

# Diameter of Superior Rectal Vein – CT Predictor of KRAS mutation in Rectal Carcinoma

**Chenyu Song**

The first affiliated hospital, Sun Yat-sen University

**Bingqi Shen**

Sun Yat-sen University, First affiliated Hospital

**Zhi Dong**

Sun Yat-sen University First Affiliated Hospital

**Zhenzhen Fan**

Sun Yat-sen University First Affiliated Hospital

**Ling Xu**

faculty of medicine and dentistry, university of western Australia

**Zi-Ping Li**

Sun Yat-sen University First Affiliated Hospital

**Yin Li**

Sun Yat-sen University, First Affiliated Hospital

**Shi-Ting Feng** (✉ [fengsht@mail.sysu.edu.cn](mailto:fengsht@mail.sysu.edu.cn))

Sun Yat-sen University First Affiliated Hospital <https://orcid.org/0000-0002-0869-7290>

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## Research article

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# Abstract

**Background** The purpose of this study was to investigate the feasibility of CT parameters to predict the presence of KRAS mutation in rectal cancer patients. The relationship between KRAS mutation and pathological findings was evaluated simultaneously.

**Methods** 89 patients (29 females, 60 males, age 27–90, mean  $59.7 \pm 12$  years) with pathologically proven rectal cancer were enrolled. KRAS mutation test was completed following surgery. Parameters evaluated on CT included the diameter of superior rectal vein (SRV) and inferior mesenteric vein (IMV), the presence of calcification, ulceration, lymph node enlargement (LNE), distant metastasis, tumor growth pattern (single nodule or annular thickening), enhanced pattern (homogeneous or heterogeneous), CT ratio and the length of tumor (LOT). Pathological findings included lymphovascular emboli, signet ring cell, peripheral fat interval infiltration, focal ulcer, lymph node metastasis, tumor pathological type and differentiation extent. The correlations between KRAS status and CT parameters, KRAS status and pathological findings were investigated. The accuracy of CT characteristics for predicting KRAS mutation was evaluated.

**Results** KRAS mutation was detected in 42 cases. On CT image, the diameter of SRV was significantly increased in KRAS mutation group than in KRAS wild-type group ( $4.6 \pm 0.9$  mm vs.  $4.2 \pm 0.9$  mm,  $p = 0.02$ ). And LNE was more likely to occur in KRAS mutation group (73.3% vs. 26.7%,  $p = 0.03$ ). There was no significant difference between KRAS mutation group and KRAS wild-type group on the other CT parameters (IMV, calcification, ulcer, distant metastasis, tumor growth pattern, enhanced pattern, CT ratio and LOT). In pathological findings, KRAS mutation was more likely to occur in middle differentiation group ( $p = 0.03$ ). No significant difference was found between KRAS mutation group and KRAS wild-type group in the presence of lymphovascular emboli, signet ring cell, peripheral fat interval infiltration, focal ulcer, lymph node metastasis, tumor pathological type. The AUC of SRV to predict KRAS mutation was 0.63.

**Conclusion** It was feasible to use the diameter of SRV to predict KRAS mutation in rectal cancer patients, and LNE also can be regarded as an important clue on preoperative CT images.

## Background

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world [1]. Rectal carcinoma accounts nearly for 30–35% of all the CRC cases [2]. In China, the incidence of CRC was approximately 37.6 per 100,000, with a mortality of 19.1 per 100,000 [3]. From 1972 to 2005, the rates of rectal cancer have increased from 7.68 and 6.51 to 11.45 and 8.28 per 100,000 in males and females, respectively [4]. Nevertheless, with the improvement of therapeutic regimen, decreasing rectal cancer mortality have been observed [5]. Anti-EGFR (epidermal growth factor receptor) drug is proven effective to rectal cancer. However, tumor response to anti-EGFR drug is significantly related to presence of KRAS (kirsten rat sarcoma viral oncogene homologue)

mutation. Generally, metastatic CRC patients with KRAS mutation tend to be resistant to anti-EGFR therapy [6, 7]. According to American society of clinical oncology, if KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment [8]. For this reason, KRAS mutation evaluation shows great importance for rectal cancer patients before pharmaceutical treatment is commenced.

Commonly, KRAS status (mutated type or wild type) is tested in postoperative pathology specimens. However, patients with advanced or metastatic rectal carcinoma may not receive surgery treatment or obtain specimens for testing. Biopsy through colonoscopy is one of the main invasive methods of specimen acquisition for KRAS status testing. The accuracy is influenced by sampling error and tumor heterogeneity. According to Jahn, Stephan W et al., different metastatic lymph nodes could be segregated into multiple intra-tumoral KRAS mutations [9]. And despite the clinical success in gene testing, potential loss of gene information during DNA extraction process is still an unavoidable factor.

