Flashy Science: the radiobiology of FLASH therapy

Michael J Baine, MD, PhD
Department of Radiation Oncology

University of Nebraska Medical Center
Nebraska Medicine

Disclosures

Scientific steering committee on advanced prostate cancer- Sanofi

Outline

- Basics of FLASH
- Comparison to Conventional RT
- Unique radiobiological effects
- Unanswered questions
- Clinical research
- Conclusions

Basics of FLASH

- Ultra-high dose rate ($\geq$ 40 Gy/s; compared to approx. 5 Gy/min for conventional RT)
- Most data in electrons
  - Data in photons, protons, and heavy ions are growing

FLASH vs Conventional RT

Tumor:

- Equivalent or better control
  - Seen in lung, breast, and HNSCC mouse models[1]
  - Notably, higher control seen in papers using non-equivalent doses between FLASH and conventional
    - ex 28 Gy FLASH led to 70% control in a lung tumor model while 15 Gy conventional RT led to 20% control[1]

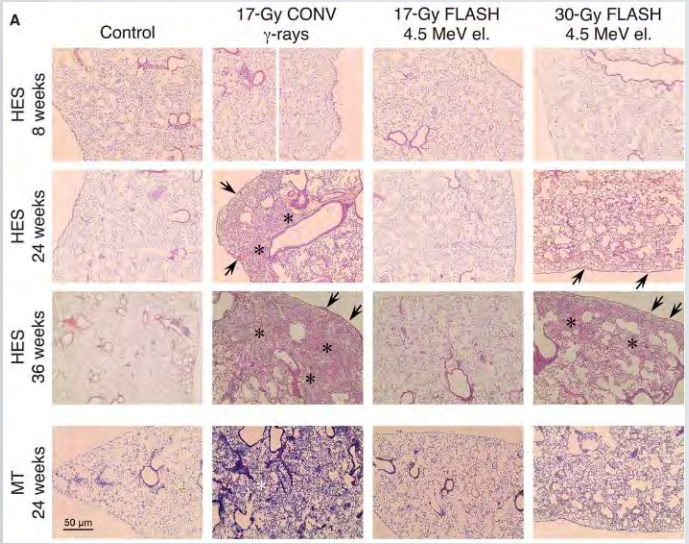
Normal Tissue:

- Increased sparing
  - Need almost double the dose of FLASH RT to induce similar lung fibrosis as conventional RT (30 vs 17 Gy)[1]
  - Juvenile mice exposed to 8 Gy whole brain FLASH RT remain indistinguishable from controls but have significant detriments if conventional RT used[2]
  - Similar results in GI tract and skin[3-5]
  - A pig skin necrosis experiment suggests that FLASH has a dose modifying factor for equivalent toxicity as conventional of 1.36[6]

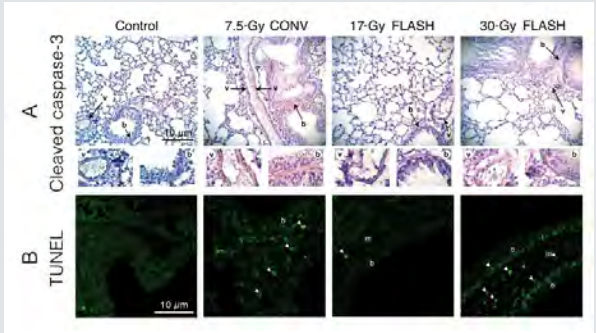
Normal vs Tumor effects

C57bl and nude mouse orthotopic lung tumor models[1]

