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REVIEW ARTICLE

Biological effects of static magnetic field exposure in the context of MR-guided radiotherapy

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ABSTRACT

The clinical introduction of MRI-guided radiotherapy has prompted consideration of the potential impact of the static magnetic field on biological responses to radiation. This review provides an introduction to the mechanisms of biological interaction of radiation and magnetic fields individually, in addition to a description of the magnetic field effects on megavoltage photon beams at the macroscale, microscale and nanoscale arising from the Lorentz force on secondary charged particles. A relatively small number of scientific studies have measured the impact of combined static magnetic fields and ionising radiation on biological endpoints of relevance to radiotherapy. Approximately, half of these investigations found that static magnetic fields in combination with ionising radiation produced a significantly different outcome compared with ionising radiation alone. strength static magnetic fields appear to modestly influence the radiation response via a mechanism distinct from modification to the dose distribution. This review intends to serve as a reference for future biological studies, such that understanding of static magnetic field plus ionising radiation synergism may be improved, and if necessary, accounted for in MRI-guided radiotherapy treatment planning.

INTRODUCTION

Image-guided radiotherapy (IGRT) aims to minimise uncertainties in treatment delivery through the use of medical imaging at frequent intervals throughout the patient's treatment course. One recent IGRT development has been the integration of MRI with a radiotherapy treatment machine.¹

The first patient treatments were recently completed with the Elekta Atlantic MR-Linac,² a device consisting of a 1.5 T Philips MRI system and a 7 MV accelerator. The ViewRay MRIdian system (0.35 T MRI and three Co-60 sources) has been used to treat patients since 2014³ and a 6 MV linac version of the MRIdian system was recently introduced.⁴ Two 6 MV MR-Linac systems currently being developed in Australia⁵ and Canada⁶ feature 1 T and 0.5 T MRI systems respectively.

Starting from current understanding of the individual effects of ionising radiation and strong magnetic field, this review is evaluating the evidence concerning a range of biological effects of the combination of static magnetic field (SMF) and ionising radiation (IR) for magnetic field strengths and radiation qualities of relevance to MR-guided radiotherapy (MRgRT). This will enable an assessment of the likelihood of altered radiobiological response in patients treated by MRgRT and will help designing studies to investigate possible synergetic effects.

RADIOBIOLOGY: TARGETED AND NON-TARGETED EFFECTS

Biological injury resultant from IR exposure has long been understood to be primarily mediated by lethal or misrepaired deoxyribonucleic acid (DNA) damage. Such DNA damage may lead to loss of a cell's proliferative capacity, a result seized upon for the treatment of cancer with radiation.

Megavoltage photon beams produce energetic free electrons via interaction with matter, which in turn produce a large number of ionisations along their tracks. In the classical paradigm, IR is capable of damaging the DNA molecule by two processes; (1) *direct action*, whereby energy is transferred from an incident ionising particle to the DNA molecule, resulting in a DNA lesion and (2) *indirect action* which involves the interaction of an IR-generated reactive species (e.g. $\cdot\text{OH}$ produced via radiolysis of water) with DNA, resulting in a DNA lesion. Indirect action accounts for 65% of DNA lesions induced by low linear energy transfer (LET) radiation sources such as MV photon beams.⁷

DNA lesions induced by IR can take several forms, such as single DNA strand breaks (SSBs), double DNA strand breaks (DSBs) and a variety of base modifications which may lead to SSBs and DSBs. The formation of two or more lesions within 10 to 20 base pairs located either tandemly or on opposing strands is termed clustered damage, of which DSB is an example. For low LET radiation, approximately 30% of the deposited energy yields clustered damage.⁸ Two DSB repair mechanisms exist; homologous recombination and non-homologous end joining. The mechanism underlying the choice of repair pathway is not fully understood, but is thought to relate to chromatin complexity in the region of the DSB.⁹

Whilst DNA is considered the predominant site of IR-induced lethality, IR has also been shown to induce biologically significant changes to cellular lipids and proteins.¹⁰

