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THERMO-CHEMORADIATION INDUCED MR DIFFUSION CHANGES AFTER BRAIN GLIOMA TREATMENT

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ABSTRACT

Background: Glioblastoma multiform (GBM) is a common brain-tumour. We expanded hyperthermia (HT) experiments over the changes of the apparent diffusion coefficient (ADC) in MR imaging to assess thermal beneficial effect in combination to chemo-radiation therapy.
Patients and methods: There were 34 GBM patients in two equal groups of chemo-radiation therapy (RT) and chemo radiation therapy plus HT (RHT), and each group age ranging from 26 to 76 years. HT was done in 10 sessions for RHT group after initial calibration. ADC values thermal enhancement factor were calculated after treatments for both tumour and normal brain tissues.
Result: There was a significant difference of ADC values between before and after treatments in tumour region of RHT group (P =0.002) and it wasn't significant in normal part of the brain tissue and TEF based on ADC values was 1.33.
Conclusion: This preliminary study shows promising result with hyperthermia in term of ADC changes.

Keywords: Hyperthermia, Glioblastoma multiform, Radiotherapy, Apparent Diffusion Coefficient, Chemotherapy, Thermal enhancement factor, Celsius, Diffusion weighted imaging

1. INTRODUCTION

Hyperthermia (HT) is known as a procedure of thermalyzing tissue volume to about 41-45 ^{o}C within the body. This method of treatment is mostly used for malignant disorders in combination to radiotherapy (RT) and/or chemotherapy (CT) because it is scientifically believed that hyperthermia can change their efficacies significantly in a positive manner (1-6).
Brain glioma (BG) forms 25-30% of all brain malignant tumors and they are accounted as a major challenge in neuro-oncology (7). Standard treatment of brain-glioma is consisted of surgical resection, when feasible, followed by chemo-radiotherapy. Three retrospective studies of the Radiation Therapy Oncology Group (RTOG) included 1578 patients from 1974-1989 and updated in 1991, show overall survival of Glioblastoma multiform (GBM) 13.7 months and 9.7 months for patients under the age of 50 years and older, respectively (8). Results of studies and clinical trials confirm the promising thermal effects of concomitant HT and RT, however, many of the micro structural and molecular mechanisms of the HT combination to RT and CT are still not understood enough (9, 10, 11, 12).

Magnetic resonance imaging (MRI) is used to study various diseases and benign brain tissue and to determine the most appropriate treatment for glioma, the development of techniques that can accurately indicate in vivo Tumoral changes and/or response is crucial (13-18). Currently, the only MR imaging technique which can provide such an information is Diffusion-weighted image (DWI) that allows microscopic evaluation of water diffusion within tissues by obtaining the apparent diffusion coefficient (ADC) data (19-21). In the biological tissue, the ADC involves Brownian motion (incoherent motion) and capillary blood circulation (coherent motion) (15). It was shown that, generally, ADC values for brain tumor measured over a normal b-factor range (about 1,000 sec/mm^2), is more than ADC values of normal gray and white matters (22).

In the present preliminary study, we expanded our hyperthermia experiments, for the treatment of GBM tumor, over the change of the ADC parameter to further assess the possible beneficial effects of hyperthermia technology in treatment of GBM.

2. SUBJECTS AND METHODS

The study population was consisted of 34 GBM patients in two groups of chemo-radiation therapy (simply here is called RT group) and chemo-radiation plus hyperthermia (simply here is called RHT group).

All the thirty-four patients were planned for external beam radiotherapy (three dimensional conformal radiotherapy or 3DCRT) and they were treated for 60 Gy megavoltage x-ray beam within 30 fractions under same radiotherapy facility. All patients had concomitant chemotherapy during radiotherapy course with dose of 75 mg/m^2 Temozolomide (TMZ). Three to four weeks after radiotherapy another course of adjuvant TMZ is started, routinely, with a dose of 150-250 mg/m^2 and it is continued for 6 to 8 courses.

2.1 Hyperthermia

Electro-HT with frequency of 13.56 MHz (Celsius 42+ GmbH, Germany) was applied by capacitive coupling technique after initial calibration based on ESHO protocol. Patients were treated with hyperthermia for 10-12 sessions (twice weekly) and treatment time was selected according to the protocol dedicated by Courtesy from Dr Huseyin Sahinbas (Praxis- Klinik Hperthermie & Support Care, Institute Fur Hyperthermieforschung des Marienhospitals Herne, Klinikum der Ruhr-Universitat Bochum). In order to quantify the hyperthermia effect we used thermal enhancement factor (TEF) based on ADC values. TEF in term of ADC is defined as the ratio of the ADC in RHT to the RT group (equation 1) and it can show how much thermal therapy can improve the result of a radiotherapy regime.

