Original paper

Impact of a 1.5 T magnetic field on DNA damage in MRI-guided HDR brachytherapy

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ABSTRACT

Purpose: Some studies have suggested that the presence of a static magnetic field (SMF) during irradiation alters biological damage. Since MRI-guided radiotherapy is becoming increasingly common, we constructed a DNA-based detector to assess the effect of a 1.5 T SMF on DNA damage during high dose rate (HDR) brachytherapy irradiation.

Methods: Block phantoms containing a small cavity for the placement of plasmid DNA (pBR322) samples were 3-D printed with biocompatible tissue equivalent material. The phantom was CT scanned and an HDR brachytherapy treatment plan was designed to deliver 20 Gy and 30 Gy doses to the DNA samples in the presence and absence of a 1.5 T SMF. Relative yields of single- and double-strand breaks (SSBs and DSBs, respectively) were computed from gel electrophoresis images of the DNA band intensities and averaged over sample sizes ranging from 12 to 30. Radiation dose was also measured in the presence and absence of the 1.5 T SMF using GafChromic™ EBT3 film placed in the coronal, sagittal, and axial planes.

Results: The average yield of DNA with SSBs and DSBs in the presence and absence of the SMF showed no statistically significant differences (all $p \geq 0.17$). Differences in the net optical densities of the EBT3 films for each plane were within experimental uncertainty, suggesting no dose difference in the presence and absence of the SMF.

Conclusions: HDR irradiation in the presence of the 1.5 T SMF did not alter dose deposition to the DNA cavity nor change SSB and DSB DNA damage.

1. Introduction

Due to the superior soft-tissue image quality that magnetic resonance imaging (MRI) provides compared to other image-guided radiotherapy (IGRT) modalities, recent developments in IGRT for cancer treatment have led to the development of commercial systems that integrate MRI with radiotherapy delivery. This in-room magnetic resonance image-guided radiotherapy (MR-IGRT) has been implemented in both external beam radiotherapy systems (e.g., Elekta Unity MR-Linac® [1] and ViewRay's MRIdian® MR-Cobalt) and brachytherapy [2–5] treatment modalities.

MR-image guidance in brachytherapy has been used in both low dose rate and high dose rate (HDR) modalities; however, due to practical and patient care advantages, HDR brachytherapy has become increasingly common in the United States [6]. MR-guided HDR brachytherapy (MRgHDRb) has been mainly applied for prostate and

gynecologic cancers [4]. As prostate cancer is the leading cancer type with the second highest number of fatalities in men, and gynecologic cancers are a leading form of new cancer cases and deaths in women [7], MRgHDRb has an important role in improving treatment outcomes. Furthermore, MRgHDRb is likely to become an image-guided technology of choice for identifying tumor regions of concern and providing treatment verification with the overall goal of enhancing cure rates and minimizing normal tissue complication [5,8,9]. MRI has also demonstrated significant potential to identify prostate cancer sub-volumes that present an increased risk of recurrence allowing for the possibility of dose escalation to these regions [4]. In its application to gynecologic cancers, MRgHDRb allows for an individually tailored brachytherapy boost to the residual tumor volume after external beam radiotherapy for high-risk cervical cancer, offering significant improvement in clinical outcome [10,11].

