Role of Vascular Damage and Tumor Microenvironment in the Response of Tumors to SBRT and SRS

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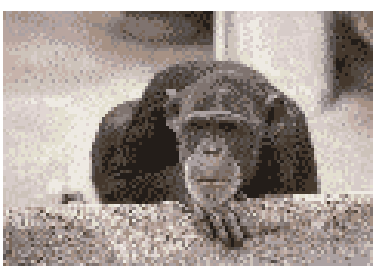
SBRT and SRS

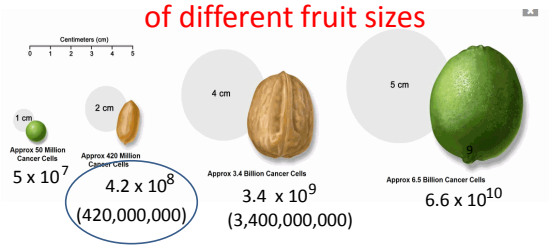
15 - 50 Gy in 1- 5 fractions

Is this enough to kill all the clonogenic tumor cells via direct DNA damage alone ?



NO !!!!

Numbers of cancer cells in tumors of different fruit sizes

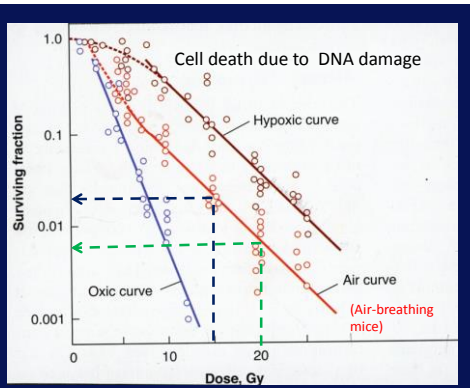


5×10^7

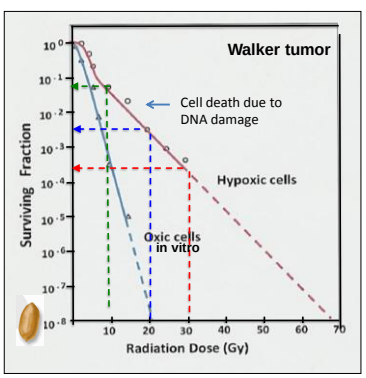
4.2×10^8 (420,000,000)

3.4×10^9 (3,400,000,000)

6.6×10^{10}



S. Rockwell. In E. Hall: Radiobiology for the Radiologist

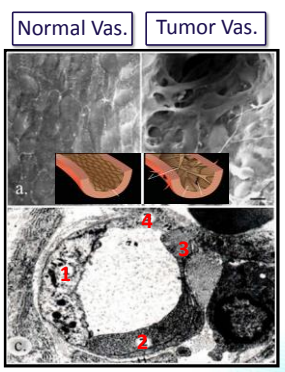


20 Gy kills only 3 logs of tumor cells through DNA damage whereas 8 logs of tumor cells should be killed to control peanut size tumors.

Are there more than DNA double strand breaks in controlling tumors with SRS and SBRT ?

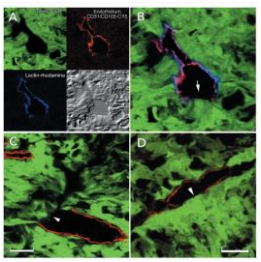
New Radiobiology is involved In SBRT/SRS

- SBRT/SRS cause vascular damages in tumors, thereby inducing ischemic/indirect cell death, in addition to causing direct cell death.
- SBRT/SRS increase anti-tumor immunity.



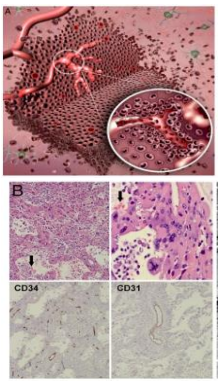
Tumor blood vessels are immature and mosaic

