Radiomics Texture Features in Advanced Colorectal Cancer: Correlation with BRAF Mutation and 5-year Overall Survival

Adrian A. Negreros-Osuna, MD • Anushri Parakh, MD • Ryan B. Corcoran, MD, PhD • Ali Pourvaziri, MD • Avinash Kambadakone, MD • David P. Ryan, MD • Dushyant V. Sahani, MD

From the Abdominal Imaging Division, Department of Radiology (A.A.N., A. Parakh, A. Pourvaziri, A.K., D.V.S.), and Cancer Center (R.B.C., D.P.R.), Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114; and Faculdad de Medicina y Hospital Universitario “Dr. José E. González,” Universidad Autónoma de Nuevo León, Monterrey, Mexico (A.A.N.). Received October 21, 2019; revision requested November 11; revision received March 31, 2020; accepted May 6. Address correspondence to D.V.S., Department of Radiology, University of Washington, 1959 NE Pacific St, Health Sciences Building, Room RR-218, Seattle, WA 98195 (e-mail: dsahani@uw.edu).

Conflicts of interest are listed at the end of this article.

Radiology: Imaging Cancer 2020; 2(5):e190084 • https://doi.org/10.1148/rycan.2020190084 • Content codes: [G1 I0]

Purpose: To explore the potential of radiomics texture features as potential biomarkers to enable detection of the presence of BRAF mutation and prediction of 5-year overall survival (OS) in stage IV colorectal cancer (CRC).

Materials and Methods: In this retrospective study, a total of 145 patients (mean age, 61 years ± 14 [standard deviation (SD)]; 68 female patients and 77 male patients) with stage IV CRC who underwent molecular profiling and pretreatment contrast material–enhanced CT scans between 2004 and 2018 were included. Tumor radiomics texture features, including the mean, the SD, the mean value of positive pixels (MPP), skewness, kurtosis, and entropy, were extracted from regions of interest on CT images after applying three Laplacian-of-Gaussian filters known as spatial scaling factors (SSFs) (SSF = 2, fine; SSF = 4, medium; SSF = 6, coarse) by using specialized software; values of these parameters were also obtained without filtration (SSF = 0). The Wilcoxon rank sum test was used to assess differences between mutated versus wild-type BRAF tumors. Associations between radiomics texture features and 5-year OS were determined by using Kaplan–Meier estimators using the log-rank test and multivariate Cox proportional-hazards regression analysis.

Results: The SDs and MPPs of radiomic texture features were significantly lower in BRAF mutant tumors than in wild-type BRAF tumors at SSFs of 0, 4, and 6 (P = .006, P = .007, and P = .005, respectively). Patients with skewness less than or equal to −0.75 at an SSF of 0 and a mean of greater than or equal to 17.76 at an SSF of 2 showed better 5-year OS (hazard ratio [HR], 0.53 [95% confidence interval {CI}: 0.29, 0.94]; HR, 0.40 [95% CI: 0.22, 0.71]; log-rank P = .025 and P = .002, respectively). Tumor location (right colon vs left colon vs rectum) had no significant impact on the clinical outcome (log-rank P = .53).

Conclusion: Radiomics texture features can serve as potential biomarkers for determining BRAF mutation status and as predictors of 5-year OS in patients with advanced-stage CRC.

Supplemental material is available for this article.

©RSNA, 2020

Colorectal cancer (CRC) is the third most common cancer and ranks third as the cause of death among malignant neoplasms (1). Up to 21% of patients with CRC demonstrate distant disease at the time of diagnosis with a relative 5-year survival rate of 14% (1). Contrast material–enhanced CT is the diagnostic modality of choice for initial workup, staging, restaging, assessment of treatment response, and surveillance according to the National Comprehensive Cancer Network guidelines (2).

Patients with CRC with specific mutation profiles may benefit from tailored therapies, and evidence-based guidelines for determination of tumor biomarkers such as BRAF, KRAS, NRAS, and microsatellite instability status were recently published (3). Tumors with BRAF mutation are resistant to anti–epidermal growth factor receptor therapeutic agents, leading to a poorer prognosis, whereas tumors with microsatellite instability have been shown to have a better prognosis (4,5). In one study, BRAF-mutated CRC tumors showed histopathologic features that were distinct from those of wild-type BRAF tumors, independent of microsatellite instability status (6). Typically, BRAF mutation is determined through generic molecular profiling by sampling the tumor. However, biopsy is invasive, fraught with sampling-error limitations, and often does not represent the complete tumor heterogeneity.

Interest in image biomarker development and validation in patients with cancer has led to substantial research efforts for extracting tumor radiomics features using computational models. These radiomics features have been shown to be a quantitative tool that relays information about tumor phenotype as well as clinical and genotypic end points (7–11). Preliminary studies have shown that CT radiomic features correlate with clinical outcomes in esophageal cancer, tumor grade in melanoma, tumor histologic findings in renal cell carcinoma, tumor hypoxia, and angiogenesis in non–small-cell lung cancer (12–15). The value of radiomics in predicting malignant potential in pulmonary nodules was verified by Digumarthy et al (16). In another study, Meyer et al (17) demonstrated that
Radiomics Texture Features in Advanced CRC

Abbreviations
Cl = confidence interval, CRC = colorectal cancer, HR = hazard ratio, MPP = mean value of positive pixels, OS = overall survival, ROC = receiver operating characteristic curve, SD = standard deviation, SSF = spatial scaling factor

Summary
Radiomics texture features from CT images can potentially be used to differentiate wild-type BRAF colorectal cancer tumors from those with BRAF mutation and to predict overall survival in advanced-stage disease.