Although MR-IGRT provides obvious clinical benefits for

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radiotherapy cancer treatment, some studies have suggested that for the same absorbed dose, changes in microscopic distributions of energy deposition due to the Lorentz force of the SMF [12] and/or potential changes in radiochemical transport [13] may alter radiobiological damage to the extent that its effect may have clinical relevance. A recent review article by Mohajer et al. on this topic summarized 29 experimental studies of the biological effects of the presence of an SMF before, during, or after irradiation for different endpoints and biological systems. Fifteen of them showed some altered biological effect [14]. However, none of these 15 studies satisfied all of the radiotherapy delivery conditions, i.e., typical radiotherapy beam types and energies, and an SMF ≥ 0.35 T during irradiation. Furthermore, only one of the 29 studies, Wang et al. [15], satisfied all of these conditions. Wang et al.'s study investigated clonogenic cell survival using human head and neck and lung cancer cells lines (H460, H1299, HN5, UMSCC47) irradiated with a 6 megavoltage (MV) x-ray beam in the presence of a 1.5 T SMF [15]. However, Mohajer et al. noted that Wang et al.'s study failed to reproduce well-established differences in survival in response to dose fractionation in the absence of an SMF, which casts doubt upon its ability to detect small differences caused by the SMF [14]. In another more recent *in vitro* clonogenic cell survival study, Yudhistiara et al. [16] applied a 1.0 T SMF during irradiation of TK6 human lymphoblastoid cells with a 6 MV x-ray beam, and they also found no decrease in cell survival in the presence of a clinically pertinent x-ray energy and SMF. However, a conclusion by Yudhistiara et al. was that ongoing research on the interaction of the SMF during radiotherapy is warranted [16].

In this study, we have taken the following three novel approaches to studying the potential combined effect of an SMF during irradiation: 1) We considered the effect in the context of the lower HDR Ir-192 brachytherapy x-ray energy ($E = 380\text{keV}$), as the possibility of increased DNA damage due to the Lorentz mechanism is expected to be more significant in MRgHDRb than at MeV Linac energies [12]; 2) As DNA is the critical target for reproductive cell death from radiation [17], we constructed and characterized a DNA-based detector to investigate the matter at the more fundamental level of induced DNA damage; 3) To distinguish any observed increase in DNA damage due to altered radiobiological effects in the presence of an SMF versus possible changes in macrodosimetry that can occur with an SMF, we measured relative dose changes in the presence and absence of the SMF using radiochromic film. In the context of MRgHDRb, it is not clear from previous studies whether the presence of a 1.5 T SMF during irradiation would undermine the goal of MRgHDRb, which is to provide superior delineation of the tumor target and normal tissues during treatment to ensure that the intended treatment is delivered with minimal adverse effects. This study is the first to experimentally determine if the presence of a strong SMF during MRgHDRb may undermine this goal by increasing DNA damage.

2. Methods and Materials:

2.1. Phantom design

We designed three phantoms for the DNA and film irradiation measurements using the computer-aided design software Tinkercad® (Autodesk, Inc.). The phantoms were 3D printed using a stereolithography 3D printer (Viper SI) and a biocompatible plastic (Accura® ClearVue™ Plastic Material) with a density of 1.17 g/cm^3 , both from 3D Systems, Inc.

The phantom used for the DNA measurements was assembled from three individual 3D printed block components (Fig. 1(a)). The mid-block component in Fig. 1(a) was 3D-printed with a $16\text{ }\mu\text{l}$ cuboid cavity at the center to hold the DNA sample (Fig. 1(b)), and six copies of this mid-block were made to perform the DNA measurements for the following groups: (0 Gy, 0 T), (0 Gy, 1.5 T), (20 Gy, 0 T), (20 Gy, 1.5 T),

(30 Gy, 0 T), and (30 Gy, 1.5 T). All of the blocks had 3.0 mm diameter holes at both ends for the insertion plastic threaded rods and end bolts to hold the blocks together, and 2.5 mm diameter holes on both sides of the cavity for the insertion of the HDR transfer tube (Fig. 1).

The two phantoms used for the radiochromic film measurements were the same dimensions as the DNA cavity phantom shown in Fig. 1(a), except that the block shapes and sizes were redesigned to exclude the DNA cavity block and instead sandwich the film strips in such a way that they passed through the midpoint coordinates of where the DNA cavity would be located. Hence, we designed the phantoms to measure the mean doses in the coronal, sagittal, and axial planes.

2.2. Phantom simulation and treatment plan

We acquired a CT scan of the assembled phantom containing the DNA cavity block and used an HDR treatment planning system (Oncentra® Brachy, Elekta) to construct two radiation treatment plans to deliver doses of 20 Gy and 30 Gy to the plasmid DNA samples placed in the phantom cavities. The doses were delivered with an Ir-192 HDR brachytherapy unit (microSelectron® Digital, Elekta) using nine source-dwell positions on both the left and right sides of the DNA cavity to achieve a uniform dose ($\pm 3\%$) over the cavity (Fig. 2). At the time of dose delivery, the Ir-192 source activity was 6.86 Ci and the average dose rate at the DNA sample position was approximately 5.78 Gy/min .