As non-invasive methods, medical imaging could be adapted for further assessment of neoplastic features. Though, MRI (magnetic resonance imaging) has been regarded as the first choice of local staging in rectal carcinoma, for patients with MRI contraindications, contrast enhanced CT also presents its great value for diagnosis. There has been an increasing amount of studies exploring the correlation between cancer biological markers and imaging findings. A few studies have focused on predicting KRAS mutation through various imaging methods such as PET-CT (positron emission tomography–computed tomography) [10, 11] and MRI (Magnetic resonance imaging) [12]. However, little research has been performed on predicting KRAS mutation in rectal carcinoma by preoperative MSCT (multi-slice computed tomography) examination. Our study set out to assess the effect of CT parameters to predict KRAS mutation in patients with rectal carcinoma, including observed CT features and anatomical based measurement. Meanwhile, SRV (superior rectal vein) only receives the blood flow from rectum, making SRV particularly sensitive to any factors influencing the biological process of rectum. And SRV has been proved significantly increased in rectal cancer with lymphovascular invasion [13]. In our study, CT parameters, especially SRV, have been assessed to predict KRAS mutation. Lymph node enlargement (LNE), distant metastasis, enhanced pattern, CT ratio and the length of tumor were supposed to imply the different invasive behaviors of rectal carcinoma [5]. And the correlation between pathological findings and KRAS status has also been evaluated.

## Methods

### Patients

This study was conducted in accordance with ethical guidelines for human research and received Institutional Review Board (IRB) or ethical committee approval. Written informed consent was obtained from all patients in the study.

The inclusion criteria are as follows:(1) preoperative CT data;(2) no preoperative chemotherapy or radiation therapy;(3) surgical treatment commenced within 1 week after CT examination;(4) pathological

proven rectal carcinoma;(5) KRAS mutation testing was performed after surgery. The exclusion criteria are as follows: (1) presence of other malignant, infectious, or vascular disease in the abdominopelvic area instead of rectal carcinoma;(2) poor imaging quality for measuring the CT predictors.

A total of 285 patients with surgical proven rectal carcinoma from December 2015 to September 2017 in First Affiliated Hospital of SunYat-Sen University were enrolled in this retrospective study. 187 patients without KRAS mutation evaluation, 3 patients with incompleting CT images, and 6 patients with other malignant tumors were excluded. A total of 89 patients (29 females, 60 males, age 27-90, mean  $59.7 \pm 12$  years) were enrolled in accordance to the above inclusion and exclusion criteria. (Figure1)

## **CT protocol**

All patients underwent enema preparation and fasting 6~8 hours before the CT scan. To expand the intestinal carefully, patients was given 1.6~2.0L 2.5% isotonic mannitol solution 1 hour before the CT scan; 0.4~0.5L 2.5% isotonic mannose at 45min, 30min, and 15min before the CT scan; and 300~500ml saline enema immediately before the CT scan.

All patients were scanned using a 320-detector row CT machine (Aquilion ONE, Toshiba Medical System, Tokyo, Japan), with the same scanning parameters as follow: tube voltage, 120 kV; tube current, 250mA; standard value, 320×0.5mm; slice thickness, 1 mm; slice gap, 1mm. All patients were in supine position, with CT scan range from the top of the diaphragm to the level of the ischial tubercle. Iopromide (Ultravist 300, Schering, Berlin, Germany) was selected as the contrast agent with an injection flow rate of 3.5 mL/s. Unenhanced and enhanced CT scans were taken at 32s and 60s after injecting iopromide respectively. All data were later delivered to the work station (Vitrea2, Toshiba Medical System, Tokyo, Japan) for processing.

## **CT features**

The preoperative CT data of all patients were interpreted independently by two diagnostic radiologists with 15 and 25 years of experience respectively, who were blinded to patients' pathological diagnosis. The diameter of SRV and IMV (inferior mesenteric vein) was measured on preoperative CT images during venous phase. (The minimum diameter of the relevant level was measured.) The diameter of the SRV was measured on the second sacral vertebral plane (Better differentiation of SRV from surrounding adipose tissue due to its position in transverse plane at this level). The diameter of the IMV was measured at 5 mm from its root into the superior mesenteric vein or splenic vein (Figure2, Figure3). Enhanced ratio (ER, the ratio of CT value between lesion and aorta or branch artery at the same plane) and the length of tumor (LOT, length on the sagittal plane) were measured during venous phase. The final data above was taken as the mean value of the two specialists' readings. The presence of calcification and ulcer was observed on unenhanced phase and venous phase, respectively. Tumor shape was divided into two types, nodular shape and annular thickening. Tumor density was observed on unenhanced and enhanced phases, respectively. Unclear boundary of serosa means increased density of the fat interval besides the tumor. The definition of lymph node enlargement is the short axis of lymph node more than

8mm. And lymph node density is also observed on venous phase. The presence of distant metastases refers to carcinoma lesions present in other distant organs or tissues. If two radiologists had any disagreement on above observed CT features, the debating feature would be reread until a consensus.

