Abstract

OBJECTIVES: Recently, Atuegwu et al. proposed a mathematical model based on ADC_{mean} and ADC_{min} to calculation of cellularity. Our purpose was to compare the calculated cellularity according to the formula with the estimated cell count by histopathology in different tumors. METHODS: For this study, we re-analyzed our previous data regarding associations between ADC parameters and histopathological findings. Overall, 134 patients with different tumors were acquired for the analysis. For all tumors, the number of tumor cells was calculated according to Atuegwu et al. 2013. We performed a correlation analysis between the calculated and estimated cellularity. Thereby, Pearson's correlation coefficient was used and \( P < .05 \) was taken to indicate statistical significance in all instances. RESULTS: The estimated and calculated cellularity correlated well together in HNSCC (\( r = 0.701, P = .016 \)) and lymphomas (\( r = 0.661, P = .001 \)), and moderately in rectal cancer (\( r = 0.510, P = .036 \)). There were no statistically significant correlations between the estimated and calculated cellularity in uterine cervical cancer, meningiomas, and in thyroid cancer. CONCLUSION: The proposed formula for cellularity calculation does not apply for all tumors. It may be used for HNSCC, cerebral lymphomas and rectal cancer, but not for uterine cervical cancer, meningioma, and thyroid cancer. Furthermore, its usefulness should be proved for other tumors.

Introduction

Magnetic resonance imaging (MRI) is used as a staging investigation in numerous malignant diseases. Some MRI techniques, for instance, diffusion weighted imaging (DWI), are influenced by histological composition of investigated tissue, and, therefore, can be used as marker of tissue architecture [1–4]. DWI measures the random motion of water molecules in tissues [1,2]. The water diffusion can be quantified by a parameter, defined as the apparent diffusion coefficient (ADC) [1–4]. ADC reflects the mobility of water within tissues and documents quantitatively restriction of water diffusion by several barriers, such as cell membranes [1–4]. Therefore, ADC can indirectly provide information about cell density [1].

Previously, numerous experimental and clinical studies reported data regarding associations between DWI and histopathological features in different tumors and tumor like lesions [3–7]. In most publications, different ADC fractions, especially minimum ADC (ADC_{min}) and mean ADC (ADC_{mean}) showed statistically significant inverse correlations with cell count in several tumors [5–7].

Recently, Atuegwu et al. proposed a mathematical model based on ADC_{mean} and ADC_{min} to calculation of cellularity [8]. The authors observed a strong and significant Pearson correlation and a strong concordance correlation between the estimated and the simulated number of tumor cells [8]. However, the proposed formula was not proven by histopathological examination, and, therefore, it is unclear, if the mathematical model provides real cell count or not.

Therefore, our purpose was to compare the calculated cellularity according to the formula with the estimated cell count by histopathology in different tumors.

Materials and Methods

Estimated Cellularity

For this study, we re-analyzed our previous data regarding associations between ADC parameters and histopathological findings...
Overall, 134 patients with different tumors were acquired for the analysis (Table 1). In all cases, the diagnosis was confirmed by histopathological examination. For every tumor entity, cellularity was estimated as an average cell count per 2–5 high power fields (×400; 0.16 mm² per field). All images were analyzed by using a research microscope Jenalumar, with camera Diagnostic instruments 4.2 as reported previously [6,9].

Furthermore, in all cases the tumors were investigated by DWI. Thereby, different equipment and b values were used (Table 1).

**Cell Number Calculation**

For all tumors, the number of tumor cells was calculated according to Atuegwu et al. 2013 [8]. In this study, ADC values were converted to tumor cell number N using following equation:

\[
N = \theta \left(\frac{\text{ADC}_w - \text{ADC}_{\text{mean}}}{\text{ADC}_w - \text{ADC}_{\text{min}}}\right)
\]

(8)

Where \(\text{ADC}_w\) is the ADC of free water (\(\text{ADC}_w = 3 \times 10^{-2} \text{ mm}^2/\text{s}\)); \(\text{ADC}_{\text{min}}\) is the minimum and \(\text{ADC}_{\text{mean}}\) the mean ADC value within the ROI, respectively. \(\theta\) is the carrying capacity which can be interpreted as the maximum number of cells that can be contained within a given volume [15]. Due to varied imaging voxel sizes for different entities, we converted the given volumes to a standard volume of 1 mm³. To calculate \(\theta\), we used the tumor cell volume of 4189 μm³ [8].

**Statistical Analysis**

Because the fact that the formula calculated cells in a volume and previously reported data were based on cell count on high power fields, we performed a correlation analysis between the calculated and estimated cellularity. Thereby Pearson’s correlation coefficient was used and \(P < .05\) was taken to indicate statistical significance in all instances.

**Results**

Table 1 shows the results of the performed correlation analysis between the calculated and estimated cellularity. In the total sample, the calculated cellularity did not correlated with the estimated cell count. The subgroup analysis showed the following. Both parameters correlated well in HNSCC and lymphomas, and moderately in rectal cancer (Table 2). There were no statistically significant correlations between the estimated and calculated cellularity in uterine cervical cancer, meningiomas, and in thyroid cancer.

**Discussion**

Our study provides data about calculated and estimated cellularity in different tumors. As seen, the estimated and calculated cellularity correlated statistically significant in HNSCC, lymphoma and rectal cancer.

The proposed formula does not consider the fact that several tumors and tumor-like lesions have different cell and nucleic sizes. Therefore, it cannot be used for all tumors. However, our study showed that it provides results, which are concordant with the estimated cell count for HNSCC, cerebral lymphoma and rectal cancer. Clearly, further investigations with different tumors are needed to proof the usefulness of the formula in other malignancies. We hypothesize that in future, more sensitive ADC-based mathematical models adjusted for every tumor entity may better reflect cellularity than a general formula. Furthermore, these models may include other ADC parameters than \(\text{ADC}_{\text{mean}}\) and/or \(\text{ADC}_{\text{min}}\). Recently, some reports showed that histogram analysis of ADC maps provided other parameters, which better correlated with tumor cell count [19,20].
The present study has several limitations. Firstly, it is retrospective. Secondly, the analyzed tumor groups had small number of patients.

In conclusion, our results suggested that the proposed formula for cellularity calculation does not apply for all tumors. It may be used for HNSCC, cerebral lymphomas and rectal cancer, but not for uterine cervical cancer, meningioma, and thyroid cancer. Furthermore, its usefulness should be checked for other tumors.

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