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Imaging features associated with survival outcomes among colorectal cancer patients with and without KRAS mutation

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Abstract

Background: Mutations in Kirsten rat sarcoma proto-oncogene (KRAS) have been shown to be associated with advanced-stage colorectal cancer (CRC), negative disease outcomes, and poor response to treatment. The purpose of this study was to investigate which CT features are biomarkers for KRAS gene mutation and impact the survival outcomes of colorectal cancer patients.

Results: Of the 113 CRC patients included in the study, 46 had KRAS mutations (40.71%) and 67 had no mutations (59.29%). Regional lymph node necrosis was the only imaging feature significantly associated with KRAS mutation ($P = 0.011$). Higher T staging and liver, lung, and distant metastasis were prognostic factors for CRC ($P = 0.014$, $P < 0.001$, $P = 0.022$, $P < 0.001$, respectively). There were no significant differences in overall survival between patients with KRAS mutations and those without ($P = 0.159$). However, in patients with no KRAS mutation, those with CRC on the left side had a significantly higher rate of survival than those with CRC on the right ($P = 0.005$).

Conclusion: Regional lymph node necrosis may be an imaging biomarker of CRC with KRAS mutation, possibly indicating poor prognosis.

Keywords: Colorectal cancer, KRAS mutation, CT, MRI

Background

There are approximately 1,000,000 annual cases of colorectal cancer (CRC) causing more than 600,000 deaths worldwide [1]. Mutations in Kirsten rat sarcoma (KRAS) proto-oncogene have been shown to be associated with the disease, and tumors with these mutations are likely to be resistant to anti-epidermal growth factor receptor (EGFR) therapy [2–14]. Mutations in human KRAS are discovered in around 40% of metastatic colorectal cancer patients [15, 16]. However, a combination of KRAS and b-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation is found in only 0.001% of cases [17]. Many studies have found that some genetic mutations are associated with more advanced stage of disease at onset, leading to limited treatment options, poor treatment response, and worse disease outcomes [4, 14]. Few randomized controlled trials such as CRYSTAL, PEAK, and PRIME have found adverse effects from a combination of anti-EGFR drugs and chemotherapy [16, 18, 19]. Studies have also found that KRAS mutations that involve codons 12 and 13 are associated with poorer overall survival rates [20–25].

National Comprehensive Cancer Network (NCCN) guidelines recommend testing for KRAS mutations in the initial diagnostic workup for metastatic colorectal cancer [5, 21, 26–28] as KRAS mutation is an important prognostic biomarker predicting survival outcomes in these patients [4, 14, 29]. Advancement of molecular biology and associated technologies has helped in the

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development of new chemotherapy regimens and novel targeted therapeutic agents for rectal cancer [3].

As far as imaging correlates between CRC and KRAS mutation, changes have been reported on magnetic resonance imaging (MRI) [30] between tumors with KRAS mutation than wild type. Published studies have found that the size of the primary rectal carcinomas differed significantly in patients with and without KRAS mutations [31]; certain MRI texture features were significantly associated with KRAS mutation status in patients with rectal cancer [32]. Rectal carcinoma with KRAS mutation were associated with higher N stage, polypoid mass with greater tumor length on MRI [33]. The parameter of apparent diffusion coefficient (ADC) of KRAS mutation colorectal cancer has also been shown to be lower compared to wild-type tumor groups [34]. Some studies have shown that colorectal cancer patients with KRAS mutations had a higher maximum standardized uptake value (SUV_{max}) on FDG-PET than those without [35–39]. Although imaging modalities are crucial in preoperative evaluation and treatment planning, there is no consensus as to the associations between pretreatment imaging, especially computed tomography (CT) and these genetic mutations.

Further imaging findings that link KRAS mutations and patient survival may aid in determining treatment options and targeted therapeutics for advanced colorectal cancer. The aim of this study was to investigate CT features associated with survival outcomes among colorectal cancer patients with and without KRAS mutation.

Methods

Patients

This retrospective analytical study was approved by our institutional review board, and the requirement for patient consent was waived. At the tertiary care cancer center hospital at which this study was conducted, there were a total of 367 patients identified with pathologically proven CRC from January 1, 2009, to January 1, 2019. Of these, 113 patients were tested for KRAS gene mutations and also underwent rountine staging abdominal CT studies. Two hundred fifty-four were excluded due to having received previous treatment (surgery, chemotherapy, or radiotherapy), inadequate image quality, inadequate KRAS genetic mutation test results, and inadequate survival data.

