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ORIGINAL ARTICLE



Capacitive hyperthermia as an alternative to brachytherapy in DNA damages of human prostate cancer cell line (DU-145)

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ABSTRACT

Purpose: The aim of this study was the evaluation of induced DNA damages of human prostate cancer cells, DU-145, treated with a combination of radiofrequency capacitive hyperthermia (HT) and teletherapy (EBRT) compared to a combination of teletherapy with high-dose rate brachytherapy (BR).

Materials and methods: DU-145 cells were cultured as spheroids in 300 micron diameter. Then the following treatments were conducted: (a) EBRT at doses of either 2 Gy or 4 Gy of photon 15 MV, (b) HT for 0, 30, 60, and 90 minutes duration at 43 °C from a 13.56 MHz radiofrequency capacitive heating device (Celsius TCS), (c) BR with Ir-192 seed at doses of either 2 Gy or 5.5 Gy, (d) The mentioned HT followed by EBRT (HT + EBRT) and (e) EBRT followed by BR (EBRT + BR). Alkaline comet assay was performed to measure tail moment.

Results: The induced DNA damages of DU-145 cells treated by adding HT to EBRT compared with EBRT alone, showed a significant enhancement; 3.28 and 5.14 times respectively for 30 and 60 minutes HT. By plotting dose-response curves, we could find a range of doses, which create radiobiological iso-effect in HT + EBRT and EBRT + BR treatments.

Conclusions: This study suggests that about DNA damages of DU-145 cells, HT + EBRT could partly be considered as an alternative to EBRT + BR.

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teletherapy;
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1. Introduction

The treatment of prostate cancer by external radiation is frequently combined with other modalities to increase efficiency. The selection of these combinations has been notably based on experimental studies with cells in culture. These studies were designed to get insight to the mechanisms of interaction and to derive quantitative information on potential methods of enhancing effectiveness through assessing the cell damages.

As shown by the results of randomized trials, mild hyperthermia (HT) can be considered as a radio-sensitizer (Franckena et al. 2008). Mild hyperthermia as a cancer treatment method increases the temperature of tumor volume to a level between 42°C and 45°C. This range of temperature can hurt and kill cancer cells with low damage to normal tissues. According to researcher findings, heat in this temperature range has the potential to denature DNA repair enzymes, consequently prevents repairing sub-lethal damages of DNA. Therefore, in combination with radiotherapy, heat enhances cancerous cell damages (Hall and Giaccia 2006).

The electro-hyperthermia system Celsius Tumor Cell Solution (TCS) (Celsius42+ GmbH Company, Cologne, Germany), a radiofrequency capacitive hyperthermia system at 13.56 MHz frequency, creates a uniform electrical field between the application's electrodes. The patient's body as the dielectric material is placed between the electrodes. Through electromagnetic current and rotation of dipoles in tissue, heat is generated and consequently it damages the cells (Baker-Jarvis and Kim 2012).

From the other side, high-dose-rate brachytherapy (HDR) in the treatment of patients with high-risk prostate cancer as a boost followed by external beam radiotherapy (EBRT) shows satisfactory results of survival rates and disease control (Zaorsky et al. 2014; Spratt et al. 2017). However, some patients are not able to tolerate brachytherapy for medical or other reasons. For these patients, it is needed as an alternative form of treatment. Our study is also an attempt to this end. Here, we have used teletherapy, RF capacitive hyperthermia, and HDR brachytherapy treatments alone and in some combinations on DU-145 human prostate cancer cells in spheroid model. The

alkaline Comet assay was conducted to evaluate DNA damages following each treatment.

The aim of this study is to quantitatively compare RF capacitive hyperthermia combined with EBRT to biologically equivalent single-fraction HDR boosts in combination with EBRT on DU-145 spheroids.

2. Materials and methods

2.1. Cell line and spheroid culture

For this study, human prostate carcinoma cell line, DU-145 which grew in Roswell Park Memorial Institute (RPMI-1640; Gibco, New York, USA) was provided by the Pasteur Institute of Iran (Tehran, Iran). The DU-145 was supplemented with 10% heat-activated fetal bovine serum (FBS; Gibco, New York, USA), 100 U/ml of penicillin and 100 mg/ml of streptomycin (Biowest, Nuaille, France).

Based on the liquid overlay technique, cells were cultured for multicellular spheroid formation. A total of 5×10^5 cells was seeded in 100 mm petri dishes (Jet Biofil Co., Ltd., Guangzhou, China) coated with a thin layer of 1% agar (Sigma-Aldrich, St. Louis, MO, USA) along with 10 ml of RPMI-1640 supplemented with 10% FBS. The plates were incubated at 37 °C in a humidified atmosphere of 5% CO₂. Half the culture medium was exchanged with a fresh medium twice per week. As a result, spheroids grew exponentially with an apparent volume doubling time of 4.4 days. The spheroids, with a mean diameter of 300 µm, were treated with teletherapy, heat, brachytherapy, or some combinations of them.

