FLASH Therapy – Physics, Biology, Clinical implications and future

DR DURGAPOORNA

ASTER MEDCITY, KOCHI, KERALA

Google Scholar

flash radiotherapy

Articles

About 21,700 results (0.05 sec)

My profile   My library

Any time
Since 2021
Since 2020
Since 2017
Custom range...

Sort by relevance
Sort by date

Any type
include patents
include citations

Review articles

Create alert

Treatment of a first patient with FLASH-radiotherapy
J Bourhis, WJ Sozzi, PG Jorge, O Gaide, C Bailat… - Radiotherapy and …, 2019 - Elsevier
Background When compared to conventional **radiotherapy** (RT) in pre-clinical studies, **FLASH**-RT was shown to reproducibly spare normal tissues, while preserving the anti-tumor activity. This marked increase of the differential effect between normal tissues and tumors …
☆ 99 Cite Cited by 183 Related articles All 5 versions

Clinical translation of FLASH radiotherapy: Why and how?
[PDF] gortec.net
J Bourhis, P Montay-Gruel, PG Jorge, C Bailat… - Radiotherapy and …, 2019 - Elsevier
Over the past decades, technological advances have transformed radiation therapy (RT) into a precise and powerful treatment for cancer patients. Nevertheless, the treatment of radiation-resistant tumors is still restricted by the dose-limiting normal tissue complications. In this …
☆ 99 Cite Cited by 147 Related articles All 6 versions

The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients
[PDF] aacrjournals.org
Free from Publisher
MC Vozenin, P De Fornel, K Petersson… - Clinical Cancer …, 2019 - AACR
Purpose: Previous studies using **FLASH radiotherapy** (RT) in mice showed a marked increase of the differential effect between normal tissue and tumors. To stimulate clinical transfer, we evaluated whether this effect could also occur in higher mammals. Experimental …
☆ 99 Cite Cited by 229 Related articles All 5 versions

Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species
[PDF] pnas.org
Free from Publisher
P Montay-Gruel, MM Acharya… - Proceedings of the …, 2019 - National Acad Sciences
Here, we highlight the potential translational benefits of delivering **FLASH radiotherapy** using ultra-high dose rates (> 100 Gy· s− 1). Compared with conventional dose-rate (CONV; 0.07–0.1 Gy· s− 1) modalities, we showed that **FLASH** did not cause radiation …
☆ 99 Cite Cited by 147 Related articles All 11 versions

Related searches

flash radiotherapy **high dose rate**   flash radiotherapy **varian**

Rationale

60–70% of cancer patients need RT

Dose delivered limited by normal tissue toxicity

Baumann M, Krause M, Overgaard J, Debus J, Bentzen SM, Daartz J, et al. Radiation Oncology in the Era of Precision Medicine. Nat Rev Cancer (2016) 16:234–49.

Concept

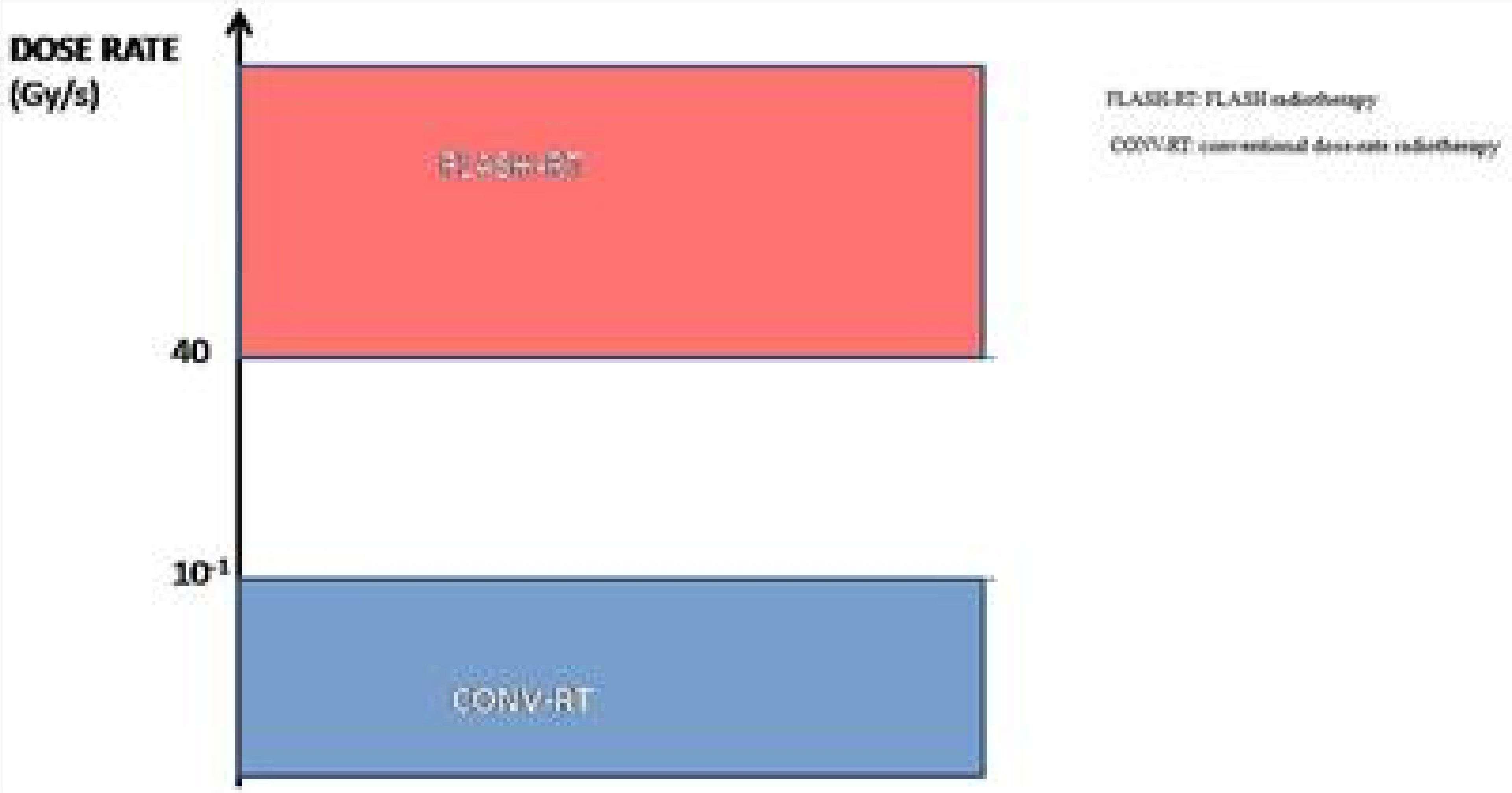
RT Delivery at ultra-high speeds; duration shorter than 0.1 s.