Key Points
- Colorectal cancer (CRC) tumors with BRAF mutation show lower values of the derived radiomics texture features standard deviation and mean value of positive pixels of the tumor region of interest on CT images in comparison with wild-type BRAF.
- CRC tumors showing less radiomics texture heterogeneity behave more aggressively than those showing more heterogeneity, and this is associated with unfavorable 5-year overall survival.

Radiomics features correlated with tumor aggressiveness in malignant head and neck tumors.

Radiomics texture analysis is a computational method that extracts multiple features from radiologic images on the basis of the pixel gray-level distribution histogram (18–20). Only a few pilot studies have explored the utility of texture features in patients with CRC for predicting survival, treatment response, and tumor mutations (8,9,21). These studies were limited because of their small sample size, heterogeneous tumor types, and genetic mutations. Therefore, it is desirable to investigate the utility of tumor texture features on CT images for predicting specific oncogenic mutations and patient outcomes in a larger patient cohort. Accordingly, the aim of this study was to explore the potential of radiomics texture features to enable identification of the presence of BRAF mutation and prediction of 5-year overall survival (OS) in stage IV CRC.

Materials and Methods

Study Design
The requirement for informed consent was waived in this Health Insurance Portability Accountability Act–compliant, institutional review board–approved retrospective study. All patients (n = 331) with colorectal carcinoma diagnosed between June 2004 and March 2018 who underwent genetic profiling of a primary resected tumor were identified; findings from the patients included in this study have not been published elsewhere. The TNM staging per the seventh edition of the American Joint Committee on Cancer staging manual was used to classify the patients. Inclusion criteria for the final study cohort (Fig 1) were at least 18 years of age, no known previous malignancy, contrast-enhanced abdominopelvic CT performed prior to treatment in the portal venous phase, and stage IV disease at the time of diagnosis. The exclusion criteria were unavailable portal venous phase (n = 19), synchronous malignancies (n = 2), no CT images on the institutional picture archiving communication system (n = 125), stages I–III at diagnosis (n = 33), and/or tumor not discernable on CT images (n = 7). The final study cohort comprised 145 (mean age, 61 years ± 14; 68 women and 77 men) patients (Fig 1).

Sex, age, mutation status (BRAF, KRAS, NRAS, and others), and microsatellite instability status based on tumor genetic profiling, location of the primary tumor, site of metastasis, and time from diagnosis to death were collected from the hospital information system. A 5-year follow-up was available for 55% (80 of 145) of patients. For patients who did not have an event (death) during the study (44.8% [65 of 145]), right censoring or end-of-study censoring was performed, and time between diagnosis and the last visit was used as censored data.

CT Imaging
All CT scans were performed with a tube voltage of either 100 or 120 kVp, and axial-plane images were reconstructed at a slice thickness of 5 mm and increment of 5 mm. A weight-based protocol was used to determine the amount of intravenous contrast media (Isovue, 370 mg; Bracco Diagnostics, Princeton, NJ) administered to the patient (61 kg = 80 mL; 61–90 kg = 90 mL; 91–113 kg = 120 mL). This was followed by a 40–mL saline chaser at 3 mL/sec. The portal venous phase was acquired using automated bolus tracking when a threshold attenuation of 150 HU was attained within the suprascapular abdominal aorta. Nine hundred milliliters of barium-based positive oral contrast material (2% wt/vol Readi-Cat 2; E-Z-EM Canada for Bracco Diagnostics, Monroe, NJ) was administered 45–60 minutes prior to scanning in all patients. We used a variety of scanners from different vendors, and a full table of the specific models used in the study can be found in Table E1 (supplement).

Radiomics Texture Analysis
A single radiologist (A.A.N., with 5 years of experience), blinded to genetic profiling and patient outcome, identified the primary tumor on the CT studies and uploaded the images to commercially available software for texture analysis (TexRAD [https://www.texrad.com]; Feedback, Cambridge, England). This software was selected because of its availability in our institution. Radiomics texture measurements were obtained by drawing a region of interest around the primary tumor at its largest cross-sectional area on a single axial slice. Three Laplacian-of-Gaussian filters known as spatial scaling factors (SSFs) (SSF = 2, fine; SSF = 4, medium; SSF = 6, coarse) were applied to retrieve quantitative values for the following radiomics texture features within the regions of interest: mean, standard deviation (SD), mean value of positive pixels (MPP), skewness, kurtosis, and entropy. Values of these parameters were also obtained without filtration (SSF = 0). The purpose of filtration is to reduce noise and highlight structures of a particular size within a region of interest. The filtration corresponds to the size of object radii in millimeters (eg, an SSF of 2 = 2-mm structures).