2.3. Static Magnetic Field (SMF)

A bipolar electromagnet (SES Instruments Pvt. Ltd., EMU-75) and a Constant Current Power Supply (SES Instruments Pvt. Ltd., DPS-175) were used to produce a 1.5 T SMF. The two magnetic poles tapered down to a diameter of 2.5 cm at their ends. The magnetic field strength could be adjusted by altering the current and separation of the poles, and a current and pole separation of approximately 4 A and 9 mm, respectively, was used to produce a uniform static 1.5 T magnetic field in the space between the two magnetic poles where the DNA cavity was centered (Fig. 3). The maximum $\sim 9\text{ mm}$ pole separation restricted our phantoms to a width of 8 mm. An MG-4D Handheld Hall Effect Gaussmeter (Walker LDJ Scientific, Inc.) was used to verify a uniform magnetic field over the pole ends. The Gaussmeter was also used to set and monitor the magnetic field strength before and after the irradiation of each sample, to verify that it remained constant over consecutive sample readings.

All irradiations in the absence and presence of the SMF were performed with the DNA and film phantoms placed between the poles of the bipolar electromagnet to ensure the same experimental conditions and thereby control for any possible alterations in the radiation field due to the presence the electromagnet (e.g., x-ray scatter from the poles of the magnet).

2.4. Film measurements and analysis

Since the average range of electrons set into motion from an Ir-192 HDR source is $< 0.5\text{ mm}$, we did not expect meaningful changes in macrodosimetry patterns due to the magnetic field's influence on electron track structure. However, as the DNA sample dimensions are on the millimeter scale, to ensure that mean dose did not change in the region of the DNA cavity we irradiated Gafchromic™ EBT3 film (Ashland, USA) strips in the coronal, sagittal, and axial planes intersecting the point at which the DNA samples were placed in the magnetic field (Fig. 4).

Each coronal, sagittal, axial film was irradiated to a dose of 5 Gy and the measurements were performed in triplicate both in the presence and absence of the 1.5 T SMF, yielding a total of twelve film dose measurements. The irradiated films were scanned 48 h after exposure using an ArtixScan 1800f scanner and ScanWizard™ Pro scanner controller program (Microtek International, Inc.). Three unexposed films of size

Fig. 1. (a) Assembled phantom containing the DNA cavity in the mid-block. The total height, length, and width of the phantom was $126 \times 100 \times 8 \text{ mm}^3$. (b) Top and side view schematics of the mid-block.

$3 \times 3 \text{ cm}^2$ were also scanned. The rectangular selection tool in ImageJ [18] was used to measure the mean transmitted light intensities in the coronal, sagittal, and axial films over the regions of interest (ROIs) consisting of the DNA cavity position in the irradiated films (Fig. 4) and the central $1 \times 1 \text{ cm}^2$ region of the unexposed films. The mean net optical densities of the three film planes were computed using the following equation:

$$\text{netOD} = \log_{10} \left(\frac{\bar{I}_0}{\bar{I}} \right), \quad (1)$$

where $\bar{I}_0$ and $\bar{I}$ are the mean transmitted light intensities of the ROIs for the unexposed and irradiated films, respectively, averaged over the

Fig. 3. Top and side view schematics of the block phantom placed within the poles of the bipolar magnet showing the position of the DNA cavity centered within the uniform magnetic field B .

Fig. 2. Treatment plan applied to the block phantom showing the isodose lines covering the DNA sample in the cavity within $\pm 3\%$ in the coronal, sagittal, and axial planes.

Fig. 4. Left: Schematic of the Gafchromic™ EBT3 film planes intersecting the DNA cavity centered at the origin. Right: Representative EBT3 film images that were irradiated in the three planes. The white dashed line shapes show the regions of interest (ROIs) of the same dimension and at the same position as the DNA cavity. The net optical densities were computed for these ROIs.

triplicate films for each plane. Their associated standard deviations (SDs) were also computed. Differences in the mean optical densities over the ROIs between the films irradiated in the presence and absence of the SMF were compared.

