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Thermal enhancement effect on chemo-radiation of glioblastoma multiform

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ABSTRACT

Background: Hyperthermia plays a significant role in the chemo-radiotherapy effect in different malignancies. In this research, we treated Glioblastoma multiform (GBM) patients with hyperthermia (HT) along with the chemoradiation, in order to evaluate HT efficacy in terms of tumor volume changes, survival time, and probability. ***Materials and Methods:*** Thirty-eight GBM patients were distributed into two groups identified as chemoradiation (CRT), and also CRT plus HT (CRHT). The Karnofsky Performance Status Scale (KPS) was done before, immediately and three months after treatments. Capacitive hyperthermia device was used at frequency of 13.56 MHz (Celsius 42+ GmbH, Germany) for HT one hour before the radiotherapy for 10-12 sessions. Patients in both groups underwent MR imaging (1.5 Tesla) before, 3 and 6 months after the treatments. Thermal enhancement factors (TEF) were attained in terms of clinical target volume changes, *TEF(CTV)*, and survival probability *(SP)* or *TEF(SP)*. ***Results:*** Age ranges were from 27-73 years (Mean=50) and 27-65 years (Mean=50) for CRT and CRHT groups, respectively. For 53% and 47% of cases biopsy and partial resection were accomplished in both groups, respectively. Means and standard deviations of tumor volumes were 135.42±92.5 and 58.4±104.1cm^3 before treatment in CRT and CRHT groups, respectively, with no significant difference (P= 0.2). *TEF(CTV)* value was attained to be as 1.54 and 1.70 for three and six months after treatments, respectively, *TEF(SP)* was also equal to the 1.90. ***Conclusion:*** HT enhanced the chemoradiation effects throughout the patient survival probability and KPS. TEF may reflect the hyperthermia efficacy for a given radiation dose.

Keywords: *Hyperthermia, GBM, chemoradiotherapy, thermal enhancement factor.*

► ***Original article***

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INTRODUCTION

Glioblastoma multiform (GBM) is still considered as a devastating brain disease. Surgery and chemoradiation have not improved the patient's survival time and quality of life, significantly, in comparison with other malignancies. Glioma forms 25–33% of all brain malignancies, and malignant glioma often relapses quickly after the surgery alone [1]. Malignant glioma patients only would survive for an average of 17 weeks without treatment, and their life span can also be prolonged to 30 weeks after surgery and chemotherapy. Radiotherapy is able to increase the rate of GBM patient's survival; however, the quality of life and those complications after radiation are severely influenced by the high dose radiotherapy.

Hyperthermia has presented its major role in radiation and chemotherapy effects enhancing for various diseases, like cervical cancer, recurrent rectal cancer, bladder, and also in soft tissue sarcomas [2]. Different approaches have been accomplished in order to quantitatively determine the thermal effect, for example the thermal enhancement ratio, which measures thermal effect for different radiation doses with same biological effect [3]. Recent retro clinical research for GBM by adjuvant electro-hyperthermia indicated that oncothermia has potential for anaplastic astrocytoma and Glioblastoma multiform treatment, and it can possibly be considered as a method in order to overcome to the present difficulties in the way of having a successful treatment for the brain glioma [4].

Those clinical parameters that were used in this study in order to quantify thermal enhancement effect are including: Karnofsky performance status scale (KPS), tumor volume, and patients survival. These parameters are influenced by the treatment methods and procedures directly [5]. We evaluated the 13.56 MHz radiofrequency capacitive hyperthermia enhancement effect on the GBM patients chemo-radiation therapy from the points of clinical outcomes including; survival probability, physical performance, and tumor volume changes.