### **Pathological data and KRAS testing**

The presence of lymph node metastasis, signet ring cell, lymphovascular emboli, focal ulcer and tumor differentiation degree were all confirmed on pathological examination. Peripheral fat interval infiltration refers to the rectal cancer cell breaking through the serosal layer into the perirectal fat interval. Tumor pathological types include adenocarcinoma, mucinous adenocarcinoma and mixed type with well, moderate, and poor differentiation three differentiation extents.

KRAS mutation evaluation was carried out using DNA extracted from paraffin sections (pathological tissue acquired after surgery). Mutational analysis for KRAS was performed using the CFX96 Real-Time PCR Detection System (Bio-Rad, Philadelphia, PA, USA) with PNA clamp™ KRAS mutation detection kit (Panagene, Inc., Daejeon, Korea). Codon 12 and codon 13 were detected.

### **Statistical analysis**

All analyses were performed using SPSS version 25. Two independent sample *T*-test was used in continuous variables between KRAS mutation and KRAS wild type groups when continuous variables were consistent with normal distribution. When continuous variables were not consistent with normal distribution, nonparametric t-test were used in these continuous variables. The difference between KRAS mutation and KRAS wild type groups was analyzed using Chi-squared test for categorical variables, and Fisher's exact test was applied when categorical variables were not consistent with the conditions of the Chi-squared test. Difference with  $p < 0.05$  was considered as statistically significant. Binary logistics regression was used to select variables and the receiver operating characteristic (ROC) curve was used to evaluate the effectiveness of diagnosis through the area under the curve (AUC).

## **Results**

### **CT parameters and KRAS mutation**

The diameter of SRV was significantly increased in KRAS mutation group than in KRAS wild-type group ( $4.6 \pm 0.9$ mm vs.  $4.2 \pm 0.9$ mm,  $p = 0.02$ ). And LNE was more likely to occur in KRAS mutation group (73.3% vs. 26.7%,  $p = 0.03$ ; Figure4, Figure5). No significant difference was found between KRAS mutation group and KRAS wild-type group on the other CT parameters (the diameter of IMV, calcification, ulcer, distant metastasis, tumor growth pattern, enhanced pattern, CT ratio and LOT) (Table 1, Table 2).

### **Pathological findings and KRAS mutation status**

In pathological findings, KRAS mutation was more likely to occur in middle differentiation group ( $p=0.03$ ). No significant difference was found between KRAS mutation group and KRAS wild-type group in the presence of lymphovascular emboli, signet ring cell, peripheral fat interval infiltration, focal ulcer, lymph node metastasis, tumor pathological type (Table 3).

## Discussion

Over the past two decades, the specific clinical significance of KRAS mutation for patients' individual medical management has been studied and applied to patient management [14]. There is a consensus that anti-EGFR antibody therapy is an effective choice for some metastatic rectal carcinoma patients without KRAS mutation [15]. Reasons for patients who cannot benefit from anti-EGFR therapy may be explained by the heterogeneity of tumor. However, medical imaging methods may disclose certain features associated with KRAS mutation. The feasibility of combining medical imaging parameters to predict KRAS mutation has been proven in some previous studies [16, 17, 18]. In the study of Pierre Lovinfosse et al. (19), rectal cancers with KRAS or NRAS mutations display a significantly higher glucose metabolism than wild-type cancers with  $^{18}\text{F}$ -FDG PET/CT imaging. Kenji Kawada et al. [10, 20], found  $^{18}\text{F}$ -FDG accumulation into metastatic CRC assessed by SUVmax (the maximum standardized uptake value for the primary tumor) was associated with KRAS status. As for MRI, Yanyan Xu et al. [21], found that lower mean-ADC (apparent diffusion coefficient) and higher  $D^*$  (pseudodiffusion coefficient) value on MRI with KRAS mutation in rectal carcinoma. And the study of YU RI SHIN et al. [5], showed that KRAS mutation was associated with N stage, gross tumor pattern, axial length of the tumor, and the ratio of the axial to the longitudinal dimensions of the tumor on MRI. So far as we know, there is no study focuses on the correlation between CT image features and KRAS status of rectal cancer.

Our study took in both observed CT features and anatomical based measurement on preoperative CT images and found that the diameter of SRV was significantly increased in positive KRAS mutation patients. However, no significant difference was found between KRAS mutation group and KRAS wild type group in the diameter of IMV. This can be explained by the anatomical characteristics that SRV is the direct vein for rectum. The key point that SRV only receives the blood flow from rectum making SRV particularly sensitive to any factors influencing the biological process of rectum. However, IMV receives blood from both SRV and sigmoid vein, there is decreased accuracy of IMV to predict hemodynamics changes of rectum.

It is well known that the obstruction of proximal vein and increased distal blood flow are two major mechanisms for venous dilatation. Our study excluded patients with other neoplastic, infectious, or vascular diseases to ensure the specificity of SRV predicting a blood flow change of rectum. Earlier researches have reported the close relationship between tumor evasiveness of colorectal cancer and its drainage vein diameters. Chih-Chun Wu et al. [13] found that rectal cancer patients with positive lymphovascular invasion showed a significantly increased mean superior haemorrhoidal vein diameter. The study of Aman N. Khan further supported this finding where patients with right hemicolon cancer showed a significantly increased mean SMV (superior mesenteric vein) diameter at presentation [22].

