Assessment of Primary Colorectal Cancer Heterogeneity by Using Whole-Tumor Texture Analysis: Contrast-enhanced CT Texture as a Biomarker of 5-year Survival[1]

Francesca Ng, FRCR
Balaji Ganeshan, PhD
Robert Kozarski, MSc
Kenneth A. Miles, MD, FRCR
Vicky Goh, MD, FRCR

Purpose: To determine if computed tomographic (CT) texture features of primary colorectal cancer are related to 5-year overall survival rate.

Materials and Methods: Institutional review board waiver was obtained for this retrospective analysis. Texture features of the entire primary tumor were assessed with contrast material–enhanced staging CT studies obtained in 57 patients as part of an ethically approved study and by using proprietary software. Entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram were derived from CT images without filtration and with filter values corresponding to fine (1.0), medium (1.5, 2.0), and coarse (2.5) textures. Patients were followed up until death and were censored at 5 years if they were still alive. Kaplan-Meier analysis was performed to determine the relationship, if any, between CT texture and 5-year overall survival rate. The Cox proportional hazards model was used to assess independence of texture parameters from stage.

Results: Follow-up data were available for 55 of 57 patients. There were eight stage I, 19 stage II, 17 stage III, and 11 stage IV cancers. Fine-texture feature Kaplan-Meier survival plots for entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram were significantly different for tumors above and below each respective threshold receiver operating characteristic (ROC) curve optimal cutoff value ($P = .001$, $P = .018$, $P = .032$, $P = .008$, and $P = .001$, respectively), with poorer prognosis for ROC optimal values *(a)* less than 7.89 for entropy, *(b)* at least 0.01 for uniformity, *(c)* less than 2.48 for kurtosis, *(d)* at least −0.38 for skewness, and *(e)* less than 61.83 for standard deviation. Multivariate Cox proportional hazards regression analysis showed that each parameter was independent from the stage predictor of overall survival rate ($P = .001$, $P = .009$, $P = .006$, $P = .02$, and $P = .001$, respectively).

Conclusion: Fine-texture features are associated with poorer 5-year overall survival rate in patients with primary colorectal cancer.

Supplemental material: *http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.12120254/-/DC1*

[1] From the Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, England (F.N., V.G.); Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, Falmer, Sussex, England (B.G., K.A.M.); CliCr, University of Hertfordshire, Hatfield, Hertfordshire, England (R.K.); and Division of Imaging Sciences and Biomedical Engineering, King's College London, St Thomas' Hospital, Lambeth Palace Road, Imaging 2, Level 1, Lambeth Wing, London SE1 7EH, England (V.G.). Received January 31, 2012; revision requested March 23; revision received May 1; accepted May 17; final version accepted July 17. **Address correspondence to** V.G. (e-mail: *Vicky.goh@kcl.ac.uk*).

Colorectal cancer is one of the commonest cancers in the Western world (1). Surgical resection of the primary tumor with curative intent is appropriate in approximately 70% of patients. However, up to 30% of patients who undergo surgical resection of the primary tumor experience a subsequent relapse, usually within 3 years, with a median time from recurrence to death of 12 months (2–4). Overall prognosis is poor once recurrence has occurred, with liver metastases in 40%–50% of these patients (5). Better methods of tumor characterization and risk stratification in patients for treatment at initial staging to guide subsequent surveillance is still needed, and this was highlighted as an important area for research in an American Society of Clinical Oncology practice guideline (6).

The TNM classification is the most widely used staging system. In patients with colorectal cancer, this classifier is based on the depth of tumor invasion, lymph node involvement, and metastatic spread, but it does not take into account spatial heterogeneity. Heterogeneity is a well-recognized feature of malignancy that reflects areas of high cell density, necrosis, hemorrhage, and myxoid change (7). However, much of the heterogeneity visible on computed tomographic (CT) images represents photon noise, which can mask any underlying biologic heterogeneity. By using filters that select for image features at larger scales, CT texture analysis can reduce the effect of photon noise while enhancing biologic heterogeneity. Heterogeneity at relevant scales can be quantified by using a range of parameters, including entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram.

Previous studies in patients with colorectal cancer that have focused on hepatic texture have shown that higher hepatic entropy and lower uniformity (8,9) may predict poorer survival; however, to date, few studies have been performed to assess the texture features of primary colorectal cancer and to determine if tumor texture is related to overall survival. The aim of this study was to determine if CT texture features of primary colorectal cancer are related to 5-year overall survival rate.

