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Texture analysis parameters derived from T1-and T2-weighted magnetic resonance images can reflect Ki67 index in soft tissue sarcoma

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ABSTRACT

Background and objectives: Texture analysis derived from morphological magnetic resonance (MR) images might be associated with histopathology in tumors. The present study sought to elucidate possible associations between texture features derived from T1-and T2-weighted images with proliferation index Ki67 in soft tissue sarcomas.
Methods: Overall, 29 patients (n = 13, 44.8% female) with a median age of 52 years were included into this retrospective study. Several soft tissue sarcomas were investigated. Texture analysis was performed on pre-contrast T1-weighted and T2-weighted images using the free available Mazda software.
Results: The best correlation coefficients with Ki67 index were identified for the following parameters: T1-weighted images "45dgr_RLNonUni (p = 0.50, P = 0.006), T2-weighted images "S (4,0)SumAverg" (p = −0.45, P = 0.02). A ROC analysis was performed for Ki67-index with a threshold of 10%. The highest area under the curve (AUC) was found for the parameter "T1_WavEnHL_s-7" with an AUC of 0.90. For the threshold of Ki67 = 20% the highest AUC was identified for the parameter „T2_S (1,1)Entropy" with an AUC of 0.77.
Conclusion: Several texture features derived from T1-and T2-weighted images correlated with proliferation index Ki67 and might be used as valuable novel biomarkers in soft tissue sarcomas.

1. Introduction

Texture analysis is a novel diagnostic method, which can quantitatively evaluate radiological images and provide imaging-based statistical parameters [1–4]. It can be divided into first and second order statistics [1–4]. In the first order statistics imaging parameters like signal intensities are issued into a histogram without concern of their spatial relationships [1–4]. Recent studies showed that histogram based parameters, such as skewness, kurtosis and entropy can reflect different histopathological features in several tumor entities [4–7]. Moreover, histogram analysis parameters can predict treatment response and can also aid in the differential diagnosis between tumor types [4,8–11]. Altogether, these parameters have been shown to be reliable enough for clinical translation. Possible correlations with histopathology can help to better characterize tumors by radiological imaging [4]. Interestingly, every radiological modality is principle applicable for this technique [1–4].

The next important analysis method is acquisition of second order statistic data of images. They describe spatial relationships between voxels with similar gray levels within a lesion [2,3]. The parameters of this analysis provide a measure of intralesional heterogeneity. Most frequently used parameters are the Gray Level Co-occurrence Matrix, the Gray Level Run-Length Matrix, and the Gray Tone Difference Matrix. Finally, higher-order statistics impose filter grids on an image to extract repetitive or non-repetitive patterns [2,3].

Texture analysis has been used in various studies with very promising results, especially in oncologic imaging. For instance, in a large cohort of 1019 lung and head and neck cancer patients, texture analysis derived from CT images was capable to stratify patients according to their prognosis and could generate a novel imaging-based phenotypical tumor characterization [12].

To date, only few studies used this imaging technique in soft tissue sarcomas [13–16]. For instance, in a preliminary study with 20 lesions, texture features derived from unenhanced CT images could reflect micro vessel density and expression of vascular endothelial growth factor (VEGF) [13]. Thus, texture analysis can provide crucial

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information regarding tumor angiogenesis [13]. In another recent study, texture analysis parameters derived from diffusion-weighted imaging (DWI) could help to distinguish intermediate from high-grade lesions with an accuracy of 0.88 [14]. Furthermore Lisson et al. identified that several first order parameters might differentiate enchondroma and low grad osteosarcoma [15]. Presumably, texture analysis can reflect microstructure differences between these tumor entities and, therefore, aid in clinical decision making.

Proliferation index Ki67 index is a very important and widely used histopathological parameter in different malignancies [17]. For example, in sarcomas, it aids in differential diagnosis between low-grade and high-grade sarcomas and can predict treatment response on neoadjuvant radiotherapy [18,19]. Moreover, it can also predict metastasis-free survival and disease-specific overall survival in sarcomas [20].

Previously, possible prediction of Ki67 index on imaging features was predominantly investigated by using DWI [21]. However, only an overall moderate inverse association between DWI and expression of Ki67 could be identified [21].

In clinical routine, it might be of benefit to predict noninvasively proliferation activity based on imaging findings because imaging can be obtained serially and can display the whole tumor, whereas histopathology is can be acquired only with small tumor biopsies, which might not always be representative of the whole tumor.

