Derivation of G-factor used in Table 2

Generalized Linear-Quadratic model (GLQM) for an arbitrary dose-rate function has been described by (*1*)

$$\ln SF(T) = -\alpha D_T(T) - 2\beta \int_0^T dt\, \dot{D}(t) \int_0^t \dot{D}(\omega)\, R(t-\omega)\, d\omega\,, \qquad \text{(S1)}$$

where α and β are the intrinsic radiosensitivity parameters, D_T is the total physical dose accumulated up to time T, $\dot{D}(t)$ is the dose-rate function and $R(t)$ is the repair function of sublethal damage. $R(t)$ has commonly been treated as behaving exponentially, i.e. $R(t) = e^{-\mu t}$, which assumes the repair rate is constant up to time T with μ as the repair constant, in the literature (*2*). Based on this generalized model, Lea-Catcheside factor, G, is then defined as the ratio of the second term in Eq.(S1) with repair to the same term without repair

$$G = \frac{\int_0^T dt\, \dot{D}(t) \int_0^t \dot{D}(\omega)\, R(t-\omega)\, d\omega}{\int_0^T dt\, \dot{D}(t) \int_0^t \dot{D}(\omega)\, d\omega}. \qquad \text{(S2)}$$

Since trapezoidal integration is used to assess the cumulative activity reported in Table 2, the activity function assumed is

$$\begin{aligned} A(t) &= m_1 t, t \leq 1 \\ &= m_1 + m_2 t, 1 < t \leq 24 \end{aligned} \qquad \text{(S3)}$$

where t is the time (in hour), m_1 and m_2 are the slopes connecting from $t = 0$ to $t = 1$ and from $t = 1$ to $t = 24$, respectively. The dose-rate function is then defined as

$$\dot{D}(t) = A(t) \times S \qquad \text{(S4)}$$

where S is the simulated S-value. Therefore, the G-factor after 1 hour is

$$G = \frac{S^2 \int_0^1 dt\, m_1 t \int_0^t m_1 \omega\, e^{-\mu(t-\omega)} d\omega}{\frac{1}{2} S^2 \left(\frac{1}{2} m_1\right)^2}$$

$$= 8 \times \int_0^1 t \left(\frac{ut + e^{-ut} - 1}{u^2}\right) dt$$

$$= 8 \times \left(\frac{6 - 3\mu^2 + 2\mu^3 - 6(1+\mu)e^{-\mu}}{6\mu^4}\right), \quad \text{(S5)}$$

which is a function dependent only on the repair constant μ where μ is the reciprocal of repair half-time, T_{rep} times ln 2. T_{rep} is assumed to be 1.5 hour for Table 2 (*3, 4*) and thus $G = 0.89$. Similarly, the G-factor after 24 hours can be derived.

$$G = \frac{S^2 \left(\int_0^1 dt\, m_1 t \int_0^t m_1 \omega\, e^{-\mu(t-\omega)} d\omega + \int_1^{24} dt\, (m_1 + m_2 t) \int_0^t (m_1 + m_2 \omega) e^{-\mu(t-\omega)} d\omega \right)}{\frac{1}{2} S^2 \left[\frac{1}{2} m_1 + 23 m_1 + \frac{23}{2} m_2\right]^2}$$

$$= \frac{2}{\left[\frac{1}{2} m_1 + 23 m_1 + \frac{23^2}{2} m_2\right]^2} \times \left[{m_1}^2 \left(\frac{6 - 3\mu^2 + 2\mu^3 - 6(1+\mu)e^{-\mu}}{6\mu^4}\right) + K \right] \quad \text{(S6)}$$

where K is

$$K = \int_1^{24} (m_1 + m_2 t) \left[\left(\frac{m_1 - m_1 e^{-\mu t}}{\mu}\right) + m_2 \left(\frac{\mu t + e^{-\mu t} - 1}{\mu^2}\right) \right] dt$$

$$= \frac{1}{6\mu^4} \times \left[-6 e^{-24\mu} (m_2 - m_1 \mu)(m_2 + m_1 \mu + 24 m_2 \mu) + 6 e^{-\mu} (m_2 - m_1 \mu)(m_2 + (m_1 + m_2)\mu) + 23\mu^2 \left(6 {m_1}^2 \mu + 6 m_1 m_2 (25\mu - 1) + {m_2}^2 (1202\mu - 75)\right) \right].$$

(S7)

Then one can easily calculate G-factor for different cell compartments, which have different uptake behavior, of each cell line based on empirical internalization data. G-factors after 24 hours for the cell lines studied in this work have been compiled in Supplemental Table 3.