Defined - Single ultra-high dose-rate ($\geq$ 40 Gy/s) radiotherapy.

RT Sparing healthy tissues without compromising anti-tumour action.

Acute O2 depletion.

Michaels, H.B., Epp, E.R., Ling, C.C. and Peterson, E.C., 1978. Oxygen sensitization of CHO cells at ultrahigh dose rates: prelude to oxygen diffusion studies. Radiation research, 76(3), pp.510-521.


DOSE RATE
(Gy/s)
40
10-1
CONV-RT
FLASH-RT: FLASH radiotherapy
CONV-RT: conventional dose-rate radiotherapy

Since 1959

First reported by Dewey & Boag

Ultra-high dose-rate (10-20 kilorads/2 µs) protect bacteria vs Conventional (1000 rads/min)

Town - 3.5×10^9 rad/s – one versus two pulses

Berry - similar results in hamster & HeLa cells - 1,000 rads for 15-ns pulse

Dewey, D.L. and Boag, J.W., 1959. Modification of the oxygen effect when bacteria are given large pulses of radiation. Nature, 183(4673), pp.1450-1451.
Town, C.D., 1967. Effect of high dose rates on survival of mammalian cells. Nature, 215(5103), pp.847-848.
Berry, R.J., Hall, E.J., Forster, D.W., Storr, T.H. and Goodman, M.J., 1969. Survival of mammalian cells exposed to x rays at ultra-high dose-rates. The British journal of radiology, 42(494), pp.102-107.

Skin reactions

67 Gy/s less than 1 or 0.03 Gy/s.

Ten 26 mm diameter circular patches of skin on a single mini-pig to five different dose levels - 22 to 34 Gy- FLASH-RT (300 Gy/s) vs CONV RT 0.083 Gy/s – Assessed at 48 wks post RT

Field, S.B. and Bewley, D.K., 1974. Effects of dose-rate on the radiation response of rat skin. International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine, 26(3), pp.259-267.
Harrington, K.J., 2019. Ultrahigh dose-rate radiotherapy: next steps for FLASH-RT. Clinical Cancer Research, 25(1), pp.3-5.

In 2014

Lung tumors -17 Gy at 0.03 Gy/s – “moderate” and “severe” pulmonary fibrosis at 36 wks

Same dose at 40-60 Gy/s – much less; 30Gy needed for same fibrosis

TGFβ signaling cascade much less in FLASH

Favaudon, V., Caplier, L., Monceau, V., Pouzoulet, F., Sayarath, M., Fouillade, C., Poupon, M.F., Brito, I., Hupé, P., Bourhis, J. and Hall, J., 2014. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science translational medicine, 6(245), pp.245ra93-245ra93.

Brain

Mice exposed to varying dose rates- 0.1 Gy/s to 10 Gy delivered in a single 1.8 µs pulse

Single fraction of 10Gy

Novel object recognition test at 2 months

0.1 Gy/s worse than no RT; improved at >= 30Gy/s

No diffce b/n >=100Gy/s vs no RT

Montay-Gruel, P., Petersson, K., Jaccard, M., Boivin, G., Germond, J.F., Petit, B., Doenlen, R., Favaudon, V., Bochud, F., Bailat, C. and Bourhis, J., 2017. Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s. Radiotherapy and Oncology, 124(3), pp.365-369.

Mice, piglets, cats

SCC nasal cavity in mice - single fraction 25–41 Gy- Tumour control rate 84% at 1 yr, no early/ late effects.

Montay-Gruel, P., Acharya, M.M., Jorge, P.G., Petit, B., Petridis, I.G., Fuchs, P., Leavitt, R., Petersson, K., Gondré, M., Ollivier, J. and Moeckli, R., 2021. Hypofractionated FLASH-RT as an effective treatment against glioblastoma that reduces neurocognitive side effects in mice. Clinical Cancer Research, 27(3), pp.775-784.
Vozenin, M.C., De Fornel, P., Petersson, K., Favaudon, V., Jaccard, M., Germond, J.F., Petit, B., Burki, M., Ferrand, G., Patin, D. and Bouchaab, H., 2019. The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients. Clinical Cancer Research, 25(1), pp.35-42.
Vozenin MC, Hendry JH, Limoli CL. Biological benefits of ultra-high dose rate FLASH radiotherapy: sleeping beauty awoken. Clin Oncol. (2019) 31:407–15.

No Significant Sparing

Whole & partial body synchrotron FLASH RT to mice

WBRT

Beyreuther, E., Karsch, L., Laschinsky, L., Leßmann, E., Naumburger, D., Oppelt, M., Richter, C., Schürer, M., Woithe, J. and Pawelke, J., 2015. Radiobiological response to ultra-short pulsed megavoltage electron beams of ultra-high pulse dose rate. International journal of radiation biology, 91(8), pp.643-652.

Oppelt, M., Baumann, M., Bergmann, R., Beyreuther, E., Brüchner, K., Hartmann, J., Karsch, L., Krause, M., Laschinsky, L., Leßmann, E. and Nicolai, M., 2015. Comparison study of in vivo dose response to laser-driven versus conventional electron beam. Radiation and environmental biophysics, 54(2), pp.155-166.

Smyth, L.M., Donoghue, J.F., Ventura, J.A., Livingstone, J., Bailey, T., Day, L.R., Crosbie, J.C. and Rogers, P.A., 2018. Comparative toxicity of synchrotron and conventional radiation therapy based on total and partial body irradiation in a murine model. Scientific reports, 8(1), pp.1-11.

Venkatesulu, B.P., Sharma, A., Pollard-Larkin, J.M., Sadagopan, R., Symons, J., Neri, S., Singh, P.K., Tailor, R., Lin, S.H. and Krishnan, S., 2019. Ultra high dose rate (35 Gy/sec) radiation does not spare the normal tissue in cardiac and splenic models of lymphopenia and gastrointestinal syndrome. Scientific reports, 9(1), pp.1-9.

Same Anti Tumour Response

Breast, H & N CA xenograft; Human GBM

Mouse lung CA

Murine GBM cells – multiple RT Schedules

Lung CA - T lymphocytes in tumor microenvironment

Bourhis, J., Montay-Gruel, P., Jorge, P.G., Bailat, C., Petit, B., Ollivier, J., Jeanneret-Sozzi, W., Ozsahin, M., Bochud, F., Moeckli, R. and Germond, J.F., 2019. Clinical translation of FLASH radiotherapy: Why and how?Radiotherapy and Oncology, 139, pp.11-17.

Favaudon, V., Caplier, L., Monceau, V., Pouzoulet, F., Sayarath, M., Fouillade, C., Poupon, M.F., Brito, I., Hupé, P., Bourhis, J. and Hall, J., 2014. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science translational medicine, 6(245), pp.245ra93-245ra93.

