Whole lesion Histogram analysis derived from morphological MRI sequences might be able to predict EGFR- and Her2-expression in cervical cancer

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Aims and objectives

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide (1).

Due to its excellent soft tissue contrast, magnetic resonance imaging (MRI) has been established as the best imaging modality for staging of cervical cancers (2). Thus it is widely clinically used for local tumor staging for this entity.

Nowadays, radiological images can further be investigated quantitatively by advanced imaging analyses. One of these techniques is a histogram based approach (3). This method includes every voxel in a region of interest (ROI) that results in a histogram and, thusly, statistically information about the tumor can be provided (3). Thereby, multiple parameters, namely percentiles, mean, maximal, minimal and median values, mode, skewness, kurtosis and entropy can be acquired. It is believed that heterogeneity displayed by the histogram might also reflect heterogeneity of tumor microstructure and, therefore, a better prediction of tumor biology might be possible using non-invasively imaging methods (3).

The reflection of histopathological features by imaging analysis might be crucial for modern oncology because imaging can be performed serially and noninvasively contrary to histopathology and might, therefore, be of potential benefit in regard of tumor response evaluation. This might be especially of interest because conventional morphological sequences are routinely acquired during every MR investigation of the pelvis and are not associated with additional investment of time or technical resources.

Therefore, the aim of this study was to elucidate possible associations between histogram based parameters derived from morphological sequences and expression of EGFR, Hif1-alpha, VEGF, Her 2 receptor and Histone 3 in cervical cancer.
Methods and materials

Patients

Overall, 18 female patients (age range 32-79 years; mean age 55.4 years) with histopathological confirmed squamous cell cervical carcinoma were enrolled into the study.

MRI

In all cases, pelvic MRI was performed. Our investigation protocol included the following sequences: an axial T2 weighted (T2w) turbo spin echo (TSE) sequence (TR/TE: 5590/105), a sagittal T2w TSE sequence (TR/TE: 4110/131), an axial T1 weighted (T1w) TSE sequence (TR/TE: 1310/12), an axial T1 TSE sequence after intravenous application of contrast medium (0.1 mmol/kg body weight Gadobutrol, Bayer Healthcare, Germany) (TR/TE: 912/12), and a sagittal post contrast T1 TSE TR/TE: 593/12). Figures 1-6 show an exemplary patient of our patient sample with the corresponding histograms.

Histogram analysis

The histogram analysis of the axial T2w and was performed with custom-made Matlab-based application (The Mathworks, Natick, MA). The volume of interest (VOI) was drawn at the tumor’s boundary, in accordance to the t2-weighted images (whole lesion measurement) and the VOI was transferred to the t1 pre- and t1 postcontrast enhanced images. Mean, maximum, minimum, median, 10th, 25th, 75th, 90th percentile, and mode, kurtosis, skewness and entropy were calculated.

Histopathological analysis

In all cases the diagnosis was confirmed histopathologically by tumor biopsy. The histological slices were stained by epidermal growth factor receptor (EGFR, EMERGO Europe, clone 111.6, dilution 1:30), vascular endothelial growth factor (VEGF, EMERGO Europe, clone VG1, dilution 1:20), hypoxia-inducible factor (HIF-1# Biocare Medical, 60 Berry Dr Pacheco, CA 94553; clone EP1215Y, dilution 1:100), Human epidermal growth factor receptor-2 (Her 2, clone 4B5, Roche Diagnostics, 6mkg/ml). The histopathological images were further analyzed by using the ImageJ software 1.48v (National Institutes of Health Image program). Expression of EGFR, VEGF, and HIF-1# (Figures 1f-i) were
estimated as a percent of stained areas per high power field. The tumors were divided according to the Her2-status in Her2-positive and Her2-negative.

**Statistical analysis**

Statistical analysis was performed using SPSS 23.0 (SPSS Inc, Chicago, IL).

Collected data were evaluated by means of descriptive statistics. Spearman's correlation coefficient (#) was used to analyze associations between investigated parameters and the Benjamini-Hochberg correction was used for multiple testing. Mann-Whitney test was used for group comparisons. A receiver operating characteristic curve was used for prediction of Her 2-status. P values< 0.05 were taken to indicate statistical significance.
**Fig. 1:** An explanatory patient of the investigated patient sample. Representative axial slide of the t1-weighted sequence. The tumor is relatively homogenous hypointense compared to the surrounding tissue. The measurement was performed as a whole lesion measurement on every slide of the tumor.

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Fig. 2: The corresponding histogram of the t1-weighted image.
Fig. 3: Representative axial slide after contrast media application. The tumor shows a moderate, homogenous enhancement.

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Fig. 4: On the corresponding histogram, the enhancement is seen as an overall higher signal intensity on the histogram. Furthermore, the histogram shows a higher entropy.

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Fig. 5: The representative axial slide of the t2-weighted sequence. The tumor is relatively homogenous with little hypointense areas.

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Fig. 6: The corresponding histogram of the t2-weighted image.

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Results

Correlation analysis

An overview about the Spearman's correlation analysis with Benjamini-Hochberg correction is given by figure 7. Several pre- and postcontrast derived t1-weighted parameters correlated inversely with EGFR expression. For precontrast t1- weighted images, the strongest correlation was found for p90 (#=-0.77, p=0.004). For postcontrast t1 weighted images, the strongest correlation was observed for minimum (#=-0.64, p=0.021) (figure 8).

For t2 weighted images, mean, p25, p75, p90 and median correlated with EGFR expression.

No statistically significant correlations were identified between histogram analysis parameters and cell count, Ki67 index or expression of Histone 3, Hif1-alpha, VEGF or p53.

Her 2 prediction

Several parameters derived from t2-weighted images were statistically significant different between Her2-positive and Her2-negative tumors. Skewness had the best p-value (p=0.004) (figure 9). Furthermore, receiver operating characteristic (ROC) analysis identified the highest area under the curve (AUC) for t2-weighted skewness (0.94) (figure 10). In addition, a threshold value of 0.32 for t2-weighted skewness had a sensitivity of 100% and a specificity of 81% for distinguishing between Her2-positive and Her2-negative tumors.
**Fig. 7:** The color-coded correlation heat map. Statistically significant correlations are highlighted with a point.

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**Fig. 8:** Correlation between percentile p90 derived from t1-precontrast weighted images and EGFR expression. The correlation coefficient is $r=-0.77$, $P=0.004$.

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**Fig. 9:** Boxplot graph displaying the difference between Her2-positive and Her2-negative tumors in regard to their skewness derived from t2-weighted images (p=0.004, Mann-Whitney test).

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Fig. 10: ROC-analysis of several histogram parameters in discriminating the tumors according to the Her2-status. The highest area under the curve (AUC) was achieved by skewness derived from t2-weighted images (AUC=0.94).

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Conclusion

The purpose of this study was to elucidate possible associations between histogram analysis derived from morphological MRI sequences and histopathological features in uterine squamous cell carcinomas. Overall, the present study showed that histogram analysis can provide crucial information for tumor characterizing.

Histogram analysis parameters of T1w and T2w images reflect Her2-status and EGFR expression in cervical cancer but cannot predict cell count, proliferation index or angiogenesis related histopathological features.
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