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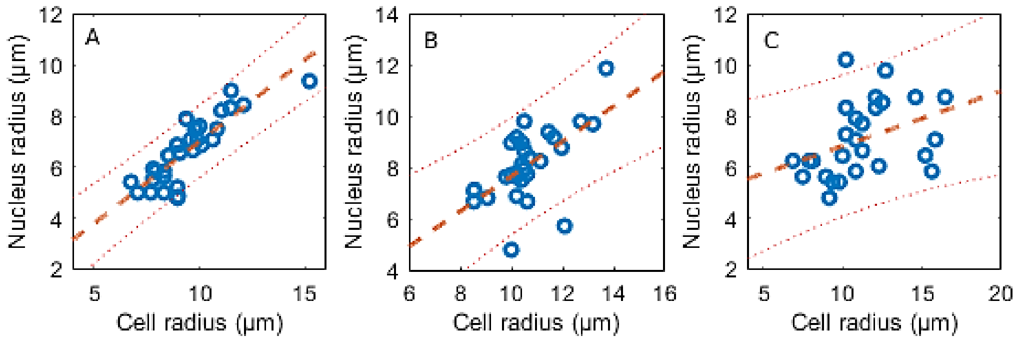
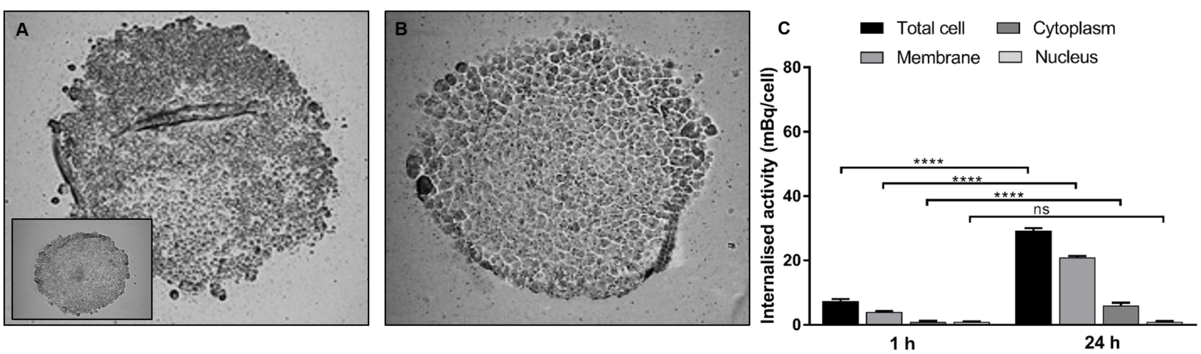
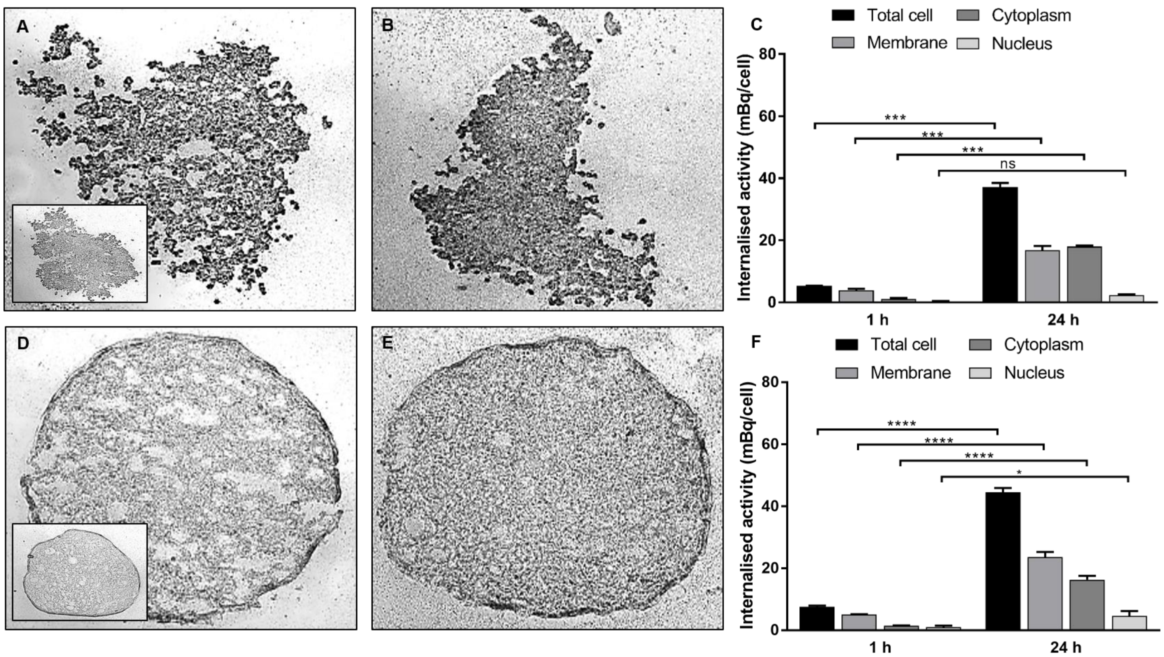