Advances in Knowledge

- Kaplan-Meier survival plots for tumor fine-texture entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram were significantly different for tumors above and below each threshold value (receiver operating characteristic [ROC] optimal cutoff value of $P = .001$, $P = .018$, $P = .032$, $P = .008$, and $P = .001$, respectively); poorer survival was noted for ROC optimal cutoff values (≤ 7.89, > 0.01, ≤ 2.48, > -0.38, and ≤ 61.83 for entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram, respectively).
- Cox regression analysis with stage as a dependent covariate showed texture features were an independent predictor of 5-year overall survival rate.

Materials and Methods

The University of Sussex, England, provided the software used for analysis. One author (B.G.) is Scientific Director of TexRAD (Brighton, England), and another (K.A.M.) is the Clinical Director. All other authors had control of the data and information submitted for publication.

Patients

Ethical approval was obtained for this retrospective analysis of data acquired during a previously published prospective imaging research perfusion CT study conducted from October 2001 to September 2005 for which patients gave informed consent (Fig 1) (10). As part of their standard imaging staging, 62 consecutive patients (30 men; mean age, 69.1 years; age range, 34.9–83.6 years; 32 women; mean age, 66.8 years; age range, 28.1–84.7 years) with primary colorectal cancer underwent standard staging contrast material–enhanced portal venous CT in addition to research perfusion CT. This clinical staging contrast-enhanced CT study was retrievable from the archive in 57 of the 62 patients, and these patients comprised the study group. In each patient, localization of the tumor had been performed at previous colonoscopy and perfusion CT, and the tumor was visible on the staging CT image, which was of good quality and was without substantial patient motion (Fig 1).

CT examination.— Contrast-enhanced CT of the chest, abdomen, and pelvis was performed with a four–detector row CT scanner (GE Lightspeed Plus; GE Healthcare, Amersham, England) by using the following parameters: 120 kV; 280 mAs; 0.6-second rotation time; 5-mm section collimation; field of view, 300; matrix, 512; pixel size, 0.68 × 0.68 mm; 75-second delay after administration of 100 mL of 340 mg/mL iodinated contrast material (Niopam 340; Bracco, Milan, Italy) at a 5 mL/sec injection rate with a pump injector (Percupump Touchscreen; E-Z-Em, Westbury, NY). The staging CT was reported, as per

Implication for Patient Care

- The addition of texture analysis to staging contrast-enhanced CT may improve prognostication in patients with primary colorectal cancer.

Published online before print
10.1148/radiol.12120254 **Content code:** GI

Radiology 2013; 266:177–184

Abbreviations:
ROC = receiver operating characteristic
ROI = region of interest

Author contributions:
Guarantors of integrity of entire study, F.N., V.G.; study concepts/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; literature research, F.N., B.G.; clinical studies, F.N.; statistical analysis, F.N., B.G., R.K., K.A.M.; and manuscript editing, F.N., B.G., K.A.M., V.G.

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

usual institutional clinical practice, at the time of acquisition.

Texture analysis.—The contrast-enhanced CT studies were retrieved from the institution archive and loaded to a standard workstation for further textural analysis. This was performed by one observer (F.N., a radiologist with 5 years of experience with abdominal CT) who was blinded to clinical outcome. The technique comprised an initial filtration step in which a Laplacian of Gaussian spatial band-pass filter was used to selectively extract features of different sizes and intensity variations (Appendix E1 [online]). This resulted in a series of derived images displaying features at different spatial scales from fine to coarse texture within a region of interest (ROI) drawn around the colorectal tumor (Fig 2). The scale was selected by tuning the filter parameter between 1.0 and 2.5, where 1.0 indicates fine texture (features of approximately 4 pixels or 2.72 mm in width), 1.5 and 2.0 indicate degrees of medium textures (features of approximately 6 pixels or 4.08 mm and approximately 10 pixels or 6.8 mm in width, respectively), and 2.5 indicates coarse texture (features of approximately 12 pixels or 8.16 mm in width). An ROI was delineated initially around the tumor outline for the largest cross-sectional area. The ROI was then propagated automatically by the software to include the entire tumor volume. The ROI was further refined by the exclusion of areas of air with a thresholding procedure that removed from analysis any pixels with attenuation values below −50 HU. Where necessary, the ROI was further adjusted manually at each individual level or section. This was performed in no more than 45% of sections in every patient. Heterogeneity within this ROI was quantified with and without image filtration, calculating entropy (irregularity) and uniformity (distribution of gray level), kurtosis (magnitude of pixel ditribution), skewness (skewness of pixel distribution), and standard deviation of the pixel distribution histogram (Appendix E1 [online]). In general, higher entropy, lower uniformity, higher standard deviation of the pixel distribution histogram, higher kurtosis, and lower skewness represent increased heterogeneity.