1. Endothelial cell
2. Perycyte
3. Tumor cell
4. Gap



Mosaic Blood Vessels

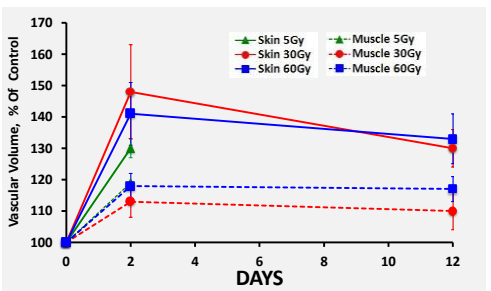
LS174T colon carcinoma (GFP) xenograft



Vasculogenic Mimicry

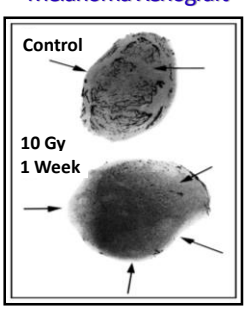
Human Glioma

Normal tissue vessels are radioresistant



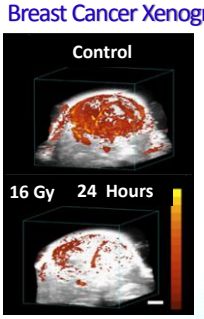
Song et al. Radiology. 94:445-447. 1970.

Melanoma Xenograft

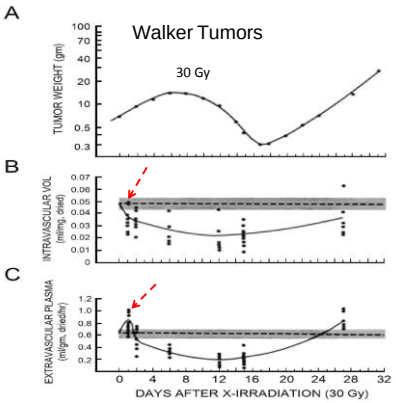


Solevik et al.
Rad Res. 165, 2006

Breast Cancer Xenograft



Kaffas et al.
Angiogenesis ,16: 443, 2013



(Review)

Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS).

Radiat. Res. 177, 311-327, 2012

Tumors and Sites	Methods	Vascular Changes	Authors, (Years)(Ref)
Human cervical carcinoma. 143 Patients	Colpophotography	Irradiation with 1700 R in 10 -12 fr in 15 days, in general, slightly increased surface vascularity at the end of fractionated radiation therapy.	P. Bergsjo (1968) (16)
Human superficial metastatic tumors. 43 patients with 48 tumors	^{133}Xe clearance	Tumors were irradiated with 1100 -3000 rad/wk in 5 fr/wk. Blood flow increased during the 1st wk of treatment and decreased from the 2nd wk of the treatment. In a longer follow up, the tumor blood flow continuously decreased.	M. Mantyla et al. (1982) (17)
Human advanced cervical carcinoma, 14 atients	Color Doppler, Ultrasound	Irradiated with 30 – 65 Gy at 1.9 Gy/fr and 5 fr/wk. In 11 out of 14 tumors, vascularity and blood flow significantly decreased.	J. Pirhonene et al. (1995) (18)
Human squamous carcinoma (14) and adenocarcinomas (3) of cervix	MR imaging	Irradiated with 40-45 Gy/4-5 wk, 5fr/wk. Some tumors showed increased blood perfusion during the first 2 wk, but the perfusion decreased thereafter.	N. Marry et al. (1996) (19)
Human non-small-cell lung cancer. 16 patients	Volumetric perfusion computed tomography	Vascular blood volume and permeability were greater in tumor rim than tumor center. After irradiation with 9 Gy in 2 fr, 18 Gy in 4 fr and 27 Gy in 6 fr, vascular volume increased significantly in tumor rim and slightly in tumor center. Vascular permeability also increased in tumor rim, but not in tumor center.	Q. NG et al. (2007) (20)
Human rectal cancer, 23 patients	Perfusion CT imaging	Irradiated with 25 Gy in 5 fractions (5 Gy x 5) in 1 week. From 3 days after the hypofractionated treatment, trans-endothelial volume constant (K trans)(permeability) slightly increased.	M. Jansen et al. (2009) (21)
Human melanoma xenograft in athymic nude mice in the flank	Angiography	In 1 wk after irradiation with 10.0 – 15.0 Gy, about 35 -45% of 5-15 μm diameter vessels were nonfunctional. The doses required for loss of 50% of the functional vessels with diameters of 5-15, 15-25, and	O. Solewvik (1984) (22)