Therefore, drainage vein diameters may become an effective predictor for evaluation of colorectal cancer. In our study, we further investigated the possibility of SRV diameter for predicting KRAS mutation of rectal cancer.

Pathologically, increased venous blood flow and emerging collateral vessels in rectal cancer are two leading reasons for the increased diameter of the SRV. Destruction of microcirculation in the tumor increases the venous blood in the vein, and demand for increased blood supply promotes the development of collateral vessels. VEGF is found to be the strongest mitogen of endothelial cells, which is a key regulator of tumor angiogenesis, vascular remodeling and vascular sprouting. Vega-Avila E et al. [23] found that VEGF helped vascular proliferation during cancer development, leading to increased blood supply to the tumor. Previous research has proved that KRAS mutation supports the production of VEGF and decline of angiogenesis inhibitors thrombospondin [24, 25, 26]. According to the research by Dong-MyungYeo [12], the microvessel density (MVD) evaluated on DCE-MRI correlates with the expression level of VEGF, which is consistent with the KRAS mutation [24]. And the study carried out by Milena Krajnović et al. [27] found that the simultaneous presence of KRAS mutations and high VEGF expression were related to worse response to chemoradiotherapy (CRT), frequent appearance of local recurrences, distant metastasis and shorter overall survival in rectal cancer.

In our study, LNE was also more likely to occur in rectal cancer patients with KRAS mutation. This could be explained by two mechanisms. One is that at the same time of increased blood flow of rectum, lymphatic system homeostasis was maintained by lymphangiogenesis, offering more chances for tumor cells to spread. The other explanation is lymph node metastases. However, according to the pathological results, there was no significant difference in lymph node metastases between KRAS mutation and wild-type groups. This suggest that hemodynamic factors might have an earlier influence on the enlargement of lymph node.

In our pathological findings, there was no significant difference between KRAS mutation group and KRAS wild type group in the presence or absence of lymphovascular emboli, signet ring cell, histological type. This should be interpreted with caution due to the small number of patients with evidence of lymphovascular emboli, signet ring cell, which were three, one, and five patients respectively. In the part of differentiation extent ( $p = 0.03$ ), considering the case number of high and low differentiation group, further research still needed. In our study, there was no significant difference between KRAS mutation group and KRAS wild type group in the presence and absence of peripheral fat interval infiltration. This might be explained by that local tumor aggressiveness was driven by multiple oncogenes and among which KRAS was not the only determining factor [28]. It was suggested in a study conducted by Weihua Li [29] that poor tumor cellularity, tumor heterogeneity, and adjuvant therapy may confound the molecular diagnosis of CRC and should be highlighted in prospective assessment. In the process of diagnosis, imaging characteristics could show focus besides the rectum and provide complementary information to gene testing. There are still many unanswered questions about the association between the mutation at gene level and medical imaging parameters that we can measure. Future studies are still required to explore these possibilities. In medical imaging aspects, MSCT, MRI, and 18F-FDG-PET/CT are all

important examinations for us to have further insight into the role of KRAS mutation in rectal carcinoma. Positive results have already been seen on MRI [5, 12, 21] and 18F-FDG-PET/CT [11, 19] for predicting KRAS mutation in colorectal carcinoma. However, CT predictors of KRAS mutation in rectal carcinoma had not been described previously. In this study, increased diameter of SRV and LNE were found in KRAS mutation group.

However, there are some limitations for this study. First, LOT was measured on a single plane, unavoidable factor including the corrugation and crooked distribution of the rectal wall. Due to the relatively small sample size of 89 patients, statistical bias cannot be excluded in this retrospective study and no test was set to verify our result. Thus, further studies are still required to explore other potential imaging predictors and apply to larger population to provide stronger clinical evidence.

In conclusion, this study has demonstrated feasibility in using the diameter of SRV to predict KRAS mutation in rectal cancer patients, and LNE on preoperative CT images can also be one of the important indicators.

## Abbreviations

KRAS

kirsten rat sarcoma viral oncogene homologue

MSCT

multi-slice computed tomography

LNE

lymph node enlargement

SRV

superior rectal vein

IMV

inferior mesenteric vein

ER

enhanced ratio

LOT

length of tumor

CRC

colorectal cancer

EGFR

epidermal growth factor receptor

VEGF

vascular endothelial growth factor

ROI

region of interest

DCE-MRI

dynamic contrast-enhanced magnetic resonance imaging

HIPAA

Health Insurance Portability and Accountability Act

IRB

Institutional Review Board

AUC

area under the curve

ROC

receiver operating characteristic

CRT

chemoradiotherapy

MVD

microvessel density

## Declarations

### Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-Sen University and informed consent was achieved from each participant<sup>1</sup>

### Consent for publication

Not applicable

### Availability of data and materials

All the data concerning this study is available from the corresponding author (Shi-Ting Feng, fengsht@mail.sysu.edu.cn).