2.2. Treatment procedures for cells

2.2.1. Teletherapy (EBRT)

The DU-145 cells, as spheroids in diameter of 300 µm, were transferred to a sterile T-12.5 flask (Jet Biofil Co., Ltd., Guangzhou, China) or a sterile blood tube (Greiner Bio-One GmbH, Kremsmünster, Austria). For all radiation treatments, we put the prepared samples in the center of a water phantom (dimensions: 30 × 30 × 15 cm), after which they were exposed to 15MV X-rays at multiple doses (0, 2, and 4 Gy). Following that, irradiation of the samples was performed using a linear accelerator (Siemens Primus, Erlangen, Germany). The sample that was not irradiated (0 Gy) was considered the control.

2.2.2. Brachytherapy (BR)

The sterile blood tube (Greiner Bio-One GmbH, Kremsmünster, Austria) that contained 300 µm spheroids were sealed with parafilm. For all radiation treatments at room temperature, we placed the prepared tubes at a specific distance from the center of the water phantom (dimensions: 20 × 20 × 20 cm), which was based on the treatment planning data. The tubes were exposed to gamma rays at doses of either 2 Gy or 5.5 Gy. We used an Ir-192 remote after loading brachy system, the *Flexitron* (Isodose Control BV, the Netherlands) for irradiation. The third sample did

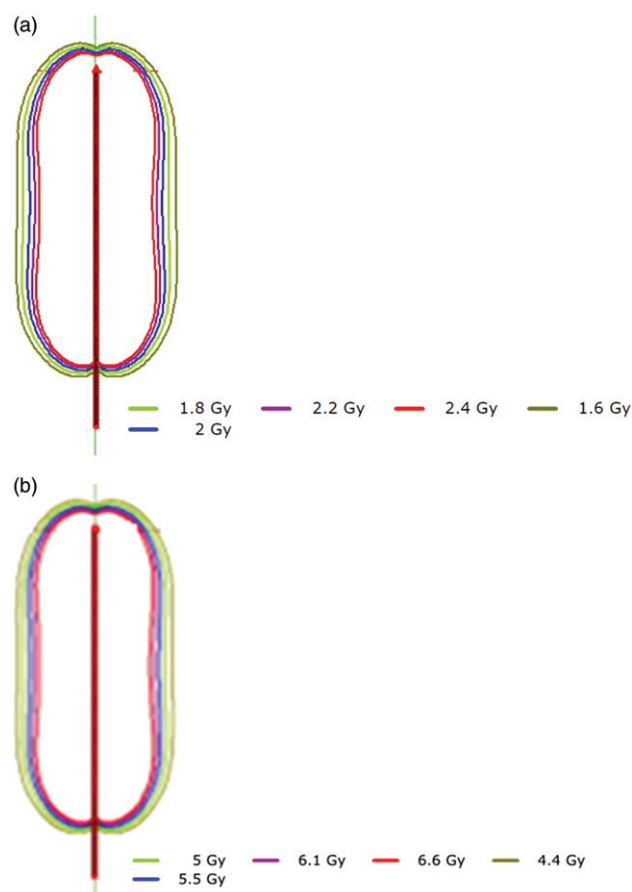


Figure 1. The radiation dose distribution of (a) 2 Gy, (b) 5.5 Gy for brachytherapy, calculated with the treatment planning computer at the reference points. The linear arrangement with a length of 40 mm is simulated by using an iridium-192 point source. Dose points are arranged at 12 mm depth from each source point. The average activity of the source was 2.5 Ci.

not irradiate (0 Gy) as the control. Figure 1 shows the dose of radiation distribution for brachytherapy, based on treatment planning data.

2.2.3. Hyperthermia (HT)

Hyperthermia treatments for 0, 30, 60, and 90 minutes at 43 °C were delivered by a radiofrequency capacitive hyperthermia system, Celsius TCS (Celsius42+, GmbH Company, Cologne, Germany) that operated at a frequency of 13.56 MHz. The size of each of the two electrodes was 25 cm in diameter.

A T-12.5 flask that contained the spheroids was covered by a dry towel placed between two electrodes of the capacitive hyperthermia system as the dielectric material. Hyperthermia was delivered in accordance with the protocol that was obtained in our previous work (Esfahani et al. 2017). It showed that the temperature inside the flask remained at 43 °C ± 0.1 for the entire duration of hyperthermia. Cells exposed to a temperature of 37 °C were considered as the control. We used Teflon-coated thermocouples to record the temperature in the center of the flask. The accuracy of the thermometer was ±0.05 °C.

