Impact of Superparamagnetic Iron Oxide Nanoparticles on *In Vitro* and *In Vivo* Radiosensitisation of Cancer Cells

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Research

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Abstract

Purpose

The recent implementation of MR-Linacs has highlighted theranostic opportunities of contrast agents in both imaging and radiotherapy. There is a lack of data exploring the potential of superparamagnetic iron oxide nanoparticles (SPIONs) as radiosensitisers. This study aimed to characterise the uptake and radiobiological effects of SPIONs in tumour cell models *in vitro* and to provide proof-of-principle application in a xenograft tumour model.

Methods

SPION uptake was measured using ICP-MS in 6 cancer cell lines; H460, MiaPaCa2, DU145, MCF7, U87 and HEPG2. The impact of SPIONs on radiobiological response was determined by measuring DNA damage using 53BP1 immunofluorescence and cell survival. Measured dose enhancement factors (DEFs) were with the predicted DEFs based on physical absorption estimations. *In vivo* efficacy was demonstrated using a subcutaneous H460 xenograft tumour model in SCID mice by following intra-tumoural injection of SPIONs.

Results

SPIONs significantly increased DNA damage in all cell lines with the exception of U87 cells at a dose of 1 Gy, 1 hr post-irradiation. Levels of DNA damage correlated with the cell survival, in which all cell lines except U87 cells showed an increased sensitivity *($P < 0.05$)* in the linear quadratic curve fit for 1 hr exposure to 0.1 mM SPIONs. There was also a 30.1 % increase in the number of DNA damage foci found for HEPG2 cells at 2 Gy. No strong correlation was found between SPION uptake and DNA damage at any dose, yet the biological consequences of SPIONs on radiosensitisation were found to be much greater, with DEFs up to 1.28 ± 0.03, compared with predicted physical dose enhancement levels of 1.0001. *In vivo*, intra-tumoural injection of SPIONs combined with radiation showed significant tumour growth delay compared to animals treated with radiation or SPIONs alone *($p < 0.05$).*

Conclusions

SPIONs showed radiosensitising effects in 5 out of 6 cancer cell lines. No correlation was found between the cell-specific uptake of SPIONs into the cells and DNA damage levels. The *in vivo* study found a significant decrease in the tumour growth rate.

Full Text

This preprint is available for download as a PDF.