Non-targeted effects comprise IR-mediated pathways that lead to biological responses in cells other than those irradiated. Growing evidence of such effects *in vitro*¹¹ and *in vivo*¹² has challenged the dogma that IR may only elicit a cellular response via energy deposition within its nucleus. Increased frequency of phenomena such as chromosomal changes, carcinogenesis and cell death have been observed in both the direct descendants of irradiated cells (radiation-induced genomic instability) and cells that have communicated with irradiated cells (radiation-induced bystander effects).^{13,14}

MAGNETOBIOLOGY

Three well-established, experimentally verified classes of physical interaction of SMF with biological systems exist^{15,16}:

- (1) *Electrodynamic interactions*. Electric potentials and current induced by interaction of magnetic dipoles with SMF. The Lorentz force, exerted perpendicularly to the direction of the magnetic field $\mathbf{B}$ and the velocity of moving charges $\mathbf{v}$ is associated with an electric field $\mathbf{E} = \mathbf{v} \times \mathbf{B}$. The separation of charged particles (e.g. electrolytes in the blood) due to the electric field results in the establishment of electrical potentials.
- (2) *Magnetomechanical effects*. Torque and forces which may give rise to translational motion exerted on materials due to SMF, associated with mechanical stress and strain. An object with magnetic susceptibility χ placed in a magnetic field gradient experiences a force proportional to χ and the gradient of B^2 . The force is towards the field maximum for paramagnetic (positive χ) objects and in the opposite

direction for diamagnetic (negative χ) objects. Materials with anisotropic susceptibility experience SMF-induced torque towards the orientation which represents a minimum energy state. Additionally, the retarding force on blood flow arising from the influence of the Lorentz force on moving electrolytes may be classified as a magnetomechanical effect.

- (3) *Effects on electron spin states of reaction intermediates*. Alteration to rates of chemical reactions involving free radical intermediates via the influence of SMF on the electron spin states of the radicals. SMF impacts the rate of intersystem crossing between the singlet and triplet spin states via mechanisms originating from the splitting of Zeeman energy levels.¹⁷

The World Health Organization reviewed the evidence concerning biological effects of 0 to 14 T SMF, collecting *in vitro*, animal, laboratory human and epidemiological studies.¹⁵

A wide range of biological end points have been studied in mammalian cells, including; cell orientation and morphology, cell metabolic activity, cell growth, cell cycle distribution, cell membrane physiology, gene expression and genotoxicity. The influence of strong SMF (greater than 1 T) on the orientation of cells *in vitro* via magnetomechanical effects is well-documented,¹⁵ whereas evidence for the SMF dependence of other end points *in vitro* is less clear. For almost all of the end points studied, SMF has been shown to either have a positive, negative or null effect suggesting a strong dependency upon the combination of the exposure conditions (field strength, time) and biological system under investigation.

Many animals are susceptible to the geomagnetic field and utilise this ability for their navigation.¹⁸ In the case of migratory birds, two distinct magnetoreceptive mechanisms appear to take place; an SMF dependent radical-pair mechanism involving a photo-active protein in the eye¹⁹ and magnetite-based receptors in the beak susceptible to SMF torque.²⁰ Some *in vivo* studies have demonstrated that strong SMF (0.1 to 1 T) generates measurable flow potentials around the heart and major blood vessels of animals and humans, however the physiological impacts of such potentials are unclear.¹⁵ Based on those current *in vivo* and *in vitro* evidences, the World Health Organization concluded that other hypotheses regarding SMF effects in animals and humans, such as stimulated bone growth, endocrine responses, blood pressure, microcirculation, haematopoiesis, carcinogenesis, reproduction and development were not well supported by reproducible evidence.¹⁵

MAGNETIC FIELD EFFECTS ON MV PHOTON BEAM DOSE DISTRIBUTIONS

The recent interest in MRgRT has motivated study of the impact of the strong SMF ($B=0.35$ to 1.5 T) on the radiation dose distribution to account accordingly for effects during radiotherapy treatment planning.^{21–29} However, interest in this question pre-dates MRI, as researchers as early as 1950 considered whether magnetic fields could be exploited to confine radiotherapy treatment fields, minimising healthy tissue damage.^{30–39}