Figure 1

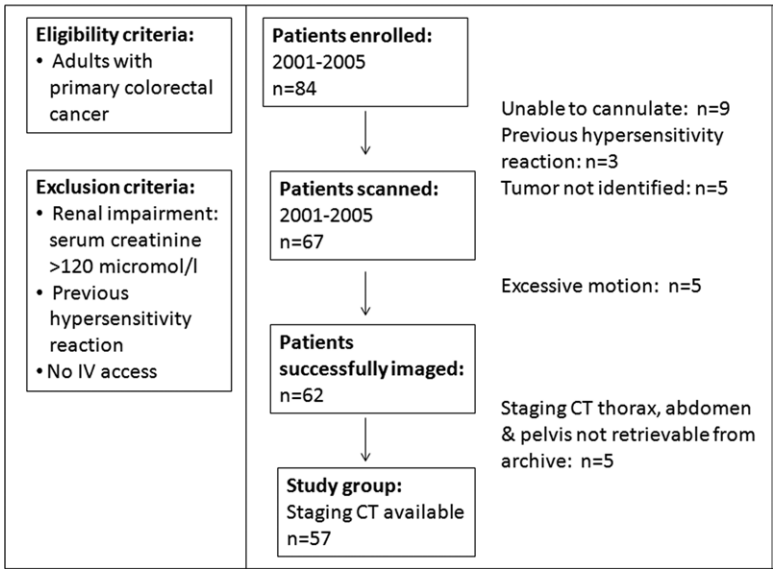

Figure 1: Schematic shows recruitment pathway of patients for this study. *IV* = intravenous.

Staging and follow-up.—The overall tumor stage of each patient was recorded as part of the original imaging research study and derived from pathologic staging (local-regional) and CT staging (distant). Stage grouping was derived from the TNM stage, as per the American Joint Committee on Cancer (11). Patients were followed up as part of the research study, and data were censored 5 years after imaging if patients were still alive.

Statistical Analysis

Texture features were compared between aggregated stage I/II and stage III/IV tumors based on the original staging information (from pathologic analysis and imaging) recorded as part of the original research study by using the Mann-Whitney test. Receiver operating characteristic (ROC) curve and Kaplan-Meier analyses were performed to determine the relationship, if any, between CT texture features of the tumor, tumor stage, and 5-year overall survival rate. For the purpose of analysis, each texture parameter at the different filter values (fine, medium, and coarse) was dichotomized with respect to the ROC optimum point. Multivariate Cox proportional hazards regression analysis was performed to assess whether any of the Kaplan-Meier significant texture parameters were independent predictors of overall survival next to the tumor stage. Correlations between texture features were assessed by using Spearmann rank correlation. A two-tailed *P* value of less than .05 was considered to indicate a significant difference. A power calculation was also performed. All statistical analysis was performed by a statistician (R.K.) using R software (version 2.14.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Follow-up data were available in 55 of 57 patients. There were eight stage I, 19 stage II, 17 stage III, and 11 stage IV cancers. Of these, 26 were in the rectum, 12 were in the sigmoid colon, two were in the descending colon, one was in the transverse colon, three were in the ascending colon, and 11 were in the cecum. Twenty-six of the 55 patients died within 45 months of the initial CT