Figures

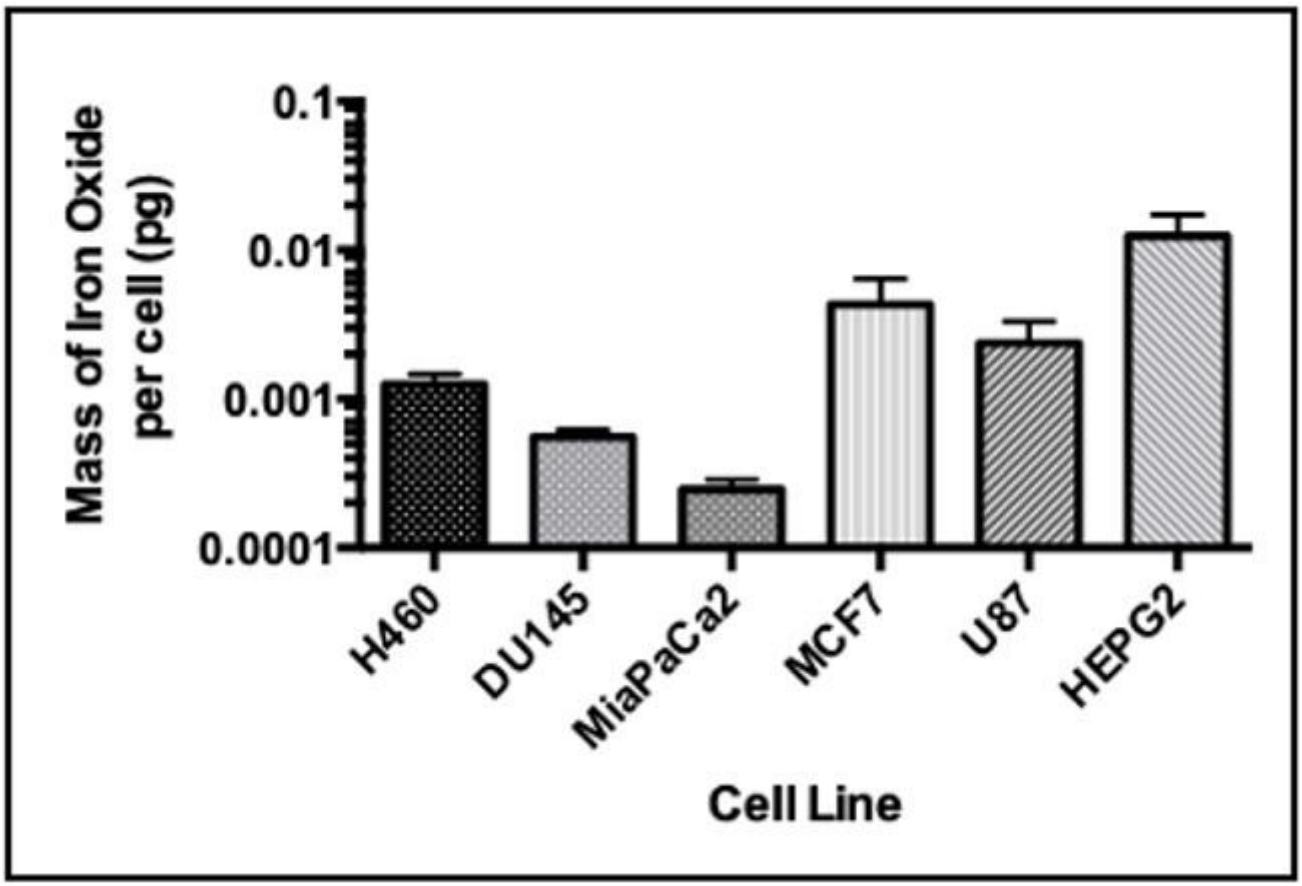

Figure 1

Uptake measurements performed using ICP-MS, representing the mass of iron oxide taken up per cell by each cell lines, for an added concentration of 0.1 mM, presented as mean ± SEM. (n=3)

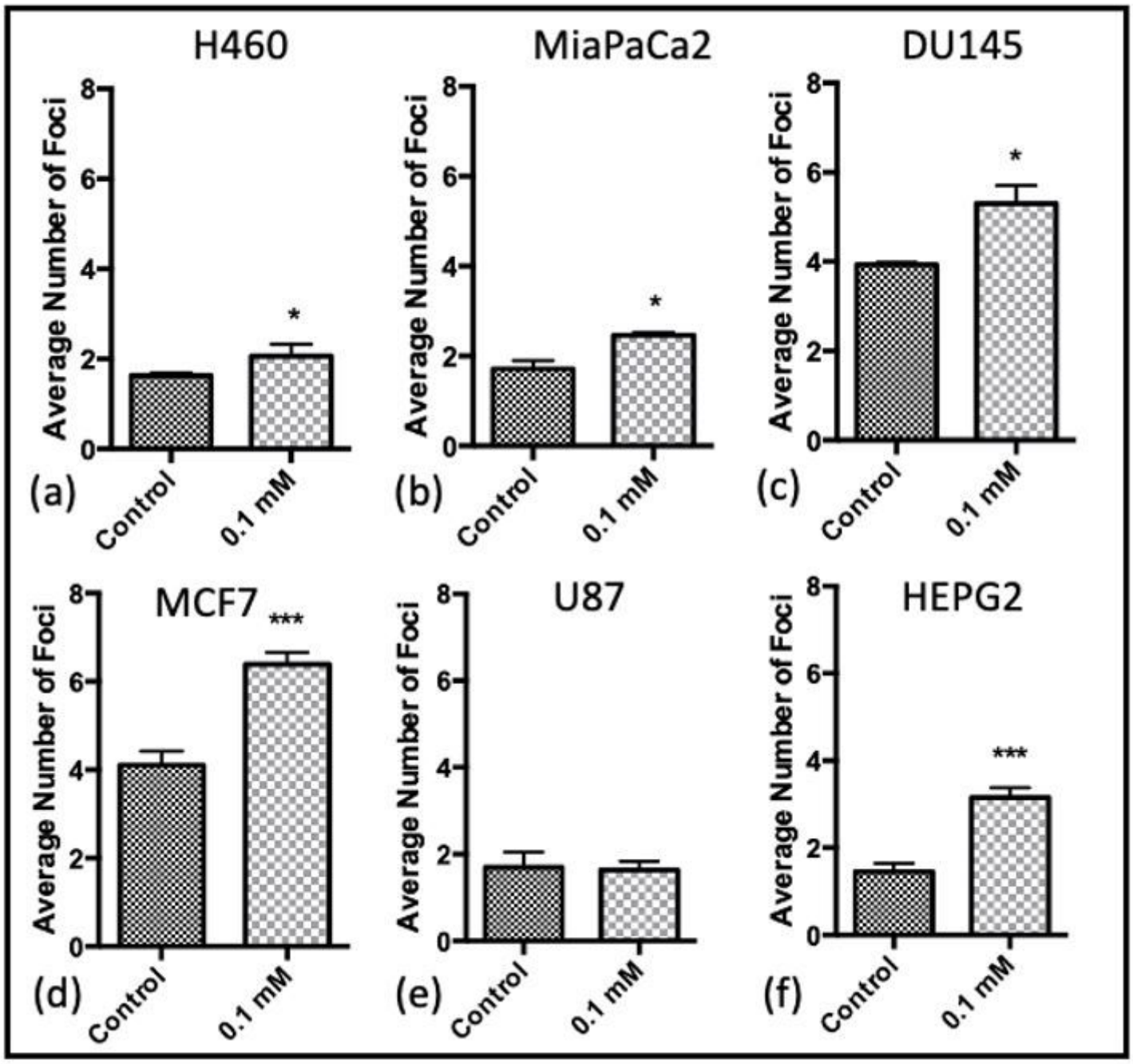

Figure 2

Average number of DNA damage foci counted for each cell line when treated with 0.1 mM SPIONs in the absence of radiation. (a) H460, (b) MiaPaCa2, (c) DU145, (d) MCF7, (e) U87 and (f) HEPG2. (n=3) Presented as mean ± SD with statistical significance represented as; $P < 0.05$: *; $P < 0.001$: **; $P < 0.0001$: ***.

