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Texture analysis of non-contrast enhanced CT for assessing angiogenesis and survival of soft tissue sarcoma

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Abstract

Objective—To evaluate the role of computed tomographic texture analysis (CTTA) in assessing tumor angiogenesis and survival of soft tissue sarcoma (STS).

Methods—In twenty patients with STSs, tumor texture parameters, which were measured on pre-therapeutic CT using CTTA software with the spatial scale filter (SSF) extracting fine to coarse texture, were compared with microvessel density (MVD), plasma VEGF, soluble VEGF receptor-1 (sVEGFR-1), and overall survival (OS).

Results—Mean of positive pixels (MPP) showed a positive correlation with MVD (P=0.02). Entropy at medium texture scales (SSF=3,4,5) showed positive correlations with VEGF (P=0.03, P=0.009, P=0.02, respectively), and entropy without filtration showed a positive correlation with sVEGFR-1 (P=0.02). In univariate analysis, kurtosis at a medium texture scale and MPP showed significant correlations with OS (P=0.04, P=0.007), and multivariate analysis demonstrated that MPP was an independent prognostic factor (P=0.01).

Conclusion—Texture parameters are associated with tumor angiogenesis and OS in STS.

Keywords

computed tomography; soft tissue sarcoma; texture analysis; heterogeneity; angiogenesis

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Conflicts of Interest

All other authors have no conflict of interest.

INTRODUCTION

Heterogeneity in the structure or blood supply is a well-recognized feature of malignancy.[1,2] One way for noninvasive assessment of tumor heterogeneity is computed tomographic (CT) texture analysis (CTTA). CTTA is an image processing algorithm that can be used to quantify the heterogeneity within the tissue by assessing the distribution of texture coarseness and irregularity within a lesion. In previous studies, CTTA of tumors on contrast–enhanced (CE) CT or non-CECT images have been reported to have a correlation with survival in non–small cell lung cancer, esophageal cancer, hepatocellular carcinoma, colon cancer, and metastatic renal cell carcinoma.[1,3–6] Furthermore, CTTA has successfully demonstrated biological associations with glucose metabolism, hypoxia, and angiogenesis.[3,4,7]

Soft tissue sarcomas (STSs) are a heterogeneous group of rare tumors that arise from mesenchymal cells at all body sites, and neoadjuvant therapy provides several advantages in the treatment of STSs.[8] Treatment-induced cytoreduction potentially facilitates a less radical surgical resection, thus decreasing the operative and postoperative morbidity. Moreover, the addition of radiotherapy (RT) has been prospectively demonstrated to decrease the incidence of local recurrence.[9–11] and recently, neoadjuvant therapy with the combination of bevacizumab (BV) and RT showed that BV increased the efficacy of RT against STS and might reduce the incidence of local recurrence.[12]

Given the emerging benefit of neoadjuvant therapy in STS, predicting treatment response prior to the therapy is of great importance. Thus, we hypothesize that CTTA, which reflects tumor biology, can predict clinical outcome in STS treated with neoadjuvant BV and RT. In this preliminary study, our aim was to evaluate the heterogeneity of STS by means of CTTA in patients treated with neoadjuvant BV and RT. We particularly assessed correlations of the texture parameters with angiogenesis and survival.

MATERIALS AND METHODS

Patient population

This preliminary study was part of the phase II clinical trial on STS[12], which was in compliance with Health Insurance Portability and Accountability Act regulations, and was approved by the institutional review board at Dana-Farber/Harvard Cancer Center (Boston, MA). All patients were required to provide written informed consent before study participation according to institutional and federal guidelines. The eligibility and treatment schedule have been detailed previously.[12] Briefly, the patient eligibility criteria included the following; (i) patients had histopathologically proven measurable primary STS or an isolated local recurrence of STS after previous surgery; (ii) they had no metastatic disease; (iii) they had no surgery, chemotherapy, immunotherapy, experimental therapy, or radiotherapy within 4 weeks of first day of study drug dosing; and (iv) they had adequate renal function (serum creatinine level ≤ 1.4 mg/dl). Exclusion criteria included the following: (i) significant medical comorbidities; (ii) clinically significant cardiovascular disease including uncontrolled hypertension, myocardial infarction, and unstable angina; (iii) pregnancy or lactation; (iv) known history of deep vein thrombus or pulmonary embolus; and (v) an

inability to give written informed consent. 20 patients with STSs were enrolled in this study from August 2006 to June 2009. The median follow-up time was 53.11 months.