Figure 2

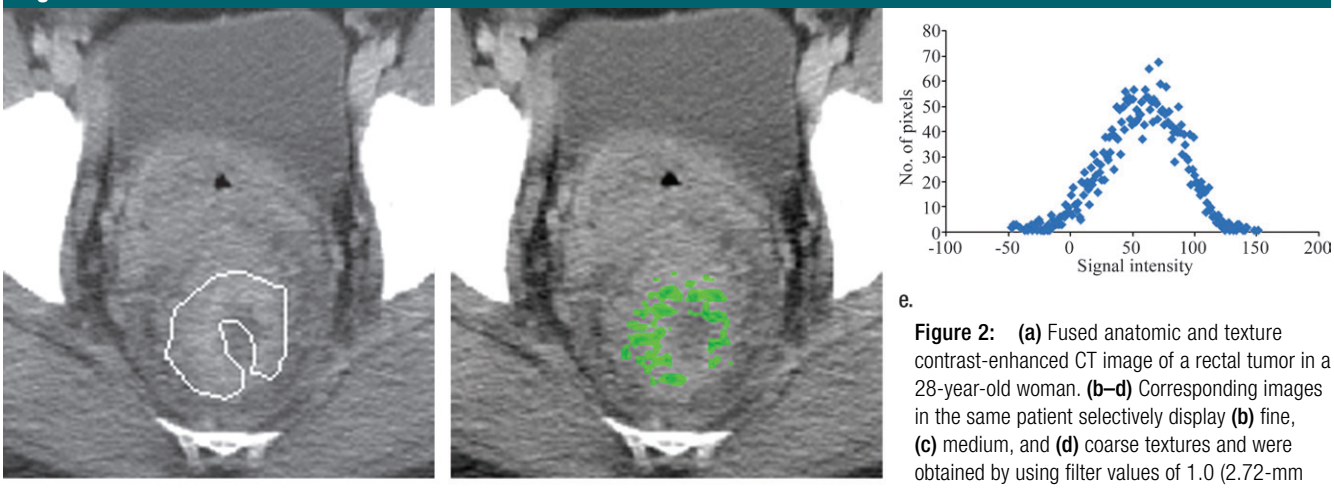

Figure 2: **(a)** Fused anatomic and texture contrast-enhanced CT image of a rectal tumor in a 28-year-old woman. **(b–d)** Corresponding images in the same patient selectively display **(b)** fine, **(c)** medium, and **(d)** coarse textures and were obtained by using filter values of 1.0 (2.72-mm width, 4 pixels), 1.5 (4.08-mm width, 6 pixels), and 2.5 (8.16-mm width, 12 pixels). **(e)** Histogram shows pixel distribution in this patient.

Table 1

Entropy, Uniformity, Kurtosis, Skewness, and Standard Deviation of Pixel Distribution Histogram without Filtration and for Absolute Filter Scale Values Depicting Fine, Medium, and Coarse Textures

Filter Scale Values	Entropy	Uniformity	Kurtosis	Skewness	Standard Deviation of Pixel Distribution Histogram
No filtration	7.06 ± 0.19	0.01 ± 0.001	0.54 ± 1.23	−0.47 ± 0.43	34.91 ± 4.71
1.0 (fine)	7.88 ± 0.22	0.01 ± 0.001	1.88 ± 1.57	−0.34 ± 0.44	60.43 ± 9.75
1.5 (medium)	7.88 ± 0.26	0.01 ± 0.001	1.79 ± 1.66	−0.50 ± 0.50	62.15 ± 12.33
2.0 (medium)	7.88 ± 0.29	0.01 ± 0.001	1.49 ± 1.63	−0.52 ± 0.55	63.06 ± 13.66
2.5 (coarse)	7.83 ± 0.33	0.01 ± 0.001	1.29 ± 1.64	−0.53 ± 0.57	62.14 ± 15.05

Note.—Data are mean ± standard deviation.

examination. Median survival for patients with stage III/IV disease was 20.9 months. The shortest survival time was 1 month. Median survival for patients with stage I/II disease was not reached in the study period. Of the 26 patients who died, 17 were found to have distant metastases (nine at staging, eight subsequent to treatment), and one had a synchronous tumor.

Texture Features

There was no significant difference in entropy (P = .44 to P = .92), uniformity (P = .39 to P = .91), kurtosis (P = .19 to P = .99), skewness (P = .18 to P = .96), or standard deviation of the pixel distribution histogram (P = .36 to P = .97) when aggregated stage I/II and stage III/IV tumors were compared at all filter levels (Table 1).

Kaplan-Meier curves were significantly different for all parameters for fine texture (Fig 3, Table 2). Kaplan-Meier analysis also enabled us to confirm that tumor stage (stage I/II vs stage III/IV) was a predictor of overall survival (Fig 4). The multivariate Cox PH regression analysis indicated that at a filter value of 1.0, entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram were separately independent predictors of overall survival,