Rama, N., Saha, T., Shukla, S., Goda, C., Milewski, D., Mascia, A.E., Vatner, R.E., Sengupta, D., Katsis, A., Abel, E. and Girdhani, S., 2019. Improved tumor control through t-cell infiltration modulated by ultra-high dose rate proton flash using a clinical pencil beam scanning proton system. International Journal of Radiation Oncology, Biology, Physics, 105(1), pp.S164-S165.

Physics

Modify gun current

Modulator charge rate

Beam steering values

Disabled the interlocks

Unstable

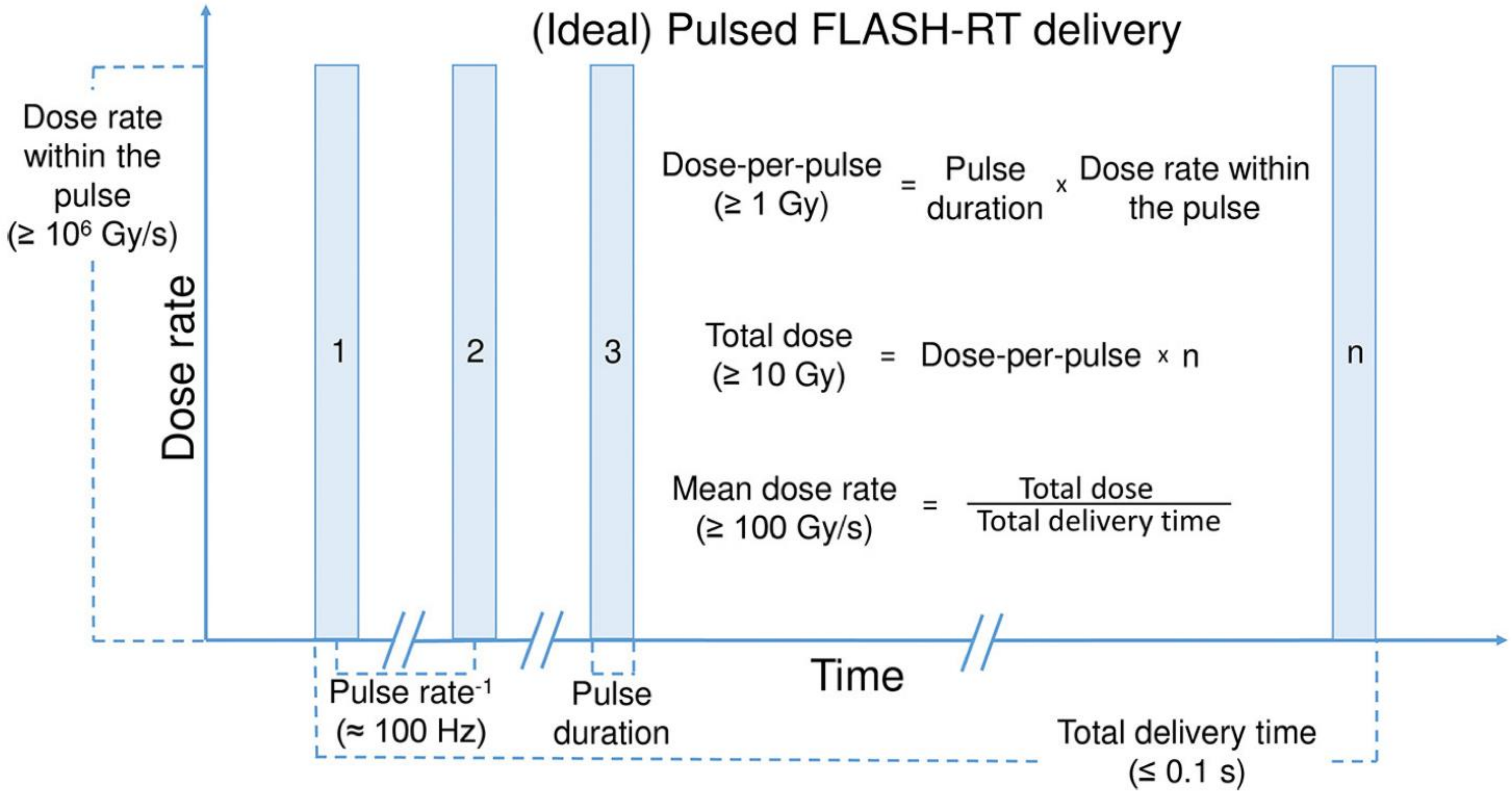


FIGURE 1 | (Ideal) Pulsed FLASH-RT delivery. A schematic view of a pulsed beam delivery, specifying some parameters which seems to be important for inducing the FLASH effect.

