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MD Anderson
~~Cancer~~ Center
Making Cancer History®

FLASH Photon: One small step for Physics, One huge leap for cancer therapy

Julianne Pollard-Larkin, PhD

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Holthusen's Hypothesis

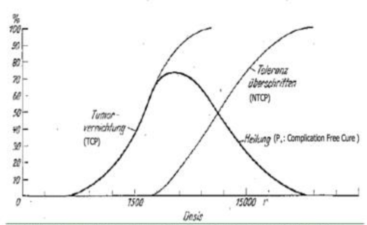

Figure 2.1: Sigmoid shape dose-response curves for tumor control and normal tissue complications. Adapted from Holthusen [Holthusen, Strahlentherapie, 1936].

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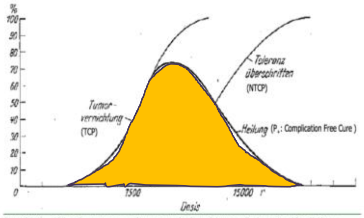
Holthusen’s Hypothesis



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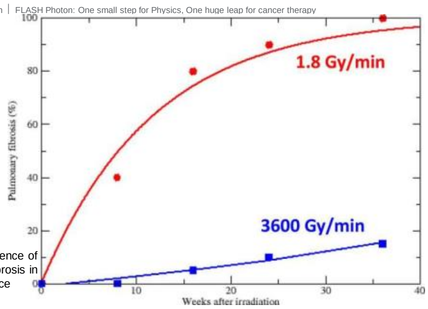
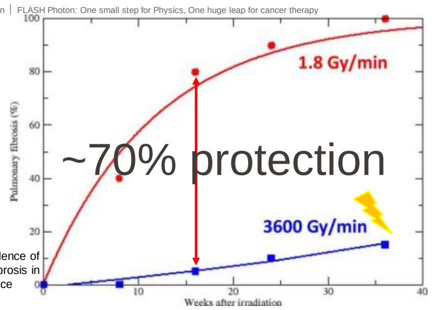
Lausanne University Hospital (CHUV)



Time dependence of pulmonary fibrosis in C57BL/6J mice

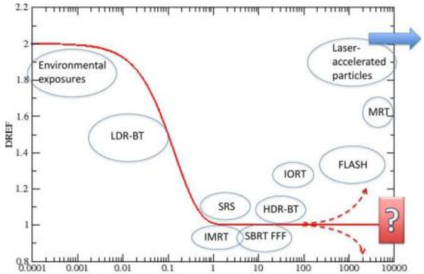
Br J Radiol. 2018 Feb; 91(1082): 20170628.



~70% protection

Time dependence of pulmonary fibrosis in C57BL/6J mice

Br J Radiol. 2018 Feb; 91(1082): 20170628.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5965780/figure/f2/

FLASH History

1959: Oxygen Effect Reduction:
Dewey and Boag noted reduced oxygen effect in bacteria during pulsed e- beams

1971: High Dose Rate RT causes Hypoxia:
Hornsey and Bewley showed evidence that high dose rate (6krads/min) electron beams induces hypoxia

2014: FLASH is reborn:
Favaudon et al published report on differential response to FLASH (≥ 40 Gy/sec) between normal and tumor tissue in mice

Oxygen Effect 1968

PULSED IRRADIATION OF CELLS IN OXYGEN 323

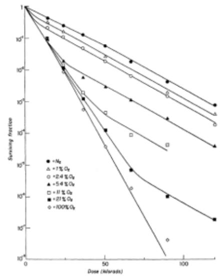


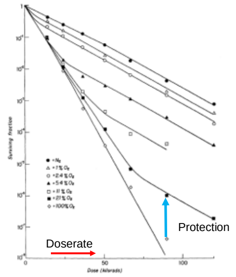
FIG. 2. Survival of *E. coli* B/r irradiated with high-intensity pulsed electrons in the presence of various concentrations of oxygen: dose delivered in single pulses of time duration of about 30 nanoseconds.

RADIATION RESEARCH **34**, 320–325 (1968)

Oxygen Effect 1968

Survival increases with dose rate and decreasing O2

PULSED IRRADIATION OF CELLS IN OXYGEN 323



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RADIATION RESEARCH **34**, 320–325 (1968)

Requirements to see FLASH Effect

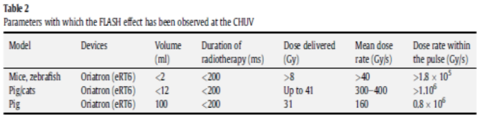


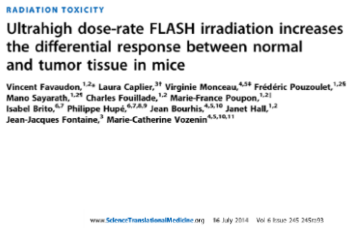
Table 2

Parameters with which the FLASH effect has been observed at the CHUV

Model	Devices	Volume (ml)	Duration of radiotherapy (ms)	Dose delivered (Gy)	Mean dose rate (Gy/s)	Dose rate within the pulse (Gy/s)
Mice, zebrafish	Oriatron (eRT6)	<2	<200	>8	>40	$>1.8 \times 10^5$
Pig/cats	Oriatron (eRT6)	<12	<200	Up to 41	300–400	$>1.10^6$
Pig	Oriatron (eRT6)	100	<200	31	160	0.8×10^6

M.-C. Vozenin et al. / Clinical Oncology 31 (2019) 407–415

FLASH RT Spares Lung and is Toxic to Tumors!



RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2||] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

www.ScienceTranslationalMedicine.org 16 July 2014 Vol 6 Issue 245 245ra93

FLASH vs CONV in Orthotopic Lung Tumor Model

Evolution of TC-1 Luc+ orthotopic lung tumors after CONV (4.5 MeV e- 0.03 Gy/s) versus FLASH (4.5 MeV e- 60 Gy/s) irradiation.

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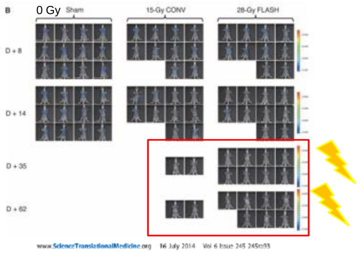


www.ScienceTranslationalMedicine.org 16 July 2014 Vol 6 Issue 245 245ra93

FLASH RT Spares Memory!

Radiotherapy and Oncology 124 (2017) 365–369

Contents lists available at ScienceDirect

Radiotherapy and Oncology

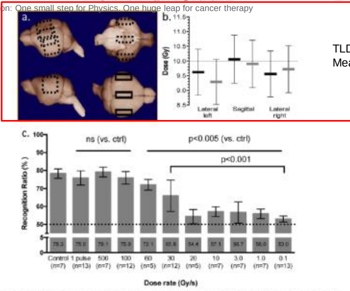
journal homepage: www.thegreenjournal.com

Flash irradiation

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

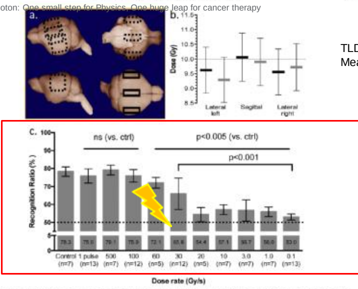
Pierre Montay-Gruel[a,b,1], Kristoffer Petersson[c,1], Maud Jaccard[c], Gaël Boivin[a], Jean-François Germond[c], Benoit Petit[a], Raphaël Doenlen[d], Vincent Favaudon[b], François Bochud[c], Claude Bailat[c], Jean Bourhis[a,1], Marie-Catherine Vozenin[a,*,1]

[a] Department of Radiation Oncology/DO/CHUV, Lausanne University Hospital, Switzerland; [b] Institut Curie, INSERM U1021/CNRS UMR3347, Université Paris-Saclay, Orsay, France; [c] Institute of Radiation Physics (IRA), Lausanne University Hospital; and [d] Faculty of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Switzerland



TLD Measurements

Fig. 1. TLD measurements in the brain of a mouse cadaver. a: TLD chips positions at the center of the brain (sagittal) and at either side of the brain (Lateral left and right); b: measurement results for a 10 Gy WBI delivery with a single 1.8 μs electron pulse (filled markers) and at a 0.1 Gy/s dose rate (open markers). Error bars represent the (expanded, k = 2) uncertainty in the absorbed dose measurements with the TLD; c: Evaluation of the Recognition Ratio (RR) two months post irradiation for groups of mice that received sham irradiation (Control) and 10 Gy WBI with a dose rate of 0.1, 1.0, 3, 10, 20, 30, 60, 100, or 500 Gy/s, or with a single 1.8 μs electron pulse (1 Pulse). Bars represent mean values and whiskers the standard deviations.



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Phase I FLASH RT Cat Dose Escalation Trial

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375

Clinical Trial Brief Report

Clinical Cancer Research

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1,6], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]

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6 cats with SCC of nasal planum (stage 4-T2, 2-T3, 25-41 Gy)

Dosimetry:
TLDs or alanine pellets for dosimetry

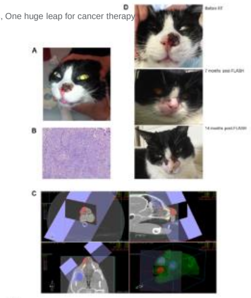


Figure 2.

