 0.019$), (b) in diameter < 70-mm lesions (46 of 62 [74.2%]) than in ≧ 70-mm lesions (16 of 62 [25.8%]) ($p = 0.003$), and (c) in well-defined lesions (49 of 62 [79.0%])

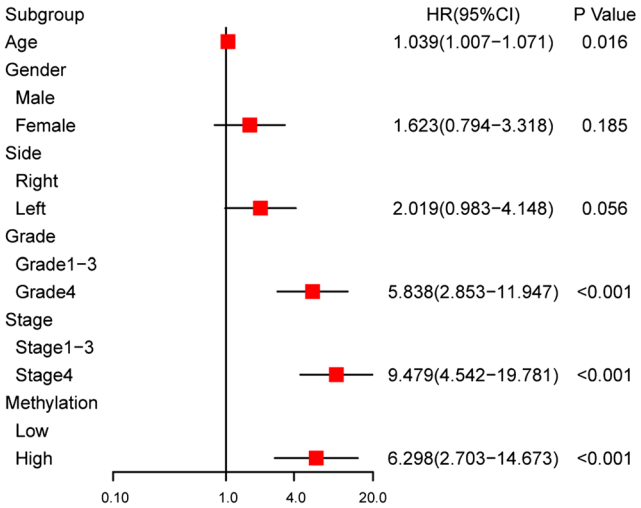


**Fig. 1** OS were assessed using Kaplan-Meyer analysis (log rank = 23.723; $p < 0.001$)

than in ill-defined lesions (13 of 62 [21.0%]) ($p = 0.026$) and (d) in absence of intratumoral vascularity lesions (48 of 62 [77.4%]) than in presence of intratumoral vascularity lesions (14 of 62 [22.6%]) ($p = 0.002$).

On univariate logistic regression analysis, side (left vs. right, odds ratio [OR] 2.569; $p = 0.02$; 95% CI 1.160–5.690) and long diameter (≧ 70 mm vs. < 70 mm, OR 3.450; $p =$ 0.003; 95% CI 1.516–7.849), margin (ill-defined vs. well-defined, OR 2.609; $p = 0.028$; 95% CI 1.107–6.150), and intratumoral vascularity (yes vs. no, OR 3.755; $p = 0.002$; 95% CI 1.622–8.692) were associated with high methylation subtype. Results from all risk analyses are summarized in Fig. 4.

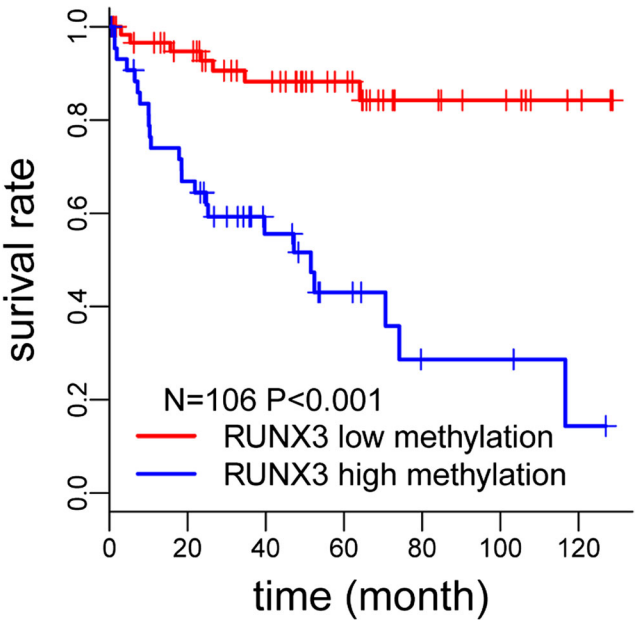


**Fig. 2** Univariate Cox regression analysis of prognostic factors for overall survival is summarized

**Table 1** Patient demographics and RUNX3 promoter methylation status information

| Variables | |
|---|---|
| Gender | |
| Female | 33.0% (35/106) |
| Male | 67.0% (71/106) |
| Side | |
| Left | 43.4% (46/106) |
| Right | 56.6% (60/106) |
| Stage | |
| Stage I | 50.9% (54/106) |
| Stage II | 8.5% (9/106) |
| Stage III | 21.7% (23/106) |
| Stage IV | 18.9% (20/106) |
| Lymph node | |
| N0 | 38.7% (41/106) |
| N1 | 1.9% (2/106) |
| Nx | 59.4% (63/106) |
| History neoadjuvant treatment | |
| No | 97.2% (103/106) |
| Yes | 2.8% (3/106) |
| Fuhrman grade | |
| Grade 1 | 36.8% (39/106) |
| Grade 2 | 1% (1/106) |
| Grade 3 | 44.3% (47/106) |
| Grade 4 | 17.9% (19/106) |
| RUNX3 promoter methylation status | |
| High methylation | 41.50% (44/106) |
| Low methylation | 58.50% (62/106) |