Influenced by

Dose rate

Total dose

Pulse rate

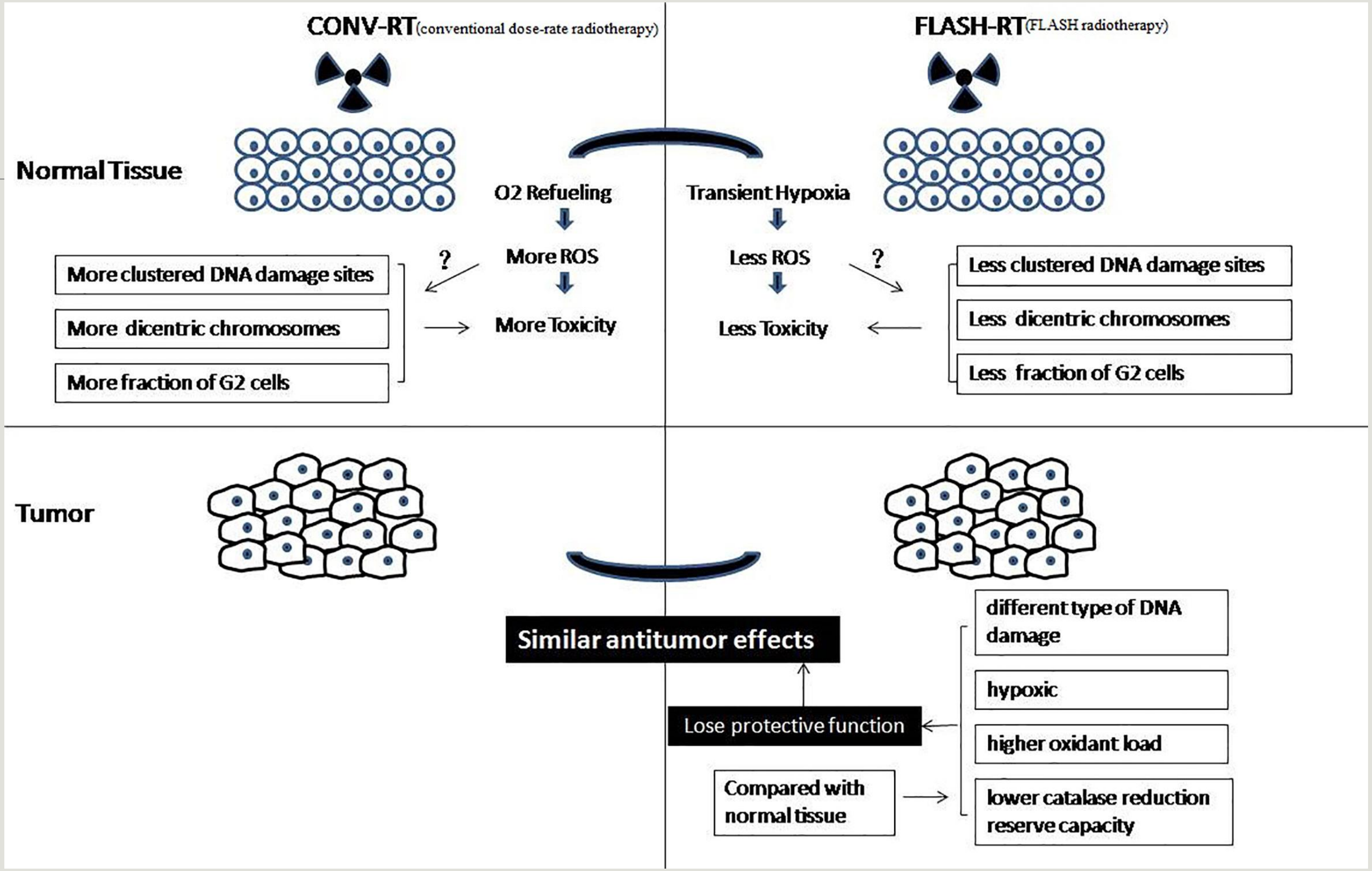
Fractionation

Modality of radiation

Duration (FLASH effect disappears as pulse duration increases from <1 second to 10 seconds)

Capillary Oxygen Tension

Biology



CONV-RT(conventional dose-rate radiotherapy)
FLASH-RT(FLASH radiotherapy)
Normal Tissue
O2 Refueling
More ROS
More Toxicity
?
More clustered DNA damage sites
More dicentric chromosomes
More fraction of G2 cells
Transient Hypoxia
Less ROS
Less Toxicity
?
Less clustered DNA damage sites
Less dicentric chromosomes
Less fraction of G2 cells
Tumor
Similar antitumor effects
Lose protective function
Compared with normal tissue
different type of DNA damage
hypoxic
higher oxidant load
lower catalase reduction reserve capacity

Findings

Induce hypoxia -> protection

Number of DNA damage sites less

Fewer dicentric chromosomes; G2 cell cycle arrest

Myosin light chain activation

Bourhis, J., Montay-Gruel, P., Jorge, P.G., Bailat, C., Petit, B., Ollivier, J., Jeanneret-Sozzi, W., Ozsahin, M., Bochud, F., Moeckli, R. and Germond, J.F., 2019. Clinical translation of FLASH radiotherapy: Why and how?. Radiotherapy and Oncology, 139, pp.11-17.

Auer, S., Hable, V., Greubel, C., Drexler, G.A., Schmid, T.E., Belka, C., Dollinger, G. and Friedl, A.A., 2011. Survival of tumor cells after proton irradiation with ultra-high dose rates. Radiation Oncology, 6(1), pp.1-8.

Kim, Y.E., Gwak, S.H., Hong, B.J., Oh, J.M., Choi, H.S., Kim, M.S., Oh, D., Lartey, F.M., Rafat, M., Schüler, E. and Kim, H.S., 2021. Effects of Ultra-high doserate FLASH Irradiation on the Tumor Microenvironment in Lewis Lung Carcinoma: Role of Myosin Light Chain. International Journal of Radiation Oncology Biology* Physics, 109(5), pp.1440-1453.*

Differential responses b/n tumour & Normal

- Different types of DNA damage
- Solid tumors are hypoxic
- Different abilities to scavenge hydrogen peroxide products
- Immune mediated

Favaudon, V., Caplier, L., Monceau, V., Pouzoulet, F., Sayarath, M., Fouillade, C., Poupon, M.F., Brito, I., Hupé, P., Bourhis, J. and Hall, J., 2014. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science translational medicine, 6(245), pp.245ra93-245ra93.

Bourhis, J., Montay-Gruel, P., Jorge, P.G., Bailat, C., Petit, B., Ollivier, J., Jeanneret-Sozzi, W., Ozsahin, M., Bochud, F., Moeckli, R. and Germond, J.F., 2019. Clinical translation of FLASH radiotherapy: Why and how?. Radiotherapy and Oncology, 139, pp.11-17.

Spitz, D.R., Buettner, G.R., Petronek, M.S., St-Aubin, J.J., Flynn, R.T., Waldron, T.J. and Limoli, C.L., 2019. An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses. Radiotherapy and Oncology, 139, pp.23-27.

Probable Mechanisms

All O2 consumed -> more ele liberated -> more ionisation events -> Maximise the diffces in redox metabolism & free radical chemistry.

Prevention of CK activation- TGF -β not released in normal lung after FLASH.

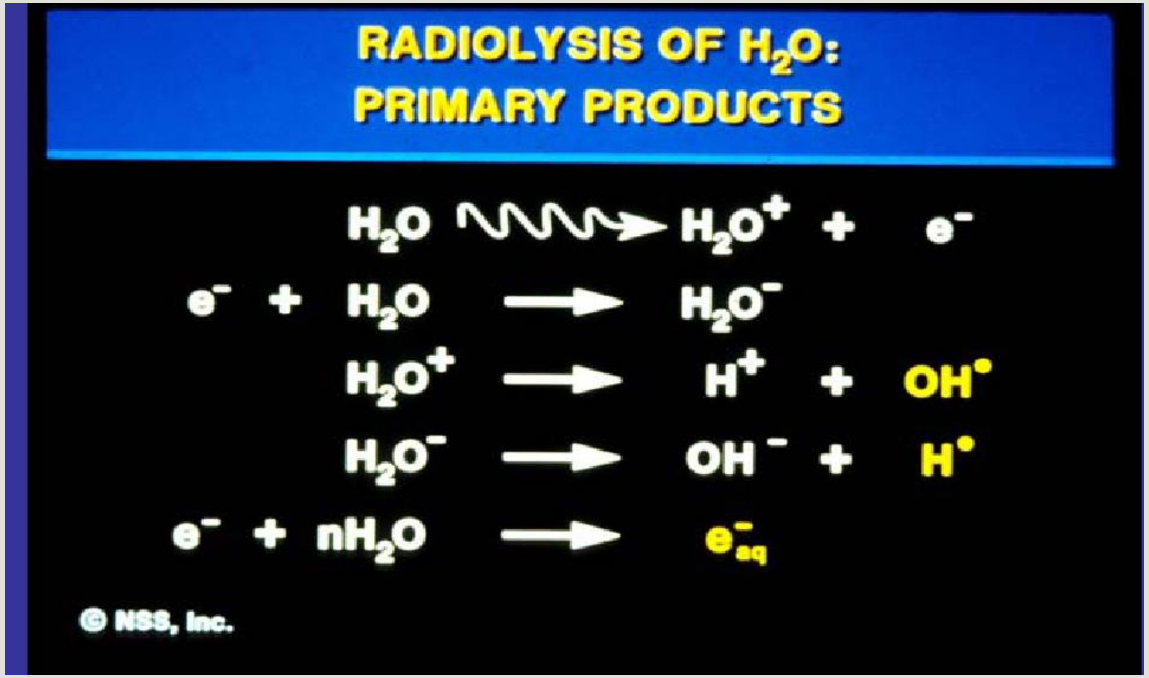
More effective killing of hypoxic cancerous cells with added sparing normal tissue.