Figure 3

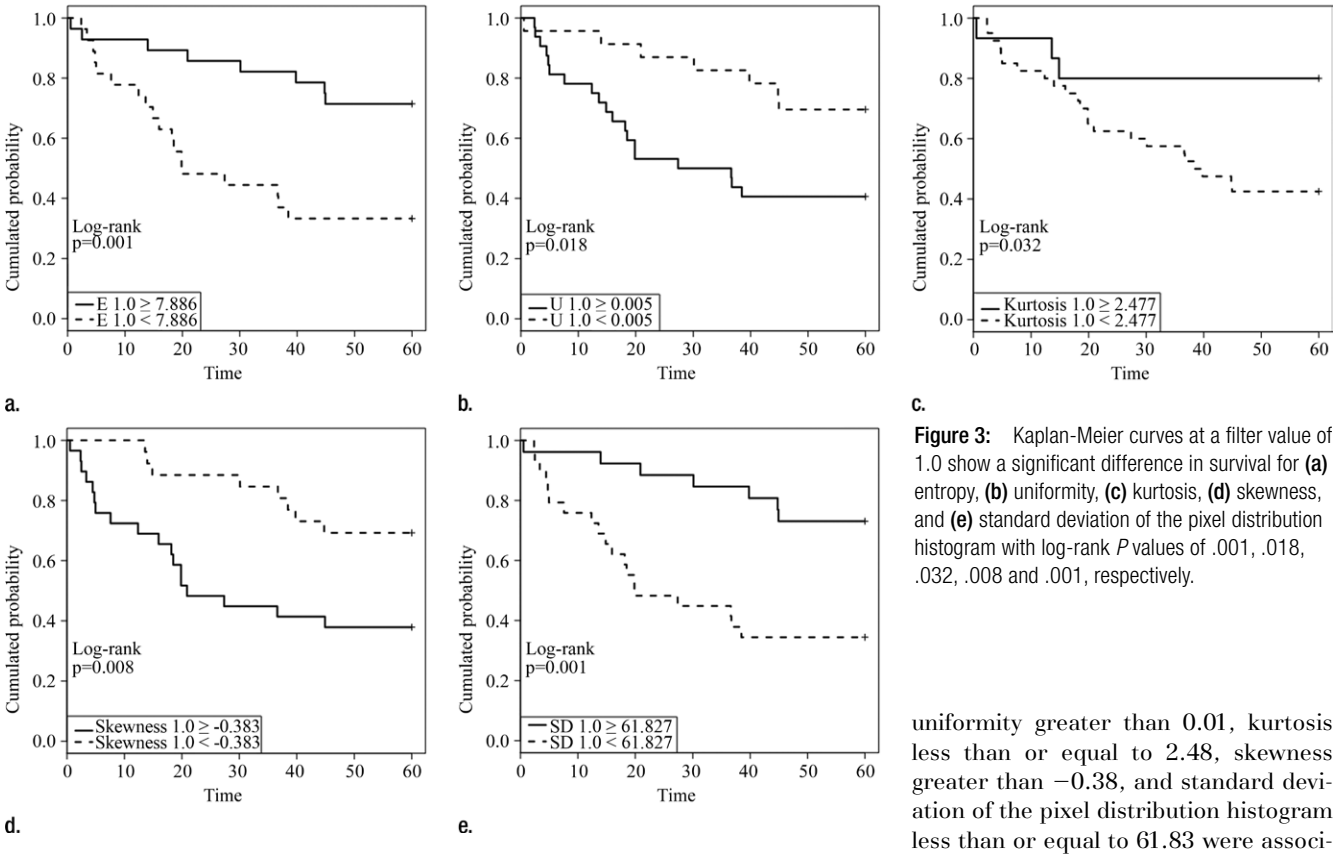

Figure 3: Kaplan-Meier curves at a filter value of 1.0 show a significant difference in survival for **(a)** entropy, **(b)** uniformity, **(c)** kurtosis, **(d)** skewness, and **(e)** standard deviation of the pixel distribution histogram with log-rank *P* values of .001, .018, .032, .008 and .001, respectively.

Figure 4

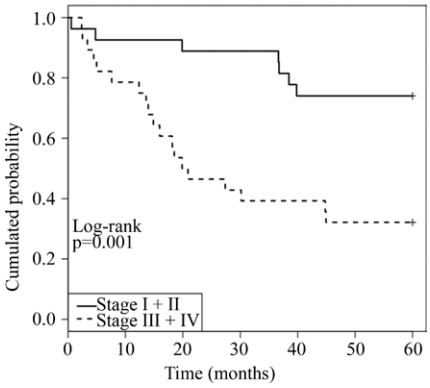

Figure 4: Kaplan-Meier curves show a significant difference in survival for stage, with log rank *P* value of .001.

in addition to the aggregated tumor stage (stage I/III vs stage III/IV) (Table 3). Strong negative correlations were noted between entropy and uniformity ($r = -0.98$, $P < .001$) and between uniformity and standard deviation of the pixel distribution histogram ($r = -0.94$, $P < .001$); strong positive correlation was noted between entropy and standard deviation of the pixel distribution histogram ($r = 0.98$, $P < .001$), and moderate negative correlation was noted between kurtosis and skewness ($r = -0.40$, $P = .003$) (Table 4).