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

ZPL, YL, and STF came up with the concept and designed this study. CS, BS and ZD analyzed and interpreted the patient data. ZF performed the histological examination. CS and LX contributed in writing

the manuscript.

## Acknowledgements

Not applicable

## References

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683–91.
2. Migliore L, Migheli F, Spisni R, Coppedè F. Genetics, Cytogenetics, and Epigenetics of Colorectal Cancer. *Journal of Biomedicine & Biotechnology* 2011; 2011(Suppl 2):792362.
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115–32.
4. Li HL, Gao YT, Zheng Y, Zhang W, Gao LF, Xu B, Xiang YB. Incidence trends of colorectal cancer in urban Shang-hai, 1973–2005. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2009;43:875–9.
5. Shin YR, Kim KA, Im S, Hwang SS, Kim K. Prediction of KRAS Mutation in Rectal Cancer Using MRI. *Anticancer Res*. 2016;36(9):4799.
6. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer (2016)-NCCN Evidence Blocks. National Comprehensive Cancer Network Web site. [http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf). Published February 8, 2016.
7. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer (2016)\ National Comprehensive Cancer Network Web site. [http://www.nccn.org/professionals/physician\\_gls/pdf/rectal.pdf](http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf). Published November 4, 2015.
8. Allegra CJ, Jessup JM, Somerfield MR, Hamilton SR, Hammond EH, Hayes DF, McAllister PK, Morton RF, Schilsky RL. American Society of Clinical Oncology Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy. *J Clin Oncol*. 2009;27(12):2091–6.
9. Jahn SW, Winter G, Stacher E, Halbwedl I, Gattenlöhner S, Stockinger R, Spreitzer S, Waldispuehl-Geigl J, Geigl JB, Offner F, Hoefler G. Multiple intratumoral KRAS mutations can clonally segregate to different lymph node metastases in colon cancer. *Histopathology* 2011; 59(2):342–345.
10. Kawada K, Toda K, Nakamoto Y, Iwamoto M, Hatano E, Chen F, Hasegawa S, Togashi K, Date H, Uemoto S, Sakai Y. Relationship Between 18F-FDG PET/CT Scans and KRAS Mutations in Metastatic Colorectal Cancer. *Journal of Nuclear Medicine Official Publication Society of Nuclear Medicine*. 2015;56(9):1322.
11. Miles KA, Ganeshan B, Rodriguez-Justo M, Goh VJ, Ziauddin Z, Engledow A, Meagher M, Endozo R, Taylor SA, Halligan S, Ell PJ, Groves AM. Multifunctional imaging signature for V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations in colorectal cancer. *J Nucl Med*. 2014;55(3):386–91.

12. Yeo DM, Oh SN, Jung CK, Lee MA, Oh ST, Rha SE, Jung SE, Byun JY, Gall P, Son Y. Correlation of dynamic contrast-enhanced MRI perfusion parameters with angiogenesis and biologic aggressiveness of rectal cancer: Preliminary results. *J Magn Reson Imaging*. 2015;41(2):474–80.
13. Wu CC, Lee RC, Chang CY. Prediction of lymphovascular invasion in rectal cancer by preoperative CT. *Ajr American Journal of Roentgenology*. 2013;201(5):985.
14. Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, Milton DT, Strawn JR, Wakelee HA, Giaccone G. American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal Growth Factor Receptor (EGFR) Mutation Testing for Patients With Advanced Non–Small-Cell Lung Cancer Considering First-Line EGFR Tyrosine Kinase Inhibitor Therapy. *J Clin Oncol*. 2016;29(15):2121–7.
15. Brand TM, Wheeler DL. KRAS mutant colorectal tumors: past and present. *Small Gtpases*. 2012;3(1):34.
16. Ganeshan B, Mandeville H, Burke M, Bell A, Townsend E, Hoskin P, Goh V, Miles K. CT of Non-Small Cell Lung Cancer (NSCLC): Histopathological Correlates for Texture Parameters. *Radiological Society of North America 2010 Scientific Assembly and Meeting*. 2010.
17. Ganeshan B, Miles KA, Young RC, Chatwin CR. In search of biologic correlates for liver texture on portal-phase CT. *Academic Radiology*. 2007;14(9):1058–68.
18. Singh D, Miles K. Multiparametric PET/CT in oncology. *Cancer Imaging the Official Publication of the International Cancer Imaging Society*. 2012;12(2):336.
19. Lovinfosse P, Koopmansch B, Lambert F, Jodogne S, Kustermans G, Hatt M, Visvikis D, Seidel L, Polus M, Albert A, Delvenne P, Hustinx R. (18)F-FDG PET/CT imaging in rectal cancer: relationship with the RAS mutational status. *Br J Radiol*. 2016;89(1063):20160212.
20. Kawada K, Nakamoto Y, Kawada M, Hida K, Matsumoto T, Murakami T, Hasegawa S, Togashi K, Sakai Y. Relationship between 18F-fluorodeoxyglucose accumulation and KRAS/BRAF mutations in colorectal cancer. *Clin Cancer Res*. 2012;18(6):1696–703.
21. Xu Y, Xu Q, Sun H, Liu T, Shi K, Wang W. Could IVIM and ADC help in predicting the KRAS status in patients with rectal cancer? *Eur Radiol*. 2018;28(7):3059–65.
22. Khan AN, Botchu R, Patel R, Elabassy M. Dilated SMV in Colon Cancer—Is There any Significance. *Journal of Gastrointestinal Cancer*. 2012;43(2):288.
23. Vega-Avila E, Pugsley MK. An overview of colorimetric assay methods used to assess survival or proliferation of mammalian cells. *Proc West Pharmacol Soc*. 2011;54(54):10–4.
24. Volpert OV, Dameron KM, Bouck N. Sequential development of an angiogenic phenotype by human fibroblasts progressing to tumorigenicity. *Oncogene*. 1997;14(12):1495.
25. Rak J, Mitsushashi Y, Bayko L, Filmus J, Shirasawa S, Sasazuki T, Kerbel RS. Mutant ras Oncogenes Upregulate VEGF/VPF Expression: Implications for Induction and Inhibition of Tumor Angiogenesis. *Can Res*. 1995;55(20):4575–80.
26. Figueras A, Arbos MA, Quiles MT, Viñals F, Germà JR, Capellà G. The impact of KRAS mutations on VEGF-A production and tumour vascular network. *BMC Cancer*. 2013;13(1):1–11.