Multivariate logistic regression analysis found that three risk factors (side: left vs. right, OR 2.696; $p = 0.024$; 95% CI 1.138–6.386; margin: ill-defined vs. well-defined, OR 2.685; $p = 0.038$; 95% CI 1.057–6.820; and intratumoral vascularity: yes vs. no, OR 3.286; $p = 0.008$; 95% CI 1.367–7.898) were significant independent predictors of high methylation subtype (Table 3 and Fig. 5). This model had an area under the receiver operating characteristic curve (AUC) of 0.725 (95% CI 0.623–0.827; Fig. 6).

## Discussion

Kidney cancer is a genetically heterogeneous and biologically diverse disease. Aberrant DNA methylation in promoter region is increasingly thought to be a common event in primary human cancers and has been associated with silencing of important tumor suppressor genes [35, 36]. In this study, we investigated associations between CT imaging features, RUNX3 methylation level, and survival in ccRCC. Our proposed model showed good performance (AUC 0.725), suggesting that presence of intratumoral vascularity, ill-defined margin, and left side tumor were significant independent predictors of high methylation level of RUNX3 gene. What's more, higher levels of RUNX3 methylation are associated with shorter survival in ccRCC patients.

The relation between DNA methylation and prognosis has been investigated [37]. Previous studies reported that distinct overall survival advantage was associated with the RUNX3 methylation level [17, 18]. In this study, patients with lower levels of methylation, compared with patients with higher levels, had longer median overall survival months. This is consistent with previous studies [17, 18]. As the use of clinic-pathologic genomic profiling has grown, the practice of correlating radiological images with genomic features of tumors has also expanded [38–40].

CT imaging can noninvasively visualize tumor phenotype characteristics at the macroscopic level [16]. Previous study confirmed that presence of intratumoral vasculature can be potential prognostic feature to screen patients for unfavorable prognosis of ccRCC patients [16, 41]. Radiogenomics may be an attractive alternative tool to identify disease genomics by

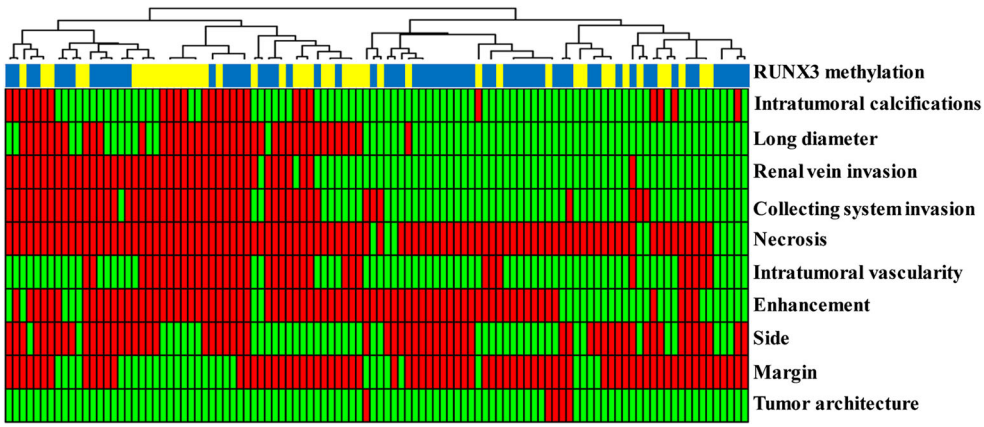


**Fig. 3** Hierarchical clustering yielded distinct groups of RUNX3 promoter methylation status and CT features. Red-positive green-negative