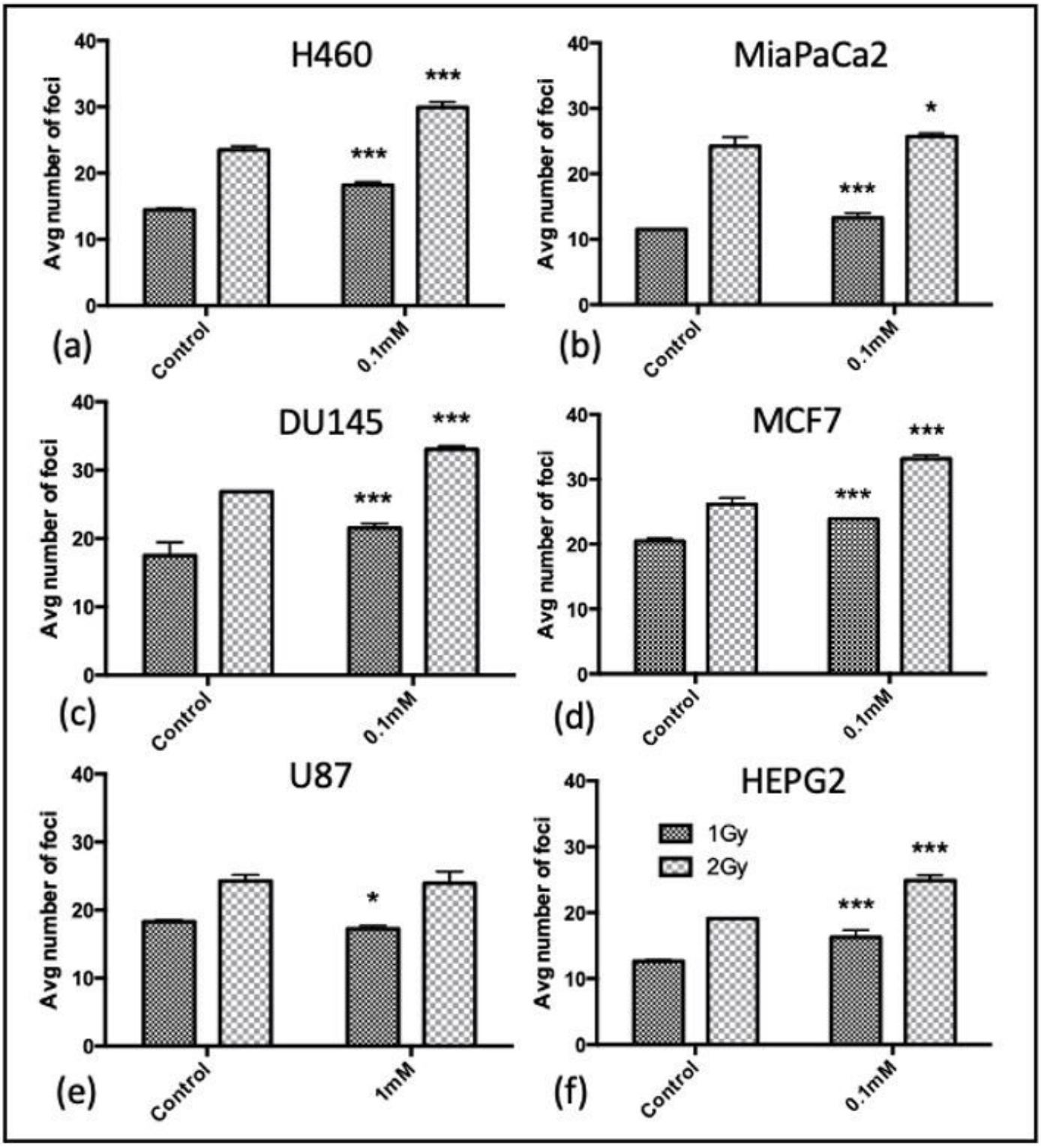

Figure 3

Average number of DNA damage foci counted for cells treated with 0.1 mM SPIONs 1 hr after exposure to 1 Gy or 2 Gy of X-rays. (a) H460, (b) MiaPaCa2, (c) DU145, (d) MCF7, (e) U87 and (f) HEPG2. (n=3) Presented as mean ± SD with statistics represented as; P < 0.05 : *; P < 0.001 : **; P < 0.0001 : ***.