2.2.4. Hyperthermia + teletherapy (HT + EBRT)

The procedure of HT applied before EBRT has been described in our last work (Esfahani et al. 2017; Mahdavi et al. 2017) and is briefly summarized here. A period of 0, 30, 60, or 90 minutes of HT was followed by external X-ray irradiation with 15 MV at 2 Gy or 4 Gy doses. The interval between the HT and radiation exposure was about 15 minutes.

2.2.5. Teletherapy + brachytherapy (EBRT + BR)

In the case of the combination of teletherapy and brachytherapy, cell samples in medium were poured into tubes to the volume of 4 ml and were transferred to the radiotherapy center. According to the protocol mentioned above, the samples were irradiated with external radiation of 15 MV photon doses at 2 Gy or 4 Gy. Then, the samples were irradiated in accordance with the brachytherapy protocol in the previous section (samples treated with dose mixtures of 2 Gy and 2 Gy, 4 Gy and 2 Gy, 2 Gy and 5.5 Gy, 4 Gy and 5.5 Gy, each pair belonging to teletherapy and brachytherapy doses, respectively).

2.3. Alkaline comet assay

Following each treatment, the alkaline comet assay was applied to evaluate the DNA damages, which this method was a modification of the method described by Singh et al. (Singh et al. 1988). Ordinary microscope slides were covered with agarose having 1% normal melting point. Around 1000 cells were resuspended in 100 μ L of 0.5% low-melting-point agarose. The mixture was then rapidly shed onto the first agarose layer. The slides were allowed to toughen, transferred to freshly prepared lysis buffer (2.5 M NaCl, 100 mM EDTA, 10 mM Tris-base with 1% Triton X-100, pH = 10), and then were incubated for 1 h at 4 °C. Following that, the slides were transferred to fresh denaturation buffer (300 mM NaOH, 1 mM EDTA, pH = 13) in a dark room. After 30 minutes, they were transferred to a horizontal gel electrophoresis tank filled with the same denaturation buffer. Electrophoresis was conducted for 30 minutes using a voltage of 24 V and a current of 300 mA. Following electrophoresis, to neutralize the excess alkali, the slides were washed in Tris buffer (0.4 M Tris-HCl, pH = 7.5). Finally, the slides were stained with 20 μ g/mL ethidium bromide. The individual cells or comets were photographed using a fluorescent microscope (Bell, INV-100-FL, Italy), and the photographs were analyzed by the Comet Score[®] software (TriTek, Corp Sumerduck, VA, USA). DNA damages were quantified as tail moment, the product of the amount of DNA (fluorescence distributions) in the tail and the distance between the middle of the head and end of the tail.

2.4. Dose-response curves and thermal enhancement ratio (TER)

In order to plot the dose-response curves based on the information about the DNA damages, the tail moment

values obtained from the experiments were intended as a response. These values were then determined versus dose on the chart. A sigmoid fitting was performed on the values.

A method of examining the radiosensitizing effect of HT is to compare the levels of dose achieved for radiation alone with a combination of HT and RT in the same response. The ratio of the two doses is defined as the thermal enhancement ratio (TER).

2.5. Statistical analysis

Each experiment was repeated three times. Data were displayed as mean $\pm$ standard error of mean and were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's test. A value of $p < .05$ was assumed statistically significant.

3. Results

3.1. Analysis of dose-response curves of HT + EBRT vs. EBRT

The mean comet tail moment values were measured from treatments (Figure 2). The data from the experimental series of hyperthermia treatments at 0, 30, 60, and 90 minutes are shown in Figure 3. A significant level of DNA damage was detected after 90 minutes of HT compared with control (p -value $< .001$). Figure 3 shows that tail moment is growing exponentially with heating time.

The dose-response curves for the irradiation of cells with and without heating are represented as a function of radiation dose in Figure 4. The thermal enhancement ratios are calculated and displayed in Figure 4. At the damage level of an average score of 0.25 (i.e., Iso-effect line B on Figure 4), TERs of 3.28 at 30 minutes HT group, and 5.14 for the 60 minutes HT group were obtained. It was not possible to calculate TER of 90 minutes HT group because the two graphs did not have any same effect. The radiosensitizing effect of HT was more prominent after the 60 minutes HT than 30 minutes HT. Linear changes in TER is visible in Figure 5. The TER of 0 minute HT + EBRT group, as control group, was assumed 1, due to non-significant enhancement in DNA damages compared with EBRT alone (p -value $< .05$), and so after that, the information about 0 minute HT was not used in drawing dose-response curves.