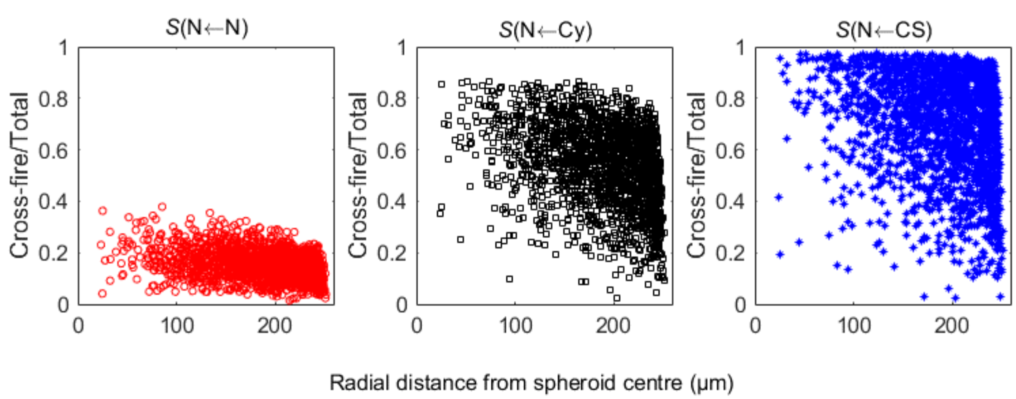
Supplemental Figure 1. Experimental distribution of cell and nucleus radii for (A) MDA-MB-468, (B) SQ20B and (C) 231-H2N cell lines. The linear fit to the data (dashed line) and the 95% confidence intervals (dotted lines) of each given dataset are shown.



Supplemental Figure 2. Spatial distribution of ^{111}In-EGF in 231-H2N spheroids, showing microautoradiograms of 8 μm spheroid sections after (A) 1 h (insert shows control) and (B) 24 h treatment. (C) Internalized activity (mBq/cell) determined at 1 and 24 h incubation. *P<0.05, ns = not significant.



Supplemental Figure 3. Spatial distribution of ^{111}In-Tz in MDA-MB-468 and SQ20B spheroids, showing microautoradiograms of 8 µm spheroid sections after (A and D) 1 h (insert shows control) and (B and E) 24 h treatment. (C and F) Internalized activity (mBq/cell) determined at 1 and 24 h incubation.



Supplemental Figure 4. The contribution of dose deposited by other cells (cross dose) to the total dose (self-dose plus cross dose) as a function of radial distance to the spheroid center for radioactive sources originating from the nucleus, cytoplasm and cell surface in the 231-H2N cell line.

Supplemental Table 1

Ratio of cross dose to total dose for different source locations.

	Cross dose to total dose ratio for cells in cluster – RCP		
	S(N←N)	S(N←Cy)	S(N←Cs)
MDA-468	0.168 ± 0.059	0.519 ± 0.126	0.643 ± 0.153
SQ20B	0.200 ± 0.069	0.542 ± 0.132	0.657 ± 0.151
231-H2N	0.151 ± 0.055	0.542 ± 0.158	0.697 ± 0.204

Supplemental Table 2

G-factor after 24 h for different compartments of each cell line. Average values were used in the calculations.

		Membrane	Cytoplasm	Nucleus	Average
^{111}In-EGF	MDA-MB-468	0.180	0.176	0.172	0.176
	SQ20B	0.171	0.214	0.167	0.184
	231-H2N	0.209	0.203	0.182	0.198
^{111}In-Tz	MDA-MB-468	0.188	0.221	0.206	0.205
	SQ20B	0.190	0.214	0.199	0.201
	231-H2N	0.193	0.186	0.168	0.182