Transformative Technology for FLASH Radiation Therapy

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Review

Transformative Technology for FLASH Radiation Therapy

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Featured Application: We report on new accelerator technology that has applications in FLASH radiation therapy. FLASH radiation therapy may have profound implications in cancer therapy because it may significantly spare normal tissues and solve the problem of tumors in motion due to the short time interval (sub-second) during which it is delivered.

Conventional and FLASH Radiotherapy

~2/3 OF US CANCER PATIENTS UNDERGO RADIATION THERAPY; OFTEN THE PRIMARY COURSE OF TREATMENT

Radiation therapy is driven by new technologies and innovation

PHOTON AND ELECTRON BEAM THERAPY – used to treat the majority of cancer patients

- Bremsstrahlung photons and ≤10 MeV low energy electrons
  - Produced using a 10-20 MeV pulsed electron linac, photons from e-beam on target
  - Sophisticated, compact and inexpensive beam delivery systems (<0.1 Gy/sec on average)
- High integral dose to normal tissue (dose limited by early & late toxicity)

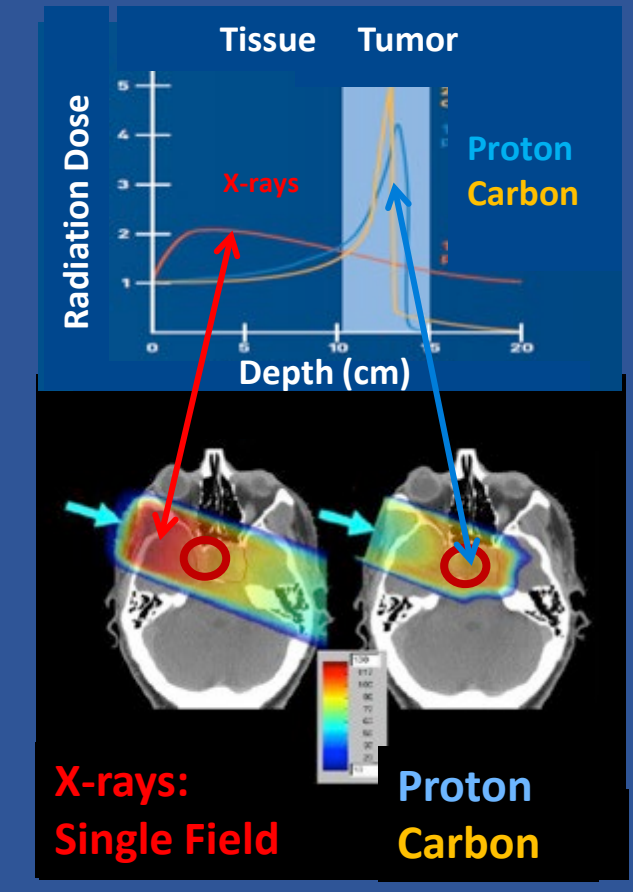
PROTON AND ION BEAM THERAPY

- Highly conformal dose distribution; biological advantage for high LET ions
  - enhanced local tumor control; Bragg peak maximizes energy deposition at tumor site;
  - Overall better sparing of normal tissue and organs at risk
- Important for pediatric tumors, retreatment, organs at risk (brain, spinal cord)
  - Delivered dose ~2 Gy/treatment < 3 Gy/min, typical is 20-40 treatment fractions
  - Reduced early and late toxicity response

FLASH THERAPY NEW!

- Acute dose of radiation delivered in a fraction of a second
  - Many preclinical and clinical results indicate a dramatic reduction of toxicity response
  - First patient treated (T-cell lymphoma, recurring), complete response, minimal toxicity[1]
  - Even after multiple non-FLASH skin irradiation and damage from photons and electrons!

[1] Bourhis J, et al. doi: 10.1016/j.radonc.2019.06.019



The FLASH effect

THERE IS A STRIKING REDUCTION IN TOXICITY AT VERY HIGH DOSE RATES WHILE MAINTAINING TUMOR RESPONSE

FLASH dose rates far exceed those in conventional therapies

EARLY EVIDENCE OF SPARING AT HIGH DOSE RATES (1969)

- In vitro mammalian cells (noncancerous) irradiated with X-rays[1]
  - Cells irradiated with nanosecond pulses ($7x10^{10}$ rad/sec or ~10^8 Gy/sec instantaneous) remained viable; while lower rates decreased cell survival

RE-DISCOVERED IN RADIATION INDUCED LUNG FIBROSIS (2014)