3.2. Assessment of dose-response curves of HT + EBRT vs. EBRT + BR

To get the radiobiological iso-effective dose, we compared dose-response curves plotted for EBRT + BR and HT + EBRT treatments. A horizontal line was drawn parallel to the dose axis to cross both the dose-response curves. The dose of intersection of the line with curves is called the iso-effective dose.

The response of the combination of teletherapy at a dose of 2 Gy with brachytherapy at doses of 0, 2, 5.5 Gy (EBRT (2Gy) + BR) and HT + EBRT against radiation dose are

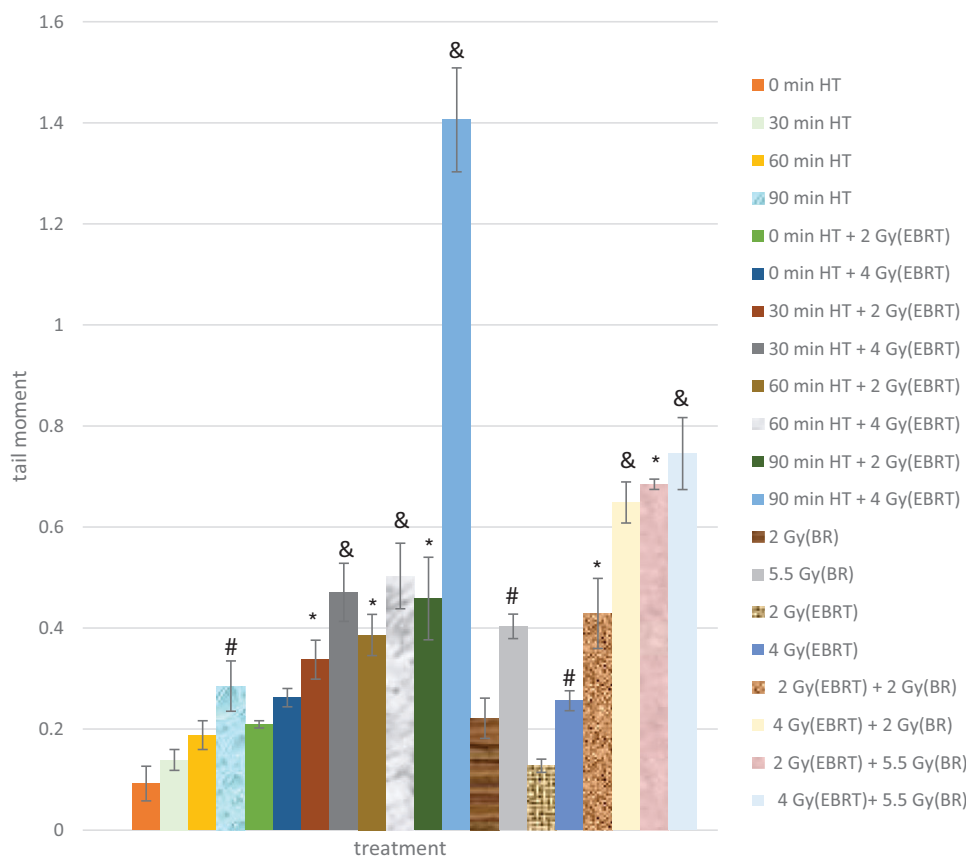


Figure 2. The amount of tail moments of DU 145 cells treated with hyperthermia (HT) (0, 30, 60, 90 minutes at 43 °C), teletherapy (EBRT) (2, 4 Gy), brachytherapy (BR) (2, 5.5 Gy), HT + EBRT, and EBRT + BR. Tail moments, an evaluation of DNA strand breaks were determined by the alkaline comet assay, are normalized to control group values. Data are presented as mean $\pm$ standard error of mean. #: $p < .05$ significant difference compared to control. *: $p < .05$ as compared to EBRT(2 Gy). &: $p < .05$ as compared to EBRT(4 Gy). (one-way ANOVA, followed by Tukey post-test).

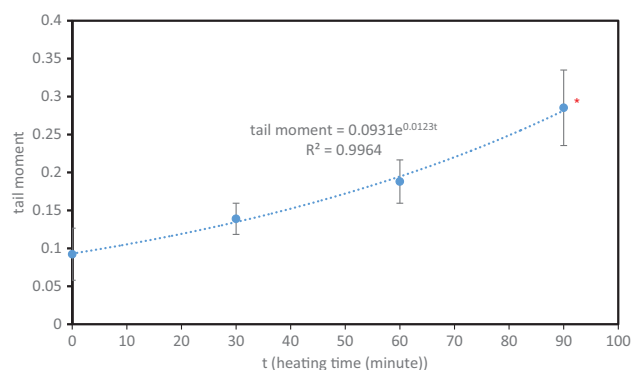


Figure 3. Changes in the value of tail moment after the treatment of hyperthermia alone with increasing duration of heating. The experiments were repeated three times. (Data are presented as mean $\pm$ standard error of mean.) (*: significant difference compared to the control group (p -value $< .001$)).

plotted in Figure 6. Similarly, response of the combination of teletherapy at a dose of 4 Gy with brachytherapy at doses of 0, 2, 5.5 Gy (EBRT (4 Gy) + BR) and HT + EBRT versus radiation dose also shown in Figure 7. Radiation dose quantities separation for teletherapy and brachytherapy was done to determine the dose of each treatment with the same effect.