MATERIALS AND METHODS

Patients

The study population was consisted of 38 GBM patients in two chemoradiation (CRT) and hyperthermia (CRHT) groups, and each group has 19 patients. Patients were selected after getting written consent about the hyperthermia and its procedure and potential effect on the chemoradiation therapy (Ethics code: IR.IUMS.REC.1397.089). There were 11 males and 8 females in CRT, and also 8 males and 11 females in CRHT groups. Tumors have been positioned in different brain lobes, and mostly in frontal lobe. All tumors were pathologically diagnosed as primary GBM (grade 4) in 38 patients. Nine patients with GBM underwent surgery, and ten of them underwent biopsy in each of the groups. Each patient was followed up after the treatment termination for eighteen months.

Karnofsky performance status

The Karnofsky Performance Status Scale (KPS) is an extensively used method for evaluating the cancer patient's physical status. The KPS value is an 11-points rating scale, which ranges from zero to 100 for a dead to normal functioning case, respectively [5]. We used KPS findings in this research in order to assess hyperthermia synergic effects for GBM patients. Patients KPS were evaluated before, right after the treatment, and also three months post treatment.

Radiation therapy

All thirty-eight patients were planned for three dimensional conformal radiotherapy (3DCRT) by a dedicated treatment planning software (TiGRT, ver. 1.0.8545, Linatech, LLC. www.LinaTech.com) and also they were treated with 60 Gy megavoltage X-ray beam from high energy linear accelerator (Siemens-primus, Siemens Co., Germany) within 30 fractions in either one or two phases. All patients had concomitant 75 mg/m^2 Temozolomide (TMZ-

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daily) chemotherapy during the time of radiotherapy course. Another course of adjuvant TMZ is usually started with dose of 150-250 mg/ m^2, which is continued for 6 to 8 courses by passing three to four weeks from the radiotherapy.

Hyperthermia

Capacitive hyperthermia was applied at the frequency of 13.56 MHz (Celsius 42+ GmbH, Germany) and by two electrodes coupling technique. Temperature of the treated volume reaches to about 41˚c, while the skin surface temperature should be kept under the 20˚c, during hyperthermia accomplishing. The applied power ranges between 30 to 140 watts in a step –up heating pattern. The system was calibrated before the study according to the European society for Hyperthermia Oncology (ESHO) quality assurance guidelines. Patients were treated by hyperthermia one hour before radiotherapy for 10-12 sessions. At first session, hyperthermia was started with 30 watt for 10 minutes, and then it was raised up to 40 watt for another 10 minutes; hyperthermia regime was changed for the next sessions. The maximum power changes to 140 watts for the last ten minutes by passing six sessions, and overall treatment time was 60 minutes. HT was performed for two sessions per week which it was accomplished according to the protocol by Dr Huseyin Sahinbas (Praxis- Klinik Hperthermie & Support Care, Institut Fur Hyperthermieforschung des Marien hospitals Herne, Klinikum der Ruhr-Universitat Bochum) [6].

Magnetic resonance imaging

Patients in both groups underwent MR imaging before the beginning of the treatment (as a baseline), and also at 3 and 6 months after the treatments. Imaging was performed on a 1.5 Tesla MR machine (Philips Co.), and along with that T2 weighted (FLAIR) images were acquired in the axial plane.

A team of radiologist, radiation oncologist and medical physicist accomplished the qualitative and quantitative image analysis. MR imaging was repeated three times: once before treatment, and then three and six months after treatments.

Statistical analysis

For statistical analysis “student T test” was used in order to compare the variables in two groups, and also actuarial analysis (Kaplan-Meyer) for survival probability calculation.

Thermal enhancement factor (TEF)

TEF is a factor for determining the thermal effect efficacy in combination with chemoradiation, when the radiation-absorbed dose is kept clinically constant. In this research, we obtained TEF in terms of the clinical target volume (CTV), TEF(CTV), and actuarial analysis or survival probability *(SP),* TEF(SP), from equitations. (1) and (2):

$$TEF(CTV) = \frac{[\frac{V_2}{V_1}](CRT)\,for\ 60\ Gy\ radiation\ dose}{[\frac{V_2}{V_1}](CRHT)\,for\ the\ same\ dose} \quad (1)$$

$$TEF(SP) = \frac{SP\,for\ CRHT\ at\ month\ 18\ for\ 60\ Gy}{SP\,for\ CRT\ at\ the\ same\ and\ dose} \quad (2)$$

Where, $[\frac{V2}{V1}](CRHT)$ and $[\frac{V2}{V1}](CRT)$, stand for relative tumor volume changes at three and six months after treatment (V2), in association with tumor volume before any treatment (V1) in CRHT and CRT groups, respectively. TEF(SP) is the survival times ratio for equal survival fraction in both CRHT and CRT groups, respectively.