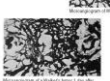
Walker tumor of rat

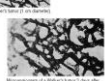
Rubin & Casarett. 1966

10 Gy

Control

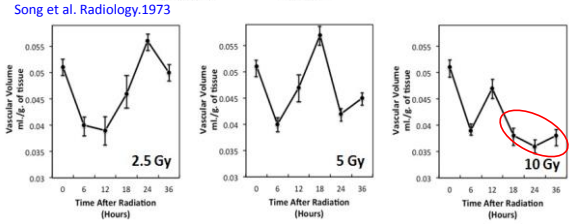
1 Day

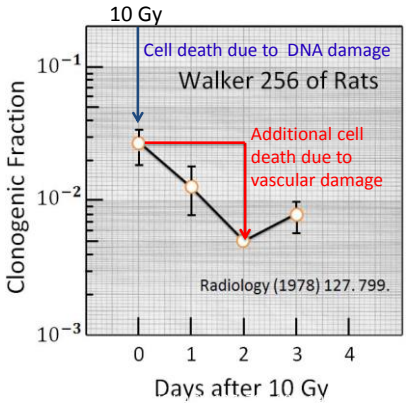


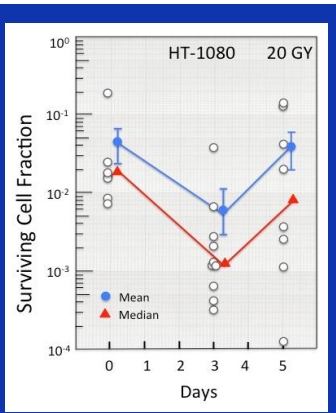


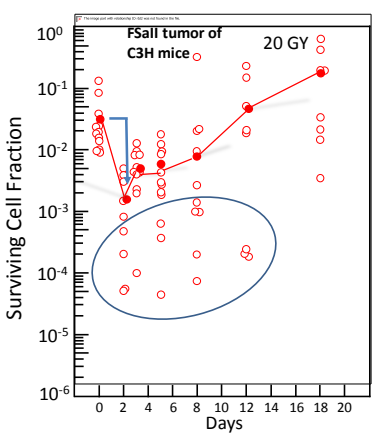
3 Day

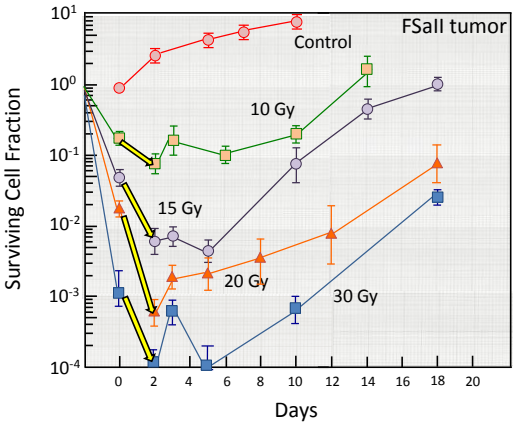
Song et al. Radiology.1973

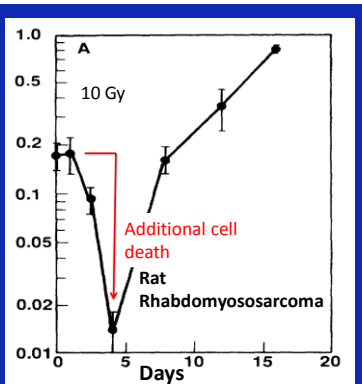



10 Gy
Cell death due to DNA damage
Walker 256 of Rats
Additional cell death due to vascular damage
Radiology (1978) 127. 799.
Clonogenic Fraction
10^{-1}
10^{-2}
10^{-3}
0 1 2 3 4
Days after 10 Gy


HT-1080
20 GY
Surviving Cell Fraction
Mean
Median
0 1 2 3 4 5
Days


FSall tumor of C3H mice
20 GY
Surviving Cell Fraction
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
0 2 4 6 8 10 12 14 16 18 20
Days





T. S. Tenforde et al. Rad Res. 123, p37, 1990

Indirect Tumor Cell Death After High-Dose Irradiation (I)

W Cramer (1932), Vascular damage played an important role in the response of tumors to radiotherapy.

I Lasnitzki (1947), In mouse adenocarcinoma, two-third of tumor cell death after 2000 r irradiation was due to indirect action.

R Merwin and G Algire (1950), In mammary adenocarcinoma of C3H mice, significant fractions of tumor cell death 2-5 days after 2000 -3000 r was due to vascular obstruction.