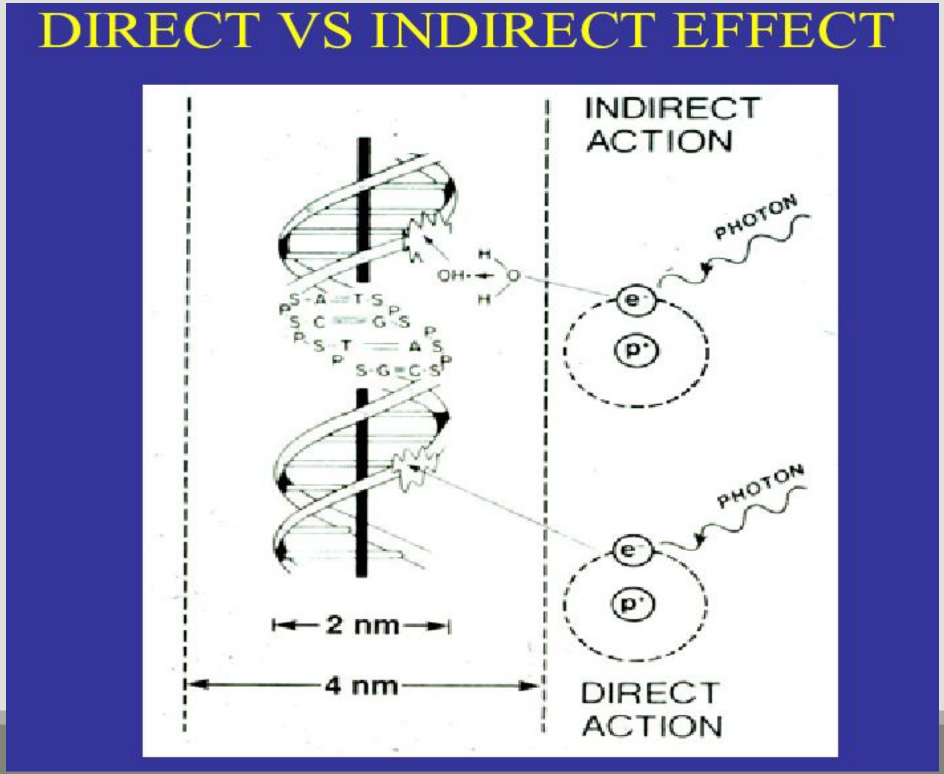
Symonds, P. and Jones, G.D.D., 2019. FLASH radiotherapy: the next technological advance in radiation therapy?. Clinical Oncology, 31(7), pp.405-406.

O2 Depletion

Low LET -> Indirect damage – fixed by O2 – Peroxyl radical

O2 depletion at ultra-high dose rates ->radioresistance





Significantly deplete O_2 before it can replenish -> small window of radiobiological hypoxia.

As dose rate inc, cellular survival mimics cells irradiated in hypoxic conditions.

At physiological O_2 levels (1.6–8.3%) - the sparing effect depends on oxygen concentration

Weiss, H., Epp, E.R., Heslin, J.M., Ling, C.C. and Santomasso, A., 1974. Oxygen depletion in cells irradiated at ultra-high dose-rates and at conventional dose-rates. International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine, 26(1), pp.17-29.

Adrian, G., Konradsson, E., Lempart, M., Bäck, S., Ceberg, C. and Petersson, K., 2020. The FLASH effect depends on oxygen concentration. The British journal of radiology, 92(1106), p.20190702.

Physoxia

Physiologically relevant oxygen concentrations – 3.4 to 6.8% O2

Increases with depth from the surface of the skin

McKeown, S.R., 2014. Defining normoxia, physoxia and hypoxia in tumours—implications for treatment response. The British journal of radiology, 87(1035), p.20130676.
Carreau, A., Hafny-Rahbi, B.E., Matejuk, A., Grillon, C. and Kieda, C., 2011. Why is the partial oxygen pressure of human tissues a crucial parameter? Small molecules and hypoxia. Journal of cellular and molecular medicine, 15(6), pp.1239-1253.