Equation 1:

$$TEF(ADC) = \frac{ADC for\ RHT\ after\ treatments}{ADC for\ RT\ after\ treatments}$$

2.2 MRI Protocol

Patients underwent MR imaging pre-treatment and 3 months post treatment in both groups. Imaging was performed by a 1.5 Tesla MR machine. T2 weighted (FLAIR) images were acquired in the axial plane with TR = 3548 ms, TE = 97.51 ms, FOV = 24 cm, matrix of 256×219, ST = 2.5 mm with 5 mm gap and number of excitations (NEX) of 2. The DWIs were acquired (b values 0 and 1000) by using the echo-planar imaging (EPI) sequence.

We then obtained ADC maps for each patient. The ADC maps and values were calculated with a commercially available software package (ITK-SNAP VERSION 3.6.0 APR., 1, 2017). We calculated the means and standard deviations of the ADC both for tumour and benign brain tissue area. Qualitative and quantitative assessments were done on the images by an expert team of radiologist, radiation oncologist and medical physicist.

Finally, The Wilcoxon signed rank test was used for analysing the mean ADC values significant differences between tumoral and non-tumoral brain tissue for both RT and RHT groups.

3. RESULTS

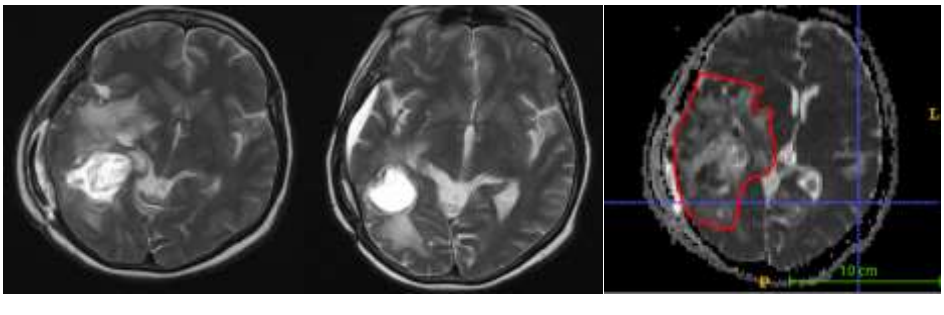
The study population was consisted of 34 patients in two groups (34 GBM tumors) 17 patients in each group ranging in age from 26 to 76 years with means 58.1 year and 45.5 year for RT and RHT groups, respectively. Eight patients with Glioblastoma underwent surgery, and nine underwent biopsy in both groups. MRI data before and after treatments were obtained for all patients and Fig. 1 shows the overall changes in the treated volume for a typical case in T2-weighted and ADC images. Quantitative assessment of MR images demonstrates clinical target volume (CTV) variation after RT plus HT and RT treatments. The means and standard deviations of CTVs for RT+HT and RT groups after treatments are 104.15±58.45 and 137.63 ±113.93 cm^3, respectively, and there is a significant difference of CTV changes between two groups (P=0.048). All patients had histo-pathologically diagnosed high grade glioma or Glioblastoma multiform

compatible with WHO *IV* grading. The summary of the tumor histology, male-female distribution, patient age, and tumor ADCs are presented in Table 1.

The pre-treatment mean ADC value of normal brain tissue for RT group was 0.91±0.45 mm^2/s and for post treatment it was 0.93±0.34. For malignant lesions, the mean ADC values were 1.40±0.42 mm2/s and 1.43±0.33 mm^2/s pre and post treatment, respectively.

The mean ADC values for benign brain tissue in RHT group pre and post treatments were 0.91±0.44mm^2/s and 0.93±0.34 mm^2/s, respectively. These values for malignant sites pre and post treatment were also 1.38±0.43 mm^2/s and 1.89±0.39 mm^2/s, respectively.

According to the results, there are differences between the ADC values of various groups and it is obvious that the amounts of ADC values were increased after treatments in both groups. However, as a remarkable result of this study, there is a reportable significant difference of ADC values between before and after treatments in tumor part of the brain in RHT group (P=0.002). In spite of the increased ADC values in normal part of the irradiated brain tissue, changes between pre and post irradiation have not shown significant difference. TEF calculation based on ADC values was done and it was calculated to be 1.33 in this study which is comparable with the TEF and/or Thermal enhancement ratios (TER) from other techniques and studies.



(A) (B) (C)

Figure1: Typical changes in MRI features are demonstrated in the images

A) Prior to commencing any treatment,

B) After completing chemo-RT and HT, the clinical target volume decreased to about 32% of its initial volume in this specific case.

C) Shows ADC map of brain before treatment.

4. DISCUSSION

This study was run on a small population of GBM patients in two groups of chemo-radiotherapy and a combination of chemo-radiotherapy and local hyperthermia to assess the apparent diffusion coefficient changes in clinical target volume. Diffusion weighted imaging and/or ADC by MRI is an efficient functional imaging technique that provides information about cellular microstructure and specific changes in tissue cellularity and water movement in malignant tumors. In fact, movement restriction of the water molecules can be characterized by decreased ADC values. ADC may be used to stratify the aggressiveness of a tumor and ADC value is of importance to predict the degree of the response to the treatment. MR diffusion imaging is able to provide some tissue information that, otherwise, it has be obtained by invasive methods such excisional biopsy (23).