P Rubin and G Cesarett (1966), Vascular damage preceded tumor cell death in Walker tumor of rat suggesting the tumor cell death was due to the vascular damage.

Indirect Tumor Cell Death After High-Dose Irradiation (II)

B Nicolas and J McNally (1973), Cell death in rat fibrosarcoma RIB5 after 2000 r calculated from the tumor growth delay was 10 times greater than that determined with in vivo-in vitro excision assay method immediately after irradiation. Lack of nutrients caused the post-irradiation secondary cell death leading to tumor growth delay.

J Clement et al (1976), In SCL carcinoma of A/J mice, 1000 or 2000 rad in a single dose markedly decreased the number of living cells/g of tumor in 3 days.

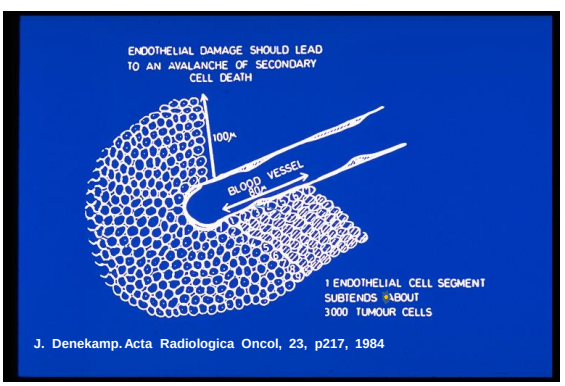
J Clement et al. (1978), In Walker carcinoma of rat irradiated with 1000 r, vascular damage caused significant indirect tumor cell death in 2-3 days.

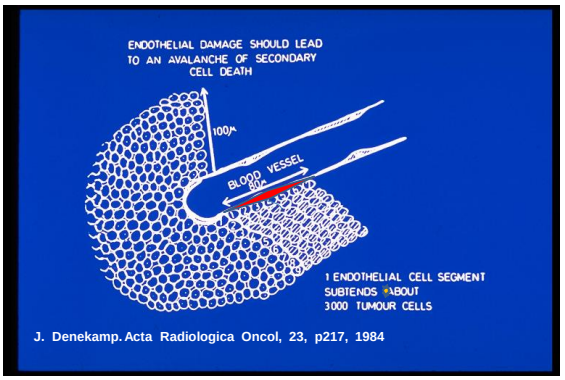
Indirect Tumor Cell Death After High-Dose Irradiation (III)

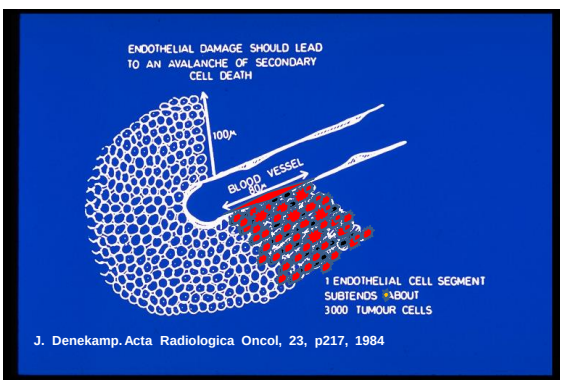
R P Hill (1980), In mouse KHT sarcoma, the absolute numbers of clonogenic cells (tumor-surviving fraction) decreased by a factor of 3-4 for a few days when tumors were left in situ after 2000 rads.

J Denekamp (1984), Endothelial damage leads to an avalanche of secondary tumor cell death.

T S Tenforde et al. (1990), In R2C5 rhabudomyosarcoma of rat, a significant 12-fold decrease in the surviving fractions occurred between days 2 and 4 following 10 Gy irradiation.







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Indirect Tumor Cell Death After High-Dose Irradiation (IV)

M. Kocher (2000), In addition to the direct cytotoxic action, delayed vascular occlusion followed by ischemic tumor cell death contributed to the effect of radiosurgery. The indirect cell death contributed 19-33% of the overall effect of single dose radiotherapy.

G Szeoffert (2002), In human intracranial neoplasm treated with gamma knife radiosurgery, microvascular endothelial cells were the primary target of the high-dose radiation.