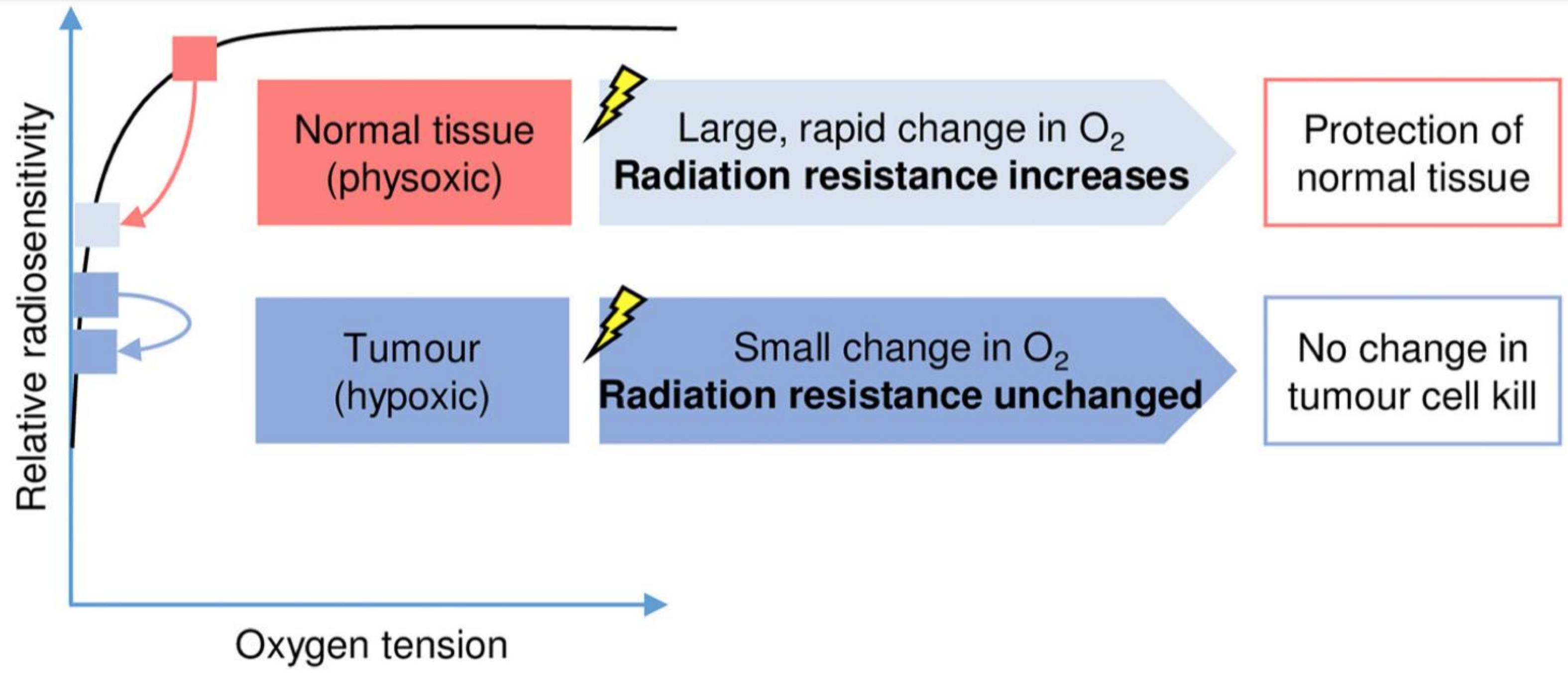


FIGURE 2 | The oxygen depletion hypothesis. The relationship between oxygen tension (horizontal axis) and radiation sensitivity (vertical axis) is shown schematically and has been widely reported (40, 41). In response to FLASH-RT, the physiological level of oxygen (physoxic) found in normal tissues decreases rapidly (pink arrow) and has an important impact on radiation sensitivity. This temporary or transient hypoxia protects the normal tissues as radiation resistance increases. In contrast, oxygen levels are low (hypoxic) in tumor tissues and consequently FLASH-RT has less of an impact on radiation sensitivity.

Reduced ROS

No cognitive impairment at >100 Gy/s - Increasing local O2 with Carbogen breathing nullified this

Zebrafish embryos -> FLASH-RT + ROS scavenger (NAC, amifostine) - no effect on zebrafish length 5 days post-RT

CONV-RT alone shorter than RT+ ROS scavenger

Montay-Gruel, P., Acharya, M.M., Petersson, K., Alikhani, L., Yakkala, C., Allen, B.D., Ollivier, J., Petit, B., Jorge, P.G., Syage, A.R. and Nguyen, T.A., 2019. Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species. Proceedings of the National Academy of Sciences, 116(22), pp.10943-10951.

Maintained Tumour Control

Higher labile iron in tumor vs normal tissue

Differences in oxidative metabolism b/n normal & tumor

More rapid removal & decay of organic hydroperoxides & free radicals derived from peroxidation chain reactions in normal

Spitz, D.R., Buettner, G.R., Petronek, M.S., St-Aubin, J.J., Flynn, R.T., Waldron, T.J. and Limoli, C.L., 2019. An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses. Radiotherapy and Oncology, 139, pp.23-27.

DNA repair proficiency

Hypoxia -> repression of DNA repair pathways - homologous recombination (HR), non-homologous end joining (NHEJ), and base excision repair (BER)

Reoxygenation by diffusion after FLASH-RT occurs at 10^{-3} s

Chemical marker of hypoxia eg pimonidazole

Chan, N. and Bristow, R.G., 2010. "Contextual" synthetic lethality and/or loss of heterozygosity: tumor hypoxia and modification of DNA repair. Clinical Cancer Research, 16(18), pp.4553-4560.

Ling, C.C., Michaels, H.B., Epp, E.R. and Peterson, E.C., 1978. Oxygen diffusion into mammalian cells following ultrahigh dose rate irradiation and lifetime estimates of oxygen-sensitive species. Radiation research, 76(3), pp.522-532.