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375

FLASH RT Spares Pig Skin

FLASH RT ~ 300 Gy/sec

Gafchromic EBT3 and alanine pellets for dosimetry

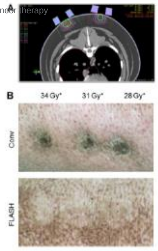
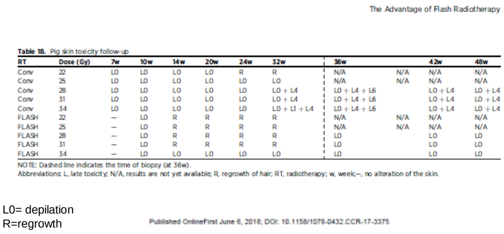


Figure 1.
A, Dose distributions calculated in XiO for the mini pig irradiation; a transversal slice reconstructed from the CT-scan showed beam apertures and dose distributions. **B,** Thirty-six weeks postradiotherapy, macroscopic visualization showed severe fibronecrotic lesions in Conv-irradiated spots and the normal appearance of the skin in FLASH-irradiated spots (*, maximal dose at 12 mm; ref. 5). (*Continued on the following page.*)

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375

FLASH RT Spares Pig Skin



The Advantage of Flash Radiotherapy

Table 1B. Pig skin toxicity follow-up

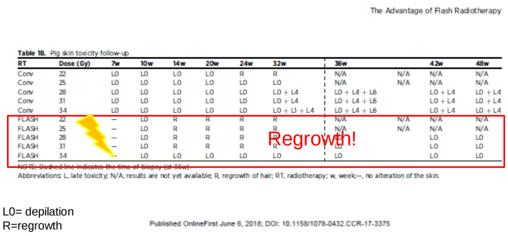
RT	Dose (Gy)	7w	10w	14w	20w	24w	32w	36w		42w	48w
Conv	22	L0	L0	L0	L0	R	R	N/A	N/A	N/A	N/A
Conv	25	L0	L0	L0	L0	L0	L0	N/A	N/A	N/A	N/A
Conv	28	L0	L0	L0	L0	L0	L0 + L4	L0 + L4 + L6		L0 + L4	L0 + L4
Conv	31	L0	L0	L0	L0	L0	L0 + L4	L0 + L4 + L6		L0 + L4	L0 + L4
Conv	34	L0	L0	L0	L0	L0	L0 + L1 + L4	L0 + L4 + L6		L0 + L4	L0 + L4
FLASH	22	—	L0	R	R	R	R	N/A	N/A	N/A	N/A
FLASH	25	—	L0	R	R	R	R	N/A	N/A	N/A	N/A
FLASH	28	—	L0	R	R	R	R	L0		L0	L0
FLASH	31	—	L0	R	R	R	R	L0		L0	L0
FLASH	34	—	L0	L0	L0	L0	L0	L0		L0	L0

NOTE: Dashed line indicates the time of biopsy (at 36w).
Abbreviations: L, late toxicity; N/A, results are not yet available; R, regrowth of hair; RT, radiotherapy; w, week;—, no alteration of the skin.

L0= depilation
R=regrowth

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375

FLASH RT Spares Pig Skin



The Advantage of Flash Radiotherapy

Table 1B. Pig skin toxicity follow-up

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Conv	25	L0	L0	L0	L0	L0	L0	N/A	N/A	N/A	N/A
Conv	28	L0	L0	L0	L0	L0	L0 + L4	L0 + L4 + L6		L0 + L4	L0 + L4
Conv	31	L0	L0	L0	L0	L0	L0 + L4	L0 + L4 + L6		L0 + L4	L0 + L4
Conv	34	L0	L0	L0	L0	L0	L0 + L1 + L4	L0 + L4 + L6		L0 + L4	L0 + L4
FLASH	22	—	L0	R	R	R	R	N/A	N/A	N/A	N/A
FLASH	25	—	L0	R	R	R	R	N/A	N/A	N/A	N/A
FLASH	28	—	L0	R	R	R	R	L0		L0	L0
FLASH	31	—	L0	R	R	R	R	L0		L0	L0
FLASH	34	—	L0	L0	L0	L0	L0	L0		L0	L0

Regrowth!

NOTE: Dashed line indicates the time of biopsy (at 36w).
Abbreviations: L, late toxicity; N/A, results are not yet available; R, regrowth of hair; RT, radiotherapy; w, week;—, no alteration of the skin.

L0= depilation
R=regrowth

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375

Oriatron

High dose-per-pulse electron beam dosimetry: Commissioning of the Oriatron eRT6 prototype linear accelerator for preclinical use

Maud Jaccard, Maria Teresa Durán, Kristoffer Petersson, and Jean-François Germond
Institute of Radiation Physics, Lausanne University Hospital, Lausanne, Switzerland
Philippe Liger
PMB-Alcen, Peynier, France
Marie-Catherine Vozenin and Jean Bourhis
Department of Radiation Oncology, Lausanne University Hospital, Lausanne, Switzerland
Radio-Oncology Laboratory, DO/CHUV, Lausanne University Hospital, Lausanne, Switzerland
François Bochud and Claude Bailat[a)]
Institute of Radiation Physics, Lausanne University Hospital, Lausanne, Switzerland

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Fig. 2. Oriatron eRT6 linac and irradiation bench: set-up for film dosimetry at the surface of the solid water phantom at an SSD of 1 m.