Reference Standard
The diagnosis in all patients was confirmed with colonoscopy and histopathologic findings of the primary tumor. Molecular
Figure 1: Patient selection process. I.V. = intravenous, PACS = picture archiving communication system.

Table 1: Demographics, Clinical-Pathologic, and Molecular Characteristics of the Study Population

| Variable          | Value           |
|-------------------|-----------------|
| No. of patients   | 145             |
| Sex               |                 |
| Men               | 77 (53.1)       |
| Women             | 68 (46.9)       |
| Age (y)           |                 |
| Men               | 63 ± 13         |
| Women             | 59 ± 14         |
| Combined age      | 61 ± 14         |
| BRAF mutant       | 21 (14.5)       |
| Wild-type BRAF    | 124 (85.5)      |
| KRAS mutant       | 56 (38.6)       |
| NRAS mutant       | 3 (2.1)         |
| Other mutations   | 65 (44.8)       |
| Microsatellite stability |     |
| MSS               | 131 (90.3)      |
| MSI               | 14 (9.7)        |
| Location          |                 |
| Right colon       | 53 (36.6)       |
| Left colon        | 53 (36.6)       |
| Rectum            | 39 (26.9)       |
| Site of metastasis|                 |
| Liver             | 116 (80.0)      |
| Lymph nodes       | 35 (24.1)       |
| Lung              | 18 (12.1)       |
| Peritoneum        | 8 (5.5)         |
| Brain             | 5 (3.5)         |
| Muscle            | 1 (0.7)         |

Note.—Data are either number of patients with percentages in parentheses or mean ± standard deviation. MSI = microsatellite instability, MSS = microsatellite stable.

Statistical Analysis

For assessing the differences in radiomics texture features between BRAF mutant versus wild-type BRAF tumors, a two-sample Wilcoxon rank sum (Mann-Whitney) test with Bonferroni correction was performed. A P value less than .0083 was considered a significant difference. Empirical optimal cut points using the Youden method for BRAF mutation status were calculated. Receiver operating characteristic curve (ROC) analysis was applied to obtain the area under the ROC and values of sensitivity and specificity. Associations between radiomics texture features and OS were determined by creating quartiles (the study cohort was divided into four equal groups according to the distribution of values in order of magnitude for each texture feature), and then Kaplan-Meier curves estimators were applied, considering a log-rank test P value less than .05 as significant. Multivariate Cox proportional-hazards regression analysis was applied to obtain the hazard ratios (HRs) and confidence intervals (CIs) in each quartile for the parameters that showed a significant difference in the survival curves by the log-rank test. The analysis was performed for all six texture features at four SSF levels (0, 2, 4, and 6). All statistical analysis and graphics generation was performed using Stata Statistical Software (release 15, 2017; Stata, College Station, Tex).

Results

Study-Cohort Profile

A total of 145 patients with stage IV CRC were included in the final study cohort (mean age, 61 years ± 14; 68 women and 77 men). The demographic, clinical-pathologic, and molecular characteristics are summarized in Table 1. A total of 36.6% (53 of 145) of tumors were located in the right colon, 36.6% (53 of 145) were located in the left colon, and 26.9% (39 of 145) were located in the rectum. Metastatic lesions were present in the liver (80% [116 of 145]), lymph nodes (24.1% [35 of 145]), lung (12.1% [18 of 145]), peritoneum (5.5% [eight of 145]), brain (3.5% [five of 145]), bone (2.8% [four of 145]), and muscle (0.7% [one of 145]). A total of 37.9% (55 of 145) of patients were smokers.

BRAF mutation was observed in 14.5% (21 of 145) of tumors, and 85.5% (124 of 145) of tumors were wild-type BRAF tumors. Of the wild-type BRAF tumors, 38.6% (56 of 145) had KRAS mutation, 2.1% (three of 145) had NRAS mutation,
and 44.8% (65 of 145) had other mutations (eg, PIK3CA and TP53) but had no mutations in BRAF, KRAS, or NRAS. A total of 9.7% (14 of 145) of patients showed microsatellite instability, and 90.3% (131 of 145) were microsatellite stable. There were no statistically significant differences between wild-type BRAF and BRAF mutant tumors in terms of the locations of metastases: liver (81.5% [101 of 124] vs 71.4% [15 of 21]; \( P = .29 \)), lung (12.9% [16 of 124] vs 9.5% [two of 21]; \( P = .66 \)), bone (3.2% [four of 124] vs 0% [0 of 21]; \( P = .4 \)), peritoneum (4.8% [six of 124] vs 9.5% [two of 21]; \( P = .38 \)), lymph nodes (24.2% [30 of 124] vs 23.8% [five of 21]; \( P = .97 \)), brain (3.2% [four of 124] vs 4.8% [one of 21]; \( P = .72 \)), and muscle (0.8% [one of 124] vs 0% [0 of 21]; \( P = .68 \)).