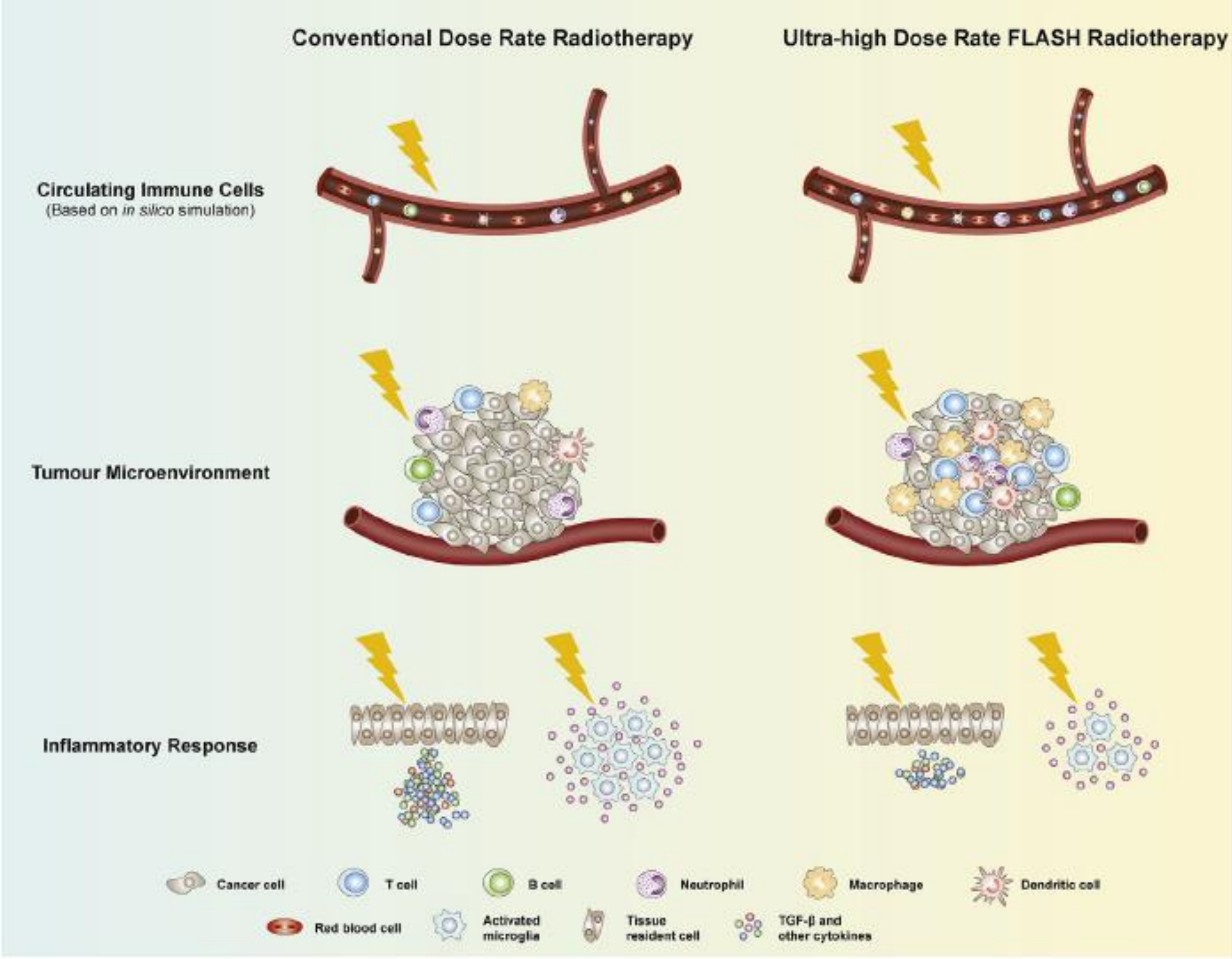
Modified Immune Response in vivo

After 2Gy x 30, 98.8% of the blood pool exposed to > 0.5Gy - chromosomal aberrations

Less immune system wide activation & maturation

Improved recruitment of T lymphocytes into tumor microenvironment after FLASH RT

Durante, M., Bräuer-Krisch, E. and Hill, M., 2018. Faster and safer? FLASH ultra-high dose rate in radiotherapy. The British journal of radiology, 91(1082), p.20170628.
Yovino, S., Kleinberg, L., Grossman, S.A., Narayanan, M. and Ford, E., 2013. The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells. Cancer investigation, 31(2), pp.140-144.



Conventional Dose Rate Radiotherapy
Ultra-high Dose Rate FLASH Radiotherapy
Circulating Immune Cells
(Based on *in silico* simulation)
Tumour Microenvironment
Inflammatory Response
Cancer cell
T cell
B cell
Neutrophil
Macrophage
Dendritic cell
Red blood cell
Activated microglia
Tissue resident cell
TGF-β and other cytokines

Radiobiology…

Too short for reoxygenation, repopulation, redistribution

Needs higher dose to cause same degree toxicity - α/β of healthy tissue change.

Killing of the highly “dose-per-fraction-sensitive” intratumor endothelial cells

Lin, B., Gao, F., Yang, Y., Wu, D., Zhang, Y., Feng, G., Dai, T. and Du, X., 2021. FLASH Radiotherapy: History and Future. Frontiers in Oncology, 11, p.1890.

Bodo, S., Campagne, C., Thin, T.H., Higginson, D.S., Vargas, H.A., Hua, G., Fuller, J.D., Ackerstaff, E., Russell, J., Zhang, Z. and Klingler, S., 2019. Single-dose radiotherapy disables tumor cell homologous recombination via ischemia/reperfusion injury. The Journal of clinical investigation, 129(2), pp.786-801.

Clinical Implications

Dose escalation in radioresistant

Normal tissue protection in radiosensitive with high toxicity

Wide variation in studies - total dose; Single fraction; control group

Dose-modifying factor of about 20–40% in FLASH-RT vs CONV-RT – only at >= 10Gy (6-8Gy Conv)

Vozenin, M.C., Hendry, J.H. and Limoli, C.L., 2019. Biological benefits of ultra-high dose rate FLASH radiotherapy: sleeping beauty awoken. Clinical oncology, 31(7), pp.407-415.

In 2019

75/M
Multiresistant CD30+ T cell

Cutaneous T cell Lymphoma

106 Gy/s in each

Ten discreet 1 µs pulses

Total dose of 15Gy

Grade I Skin rxn

Bourhis, J., Sozzi, W.J., Jorge, P.G., Gaide, O., Bailat, C., Duclos, F., Patin, D., Ozsahin, M., Bochud, F., Germond, J.F. and Moeckli, R., 2019. Treatment of a first patient with FLASH-radiotherapy. Radiotherapy and oncology, 139, pp.18-22.

?Role of Chemo??

Single versus multiple fractions

Motion management

Adaptive RT

Role of Sx?

Future

Mice – Lungs – FLASH with Ele; Conv with Cs 137 photons

Mice – Brain – FLASH with circular; Conv with Square fields; same area

Favaudon, V., Caplier, L., Monceau, V., Pouzoulet, F., Sayarath, M., Fouillade, C., Poupon, M.F., Brito, I., Hupé, P., Bourhis, J. and Hall, J., 2014. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science translational medicine, 6(245), pp.245ra93-245ra93.

Montay-Gruel, P., Bouchet, A., Jaccard, M., Patin, D., Serduc, R., Aim, W., Petersson, K., Petit, B., Bailat, C., Bourhis, J. and Bräuer-Krisch, E., 2018. X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. Radiotherapy and Oncology, 129(3), pp.582-588.

Definitely Maybe..

One pulse better than 2

If 4.5–20 MeV electron beams, only superficial lesions

For deep seated, protons- scattered or scanned – decreases dose rate

Berry, R.J., Hall, E.J., Forster, D.W., Storr, T.H. and Goodman, M.J., 1969. Survival of mammalian cells exposed to x rays at ultra-high dose-rates. The British journal of radiology, 42(494), pp.102-107.
van Marlen, P., Dahele, M., Folkerts, M., Abel, E., Slotman, B.J. and Verbakel, W.F., 2020. Bringing FLASH to the clinic: treatment planning considerations for ultrahigh dose-rate proton beams. International Journal of Radiation Oncology Biology* Physics, 106(3), pp.621-629.*

Too Complex?

Multiple-field conformal radiation

Too short time for movement of MLC & mechanical gantry rotation, so multi-mechanical gantry

Real time adaptation

Maxim, P.G., Tantawi, S.G. and Loo Jr, B.W., 2019. PHASER: A platform for clinical translation of FLASH cancer radiotherapy. Radiotherapy and Oncology, 139, pp.28-33.

Modified Systems

Electron linacs - 4.5 MeV and 6 MeV ele beams

Synchrotron – ultra HDR microbeam RT - 18000 Gy/s

Proton accelerators - dose-rate > 40 Gy/ s

Favaudon, V., Caplier, L., Monceau, V., Pouzoulet, F., Sayarath, M., Fouillade, C., Poupon, M.F., Brito, I., Hupé, P., Bourhis, J. and Hall, J., 2014. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science translational medicine, 6(245), pp.245ra93-245ra93.

Montay-Gruel, P., Bouchet, A., Jaccard, M., Patin, D., Serduc, R., Aim, W., Petersson, K., Petit, B., Bailat, C., Bourhis, J. and Bräuer-Krisch, E., 2018. X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. Radiotherapy and Oncology, 129(3), pp.582-588.