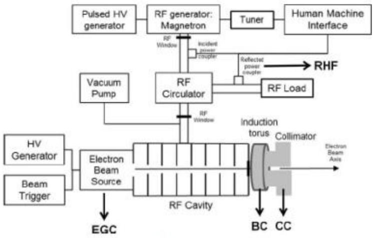

Fig. 3. Design of the Oriatron eRT6 accelerator. Main components of the linac and origin of the signals used to monitor the output: the beam current (BC), the collimator current (CC), the reflected high-frequency (RHF) power, and the electron gun current (EGC).

Table I. Parameter definitions and corresponding dose-rates (at a SSD of 1 m and at the depth of dose maximum in water) of the Flash and Conv functioning modes of the eRT6.

	Flash	Conv
GT (V)	300	100
w (μs)	2.2	1.0
f (Hz)	200	10
$\dot{D}_m$ (Gy/s)	200	0.05
$\dot{D}_p$ (Gy/s)	4.5×10^5	4.9×10^3

Beam Monitoring System for Oriatron

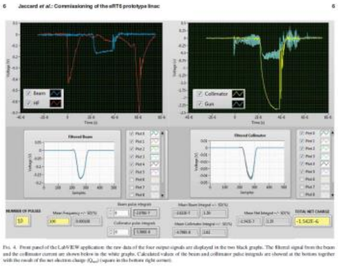
6 Jaccard *et al.*: Commissioning of the eRT6 prototype linac 6

Fig. 4. Front panel of the LabVIEW application: the raw data of the four output signals are displayed in the two black graphs. The filtered signal from the beam and the collimator current are shown below in the white graphs. Calculated values of the beam and collimator pulse integrals are showed at the bottom together with the result of the net electron charge (Q_{net}) (square in the bottom right corner).

FLASH and Conv Output Drift in Oriation

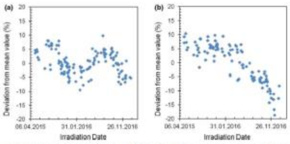

FIG. 8. Long-term reproducibility in: (a) Flash mode and (b) Conv mode. Daily variation with respect to the average output value. Each point was obtained averaging over ten repeated measurements with the Advanced Markus chamber.

Dosimetry for Oriatron

- **EBT3 Gafchromic**
- **Advanced Markus plane parallel chamber (PTW)**
- **TLDs**

Doserate Independence of EBT3

"No energy dependence of EBT3 between 4-12 MeV between 0.25-30 Gy"

Med. Phys. 44 (2), February 2017 0094-2405/2017/44(2)/725/11

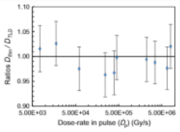

FIG. 5. Ratios of film and TLD doses (D_{film} / D_{TLD}) and corresponding uncertainties for different dose rate in pulse ($\dot{D}_p$). [Color figure can be viewed at wileyonlinelibrary.com]

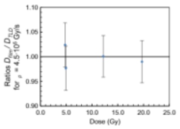

FIG. 6. Ratios of film and TLD doses (D_{film} / D_{TLD}) and corresponding uncertainties for different doses and a fixed dose rate in pulse ($\dot{D}_p$) of 4.5×10^5 Gy/s. [Color figure can be viewed at wileyonlinelibrary.com]

FLASH Requires Unique Dosimetry

High dose-per-pulse electron beam dosimetry — A model to correct for the ion recombination in the Advanced Markus ionization chamber

Kristoffer Petersson,[a] Maud Jaccard, Jean-François Germond, Thierry Buchillier, and François Bochud
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Jean Bourhis and Marie-Catherine Vozenin
CHUV, Service de Radio-Oncologie, Rue du Bugnon 46, CH - 1011 Lausanne, Switzerland

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(Received 23 June 2016; revised 11 January 2017; accepted for publication 11 January 2017; published 16 March 2017)

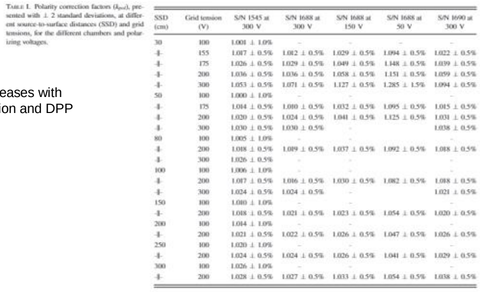

TABLE I. Polarity correction factors (k_{pol}), presented with ± 2 standard deviations, at different source-to-surface distances (SSD) and grid tensions, for the different chambers and polarizing voltages.