RESULTS

Patient’s demographic data is displayed in table 1. At first 40 patients were entered into the study, but two of them left the project because of their own personal reasons, consequently, 38 cases were prospectively studied finally with equal numbers in two groups that identified as CRT and CRHT groups. Age ranges from 27 to 73 years old (Mean= 50 years), and 27-65 years old (Mean= 50 years) for CRT and CRHT groups, respectively. There were 11(58%) males and 8

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(42%) females in CRT group, along with 8 (42%) males and 11 (58%) females in CRHT group. Tumors have been located in the different brain lobes, but they were within the frontal and parietal lobes in the majority of cases (table 1). Total resection was not performed for none of the cases, however, 53% of cases had a biopsy, and also 47% of cases had partial resection in both groups.

Hyperthermia was done two times per week according to protocol and typical MR imaging for CRHT and CRT patients are shown in figure 1. Typical images at three different time points show target volume changes in two groups.

Table 1. Demographic data for the patients in both groups of CRT and CRHT are shown.

Characteristic	RT+HT GROUP	RT GROUP
Gender (%) No	male (42%) 8 female (58%) 11	male (58%) 11 female (42%) 8
Range(median)	26-75 years(50)	27-73 years(50)
Tumor location (%) No.	Frontal (37%) 7 Temporal (37%) 7 Parietal (21%) 4 Other (5%) 1	Frontal (32%) 6 Temporal (42%) 8 Parietal (21%) 4 Other (5%) 1
KPS:	KPS (%) No	
KPS<60	(5%) 1	(11%) 2
KPS=60	(5%) 1	(5%) 1
KPS=80	(21%) 4	(26%) 5
KPS=90	(47%) 9	(42%) 8
KPS=100	(21%) 4	(16%) 3
Biopsy	(53%) 10	(53%) 10
Subtotal resection	(47%) 9	(47%) 9

