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Multiparametric MRI in distinguishing high-grade gliomas from solitary brain metastasis: MR spectroscopy, diffusion weighted imaging and dynamic susceptibility contrast imaging

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Purpose: The purpose of this study is to determine the utility of diffusion weighted imaging (DWI), MR spectroscopy (MRS) and dynamic susceptibility contrast imaging (DSCI) at peritumoral area and contrasted tumor on the basis of cellularity, vascularity and metabolite levels in distinguishing high-grade gliomas (HGG) from solitary metastasis (SM).

Method: MRS, DSCI and DWI were applied on 56 patients with solitary brain tumor (39 HGG, 17 SM). ADCMIN, ADCMAX, ADCMEAN, rCBVMax rates, Cho/Cr, Cho/NAA and NAA/Cr metabolite rates were measured from contrasted tumor and peritumoral area. In terms of the distinction between SM and HGT, Mann Whitney U test and independent samples T test were used to find out whether all these parameters had statistical difference and receiver operating characteristic (ROC) curve analysis was conducted to find out the cutoff values of these parameters.

Results: In the distinction between SM and HGG, the differences in all ADC rates in the peritumoral area, rCBVMAX rate and differences between Cho/Cr, Cho/NAA and NAA/Cr metabolite rates were statistically significant (NAA/Cr $p<0.009$ other parameters $p<0.0001$). However, in the distinction between the two groups, all these parameters were shown to have no statistical difference in the contrasted tumor ($p>0.05$). According to ROC curve analysis, in distinguishing SM lesions from HGGs, cutoff values for ADCMIN, ADCMAX, ADCMEAN, rCBVMAX, Cho/Cr, Cho/NAA and NAA/Cr were 1,327, 1,483, 1,439, 0,61, 1,29, 1,16, 1,33, respectively in the peritumoral area, while sensitivity, specificity and AUC values were 82,4%, 89,7%, 0,920; 82,4%, 83,1%, 0,863; 82,4%, 87,2%, 0,888; 94.1%, 87,2%, 0,949; 88,2%, 82,1%, 0,897; 94,1%, 79,5%, 0,952; 82,4%, 74,4%, 0,762, respectively.

Conclusion: DWI, MRS and DSCI can show the tumor infiltration around the contrasted area and provide diagnostic information in the distinction between SM and HGG. In addition, the highest sensitivity and specificity was found in the peritumoral rCBVMAX rates in the distinction between tumors.

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Pharmacological inhibition of the epigenetic writer EZH2 in castration resistant prostate cancer

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Pharmacological inhibition of the methyltransferase EZH2 has been proposed as a promising anticancer strategy. Selective small-molecule inhibitors that disrupt EZH2 enzymatic activity preferentially suppress the growth of lymphoma cells with activating mutations in EZH2 gene. Although substantial evidence indicates a vital role of EZH2 in driving the aggressive features of cancer cells, it is unknown whether these EZH2-targeting compounds have inhibitory effects in solid tumors that generally do not carry somatic mutations of the methyltransferase. We tested two distinct EZH2 inhibitors in a panel of human prostate cell lines, and found that both were effective in blocking the proliferation of cancer cells with competent androgen receptor (AR) signaling, especially the castration resistant prostate cancer (CRPC) cells. Quantitative ChIP-Seq revealed a significant reduction in global H3K27 trimethylation (H3K27me3) levels in both sensitive and irresponsive prostate cancer cells upon the inhibitor treatment. In sensitive CRPC cells, however, both drugs induced a specific gene signature that is highly associated with AR signaling. Compound treatment disrupted the interaction between EZH2 and AR, and impaired AR recruitment to its target gene loci. EZH2 inhibitor showed significant efficacies in CRPC xenograft mouse models as monotherapy, and was even more effective in hindering the androgen-independent growth of CRPC cells when combined with second-generation anti-androgens. Our data demonstrate that pharmacological inhibition of EZH2 activity, either alone or in combination with AR antagonists, represents a promising strategy for the treatment of advanced prostate cancer.

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