**Table 2** Association between RUNX3 promoter methylation status and CT features (chi-square test and univariate logistic regression analysis)

| | Low-Methy | High-Methy | $\chi^2$ | *p* | Univariate OR |
|---|---|---|---|---|---|
| Side | | | 5.517 | 0.019 | |
| Right | 41 (66.1) | 19 (43.2) | | | Ref |
| Left | 21 (33.9) | 25 (56.8) | | | 2.569 |
| Long diameter | | | 9.047 | 0.003 | |
| < 70 mm | 46 (74.2) | 20 (45.5) | | | Ref |
| ≧ 70 mm | 16 (25.8) | 24 (54.5) | | | 3.450 |
| Necrosis | | | 4.515 | 0.043 | |
| No | 9 (14.5) | 1 (2.3) | | | Ref |
| Yes | 53 (85.5) | 43 (97.7) | | | 7.302 |
| Intratumoral vascularity | | | 9.986 | 0.002 | |
| No | 48 (77.4) | 21 (47.7) | | | Ref |
| Yes | 14 (22.6) | 23 (52.3) | | | 3.755 |
| Calcification | | | 2.160 | 0.142 | |
| No | 50 (80.6) | 30 (68.2) | | | Ref |
| Yes | 12 (19.4) | 14 (31.8) | | | 1.944 |
| Margin | | | 4.946 | 0.026 | |
| Well-defined | 49 (79.0) | 26 (59.1) | | | Ref |
| Ill-defined | 13 (21.0) | 18 (40.9) | | | 2.609 |
| Renal vein invasion | | | 1.600 | 0.206 | |
| No | 40 (64.5) | 23 (52.3) | | | Ref |
| Yes | 22 (35.5) | 21 (47.7) | | | 1.660 |
| Collecting system invasion | | | 2.094 | 0.148 | |
| No | 37 (59.7) | 20 (45.5) | | | Ref |
| Yes | 25 (40.3) | 24 (54.5) | | | 1.776 |
| Tumor architecture | | | 0.005 | 1 | |
| Multicystic | 3 (4.8) | 2 (4.5) | | | Ref |
| Solid | 59 (95.2) | 42 (95.5) | | | 1.068 |
| Enhancement | | | 0.057 | 0.811 | |
| Homogeneous | 17 (27.4) | 13 (29.5) | | | Ref |
| Nodular | 45 (72.6) | 31 (70.5) | | | 1.110 |

analyzing amounts of features extracted from medical images [42].

Radiogenomics aims to correlate imaging characteristics with gene expression patterns, gene mutations, and other genome-related characteristics and is designed to facilitate a deeper understanding of tumor biology and capture the intrinsic tumor heterogeneity [23, 43]. In previous studies, Lan [26] found that m1-subtype rates (mRNA-based subtyping) were significantly higher in well-defined margin tumors. And Lan [26] also revealed that m3-subtype rates were significantly higher in collecting system invasion lesions and ill-defined margin lesions. Karlo [27] found that mutations of VHL were significantly associated with gross appearance of intratumoral vascularity, nodular tumor enhancement, and well-defined tumor margins. Karlo [27] also revealed that mutations of BAP1 and

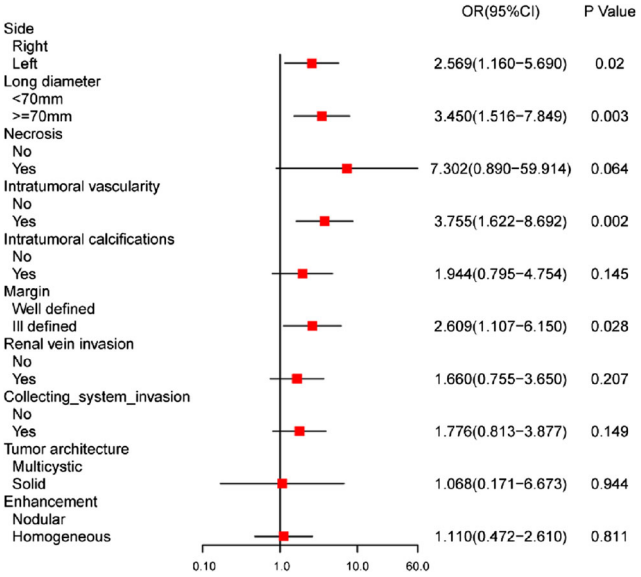


**Fig. 4** Univariate logistic regression analysis demonstrated that four risk factors were significantly associated with high methylation subtype