Imaging analysis and data collection

All patients' epidemiological data and KRAS test results were obtained from the hospital's electronic medical records health object (HO).

An experienced radiologist with more than 10 years of experience in abdominal imaging along with early career radiologist with 2 years of abdominal imaging experience evaluated the abdominal staging CT in consensus using a 2000 × 2000 picture archiving and communication system (PACS) workstation. Scans closest to the surgery were analyzed in random order with the researchers blinded to all clinical information. Features analyzed included tumor diameter, tumor length, tumor morphology, and tumor margin, pattern of tumor enhancement, local invasion of the peritoneum or an adjacent organ, regional or distant lymphadenopathy, and distal metastasis. All measurements were recorded in millimeters. Tumor location was recorded in relation to the cecum, ascending colon, hepatic flexure colon, transverse colon, splenic flexure colon, descending colon, sigmoid colon, and rectum. Tumors were considered left sided if located in distal 2/3 of the transverse colon to anorectal region and right sided if located from cecum to proximal 2/3 of the transverse colon [40].

The tumor sizes were measured in axial tumor length (ATL) on axial image and longitudinal tumor length (LTL) on coronal image; then, ATL/LTL were calculated. Tumor morphology was classified into polypoid, ulcerated, and circumferential wall thickening. The margin of the tumor was classified as either smooth, lobulated, or infiltrating. The enhancement pattern was classified as either homogeneous enhancement, heterogeneous enhancement in less than 50% of the tumor, and heterogeneous enhancement in 50% or more of the tumor.

Lymphadenopathy was defined as presence of any lymph node more than 5 mm or larger in short axis diameter and if there was presence of necrosis or heterogeneous enhancement within the enlarged lymph nodes or irregular border of the lymph node.

Finally, tumor (T), nodes (N), and metastases (M) staging was determined following the 8th TNM staging system proposed by the American Joint Committee on Cancer.

Imaging protocol

CT imaging protocol

There were 90 patients in which abdominal CT imaging was performed using one of two spiral CT scan machines: a 128 spiral CT scanner (Brilliance iCT SP 128 slice, Philips Medical Systems, Netherland) with a slice thickness of 2 mm, 80 mm of detector cover, 0.27 s of rotation time, and 700 mm gantry aperture or a 256 slice spiral dual source dual energy CT scanner (Somatom Definition Flash 256 slice, Siemens Medical Solutions, Erlangen, Germany) with a slice thickness of 2 mm, 78 mm of detector cover, 0.28 s of rotation time, and 780 mm gantry aperture. The abdominal CT protocol included a pre-contrast scan and portal venous phase (70–

Table 1 Baseline characteristics of studied populations

Baseline characteristics	Negative KRAS mutation	Positive KRAS mutation	*P* value
No. (%)	67 (59.29%)	46 (40.71%)	
Sex (%)			0.859
Male	39 (58.21)	26 (56.52)	
Female	28 (41.79)	20 (43.48)	
Age, years			0.555
Mean (SD)	58.21 (11.28)	59.39 (9.05)	
Median (min-max)	59 (29–86)	59.5 (42–82)	

80 s after contrast injection). The contrast injection rate was about 5 ml/s (2 ml/kg; not more than 120 ml). The remainder 23 patients underwent abdominal CT imaging at an outside institution. Pre-contrast and portal venous-phase images were evaluated using a PACS.

Evaluation of overall survival

Overall survival was calculated based on the duration from pre-treatment abdominal CT until the date of death or the end of data collection (January 1, 2019). Median overall survival outcome is presented in months.