Treatment

The treatment schedule and the dose modification schema have been detailed previously.[12] Briefly, patients received four doses of BV (5 mg/kg) every 2 weeks. RT was started with the second dose of BV to a total dose of 50.4 Gy in 28 fractions within 5.5 weeks. Surgical resection of the tumor was performed with curative intent at 6–7 weeks after RT completion and 8–9 weeks after the last dose of BV.

Pathological analysis

Tumor samples were obtained by image guided core needle biopsy before the therapy. Tumor grade was assessed according to French Federation of Cancer Centers Sarcoma Group (FNCLCC) guideline. Microvessel density (MVD) was also assessed by immnohistochemical analysis using an antibody against CD31 as previously described.[12] After the surgery, all surgical specimens were evaluated in a standard fashion. The extent of necrosis was assessed relative to the percentage of residual viable tumor in each case and in an identical manner to that established for bone tumors.[8,13] The percentage of necrosis ranged from 0% to 100%.

Plasma markers of angiogenesis

The plasma marker analysis has been detailed previously.[12] All blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-containing Vacutainer tubes and spun at 1000g for 15 min, and plasma was aliquoted and frozen immediately before the. The plasma samples were analyzed using multiplex array plates from Meso-Scale Discovery (Gaithersburg, MD) for serial measurements of the VEGF, soluble VEGF receptor-1 (sVEGFR-1).

Imaging acquisition and analysis

All patients were examined on a 16/64-section multi-detector row CT (MDCT) scanner (Light Speed/Discovery; GE Medical Systems, Milwaukee, WI) within 2 weeks before the therapy. The following CT parameters were used for acquisition of volume data: 100 kVp; 150–200 mA; 0.5-second rotation time; field of view, 220–360 mm; matrix, 512 mm; 5 mm reconstructed slice thickness. Tumor size was measured in the longest cross-sectional dimension for each lesion based on RECIST 1.1 guidelines.[14]

CT Texture analysis (CTTA)

CTTA was performed on the non-CECT patient images using TexRAD (TexRAD Ltd, Somerset, UK, www.texrad.org), a novel commercially available research software for image heterogeneity assessment. This CTTA algorithm has been previously reported in other tumor applications.[1,3–5,7,15,16] The single axial CT slice with the largest cross-sectional area of the tumor was used for CTTA. A freehand region of interest (ROI) was carefully drawn contouring the periphery of the tumor (Figure 1A) by a single reader (K.H., with 10 years of experience in CT interpretation), who was blinded to the clinical and

survival data. Mean ROI size was 9988 pixels (range, 2875–34944 pixels). The CTTA algorithm had an additional thresholding procedure that excluded any pixels with attenuation values below −50HU. CTTA comprised an image filtration technique using a Laplacian of Gaussian spatial band-pass filter to produce a series of derived images extracting and enhancing features of different sizes and intensity variations at different spatial scale filter (SSF) values highlighting fine (SSF=2, features of 2mm in radius, Fig. 1B), medium (SSF=3, 4, 5, features of 3mm, 4mm – Fig. 1C, 5mm in radius) and coarse (SSF=6, features of 6mm in radius, Fig. 1D) texture scales, and was followed by texture (heterogeneity) quantification using entropy (a measure of irregularity), mean value of positive pixels (MPP; the average value of all the pixels with positive values), skewness (a measure of asymmetry of the histogram) and kurtosis (a measure of peakedness and tailedness). In addition these histogram parameters were also quantified from the conventional CT image without filtration (i.e. SSF=0). A recent article further described what these texture parameters mean in terms of image features.[17] To assess interobserver variability, the other reader (F.T., with 14 years of experience in CT interpretation), who was blinded to the clinical and survival data, independently evaluated CTTA of STS in the same manner as first reader.