The log-rank test power, assuming 5% significance, was between 52% for kurtosis and 84% and 87% for standard deviation of the pixel distribution histogram and entropy, respectively.

Discussion

In our study, we used whole-tumor volumetric textural analysis and found that tumors demonstrating less heterogeneity at fine filter levels were associated with poorer survival and that tumor entropy less than or equal to 7.89, uniformity greater than 0.01, kurtosis less than or equal to 2.48, skewness greater than −0.38, and standard deviation of the pixel distribution histogram less than or equal to 61.83 were associated with poorer 5-year overall survival.

Assessment of tumor heterogeneity is relevant to everyday clinical practice. It has been proposed that greater biologic heterogeneity may be associated with oxidative stress, promotion of survival factors, and genomic instability (7,12,13). To date, no studies have directly addressed primary colorectal cancer heterogeneity; however, several studies have suggested that increasing heterogeneity is associated with malignancy. One study of 220 nodes in patients with colorectal cancer suggested that CT texture features of malignant and benign nodes may differ, with greater heterogeneity noted in malignant nodes (14). In a study of 21 patients with primary esophageal cancer (15), correlating unenhanced CT texture analysis with positron emission tomography standardized uptake value (SUV) and clinical staging, coarse texture uniformity correlated negatively and entropy correlated positively with

standardized uptake value, while higher-stage tumors demonstrated greater heterogeneity at medium (3.92-mm pixel width in this study) but not fine textures (15). In a study of 17 patients with non–small cell lung cancer, unenhanced CT texture analysis coarse texture uniformity also correlated negatively with tumor stage (16); however, uniformity correlated negatively with the standardized uptake value. Other studies focusing on hepatic texture in patients with colorectal cancer have found a more heterogeneous liver texture at coarse textures is related to the presence of occult malignancy and a poorer prognosis (17,18).

Our study results differ from the results of other published studies, for which there may have been several factors: First, in our study, the whole tumor was assessed rather than a single axial level, as was the case in previous studies. This theoretically provides a more representative picture of tumor heterogeneity than that provided by single-level analysis. Second, these were contrast-enhanced CT images rather than unenhanced CT images. Third, this may reflect the differences in underlying tumor biology between different tumor types. Our findings and the findings of other studies highlight that there are key differences in texture features at different scales and between unenhanced and contrast-enhanced CT images. At a coarse scale, heterogeneity has been ascribed predominantly to the heterogeneity of the tumor vascular supply; this has been supported by computer simulation studies (19). At a fine scale, texture features may reflect cellular distribution on unenhanced images; however, on contrast-enhanced images, texture features will also reflect the distribution of the contrast agent between the intra- and extravascular extracellular space. A hypothesis is that our contrast-enhanced CT findings may be related to the effects of tumor vascular permeability. Tumors demonstrating higher vascular permeability and leading to greater parenchymal enhancement and lower contrast resolution between parenchyma and adjacent vessels may actually demonstrate less heterogeneity at texture analysis. Previous histologic studies have shown, for example, that poor pericyte coverage of tumor vessels (leading to increased vascular leakiness) is associated with an increased likelihood of nodal and distant metastases and a reduced survival rate (20).

In our study, we found that primary tumors that demonstrated greater homogeneity at a fine-texture level were associated with a poorer prognosis, leading us to hypothesize that these might be tumors with greater cell packing and more uniform distribution of vascularization and contrast enhancement. Given that the majority of colorectal tumors show moderate differentiation, this texture feature may augment current characterization and is promising as an additional prognostic biomarker to tumor stage. This may be particularly pertinent

Table 2

Summary of ROC and Kaplan-Meier Analysis for Entropy, Uniformity, Kurtosis, Skewness, and Standard Deviation of Pixel Distribution Histogram