Table 2 The association between imaging characteristic and KRAS mutation based on an independent sample *t* test or Mann-Whitney *U* test

Imaging variable	Negative KRAS mutation	Positive KRAS mutation	*P* value
Axial tumor length (ATL) (cm)	(*n* = 69)	(*n* = 46)	
Median (min-max)	1.9 (1.0–6.4)	2.2 (1.1–7.7)	0.815
Mean (SD)	2.37 (1.12)	2.35 (1.08)	0.937
Longitudinal tumor length (LTL) (cm)	(*n* = 69)	(*n* = 46)	
Median (min-max)	6.3 (1.3–15.0)	6.0 (1.28–16.0)	0.564
Mean (SD)	6.67 (2.90)	6.48 (2.87)	0.723
ATL/LTL	(*n* = 69)	(*n* = 46)	
Median (min-max)	0.35 (0.12–1.75)	0.38 (0.08–2.19)	0.521
Mean (SD)	0.42 (0.29)	0.43 (0.31)	0.888
Tumor locations (%)	(*n* = 69)	(*n* = 46)	0.584
Left side	61 (88.41)	39 (84.78)	
Right side	8 (11.59)	7 (15.22)	
Tumor gross patterns (%)	(*n* = 69)	(*n* = 46)	
Polypoid	30 (43.48)	23 (50)	0.568
Ulcerative	3 (4.35)	1 (2.17)	0.649
Circumferential wall thickening	42 (60.87)	23 (50)	0.258
Tumor margin (%)	(*n* = 69)	(*n* = 46)	0.390
Smooth	0 (0.00)	1 (2.17)	
Lobulate	69 (92.54)	43 (93.48)	
Infiltrating	5 (7.46)	2 (4.35)	
Tumor enhancement patterns (%)	(*n* = 69)	(*n* = 46)	0.736
Homogenous	7 (10.14)	4 (8.70)	
Heterogeneous < 50%	25 (31.88)	12 (26.09)	
Heterogeneous ≥ 50%	40 (57.97)	30 (65.22)	
T stage (%)	(*n* = 68)	(*n* = 46)	0.955
2	30 (43.48)	21 (45.65)	
3	24 (34.78)	16 (34.78)	
4	15 (21.74)	9 (19.57)	

Table 3 The association between imaging characteristics and KRAS mutation according to a Pearson's Chi-square or Fisher's exact test

Imaging variable	KRAS mutation (-)	KRAS mutation (+)	*P* value
Regional lymph node metastasis (%)	(*n* = 67)	(*n* = 46)	0.736
No	6 (8.96)	5 (10.87)	
Yes	61 (91.04)	41 (89.13)	
Necrosis	**(*n* = 61)**	**(*n* = 41)**	**0.011**
No	19 (31.15)	4 (9.76)	
Yes	42 (68.85)	37 (90.24)	
Distant lymph node metastasis (%)			0.790
No	51 (76.12)	34 (73.91)	
Yes	16 (23.88)	12 (26.09)	
Liver metastasis (%)			0.167
No	29 (43.28)	26 (56.52)	
Yes	38 (56.72)	20 (43.48)	
Lung metastasis (%)			0.166
No	61 (91.04)	37 (82.22)	
Yes	6 (8.96)	8 (17.78)	
Bone metastasis (%)			> 0.999
No	66 (98.51)	44 (97.78)	
Yes	1 (1.49)	1 (2.22)	

Statistical analysis

Continuous variables, including age and diameter of tumor, were compared between groups using an independent sample *t* test or Mann-Whitney *U* test as appropriate. Categorical variables, including KRAS mutation, sex, T stage, location of the tumor, lymph node metastasis, liver metastasis, lung metastasis, bone metastasis, peritoneal invasion, and distant metastasis, were compared between groups using Pearson's Chi-square or Fisher's exact test. Survival outcomes and recurrence rates were compared using a log-rank test. Survival was compared using a Kaplan-Meier graph. All statistical analyses were performed using STATA (version 10.1. Stata Corp LP, 4905, Lakeway Drive College Station, TX, USA).

Results

Baseline and population characteristics

Among the 113 (65 male and 48 female) CRC patients included in this study, 40.71% (46; 56.52% male; 43.48% female) had KRAS genetic mutations (age range 42 to 82 years; mean 59.39 ± 9.05 years), and 59.29% (67; 58.21% male; 41.79% female) in age from 29 to 86 years