2.5. Agarose gel electrophoresis

The pBR322 plasmid DNA (Thermo Fisher Scientific, Inc.) used in this study had an initial concentration of 0.5 $\mu\text{g}/\mu\text{l}$ in 1 $\times$ TE storage buffer (10 mM Tris–HCl, pH 8.0, 1 mM EDTA). The DNA can exist in supercoiled (S), open circular (C), and linear (L) conformations, and it was supplied with approximately 90% in S form. The three possible pBR322 conformations are all the same length, 4361 base pairs (bp), and radiation-induced SSBs and DSBs cause the S conformation to transform to the C or L conformation, respectively. Hence, these three possible conformations form the basis for quantifying DNA strand breaks using agarose gel electrophoresis (AGE) [19,20]. That is, given a known initial concentration of S, C, and L DNA, the final concentration of the three conformations can be assessed by staining an irradiated sample of the inherently negatively charged DNA and measuring the relative mobility of the three conformations through an agarose gel in the presence of an applied electric field. In this way, AGE produces three quantifiable bands representing the relative concentrations of the three DNA conformations (Fig. 5).

Prior to irradiation, the DNA sample was initially diluted with potassium phosphate (PP) to 18 ng/ μl , and 12 μl were pipetted into each phantom cavity for all the cases tested. Post-irradiation, at least 10 μl of the sample was retrieved from each cavity, and PP was used to dilute the samples further to a DNA concentration of 6 ng/ μl . Next, 10 μl of TE buffer and 10 μl of loading dye were added to the diluted samples to form the solution used in the AGE runs.

To perform AGE, four 0.9% agarose gel slabs were prepared with 25 lanes each and two gels at a time were placed in the gel tank of the ENDURO™ Gel XL electrophoresis system (Labnet International, Inc.). They were topped with 1 $\times$ TAE buffer (40 mM Tris, 20 mM acetic acid, 1 mM EDTA). Each gel lane was seeded with 2.5 μl of the solution

Fig. 5. A representative agarose gel electrophoresis image showing the intensities of the open circular (C), linear (L), and supercoiled (S) DNA conformation bands for the different radiation doses and in the presence and absence of the 1.5 T static magnetic field.

containing 9 ng of DNA. The samples were run at 80 V and 100 mA for 80 min. Next, the gels were post-stained with SYBR® Green I Nucleic Acid Gel Stain (Thermo Fisher Scientific, Inc.), and placed on an UltraBright LED Transilluminator (MaestroGen, Inc.) with a SMART-DOC™ imaging enclosure (Accuris Instruments) to visualize the DNA bands in the absence of ambient light. The iPhone X's 12-megapixel camera (Apple, Inc.) was used to acquire images of the gel bands in jpeg format. A calibration gel containing DNA band signals averaged over 12 runs for a range of DNA concentrations (i.e., 0.04, 0.2, 0.4, 2, 2.4, 2.8, 3.2, 3.6 ng/ μl) was done to ensure that the imaging system response to the DNA band signals was linear over the relevant range of signals observed in the irradiated samples.

2.6. Analysis of gel bands

Images of the gel bands were analyzed using GelAnalyzer 2010a AGE image analysis freeware (<http://www.gelanalyzer.com/index.html>). GelAnalyzer 2010a allows the user to select a rectangular region of interest around the DNA bands of each lane and produces an averaged profile plot of the bands, from which the user can select the background signal to exclude when quantifying the area under the profile (i.e., band intensities). Upon obtaining the band intensities for a given lane corresponding to one of the experimental groups, the relative yield of each DNA conformation was computed as the S, C, or L band intensity divided by the sum of the three band intensities in the lane. The average and standard deviation of these DNA conformation yields for each experimental group was calculated and used to compare the groups.