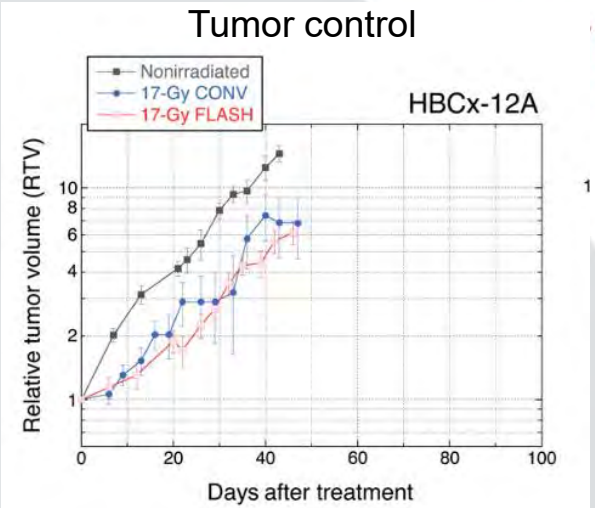
Fibrosis

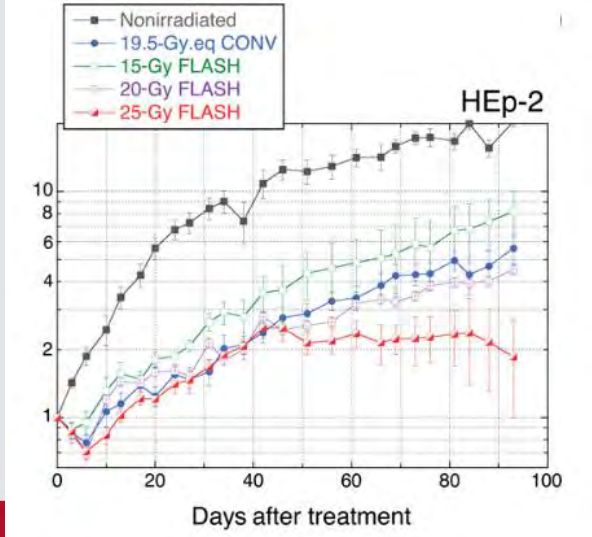


SM Apoptosis



Tumor control





Radiobiological mechanisms

Not completely understood, but generally 4 mechanisms:

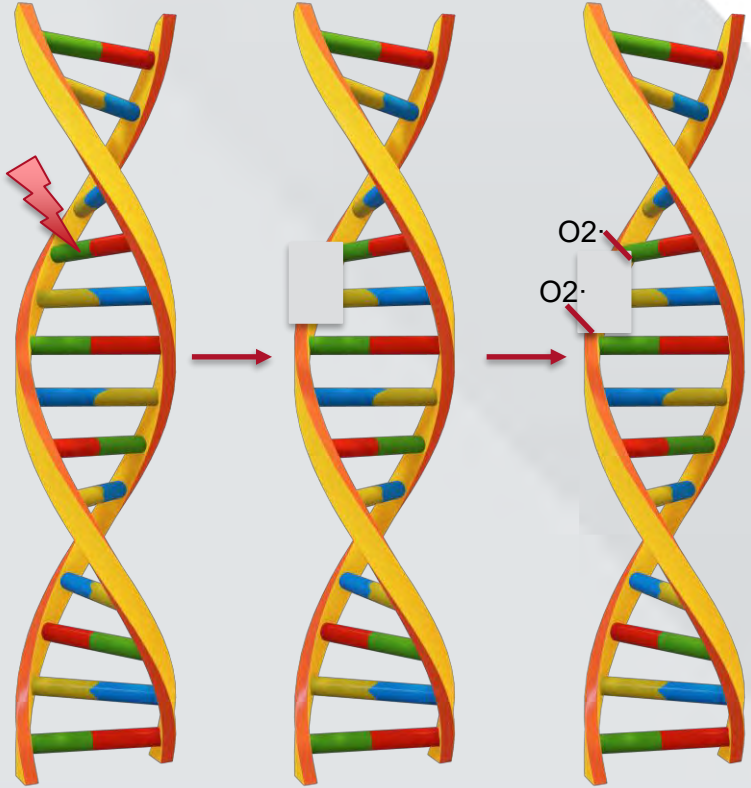
- Oxygen depletion
- Altered inflammatory process
- Redox biology
- Differential effect dependent on tissue type (tumor vs healthy)

Note: likely all inter-related and not independent mechanisms

Radiobiological mechanisms

Oxygen depletion:

- 70% of DNA damage with conventional RT is indirect via ROS (ie hydroxyl radicals) which is then “fixed” in place with the help of intracellular oxygen
- With FLASH dose rates, local O2 is depleted faster than it can be replenished[7]
  - Leads to focal transient hypoxia which reduces fixing of the damage from the ROS
  - So, FLASH leads to less permanent DNA damage and its downstream effects
- This seems to be dependent on O2 concentration
  - Improved cell survival in *in vitro* expts with FLASH if O2 was between 1.4-4.5% but not if 8.3% or higher[8]



Radiobiological mechanisms

Altered inflammatory processes:

