Metastatic Hepatic Neuroendocrine Tumors: Correlation of Quantitative Diffusion and Dynamic Contrast Enhanced MRI with Tumor Grade

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Target audience: Radiologists, physicists and technologists with interest in oncology.

Purpose: Neuroendocrine tumors (NETs) arise from enterochromaffin cells and are predominantly found in the gastrointestinal tract. The most common metastatic site from these tumors is the liver (up to 60% of cases) [1]. Optimized therapy of patients with metastatic NET is based on histopathologic tumor aggressiveness. Therefore, development of optimal treatment strategies based on non-invasive characteristics of NET as well as new active agents is warranted. ADC measured with DWI has shown utility in predicting the grade of a variety of neoplasms, with an inverse correlation between ADC and tumor cellularity reported [2-4]. There are very few reports about the relationship between ADC and grade of differentiation in NET, with no data on liver metastatic NET. The purpose of this study was to evaluate the value of ADC and dynamic contrast-enhanced MRI in predicting histopathologic characteristics of liver metastatic NET.

Methods: 18 patients (M/F 8/10, mean age 62.5 y) with pathology proven metastatic NET to the liver who underwent abdominal CE-MRI including DWI from October 2009 to July 2014 before treatment were included in this IRB approved study. One radiologist placed regions of interest (ROIs) in normal liver parenchyma and liver lesions to measure SI on pre and post-CE dynamic imaging phases and on DWI using two b values (0, 500 s/mm^2) to measure mean ADC. Enhancement ratio (ER) for NET lesions was calculated as ER=[(SI post - SI pre)/SI pre] x100%. Histopathologically, tumor differentiation was categorized based on WHO 2010 classification as follow: G1, G2, and G3. ADC and CE-MRI parameters (ER on arterial phase, ER-ART) were compared between different tumor grades. The correlation between each of ADC and ER with tumor grade, mitotic count, Ki-67 labeling index (index of cell growth) and tumor size were analyzed with Spearman correlation test. The diagnostic performance of ADC values and ERs to predict pathologic grade was evaluated using ROC analysis.

Results: 18 patients with a total of 46 NET metastatic liver lesions were analyzed (mean size 3.5 cm, range 1-17 cm), as follows: G1 (n=23), G2 (n=13) and G3 (n=10). ADC (x10^{-3} mm^2/sec) of G3 tumors (1.10 ± 0.48) was significantly lower than those of G1 (1.62 ± 0.47) and G2 tumors (1.60 ± 0.57, p=0.01) **(Table, Fig. 1).** ERs were significantly higher in G3 versus G1-G2 tumors (p=0.01) **(Table).** A significant negative correlation was observed between ADC and mitotic count (r=-0.40, p=0.005), Ki-67 (r=-0.35, p=0.01) and tumor grade (r=-0.34, p=0.02). A significant correlation was also observed between ER and mitotic count (r=0.38, p=0.006), Ki-67 (r=0.55, p=0.00002) and tumor grade (r=0.49, p=0.0002). No significant correlation was found between ADC or ER and tumor size. AUC for the prediction of G3 vs. G1-G2 was 0.76 for ADC and 0.77 for ER-ART, and 0.88 for the combination of ADC and ER. Threshold ADC to distinguish between NET G1- G2 and G3 was 1.34 x 10^{-3} mm^2/sec (sensitivity 80%, specificity 67%).

	ADC	ER-ART
Grade 1 (n=23)	1.62 ± 0.47	21.3 ± 19.6
Grade 2 (n=13)	1.60 ± 0.57	45 ± 37.5
Grade 3 (n=10)	1.10 ± 0.48	77.8 ± 54.1
p	**0.012**	**0.002**
****p***	0.9	**0.01**

Tumor ADC and arterial enhancement ratios (ER-ART) in 46 NET metastatic liver lesions.
**p*: Grade 1+2 vs. 3 ; **p=Grade 1 vs.2+3

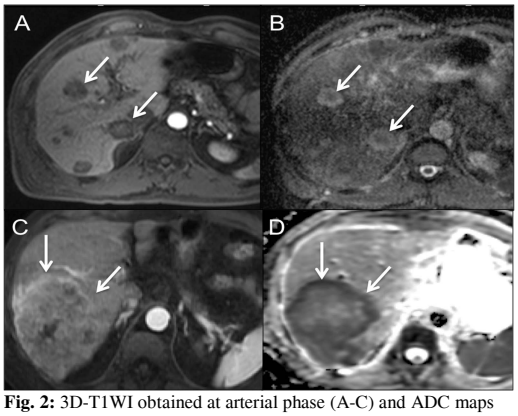

Fig. 2: 3D-T1WI obtained at arterial phase (A-C) and ADC maps (B-D) in 2 different patients with metastatic liver NET: grade 1 (top row) and grade 3 (lower row). G3 liver metastasis demonstrates higher arterial enhancement (ER-ART=132.4%) and lower ADC values (1.2 x10^{-3} mm^2/s) than G1 NET (ER-ART=23.5% and ADC=2.1 x10^{-3} mm^2/s).

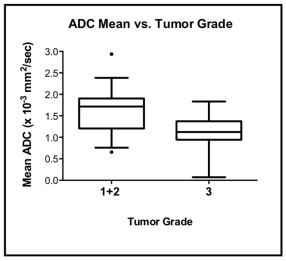

Fig.1: Box Plot distribution showing lower ADC Mean values in Grade 3 NEC compared to Grade 1 and 2 NET.

Discussion: In this study we demonstrated that neuroendocrine carcinoma (G3) liver metastases had significantly lower ADC and higher arterial enhancement than Grade 1-2 tumors **(Fig.2)**. In addition, significant negative correlation was observed between ADC and ER with histopathologic characteristics. These results are in agreement with a prior study by Wang et al [2], who analyzed ADC data on 18 patients with pancreatic NET and found that ADC correlates with Ki-67 and may help to predict growth of NET. Based on our results, we suggest that DWI and CE-MRI provide important information on characterization of NET liver metastases, which is critical for treatment planning and prognostication. The presence of hepatic metastasis is the most important predictor of poor survival in patients with NET, with extent of liver metastases correlating with subsequent survival. Therefore, ADC and enhancement/perfusion could be become valuable biomarkers of tumor aggressiveness in patients with metastatic NET.

Conclusion: ADC and enhancement quantification may be useful in predicting tumor grade in metastatic liver NET. These results need to be confirmed in a prospective study.

References
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