Statistical analysis

Statistical analyses were carried out using the JMP 10.0 (SAS Institute, Inc., Cary, NC, USA), and for all comparisons, $P < 0.05$ was considered to indicate a statistically significant difference. Interobserver agreement of CTTA analysis was assessed by means of spearman's rank correlation coefficient. Correlations between texture parameters and markers of angiogenesis were also analyzed using spearman's rank correlation coefficients. The association of the continuous variables with overall survival (OS) was evaluated using the Cox proportional hazards regression model. In the univariate analyses, each variable was included in a Cox regression model alone. In the multivariable analyses, each continuous variable was added to a Cox regression model, and the influence of each variable was assessed. Kaplan-Meier analysis was also performed for OS analysis, and the log-rank test was employed. Kaplan-Meyer survival analysis identified the respective optimal threshold based on an iterative method for each parametric threshold that can best separate the patients into poor and good survival groups (indicated by the best P-value from log-rank test).

RESULTS

Patient Characteristics

A total of twenty patients were eligible in the current study. The subjects included sixteen men and four women, with a median age of 58.5 years (range 26–75 years). The histologic subtypes of tumors were, fibroblastic sarcoma (n=8), liposarcoma (n=6), leiomyosarcoma (n=4), fibroblastic osteosarcoma (n=1) and undifferentiated sarcoma (n=1). Tumors of fourteen patients were located in the extremity, and six in the retroperitoneum. Patients' characteristics were summarized in Table 1.

Interobserver agreement of CTTA

Interobserver agreement was assessed by comparing the two sets of CTTA parameters of STS tumors measured by two independent readers. Interobserver agreement for CTTA

parameters was summarized in Table 2. CTTA parameters showed good correlations between two readers (Spearman's correlation coefficient, 0.698–0.990).

Texture parameters and biological markers of angiogenesis

Correlations of texture parameters with MVD, plasma VEGF, sVEGFR-1 were shown in Table 3. MVD showed a positive correlation with MPP with no filtration (R=0.516, P=0.02). Entropy at medium texture scales (SSF=3,4,5) showed positive correlations with VEGF (R=0.507, P=0.03; R=0.595, P=0.009; R=0.521, P=0.02; respectively), and entropy without filtration showed positive correlations with sVEGFR-1 (R=0.541, P=0.02). Other texture parameters showed no significant correlations with the biological markers.

Univariate analysis of correlations between texture parameters and OS

In univariate analysis, MPP with no filtration (SSF=0), kurtosis at a medium texture scale (SSF=5) showed significant associations with OS (P=0.007, P=0.04, respectively) (Table 4). For these two texture parameters, survival curves were analyzed with use of Kaplan-Meyer analysis (Fig. 2). Patients with tumor showing lower MPP (≤ 34.65) with no filtration (SSF=0) showed better survival (P = 0.009). Patients with higher kurtosis (> 0.58) at medium texture scale (SSF=5) also showed a good correlation with OS, but this tendency was not significant (P = 0.05).

The influence of MPP on OS in multivariate analysis

MPP with no filtration showed a best correlation with OS, and therefore, we assessed the influence of MPP on OS using the Cox proportional hazards regression model in comparison with clinicopathologic features (age, size, necrosis, tumor grade) that were reported as prognostic markers of STS in previous studies.[18–24] In the multivariate analyses, MPP was identified an independent factor for OS (P=0.01; hazards ratio, 1.27; 95% CI, 1.03–1.77) (Table 5).