2.7. Characterization of DNA-based detector response

A robust mathematical model by McMahon and Currell [21] was used to characterize the DNA-based dosimeter response by computing the rate of SSBs (β_S) and DSBs (β_D) per Gy from the S, C, and L yields at all the measured doses. In this model, ionizing events, which have some probability of causing SSBs or DSBs, are taken to occur randomly and increase with absorbed dose (D). The model also assumes some probability that multiple SSBs occurring within a sufficiently close distance (~ 10 bp) can form DSBs with probability ρ , which is the ratio of the distance between two SSBs that can result in a DSB and the length of the DNA used [21]. Hence, in this study $\rho = 10/4361$. The method uses nonlinear regression to simultaneously fit analytically derived dose–response curves (Eqs. (2)–(4)) to observed yields of the S, C, and L DNA conformations. That is,

$$S = S_0 e^{-(\beta_S + \beta_D)D} \quad (2)$$

$$C = e^{-\beta_D D} (C_0 e^{-\frac{1}{2}\beta_S^2 \rho D^2} + S_0 (e^{-\frac{1}{2}\beta_S^2 \rho D^2} - e^{-\beta_S D})) \quad (3)$$

$$L = 1 - (C_0 + S_0) e^{-(\beta_D D + \frac{1}{2}\beta_S^2 \rho D^2)} \quad (4)$$

where S_0 and C_0 are the initial zero dose yields of S and C DNA forms, respectively, found from the control group (0 Gy, 0 T). Eqs. (2)–(4) were fitted simultaneously by using the Excel Evolutionary nonlinear solver to find β_S and β_D that gives the chi-squared minimization of the following arithmetic mean: [21]

$$\chi^2 = \frac{1}{3}((\chi_S^2 + \chi_C^2) + (\chi_S^2 + \chi_L^2) + (\chi_C^2 + \chi_L^2)) = \frac{2}{3}(\chi_S^2 + \chi_C^2 + \chi_L^2) \quad (5)$$

where

$$\chi_x^2 = \sum_{i=0}^{N-1} \left(\frac{y_i - y(D_i; \beta_S, \beta_D)}{\sigma_i} \right)^2, \quad (6)$$

y_i is an average measured yield at dose D_i with associated uncertainty σ_i , taken to be the standard deviation, x is S, C, or L, and $y(D_i; \beta_S, \beta_D)$ is the value predicted by the model function that is being fitted to the measurement.

2.8. Statistical analysis

Data normality was tested and confirmed with the Shapiro-Wilk test using the Real Statistics Resource Pack (<http://www.real-statistics.com/>) add-in for Excel (Microsoft Corp.). For each radiation dose data group Welch's two-tailed t -test (Analysis ToolPak add-in for Excel) was applied, to compare the means of the DNA strand break yields in the presence and absence of the 1.5 T SMF. The null hypothesis, i.e., no difference between the means of the two data sets (with and without the SMF) at a given dose, was tested with statistical significance given by $p < 0.05$.

3. Results:

3.1. Film measurements

Table 1 shows that the differences in the means of the net optical densities ($OD_2 - OD_1$) for the ROIs of the coronal, sagittal, and axial films in the presence and absence of the SMF have no consistent trend and are comparable to the associated uncertainties (δ). This implies that the presence of the SMF did not change the macrodosimetry relative to radiation alone.

3.2. Characterization of DNA-based detector response

Application of the McMahon and Currell model [21] to our measured data for the Ir-192 HDR brachytherapy source yielded SSB and DSB rates of $\beta_S = 6.78 \times 10^{-2}/\text{Gy}$ and $\beta_D = 4.17 \times 10^{-3}/\text{Gy}$, respectively, in the absence of an SMF and $\beta_S = 6.88 \times 10^{-2}/\text{Gy}$ and $\beta_D = 4.46 \times 10^{-3}/\text{Gy}$, respectively, in the presence of the 1.5 T SMF. Plots of these solutions to Eqs. (2)–(4) give us the DNA conformation yields as a function of dose and show that the dose curves for the 0.0 T and 1.5 T SMF overlap well within the experimental uncertainty (Fig. 6). These plots of the modelled solutions to the data also show that the S conformation of the DNA decreases exponentially with the formation of DNA strand breaks, and the initial formation of SSBs (C-yields) are an order of magnitude greater than DSBs (L-yields) at doses less than 12 Gy. In addition, the DSBs continuously rise in a linear

Fig. 6. Interpolation/extrapolation of the relative yields of DNA conformations from the McMahon and Currell model [21] showing the DNA conformation yields as a function of radiation dose.

fashion as a function of dose matching the rate of decline in SSBs as the supercoiled DNA conformation approaches zero at doses greater than 50 Gy.