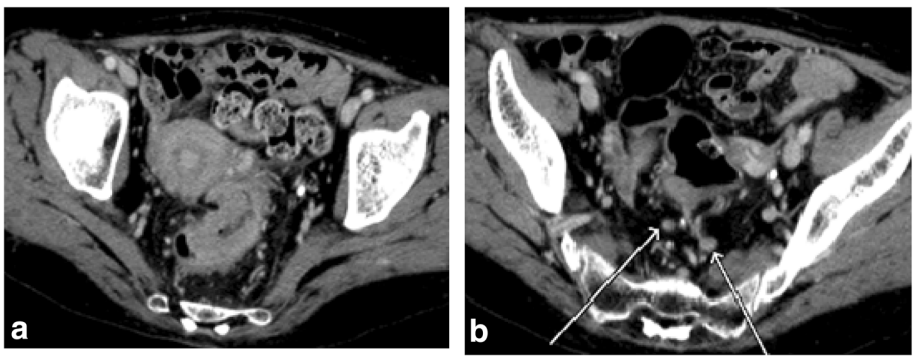

Fig. 1 A 57-year-old woman with rectosigmoid colon cancer and a wild-type KRAS mutation. The tumor exhibited a lobulated margin, circumferential wall thickening, and homogenous enhancement without adjacent organ invasion (T stage 2; **a**) and two regional lymph nodes without necrosis (N stage 2; arrow; **b**)

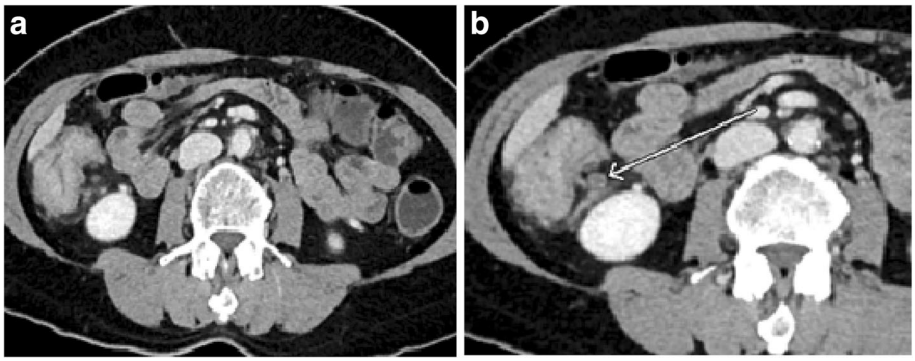

Fig. 2 A 54-year-old woman with ascending colon cancer and KRAS mutation. The tumor exhibited a polypoid appearance, lobulated margin, heterogenous enhancement less than 50 percent (T stage 3; **a**), and necrosis of the regional lymph node metastasis (arrow; N stage 2; **b**)

old with a mean of 58.21 ± 11.28 did not have the mutation. The two groups did not differ significantly in terms of sex (p = 0.859). The mean age of patients with and without KRAS mutations did not differ significantly (58.21 years and 59.39 years, respectively; P = 0.555; Table 1).

Association between imaging features and KRAS mutation

No significant difference was seen between the two groups in terms of ATL, LTL, ATL/LTL, tumor location, gross tumor patterns, tumor margins, tumor enhancement patterns, T staging, regional lymph node metastasis, distant lymph node metastasis, or distal organ metastasis (including liver, lung, and bone; Tables 2 and 3). Only necrosis of the regional lymph node differed significantly (P = 0.111; Table 3, Figs. 1 and 2).

The survival analysis outcome rates in the two groups

There was no significant difference between KRAS groups in terms of surgical outcome (P = 0.159; Fig. 3). However, those in the KRAS mutation group had a lower survival rate.

Comparison of tumor location and survival analysis between groups

No significant difference was seen in survival rate among patients with left- and right-side in the KRAS mutation group (P = 0.379; Fig. 4). However, in the KRAS-