- TGF-β less significantly induced after FLASH than conventional RT in lung fibroblasts (1.8x vs 6.5x increase at 24h)[9]
  - TGF-β is partially responsible for RT-induced chronic inflammation and fibrosis
- Pro-inflammatory cytokine levels lower after WBI in mice if FLASH used vs conventional[9]
  - 3 vs 5/10 cytokines increased
- There is more recruitment of intra-tumoral T-cells after FLASH than conventional RT in mice[10]
- Fast exposure time may also reduce blood pool being treated and thus reduce exposure of circulating immune cells[11]

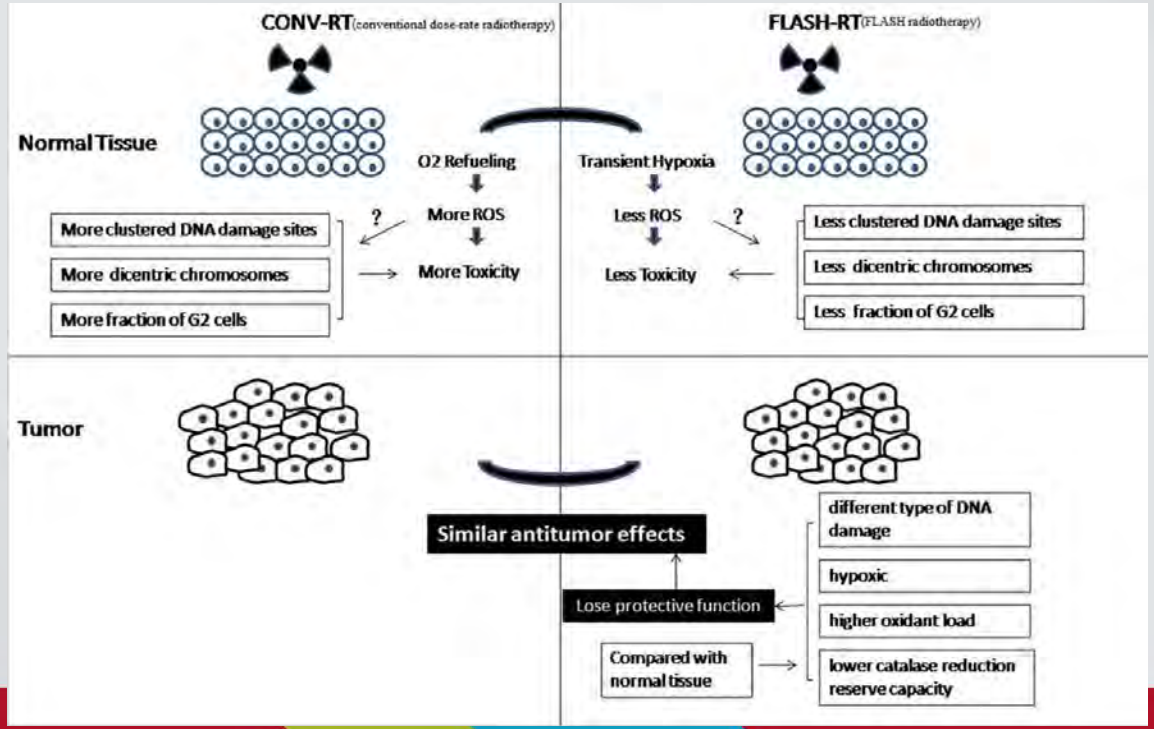
Radiobiological mechanisms

Redox biology:

- Reduced ROS
  - Zebrafish treated with FLASH produced less ROS than with conventional[12]
    - Difference ameliorated if ROS scavenges (amifostine or N-acetyl-cysteine) used pre-RT
- Normal cells have a lower ROS burden than tumor cells and are better able to sequester labile Fe
  - Thus, normal cells are better able to reduce ROS burden post-RT as well

Radiobiological mechanisms

Differential effects dependent on tissue types[13]:



Unanswered Questions

- Is the oxygen depletion effect different somehow in normal tissues vs tumor?
- Does reduced ROS production occur in tumors as well?
  - Possibly not as antioxidant mechanisms are already taxed or damaged
- Mechanism of altered TGF-β expression after FLASH
- Normal tissue vs intra-tumoral immune effects after FLASH
- True clinical relevance

Ongoing clinical research

U. of Cincinnati: FAST-Bone (FeAsibility STudy of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases)

- 10 pts; Protons
- Endpoints: evaluation of clinical workflow feasibility, treatment-related side effects. and pain relief

Conclusions

Flash is exciting...possibly a "Holy Grail"

Understanding of radiobiologic mechanisms are currently still in its infancy

- Problematic for translating to clinic?