27. Krajnović M, Marković B, Knežević-Ušaj S, Nikolić I, Stanojević M, Nikolić V, Šiljić M, Jovanović Ćupić S, Dimitrijević B. Locally advanced rectal cancers with simultaneous occurrence of KRAS, mutation and high VEGF expression show invasive characteristics. *Pathol Res Pract.* 2016;212(7):598–603.
28. Steinestel K, Lennerz JK, Eder S, Kraft K, Arndt A. Invasion pattern and histologic features of tumor aggressiveness correlate with MMR protein expression, but are independent of activating KRAS and BRAF mutations in CRC. *Virchows Arch.* 2014;465(2):155–63.
29. Li W, Qiu T, Guo L, Ying J. Major challenges related to tumor biological characteristics in accurate mutation detection of colorectal cancer by next-generation sequencing. *Cancer Lett.* 2017;410:92–9.

## Tables

**Table 1 CT Predictors and KRAS Status**

	Test of normality	KRAS status		t/z	p
		Mutated(42)	Wild(47)		
Length (mm)	0.20	43.49±16.35	45.16±13.13	0.53	0.59
SRV (mm)	0.10	4.62±0.94	4.19±0.82	-2.30	0.02
IMV (mm)	0.02	4.90(4.47,5.47)	4.98(4.42,5.54)	-0.25	0.80
CT ratio (unenhanced)	0.01	0.89(0.79,1.01)	0.94(0.76,1.12)	-0.65	0.52
CT ratio (venous phase)	0.20	0.52±0.08	0.55±0.09	1.58	0.12

**Table 2 CT Predictors and KRAS Status**

	KRAS status		Total	t / $\chi^2$	p
	Mutated	Wild			
Gender				1.10	0.29
M	26(28.3)	34(31.7)	60(60.0)		
F	16(13.7)	13(15.3)	29(29.0)		
Calcification				-	0.46
Y	2(1.4)	1(1.6)	3(3.0)		
N	40(40.6)	46(45.4)	86(86.0)		
Ulcer				0.47	0.50
Y	37(35.9)	39(40.1)	76(76.0)		
N	5(6.1)	8(6.9)	13(13.0)		
Shape				2.33	0.13
Lobulated	14(10.9)	9(12.1)	23(23.0)		
Annular thickening	28(31.1)	38(34.9)	66(66.0)		
Unenhanced density				0.12	0.73
Homogeneous	23(22.2)	24(24.8)	47(47.0)		
Heterogeneous	19(19.8)	23(22.2)	42(42.0)		
Enhanced density				0.02	0.90
Homogeneous	22(21.7)	24(24.3)	46(46.0)		
Heterogeneous	20(20.3)	23(22.7)	43(43.0)		
Boundary of serosa				0.53	0.47
Clear	13(14.6)	18(16.4)	31(31.0)		
Unclear	29(27.4)	29(30.6)	58(58.0)		
Enlarged lymph node				4.95	0.03
Y	11(7.1)	4(7.9)	15(15.0)		
N	43(39.1)	31(34.9)	74(74.0)		
Enhanced lymph node				0.06	0.80
Homogeneous	34(34.4)	39(38.6)	73(73.0)		
Heterogeneous	8(7.6)	8(8.4)	16(16.0)		
Distant metastasis				-	0.61
Y	3(2.8)	3(3.2)	6(6.0)		
N	39(39.2)	44(43.8)	83(83.0)		