Patriarca, A., Fouillade, C., Auger, M., Martin, F., Pouzoulet, F., Nauraye, C., Heinrich, S., Favaudon, V., Meyroneinc, S., Dendale, R. and Mazal, A., 2018. Experimental set-up for FLASH proton irradiation of small animals using a clinical system. International Journal of Radiation Oncology Biology* Physics, 102(3), pp.619-626.*

FLASHForward Consortium

Multiple synchronized linear accelerators

Powerful recirculating accelerator

Xray tubes

TCP assays often terminated at 80 to 180 days post RT – at least 1 yr FU.

Hendry, J., 2020. Taking care with FLASH radiation therapy. International journal of radiation oncology, biology, physics, 107(2), pp.239-242.

Very High Energy Electron (VHEE) beams

Beam energies of 100–250 MeV.

Good depth penetration; Sharp penumbra

Less sensitive to tissue heterogeneity vs conventional X-rays

Beam can be focused to the tumor volume

Bazalova-Carter, M., Liu, M., Palma, B., Dunning, M., McCormick, D., Hemsing, E., Nelson, J., Jobe, K., Colby, E., Koong, A.C. and Tantawi, S., 2015. Comparison of film measurements and Monte Carlo simulations of dose delivered with very high-energy electron beams in a polystyrene phantom. Medical physics, 42(4), pp.1606-1613.

Schüler, E., Eriksson, K., Hynning, E., Hancock, S.L., Hiniker, S.M., Bazalova-Carter, M., Wong, T., Le, Q.T., Loo Jr, B.W. and Maxim, P.G., 2017. Very high-energy electron (VHEE) beams in radiation therapy; Treatment plan comparison between VHEE, VMAT, and PPBS. Medical physics, 44(6), pp.2544-2555.

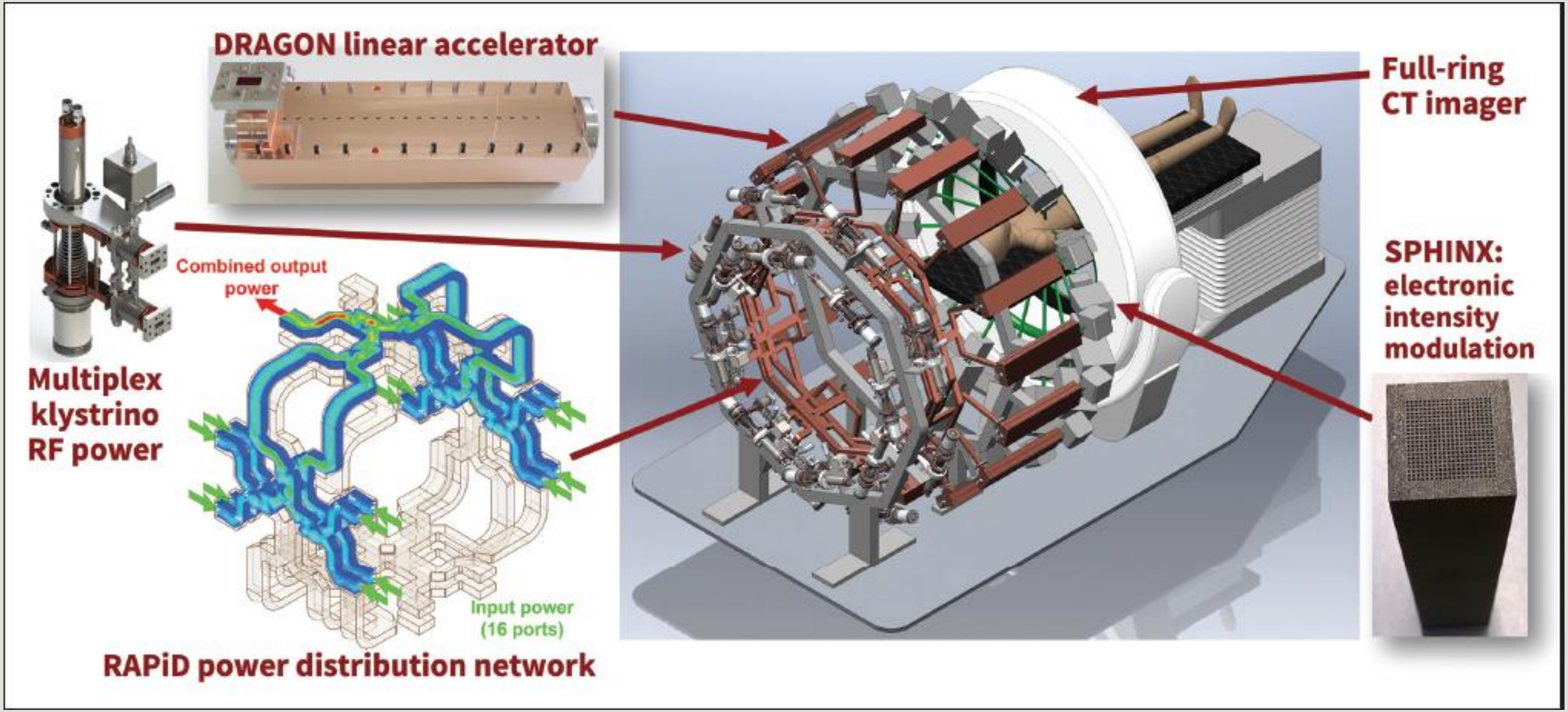
PHASER radiotherapy system

Pluridirectional High-energy Agile Scanning Electronic Radiotherapy

Highly conformal intensity modulated FLASH-RT

Highly adapted image-guidance techniques

Maxim, P.G., Tantawi, S.G. and Loo Jr, B.W., 2019. PHASER: A platform for clinical translation of FLASH cancer radiotherapy. Radiotherapy and Oncology, 139, pp.28-33.


DRAGON linear accelerator
Full-ring
CT imager
Multiplex
klystrino
RF power
Combined output
power
Input power
(16 ports)
RAPiD power distribution network
SPHINX:
electronic
intensity
modulation

Before use..

Differences between animal models and human

Acute and late toxicity

Redefine Definitive RT dose

RCT ideally

At the very least, a positive phase II, single-arm study

The first FLASH study in humans

Actively enrolling

Metastatic bone cancer

Less than 1 second

Cincinnati Children's
changing the outcome together

Treatment-related side effects

Efficacy of treatment

Pain relief

Lausanne University

Melanoma skin metastases

7-21 MeV

3.3 Gy/s

Mobetron

Ralston Paterson

(1897–1981)

"We know now with remarkable accuracy, exactly how much radiation we are giving. Indeed, our dosimetry is now a lot more exact than that of other medical sciences." (1969)[461]

drdurga.poorna@asterhospital.com
durgapoorna@gmail.com