DISCUSSION

Human tumors arise from single cells that have accumulated the necessary number and type of heritable alterations. Each such cell leads to dysregulated growth and eventually the formation of a tumor. Despite their monoclonal origin, at the time of diagnosis, most tumors show a striking amount of intratumor heterogeneity, which has implications for diagnosis, treatment efficacy, and the identification of drug targets.[25] Thus, assessment of tumor heterogeneity is relevant to everyday clinical practice, and CTTA is emerging as a method to quantify heterogeneity within the tumor. In the validation of this approach, establishment of histologic and prognostic correlates is an important step. Recently several papers about CTTA have been published, and texture parameters on CECT or non-CECT have been demonstrated their correlations with survival in non–small cell lung cancer, esophageal cancer, colon cancer, and metastatic renal cell carcinoma.[1,3–5] Furthermore, CTTA has successfully demonstrated its histological correlations with glucose metabolism, hypoxia, and tumor angiogenesis in non–small cell lung cancer and esophageal cancer.[3,4,7] However, to date, no studies have directly addressed the intratumoral heterogeneity of STS.

In this study, texture parameters were compared with biologic markers of angiogenesis, and MPP showed a positive correlation with MVD. Basically, fresh blood, including intravascular blood is typically of higher attenuation.[17] And MPP is the average brightness of positive values of the image. Based on these, the tumor with higher MVD may have more bright objects. In addition, entropy showed positive correlations with plasma VEGF and sVEGFR-1, which have been previously proposed as biomarkers for antiangiogenic therapy.[26,27] One possible reason for these correlations may be the development of hypoxia in the tumor. Entropy, which is a measure of irregularity, represents heterogeneity in tumor. Structural heterogeneity leads to a heterogeneous blood supply in the tumor, which may result in a hypoxic tumor environment. In turn, hypoxia may lead to increased plasma VEGF and sVEGFR-1.[28]

In survival analysis, patients with low MPP showed better OS, and MPP was demonstrated to be an independent prognostic factor associated with OS. Several previous studies reported a correlation between MVD and survival in patients with STS, and demonstrated that high MVD in STS correlated with poor OS.[29,30] Therefore, we assume that high MPP tumor, which tends to show high MVD, may be associated with poor OS in STS. In a previous study of non-small cell lung carcinoma, MPP on non-CECT showed a negative correlation with MVD.[7] But, in that study, MPP value was calculated with a filtration, and therefore, the association between MPP and histology may change according to the filter value. Or it may just reflect biological differences of angiogenesis between STS and non-small cell lung carcinoma.

We also observed that low kurtosis in STS associated with a poor OS. Kurtosis is a measure of the "peakedness" and “tailedness” of the histogram, and high kurtosis tends to have a distinct peak near the mean.[17] In colon cancer, Ng et al. reported that lower kurtosis of tumor on CECT associated with poorer 5-year OS.[5] They hypothesized that these might be tumors with greater cell packing and more uniform distribution in tumor structure.[5] Another assumption is that intratumoral fibrosis may affect tumor kurtosis. In lung, kurtosis has been used for the evaluation of interstitial pulmonary fibrosis, and lung with higher fibrosis has been reported to show lower kurtosis.[31,32] Given the importance of fibrotic tumor stroma in cancer progression[33–35], STS with an abundant of fibrotic tumor stroma, which leads low kurtosis in tumor, may have a poor prognosis. The influence of texture parameters on survival may change according to the tumor biology such as angiogenesis and stromal fibrosis.

Our study has several limitations. First, our findings are based on single-center data, and the sample size was very small. Our findings need to be confirmed in multicenter investigations, and a larger patient population should be studied. Second, acquisition parameters, such as tube voltage or tube current, may affect texture parameters. A previous water phantom study in which researchers used varying tube current (100–250 mAs) at 80 and 120 kV and then varying tube voltage at a fixed tube current of 150 mAs suggests this has less of an effect on a texture parameter.[16] Third, the definition of the tumor ROIs was subjective. A computerized tumor segmentation method with high reproducibility and reliability should be employed in the further studies.

In conclusion, our results suggested that the tumor texture on non-CECT image might be associated with angiogenesis and survival of STS patients treated with BV + RT. Because CT is commonly used in the staging process of STS, image post-processing techniques such as CT texture analysis can serve as a widely applicable and beneficial biomarker for predicting OS of patients with STSs. We believe that our results will provide an important insight into selecting the optimal therapeutic strategy for patients with STSs.