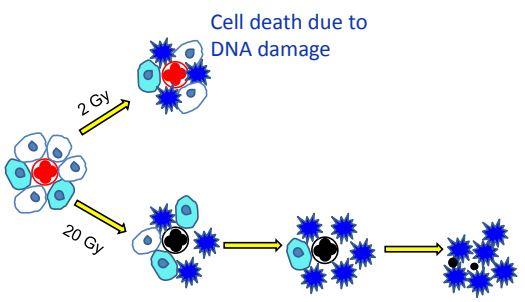
M Garcia-Barros et al. (2003), Indirect cell death due to endothelial cell apoptosis and vascular damage regulate tumor response to radiotherapy.

Indirect Tumor Cell Death After High-Dose Irradiation (V)

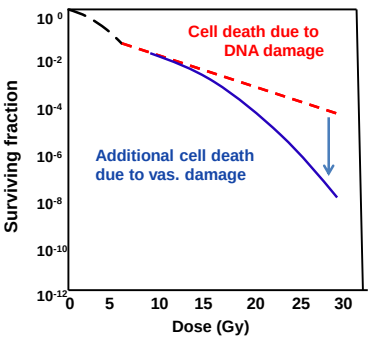
J Kirkpatrick et al. (2008), The total cell death in tumors receiving high-dose irradiation (SBRT or SRS) is the product of direct cell death and indirect cell death caused by vascular damage.

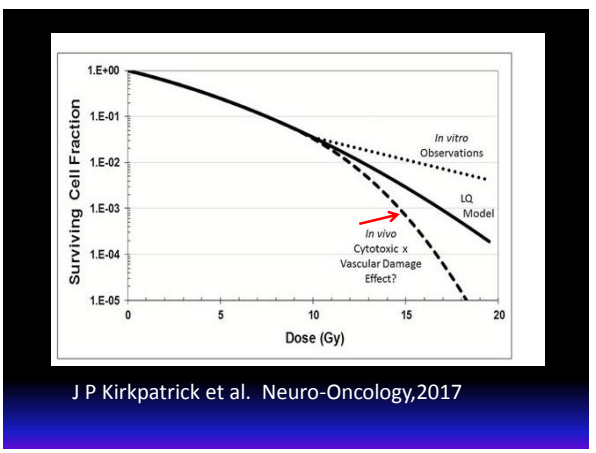
C Song et al.(2014), In HT-1080 human fibrosarcoma xenografts, the surviving cell fraction on day 3 after 20 Gy irradiation was lower than that observed immediately after irradiation by a factor of 10.

M Kim et al. (2015), Irradiation of FSaII fibrosarcoma of mouse with 10-30 Gy caused significant indirect tumor cell death in 2-5 days.

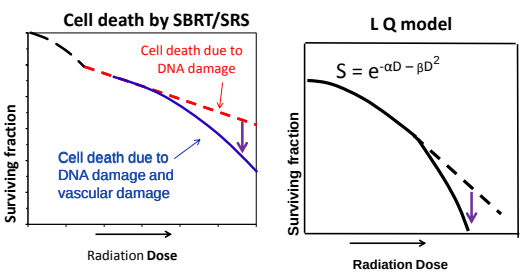


Tumor cell death in vivo





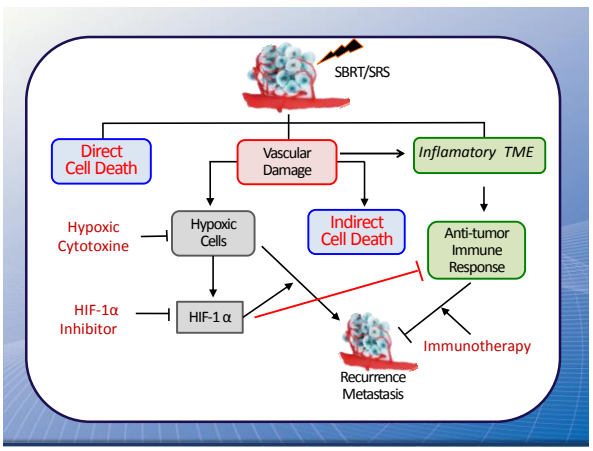
J P Kirkpatrick et al. Neuro-Oncology,2017



Indirect/additional cell death due to vascular damage may render LQ model approximates the total cell death in SBRT and SRS

Hypothesis 1.
Because LQ model (BED) works for SBRT, no new biology is involved in SBRT.

Hypothesis 2.
LQ model (BED) may work for SBRT and SRS because new biology(vascular and immunological effects) is involved..



Thank You