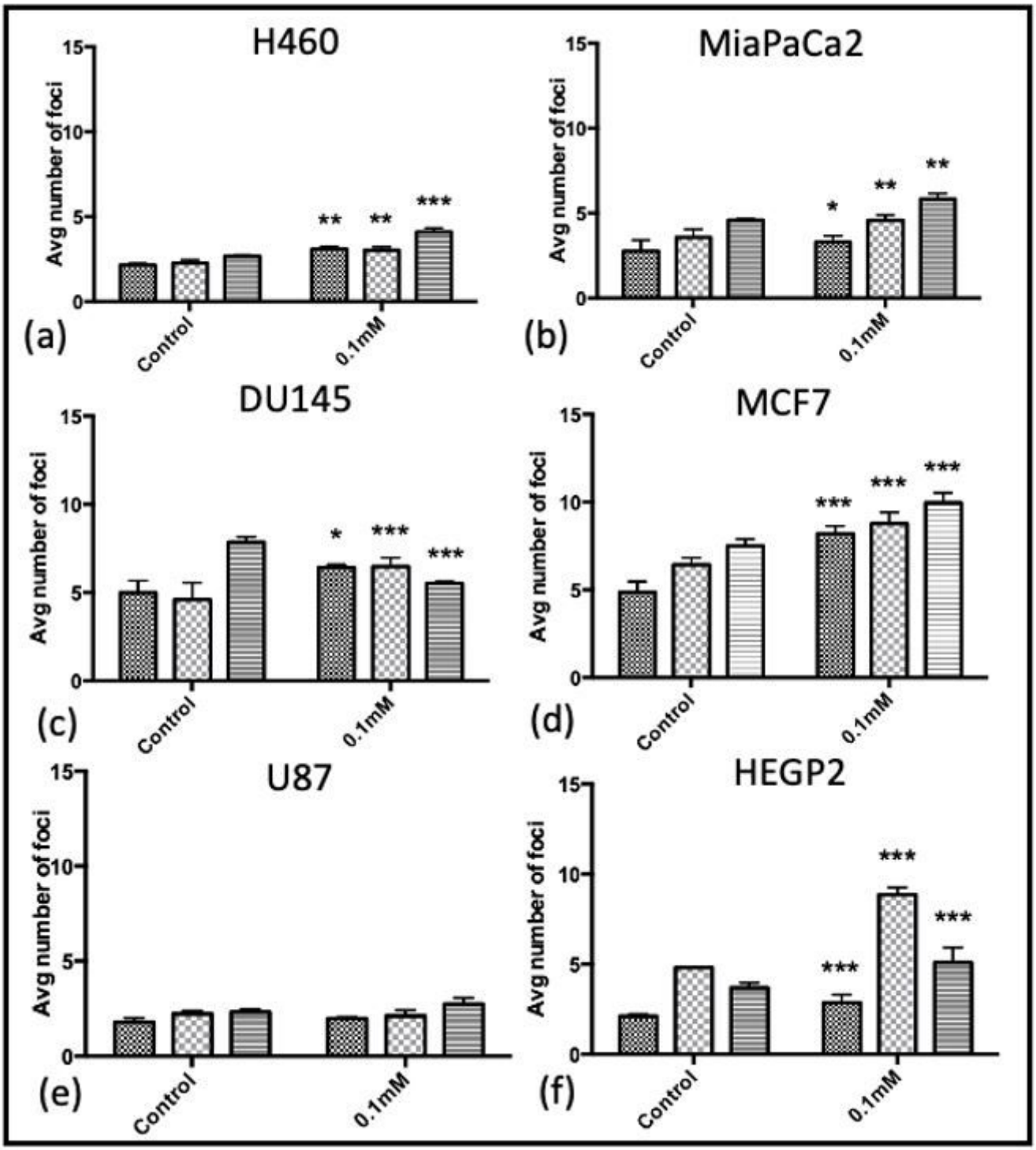

Figure 4

Average number of DNA damage foci counted for each cell line when treated with 0.1 mM SPIONs and doses of 0 – 2 Gy measured at 24 hr after irradiation. (a) H460, (b) MiaPaCa2, (c) DU145, (d) MCF7, (e) U87 and (e) HEPG2. (n=3) Presented as mean ± SD with statistics represented as; $P < 0.05$: *; $P < 0.001$: **; $P < 0.0001$: ***.