Presumably, texture analysis derived from morphological MR images, such as T1-and T2-weighted images, may reflect proliferation index in soft tissue sarcomas. Therefore, the purpose of the present study was to elucidate possible associations between texture analysis parameters and Ki67 index in soft tissue sarcomas.

2. Materials and methods

The radiological database of our university hospital was retrospectively screened for soft tissue sarcomas (STS). The study was approved by the institutional ethic committee (University of Leipzig) and informed consent was waived.

Inclusion criteria were sufficient presurgical MRI data including T1- and T2-weighted images and histopathological examination including Ki67 index.

Overall, 29 patients (female n = 13, 44.8%) with a median age of 52 years (range 6–82 years) were included into the study. In the patients, different STS were diagnosed as follows: pleomorphic sarcoma (n = 11, 37.9%), malignant peripheral nerve sheath tumors (n = 3, 10.3%), fibrosarcoma (n = 3, 10.3%), rhabdomyosarcoma (n = 2, 6.9%), chondrosarcoma n = 2 (6.9%), liposarcoma (n = 2, 6.9%), synovial sarcoma (n = 2, 6.9%), Ewing sarcoma (n = 1, 3.5%), osteosarcoma (n = 1, 3.5%), angiosarcoma (n = 1, 3.5%), and leiomyosarcoma (n = 1, 3.5%).

Ki67 index ranged from 4 to 98% with a median of 30, mean 42.4 with a standard deviation of 32.

2.1. MRI

Magnetic resonance imaging was performed using a 1.5-T MRI scanner (Magnetom Symphony 1,5T; Siemens, Germany). Several different scanning protocols were used depending on lesion localisation. MRI sequences included T2-weighted turbo spin echo images, fat-suppressed T2-weighted short tau inversion recovery (STIR) images, half-Fourier acquisition single-shot turbo spin echo (HASTE) images, T1-weighted spin echo images, T1-weighted flash 2D images.

Figs. 1 and 2 display patients of our patient sample as examples.

2.2. Texture analysis

For this study, precontrast T1-weighted spin echo images as well as T2-weighted spin echo images were analyzed. The images were transformed into DICOM format and processed with the free available texture analysis software MaZda (version 4.7, available at http://www.eletel.p.lodz.pl/mazda/) [22,23]. A polygonal region of interest (ROI) was placed on the largest, representative slide within the boundary of the tumors on the images. The T1-weighted sequence after contrast media application was used to delineate the tumor margins. For each ROI, gray-level normalization was performed, using the limitation of dynamics to $\mu \pm 3SD$ (μ gray level mean, SD standard deviation) to minimize the influence of contrast and brightness variation, as it was performed previously for similar investigations [24,25]. The extracted features were as follows: gray-level histogram (mean, variance, skewness, kurtosis, percentiles (1, 10, 50, 90, 99%), co-occurrence matrix (angular second moment, contrast, correlation, entropy, sum entropy, sum of squares, sum average, sum variance, inverse difference moment, difference entropy, difference variance (for four directions and five interpixel distances (offsets; n = 1 to 5)), run-length matrix (run-length non-uniformity, gray-level non-uniformity, long run emphasis, short run emphasis, fraction of image in runs)), absolute gradient (gradient mean, variance, skewness, kurtosis, non-zeros), autoregressive model (theta 1 to 4, sigma), and wavelet transform (energies of wavelet transform coefficients in sub-bands LL,LH,HL,HH). Altogether, 279 texture features were retrieved from every image and thus 558 texture features were retrieved for every patient.

2.3. Histopathology analysis

All sarcomas were surgically resected and histopathologically analyzed. In every case, the proliferation index was estimated on Ki67-antigen stained specimens using MIB-1 monoclonal antibody (DakoCytomation, Glostrup, Denmark). The Ki67 index was calculated as the area with the highest stained nucleic per 100 cells on a representative tumor specimen.

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA). Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Spearman's correlation coefficient (p) was used to analyze associations between texture features and Ki67 index. Differences between the tumor entities were investigated by Mann–Whitney test. A receiver operating characteristic (ROC) analysis was performed and Sensitivity, specificity and area under the receiver operating characteristic curve (AUC) value were calculated for the diagnostic procedures. In all instances, p-values $<$ 0.05 were taken to indicate statistical significance.