In Figures 6 and 7, by drawing iso-response lines G and F, a range of injuries were identified those have identical tail moment for two curves.

In Figure 6(a), in response that the G line passes through, the iso-dose for HT (30 min)+EBRT and EBRT (2 Gy)+BR were 4 Gy and 4.24 Gy, respectively. Of this 4.24 Gy, 2 Gy is related to teletherapy and 2.24 Gy is related to brachytherapy. This meant the amount of comet tail moment value (0.47 ± 0.05) measured after 30 minutes of hyperthermia combined with teletherapy at 4 Gy is the same as those receiving 2 Gy of teletherapy combined with 2.24 Gy of gamma irradiation of brachytherapy.

This description can also be used in all parts of the chart for the rest of the treatments at Figures 6 and 7. Dose quantities for each treatment, related to iso-response lines G and F, are given in Table 1. In these regimens, the radiation dose of teletherapy and brachytherapy creating the same injury has been displayed.

4. Discussion

The main purpose of applying radiation in cancer treatment is to damage DNA of cancer cells. DNA integrity is necessary for successful functioning of the cell in terms of genetic information so that alterations in this molecule may interfere with normal proliferation and leading to cell death (Baskar et al. 2012).

Studies have consistently shown that applying hyperthermia in combination with radiation resulted in a remarkable

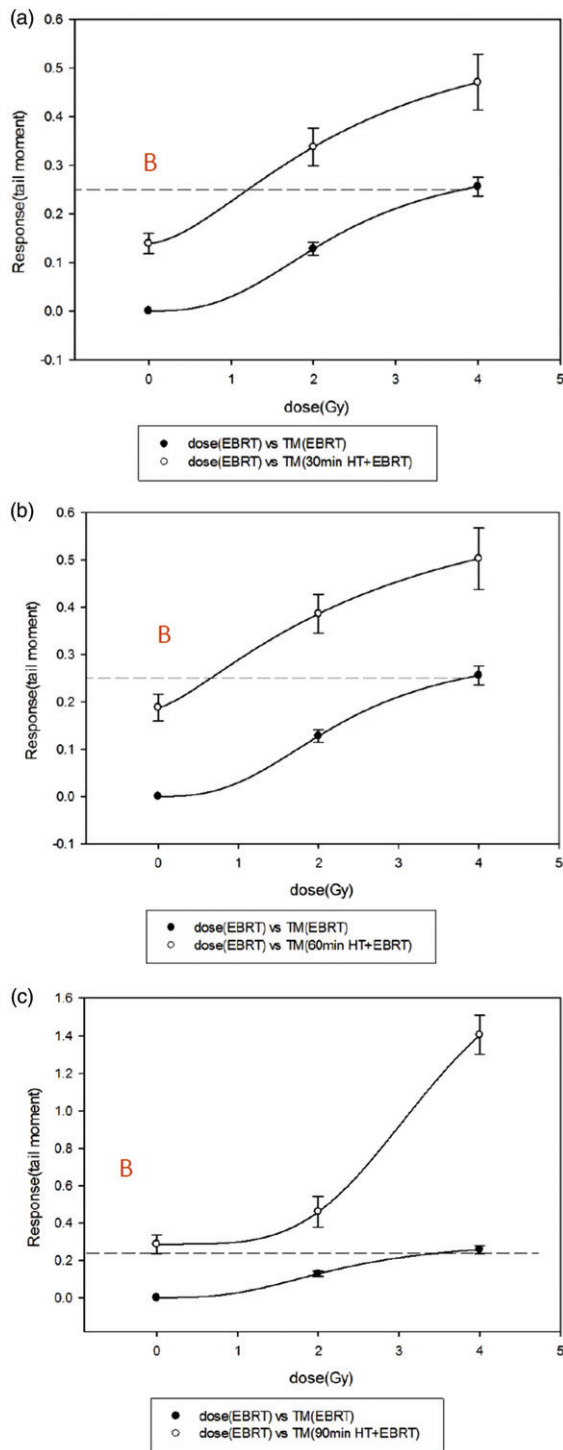


Figure 4. Dose-response curves of HT + EBRT vs. EBRT alone to calculate thermal enhancement ratio (TER), for different heating times at 43°C: (a) 30 minutes, (b) 60 minutes, and (c) 90 minutes. Curves were fitted to data as described in section 2.4. The plotted points are average values from three repeated experiments. Vertical bars are standard errors of mean.

thermal radiosensitization, which is attributed to the reduced repair of radiation-induced DNA lesions (Bergs et al. 2013).