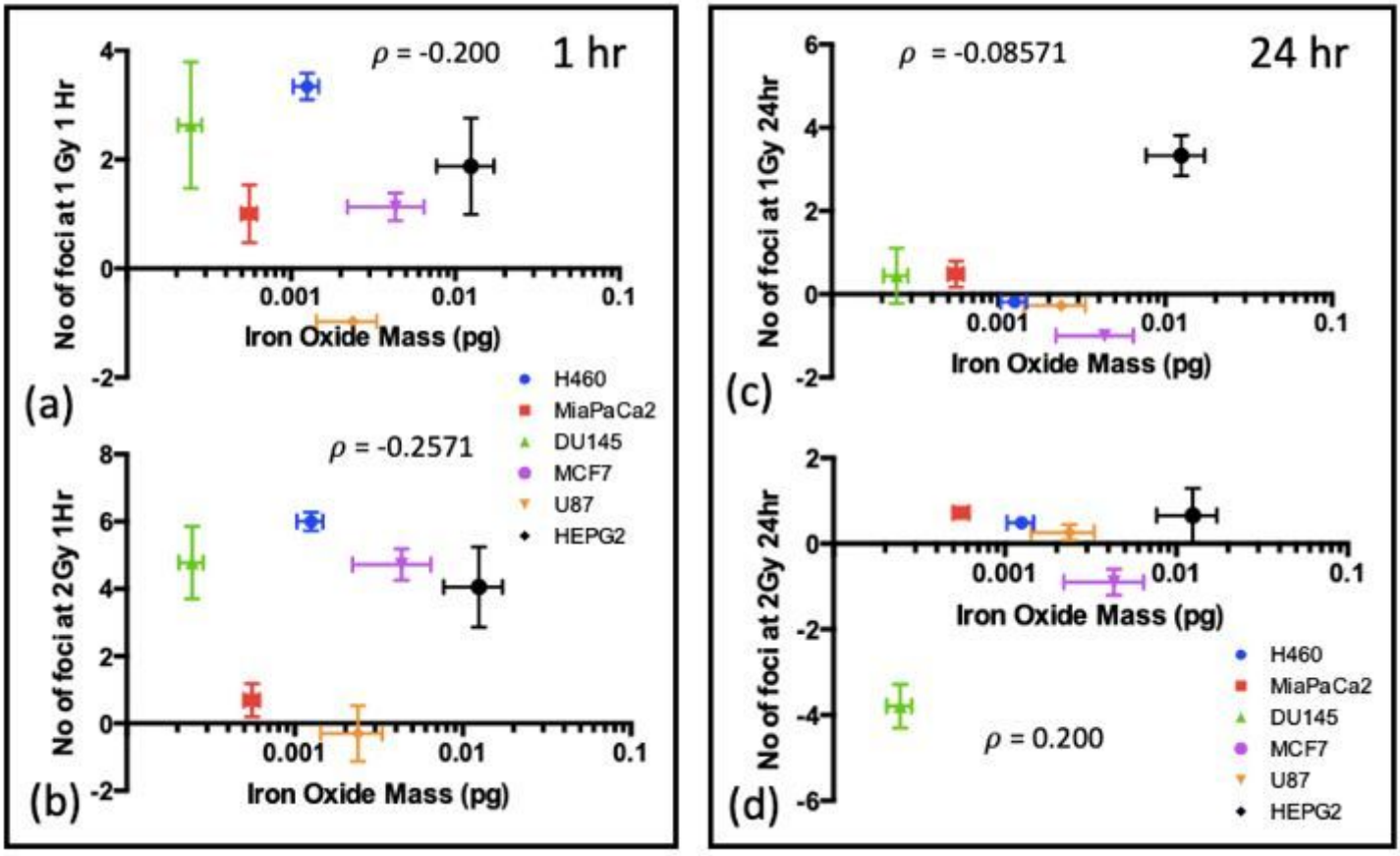

Figure 5

Mass of iron oxide detected per cell for each cell line compared to the number of foci counted, corrected for controls, and also corrected for the number of foci for cells without SPIONs, at the 1 hr timepoint (left) and 24 hr timepoint (right) after combined exposure with SPIONs and 225 kVp X-rays for; (a,c) 1 Gy and (b,d) 2 Gy. Presented as mean ± SD. Spearman Correlation coefficient, ρ, is indicated on each graph.

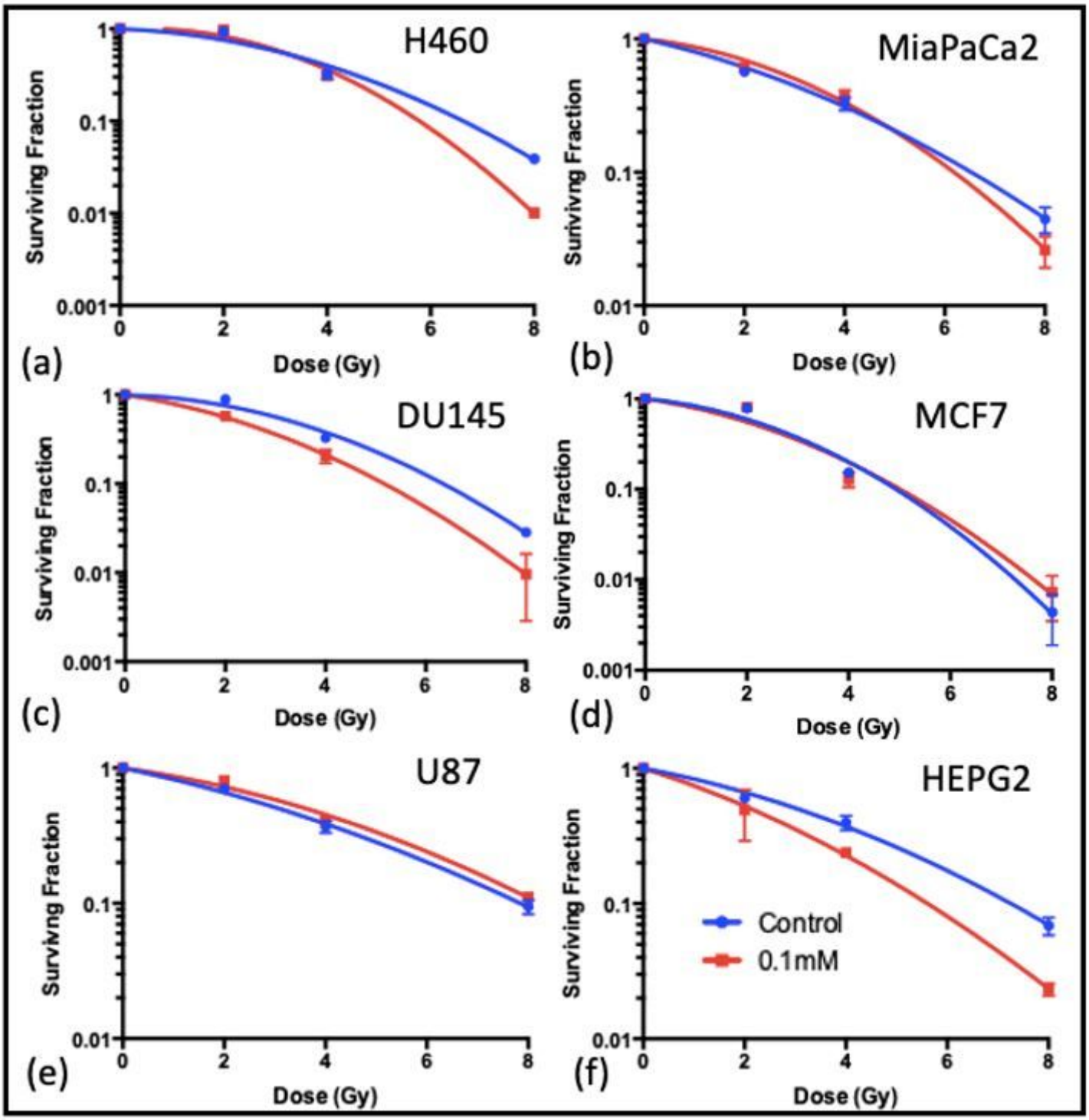

Figure 6

Clonogenic cell survival curves fitted with the linear quadratic model for the combination of 225 kVp X-rays with 0.1 mM SPIONs, for a 1 hr exposure time; (a) H460, (b) MiaPaCa2, (c) DU145, (d) MCF7, (e) U87, (f) HEPG2. (n=3) Presented as mean ± SD.