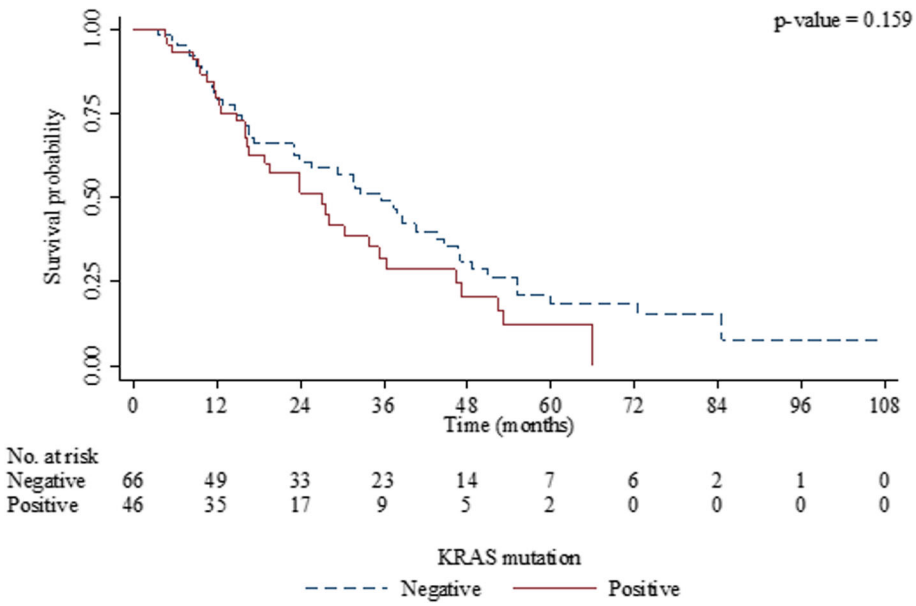

Fig. 3 Kaplan-Meier graph comparing survival rate between patients with positive and negative KRAS mutation status

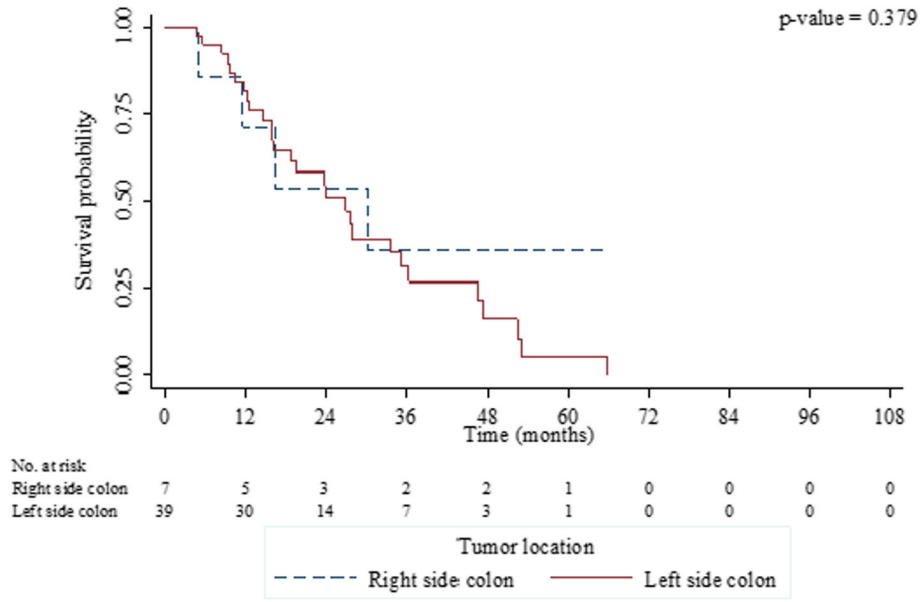

Fig. 4 Kaplan-Meier graph comparing survival rates between left- and right-side CRC in patients with positive KRAS mutation status

negative group, those with left-sided CRC had a higher survival rate (P = 0.005; Fig. 5).

Comparison of tumor staging and survival analysis between groups

There was no significant difference in T staging between the two KRAS groups

(P 0.177; Fig. 6)

Discussion

KRAS mutations are associated with multiple organ cancers including CRC [2, 15–17]. The presence of KRAS mutation in CRC is always associated with advanced tumor stage and presence of lymph node metastasis with poor response to treatment and outcome [2, 20, 23, 33, 41, 42]. For most CRC, CT is the routinely used imaging modality for tumor diagnosis, tumor staging, identifying patients who require neo-adjuvant therapy, and assessing treatment response