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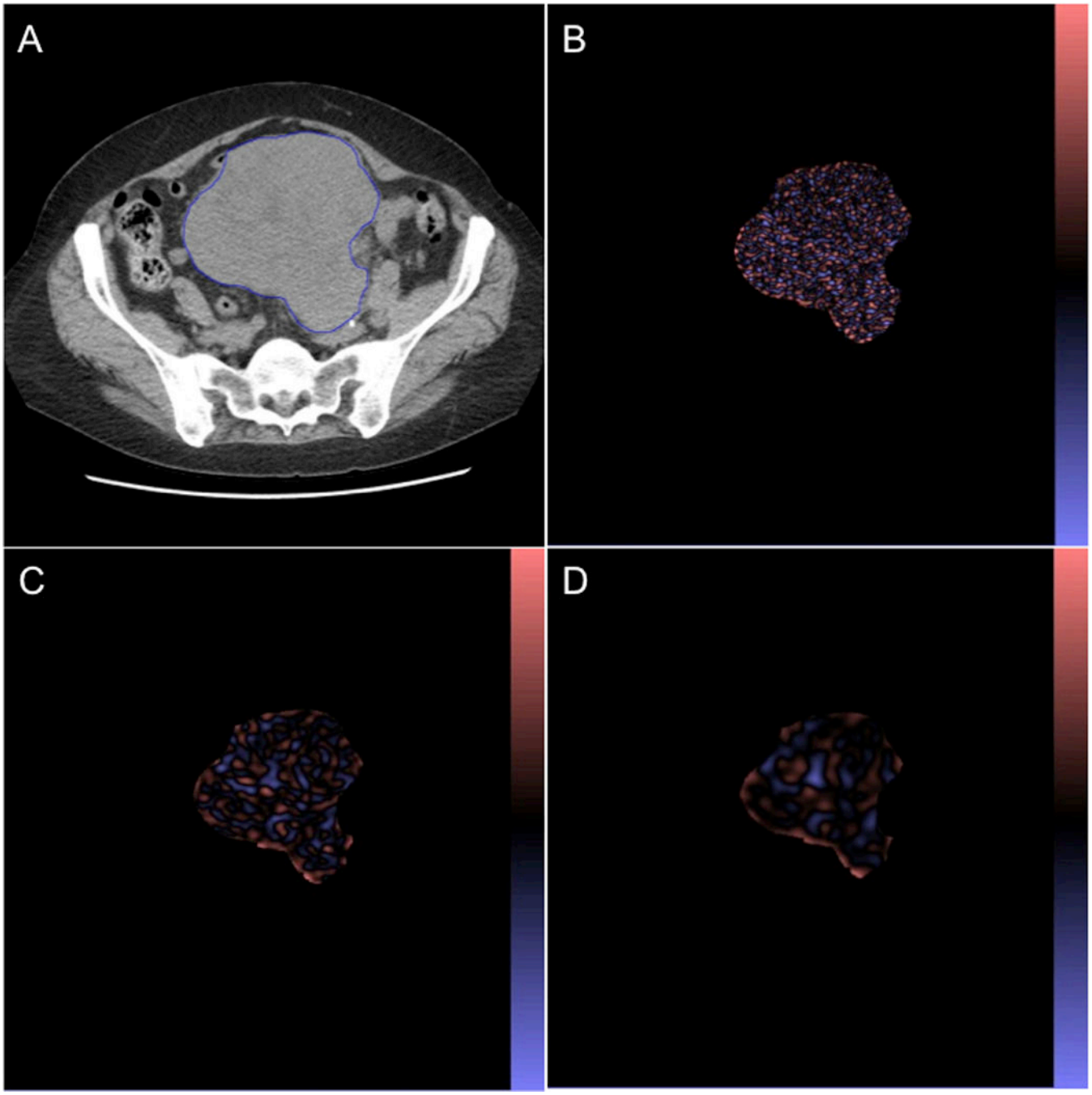

Fig. 1.
(A) Non-CECT image of 66-year-old woman with STS. Corresponding images in the same patient selectively display (B) fine, (C) medium, (D) coarse texture and were obtained by using SSF of 2mm, 4mm, and 6mm in radius.