3. Results

3.1. Correlation analysis

Table 1 displays the statistically significant correlations between texture features derived from T1-and T2-weighted images and Ki67 index. The other correlations did not reach statistically significance.

The best correlation coefficient for T1-weighted images achieved the parameter “45dgr_RLNonUni (p = 0.50, p = 0.006), and for T2-weighted images it was the parameter “S (4,0)SumAverg“ (p = -0.45, p = 0.02) (Fig. 3a and b).

3.2. ROC-analysis

A ROC analysis was performed to predict tumors with an expression of Ki67 over 10% (Fig. 4a). The highest area under the curve (AUC) was identified for the parameter “T1_WavEnHL_s-7” with an AUC of 0.90. The sensitivity is 0.70 and the specificity is 0.99 using the threshold 399.

On the next step, a ROC analysis was performed for prediction of

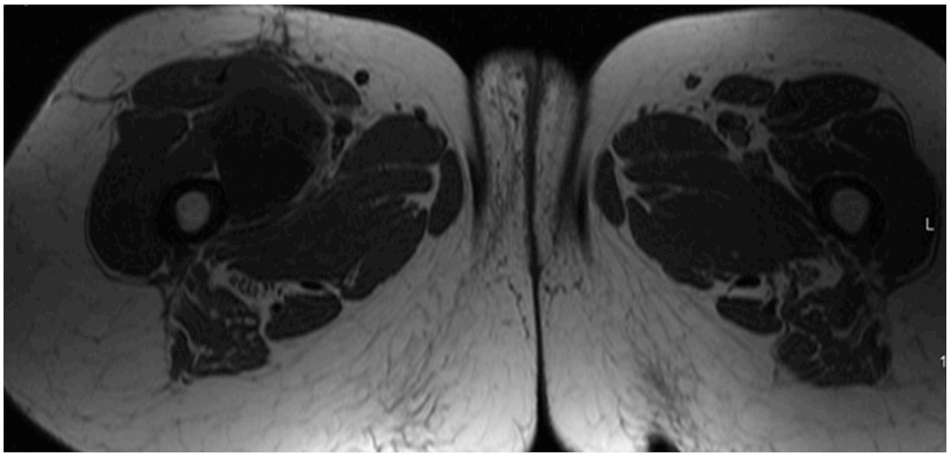

Fig. 1a. Imaging findings of a well differentiated (G1) fibromyxoid sarcoma with a low Ki67-index (5%) in a 61 years old patient. a. T1-weighted axial image shows a homogenous lesion within the right musculus quadriceps femoris. The lesion is hypointense compared to adjacent muscle tissue lesion.

tumors with an expression of Ki67 over 20% (Fig. 4b). The highest AUC was identified for the parameter "T2_S (1,1)Entropy" with an AUC of 0.77. The sensitivity is 0.80 and the specificity is 0.85 using the threshold 2.5.

Fig. 5 displays the discrimination between tumors with high and low expression of Ki67 with the threshold of 10%. The parameter „T1_WavEnHL_s-7″ was significantly higher in tumors with high Ki67 expression ($p = 0.032$). Regarding T2-weighted images, the best discrimination was found for the histogram parameter "t2_Perc.10%" ($p = 0.025$).

By using the threshold of 20% for expression of Ki67, for T1-weighed images the parameter „T1_WavEnHL_s-5″ was significantly lower in tumors with high Ki67 expression ($p = 0.048$). For T2-weighted images the best parameter was "T2_Sima", which was significantly ($p = 0.031$) lower in tumors with high Ki67-expression.

4. Discussion

The present study showed that several texture features derived from morphological MR images correlated with proliferation index Ki67 in soft tissue sarcomas. To the best of our knowledge, this is the first study of its kind. The principle finding of the study is that texture analysis might aid in discrimination of high and low proliferating sarcomas in clinical routine in a non-invasive manner.

Nowadays, texture analysis has been extensively researched, especially in oncology [1–4]. According to the literature, radiomics might be able to provide crucial information regarding tumor behavior [2,4].