**Radiomics and Mutation Status**

SDs were significantly lower in BRAF mutant tumors than in wild-type BRAF tumors at an SSF of 0 (22.31 [95% CI: 20.66, 24.62] vs 25.44 [95% CI: 22.67, 29.55]; \( P = .006 \)). MPPs were also lower in BRAF mutant tumors than in wild-type BRAF tumors at an SSF of 4 (51.54 [95% CI: 47.14, 58.99] vs 60.42

---

**Figure 2:** A. Histogram comparison shows significant differences in shape and in the mean of positive pixels (MPP; range highlighted in red) between (a, b) wild-type BRAF and (c, d) BRAF mutant colorectal tumors in the right colon. These tumors look reasonably similar on (a, c) axial CT images. Blue outlines on CT images indicate colorectal tumors. B, Boxplot shows the difference in the MPP between wild-type BRAF and BRAF mutant tumors at a spatial scaling factor of 6 (SSF 6).
Negreros-Osuna et al

Relate CT radiomics texture features and OS, the texture features were first divided into quartiles as previously explained. Kaplan-Meier curves were generated for all quartiles and compared, and Cox regression was applied to obtain HRs. Patients with tumors within the first quartile of skewness with an SSF of 0 showed better 5-year OS ($P = .041$) (Fig 3). Those within the fourth quartile of the mean with an SSF of 2 showed a better 5-year OS ($P = .025$) (Fig 3). The log-rank test demonstrated no significant differences in Kaplan-Meier curves for the remaining texture features ($P > .99$). No significant differences in OS were found on the basis of tumor location (right colon vs left colon vs rectum [$P = .53$]). After adjusting for age, sex, and mutation type, multivariate Cox hazards regression analysis showed that skewness at an SSF of 0 indicated higher risk for the patients at quartiles 2, 3, and 4 (HR, 2.34 [95% CI: 1.18, 4.64]; $P = .014$; HR, 1.83 [95% CI: 0.95, 3.55]; $P = .070$; and HR, 1.54 [95% CI: 0.75, 3.19]; $P = .24$). In contrast, the mean at an SSF of 2 indicated reduced

Radiomics and OS

The median survival time in our cohort was 48.4 months (range, 20.4–85.6 months). A total of 55.2% (80 of 145) of patients died during the follow-up. The median follow-up time among patients who were alive at the end of study (44.8% [65 of 145]) was 37.7 months (range, 16.5–63.1 months). To correlate CT radiomics texture features and OS, the texture features were first divided into quartiles as previously explained. Kaplan-Meier curves were generated for all quartiles and compared, and Cox regression was applied to obtain HRs. Patients with tumors within the first quartile of skewness with an SSF of 0 showed better 5-year OS ($P = .041$) (Fig 3). Those within the fourth quartile of the mean with an SSF of 2 showed a better 5-year OS ($P = .025$) (Fig 3). The log-rank test demonstrated no significant differences in Kaplan-Meier curves for the remaining texture features ($P > .99$). No significant differences in OS were found on the basis of tumor location (right colon vs left colon vs rectum [$P = .53$]). After adjusting for age, sex, and mutation type, multivariate Cox hazards regression analysis showed that skewness at an SSF of 0 indicated higher risk for the patients at quartiles 2, 3, and 4 (HR, 2.34 [95% CI: 1.18, 4.64]; $P = .014$; HR, 1.83 [95% CI: 0.95, 3.55]; $P = .070$; and HR, 1.54 [95% CI: 0.75, 3.19]; $P = .24$). In contrast, the mean at an SSF of 2 indicated reduced