SSD (cm)	Grid tension (V)	S/N 1545 at 300 V	S/N 1688 at 300 V	S/N 1688 at 150 V	S/N 1688 at 50 V	S/N 1690 at 300 V
30	100	1.001 ± 1.0%	–	–	–	–
-‖-	155	1.017 ± 0.5%	1.012 ± 0.5%	1.029 ± 0.5%	1.094 ± 0.5%	1.022 ± 0.5%
-‖-	175	1.026 ± 0.5%	1.029 ± 0.5%	1.049 ± 0.5%	1.148 ± 0.5%	1.039 ± 0.5%
-‖-	200	1.036 ± 0.5%	1.036 ± 0.5%	1.058 ± 0.5%	1.151 ± 0.5%	1.059 ± 0.5%
-‖-	300	1.053 ± 0.5%	1.071 ± 0.5%	1.127 ± 0.5%	1.285 ± 1.5%	1.094 ± 0.5%
50	100	1.000 ± 1.0%	–	–		–
-‖-	175	1.014 ± 0.5%	1.010 ± 0.5%	1.032 ± 0.5%	1.095 ± 0.5%	1.015 ± 0.5%
-‖-	200	1.020 ± 0.5%	1.024 ± 0.5%	1.041 ± 0.5%	1.125 ± 0.5%	1.031 ± 0.5%
-‖-	300	1.030 ± 0.5%	1.030 ± 0.5%	–		1.038 ± 0.5%
80	100	1.005 ± 1.0%	–	–		–
-‖-	200	1.018 ± 0.5%	1.019 ± 0.5%	1.037 ± 0.5%	1.092 ± 0.5%	1.018 ± 0.5%
-‖-	300	1.026 ± 0.5%	–	–		–
100	100	1.006 ± 1.0%	–	–		–
-‖-	200	1.017 ± 0.5%	1.016 ± 0.5%	1.030 ± 0.5%	1.082 ± 0.5%	1.018 ± 0.5%
-‖-	300	1.024 ± 0.5%	1.024 ± 0.5%	–		1.021 ± 0.5%
150	100	1.010 ± 1.0%	–	–		–
-‖-	200	1.018 ± 0.5%	1.021 ± 0.5%	1.023 ± 0.5%	1.054 ± 0.5%	1.020 ± 0.5%
200	100	1.014 ± 1.0%	–	–		–
-‖-	200	1.021 ± 0.5%	1.022 ± 0.5%	1.026 ± 0.5%	1.047 ± 0.5%	1.026 ± 0.5%
250	100	1.020 ± 1.0%	–	–		–
-‖-	200	1.024 ± 0.5%	1.024 ± 0.5%	1.026 ± 0.5%	1.041 ± 0.5%	1.029 ± 0.5%
300	100	1.026 ± 1.0%	–	–		–
-‖-	200	1.028 ± 0.5%	1.027 ± 0.5%	1.033 ± 0.5%	1.054 ± 0.5%	1.038 ± 0.5%

Kpol increases with
grid tension and DPP

Medical Physics, 44 (3), March 2017

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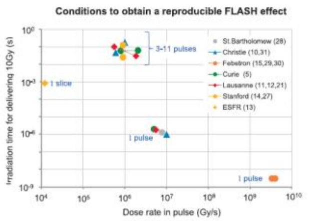

Fig. 4. Conditions to obtain a reproducible FLASH effect. Summary of the temporal dosimetry characteristics of the reported experiments' data having observed the FLASH effect in vivo [5,10–14,21,27] or oxygen depletion in vitro [15,28–31]. The horizontal axis denotes the dose-rate in pulse for electrons and in slice for synchrotron radiation, the vertical axis the total irradiation time for delivering 10 Gy. Parameters for other dose values must be changed accordingly. In mono-pulse mode, the irradiation time is governed by the pulse width, in multi-pulses mode by the pulse repetition rate (10–200 Hz).

FLASH at Stanford

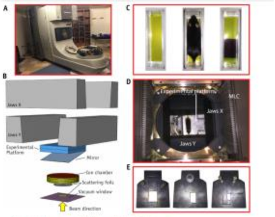

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Fig. 1. The field characteristics were determined at the position of the ion chamber, mirror, and inner jaws (Y jaws). (A) Photograph of the Varian Clinac 21EX in the 180° position, (B) generated Monte Carlo geometry model of the head of the linear accelerator, (C) animal jig used for mouse immobilization and setup, (D) photograph into the head of the linear accelerator with lead sheets and animal jig at the position of the mirror, and (E) 10-mm-thick lead sheets used for abdomen, thorax, and brain irradiation. *Abbreviation:* MLC = multileaf collimator.