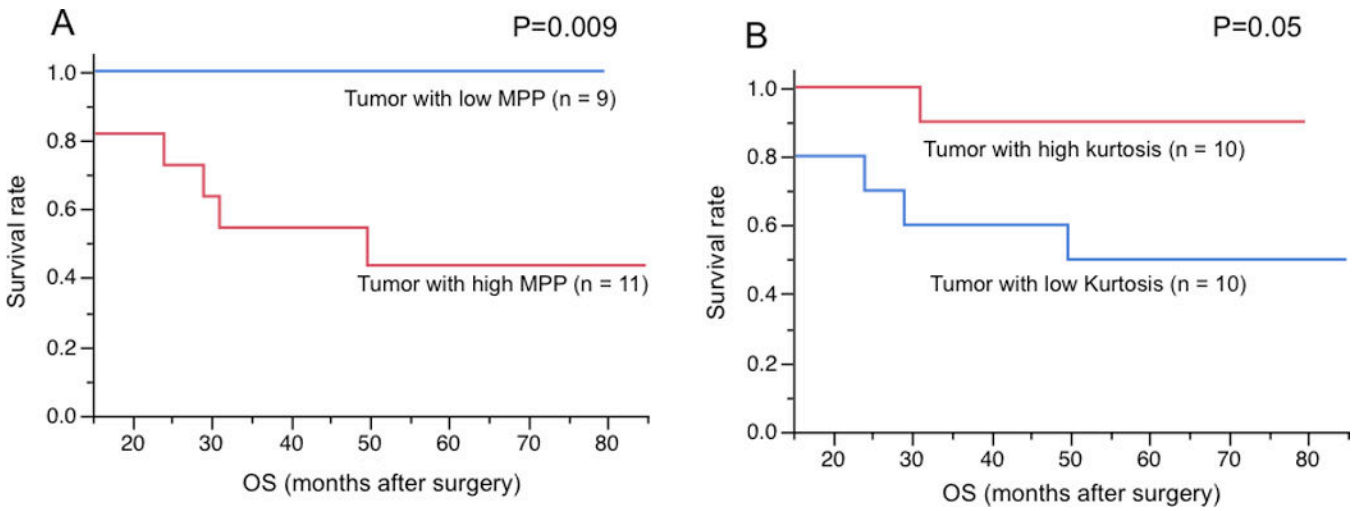

Fig. 2.

Kaplan-Meier analysis of MPP without filtration (A) and kurtosis at medium texture scale (SSF=5) (B) in OS. Patients with tumor showing lower MPP (≤ 34.65) and higher kurtosis (> 0.58) showed better survival.

Table 1

Patient characteristics

Patient Demographics	Variables	Value
Sex	Male / Female	16 / 4
Age	Median / range	54.8 / 26–75
Tumor size	Median / range	5.85 / 3.1–18.9
Tumor grade	1 / 2 / 3	2 / 8 / 10
Necrosis after the therapy (%)	Median / range	65.0 / 20–100

Table 2

Interobserver agreement (Spearman's rank correlation)

	Entropy		MPP		Skewness		Kurtosis	
SSF	R	P	R	P	R	P	R	P
0	0.964	< 0.0001	0.980	< 0.0001	0.853	< 0.0001	0.799	< 0.0001
2	0.978	< 0.0001	0.990	< 0.0001	0.909	< 0.0001	0.971	< 0.0001
3	0.928	< 0.0001	0.974	< 0.0001	0.912	< 0.0001	0.858	< 0.0001
4	0.859	< 0.0001	0.952	< 0.0001	0.898	< 0.0001	0.698	0.0006
5	0.867	< 0.0001	0.984	< 0.0001	0.938	< 0.0001	0.843	< 0.0001
6	0.942	< 0.0001	0.990	< 0.0001	0.917	< 0.0001	0.841	< 0.0001