In our study, ADC values of GBM tumors significantly are increased after hyperthermia in RHT group. Changes in ADC value might be explained by thermal effect on water diffusion, because higher temperature, increases movement of the molecules (24). It is generally accepted that there are multiple mechanisms underlying hyperthermia effects on the tissues for example increasing perfusion, permeability, metabolic activity for drug uptake, radio and/or chemo sensitization. Most of these mechanisms are capable to change diffusion imaging parameters and the consequences can be processed and analyzed according to the specific probe type.

Our study also has shown that there is no significant difference in mean ADC values between pre and post treatment in both groups within the not affected brain tissue. One possible explanation for this finding is that the lower ADC values may reflect the restriction of water mobility due to the high cellularity of brain cancer (8). Previous studies reported significant differences in mean ADC

values between pre and post radiotherapy treatment in the GBM tumor (25), but in our preliminary study they are not significant which could be due to the inferior sample size.

In the present study, the maximum b-value was 1000 mm^2/s. By using the higher B value, the ADC value is less affected by perfusion, and the ADC difference between malignant and benign lesions could be larger, since the effect of perfusion in malignant lesions is more than benign lesions due to tumor angiogenesis. However, the high b value needs a long TE and it also distorts the image. In our studies b-value between 0 and 1000 mm^2/s was sufficient to obtain image with proper quality.

Now a day, a few studies have shown changes of ADC values in brain tumor after radiotherapy compared to before treatment values and its role in evaluating therapeutic response pre and post radiotherapy observed in several recent studies (25).

In-vivo and in-vitro studies have proved that malignant cells are more sensitive to heat effect in comparison to normal cells. It has also been shown that due to blood vessel architectural damage in tumor, blood flow (input and output) are not equally distributed in tumor volume, on other hand, tumor blood vessels have a fragile and non-nervous structure that causes them more susceptible to thermal effect (8). Studies have shown that blood-brain barrier in the vicinity of the GBM tumor can be broken-down by heat, causing to facilitate Tumoral diffusion which makes them more susceptible to chemotherapy reagents and producing targeting effect. Hyperthermia has also shown that it can increase therapeutic efficacy, thanks to reducing the concentration and side effects of chemotherapy reagents (26).

In order to quantify the hyperthermia effect we get help from thermal enhancement factor (TEF). Generally, TEF defines how much thermal therapy can improve the result of a radiotherapy regime (27). Translation of thermal enhancement factor in term of ADC language might be the ratio of ADC in RHT treatment relative to RT treatment in a specific and comparative frame work including hyperthermia regime and clinical considerations (e.g. patients follow up time). Simple calculation of TEF for ADC showed that is equal to 1.33 values. Results from invitro studies have been reported by Laurie Roizin-Towle, and John P. Pirro (1991) that shows TER's for human cells ranged from 1.1 to 2.7 for hyperthermia treatments at 43°C and from 2.1 to 5.3 for cells exposed to heating at 45°C. Specific TER value for GBM invitro study is revealed to be 2.5 for one hour 43^0c hyperthermia protocol (28). In spite of the difference between enhancement effect of the GBM in present study and previous researchers, but our result is well within the range which shows it worth to work more on this method of TEF calculation. It means that hyperthermia could improve the clinical effects of radiation in term of ADC for about 33%. In the other word, ADC can be used as indicator to assess the thermal enhancement effect. However, as far as authors know, it is for first time that term "TEF based on ADC" is presented and it needs more intensive studies to validate the application of this raw definition in terms of sensitivity and specificity.

Table 1: Summary of the results of the study is presented in the table.

Tumor type	Group	Patients No. Male / Female	Age range: Male /Female	Mean Age (year)	Tumor Mean ADC ($x10^{-3}mm^2/s$) ±SD (pre)	Tumor Mean ADC ($x10^{-3}mm^2/s$) ±SD (post)	Normal Brain Mean ADC ($x10^{-3}mm^2/s$) ±SD Pre-treatment	Normal Brain Mean ADC($x10^{-3}mm^2/s$) ±SD Post-treatment
GBM	RT	17(9/8)	(50-76) /(27-68)	58.1	1.40±0.42	1.43±0.34	0.91±0.45	0.93±0.34
GBM	RHT	17(8/9)	(26-5) /(30-70)	45.5	1.37±0.43	1.89±0.39	0.91±0.44	0.93±0.33

5. CONCLUSION

The results indicating that hyperthermia induces some changes in imaging features those reflecting diffusion properties in the tumor mass of Glioblastoma multiform. Apparent diffusion coefficient values are used as proper indicator for predicting the response of chemo-irradiated malignant glioma. Further clinical investigation and evaluation are needed to remarking the relation-ship between ADC and hyperthermia effect in term of thermal enhancement factor. But this preliminary study results are more promising when it is compared to the short term clinical outcome.

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