- Mice were irradiated with 4-6 MeV electron beams[2]
  - Irradiation dose rate was ≥40 Gy/sec average in <500 ms for FLASH vs. 0.03 Gy/s Conventional
  - A 15 Gy total dose with CONV RT induced lung fibrosis, no fibrosis for 20 Gy with FLASH (other sparing effects)
  - ***HOWEVER, LUNG TUMORS SHOWED THE SAME RESPONSE TO THE TOTAL DOSE FOR FLASH AND CONVENTIONAL RT!***

PRECLINICAL FLASH STUDIES

- Electrons: Performed using 4-6 MeV electron beams from modified clinical linacs
  - Provides the strongest, consistent evidence for FLASH
- Photons: Synchrotron Radiation and keV X-rays (early study)
  - Mixed results
- Protons: CW or iso-cyclotrons (shoot-through beams, beam is not energy degraded)
  - Mixed results – better tumor control in one study

[1] Berry RJ, et al. doi: 10.1259/0007-1285-42-494-102, [2] Favaudon V, et al., doi: 10.1126/scitranslmed.3008973

Preclinical FLASH Studies with Electrons

LOW ENERGY (<10 MeV) ELECTRON BEAMS PRODUCED USING 100 Hz CLINICAL LINACS

FLASH EFFECT OBSERVED - highlights:

- Study of pulmonary fibrosis from irradiation of the lung[1]
  - Severe to moderate for conventional average dose rate of 0.03 Gy/sec, 17 Gy total dose
  - For an average dose rate of 40-60 Gy/sec, equivalent fibrosis occurred at 30 Gy total dose
- Study of neurocognitive impairment from brain irradiation[2]
  - Severe neurocognitive degeneration at an average dose rate of 0.1 Gy/sec, 10 Gy total dose
  - Improvement starts at 30 Gy/sec with no neurocognitive decline at 100 Gy/sec average dose rate for10 Gy!
- Skin irradiation (mini-pig)[3]
  - Fibrosis and necrotic lesions observe at and average dose rate of 0.08 Gy/sec, (22-37 Gy total dose)
  - Only mild depigmentation at an average dose rate of 300 Gy/sec, (22-37 total dose)!

THE PRECLINICAL ELECTRON STUDIES have established general beam conditions for FLASH

- FLASH: $\geq$40Gy/sec, $\geq$10 Gy delivered in $\leq$100 millisecs, instantaneous dose rate $\geq 10^6$ Gy/sec (during beam pulse)[4]

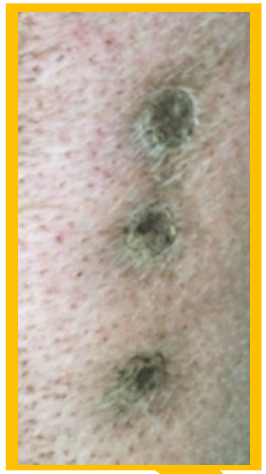
[1] Favaudon V, et al., doi: 10.1126/scitranslmed.3008973, [2] Montay-Gruel, et al., doi: 10.1016/j.radonc.2017.05.003,

[3] Harrington KJ. et al., doi: 10.1158/1078-0432.CCR-18-1796, [4] J. Wilson, et. al., doi: 10.3389/fonc.2019.01563,

FLASH Effect in Skin Irradiation with electrons

Vozenin, et al, The advantage of Flash RT confirmed in mini-pig and cat-cancer patients." Clinical Cancer Research. 2018;

	CONV	Dose	FLASH
Beam Type	Electron	28 Gy	Electron
Nominal Energy	6 MeV		6 MeV
Beam Structure	Pulsed	31 Gy	Pulsed
Pulse Rep Rate	10 Hz		200 Hz
Pulse Width	Few µs	34 Gy	1 µs
Mean Dose Rate	0.08 Gy/s		300 Gy/s



Preclinical FLASH Studies with Photons

CREATING HIGH DOSE RATES OF PHOTONS

(photon dose rates from clinical electron linacs are too low)

PHOTONS FROM LIGHT-SOURCE SYNCHROTRONS

- Synchrotron Broad-Beam Radiation therapy (SBBR)
  - One study did not show FLASH effect (37 – 41 Gy/sec, 4-28 Gy)[1]
  - Another, mouse-brain irradiation (37 Gy/sec, 10 Gy), significant cognitive sparing; (vertical beam size x20 smaller)[2]
- Microbeam Radiation therapy (MRT) – grid of "pencil" photon beams[1]
  - Parallel beam array, 25-100 μm (peak) spaced by 100-400 μm (valleys)
  - Peak average dose rate ~300 Gy/sec; valley average dose rate lower factor of ~30 and strong indicator of toxicity
  - The low dose rates, especially in valleys, conjectured to be the reason for no FLASH effect