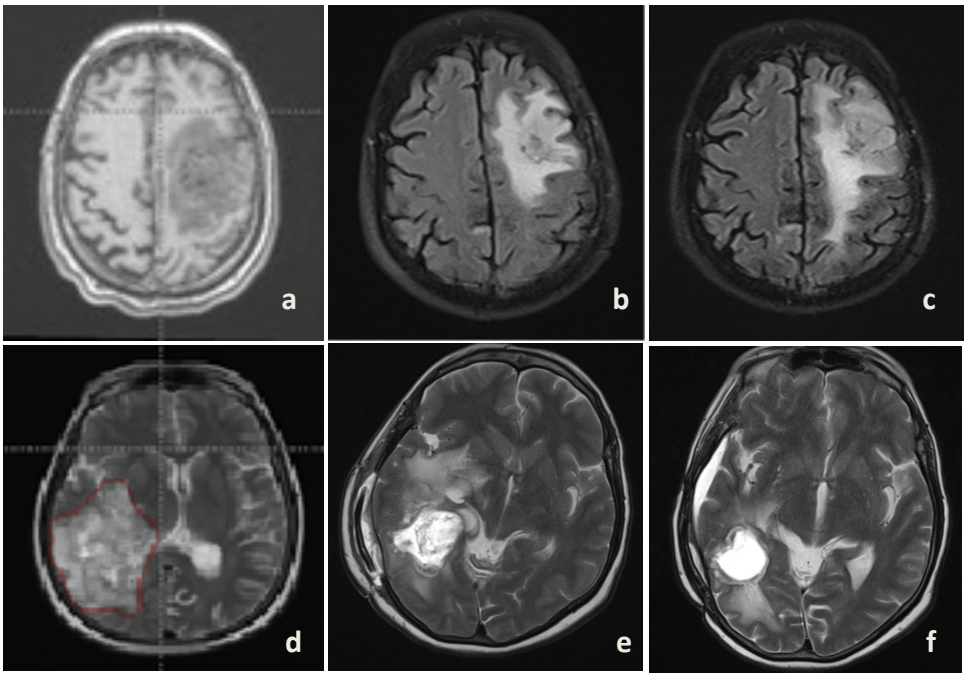

Figure 1. MR images show tumor volumes for two cases before and after treatments; **a, d)** before, **b, e)** three and **c, f)** six months after treatment in CRT and CRHT groups, respectively.

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According to this study results, volume changes in tumor were analyzed based on the imaging data. Tumor volumes means and standard deviations (Ms± SDs) are as 135.42±92.5 and 104.14±58.4 cm^3 before treatment in CRT and CRHT groups, respectively. The difference between them is not statistically significant (P= 0.2), which indicates the patients homogenous distribution in two groups from the target volume point of view. Ms± SDs of tumor volumes were 59.6±68.8, 113.9±137.63, 62.1±68.41 and 117.1±151.42 cm3 at three and six months after the treatments in CRHT and CRT groups, which is considered as statistically significant (P<0.05). Ratios of $\left[\frac{V2}{V1}\right](CRHT)$ are equal to 0.66 and 0.66 for clinical target volume (CTV) after three and six months, but ratios of $[\frac{V2}{V1}](CRT)$ after three and six months from treatment are equal to 1.02 and 1.12 for CTV, respectively. From equitation 1 the *TEF(CTV)* value is attained to be equal to 5.98 and 1.70 after three and six months treatments. The clinical results of both groups including survival times, clinical target volumes, and KPS data are displayed in table 2.

Table 2. Clinical findings in terms of survival time, tumor volume changes, and KPS are tabulated for both CRT and CRHT groups.

Group (No. of Patient)	Survival Time (months)	Tumor volume(cc)			KPS		
		Before treatment	3 months after treatment	6 months after treatment	Before treatment	After treatment	3 months after treatment
CRT (18)	14.57±4.5	135.42±92.48	137.63±113.93	151.42±117.10	84.73±12.18	84.21±13.46	78.94±19.40
CRHT (18)	15.47±4.61	104.14±58.44	68.08±59.64	68.41±62.14	86.31± 16.74	88.95±14.86	85.26± 16.45

Survival times (ST) of the patients were followed for 18 months after the thermo-chemoradiotherapy completing. Almost all of the patients survived after the follow up time. The means ± standard deviations of ST were 14.57±4.5 (median 16) and 15.47±4.6 (median 18) months from end of the treatment time for CRT and CRHT groups, respectively (tables 2). Statistically there is no significant difference between these two groups (P=0.55), however, temporal survival parameter is higher for hyperthermia patients quantitatively, which can be translated to hyperthermia positive effect that has not been fully manifested, due to the short follow up time.

Actuarial analysis (Kaplan-Meyer) was obtained in order to compare the both groups' survival probabilities (figure 2). Survival probability (SP) was obtained for 18 months after commencing the treatment for each patient. SP expresses the difference between two groups in term of overall time. SP is higher for CRHT group, but the difference is not significant for the proposed present study time (P=0.6). However, the SP for CRT and CRHT groups are 40 and 70%, respectively. According to equation 2, *TEF(SP)* was obtained for 18 months equal to 1.90.

Brain functional scoring by means of KPS is another patient dependent index for the treatment effects on the brain tissue quantifying. Means of KPS were obtained to be as 84.73, 84.21, and 79.84 for before, right after, and also three months after the CRT group treatment. KPS values for CRHT group were 86.31, 88.95, and 85.26 for similar time points. Statistically, there are no significant differences between KPS values before (P=0.6), immediately (P=0.3), and by passing three months (P=0.4) from the treatments. However, KPS values are larger for CRHT group in comparison with CRT group.