### Table 2: Radiomics Texture Features by BRAF Mutation Status

| Radiomics Texture Feature | Wild-type BRAF | BRAF Mutant | $P$ Value | Corrected $P$ Value |
|---------------------------|---------------|-------------|-----------|---------------------|
| **SSF = 0 (no filter)**   |               |             |           |                     |
| Mean                      | 62.15 (52.49, 73.86) | 59.98 (53.69, 68.13) | .33       | > .99               |
| SD                        | 25.44 (22.67, 29.55) | 22.31 (20.66, 24.62) | .006      | .036                |
| MPP                       | 64.73 (55.35, 74.98) | 61.23 (55.67, 68.8) | .23       | > .99               |
| Entropy                   | 4.54 (4.42, 4.68) | 4.45 (4.38, 4.57) | .02       | .12                 |
| Kurtosis                  | 0.765 (0.24, 1.19) | 0.79 (0.44, 1.04) | .77       | > .99               |
| **SSF = 2 (fine)**        |               |             |           |                     |
| Mean                      | 12.08 (5.58, 18.61) | 11.06 (5.39, 13.66) | .41       | > .99               |
| SD                        | 62.65 (54.14, 76.75) | 55.57 (49.71, 62.99) | .052      | .31                 |
| MPP                       | 49.75 (43.53, 57.43) | 45.26 (39.58, 50.25) | .033      | .20                 |
| Entropy                   | 5.35 (5.22, 5.47) | 5.27 (5.2, 5.36) | .14       | .84                 |
| Kurtosis                  | 0.84 (0.30, 1.9) | 0.87 (0.55, 1.14) | .96       | > .99               |
| Skewness                  | $-0.5 (-0.76, -0.15)$ | $-0.47 (-0.62, -0.04)$ | .31       | > .99               |
| **SSF = 4 (medium)**      |               |             |           |                     |
| Mean                      | 25.57 (7.61, 38.17) | 19.74 (9.24, 31.01) | .31       | > .99               |
| SD                        | 66.09 (56.39, 84.84) | 57.12 (53.84, 64.12) | .012      | .07                 |
| MPP                       | 60.42 (50.22, 75.76) | 51.54 (47.14, 58.99) | .007      | .042                |
| Entropy                   | 5.39 (5.26, 5.57) | 5.3 (5.25, 5.41) | .068      | .41                 |
| Kurtosis                  | 0.21 (0.21, 1.09) | 0.33 (0.1, 1.13) | .48       | > .99               |
| Skewness                  | $-0.43 (-0.79, -0.21)$ | $-0.42 (-0.62, -0.18)$ | .58       | > .99               |
| **SSF = 6 (coarse)**      |               |             |           |                     |
| Mean                      | 32.55 (10.29, 47.59) | 23.43 (7.64, 40.15) | .41       | > .99               |
| SD                        | 69.22 (57.63, 91.86) | 58.28 (54.56, 64.91) | .009      | .05                 |
| MPP                       | 72.29 (56.33, 84) | 57.66 (50.87, 65.29) | .005      | .03                 |
| Entropy                   | 5.41 (5.28, 5.63) | 5.29 (5.22, 5.41) | .019      | .11                 |
| Kurtosis                  | 0.04 (0.42, 0.72) | $-0.01 (-0.31, 0.79)$ | .92       | > .99               |
| Skewness                  | $-0.42 (-0.71, -0.11)$ | $-0.22 (-0.78, 0.2)$ | .18       | > .99               |

Note.—Data are shown as the median with interquartile range in parentheses. Corrected $P$ values were computed using the Bonferroni method as the $P$ value by six radiomics texture features, in which a $P$ value less than .0083 was considered significant. MPP = mean value of positive pixels, SD = standard deviation of pixels, SSF = spatial scaling factor.
risk was found for the patients at quartiles 2, 3, and 4 (HR, 0.85 [95% CI: 0.46, 1.6]; \( P = .63 \); HR, 0.96 [95% CI: 0.52, 1.75]; \( P = .90 \); and HR, 0.41 [95% CI: 0.21, 0.77]; \( P = .007 \)).

To display the data in a concise manner, cutoff points were obtained on the basis of the highest value of the first quartile of skewness (−0.75) at an SSF of 0 and the lowest value of the fourth quartile for the mean (17.76) at an SSF of 2. These cutoff values were used to compare OS. Patients with skewness less than or equal to −0.75 showed better median 5-year OS than those with skewness greater than −0.75. (71.34 vs 39.02 months; log-rank \( P = .025 \); HR, 0.53 [95% CI: 0.29, 0.94]). Patients with a mean greater than or equal to 17.76 showed better 5-year OS than those with a mean less than 17.76 (85.64 vs 37.74 months; log-rank \( P = .002 \); HR, 0.40 [95% CI: 0.22, 0.71]) (Fig 4).

**Discussion**

In the era of precision medicine to tailor therapies, predicting tumor genomics using noninvasive techniques is the desired aim, especially in patients with advanced-stage disease who may benefit from a specific molecularly targeted agent or a combination of such agents (23). Radiomics leverages high-throughput feature extraction through complex pattern recognition that is difficult for humans to perceive visually. In our investigation, \( BRAFT \) mutant CRC tumors had lower values for the derived radiomics texture features of SD and MPP than wild-type \( BRAFT \) tumors. However, tumors showing lower skewness and higher mean values were associated with better 5-year OS. Because we focused our study on a large cohort of patients with stage IV CRC, tumor genetic variability was po-