PHOTONS FROM BREMSSTRALUNG[3]

- FLASH dose rates produced by a high intensity 10-MeV SRF electron linac, tungsten target;
  - Significant FLASH effect observed for lungs and tissues[3]
  - Original 1969 study and a recent Monte Carlo Study suggests FLASH with X-ray tubes may be possible[4]

[1] Smyth LML, et al., doi: 10.1038/s41598-018-30543-1), [2] Montay-Gruel, et al., doi: 10.1016/j.radonc.2018.08.016)
[3] Gao F, et al., doi: https://doi.org/10.1101/2020.11.27.401869;, [4]Bzalova-Carter M, et al., doi: 10.1002/mp.13858.2017.05.003

Preclinical FLASH Studies with Protons

VERY HIGH PROTON DOSE RATES (CW) FROM ISO-CYCLOTRONS

(Pulsed FLASH has been proposed using large synchrotrons and fast extraction)

230-250 MEV PROTON THERAPY CYCLOTRONS – very few studies

- Requires shoot-through or non-degraded beam to achieve FLASH intensities
  - **MIXED RESULTS** (high-energy beam placed Bragg peak beyond the targeted area)[1,2]
- Individual RF (MHz) proton bunch structure may be important for proton FLASH
  - Proton RF "bunches' are fractions of a microsecond; electron RF bunches are fractions of a nanosecond
  - Proton beam is "quasi-continuous" ; 100-300 Hz electron linacs produce a microsecond "macro-pulse"
  - For proton FLASH it can be hypothesized that the instantaneous dose rate of 10^6 Gy/sec must be achieved within the RF bunch pulse
  - For pulsed electron beams the instantaneous dose rate is integrated over microsecond macro-pulse
- The 0.1 sec treatment time may not apply to quasi-continuous beams
  - CW electron linacs , like proton cyclotrons, produce a quasi-continuous beam

[1] Rama N, Saha, et al., doi: 10.1016/j.ijrobp.2019.06.187, [2] Beyreuther E, et al., doi: 10.1016/j.radonc.2019.06.024

COMPENDIUM: FLASH IN VIVO STUDIES IN NORMAL TISSUES: Irradiation parameters with outcomes for electrons (green), protons (blue) and X-rays (grey)
J. Wilson, et. al., "Ultra-high Dose Rate (FLASH) Radiotherapy Silver Bullet or Fool's Gold", Frontiers in Oncology, Vol 9, Jan 2020.

Model	Assay	FLASH dose modification factor (Bold if >1)	Total dose (Gy)	Dose rate (Gy/s)	Pulse rate (Hz)	Modality of radiation
Zebrafish embryo (16)	Fish length	**1.2–1.5**	10–12	10^6-10^7	Single pulse	Electron
Zebrafish embryo (29)	Fish length, survival, and rate of oedema	1	0–43	100	0.106 × 10^9	Proton
Whole body irradiation of mice (34)	LD50	**1.1**	8–40	17–83	400	Electron
Thoracic irradiation of mice (10)	TGFβ signaling induction	**1.8**	17	40–60	100–150	Electron
Thoracic irradiation of mice (18)	Number of proliferating cells, DNA damage, expression of inflammatory genes	**>1 Significant Differences**	17	40–60	100–150	Electron
Abdominal irradiation of mice (33)	Survival	<1 Significant Difference	16	35	Likely 300	Electron
Abdominal irradiation of mice (12)	LD50	**1.2**	22	70–210	100–300	Electron
Abdominal irradiation of mice (17)	Survival, stool formation, regeneration in crypts, apoptosis, and DNA damage in crypt cells	**>1 Significant Differences**	12–16	216	108	Electron
Whole brain irradiation of mice (25)	Novel object recognition and object location tests	**>1 Significant Differences**	30	200, 300	108, 180	Electron
Whole brain irradiation of mice (13)	Variety of neurocognitive tests	**>1 Significant Differences**	10	5.6·10^6	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**>1 Significant Differences**	10	30–5.6·10^6	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥1.4**	10	5.6–7.8·10^6	single pulse	Electron
Whole brain irradiation of mice (24)	Novel object recognition test	**>1 Significant Difference**	10	37	1,300	X-ray
Total body and partial body irradiation of mice (32)	TD50	1	3.6–28	37–41	1,388	X-ray
Thoracic irradiation of mice (11)	lung fibrosis, skin dermatitis, and survival	**>1 Significant Difference**	15, 17.5, 20	40	?	Proton
Irradiation of mouse tail skin (49)	Necrosis ND50	**1.4**	30 and 50	17–170	50	Electron
Irradiation of mouse skin (27)	Early skin reaction score	**1.1–1.6**	50–75	2.5 mean, 3 × 10^4 in the pulse	23–80	Electron
Irradiation of rat skin (26)	Early skin reaction score	**1.4–1.8**	25–35	67	400	Electron
Irradiation of mini-pig skin (15)	Skin toxicity	**≥1.4**	22–34	300	100	Electron

