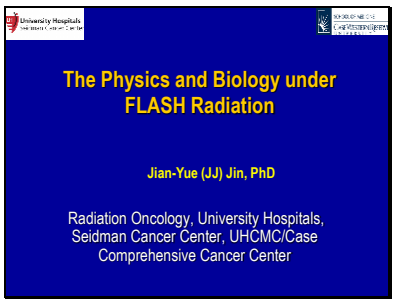
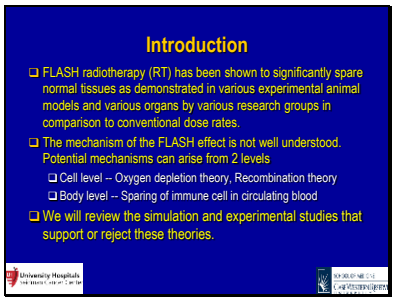
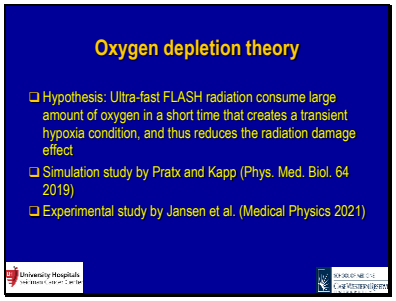
Slide 1



Slide 2

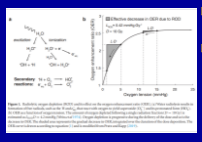


Slide 3



Slide 4

Simulation study on oxygen depletion

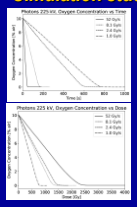


- Oxygen depletion rate is 0.21-0.42mmHg/Gy
- Without considering any Oxygen diffusion, 10Gy FLASH radiation would induce limited OER when the cell has Oxygen tension ≥15mmHg

Pratx and Kapp (Phys. Med. Biol. 64, 2019)

Slide 5

Simulation study on oxygen depletion



- Oxygen concentration in an airtight water phantom was measured before and after radiation.
- It took 150-500 Gy to reduce Oxygen concentration from 10% to 9% air pressure.

Jansen et al. (Medical Physics 2021)

Slide 6

Summary on oxygen depletion

- The amount of oxygen depleted by 10-30 Gy of radiation is very small.
- Even without considering any oxygen diffusion effect, the depleted oxygen is highly unlikely to induce a significant sparing effect in radiation damage.

Slide 7

Recombination theory

- Radiation generates radiolytic products. These products may react with O_2 to form harmful free radicals, or some products themselves are free radicals. The products may interact to each other and recombine before reacting with O_2, or the free radicals may recombine before breaking a DNA strand. The recombination become significant at FLASH radiation.
- Simulation study by Labarbe et al (Radiotherapy and Oncology 153, 2020, 303–310)
- Experimental study by Jansen et al. (Medical Physics 2021)

Slide 8

Simulation on recombination theory

Radiolysis process in water:

$H_2O \rightarrow H_3O^+$, H_2, H_2O_2, e_{aq}^-, H^*, $^*OH$

In cells: $RH \rightarrow R^* + H^*$

Radiolytic products react with cells:

$^*OH + RH \rightarrow R^* + H_2O$

To form harmful peroxyl radical ROO*

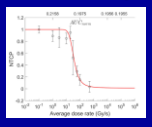
$O_2 + R^* \rightarrow ROO^*$

Recombination process:

$ROO^* + ROO^* \rightarrow ROOR + O_2$

$ROO^* + R^* \rightarrow ROOR$

$H^* + {}^*OH \rightarrow O_2$ .....