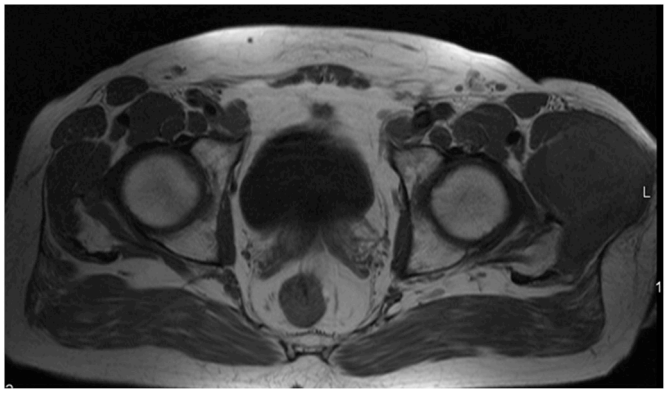

Fig. 2a. A 63 years old male patient with a tumor within the tensor fasciae latae muscle on the left side. Histopathological examination revealed an undifferentiated pleomorphic sarcoma (G3) with a Ki67 index of 90%. 2a. On the T1-weighted image the lesion appears relatively homogeneous isointense compared to the adjacent muscle.

The possibilities range from improving clinical staging classification, predict overall prognosis of the patients, and reflect histopathology microstructure and genomics-related parameters [4]. So far, radiomics might be a valuable tool for almost every aspect of modern oncologic imaging ranging from diagnosis to prognosis.

Regarding soft tissue sarcoma, recent studies investigated this

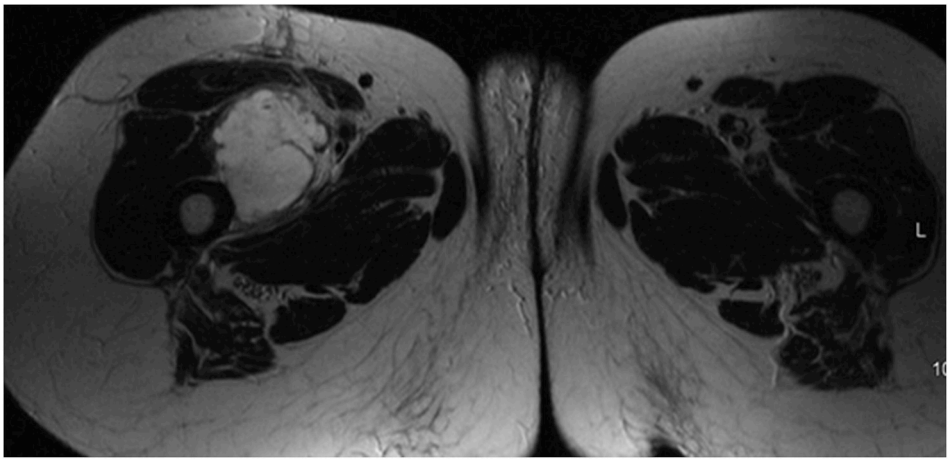

Fig. 1b. T2-weighted axial image. The lesion is hyperintense compared to adjacent muscle tissue. Multiple septs can be seen within the lesion.

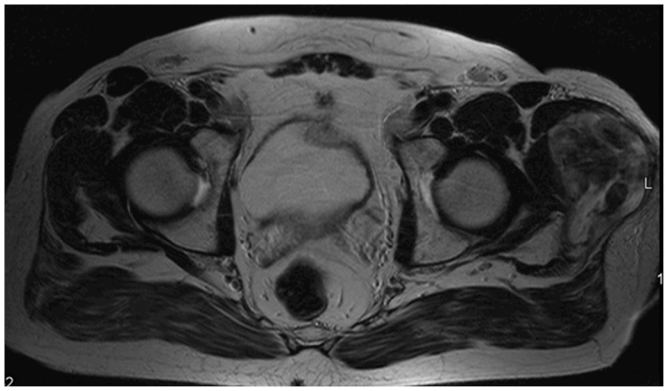

Fig. 2b. On the T2-weighted image the lesion is heterogenous hyperintense compared to the adjacent muscle.

Table 1
a. Overview of statistically significant correlations between T1-weighted texture features and Ki67 index.

Texture features	Correlation coefficient	p-value
45dgr_RLNonUni	0.50	0.006
135dr_RLNonUni	0.50	0.006
Vertl_RLNonUni	0.48	0.01
Vertl_GLevNonU	0.44	0.02
Horzl_RLNonUni	0.40	0.04
WavEnHL_s-7	0.43	0.04

Texture features	Correlation coefficient	p-value
S (4,0)SumAverg	−0.45	0.02
S (5,0)SumAverg	−0.43	0.03
S (4,-4)SumAverg	−0.42	0.03
S (3,0)SumAverg	−0.42	0.04
S (3,-3)SumAverg	−0.42	0.04
S (5,-5)SumAverg	−0.41	0.04
GrKurtosis	−0.40	0.04

technique on ADC maps derived from diffusion-weighted imaging [13–16]. It has been shown that texture analysis derived from ADC-maps could differentiate intermediate-grade soft tissue sarcomas from high-grade sarcomas [14]. High grade sarcomas had higher entropy-related features than intermediate sarcomas. However, no direct correlation with histopathology was performed in this study and so only assumptions can be made, which histopathological factors influence entropy-related texture features [14].