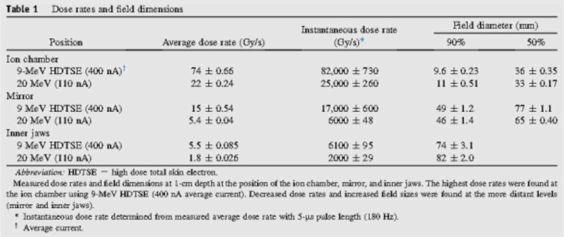


Table 1 Dose rates and field dimensions

Position	Average dose rate (Gy/s)	Instantaneous dose rate (Gy/s)*	Field diameter (mm)	
			90%	50%
Ion chamber				
9-MeV HDTSE (400 nA)†	74 ± 0.66	82,000 ± 730	9.6 ± 0.23	36 ± 0.35
20 MeV (110 nA)	22 ± 0.24	25,000 ± 260	11 ± 0.51	33 ± 0.17
Mirror				
9 MeV HDTSE (400 nA)	15 ± 0.54	17,000 ± 600	49 ± 1.2	77 ± 1.1
20 MeV (110 nA)	5.4 ± 0.04	6000 ± 48	46 ± 1.4	65 ± 0.40
Inner jaws				
9 MeV HDTSE (400 nA)	5.5 ± 0.085	6100 ± 95	74 ± 3.1	
20 MeV (110 nA)	1.8 ± 0.026	2000 ± 29	82 ± 2.0	

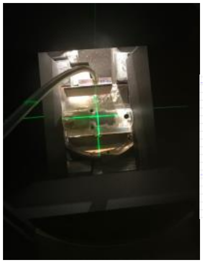
Abbreviation: HDTSE = high dose total skin electron.

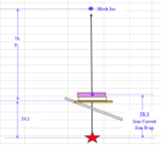
Measured dose rates and field dimensions at 1-cm depth at the position of the ion chamber, mirror, and inner jaws. The highest dose rates were found at the ion chamber using 9-MeV HDTSE (400 nA average current). Decreased dose rates and increased field sizes were found at the more distant levels (mirror and inner jaws).

* Instantaneous dose rate determined from measured average dose rate with 5-μs pulse length (180 Hz).

† Average current.

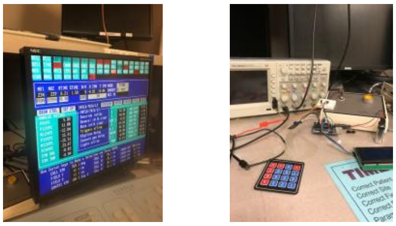
FLASH at MD Anderson on Non-Clinical Linac



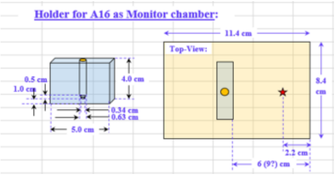


Funded by internal
Rad Onc grant

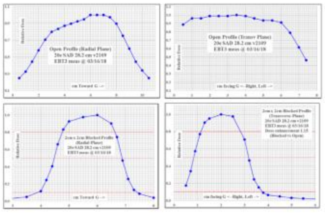
Tuned 20 MeV board



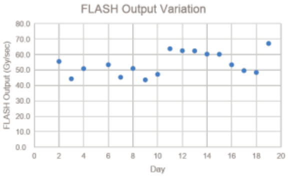
Monitor Chamber Holder



FLASH MD Anderson Beam Profiles

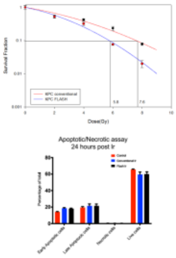


FLASH at MD Anderson



Film Meas	TLD Report	Film/TLD
1430.7	1428	1.002
993.9	964	1.031
1412.9	1352.5	1.045

40 – 60 Gy/sec Not Protective



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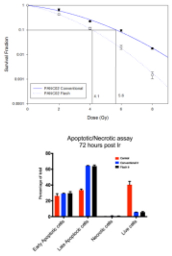

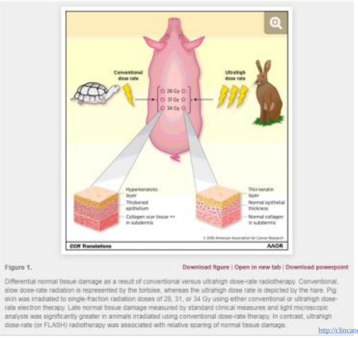

Figure 1.

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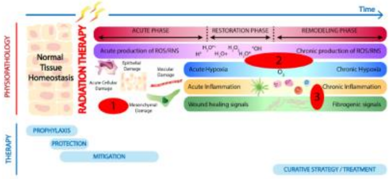
Differential normal tissue damage as a result of conventional versus ultrahigh dose-rate radiotherapy. Conventional, slow dose-rate radiation is represented by the tortoise, whereas the ultrahigh dose rate is depicted by the hare. Pig skin was irradiated to single-fraction radiation doses of 28, 31, or 34 Gy using either conventional or ultrahigh dose-rate electron therapy. Late normal tissue damage measured by standard clinical measures and light microscopic analysis was significantly greater in animals irradiated using conventional dose-rate therapy. In contrast, ultrahigh dose-rate (or FLASH) radiotherapy was associated with relative sparing of normal tissue damage.

http://clincancerres.aacrjournals.org/content/25/1/3

What Mediates FLASH?

Figure 1. Biology-driven strategy to identify therapeutic approaches. RNS, reactive nitrogen species; ROS, reactive oxygen species.