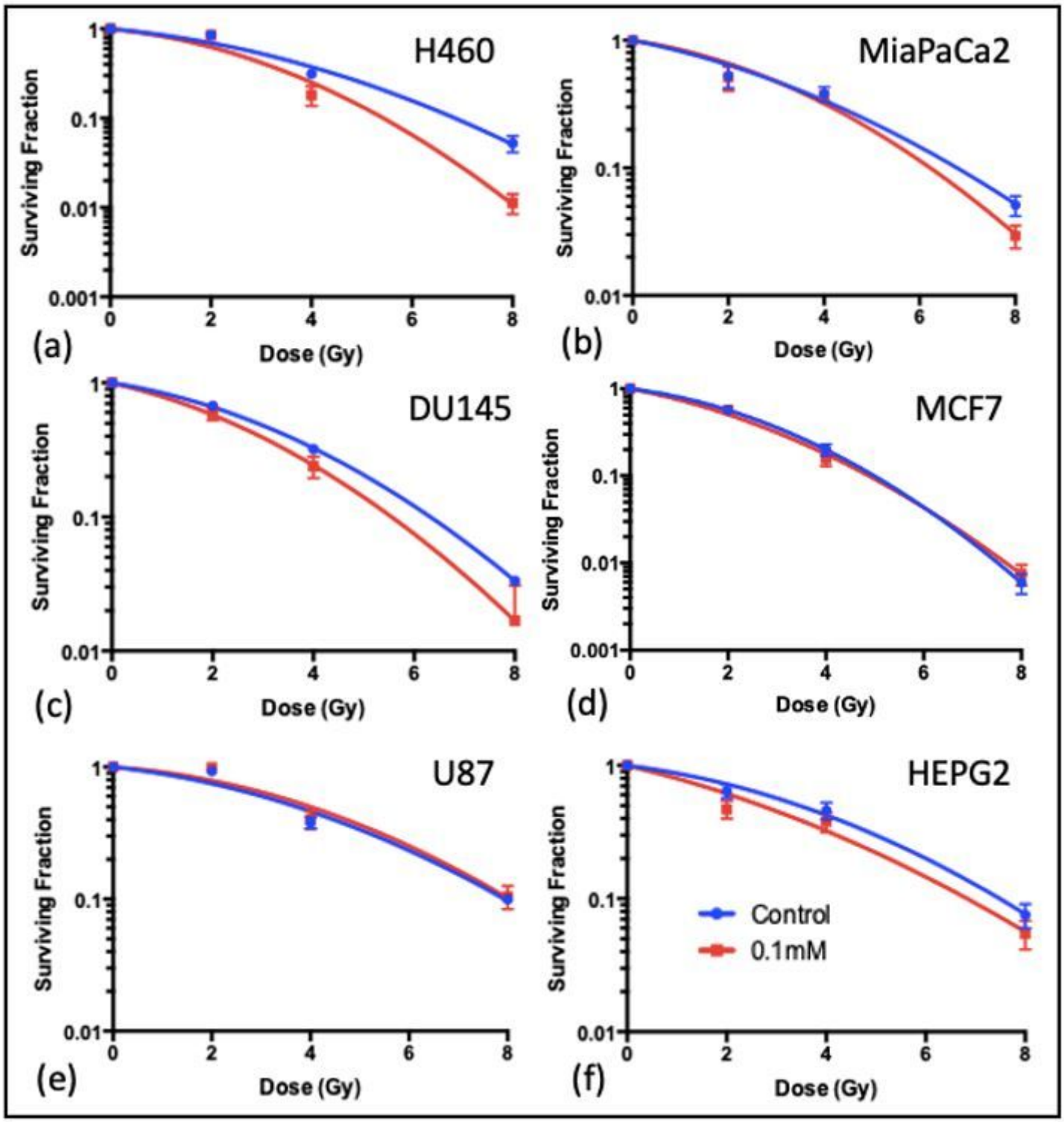

Figure 7

Clonogenic cell survival curves fitted with the linear quadratic model for the combination of 225 kVp X-rays with 0.1 mM SPIONs, for a 24 hr exposure time; (a) H460, (b) MiaPaCa2, (c) DU145, (d) U87, (f) U87 and (f) HEPG2. (n=3) Presented as mean ± SD.