In a similar recent study investigating 40 myxoid-containing sarcomas, the high-grade tumors showed significantly higher texture features, such as kurtosis, energy, correlation and homogeneity than the low-grade lesions [16].

First order statistics parameters derived from ADC-maps were also investigated in muscle lymphoma [26]. In this entity, no correlations between texture features and Ki67 could be identified, whereas several correlations were found with cell area related parameters [26], indicating that ADC can reflect cellularity in tumors. Nowadays, this fact is widely acknowledged based upon larger study samples [27].

However, only one study investigated texture analysis derived from morphological sequences in soft tissue sarcomas [15]. Enchondromas and low-grade osteosarcomas could be distinguished by using texture analysis parameters, especially T1-weighted features, such as kurtosis derived from contrast enhanced T1-weighted images and entropy derived from non-contrast enhanced T1-weighted images showed the highest accuracy in this regard [15].

Previously, only few studies investigated direct correlations between histopathology and texture analysis to elucidate how the tumor microstructure might influence texture features [25,28–31]. However, this information regarding their underlying histopathological reflection is very important to establish texture parameters as possible clinical biomarkers. For example, in thyroid cancer, several texture features derived from morphological MR images correlated with expression of p53, Ki67 and cellularity related parameters [25]. In another study, several first order texture features were associated with cellularity parameters in cerebral lymphomas [30]. Interestingly, it was identified that features derived from T1-and T2-weighted-weighted images might reflect different aspects of cellularity in tumors [31]. Presumably, T1- and T2-weighted-related texture features might also show different correlations with Ki67, as was shown in the present study. That might be the reason why different features derived from T1-and T2-weighted images showed statistically significant associations with Ki67-index.

Ki67-index is the most used proliferation marker in clinical routine in various different tumor entities [17]. In sarcomas, this index can help in distinguishing low-grade from high-grade lesions and can also aid in prediction of treatment response of neoadjuvant radiotherapy [18–20]. It might be of clinical relevance that the radiologist can predict Ki67-index by using texture analysis derived from morphological MR images used in clinical routine. For example, the radiologist might characterize tumors and depict the tumor area with the highest proliferation potential to obtain the biopsy out of this tumor area to improve the biopsy. The routinely acquired MRI images would gain a novel clinically relevant value. Clearly, the preliminary data of the presented study should be validated in a larger prospective study.

Furthermore, we performed a ROC analysis with a Ki67 threshold value of 10 and 20%. The discrimination for the 10% threshold was

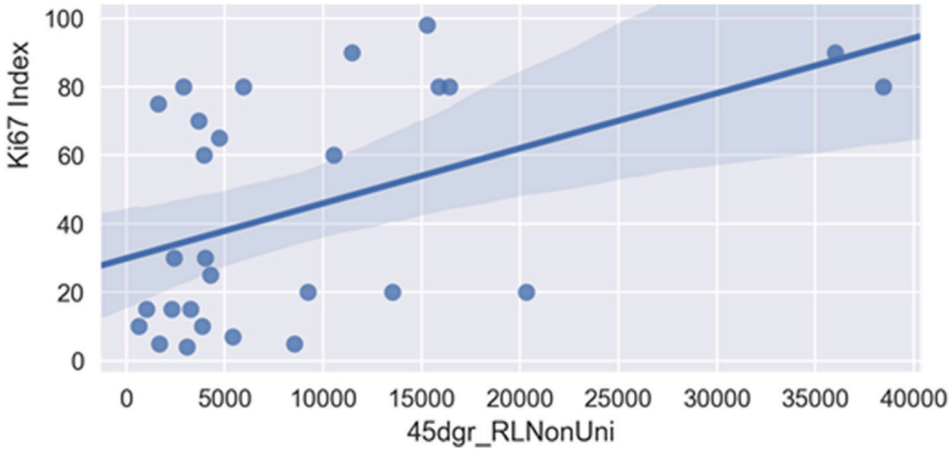

Fig. 3a. Correlation graph displaying the correlation between the parameter "45dgr_RLNonUni" derived from T1-weighted images and Ki67 index. The Spearman's correlation coefficient is p = 0.50, P = 0.006.