Complications were investigated during hyperthermia procedure, based on the patient questionnaire. We did not find any severe complication, and patients reported only mild headache, which there was no necessity for any additional medication. Although, some patients comply from treatment duration, which was continued for one hour; but all patients tolerated hyperthermia procedure well and without any directly associated side effects from hyperthermia.

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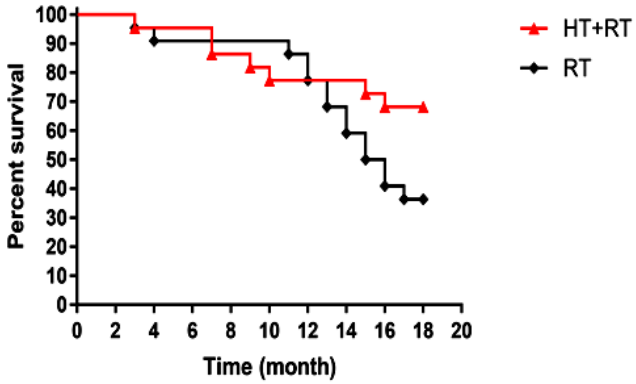

Figure 2. Kaplan- Meyer analysis was obtained for comparing the survival probability between CRT and CRHT groups.

DISCUSSION

This is a study for the hyperthermia clinical efficacy on the GBM patients' assessment in Iran. 38 GBM patients was divided in two groups of chemo-radiation and thermo-chemoradiation patients at the same time (prospectively) were the subject of this study, and we tried to obtain a thermal enhancement factor in terms of tumor volume changes and survival probability.

GBM is still the most frequent and invasive malignant brain disease, which presented in the central nervous system, and may happen in different brain lobes without any special locality. This malignancy may occur over the life span, however, mostly is happening between 45-75 years old, and there has also no preference for gender [7]. Prognosis is still poor despite of all advancements in radiotherapy techniques [8]. Glioma resistance to chemoradiation therapy partly may be from hypoxic area within the tumor. Hypoxic cells have great potential for infiltrating into the brain tissue and locally extending the tumor. Hyperthermia offers a technique in order to overcome hypoxia, which consequently may improve tumor local control [9, 10]. There are two reviews on the brain tumors hyperthermia clinical trials in which authors concluded hyperthermia as feasible, and as playing effective role in tumor response [11].

Sahinbas *et al.* [12] have accomplished a retrospective clinical study using the adjuvant oncothermia treatment in combination with chemoradiotherapy and Temozolomide (TMZ) for advanced brain glioma. That study findings indicated that median/mean survival times are equal to 19.8/31.7 months from the first diagnosis, and 6.7/10 months from the oncothermia initiation, respectively. Results also confirmed the onco-hyperthermia feasibility for advanced glioma patients. This study is in agreement with our study from the points of hyperthermia application and chemoradiation protocol for patient treatment, which revealed the survival benefit from TMZ chemo agent. Recent TMZ randomized clinical trial also indicated a significant survival improvement in TMZ group, in comparison with the that group without TMZ [13]. We studied patient's conditions for 18 months after starting the treatment in this research. During this period, there was observed no significant difference between these two groups SP, however, considerable *TEF(SP)* indicates about 90% better survival by passing 18 months. This phenomenon reveals a complex synergistic effect of hyperthermia in combination with the radiation and TMZ. Our study confirms the fact that more time is required for evaluating the thermal enhancement effect on the overall survival time, 18 months is not enough and we recommend time duration about 30 months and it can be due to increase in overall survival time of the GBM patients in thanks of chemoradiation therapy improvement.