Appears FLASH effect primarily driven by rapid transient hypoxia but how this impacts tumor vs healthy tissue differently remains unclear

At the end of the day, we need clinical trials

University of Nebraska
Medical Center

Nebraska
Medicine

References

1. Favaudon, V.; Caplier, L.; Monceau, V.; Pouzoulet, F.; Sayarath, M.; Fouillade, C.; Poupon, M.F.; Brito, I.; Hupe, P.; Bourhis, J.; et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci. Transl. Med.* **2014**, *6*, 245ra293.

2. Alaghband, Y.; Cheeks, S.N.; Allen, B.D.; Montay-Gruel, P.; Doan, N.L.; Petit, B.; Jorge, P.G.; Giedzinski, E.; Acharya, M.M.; Vozenin, M.C.; et al. Neuroprotection of Radiosensitive Juvenile Mice by Ultra-High Dose Rate FLASH Irradiation. *Cancers* **2020**, *12*, 1671

3. Vozenin, M.C.; De Fornel, P.; Petersson, K.; Favaudon, V.; Jaccard, M.; Germond, J.F.; Petit, B.; Burki, M.; Ferrand, G.; Patin, D.; et al. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. *Clin. Cancer Res.* **2019**, *25*, 35–42.

4. Levy, K.; Natarajan, S.; Wang, J.; Chow, S.; Eggold, J.; Loo, P.; Manjappa, R.; Lartey, F.; Schüler, E.; Skinner, L.; et al. FLASH irradiation enhances the therapeutic index of abdominal radiotherapy in mice. *bioRxiv [Preprint]* **2020**, 1–35.

5. Diffenderfer, E.S.; Verginadis, I.I.; Kim, M.M.; Shoniyozov, K.; Velalopoulou, A.; Goia, D.; Putt, M.; Hagan, S.; Avery, S.; Teo, K.; et al. Design, Implementation, and in Vivo Validation of a Novel Proton FLASH Radiation Therapy System. *Int J. Radiat. Oncol. Biol. Phys.* **2020**, *106*, 440–448

6. Vozenin, M.C.; Hendry, J.H.; Limoli, C.L. Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken. *Clin. Oncol.* **2019**, *31*, 407–415.

7. Hughes JR, Parsons JL. FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. *International Journal of Molecular Sciences*. 2020; 21(18):6492

8. Adrian, G.; Konradsson, E.; Lempart, M.; Back, S.; Ceberg, C.; Petersson, K. The FLASH effect depends on oxygen concentration. *Br. J. Radiol.* **2020**, *93*, 20190702

9. Simmons, D.A.; Lartey, F.M.; Schuler, E.; Rafat, M.; King, G.; Kim, A.; Ko, R.; Semaan, S.; Gonzalez, S.; Jenkins, M.; et al. Reduced cognitive deficits after FLASH irradiation of whole mouse brain are associated with less hippocampal dendritic spine loss and neuroinflammation. *Radiother. Oncol.* **2019**, *139*, 4–10.

10. Rama, N.; Saha, T.; Shukla, S.; Goda, C.; Milewski, D.; Mascia, A.E.; Vatner, R.E.; Sengupta, D.; Katsis, A.; Abel, E.; et al. Improved Tumor Control Through T-cell Infiltration Modulated by Ultra-High Dose Rate Proton FLASH Using a Clinical Pencil Beam Scanning Proton System. *Int. J. Radiat. Oncol. Biol. Phys.* **2019**, *105*, S164–S165

11. Durante, M.; Brauer-Krisch, E.; Hill, M. Faster and safer? FLASH ultra-high dose rate in radiotherapy. *Br. J. Radiol.* **2018**, *91*, 20170628.

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

13. Lin B, Gao F, Yang Y, Wu D, Zhang Y, Feng G, Dai T and Du X (2021) FLASH Radiotherapy: History and Future. *Front. Oncol.* 11:644400. doi: 10.3389/fonc.2021.644400