A particle with charge q travelling within a magnetic field $\mathbf{B}$ with velocity $\mathbf{v}$ will experience the magnetic Lorentz force $\mathbf{F}$ perpendicular to both the $\mathbf{v}$ and $\mathbf{B}$:

$$\mathbf{F} = q\mathbf{v} \times \mathbf{B} \quad (1)$$

For radiotherapy MV photon beams, this has implications for trajectories of secondary charged particles generated in the patient via photoelectric effect, Compton scattering and pair production. In vacuum, an uniform magnetic flux density of magnitude B causes particles to spiral with gyration radius:

$$r_g = \frac{mv_{\perp}}{|q|B} \quad (2)$$

with m the particle mass, $v_{\perp}$ its velocity perpendicular to the magnetic field and $|q|$ the charge magnitude. However, in media, although the particle experiences the Lorentz force, the regularity of its helical track structure is broken by discrete scattering processes. Energy losses via scattering events leads to an overall reduction in r_g , yielding a spiralling particle track. As electrons exit the patient into air, their mean free path becomes long compared to r_g , allowing the helical path to be traversed with minimal interaction. This path returns electrons to the exit surface of the patient (electron return effect, ERE), leading to a significantly enhanced dose in the region.

Regarding macrodosimetry, Geant4⁴⁰ Monte Carlo (MC) simulation of 1×1 and 5×5 cm² fields of an Elekta SLi 20 modelled 6 MV photon spectrum incident upon a water phantom in transverse $B = 1.5$ T produced asymmetric penumbra and a similar central axis depth dose profile to $B = 0$ T, shifted by 5 mm towards the entrance surface under the magnetic field.²¹ Although the field dimensions (50% isodose) were unaffected, the entire field was shifted by approximately 0.7 mm in the direction perpendicular to the SMF and the beam axis.²¹ Macrodosimetric effects are generally increased at higher magnetic field strengths.²⁴

In the presence of heterogeneities, the impact of the magnetic field is significant. The ERE was demonstrated by MC simulation of a 6 MV linac beam incident upon heterogeneous phantoms comprised of water and air regions with transverse $B = 1.5$ T.²² An increased exit dose of order 40% was observed. In addition to the exit surface, ERE also has profound implications for air cavities and low density tissues such as lung.²⁵ The problem of ERE exit dose enhancement was largely mitigated by using opposing beams²³ and clinically acceptable MR-Linac treatment plans are attainable with intensity-modulated radiotherapy inverse planning for dose optimisation.^{26,41}

At the microdosimetric level, it is pertinent to consider whether SMF significantly influences radiation quality and hence relative biological effectiveness. Kirkby et al⁴² used the MC code PENELOPE to study the energy deposition spectra within a microscopic target (10 μ m diameter water sphere) in the presence of SMF up to 1000 T. Mono-energetic electron beams (0.01, 0.025, 0.1 and 1 MeV) and secondary electron spectra obtained on the central axis, 1.5 to 3.5 cm deep in water for a simulated Varian 6 MV photon source were studied. The track-averaged

lineal energy and dose-averaged lineal energy were virtually identical at $B = 1.5$ T (both parallel and transverse orientations) to $B = 0$ T. The change in dose-averaged lineal energy relative to the $B = 0$ T case only exceeded 2% at 70 T (transverse orientation).