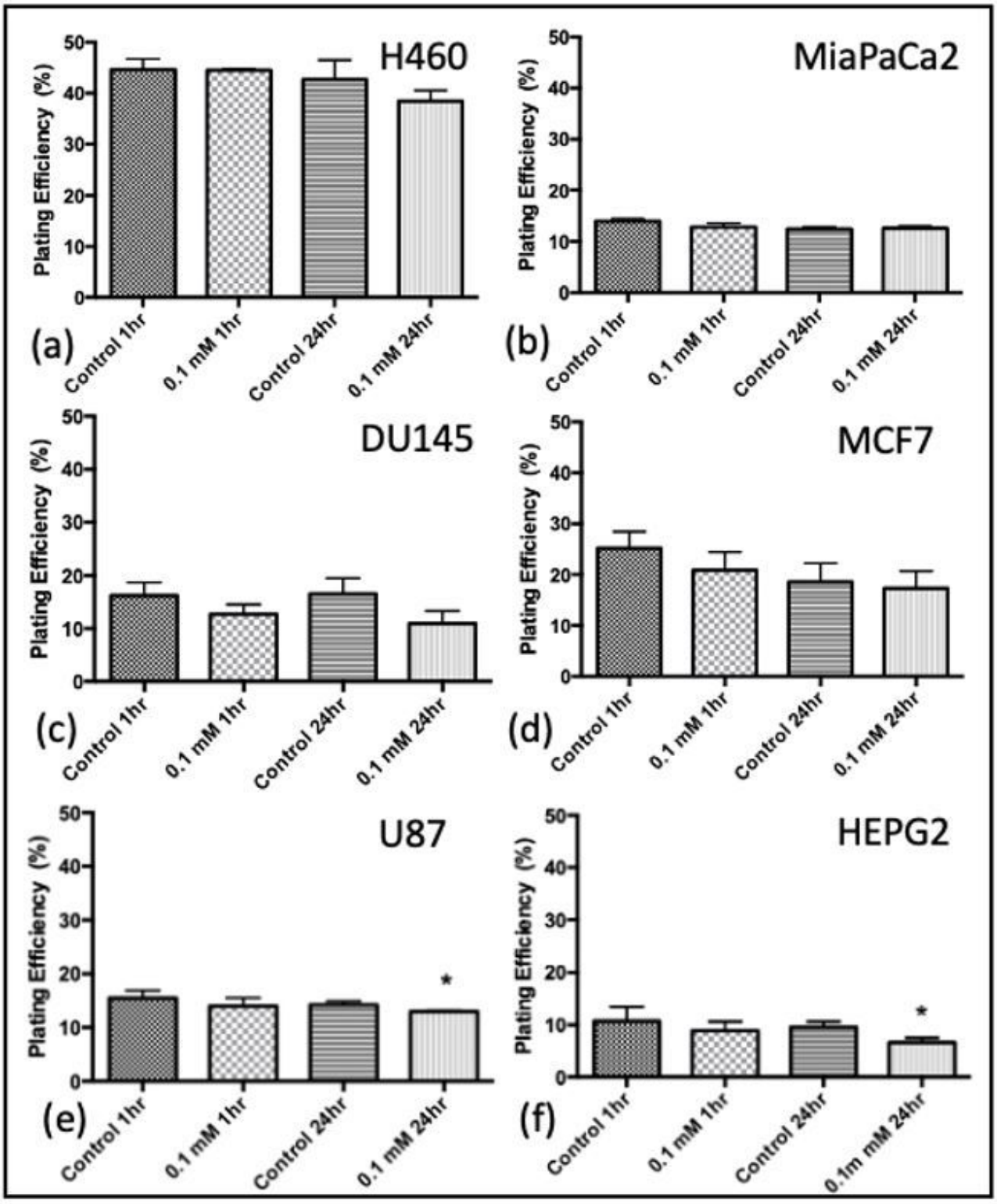

Figure 8

Plating efficiency for cell lines in the absence of radiation, for control samples and 0.1 mM SPIONs for both 1 hr and 24 hr exposure times. (a) H460, (b) MiaPaCa2, (c) DU145, (d) MCF7, (e) U87 and (e) HEPG2. (n=3) Presented as mean ± SD with statistics represented as; $P < 0.05$: *; $P < 0.001$: **; $P < 0.0001$: ***.