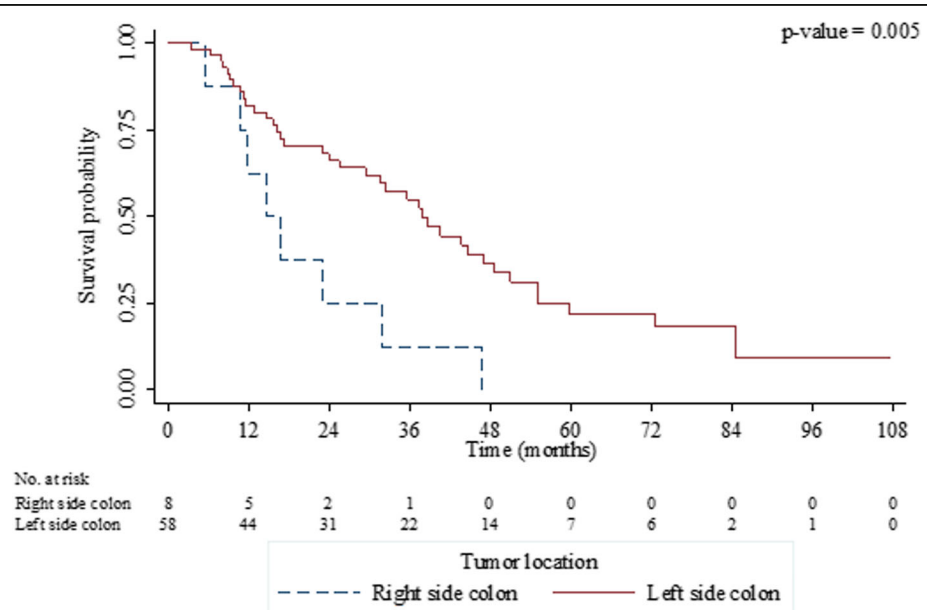

Fig. 5 Kaplan-Meier graph comparing survival rates between left- and right-side CRC in patients with negative KRAS mutation status

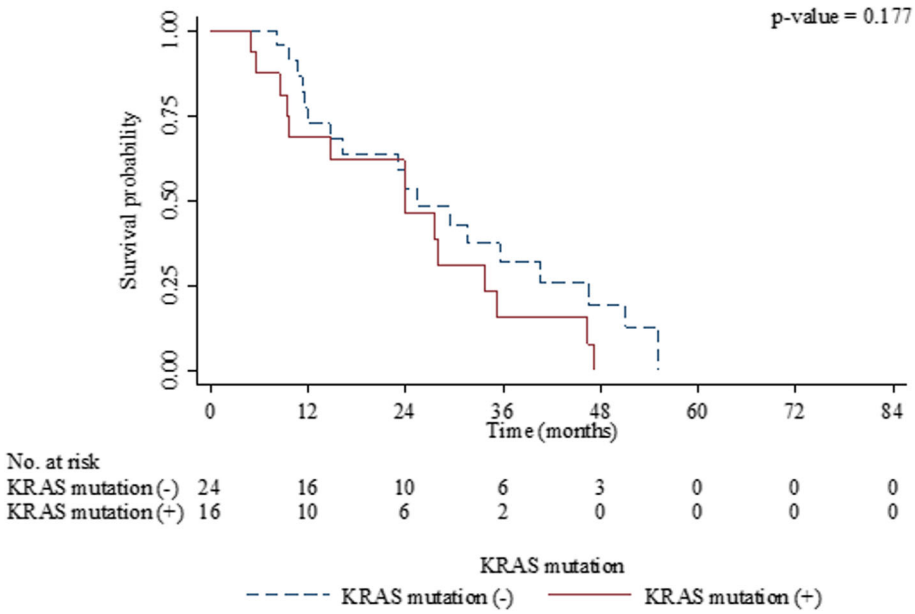

Fig. 6 Kaplan-Meier graph comparing survival by T staging between KRAS mutation groups

[43–46]. Recently, some reports have found that new generation CT scanners can offer high spatial resolution images with reliable rectal staging with low dose of radiation, particularly useful in patients who have contraindication to MRI [47, 48]. If used in conjunction with KRAS mutation status, CT may potentially be used as a noninvasive biomarker for deciding appropriate therapy selection and also predict patient prognosis.

Our study found that 90.24% of patients with KRAS mutations had necrosis of regional lymph node metastasis, whereas only 68.85% of KRAS wild type (P = 0.011) showed this finding. The results of our study were consistent with those of a study by Gonzalez et al. [49], who found cystic nodule metastasis containing tumor necrosis to be frequently associated with KRAS and BRAF mutation that have a micropapillary feature of CRC. The greater percentage of cases with nodal necrosis found in this study could be explained by using the KRAS mutation CRC base on the pathogenesis of classical adenoma-carcinoma associated pathway, which usually exhibits heterogeneous necrosis of the tumor [50, 51]. However, we found no significant difference between N and tumor staging in these KRAS mutations and wild-type groups, which differs from the results found in previous studies [20, 23, 33, 42].