It is generally accepted that cell lethality is linked to the complexity of DNA damage. The MC code Geant4-DNA was used to study the impact of transverse SMF (up to 14 T) on electron track structure in order to determine the probability distribution of the formation of nanometric ionisation clusters of a given size.⁴³ The number of ionisation events per incident primary particle within two nanoscale water targets representing a DNA segment and nucleosome were recorded for monoenergetic electron pencil beams (200 eV–10 keV). The mean ionisation cluster size and the probability of formation of at least two ionisations per incident particle inside the DNA segment deviated minimally from the $B = 0$ T case for all field strengths and primary electron energies studied. Application of the $B = 1.5$ T field led to a 2% increase in the probability of at least two ionisations occurring within the DNA segment by 5 keV electrons. However, for a polyenergetic electron spectrum, no significant difference in clustered damage formation would be expected with application of a magnetic field.⁴³ A follow-up study found that SMF (up to 10 T) had no significant influence on double strand formation probability for Geant4-DNA simulated electron (200 eV–10 keV), proton (300 keV–30 MeV) and α particle (1 MeV–9 MeV) track structures.⁴⁴ Only direct damage to DNA was considered in these works; further simulation incorporating radiochemical transport, including the effect of magnetic fields on such processes is necessary.⁴³ Moreover, there is limited evidence to support the general assumption in MC studies that SMF does not alter interaction cross-sections, only particle transport. However, Szymanowski et al reported that the partial alignment of water molecules caused by 1.5 T SMF had negligible impact on differential cross-sections for electron scattering relative to no field.⁴⁵

BIOLOGICAL EFFECTS OF COMBINED IONISING RADIATION AND STRONG STATIC MAGNETIC FIELD EXPOSURE

While there have been a wealth of studies examining the biological effects of ionising radiation and SMF individually, relatively few have investigated the effects of both agents combined (Table 1).

The earliest study retrieved reported the impact of strong SMF on the mortality of *Drosophila melanogaster* eggs irradiated with 150 kVp X-rays.⁴⁶ SMF alone did not significantly influence the ratio of hatched eggs, however when SMF was applied during irradiation the egg mortality rate was increased in 30 out of 39 experiments. SMF during irradiation was associated with a mean increase in mortality rate of $16.8 \pm 3.4\%$. Subsequent studies of *D. melanogaster* concluded that SMF during irradiation did not affect production of sex-linked recessive lethals in mature spermatozoa^{48,49} nor mean life span for flies treated with strong SMF for 30 min post-irradiation.⁴⁷

Barnothy⁵⁰ investigated the effect of SMF pre-treatment (14 days) on the mortality of whole body irradiated mice. A mortality

Table 1. Summary of investigations into the biological effects of combined static magnetic fields and ionising radiation