Filtration and Fine-Texture Feature	ROC Threshold	Median Survival (mo)		*P* Value
		Above Threshold	Below Threshold	
No filtration				
Entropy	≤7.06	60* (25)	45 (30)	.73
Uniformity	>0.01	42 (12)	60* (43)	.49
Kurtosis	>0.61	37 (19)	60* (36)	.18
Skewness	>−0.39	18 (14)	60* (41)	.004
Standard deviation of pixel distribution histogram	≤36.58	60* (18)	39 (37)	.13
Filter value = 1.0 (fine)				
Entropy	≤7.89	60* (28)	20 (27)	.001
Uniformity	>0.01	32 (32)	60* (23)	.018
Kurtosis	≤2.48	60* (15)	40 (40)	.032
Skewness	>−0.38	21 (29)	60* (26)	.008
Standard deviation of pixel distribution histogram	≤61.83	60* (26)	20 (29)	.001
Filter value = 1.5 (medium)				
Entropy	≤7.92	60* (24)	27 (31)	.01
Uniformity	>0.01	37 (13)	60* (42)	.19
Kurtosis	≤1.95	60* (16)	40 (39)	.07
Skewness	>−0.62	27 (29)	60* (26)	.03
Standard deviation of pixel distribution histogram	≤61.42	60* (24)	27 (31)	.003
Filter value = 2.0 (medium)				
Entropy	≤7.98	60* (18)	39 (37)	.049
Uniformity	>0.01	45 (35)	60* (20)	.37
Kurtosis	≤0.70	60* (42)	27 (13)	.09
Skewness	>−0.54	27 (23)	60* (32)	.15
Standard deviation of pixel distribution histogram	≤63.85	60* (24)	27 (31)	.01
Filter value = 2.5 (coarse)				
Entropy	≤7.80	60* (29)	38 (26)	.14
Uniformity	>0.01	39 (32)	60* (23)	.15
Kurtosis	>0.99	41 (26)	60* (29)	.22
Skewness	>−0.48	45 (35)	60* (20)	.59
Standard deviation of pixel distribution histogram	≤65.87	60* (17)	39 (38)	.03

Note.—Data in parentheses are numbers of patients.

* Cumulative survival probability was above 0.5 at 60 months follow-up.

Table 3

Multivariate Cox Proportional Hazards Regression Analysis of Texture Parameters with Stage as a Dependent Covariate

Fine-Texture Feature	Hazard Ratio	95% Confidence Interval	*P* Value
Entropy	0.247	0.104, 0.582	.001
Unifomity	3.193	1.328, 7.676	.009
Kurtosis	0.182	0.053, 0.619	.006
Skewness	2.709	1.168, 6.283	.02
Standard deviation of pixel distribution histogram	0.213	0.087, 0.522	<.001

Table 4

Spearman Rank Correlation for Entropy, Uniformity, Kurtosis, Skewness, and Standard Deviation of Pixel Distribution Histogram at a Filter Level of 1.0

Fine-Texture Feature	Entropy	Uniformity	Kurtosis	Skewness	Standard Deviation of Pixel Distribution Histogram
Entropy	…	−0.98 (<.001)	−0.09 (.537)	−0.11 (.424)	0.98 (<.001)
Uniformity	−0.98 (<.001)	…	0.2 (.140)	0.09 (.505)	−0.94 (<.001)
Kurtosis	−0.09 (.537)	0.2 (.140)	…	−0.4 (.003)	0.05 (.744)
Skewness	−0.11 (.424)	0.09 (.505)	−0.4 (.003)	…	−0.15 (.274)
Standard deviation of pixel distribution histogram	0.98 (<.001)	−0.94 (<.001)	0.05 (.744)	−0.15 (.274)	…

Note.—Data in parentheses are *P* values.

for stage II cancers, which might have a variable prognosis, in identifying potential at-risk stage II cancers that might benefit from additional neoadjuvant or adjuvant treatment and potentially in guiding frequency of subsequent surveillance frequency and length after treatment.

There were, however, limitations to this study that must be appreciated. Biologic correlates of fine texture have yet to be confirmed in published histologically validated studies. Thus, our proposed associations remain speculative, and this study is hypothesis generating rather than hypothesis confirming. These data are from a single center in a relatively small number of patients. The log rank test power, assuming 5% significance, was between 52% for kurtosis and 84% and 87% for standard deviation of the pixel distribution histogram and entropy, respectively. For the aggregated stage, it was 85%, indicating obtained results cannot be fully considered as representative for all test results. Generalizability has to be confirmed. There are also limitations of using the same data set to derive optimum cutoff points for survival analysis, which can lead to overestimation of results. Nevertheless, other published studies on contrast-enhanced CT (eg, in patients with renal cell cancer) have also suggested texture has potential as a prognostic biomarker. Primary tumor entropy (≤2.33) and uniformity (>0.55) at a coarse scale were related to poorer outcome (defined by shorter time to progression) in patients with metastatic renal cancer with tyrosine kinase inhibitor treatment (21).