3.3. DNA yields

Fig. 6 shows that the differences in the mean percentage relative yields of the S, C, and L DNA for each radiation dose group in the presence and absence of the SMF ranged from 0.1% to 2.2%, which lie within the standard deviations of the measurements. Furthermore, statistical analysis (Welch's t -test) of the mean relative yields in the presence and absence of the SMF confirmed no statistically significant difference in the SSBs (C yields) and DSBs (L yields) at 0 Gy, 20 Gy, and 30 Gy (see Table 2). Hence, the presence of a 1.5 T SMF alone or in addition to ionizing radiation did not appear to change the incidence SSB/DSB DNA damage compared to no SMF (Fig. 7).

4. Discussion

In this study, we have constructed and characterized the dose response of a DNA-based detector to investigate the effects of DNA damage due to the presence of a clinically relevant SMF during irradiation for the treatment of cancer (Fig. 6). Although a few studies had examined this issue experimentally in the context of megavoltage external beam radiotherapy with clonogenic cell survival as the endpoint [14–16], to our knowledge no one has experimentally investigated the possibility of an SMF effect in the keV energy range where it has been suggested the magnetic field might have a stronger influence at lower energies [12]. In addition, this study was the first to use DNA strand break damage as the endpoint to examine the SMF effect. Although this endpoint represents a more basic model than clonogenic cell survival, it lends itself naturally to the investigation of the radiobiological impact of a strong SMF during irradiation because DNA is considered the main critical target for reproductive cell death from radiation [17], and damage to DNA can be quantified with greater ease and precision ($\pm 3\%$) than clonogenic cell survival.

The following mechanisms have been proposed to explain why an

Table 1

The netOD_1 and netOD_2 are the means of the net optical densities of the EBT3 films in the presence and absence of the SMF, respectively, and SD_1 and SD_2 are the associated standard deviations computed using $SD = (I/(I_0 \cdot \ln 10)) \cdot \sqrt{\delta I/I + \delta I_0/I_0}$. The difference in the net mean optical density is given in the last column by $\text{netOD}_{2-1} = (\text{netOD}_2 - \text{netOD}_1)$, where $\delta = \sqrt{(SD_1)^2 + (SD_2)^2}$ is the associated uncertainty.

Film Plane	0.0T ($\text{netOD}_1 \pm SD_1$) $\times 10^{-1}$	1.5T ($\text{netOD}_2 \pm SD_2$) $\times 10^{-1}$	($\text{netOD}_{2-1} \pm \delta$) $\times 10^{-1}$
Coronal	1.43 $\pm$ 0.05	1.49 $\pm$ 0.04	0.06 $\pm$ 0.06
Sagittal	1.69 $\pm$ 0.06	1.60 $\pm$ 0.05	− 0.09 $\pm$ 0.08
Axial	1.59 $\pm$ 0.07	1.51 $\pm$ 0.06	− 0.09 $\pm$ 0.09

Table 2

At each radiation dose, the difference between the mean yields $\bar{Y}_2$ and $\bar{Y}_1$ of DNA computed from n samples exposed to 1.5T and 0T, respectively, and the p-value for Welch's t -test between the data sets are given.