Reference	Biological specimen	Static magnetic field	Ionising radiation	End point studied	Effect of SMF on IR response
Forssberg ⁴⁶	<i>Drosophila melanogaster</i>	0.6 T during IR	150 kVp X-rays, 1.65 Gy	Egg mortality rate	Increased mortality
Close and Beischer ⁴⁷	<i>Drosophila melanogaster</i>	1 T post-IR (30 mins)	X-rays, 36.9 Gy	Sex-linked recessive lethals	None
				Life span	None
Mittler ⁴⁸	<i>Drosophila melanogaster</i>	1.1 T during IR	200 kVp X-rays, 33 Gy	Sex-linked recessive lethals	None
Kale and Baum ⁴⁹	<i>Drosophila melanogaster</i>	3.7 T during IR	Cf-252 neutron and γ , 1.8 to 5.8 Gy	Sex-linked recessive lethals	None
Barnothy ⁵⁰	Mouse	0.42 T pre-IR (14 days)	Co-60 γ , 8 Gy	Mortality	Decreased mortality
Amer ⁵¹	<i>Tribolium confusum</i>	0.22 T, 0.36 T, 0.97 T post-IR (7 days)	250 kVp X-rays, 12 Gy	Wing abnormalities	Decreased abnormalities
Wordsworth ⁵²	Rat liver (<i>in vivo</i>)	0.6 T during IR	240 kVp X-rays, 60 Gy in nine fractions	Serum component levels associated with liver damage	Increased serum enzyme levels
Tinney and Aldridge ⁵³	<i>Saccharomyces cerevisiae</i>	0.17 T during IR	200 kVp X-rays, dose not reported	Clonogenic survival	Decreased survival
Chen et al. ⁵⁴	<i>Saccharomyces cerevisiae</i>	0.78 T during IR	Co-60 γ , 300 Gy	Clonogenic survival	None
		0.14 T during IR	120 kVp X-rays, up to 12 Gy	Clonogenic survival	None
Rockwell ⁵⁵	Mouse mammary tumour cells (EMT6)	0.14 T post-IR (up to 5 h)	120 kVp X-rays, 10 Gy in two fractions	Recovery from sub lethal damage	None
		0.14 T post-IR (up to 25 h)	120 kVp X-rays, 10 Gy	Recovery from potentially-lethal damage	None
Nath et al. ⁵⁶	Chinese hamster lung cells (CCL16)	2 T during IR	30 MV X-rays, up to 30 Gy	Clonogenic survival	None
			30 MV X-rays, up to 30 Gy in two fractions	Recovery from sub lethal damage	None
Ngo et al. ⁵⁷	Chinese hamster lung cells (V79)	0.75 T during IR	25 MeV, 43 MeV neutrons, up to 30 Gy	Clonogenic survival	None
				DNA synthesis	None
Nakahara et al. ⁵⁸	Chinese hamster ovary cells (CHO-K1)	1 T, 10 T post-IR (18 h)	X-rays, up to 4 Gy	Clonogenic survival	None
				Micronucleus formation	Increased micronucleus formation
Sarvestani et al. ⁵⁹	Rat bone marrow stem cells	0.015 T post-IR (5 h)	140 kVp X-rays, 0.5 Gy	Cell cycle distribution	Increased G2/M fraction
Politański et al. ⁶⁰	Rat lymphocytes	0.005 T post-IR (up to 2 h)	X-rays, 3 Gy	Intracellular reactive oxygen species	Increased reactive oxygen species
Takatsuji et al. ⁶¹	Human peripheral blood lymphocytes	1.1 T during IR	4.9 MeV protons and 23 MeV α particles, up to 3 Gy	Dicentric chromosome rate	Increased chromosome aberrations
Kubinyi et al. ⁶²	Human leukocytes in blood	0.16 T (homogeneous) or inhomogeneous SMFs pre or post-IR (24 h)	Co-60 γ , 4 Gy	DNA damage	None (pre)
					Decreased DNA damage (post)

(Continued)

Table 1. (Continued)

Reference	Biological specimen	Static magnetic field	Ionising radiation	End point studied	Effect of SMF on IR response
Feng et al. ⁶³	Human lung adenocarcinoma cells (A549)	0.5 T post-IR (1 h)	X-rays, up to 10 Gy	Clonogenic survival	Decreased survival
Teodori et al. ⁶⁴	Human primary glioblastoma cells	0.08 T pre-IR (0 or 6 h) plus post-IR (up to 20 h)	250 kVp X-ray, 5 Gy	Apoptosis DNA damage Mitochondrial membrane potential	Increased apoptosis Decreased DNA damage Decreased loss of mitochondrial membrane potential
Wang et al. ⁶⁵	Human head/neck and lung cancer cells (H460, H1299, HN5, UMSCC47)	1.5 T during IR	6 MV X-rays, up to 8 Gy in 1, 3 or 4 fractions	Clonogenic survival	None

DNA, deoxyribonucleic acid; IR, ionising radiation; SMF, static magnetic field;

Static magnetic field exposure times are stated in brackets. Ionising radiation nominal energies were listed if available and doses were delivered in a single fraction unless otherwise stated. Significance result noted if any SMF + IR exposure conditions produced a statistically significant difference ($p < 0.05$) in the biological endpoint measured from equivalent IR alone, as reported by the authors.

reduction of $26.7 \pm 3.2\%$ was observed for SMF treated mice compared with those exposed to a dummy magnet, possibly due to SMF stimulated leukocytosis which counterbalanced radiation-induced leukopaenia.⁵⁰ A separate study reported a deleterious effect of SMF in rats that received targeted liver doses of 60 Gy in nine daily fractions.⁵² Serum concentrations of aminotransferases and total haemolytic complement were used to assess liver damage; significantly greater elevation in serum enzyme levels was produced by irradiation with SMF than by irradiation in the absence of the field. A similar elevation of serum aminotransferases (from 70 days post-SMF treatment) was also observed in rats not exposed to ionising radiation relative to controls, prompting the conclusion that the enhanced liver damage observed in SMF plus ionising radiation exposed rats may be due to the addition of separate damage mechanisms rather than a mechanism arising uniquely from SMF plus ionising radiation synergism.⁵²