In summary, in our study, fine texture features (lower entropy, kurtosis, and standard deviation of pixel distribution; higher uniformity and skewness) were associated with a poorer 5-year overall survival rate in patients with colorectal cancer. With the shift from adjuvant to neoadjuvant chemotherapy for colorectal cancer and the ease of introducing such postprocessing tools into the clinical workflow, texture analysis shows promise as a clinical prognostic tool.

Acknowledgments: We thank the University of Sussex for the software provision. King's College London and Guy's and St Thomas' NHS Foundation Trust receive Biomedical Research Centre funding from the National Institutes of Health Research, United Kingdom.

Disclosures of Conflicts of Interest: F.N. No relevant conflicts of interest to disclose. **B.G.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is on the board of TexRAD, is employed by TexRAD, holds stock in TexRAD. Other relationships: none to disclose. **R.K.** No relevant conflicts of interest to disclose. **K.A.M.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: is on the board of TexRAD, holds stock in TexRAD. Other relationships: none to disclose. **V.G.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution has a research agreement with Siemens Healthcare, institution received payment for lectures from Siemens Healthcare. Other relationships: none to disclose.

References

1. Sargent D, Shi Q, Yothers G, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803. Eur J Cancer 2011;47(7):990–996.
2. McArdle CS, Hole D, Hansell D, Blumgart LH, Wood CB. Prospective study of colorectal cancer in the west of Scotland: 10-year follow-up. Br J Surg 1990;77(3):280–282.
3. Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005;23(34):8664–8670.
4. Sargent DJ, Patiyil S, Yothers G, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. J Clin Oncol 2007;25(29):4569–4574.

5. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 1990;77(11):1241–1246.

6. Desch CE, Benson AB 3rd, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2005;23(33):8512–8519.

7. Nelson DA, Tan TT, Rabson AB, Anderson D, Degenhardt K, White E. Hypoxia and defective apoptosis drive genomic instability and tumorigenesis. Genes Dev 2004;18(17):2095–2107.

8. Ganeshan B, Miles KA, Young RC, Chatwin CR. Hepatic enhancement in colorectal cancer: texture analysis correlates with hepatic hemodynamics and patient survival. Acad Radiol 2007;14(12):1520–1530.

9. 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.

10. Goh V, Halligan S, Wellsted DM, Bartram CI. Can perfusion CT assessment of primary colorectal adenocarcinoma blood flow at staging predict for subsequent metastatic disease? a pilot study. Eur Radiol 2009;19(1):79–89.

11. FL Greene, DL Page, ID Fleming, et al (eds). AJCC Cancer Staging Manual. 6th ed. Heidelberg, Germany: Springer-Verlag, 2002.

12. Semenza GL. HIF-1 and tumor progression: pathophysiology and therapeutics. Trends Mol Med 2002;8(4 Suppl):S62–S67.

13. Lunt SJ, Chaudary N, Hill RP. The tumor microenvironment and metastatic disease. Clin Exp Metastasis 2009;26(1):19–34.

14. Cui C, Cai H, Liu L, Li L, Tian H, Li L. Quantitative analysis and prediction of regional lymph node status in rectal cancer based on computed tomography imaging. Eur Radiol 2011;21(11):2318–2325.

15. Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. Clin Radiol 2012;67(2):157–164.

16. Ganeshan B, Abaleke S, Young RC, Chatwin CR, Miles KA. Texture analysis of non-small cell lung cancer on unenhanced computed tomography: initial evidence for a relationship with tumour glucose metabolism and stage. Cancer Imaging 2010;10:137–143.

17. Ganeshan B, Miles KA, Young RC, Chatwin CR. Texture analysis in non-contrast enhanced CT: impact of malignancy on texture in apparently disease-free areas of the liver. Eur J Radiol 2009;70(1):101–110.

18. Ganeshan B, Burnand K, Young R, Chatwin C, Miles K. Dynamic contrast-enhanced texture analysis of the liver: initial assessment in colorectal cancer. Invest Radiol 2011;46(3):160–168.

19. Bézy-Wendling J, Kretowski M, Rolland Y, Le Bidon W. Toward a better understanding of texture in vascular CT scan simulated images. IEEE Trans Biomed Eng 2001;48(1):120–124.

20. Yonenaga Y, Mori A, Onodera H, et al. Absence of smooth muscle actin-positive pericyte coverage of tumor vessels correlates with hematogenous metastasis and prognosis of colorectal cancer patients. Oncology 2005;69(2):159–166.

20. Goh V, Ganeshan B, Nathan P, Juttla JK, Vinayan A, Miles KA. Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. Radiology 2011;261(1):165–171.