COMPENDIUM: FLASH IN VIVO STUDIES IN TUMOR TISSUES: Irradiation parameters with outcomes for electrons (green), protons (blue) and X-rays (grey)
J. Wilson, et. al., "Ultra-high Dose Rate (FLASH) Radiotherapy Silver Bullet or Fool's Gold", Frontiers in Oncology, Vol 9, Jan 2020.

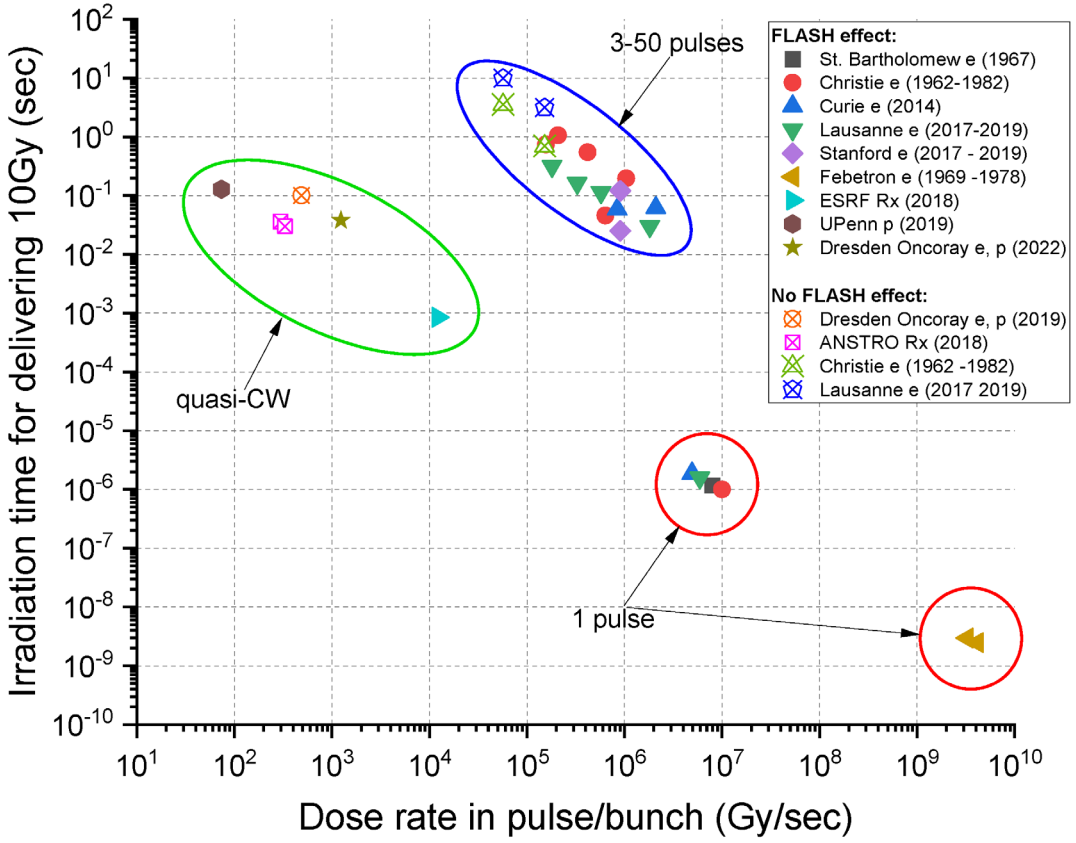
In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if >1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Thoracic irradiation of orthotopic engrafted non-small cell lung cancer (Lewis lung carcinoma) in mice (36)	Tumor size and T-cell Infiltration	**>1 Differences in tumor size (significant) and T-cell infiltration**	18	40	?	Proton
Thoracic irradiation of orthotopic engrafted mouse lung carcinoma TC-1 Luc+ in mice (10)	Survival and tumor Growth Delay	1	15-28	60	100–150	Electron
Abdominal irradiation of mice (17)	Number of tumors, tumor weights	1	12–16	216	108	Electron
Whole brain irradiation of nude mice with orthotopic engrafted H454 murine glioblastoma (8)	Tumor Growth Delay	1	10–25	$2.8–5.6 \cdot 10^6$	Single pulse	Electron
Local irradiation of subcutaneous engrafted Human breast cancer HBCx-12A and head and neck carcinoma HEp-2 in nude mice (10)	Tumor Growth Delay	1	15–25	60	100–150	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (8)	Tumor Growth Delay	1	0–35	$125–5.6 \cdot 10^6$	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (19)	Tumor Growth Delay	1	10–30	$125–5.6 \cdot 10^6$	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted Human hypopharyngeal squamous cell carcinoma ATCC HTB-43 in nude mice (35)	Tumor Growth Delay in irradiated Mice and RBE	1	20	0.008 mean, $\approx 10^9$ in pulse	<<1	Proton
Treatment of locally advanced squamous cell carcinoma (SCC) in cat patients (15)	Tumor response and survival	1 Similar response as in published studies with CONV-RT	25–41	130–390	100	Electron
Treatment of CD30+ T-cell cutaneous lymphoma T3 N0 M0 B0 in human patient (9)	Tumor response	1 Similar response as previous treatments with CONV-RT	15	167	100	Electron