---

**Table 3: Median Survival Time by Radiomics Texture Feature Quartiles**

| Radiomics Texture Feature | Median Survival (mo) | Log-Rank \( P \) Value |
|---------------------------|----------------------|-------------------------|
|                           | Q1       | Q2       | Q3       | Q4       |
| SSF = 0 (no filter)       |          |          |          |          |
| Mean                      | 34 (37)  | 58 (36)  | 39 (36)  | 62 (36)  | .24         |
| SD                        | 26 (37)  | 49 (36)  | 57 (36)  | 51 (36)  | .08         |
| MPP                       | 32 (37)  | 58 (36)  | 51 (36)  | 62 (36)  | .11         |
| Entropy                   | 26 (40)  | 57 (36)  | 47 (33)  | 58 (36)  | .07         |
| Kurtosis                  | 49 (40)  | 38 (33)  | 47 (36)  | 62 (36)  | .70         |
| Skewness                  | 71 (37)  | 31 (36)  | 49 (38)  | 41 (34)  | .041        |
| SSF = 2 (fine)            |          |          |          |          |
| Mean                      | 49 (37)  | 33 (36)  | 38 (36)  | 86 (36)  | .025        |
| SD                        | 47 (37)  | 28 (36)  | 61 (36)  | 51 (36)  | .25         |
| MPP                       | 58 (37)  | 31 (36)  | 49 (36)  | 62 (36)  | .27         |
| Entropy                   | 47 (39)  | 39 (34)  | 63 (39)  | 47 (33)  | .61         |
| Kurtosis                  | 47 (37)  | 48 (37)  | 51 (35)  | 49 (36)  | .89         |
| Skewness                  | 49 (37)  | 57 (37)  | 28 (35)  | 61 (36)  | .47         |
| SSF = 4 (medium)          |          |          |          |          |
| Mean                      | 51 (37)  | 41 (36)  | 34 (36)  | 72 (36)  | .20         |
| SD                        | 31 (38)  | 39 (35)  | 57 (36)  | 51 (36)  | .16         |
| MPP                       | 47 (37)  | 29 (36)  | 39 (36)  | 62 (36)  | .12         |
| Entropy                   | 47 (38)  | 39 (35)  | 47 (36)  | 57 (36)  | .69         |
| Kurtosis                  | 57 (38)  | 47 (36)  | 39 (35)  | 27 (36)  | .53         |
| Skewness                  | 39 (37)  | 41 (36)  | 48 (37)  | 51 (35)  | .69         |
| SSF = 6 (coarse)          |          |          |          |          |
| Mean                      | 49 (37)  | 76 (36)  | 41 (36)  | 51 (36)  | .23         |
| SD                        | 33 (37)  | 51 (36)  | 41 (36)  | 51 (36)  | .76         |
| MPP                       | 31 (37)  | 39 (36)  | 51 (36)  | 57 (36)  | .61         |
| Entropy                   | 41 (37)  | 49 (41)  | 39 (31)  | 51 (36)  | .99         |
| Kurtosis                  | 51 (38)  | 47 (35)  | 49 (37)  | 47 (35)  | .94         |
| Skewness                  | 31 (38)  | 47 (35)  | 51 (38)  | 58 (34)  | .39         |

Note.—Numbers in parentheses are the number of patients. MPP = mean value of positive pixels, SD = standard deviation of pixels, SSF = spatial scaling factor.
Nevertheless, the CRC-staging CT protocols are standardized
ferences that could have affected texture features and noise.
were performed on different scanners, leading to potential dif-
distribution of patients across the 14-year period, CT scans
within the vascular components and not within the parenchyma.
The difference between the tumors evaluated in our investigation lies
2) highlights parenchyma (28). This suggests that the main dif-
filters emphasize vasculature, whereas a fine filter (SSF =
nation between
tumor neoangiogenesis (25).
Genetic heterogeneity also influences the distribution of stro-
melanoma architecture or the function of individual tumors and, in
turn, may affect prognosis and treatment (26,27). CRC tumors
showing the lowest estimated values (first quartile) for skewness
and highest values for the mean (fourth quartile) were associated
with favorable 5-year OS in our study. This potentially implies
that tumors with less texture heterogeneity behave more aggres-
sively than tumors showing more heterogeneity; this might be
related to increased vascular permeability that allows a homoge-
neous distribution of contrast media within intra- and extravas-
ular spaces that translates into a more homogeneous texture (8).
Medium and coarse filters (SSF ≥ 4) enabled better discrimi-
nation between \( \text{BRAF} \) mutant and wild-type \( \text{BRAF} \) tumors.
These filters emphasize vasculature, whereas a fine filter (SSF =
2) highlights parenchyma (28). This suggests that the main dif-
ference between the tumors evaluated in our investigation lies
within the vascular components and not within the parenchyma.
There were a few limitations in this study. First, given the
distribution of patients across the 14-year period, CT scans
were performed on different scanners, leading to potential dif-
ferences that could have affected texture features and noise.
Nevertheless, the CRC-staging CT protocols are standardized
for injection protocols and slice thickness at our institution and
at most cancer centers. Moreover, texture analysis is indiffer-
ent to slight variations in image-acquisition protocols (29), and
the filtration step applied to the images before extracting radiomic
features can substantially reduce noise and minimize the effect of
image acquisition (30). Second, the analysis was performed on the
largest cross-sectional area of the tumor instead of on the whole
tumor volume. This could have potentially underestimated the
heterogeneity of the tumor. How-
ever, texture-analysis comparisons
from the whole tumor volume
and the largest cross-sectional area of the tumor have
related relatively similar results (7,28).
Third, another limitation
was the inherent small number of radiomics features evaluated
by using TexRAD, as this platform provides only first-order sta-
tistical features at different anatomic scales. Finally, to be con-
fident regarding the application of our findings, testing on an
unseen validation cohort would be useful. However, the small
sample size of our cohort precludes this analysis.

Despite its promise, radiomics texture analysis is currently
a research tool and entails a workflow not conducive to sup-
porting clinical practice. Seamless integration of radiomics
texture analysis into the radiologic image-interpretation work-
flow as a readily accessible tool that combines tumor metrics
with genomic and clinical information to support decision-
making should be explored (31,32). Lack of standardization
across different radiomics software platforms is also a limita-
tion, and robust and reproducible data validated from large
multicenter trials are desired (33). It is also worth mentioning
that radiomics can also be applied in the field of MRI, where it
has been used for purposes ranging from differentiating benign
from malignant tumors of mesenchymal origin (34,35) to
improving the diagnostic yield of Prostate Imaging Reporting and
Data System version 2 (36).