KRAS mutation has been found to be associated with polypoid tumor growth patterns with higher staging and with fewer cases with flat tumor gross pattern in early staging [22, 32, 33, 52–57]. In this study, neither tumor size (including mean ATL, mean LTL, and mean ATL/LTL) nor tumor morphology patterns differed significantly between CRC patients with and without KRAS mutation (P = 0.937, P = 0.723, and P = 0.888, respectively). These differences may be related to the classical pathogenesis of CRC with adenoma-carcinoma sequence pathway proposed by Fearon and Vogelstein [58] and the other serrated pathway described by Jass and Smith [59] that serrate polyps, which may be associated with KRAS mutation, are generally smaller than 5 mm of the original size.

This study also found no significant difference in the occurrence of distant lymph node or distal organ metastases between the two groups. This contrasts with the findings of Cho et al. [36], who studied the correlation between KRAS mutation and 18F-FDG uptake in stage IV colorectal cancer patients and found that those with KRAS mutations had a higher incidence of lung metastases than those without.

Our survival outcome analysis showed that patients with KRAS mutation had a lower survival rate than those without. This result could be due to the higher rate of regional lymph node necrosis in this group, which can lead to poor disease outcomes. This finding could be involved in poorly differentiated carcinoma with microsatellite instability molecular pathway of adenoma-carcinoma sequence etiology [60, 61]. Necrosis within the tumor or lymph node indicates more aggressive tumor behavior, which leads to reduced survival. However, in patients without KRAS mutation, overall survival was higher in those with left-side CRC than those with right-side CRC (P = 0.005). This difference was not found in the KRAS mutation group. Some researchers have found that serrate adenocarcinoma pathway or carcinoma with microsatellite instability is usually related to right-side CRC and that these patients

have less favorable 5-year survival outcomes [51, 62, 63]. However, our study found that tumors in both groups occurred primarily on the left side of the colon (84.78% in those with KRAS mutation and 88.41 % in those without; $P = 0.584$).

Limitations

First limitation of this study is the small number of cases of KRAS mutation compared to those with KRAS wild-type CRC, which could have affected the results.

Second, this study included patients who had undergone a KRAS mutation test but not a BRAF gene mutation test, meaning that some of the patients in this study may have had a combination of KRAS and BRAF gene mutation (which occurs in 0.001% of the population). Further studies in larger populations who have undergone gene mutation tests could yield more accurate results.

Third, this was a retrospective study with variability in CT images from different CT scanners, especially those from outside institution with a limited spatial collimation and insufficient reconstruction. Further prospective study with the same high row number MDCT scanner with thin-collimation, high spatial resolution, and multiplanar reconstructions (MPRs) is needed to minimize image variability.

Conclusion

Imaging findings indicating necrosis of regional lymph node metastasis could be a biomarker that predicts KRAS mutation among patients with CRC and lower rates of survival.

Abbreviations

CRC: Colorectal cancer; KRAS: Mutations in Kirsten rat sarcoma; EGFR: Epidermal growth factor receptor; BRAF: b-Raf murine sarcoma viral oncogene homolog B1; NCCN: National Comprehensive Cancer Network; MRI: Magnetic resonance imaging; SUV_{max}: Maximum standardized uptake value; CT: Computed tomography; HO: Health object; PACS: Picture archiving and communication system; ATL: Axial tumor length; LTL: Longitudinal tumor length; TNM: Tumor (T), nodes (N), metastases (M); MPRs: Multiplanar reconstructions

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Authors' contributions

All authors have read and approved the manuscript. J.P contributed to conceptualization, design of the study, image interpretation, writing, editing manuscript, submission and follow-up. P.C participated in design of study, imaging interpretation, data collection and manuscript writing. K.S participated in visualization and investigation. K.P participated in visualization and investigation. P.S participated in visualization and investigation. C.A participated in visualization and intestigation. R.M.L participated in visualization and intestigation. M.H contributed to supervision, reviewing and editing manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics approval was provided by the Ethics Committee of the Faculty of Medicine, Khon Kaen University, as instituted by the Helsinki Declaration, and this study was a retrospective study; for this type of study, formal consent is not required. The reference number of ethical approval is HE621442.

Consent for publication

All images in this manuscript contain no individual personal data.

Competing interests

The authors declare that they have no competing interests.

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