Beam Conditions for FLASH

- The FLASH effect has been observed for a wide range of beams – pulsed clinical electron linacs and different types of beam delivery modes from continuous beam cyclotrons and synchrotron radiation light sources. Ions are a new frontier in FLASH therapy.

Preclinical FLASH beam properties relevant to a clinical application of FLASH

Electron Beam	Min. for Observed FLASH	Optimal for FLASH
Average dose rate	30 Gy/s (now ~70 Gy/sec)	100 Gy/s
Intrapulse dose rate	~10^5 Gy/s	≥10^6 Gy/s
Total dose	<10 Gy	≥10 Gy—tissue dependent
Delivery time for 10 Gy	<1 s	1 μs–10 ms



FLASH studies at accelerator facilities with different radiation types† (right panel).

†R. Schulte and C. Johnstone, editors, "Transformative Technology for FLASH Radiation Therapy", in Appl. Sci., 13(8), Apr, 2023, pp. 5021. https://doi.org/10.3390/app13085021

FLASH versus no FLASH – Updated Preclinical Studies

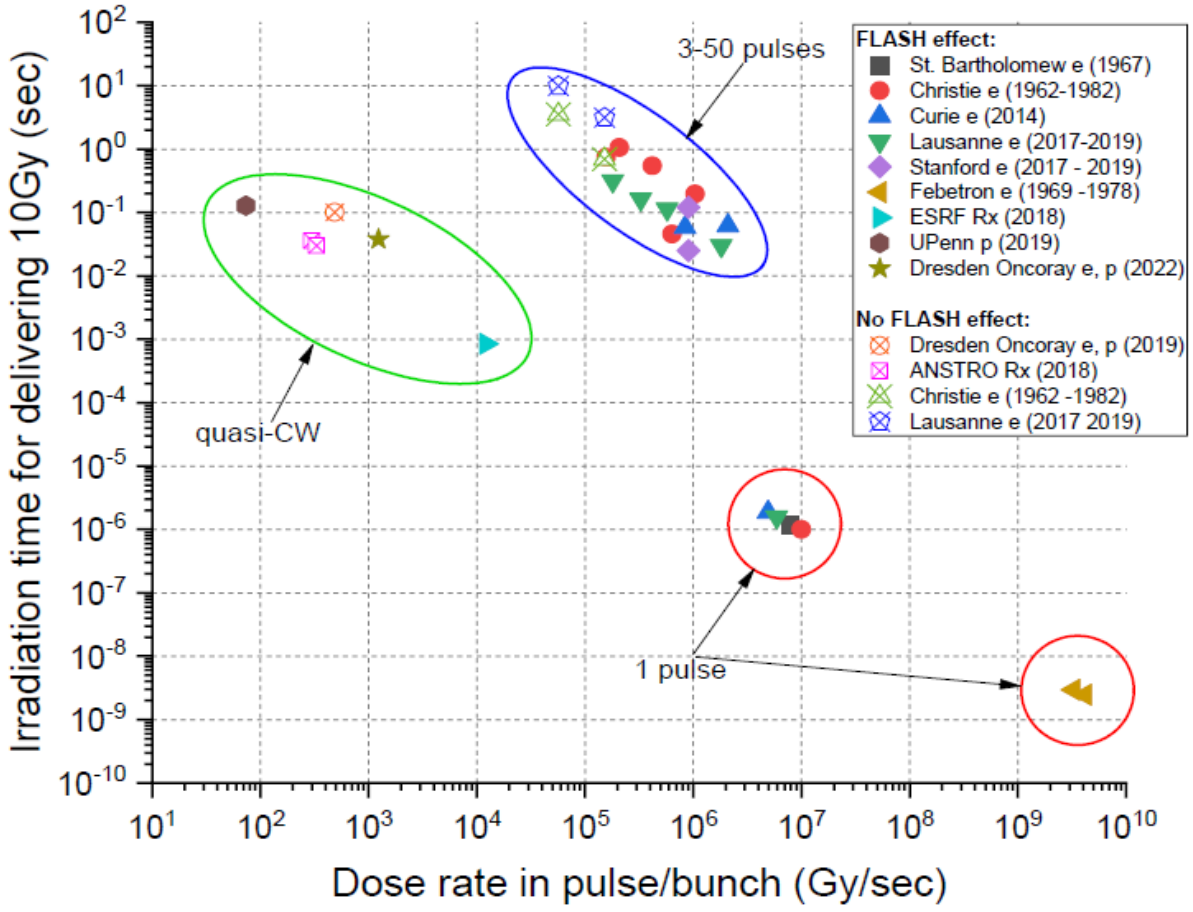
R. Schulte, et. al. https://www.mdpi.com/2076-3417/13/8/5021