- 1 Early inhibition of radiation-induced acute cell death and depletion is presented in part 1.
- 2 Regulation of the redox imbalance is presented in part 2 .
- 3 Regulation of inflammatory and fibrogenic signals are presented in part 3.

Mechanism of Action

Original Article

An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses

Douglas R. Spitz [a,*], Garry R. Buettner [a], Michael S. Petronek [a], Joël J. St-Aubin [a], Ryan T. Flynn [a], Timothy J. Waldron [a], Charles L. Limoli [b]

[a] Free Radical and Radiation Biology Program, Department of Radiation Oncology, Free Radical Metabolism and Imaging Program, Holden Comprehensive Cancer Center, The University of Iowa, United States; and [b] Department of Radiation Oncology, University of California, Irvine, United States

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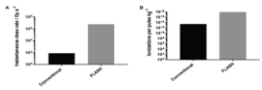


Fig. 1. Graphical representation of theoretical results comparing an instantaneous pulse from a conventional and FLASH electron beam. (A) instantaneous dose rate; and (B) number of ionizations produced following an instantaneous pulse (ionizations kg^{-1}).

Mechanism of Action

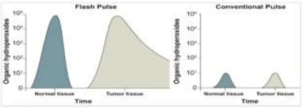


Fig. 2. Proposed mechanism for differential dissipation of organic hydroperoxide levels in FLASH vs. conventional radiation damage to normal versus tumor tissue.

Please cite this article as: D. R. Spitz, G. R. Buettner, M. S. Petronek et al., 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, https://doi.org/10.1016/j.radonc.2019.03.028

Potential Mechanisms of Action

1. **Spitz et al. suspect that FLASH may convert all endogenous oxygen into ROOH in all tissues, but this gets handled preferentially by normal cells with better antioxidant pathways.**
2. **Vozenin et al. have suggested that transient hypoxia initiated by FLASH causing bursts of free radicals trapping oxygen and conferring radioresistance, differential oxygen tensions between normal and tumor cells and differences in DNA damage created by FLASH (less clustered DNA damage than CONV).**

Challenges with Clinical Translation of FLASH

- **Few systems available to deliver FLASH (eRT6 Oriatron)**
- **Treating deep tumors would require FLASH-VHEE (Very high energy electrons), FLASH-X-Ray or FLASH-Protons (explained later by Dr. Lei Dong)**
- **Very little data on FLASH multi-fraction treatments**
- **Sophisticated dose monitoring for delivery of FLASH similar to those in high energy physics labs is needed**
- **Patient safety**

FLASH Benefits

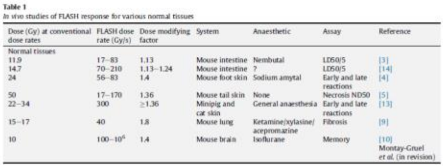


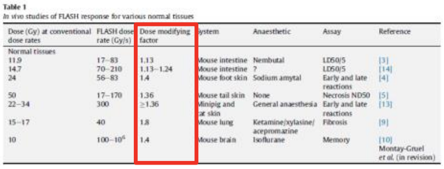
Table 1

In vivo studies of FLASH response for various normal tissues

Dose (Gy) at conventional dose rates	FLASH dose rate (Gy/s)	Dose modifying factor	System	Anaesthetic	Assay	Reference
Normal tissues						
11.9	17–83	1.13	Mouse intestine	Nembutal	LD50/5	[3]
14.7	70–210	1.13–1.24	Mouse intestine	?	LD50/5	[14]
24	56–83	1.4	Mouse foot skin	Sodium amytal	Early and late reactions	[4]
50	17–170	1.36	Mouse tail skin	None	Necrosis ND50	[5]
22–34	300	≥1.36	Minipig and cat skin	General anaesthesia	Early and late reactions	[13]
15–17	40	1.8	Mouse lung	Ketamine/xylasine/acepromazine	Fibrosis	[9]
10	$100–10^6$	1.4	Mouse brain	Isoflurane	Memory	[10] Montay-Gruel *et al.* (in revision)

M.-C. Vozenin et al. / Clinical Oncology 31 (2019) 407–415

FLASH Benefits



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M.-C. Vozenin et al. / Clinical Oncology 31 (2019) 407–415

Conclusions

- **FLASH could make motion management obsolete**
- **FLASH treatment times are economically and logistically beneficial to clinics**
- **Reduced number of overall fractions necessary due to FLASH could provide better quality of life for patients**

https://www.cryoport.com/hubfs/19JAN2017.jpg

It Takes a Village:

- **Ram Sadagopan, MS**
- **Ramesh Tailor, PhD**
- **Michael Gillin, PhD**
- **Peter Balter, PhD**
- **Steven Lin, MD**
- **Sunil Krishnan, MD**
- **Jessica Symons, BS**
- **Amrish Sharma, MD**
- **Bhanu Venkatesulu, PhD**

Questions:

1. When did the first report of ultra-high dose rates of electron radiotherapy causing hypoxia in normal tissue get published?

a. 1980s
b. 1990s
c. 2010s
d. 1970s

Answer

Answer: d. 1970s

Hornsey S, Bewley DK. Hypoxia in mouse intestine induced by electron irradiation at high dose-rates. Int J Radiat Biol Relat Stud Phys Chem Med 1971;19(5):479-483.