The alkaline comet assay detects DNA strand breaks (SB) and is useful for evaluating damages to the DNA. Here, after each treatment, the alkaline comet assay was performed to obtain the amount of tail moment. Tail moment was used as an index of DNA damage, which represents a measure of

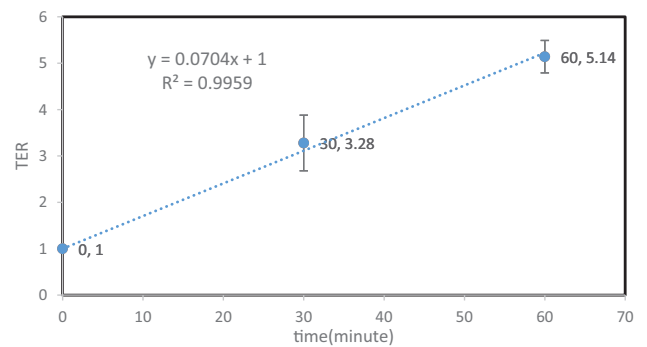


Figure 5. At a tail moment level of 0.25, thermal enhancement ratio (TER) was calculated (obtained from Figure 4). TER values increased with an increase in the duration of heating. Data are presented as mean $\pm$ standard error of mean. (Written numbers on the graph represent the amount of heating time and TER, respectively).

the length of the comet tail and the proportion of DNA to migrate into the tail (Collins et al. 2008).

This experiment was designed to compare DNA damages of HT + EBRT with EBRT + BR. Here, human prostate cancer cell line DU-145 was cultured as 300 micron spheroids by liquid overlay technique that has been used extensively to form spheroids from the DU-145 cell line (Enmon et al. 2002; O'Connor and Venczel 2005). Four heat treatments were applied: 0, 30, 60, or 90 minutes at a temperature of 43.0°C; radiation treatments exposed by X-ray from teletherapy system with energy of 15 MV and gamma ray by HDR Ir-192 seed with 380 KeV energy. The treatments were applied singly or in combination of heat and teletherapy or teletherapy and brachytherapy.

In treatments where only heat was applied, we observed that tail moment grew exponentially with heating time (Figure 3).

In our previous studies, exposure of DU-145 cells, the thermal effects of 13.56 MHz radio waves from a celsius-capacitive hyperthermia system, resulted in some significant cytotoxic and genotoxic effects; also, the effects increased with an addition of radiation (Esfahani et al. 2017; Mahdavi et al. 2017).

In this study, a dose-response relationship was detected after radiation treatment alone and HT + EBRT. The addition of hyperthermia to radiation resulted in the enhancement of the response. On the other hand, a longer heating time resulted in a larger TER; a 90 minutes HT treatment caused the most significant increase in the radiation DNA damages, which is in good agreement with previous findings (Horsman and Overgaard 2002). We found TER changes linearly as a function of heating time. Researches have shown that the amount of TER depends on the type of cell, cell cycle phase, thermal tolerance, temperature, heating time, order of the heat and radiation, and the time interval between the application of heat and radiation (Overgaard 1980).

In the present study, damages detected after brachytherapy were more severe than teletherapy. This phenomenon can be attributed to the difference in the linear energy transfer (LET) of the two radiation treatments. Lower photon energies have higher LET. This is imputable to the energy