	(0 Gy, 0 T, $n = 30$) Vs. (0 Gy, 1.5 T, $n = 12$)	(20 Gy, 0 T, $n = 13$) Vs. (20 Gy, 1.5 T, $n = 13$)	(30 Gy, 0 T, $n = 13$) Vs. (30 Gy, 1.5 T, $n = 17$)
<i>Open Circular</i>			
$\bar{Y}_2 - \bar{Y}_1$	0.009	0.017	−0.001
Welch's t -test			
Linear	$p = 0.18$	$p = 0.17$	$p = 0.90$
$\bar{Y}_2 - \bar{Y}_1$	−0.001	0.005	0.009
Welch's t -test	$p = 0.63$	$p = 0.20$	$p = 0.29$
<i>Supercoiled</i>			
$\bar{Y}_2 - \bar{Y}_1$	−0.007	−0.022	−0.008
Welch's t -test	$p = 0.36$	$p = 0.05$	$p = 0.27$

Fig. 7. The means (numbers above the bars) and sample standard deviations (error bars) of the percent relative yields of the S, C, and L DNA conformations for the different radiation doses in the presence and absence of the magnetic field.

altered biological effect may occur at certain ranges of combined radiation energies and magnetic field strengths: (1) the Lorentz force causes the nanoscale energy deposition patterns (or track structures) of the charged particles depositing radiation dose to become more densely ionizing [12,22] causing an increase in DNA DSBs and clustered damage [23,24], and resulting in more cellular damage for a given absorbed dose; (2) a change in the radiochemistry (e.g., the number of free radicals produced that escape the recombination reaction increases in the presence of a sufficiently strong SMF) [25,26].

Monte Carlo (MC) methods have been used to investigate possible changes in microdosimetry track structure resulting from the presence of a static magnetic field [13,27,28]. One group had investigated the Lorentz force mechanism of the magnetic field effect using MC-simulation to simulate DNA damage due to different types of ionizing radiation at relevant energies in the presence of magnetic field strengths of up to 14 T [13,28]. They concluded that any radiobiological effect observed in the presence of a magnetic field is likely not due to a change in charged particle track structure. Although these MC studies added valuable insights, an assumption of their simulation had been that the SMF does not alter the interaction cross-sections. These studies also did not model possible increases in DNA damage due to potential changes in radiochemistry (e.g., an increase in the quantity or lifetime of reactive oxygen species) in the presence of a strong magnetic field. In addition, a recent MC study on the sensitivity of model parameters has shown that changes in the energy threshold for direct DNA damage, the timescale of the chemical stage, and the probability of DNA damage due to reactions between the hydroxyl radicals and DNA can all cause significant changes (26%, 51%, and 71%, respectively) to computed DSB yields [29].

Although isolating the Lorentz force effect from possible altered radiochemistry was beyond the scope of this study, our experimental

findings infer two possibilities: 1) The conclusion from the MC studies [13,27,28] regarding the lack of enhanced DNA damage due to the Lorentz force mechanism is correct, implying that the assumption of an unaltered interaction cross-section is reasonable for a 1.5 T SMF. Moreover, from this possibility and the lack of altered DNA damage seen in our study we would infer that the influence of the SMF on radiochemical effects is minimal at best; 2) The Lorentz force mechanism is causing a change to the nanodosimetry, but the combined Lorentz force and altered radiochemistry effects work to cancel each other out, resulting in no change to DNA damage. Future studies at the fundamental level are needed to probe which of the above two possibilities is correct.

Another novelty of this study is that we used Gafchromic™ EBT3 film to ensure that any change to DNA damage seen with the SMF was not simply due to a change in dose because of altered electron transport into the DNA cavity, but rather a change in the linear energy transfer of secondary electrons and/or a biochemical change. As expected, results of the film measurements demonstrated that irradiation with the Ir-192 HDR source in the presence of the 1.5 T SMF does not change the microdosimetry properties of the source, implying that any differences that could have been seen in the presence versus absence of the SMF during irradiation would have been due to nanodosimetric changes caused by the Lorentz force and/or altered radiobiology.

5. Conclusion

The presence of a 1.5 T SMF in the absence of ionizing radiation (0 Gy) and during HDR brachytherapy source irradiation at 20 Gy and 30 Gy did not alter the microdosimetry to the DNA-based detector, nor did it alter SSB and DSB DNA damage. This study shows that the clinically relevant SMF strength used in MRI-guided HDR brachytherapy does not appear to alter DNA damage.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmp.2020.06.020>.

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