Amer⁵¹ studied the effect of strong SMF exposure for a duration of 7 days immediately post-irradiation on wing development in *Tribolium confusum*. SMF conferred a protective effect, yielding significantly fewer wing abnormalities in radiation exposed animals. Temperature and radiation dose were found to impact the magnitude of the SMF effect, which comprised a 11 to 36% reduction in wing anomaly occurrence across the various experiments reported.

Two studies of *Saccharomyces cerevisiae* (yeast) have provided limited evidence for an impact of SMF during X-ray irradiation on clonogenic survival.^{53,54} Tinney and Aldridge⁵³ observed 27 to 33% fewer surviving colonies in samples exposed to 0.17 T SMF during irradiation, however full details of the authors' methods were not published. In a work which carefully accounted for dose distribution modifications of a 0.78 T SMF during Co-60 irradiation, Chen et al⁵⁴ found that in five out of seven experiments the null hypothesis (*i.e.* no effect of SMF) could not be rejected (t -test $p > 0.05$). SMF was associated with a modest reduction in clonogenic survival of $3.9 \pm 2.7\%$.⁵⁴

Motivated by theoretical work on the potential for SMF confinement of radiotherapy beams,³² three studies assessed the impact of various combinations of SMF strengths, radiation qualities and mammalian *in vitro* models^{55–57} (Table 1). All concluded that survival curves for cells irradiated with and without simultaneous SMF were indistinguishable. Application of SMF during incubation post-irradiation did not influence recovery from sub lethal or potentially lethal damage. Nath et al⁵⁶ performed experiments with Chinese hamster lung cells irradiated in either aerated or hypoxic conditions. Non-parametric analysis⁶⁶ yielded a dose modifying factor of unity for SMF for both the normoxic and hypoxic experiments. Ngo et al⁵⁷ reported that the DNA synthetic rate was unaffected by the presence of SMF during fast neutron irradiation. However, DNA synthesis was slightly suppressed by longer SMF durations in non-irradiated cells, *e.g.* by approximately 10% at 3 h SMF exposure.

Nakahara et al⁵⁸ investigated whether incubation in a strong SMF (1 and 10 T) influenced the number of micronuclei produced

in Chinese hamster ovary cells exposed to X-rays. Micronuclei frequency was unaltered by SMF alone. A small yet significant increase in the micronuclei frequency of approximately 10% was observed in cells incubated in a 10 T SMF for 18 h following 4 Gy irradiation ($p < 0.05$, Fisher protected least significant difference test). For all other combinations of SMF strength and radiation dose, no significant difference in micronuclei frequency due to SMF was observed. This evidence suggests that 10 T SMF, although not in itself genotoxic, may inhibit the repair of DNA damage or intensify X-ray induced mitotic spindle apparatus damage.⁵⁸

Sarvestani et al⁵⁹ studied the cell cycle distributions of rat bone marrow stem cells irradiated with orthovoltage X-rays prior to incubation in either 0.015 T SMF or the geomagnetic field alone (60 μ T). Flow cytometry analysis revealed that 0.015 T SMF exposure increased the percentage of cells in the G2/M phase following irradiation from $14.35 \pm 0.13\%$ to $15.30 \pm 0.57\%$ ($p < 0.05$ for Student's *t*-test).⁵⁹ G2/M arrest is associated with DNA damage; hence this result suggests that moderate SMF may slightly enhance radiation induced damage. The authors posit SMF influence on electronic spin states (thereby altering kinetics of chemical reactions involving radical pairs) as the presumptive mechanism.⁵⁹ This hypothesis was supported by the work of Politański et al⁶⁰ in which measurements of intracellular reactive oxygen species (ROS) were performed in rat lymphocytes *in vitro*, subsequent to weak SMF exposure (5 mT). SMF was associated with statistically significant increases in dichlorofluorescein probe fluorescence (proportional to the ROS level) both with and without X-ray radiation (Tukey's *post hoc* test $p < 0.05$).⁶⁰