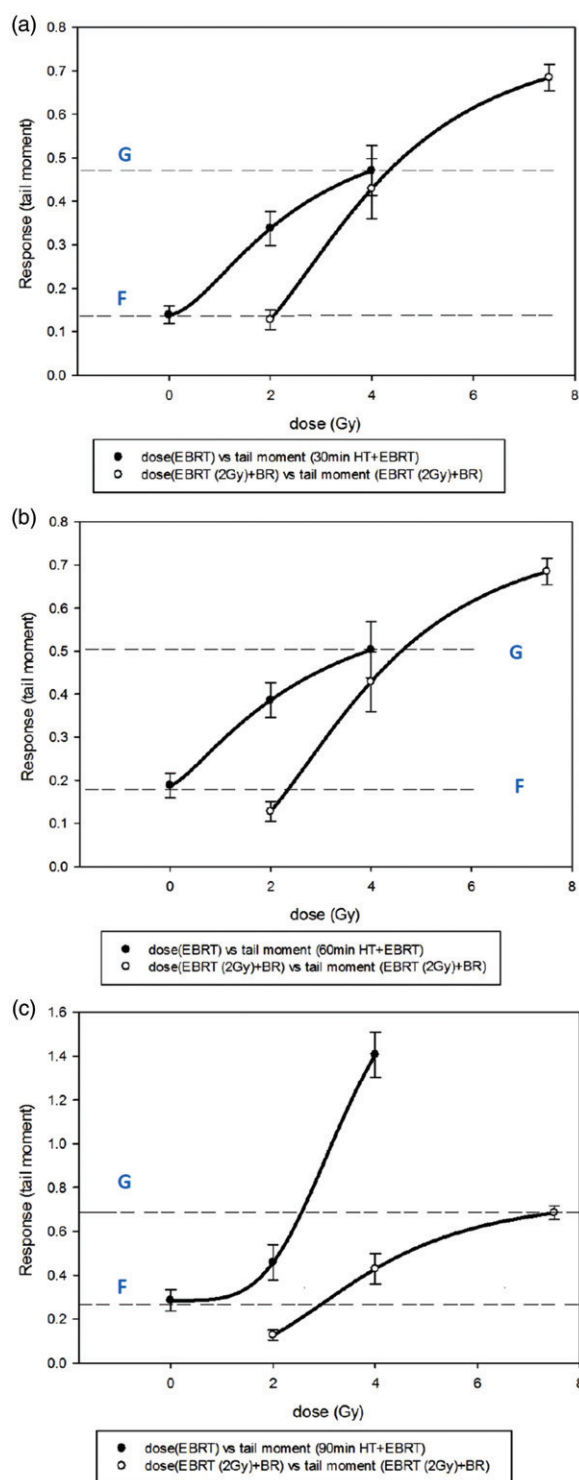


Figure 6. Dose-response curves for HT + EBRT (closed circles) and EBRT (2 Gy) + BR (open circles), for different heating time: (a) 30 minutes, (b) 60 minutes, and (c) 90 minutes. (Data are presented as mean $\pm$ standard error of mean).

deposition pattern along the secondary-electron track, which becomes more intense on the shorter distance on track-end (Matsuya et al. 2014).

Few studies have been conducted about the replacement of a conventional cancer treatment modality by hyperthermia (Franken et al. 2013; Datta et al. 2016). In some studies, which had the effects of the combination of brachytherapy