Table 3

Correlations of texture parameters with MVD, plasma VEGF, and sVEGFR-1

	Entropy		MPP		Skewness		Kurtosis	
SSF	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**
MVD								
0	−0.269	0.2	0.516	**0.02**	0.160	0.5	0.213	0.3
2	−0.376	0.1	−0.340	0.1	0.213	0.3	0.217	0.3
3	−0.373	0.1	−0.329	0.1	0.008	0.9	0.233	0.3
4	−0.233	0.3	−0.302	0.2	−0.139	0.5	0.147	0.5
5	−0.081	0.7	−0.245	0.3	−0.117	0.6	0.022	0.9
6	0.044	0.8	−0.202	0.4	−0.126	0.6	0.047	0.8
Plasma VEGF								
0	0.330	0.1	0.119	0.6	−0.302	0.2	−0.250	0.3
2	0.416	0.08	0.328	0.1	−0.326	0.1	−0.126	0.6
3	0.507	**0.03**	0.361	0.1	−0.322	0.1	−0.057	0.8
4	0.595	**0.009**	0.440	0.06	−0.074	0.7	−0.137	0.5
5	0.521	**0.02**	0.402	0.09	−0.052	0.8	−0.265	0.2
6	0.273	0.2	0.277	0.26	−0.036	0.8	0.034	0.8
sVEGFR-1								
0	0.541	**0.02**	−0.010	0.9	−0.394	0.1	−0.241	0.3
2	0.435	0.07	0.457	0.05	−0.264	0.2	−0.108	0.6
3	0.384	0.1	0.435	0.07	−0.135	0.5	0.034	0.8
4	0.242	0.3	0.398	0.1	0.122	0.6	0.038	0.8
5	−0.023	0.9	0.347	0.1	0.157	0.5	0.177	0.4
6	−0.278	0.2	0.324	0.1	−0.267	0.2	0.133	0.5

Table 4

Univariate Cox regression analysis of correlations between texture parameters and OS

Filter value / parameters	HR	95%CI	P
SSF = 0			
Entropy	2.36	0.30–25.37	0.4
MPP	1.24	1.04–1.62	**0.007**
Skewness	1.58	0.35–4.34	0.4
Kurtosis	1.12	0.61–1.67	0.6
SSF = 2			
Entropy	2.83	0.53–16.51	0.2
MPP	1.01	0.97–1.05	0.3
Skewness	1.78	0.41–6.23	0.4
Kurtosis	1.06	0.78–1.30	0.6
SSF = 3			
Entropy	4.36	0.71–29.06	0.1
MPP	1.02	0.96–1.06	0.4
Skewness	1.05	0.38–4.39	0.9
Kurtosis	0.98	0.65–1.28	0.9
SSF = 4			
Entropy	4.21	0.64–26.15	0.1
MPP	1.02	0.95–1.09	0.4
Skewness	1.19	0.57–3.03	0.6
Kurtosis	0.86	0.49–1.13	0.3
SSF = 5			
Entropy	3.07	0.55–21.56	0.2
MPP	1.03	0.95–1.09	0.3
Skewness	1.07	0.56–1.91	0.8
Kurtosis	0.47	0.12–0.98	**0.04**
SSF = 6			
Entropy	1.47	0.61–7.15	0.4
MPP	1.02	0.96–1.06	0.4
Skewness	1.50	0.68–4.51	0.3
Kurtosis	0.72	0.40–1.04	0.1

Table 5

Multivariate analysis of MPP and clinicopathological features for OS using Cox regression model

Variables	HR	95%CI	P
MPP without filtration	1.27	1.03, 1.77	**0.01**
Age	1.00	0.91, 1.11	0.9
Tumor size	0.97	0.63, 1.46	0.8
Grade	2.25	0.23, 53.94	0.5
Necrosis	0.97	0.92, 1.01	0.3