**Table 3** Binary logistic regression analysis of prognostic factors for RUNX3 promoter methylation status

| | *β* | *p* | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Left side | 0.992 | 0.024 | 2.696 | 1.138 | 6.386 |
| With intratumoral vascularity | 1.190 | 0.008 | 3.286 | 1.367 | 7.898 |
| Ill-defined margin | 0.988 | 0.038 | 2.685 | 1.057 | 6.820 |
| Constant | − 1.527 | < 0.001 | 0.217 | | |

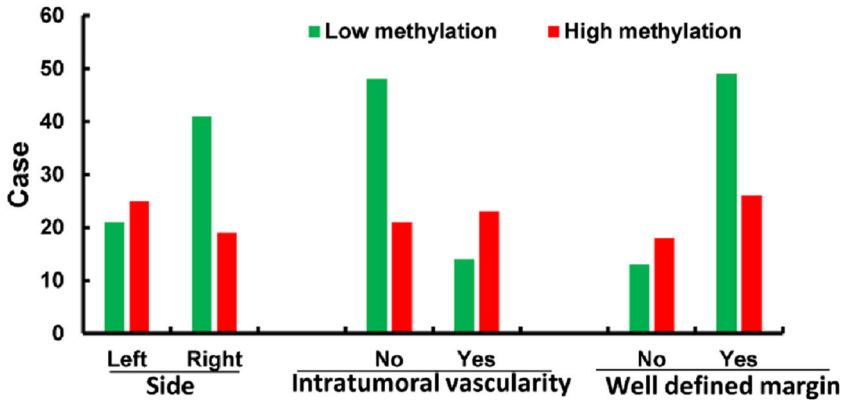


**Fig. 5** $\beta$ values for each patient regarding the classification of tumor side (left vs. right), margin (ill-defined vs well-defined), and intratumoral vascularity (yes vs. no) in subgroups

KDM5C were significantly associated with evidence of renal vein invasion. To our knowledge, this is the first study that revealed the relationship between high methylation tumors and CT imaging features. The findings have the potential to reflect tumor biology and predict prognosis [44].

There are several limitations. Firstly, this was a retrospective study and the CT data sets are also very heterogeneous in terms of CT scanner modalities, acquisition protocols, and manufacturers. Secondly, it is insufficient to just conclude that several CT features are more often seen in certain subgroups. To our knowledge, this is the first study that found the relationship between RUNX3 methylation level and CT features. For this reason, the discussion lacks an evaluation of the available literature on this topic. This work is a preliminary exploratory study. Thirdly, in trials with survival outcomes, the current practice applies an interaction testing procedure and chooses the cut point that minimizes the $p$ values for the tests. Future study will focus on external validation of the model.

In conclusion, higher levels of RUNX3 methylation are associated with shorter survival. And this preliminary exploratory study of ccRCC found associations between RUNX3 methylation level and CT features. And presence of intratumoral vascularity, ill-defined margin, and left side tumor were significant independent predictors of high methylation level of RUNX3 gene. These results should be further validated.

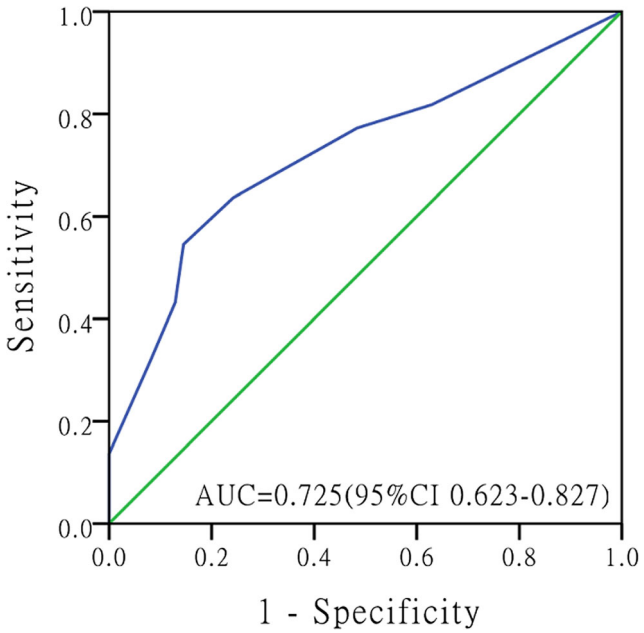


**Fig. 6** ROC curve analysis showed acceptable good discrimination (AUC = 0.725)

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Siwei Zhang.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was not required for this study.

**Ethical approval** Institutional Review Board approval was obtained.

**Methodology**
- retrospective
- prognostic study
- performed at one institution

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