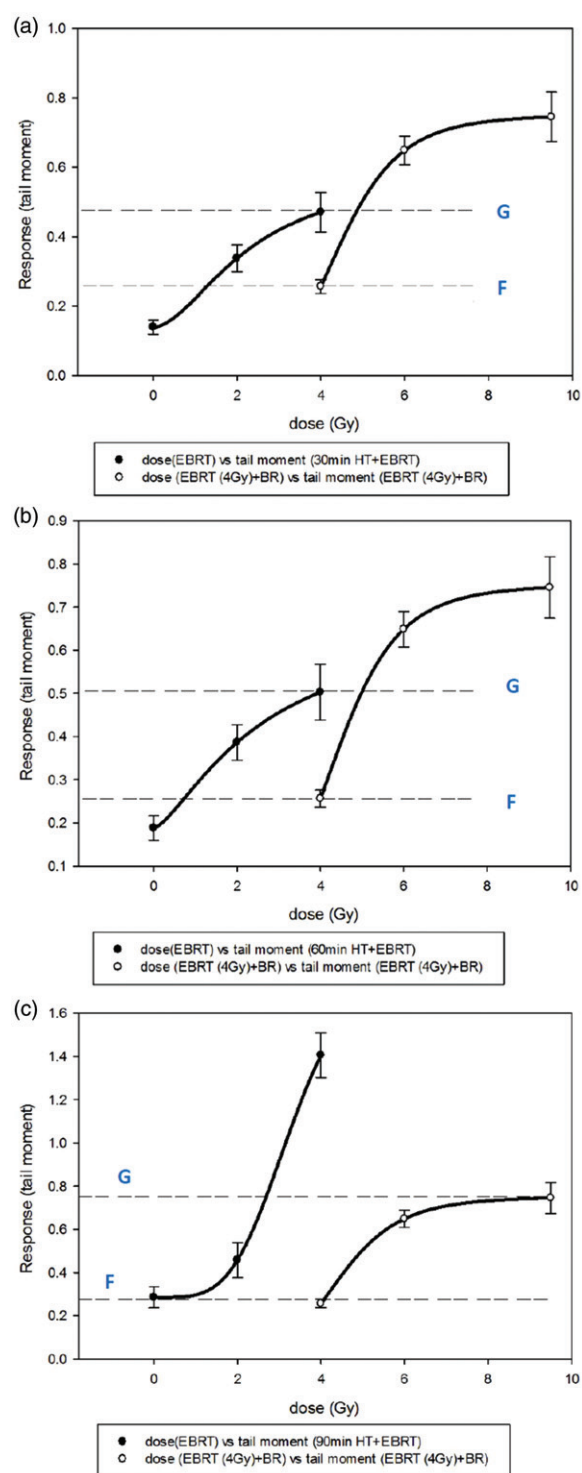


Figure 7. Dose-response curves for HT + EBRT (closed circles) and EBRT (4 Gy) + BR (open circles) versus radiation dose, for different heating time: (a) 30 minutes, (b) 60 minutes, and (c) 90 minutes. (Data are presented as mean $\pm$ standard error of mean).

and hyperthermia measured, heat was able to replace the dose of brachytherapy and to some extent can create its effects (Kaver et al. 1991; Kurosaki et al. 2001; Kudzia et al. 2015; Kukiellka et al. 2016).

Our research aimed to find a specific regimen of hyperthermia that in combination with teletherapy can cause similar DNA damages of brachytherapy on DU-145 cancer cells. In order to achieve this goal, the sigmoid fitting (R-

Table 1. Some regimens of the combination of hyperthermia with teletherapy (HT + EBRT) were obtained in this study, which are capable of being replaced by combining teletherapy with brachytherapy (EBRT + BR).

Treatment	Iso-effect line	Iso-dose from HT + EBRT curve (Gy)	Iso-dose from EBRT + BR curve (Gy)	
			Dose of EBRT	Dose of BR
HT(30 min)+ EBRT & EBRT(2 Gy)+BR	F	0	2	0
	G	4	2	2.24
HT(30 min)+ EBRT & EBRT(4 Gy)+BR	F	1.49	4	0
	G	4	4	0.78
HT(60 min)+ EBRT & EBRT(2 Gy)+BR	F	0	2	0.33
	G	4	2	2.77
HT(60 min)+ EBRT & EBRT(4 Gy)+BR	F	0.8	4	0
	G	4	4	1
HT(90 min)+ EBRT & EBRT(2 Gy)+BR	F	0	2	1
	G	2.61	2	5.5
HT(90 min)+ EBRT & EBRT(2 Gy)+BR	F	0	4	0.1
	G	2.77	4	5.5

The portion of teletherapy and brachytherapy radiation dose has been brought in front of each regimen (data from Figures 5 and 6).

square ≈ 1) was done on tail moment data to plot dose-response curves from the EBRT + BR and HT + EBRT treatments. Here, a horizontal line was drawn parallel to the dose axis as two dose-response curve hits. We read the intersection of this line with diagrams for the dose that creates a similar radiobiological effect. Finally, the radiobiological equivalent dose prescription was gained.

In the zone between G and F line, the same response can be obtained from HT + EBRT and EBRT + BR dose-response curves (Figures 6 and 7). Hence, we could find the regimens of hyperthermia which, in combination with teletherapy, produce similar DNA damages to EBRT + BR (Table 1). In fact, the same radiobiological effect was obtained.

According to dose-response curves of HT + EBRT and EBRT + BR, in those hyperthermia at 30 and 60 minutes is combined with teletherapy (Figure 6(a,b) and 7(a,b)), we observed that at low doses, the distance between the two curves HT + EBRT and EBRT + BR is large; but with increasing doses, the distance of the graphs is reduced. However, at HT (90 min)+EBRT curve (Figures 6(c) and 7(c)) at low doses, the distance between the two curves HT + EBRT and EBRT + BR is low and the gap between the two curves increases with increasing dose. Based on our findings, it can be concluded that at low doses of radiation, hyperthermia with durations of 30 and 60 minutes can be a good alternative to radiation. But in the case of hyperthermia with a duration of 90 minutes, high doses of radiation can be replaced with hyperthermia.

5. Conclusion

It was found that some regimens of hyperthermia in combination with teletherapy has the potential to produce similar DNA damages on prostate cancer cells to EBRT + BR. Substitution of brachytherapy with hyperthermia for prostate cancer treatment needs more investigation in terms of thermal dose and fractionation and may be at this stage, it is better to say that hyperthermia can enhance the radiation effect of EBRT and in some instances, it may create the effect of brachytherapy doses. So we could create the same radiobiological effect also not undesirable effects of brachytherapy.

Brachytherapy plays a key role in the treatment of many cancers. However, some patients cannot tolerate brachytherapy. For these patients, hyperthermia added to teletherapy might be offered as an alternative treatment, which requires more research.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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