Two studies of human white blood cells *in vitro* have provided additional evidence of a small influence of SMF on radiation-induced DNA damage.^{61,62} The frequency of chromosome aberrations in human peripheral blood lymphocytes exposed simultaneously to 1.1 T SMF and ionising radiation (4.9 MeV protons and 23 MeV α particles) was subtly increased.⁶¹ Regression analysis of dicentric data fitted to a linear quadratic model yielded a significant difference in α coefficients (associated with the one-track radiation damage component) for 1.1 T SMF during proton beam irradiation compared with irradiation in the absence of SMF ($p < 0.05$). For the α particle irradiations, the significance criterion was not met. The authors suggested that SMF modulation of charged particle tracks via the Lorentz force resulted in an effective increase in the linear energy transfer, with the effect more pronounced for the more sparsely ionising 4.9 MeV proton beam; however, other possible magnetobiological interaction mechanisms were not accounted for.⁶¹ Kubinyi et al⁶² assessed the impact on DNA damage of 0.16 T homogeneous SMF and a range of SMF gradients (47.7, 1.2, or 0.3 T/m) applied either before or after Co-60 irradiation of human leukocytes in their intact microenvironment in the blood. DNA damage, measured via single-cell gel electrophoresis (comet assay), was significantly reduced due to 4 h 0.16 T homogeneous SMF incubation post-irradiation compared with no SMF ($p < 0.05$). Cells incubated in the 0.012 T, 1.2 T/m gradient SMF post-irradiation exhibited a significant increase in DNA damage after 1 h. Besides these two anomalies, no significant difference in DNA damage

was observed relative to SMF non-exposed samples at all other post-irradiation incubation time points and SMF strengths.⁶²

In the last 5 years, three studies have been published on the topic of combined SMF and ionising radiation exposure in human cancer *in vitro* models.^{63–65} Viability of lung adenocarcinoma cells (cell line A549) treated with 0.5 T SMF alone for 1 to 4 h was significantly inhibited by approximately 10% relative to untreated cells ($p < 0.05$).⁶³ Gene chip analysis revealed that SMF exposure of 1 h produced alterations in gene expression associated with the promotion of cell cycle arrest and apoptosis. A549 clonogenic survival following X-ray irradiation was significantly impaired in cells exposed to SMF ($p < 0.05$), *e.g.* the survival fraction at 10 Gy was 0.24 for $B = 0$ T and 0.02 for $B = 0.5$ T. Flow cytometry analysis linked SMF exposure with an increase in the proportion of cells in phase G2 and M, the most radiosensitive phases, suggesting that SMF may act to radiosensitize A549 cells by influencing cell cycle progression via an unidentified interaction mechanism.⁶³ Teodori et al⁶⁴ studied the impact of 0.08 T SMF in combination with orthovoltage X-ray irradiation on DNA damage (comet assay) and mitochondrial membrane potential (JC-1 probe) in human primary glioblastoma cells *in vitro*. SMF exposure (24 h) without irradiation was associated with a significant increase in DNA damage ($p < 0.01$),⁶⁴ which concords with the SMF-related viability reduction observed by Feng et al.⁶³ Intriguingly, glioblastoma DNA damage was significantly reduced by 6 and 20 h SMF exposure post-irradiation ($p < 0.001$), while the inclusion of an additional 6 h SMF pre-treatment did not impact this result.⁶⁴ X-ray induced loss of mitochondrial membrane potential was diminished by exposure to SMFs during recovery, suggesting a potential link between the protection of mitochondria by SMF (possibly via SMF perturbation of the electron transport chain in mitochondria) and a reduction in radiation-induced genotoxicity.⁶⁴