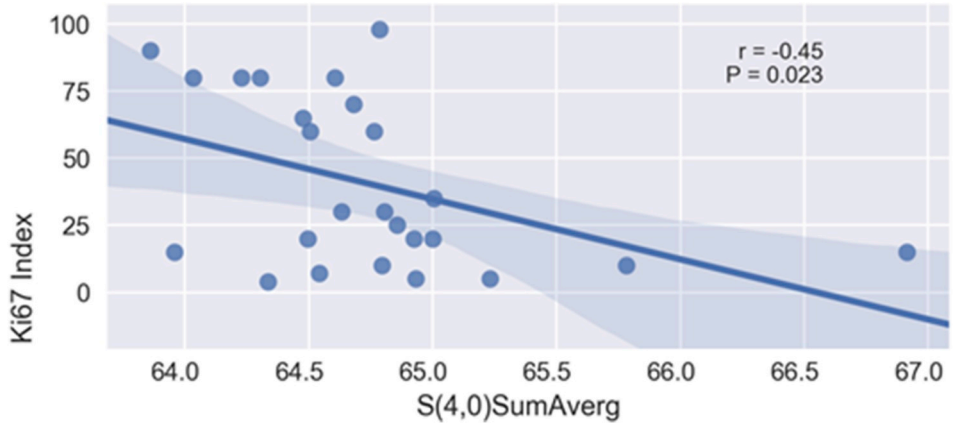

Fig. 3b. Correlation graph displaying the correlation between the parameter "S (4,0)SumAverg" derived from T2-weighted images and Ki67 index. The Spearnan's correlation coefficient is p = -0.45, P = 0.023.

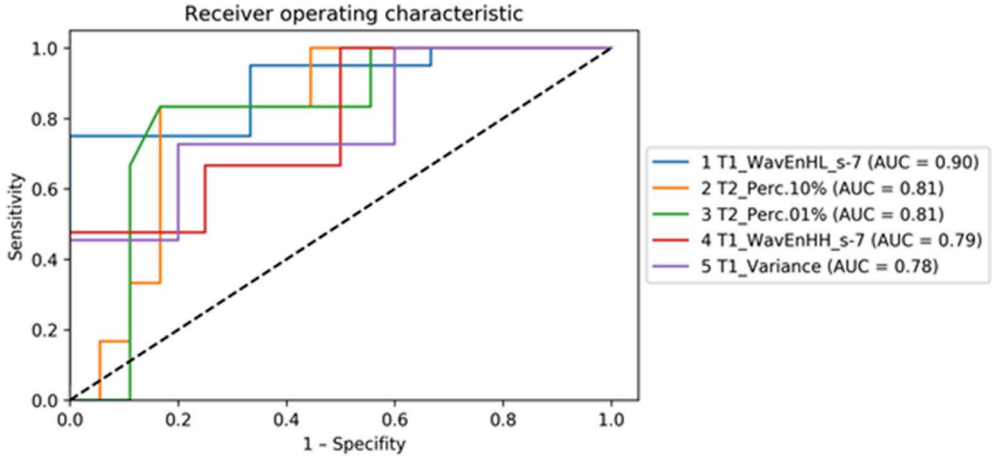

Fig. 4a. Receiver-operating-Curve for prediction of Ki67-index at the 10% threshold. The best area under the curve (0.90) was found for the parameter "T1_WavEnHL_s-7".