The FLASH effect has been observed for

- A wide Instantaneous Dose Rate (IDR) range
  - A train of electron linac pulses
  - quasi-CW bunch delivery with iso-cyclotrons and synchrotron radiation light sources.
  - Single electron pulses with IDR in the range of 10^6–10^7 Gy/s and 10^9–10^{10} Gy/s, respectively.

From

Modified from Montay-Gruel P et al. Clin Cancer Res. 2021 doi:10.1158/1078-0432.CCR-20-0894; data grouped according to delivery method with an added data point from Karsch et al, Radiother. Oncol. 2022, 173, 49–54.



Preclinical studies at different accelerator facilities and radiation types (right panel). The irradiation time for delivering 10 Gy on the vertical axis and the IDR of linac pulses or CW bunches on the horizontal axis.

Factors that Influence the FLASH effect

ABSENCE OF SYSTEMATICS in MOST STUDIES:

mean and instantaneous dose rate, total dose, pulse structure, fractionation, and radiation type

INITIAL FLASH SYSTEMATICS (wide range of dose rates)

- FLASH effects begin to appear at average dose rates >30 Gy/sec, apparent optimal at 100 Gy/sec[1]
  - FLASH effect likely tissue dependence
  - Dependence on the micro-structure of beam delivery and the uniformity of dose deposition
- Beam Delivery
  - Maximum dose delivery time for a consistent (electron) FLASH effect is $\leq$100 milliseconds
  - ***MOST positive FLASH studies used a pulsed clinical electron linac (beam pulse length of microseconds)***
  - Instantaneous (within the pulse) FLASH dose rate is 10^6 Gy/sec (again, characteristic of clinical electron linacs)
- Dosimetric issues
  - Observed Volumetric dose deposition dependence
  - Low dose-rate areas not tolerated during FLASH – toxicity reappears[2]
  - Bragg peak and pencil beam scanning questions - distal edge and penumbra issues which create lower-dose rate beam "halos"?
  - ***Can a Large Gross Tumor Volume be uniformly irradiated with FLASH?***
  - ***Instantaneous FLASH dose rate and delivery time for 10 Gy - is it consistent for all radiation types***

[1] Montay-Gruel, et al., doi: 10.1016/j.radonc.2017.05.003, [2] Smyth LML, et al., doi: 10.1038/s41598-018-30543-1

FLASH intensities translated into ion accelerator currents

Dose translated to a clinical application of ion FLASH
Derived from electron FLASH conditions
R. Schulte, et. al. https://www.mdpi.com/2076-3417/13/8/5021

Dose Delivery Mode	Protons	Helium	Carbon
Conventional: 2.6 Gy/fraction	2×10^9 p/s	5×10^8 He/s	1.7×10^8 C/s
Delivery time: 100 s	0.4 nA	0.2 nA	0.2 nA
FLASH: $\geq$10 Gy/fraction	1×10^{13} p/s	2.5×10^{12} He/s	0.8×10^{12} C/s
Delivery Time: 100 ms	1.6 μA	0.8 μA	0.8 μA