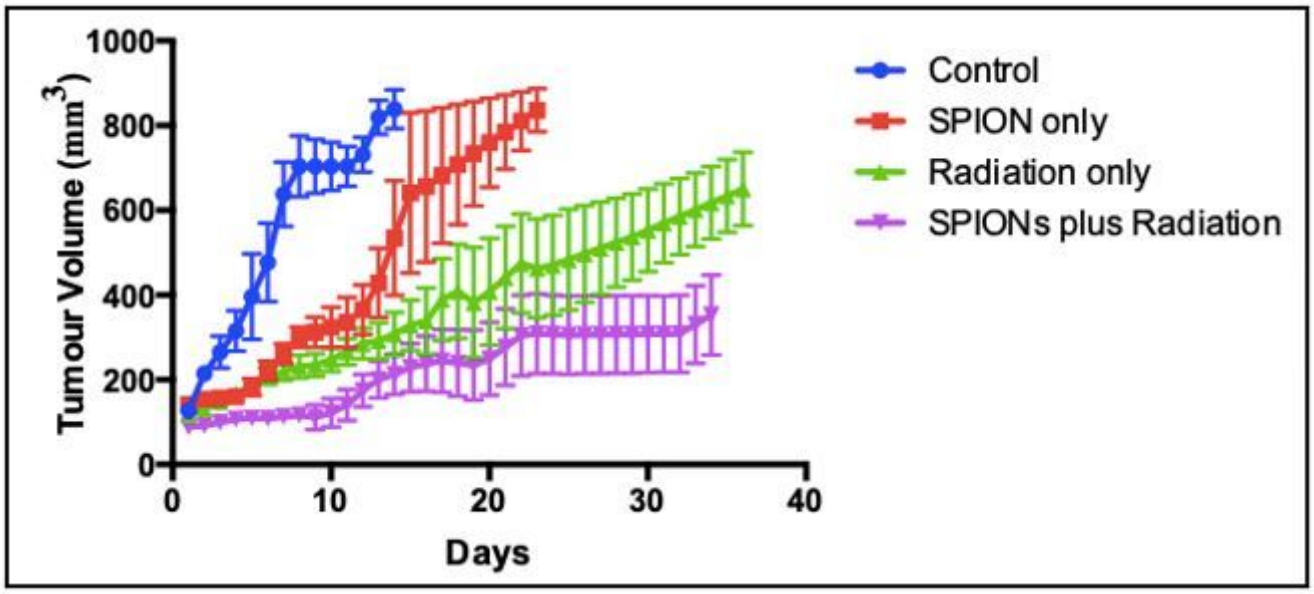

Figure 9

Tumour Volume with time for in vivo experiment for 4 subgroups; control, SPION only, radiation only, and SPIONs plus radiation, taken as the median value across all mice, using linear interpolation for days between measurements. Presented as mean ± SEM.

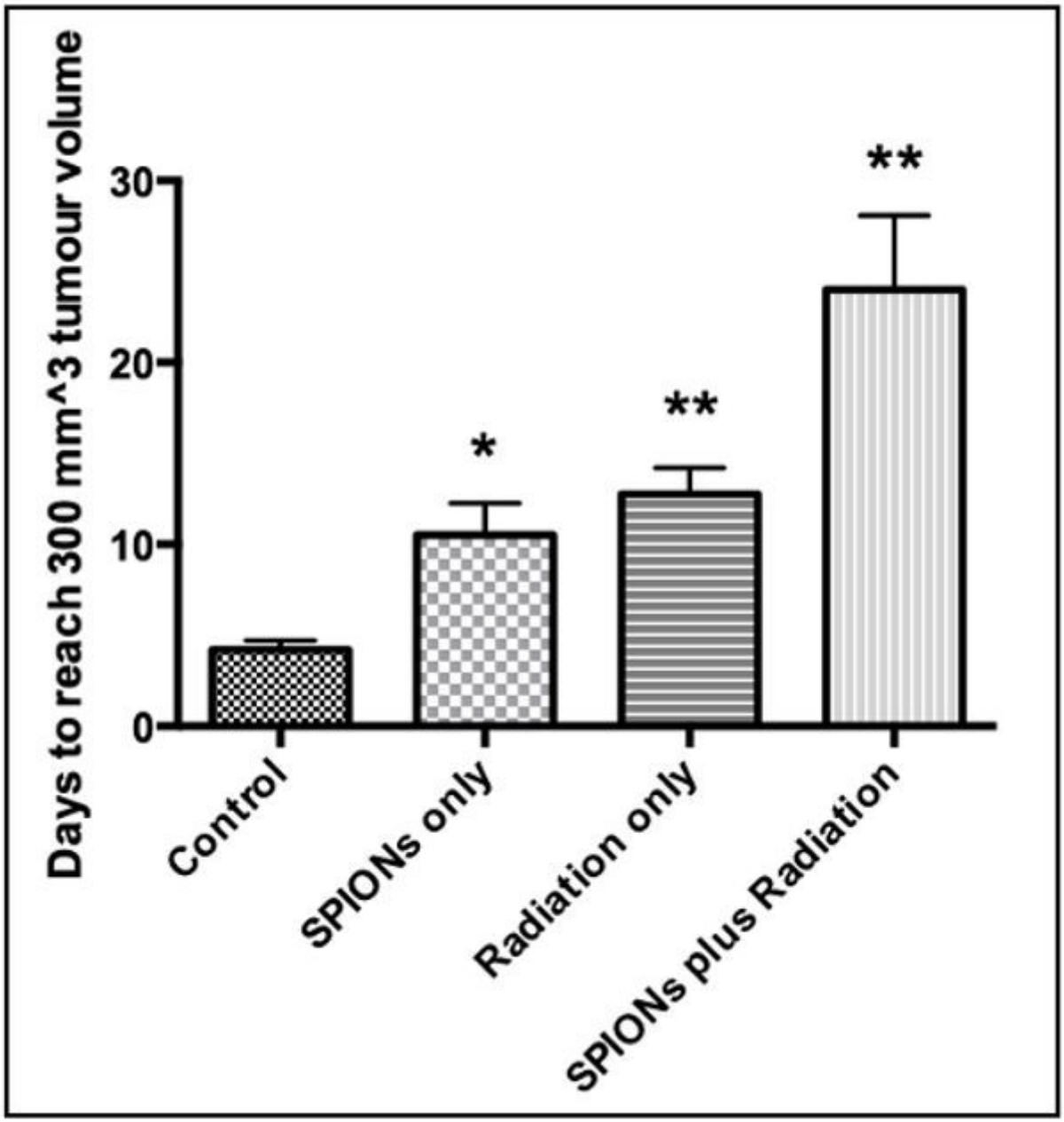

Figure 10

Average time (days) for tumour volume to reach 300 mm3 for the 4 subgroups; control, SPIONs only, radiation only, and SPIONs plus radiation. Presented as mean ± SEM with statistics represented as; P < 0.05 : *; P < 0.001 : **; P < 0.0001 : ***.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- U87authentication.pdf
- H460authentication.pdf

- MCF7authentication.pdf
- MiaPaCa2authentication.pdf
- DU145authentication.pdf
- HEPG2authentication.pdf