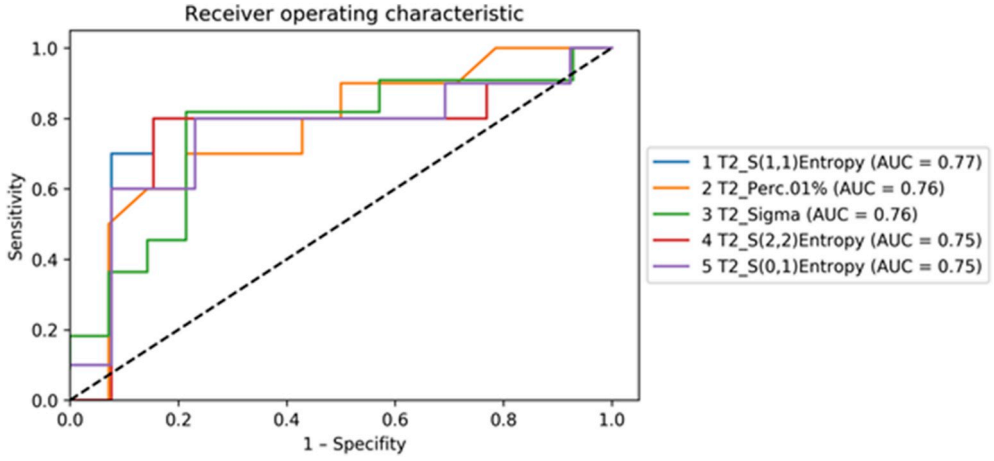

Fig. 4b. Receiver-operating-Curve for prediction of Ki67-index at the 20% threshold. The best area under the curve (0.77) was found for the parameter "T2_S (1,1) Entropy".

better with a good AUC of 0.90, compared to 0.77 for the 20% threshold. These cut-off values were evaluated in some previous studies and it was identified that these values have prognostic power to predict metastasis-free survival and disease-specific overall survival [20].

There are several limitations of the present study to address. First, it is a retrospective study with possible known inherent bias. Second, the patient sample is small, yet comparable to other similar studies. Third, different tumor entities were pooled together with small patient numbers in each group and, therefore, no subgroup analyses could be performed. Presumably, different tumors might have a different microstructure, which might influence texture features. Fourth, the Ki67-index was evaluated on a presurgical biopsy and might, therefore, not be fully representative of the whole tumor. Finally, we performed a single slide measurement on the representative slide of the tumors. For

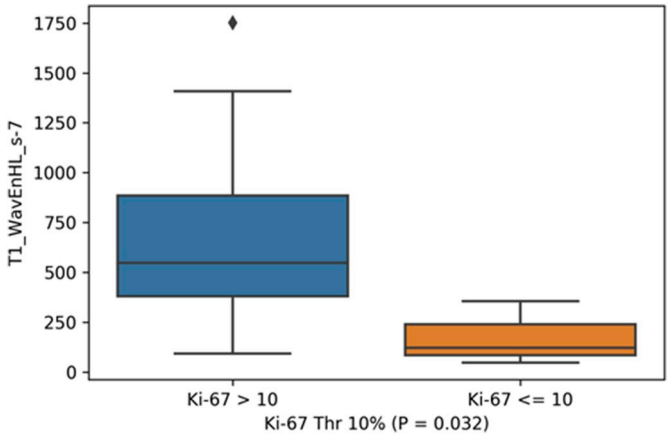

Fig. 5a. The parameter "T1_WaveEnHL_s7" was significantly higher in tumors with high Ki67 expression (p = 0.032) with the threshold of 10%.

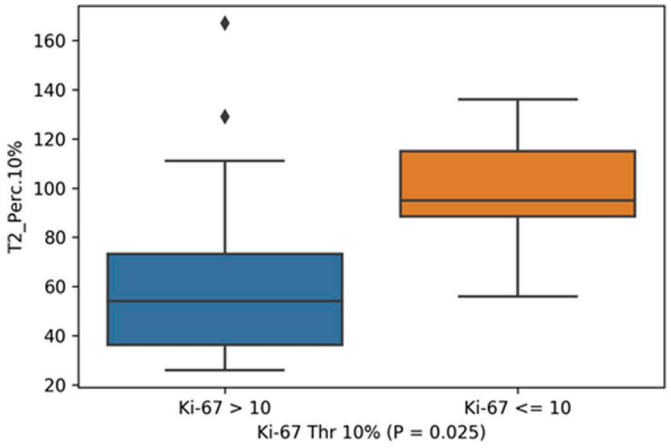

Fig. 5b. The parameter "T2_Perc.10%" was significantly lower in high Ki67 expression tumors (p = 0.025) with the threshold of 10%.

clinical routine this method is more easily to perform. However, it was shown that some texture features might differ between single slide measurement and whole tumor measurement [2].

In conclusion, the present study identified that several texture features derived from morphological T1-and T2-weighted images correlated with proliferation index Ki67 and, therefore, may be used as valuable novel biomarkers in soft tissue sarcomas.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.06.006.

Conflicts of interest

The authors declare that there are no conflict of interest.

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