The only study to have featured an MR-Linac (1.5 T SMF, 6 MV X-rays) was performed by Wang et al.⁶⁵ Two human head and neck cancer and two lung cancer cell lines were studied *in vitro*. Robust dosimetry and the use of a cell irradiation jig to ensure high dose uniformity to the cells in the presence of SMF were strengths of this work. Exposure conditions were chosen to mimic those experienced by radiotherapy patients, *i.e.* a series of relatively short (15 min) daily sessions. Cell survival was unaffected by SMF alone and all survival curves were indistinguishable for irradiations by MR-Linac or conventional 6 MV linac. SMF did not significantly impact survival whether treatment was delivered in single or multiple fractions.⁶⁵ However, the failure of the study to reproduce well-established differences in survival in response to dose fractionation without SMF casts doubt upon its ability to detect small differences caused by SMF.

DISCUSSION AND CONCLUSION

The classical paradigm of radiation-induced biological damage posits DNA as the primary site of interaction. MC track structure studies have shown that MRI strength SMF has negligible impact on radiobiologically important micro-⁴² and nanodosimetric^{43,44} quantities. Yet, approximately half of the papers comprising the scientific literature reported statistically significant difference in

the biological end point measured when SMF was combined with ionising radiation relative to ionising radiation exposure alone.

There are several possible explanations for this disparity. Many of the studies involving simultaneous SMF and ionising radiation exposure lacked thorough descriptions of radiation dosimetry or tests to characterise the macroscopic dose distribution to which biological samples were exposed, with and without simultaneous SMF. Air regions and other heterogeneities in proximity to biological material may give rise to ERE-related local dose enhancement when SMF is applied. Furthermore, the response of radiation detectors (most significantly ionisation chambers) is known to vary with magnetic field strength due to the Lorentz force on electrons within the active volume,⁶⁷ an effect which must be accounted for in order to accurately calibrate the radiation output. Differences in the experimental setup, and hence in the influence of SMF on the delivered radiation doses may be a contributing factor to the contradictory results reported in the literature. It is recommended for future studies that tests are included to confirm both the absolute dose and dose uniformity across the biological sample, with and without SMF applied, such that any differences may be taken into account when evaluating the impact of SMF.

The absence of SMF-induced changes to the yield and complexity of direct DNA damage produced by ionising radiation^{42–44} at field strengths in the range utilised in relevant biological studies in the literature (Table 1) suggests that an alternative mechanism is responsible for the SMF-related modification to radiobiological injury. This is supported by studies in which the application of SMF before or after irradiation produced a significant effect vs no SMF, thus removing possible changes to the macroscopic dose distribution as a potential variable. In such cases, it can only be inferred that SMF elicits a biological response which alters the way in which the system responds to radiation injury. The current evidence is insufficient to allow conclusion of the mechanism(s)

by which this occurs, however the following hypotheses may be considered in future studies: (1) SMF modifies one or more steps in the DNA damage response, (2) SMF influences the yield or lifetime of ROS responsible for indirect DNA damage, (3) SMF influences intercellular signalling implicated in non-targeted radiation-induced effects.

In vitro investigations utilising cells cultured in monolayers represent the majority of the scientific literature on this topic (Table 1). Emerging evidence suggests that cells cultured using three-dimensional (3D) tissue engineering constructs better reflect many *in vivo* features, such as cell–cell interactions, morphology and the development of microenvironmental niches.⁶⁸ Radiation response differs significantly in cells cultured in 3D systems compared with monolayers.^{69,70} The effect of combined SMF and ionising radiation in 3D cell cultures has not yet been investigated.

It should be noted that in the majority of studies presented in Table 1, the magnitude of any observed difference in the measured biological end point for SMF plus ionising radiation relative to ionising radiation alone was modest. However, the divergent literature on the topic highlights an important gap in understanding, *i.e.* the possibility of ionising radiation and SMF synergism involving a mechanism other than modification to radiation track structure. Further studies incorporating robust radiation dosimetry and 3D cell culture systems are needed to supplement the literature on the topic, such that underlying mechanism(s) may be elucidated and any impact of SMF on radiation treatment response accounted for during MRgRT.

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