U. Titte, MDAnderson, private communication

Clinical FLASH with Pulsed Electron Accelerators

A pulsed electron accelerator is very effective for applying clinical FLASH

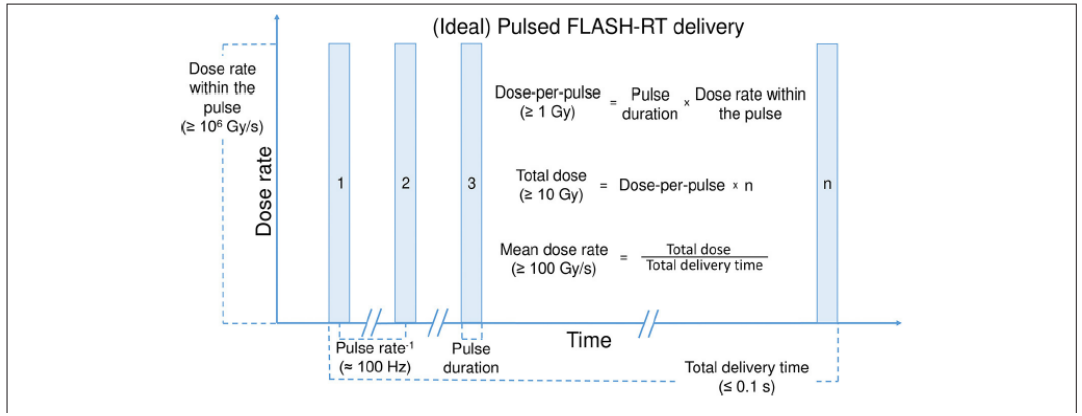


Figure 1. Schematic view of pulsed beam delivery inducing the FLASH effect

Review Electron Pulsed Beam Structure for FLASH[1]

- Schematic of pulse structure shown in Fig. 1
  - Given ≥10 Gy total dose in 100 ms, 10^6Gy/sec instantaneous
  - Calculate dose per single pulse and pulse length
  - Beam structure parameterization shown in Figure

Very High Energy Electrons (VHEE) Therapy[2]

- Tumor depths of 30 cm require 200-250 MeV electrons
  - Treatment models calculate that 10 Gy/sec ≅ 10^{11} e/sec (ref2)
  - For 200-MeV electrons delivered with a Gaussian distribution, σ=1.5 mm (ref 2)

Example: 100 Hz LINAC FOR VHEE [1,2]

- Using 10 Gy/sec ≅ 10^{11} e/sec[2]
  - Average 100 Gy/sec in 100 msec = 10 Gy dose, which is ten 1-Gy pulses @100 Hz
  - 10^6 Gy/sec instantaneous dose rate requires a 1 μsec single pulse length for a 1 Gy pulse
  - This is 10^{11} electrons delivered in 100 ms, or 10^{10} e/μsec (# electrons scales with pulse length, # of pulses inversely)
- How would you scan with a 100 Hz Linac,, 1 μsec pulse length?
  - 15 cm x 15 cm field – 10 pulses at each 1.5 mm position x (100 x 100 positions) or 100,000 pulses; 1000 sec or 17 min
  - Scan rate – 15 cm/1000 pulses or 15 cm/10 sec or 1.5 cm/sec - isn't technically challenging
  - Granted clinical electron linacs are only 10-20 MeV – so here is where advanced accelerators can play a major role

[1] J. Wilson, et. al., doi: 10.3389/fonc.2019.01563, [2] D. Bartkoski, private communication

Towards Understanding FLASH Radiobiology

What do we know about the radiobiology and radiation chemistry of FLASH?

Primary mechanism of DNA damage is radiation induction of free radicals into the DNA

- Depletion of oxygen
  - Oxygen depletion is one of the most frequent hypotheses to explain the FLASH effect
  - In healthy tissues, oxygen can be depleted from a normal level by numerous radio-chemical reactions that take place during the physico-chemical and chemical stage of irradiation, cells might be transiently hypoxic and radioresistant
  - In tumors, O2 concentration is generally lower, so tumors are not as impacted by the depletion of oxygen
- Other Explanations
  - Mitochondrial oxygen metabolism in tumor cells is mostly due to aerobic glycolysis (Warburg effect)
  - Tumors consume large amounts of glucose a mechanism insensitive to hypoxia
  - Hypoxic cells in tumors do not become more hypoxic by FLASH and remain resistant to low radiation doses
  - Puzzling, is that they seem to be more sensitive at high radiation doses, possibly to immune-sensitization.
  - The tumor's microvasculature also appears more sensitive to high single doses than normal capillaries.
  - Tissue oxygen levels return to normal (estimate is 10^{-3} sec)– pulse structure of beam may play an important role
    - Race against oxygen replenishing – maintains hypoxia environment during a short radiation pulses
    - Tumor vessels are known to be more transparent for oxygen (leaky) and replenishing could happen faster
    - This would further explain the absence of a FLASH sparing in tumors