Table 3 Pathological Findings and KRAS Status

	KRAS status		Total	t / $\chi^2$	p
	Mutated	Wild			
Lymphovascular emboli				-	0.42
Y	3(3.8)	5(4.2)	8(8.0)		
N	39(38.2)	42(42.8)	81(81.0)		
Signet ring cell				-	0.53
Y	0(0.5)	1(0.5)	1(1.0)		
N	42(41.5)	46(46.5)	88(88.0)		
Peripheral fat interval infiltration				0.02	0.88
Y	23(22.7)	25(25.3)	48(48.0)		
N	19(19.3)	22(21.7)	41(41.0)		
Ulcer				1.83	0.18
Y	19(22.2)	28(24.8)	47(47.0)		
N	23(19.8)	19(22.2)	42(42.0)		
Lymph node metastasis				0.76	0.38
Y	19(17.0)	17(19.0)	36(36.0)		
N	23(25.0)	30(28.0)	53(53.0)		
Histological type				-	0.32
Adenocarcinoma	37(38.7)	45(43.3)	82(82.0)		
Mucinous adenocarcinoma	1(0.9)	1(1.1)	2(2.0)		
Mixed	4(2.4)	1(2.6)	5(5.0)		
Differentiation extent				-	0.03
Low	0(2.8)	6(3.2)	6(6.0)		
Middle	42(38.7)	40(43.3)	82(82.0)		
High	0(0.5)	1(0.5)	1(1.0)		