Developing radiomics texture analysis as a potential quan-
titative image biomarker for predicting tumor genomic and
clinical outcomes confers many advantages, such as having a
noninvasive nature that allows for analysis of a tumor at its
largest cross-sectional area or in its entire tumor volume, acting
as a whole-tumor virtual biopsy; being a disporible technol-
y; and having a relatively low cost and good spatial resolu-
tion. Moreover, the differences detected as radiomics texture
features are virtually impossible for a radiologist to assess vi-
sually because the human eye is insufficient to discern subtle
changes in tissue attenuation. In summary, radiomics texture
features might serve as potential biomarkers for determining
\( \text{BRAF} \) mutation status and as predictors of 5-year OS in pa-
tients with advanced-stage CRC.
Acknowledgments: The authors thank Hamed Kordbacheh, Vicente Morales Oyarvide, and Priyanka Sahni.

Author contributions: Guarantors of integrity of entire study, A.A.N., D.V.S.; study concept/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure all questions related to the work are appropriately resolved, all authors; literature research, A.A.N., A. Parakh, A. Pourvaziri; clinical studies, A.A.N., A. Parakh, D.P.R., D.V.S.; statistical analysis, A.A.N., A. Pourvaziri, D.V.S.; and manuscript editing, A.A.N., A. Parakh, A. Pourvaziri, A.K., D.V.S.

Disclosures of Conflicts of Interest: A.A.N. disclosed no relevant relationships. A. Parakh disclosed no relevant relationships. R.B.C. Activities related to the present article: disclosed no relevant activities. Activities not related to the present article: author is paid as a consultant by Abbvie, Amgen, Array Biopharma/Pfizer, Astex Pharmaceuticals, Avidity Biosciences, BMS, C4 Therapeutics, Chugai, Eliion, Fog Pharma, Fourn Therapeutics/Kinnate Biopharma, Genentech, Guardian Health, Ipsen, LOXO, Merrimack, Naxera, N-of-one, Novartis, nRichDx, Revolution Medicines, Roche, Roivant, Shionogi, Shire, Spectrum Pharmaceuticals, Symphogen, Taiho, Warp Drive Bio, Zikani Therapeutics; author receives grants from AstraZeneca, Asana, and Lilly; author has stock/stock options in Avidity Biosciences, C4 Therapeutics, Fourn Therapeutics/Kinnate Biopharma, nRichDx, and Revolution Medicines. Other relationships: disclosed no relevant relationships. A. Pourvaziri disclosed no relevant relationships. A.K. Activities related to the present article: disclosed no relevant activities. Activities not related to the present article: author receives grants from GE Healthcare and Philips. Other relationships: disclosed no relevant relationships. D.P.R. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed no relevant relationships. Other relationships: author has equity in MPM Capital, Acworth Pharmaceuticals, and Thrive Earlier Detection; author advises for MPM Capital, Oncorus, Geistsone Oncology; Maverick Therapeutics, and 287 Therapeutics; author receives publishing compensation/revenues from Johns Hopkins University Press, Up-to-date, and McGraw Hill. D.V.S. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: author is a consultant for GE Healthcare; author is paid for lectures by GE Healthcare; author receives royalties from Elsevier. Other relationships: disclosed no relevant relationships.