Questions:

2. What are some of the proposed mechanisms of action to explain the protective effect conferred to normal tissues by FLASH-RT from the Vozenin team?
   - a. FLASH-RT potentially causes rapid, transient radiation-induced hypoxia.
   - b. FLASH-RT preferentially spares normal tissues due to the differential oxygen tensions between tumor and normal tissues.
   - c. FLASH-RT causes an instantaneous larger cascade of reactive species than conventional radiation which is metabolized more efficiently in normal tissues with lower pro-oxidant burdens than tumors.
   - d. All of the above
   - e. None of the above

Answer:

Answer: d. FLASH-RT causes an instantaneous larger cascade of reactive species than conventional radiation which is metabolized more efficiently in normal tissues with lower pro-oxidant burdens than tumors.

Vozenin M –C, Hendry JH, Limoli CL. Biological benefits of ultra-high dose rate FLASH radiotherapy: sleeping beauty awoken. Clin Onc 2019: (19)30151-7.

Questions:

3. Which dosimeters were utilized to confirm FLASH-RT dosimetry by Vozenin et al?
   - a. Thermoluminescent dosimeters
   - b. EBT3 Gafchromic film
   - c. Alanine pellets
   - d. A and B
   - e. B and C
   - f. All of the above

Answer:

Answer: f. (all of the above)

Vozenin M –C, Hendry JH, Limoli CL. Biological benefits of ultra-high dose rate FLASH radiotherapy: sleeping beauty awoken. Clin Onc 2019: (19)30151-7.

Favaudon V, Caplier L, Monceau V et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med 2014: 6 (245) 1-9.

Vozenin M-C, De Fornel P, Petersson K et al. The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients. Clin Canc Res 2019: 25:35-42.

References:

1. **Hornsey S, Bewley DK. Hypoxia in mouse intestine induced by electron irradiation at high dose-rates. Int J Radiat Biol Relat Stud Phys Chem Med 1971;19(5):479-483.**
2. **Vozenin M –C, Hendry JH, Limoli CL. Biological benefits of ultra-high dose rate FLASH radiotherapy: sleeping beauty awoken. Clin Onc 2019: (19)30151-7.**
3. **Harrington KJ. Ultrahigh dose-rate radiotherapy: next steps for FLASH-RT. Clin Canc Res 2019;25:3-5.**
4. **Vozenin M-C, De Fornel P, Petersson K et al. The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients. Clin Canc Res 2019: 25:35-42.**
5. **Favaudon V, Caplier L, Monceau V et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med 2014: 6 (245) 1-9.**

Thanks!

You can find me at @JulieLarkin305

jmpollard@mdanderson.org

Photo Credit

1. https://www.google.com/maps/place/Lausanne+University+Hospital/@46.5247702,6.6436515,3a,98.6y,90t/data=!3m8!1e2!3m6!1sAF1QipP-fA08yqug5cE3Lzn1Faq4JPonoP4KJQjcS-6m!2e10!3e12!6shttps:%2F%2Flh5.googleusercontent.com%2Fp%2FAF1QipP-fA08yqug5cE3Lzn1Faq4JPonoP4KJQjcS-6m%3Dw360-h239-k-no!7i800!8i533!4m8!1m2!2m1!1sInstitut+Curie+and+Centre+Hospitalier+Universitaire+Vaudois!3m4!1s0x478c2e483fa0df43:0x3ff9568528e6b139!8m2!3d46.525146!4d6.6425496

K_S vs DPP

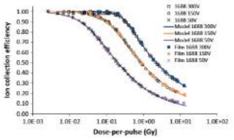

FIG. 5. The (S/N 1688) Advanced Markus ionization chamber's ion collection efficiency ($1/k_s$) as a function of the dose-per-pulse according to water phantom (1688 300 V, 150 V, and 50 V; open symbols) and simultaneous film and chamber measurements (Film 1688 300 V, 150 V, and 50 V; filled symbols), as well as the logistic function (Model 1688 300 V, 150 V, and 50 V; lines) fitted to the data points, for a polarizing voltage of 50 (50 V; cross signs), 150 (150 V; circles), and 300 V (300 V; squares). [Colour figure can be viewed at wileyonlinelibrary.com]

$$k_s = \left(1 + \left(\frac{DPP[mGy]}{k_s \cdot U[V]}\right)^{\gamma}\right)^{\delta}$$

Petersson *et al.*: An ion recombination model for the Advanced Markus **Medical Physics, 44 (3), March 2017**