## Figures

- Fisher's exact method was used

From 2015.12 to 2017.10

The First Affiliated Hospital, Sun Yat-sen University

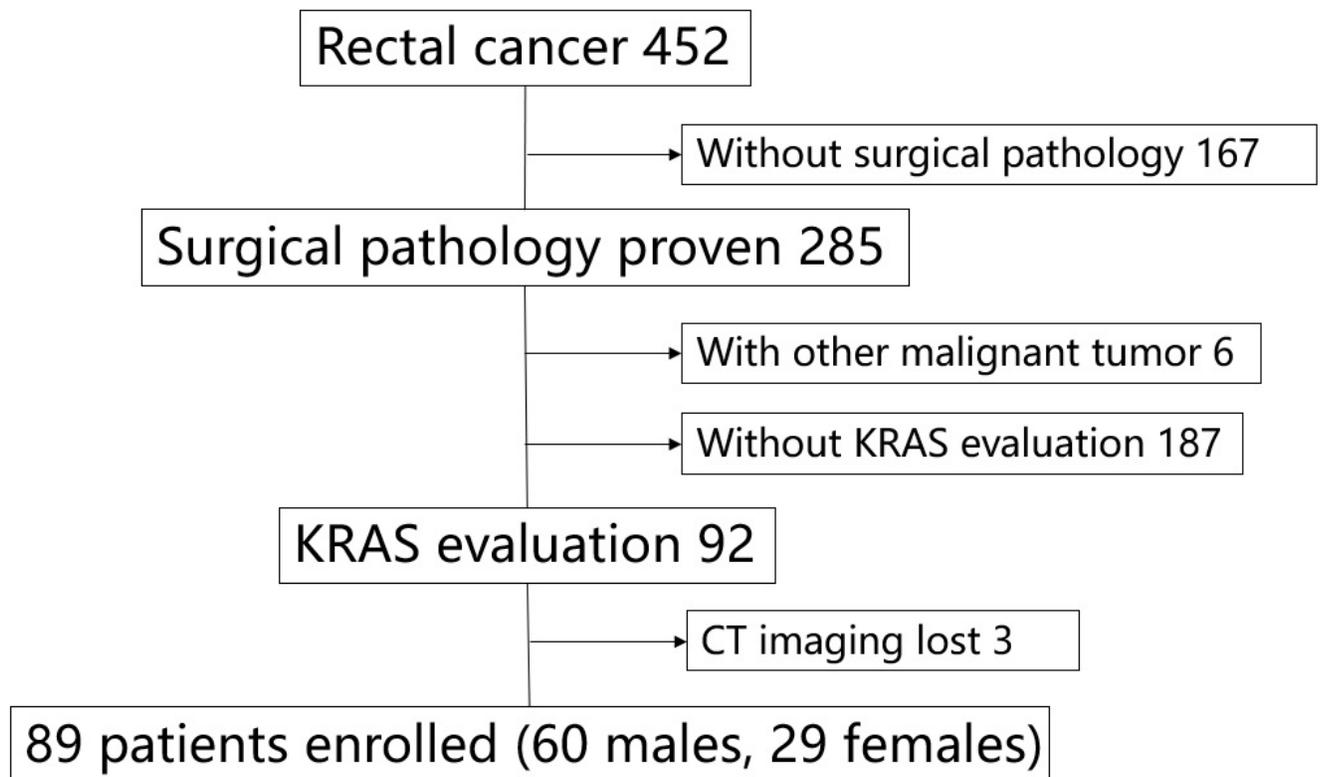


Figure 1

Data filtering process



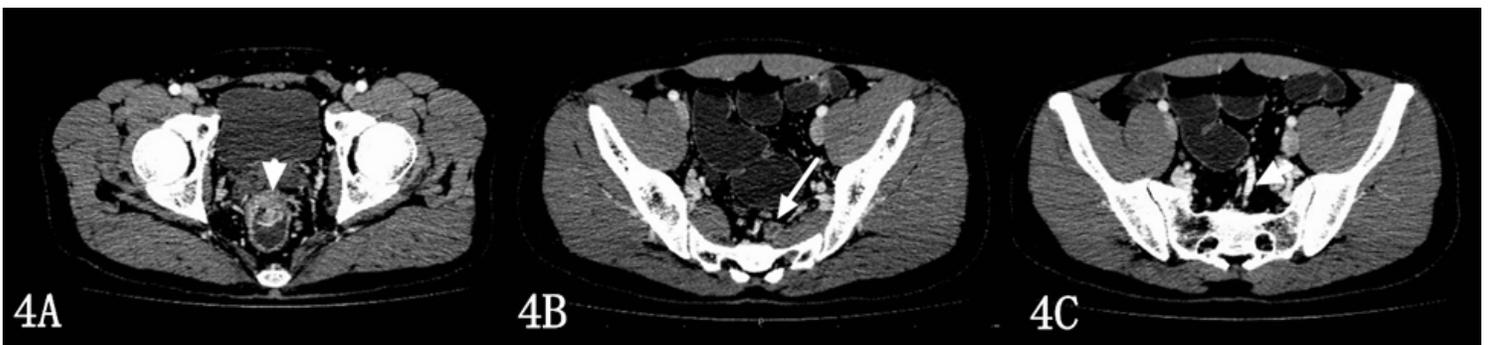
Figure 2

Position of the SRV is shown with the white arrow on the second sacral vertebral transverse plane. White line represents the diameter of the SRV.



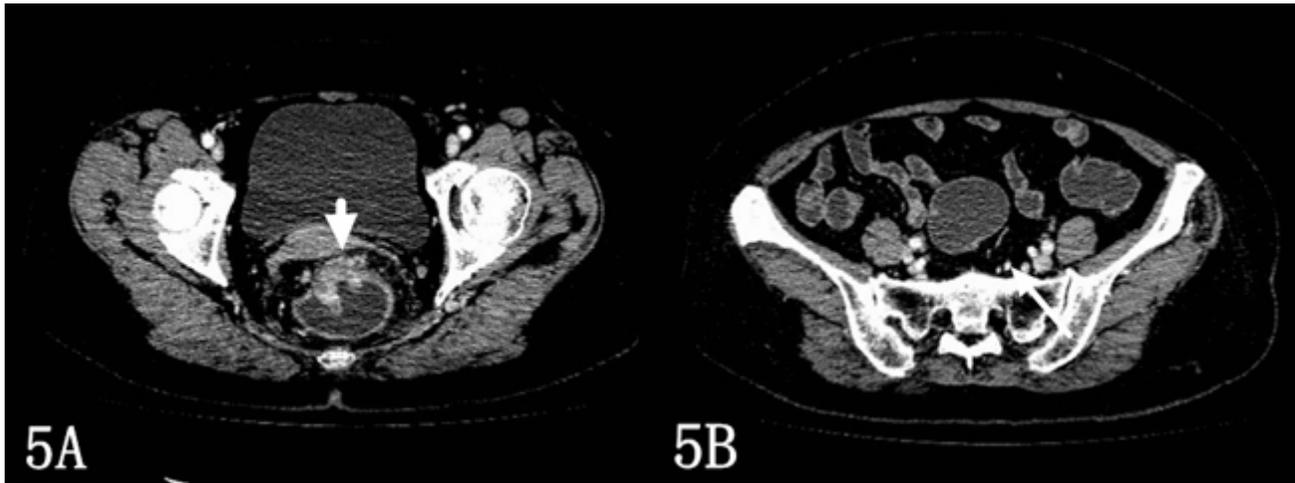
**Figure 3**

Position of IMV is shown with the white arrow.



**Figure 4**

Transverse MSCT of a forty-year-old male patient with rectal cancer with KRAS mutation, rectal carcinoma lesion (4A, white arrow with short tail) was on the anterior rectal wall with LNE (4B, white arrow with long tail). The short axis length of the enlarged lymph node was 12mm. The diameter of the SRV (4C, white arrow with short tail) was dilated (5.0mm, >4.5mm).



**Figure 5**

Transverse MSCT of a sixty-four-year-old female patient with rectal cancer without KRAS mutation; rectal carcinoma lesion (5A, white arrow with short tail) was on the anterior rectal wall without LNE. The diameter of the SRV (5B, white arrow with long tail) was normal size (3.5mm).