References
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7–30.
2. Colon cancer (version 1.2019). National Comprehensive Cancer Network Web site. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed April 3, 2019.
3. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med 2017;141(5):625–657.
4. Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S, Mal MS, Raaschou-Nielsen O, Robson M. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: a systematic review and meta-analysis. Acta Oncol 2016;55(7):822–845.
5. Popat S, Hruban R,Houlston RS. Systematic review of microsatellite instability and colorectal cancer progression. J Clin Oncol 2005;23(3):609–618.
6. Jang MH, Kim S, Hwang DY, et al. BRAF-mutated colorectal cancer exhibits distinct clinicopathological features from wild-type BRAF-expressing cancer independent of the microsatellite instability status. J Korean Med Sci 2017;32(1):38–46.
7. Lubner MG, Stabo N, Lubner SJ, et al. CT textural analysis of hepatic metastatic colorectal cancer: pre-treatment tumor heterogeneity correlates with pathology and clinical outcomes. Abdom Imaging 2015;40(7):2331–2337.
8. Ng F, Ganeshan B, Kozarski R, Miles KA, Goh V. Assessment of primary colorectal cancer heterogeneity by using whole-tumor texture analysis: contrast-enhanced CT texture as a biomarker of 5-year survival. Radiology 2013;266(1):177–184.
9. Chee CG, Kim YH, Lee KH, et al. CT texture analysis in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy: a potential imaging biomarker for treatment response and prognosis. PLoS One 2013;12(8):e28933.
10. Shin SY, Hong IK, Jo YS. Quantitative computed tomography texture analysis: can it improve diagnostic accuracy to differentiate malignant lymph nodes? Cancer Imaging 2019;19(1):25.
11. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology 2016;278(2):563–577.
12. Yip C, Landau D, Kozarski R, et al. Primary esophageal cancer: heterogeneity as potential prognostic biomarker in patients treated with definitive chemoradiotherapy and radiation therapy. Radiology 2014;270(1):141–148.
13. Smith AD, Gray MR, del Campo SM, et al. Predicting overall survival in patients with metastatic melanoma on antiangiogenic therapy and RECIST stable disease on initial posttherapy images using CT texture analysis. AJR Am J Roentgenol 2015;205(3):W283–W293.
14. Ganeshan B, Goh V, Mandeville HC, Ng QS, Hoskin PJ, Miles KA. Non-small cell lung cancer: histopathologic correlates for texture parameters at CT. Radiology 2013;266(1):326–336.
15. Deng Y, Soule E, Samuel A, et al. CT texture analysis in the differentiation of major renal cell carcinoma subtypes and correlation with Fuhrman grade. Eur Radiol 2019;29(12):6922–6939.
16. Diamantarthry S, Padole AM, Rastogi S, et al. Predicting malignant potential of subsolid nodules: can radiomics preempt longitudinal follow up? Cancer Imaging 2019;19(1):36.
17. Meyer HJ, Hamerla G, Höhn AK, Surov A. CT texture analysis-correlations with histopathology parameters in head and neck squamous cell carcinomas. Front Oncol 2019;9:444.
18. Castellano G, Bonilla L, Li LM, Cendes F. Texture analysis of medical images. Clin Radiol 2009;64(12):1061–1069.
19. Lubner MG, Smith AD, Sandrasegaran K, Sahani DV, Pickhardt PJ. CT texture analysis: definitions, applications, biologic correlates, and challenges. Radiographics 2017;37(5):1483–1503.
20. Ganeshan B, Miles KA. Quantifying tumour heterogeneity with CT. Cancer Imaging 2013;13(1):140–149.
21. Yang L, Dong D, Fang M, et al. Can CT-based radiomics signature predict KRAS/NRAS/BRAF mutations in colorectal cancer? Eur Radiol 2018;28(5):2058–2067.
22. Dias-Santagata D, Akhavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. EMBO Mol Med 2010;2(5):146–158.
23. Verma M. Personalized medicine and cancer. J Pers Med 2012;2(1):1–14.
24. Baldus SE, Schaefer KL, Ruhl T, Hartleh D, Stoecklein NH, Gabbert HE. Prevalence and heterogeneity of KRAS, BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases. Clin Cancer Res 2010;16(3):790–799.
25. Ganeshan B, Ziauddin X, Goh VJ, et al. Quantitative imaging biomarkers from PET-CT as potential correlates for angiogenesis and hypoxia in colorectal cancer. Vienna, Austria: European Society of Radiology, 2012.
26. McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. Cell 2017;168(4):613–628.
27. O’Connor JPB, Rose CJ, Waterton JC, Carano RA, Parker GJ, Jackson A. Imaging intratumor heterogeneity: role in therapy response, resistance, and clinical outcome. Clin Cancer Res 2015;21(2):249–257.
28. Ng F, Kozarski R, Ganeshan B, Goh V. Assessment of tumor heterogeneity by CT texture analysis: can the largest cross-sectional area be used as an alternative to whole tumor texture analysis? Eur J Radiol 2013;82(2):342–348.
29. Miles KA, Ganeshan B, Griffiths MR, Young RC, Chatwin CR. Colorectal cancer: texture analysis of portal phase hepatic CT images as a potential marker of survival. Radiology 2009;250(2):444–452.
30. Ganeshan B, Miles KA, Young RCD, Chatwin CR. In search of biologic correlates for liver texture on portal-phase CT. Acad Radiol 2007;14(9):1058–1068.
31. Mackie TR, Jackson EF, Giger M. Opportunities and challenges to utilization of quantitative imaging: report of the AAPPM practical big data workshop. Med Phys 2018;45(10):e820–e828.
32. Court LE, Faye X, Mackin D, et al. Computational resources for radiomics. Transl Cancer Res 2016;5(4):340–348.
33. Park JE, Park SY, Kim HJ, Kim HS. Reproducibility and generalizability in radiomics modeling: possible strategies in radiologic and statistical perspectives. Korean J Radiol 2019;20(7):1124–1137.
34. Lakhman Y, Veeraraghavan H, Chaim J, et al. Differentiation of uterine leiomyosarcoma from atypical leiomyoma: diagnostic accuracy of qualitative MR imaging features and feasibility of texture analysis. Eur Radiol 2017;27(7):2903–2915.
35. Lissom CS, Lissen CG, Floodorf K, et al. Diagnostic value of MRI-based 3D texture analysis for tissue characterisation and discrimination of low-grade choriodosarcoma from enchondroma: a pilot study. Eur Radiol 2018;28(2):468–477.
36. Wang J, Wu CJ, Bao ML, Zhang J, Wang XN, Zhang YD. Machine learning-based analysis of MR radiomics can help to improve the diagnostic performance of PI-RADS v2 in clinically relevant prostate cancer. Eur Radiol 2017;27(10):4082–4090.