Quantification of thermal effect in term of TEF or other definitions like thermal enhancement ratio (TER), and thermal risk ratio (TRR) are useful methods for the heat radiobiological effect estimating in clinic, in

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order to attain an iso-effective line for different radiation doses [14, 15]. Numbers of in vitro and *in -vivo* studies and clinical trials have revealed the hyperthermia higher response rate in combination with radiotherapy or chemotherapy for various kinds of malignancies [16]. Roizin-Towel *et al.* (1991) calculate thermal enhancement ratios for human and rodent cells for cells heated at 43 °c. They reported TER for GBM, which is equal to 2.5 for one-hour thermal treatment duration. They also reported that TER is varied from 1.1 to 2.7 for human cells at 43°C, and it also depends on the temperature [17] .

KPS is developed in order to evaluate the patient physical activity level or designing the necessary treatment. In this survey, we tried to investigate thermal effect on the KPS based on the patients' questionnaire. We found no significant improvement in CRHT group in comparison with CRT patients, and this attained result triggers the question that how much a subjective test like KPS can be considered as reliable for decision-making and treatment strategy planning. However, despite of the extensive use, a small number of systematic data confirm the existed KPS reliability or validity. Application of KPS has always been the subject of criticism, due to its subjective nature, variation in scoring between observers, and also highly dependency between scoring and acute self limited parameters [18].

It was stated that KPS popularity is in regard with its concision for patients categorizing with highly complicated clinical status, which it makes KPS appropriate for the patient condition evaluating by comparing it with the other observable parameters [19]. In the investigation done by Sneed *et al*, same range of the KPS values (60-90) were reported for patients underwent interstitial hyperthermia, and brachytherapy for recurrent malignant brain tumors [20]. However, in this research, no significant difference was reported for KPS between two groups, which can be due to same radiation treatment protocols for patients in both groups, and also the fact that hyperthermia did not induce a dramatic change into the patients.

Clinical target volume changes have been considerable in this study, and we could quantify thermal effect with *TEF (CTV)*, obtained to be as 1.54-1.70 depending on the time after treatment. In a research done by Sun J. *et al*. (2013) thirty-grade *III-IV* primary or recurrent G lioma patients (tumor diameter 3-7 cm) were treated in two groups of chemoradiation and chemoradiation plus hyperthermia [1]. A 13.56 MHz radiofrequency device was used for interstitial hyperthermia, and heat was applied for 1 hour. During three months after hyperthermia, CT or MRI examined patients every month. They reported tumor growth control or termination, and their outcomes confirmed the considerable changes of target volume in hyperthermia group. Researchers have indicated that residual tumor volume plays a significant role in the treatment prognosis and KPS. On the relatively large sample size, Bette *et al.* (*2018*) have shown that tumor size plays a significant role before and after the surgery on the pre- and post surgery KPS. Postoperative target volume was considered as an important prognostic parameter in a multivariate analysis. Although, they have concluded that surgery is the main prognostic factor for GBM, but maximum reductive excision is recommended even if total resection is not possible [21].

Hyperthermia would enhance the Tumoral chemo radiation effects because Tumoral mass has a non-homogenous and distorted architecture inherently with altered blood flow, which would lead to hypoxia and intracellular pH reduction. Cellular micro-environmental alterations are identified as the thermal sensitivity through heat deposition cause within the tumor. During hyperthermia intra-tumor, temperature may reach around 42.5 °C, which is adequate in order to maximize cell killing. From the clinical point of view, this type of cellular and Tumoral shifting can be translated to thermal enhancement factor. Thermal energy propagation in the tissue is affected by many pathophysiological parameters; some of them can be changed to improve hyperthermia response clinically like tumor perfusion, oxygenation, and extracellular pH [1].

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CONCLUSION

In this research, it has been tried to quantify the thermal enhancement effect in terms of changing clinical target volume, and Karnofsky performance status for GBM tumors. Although, there exist some limitations in the way of investigation, but TEF may reflect the magnitude of hyperthermia enhancement or efficacy for a given radiation dose, which can be useful for avoiding from the complication in normal tissue in chemo-radiotherapy. Clinical experiment with target therapy, Nano-medicine, and particle therapy novel combination are promising in order to improve therapeutic ratio for malignant glioma.

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Conflicts of interest*: *Declared none.

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