R. Schulte, Loma Linda University

Broad Clinical Application of FLASH requires VHEE beams

Deeper cancers require penetration depths up to 30 cm – a 200-250 MeV electron beam

SRF Linac

- Lower cycling time is relevant for FLASH Radiobiology (Fermilab FAST Linac)
  - FAST SRF Linac produces 5, 50, and 300 MeV electron beams
  - FAST delivers 10^{14}e/msec-pulse @5Hz;
  - 10 Gy/sec ~10^{11} e/sec for a 1.5 mm (σ) Gaussian pencil beam (10^{11}e/10 Gy)
  - The FAST Linac can delivers ≤1000 Gy/pulse @instantaneous dose rate of 10^{6} Gy/sec
  - 5 Hz represents a limitation for clinical scanning

Laser Accelerators (proton and electron)

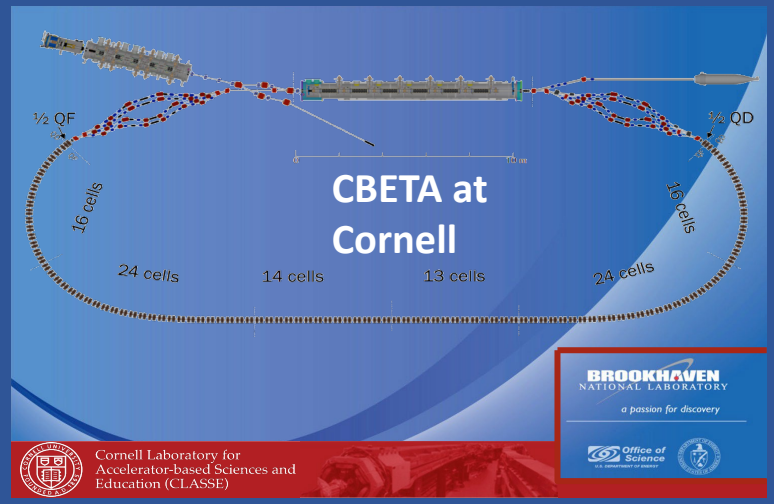
- Single intense, low-energy nanosecond pulses @1-10 Hz
  - Platform for understanding radiobiology – being pursued at BELLA with protons

CBETA – Energy Recovery Linear Accelerator (ERL): 6-150 MeV electrons

- CW 1.3 GHz linac, single FFA arc, 4 simultaneous acceleration turns
  - CW VHEE beam in a recirculating format,
  - CBETA can deliver ~10^{8} e/nsec-bunch @instantaneous dose rate of 10^{7} Gy/sec
  - CBETA can SCAN: 10^{6} Gy/sec @ 200 cm/ms at peak intensity!
  - Machine size can be dramatically reduced by replacing permanent magnets

Synchrotron Light Sources

- Produces short pulse, high intensity broad-band X and gamma rays
  - Photons are the most penetrating; ongoing preclinical studies



What about Dosimetry – *Monitoring FLASH delivery*

FLASH is ***~1000*** times faster;

FLASH dose is delivered in **< 100 ms**. For *proton*-FLASH (@40 Gy/sec) the corresponding beam luminosity is ***~6.25 x 10^{11} protons/cm^2-sec***

- ***Standard dosimetry methods do not work*** at the radiation intensity of FLASH delivery

FLASH – a groundbreaking modality in cancer treatment

FLASH targets radiobiology of tumors not healthy tissue

- **Enhanced protection of normal tissue, reduced side effects**
  - Many beam delivery questions
- ***FLASH requires state-of the art Accelerator Technologies***
  - *Proton and Ion Synchrotrons cannot produce FLASH beams*
    - Synchrotrons are not participating in FLASH preclinical trials
  - *Cyclotrons and clinical electron linacs highly limited for FLASH R&D*
    - Clinical linac electron beams cannot penetrate >few cm
    - FLASH requires ultra-high, instantaneous intensity continuous beams
    - Only (230-250 MeV shoot-through) CW proton beams achieve FLASH intensities (iso-cyclotrons, no energy degrader)

FLASH IS IN THE PRE & CLINCAL TRIAL STAGE for specific cancers

Thank you!

A special thanks to my co-authors, especially Reinhard Schulte for his patience in listening to this talk repeatedly and all the impressive researchers and pioneers in understanding and bringing the FLASH effect to the clinical stage