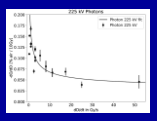
When dose rate increase to 30-50 Gy/s, recombination increases significantly, so that the number of ROO* is greatly reduced before they break the DNA strand and induce DNA damage

Labarbe et al, Radiotherapy and Oncology 153, 2020

Slide 9

Experimental study on recombination

- In the same experiment on oxygen depletion, the oxygen consumption rate is a good indicator of the remaining radiolytic products and free radicals after recombination, and the indicator of radiation effect
- The experimental data showed that oxygen consumption decreases with increasing dose rate, supporting that increasing dose rate increases recombination and reduces the radiation damage



O_2 consumption: radiolytic products react with O_2 to form free radicals:

$e_{aq}^- + O_2 \rightarrow O_2^{\bullet-}$, $H^* + O_2 \rightarrow HO_2^*$

Radiolytic products recombination:

$2e_{aq}^- + 2H_2O \rightarrow H_2 + 2OH^-$, $H^* + H^* \rightarrow H_2$

Jansen et al. (Medical Physics 2021)

Slide 10

Summary on recombination

- Both simulation and experimental studies support significant recombination at high dose rate
- Recombination is highly likely to be the mechanism responsible for the observed normal tissue sparing effect in FLASH radiation
- Because recombination is a physical process, the recombination occurs for both normal cells and tumor cells, and in water

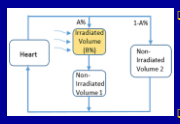
Slide 11

Immune system sparing theory

- Immune cells in circulating blood may play an important role in tumor control and normal tissue damage repair in radiotherapy. FLASH RT can froze blood flow and greatly reduce the killing of immune cells in blood
- Simulation study by Jin et al (Radiother Oncol. 2020 Aug;149:55-62)
- Experimental study to be performed

Slide 12

Compute radiation dose to blood



- Related to 2 parameters in the irradiated volume
  - A%: the percentage of blood flows into the volume
  - B%: the percentage of blood contained within the volume
- When t<T, continuity principle

$$V\% = B\% + (A\% - B\%) * t/T$$

$$D = D_0 * \frac{B\%}{V\%}$$

- When t>T, to be continue…

t: irradiation time, t = D_0/dose rate
T: blood circulation time
V%: irradiated blood volume
D_0: irradiated dose to the body
D: irradiated dose to blood

Slide 13

Blood dose volume histogram

- When t<T, V% of volume receives D, rest of blood with zero dose
- When t>T, the irradiated blood flow into the radiation region in second cycle. We assume irradiated blood is uniformly mixed with non-irradiated blood.

For a scenario of t = 2*T, the total blood can be divided into 3 parts:

1) No radiation: $i = 0, d_{i,2} = 0, v_{i,2} = (1 - A\%) * (1 - A\%)$
2) Irradiated in one cycle: $i = 1, d_{i,2} = (D_0 * \frac{B\%}{A\%})/2, v_{i,2} = 2 * (1 - A\%) * A\%$
3) Irradiated in both cycles: $i = 2, d_{i,2} = D_0 * \frac{B\%}{A\%}, v_{i,2} = A\% * A\%$

For a scenario of t = n*T, to be continue…..

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Blood dose volume histogram

For a scenario of t = n*T, the blood is irradiated with n cycles and can be divided into n+1 parts. The blood DVH can be calculated using an iterative approach:

1) $i = 0,\ d_{0,n} = 0,\ V_{0,n} = V_{0,n-1} * (1 - A\%)$
2) $i = 1,\ d_{1,n} = (D_0 * \frac{B\%}{A\%})/n,\ V_{1,n} = V_{0,n-1} * A\% + V_{1,n-1} * (1 - A\%)$

   ….

3) $i = n - 1,\ d_{n-1,n} = (n - 1) * (D_0 * \frac{B\%}{A\%})/n,$
   $V_{n-1,n} = V_{n-2,n-1} * A\% + V_{n-1,n-1} * (1 - A\%)$
4) $i = n,\ d_{n,n} = D_0 * \frac{B\%}{A\%},\ V_{n,n} = V_{n-1,n-1} * A\%$

Slide 15

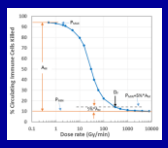
Modeling radiation killing of circulating immune cells

- Linear quadratic model to simulate the percentage of immune cell killing in blood, $\alpha = 0.4\ Gy^{-1}$, $\alpha/\beta = 2\ Gy$
- Dose rate vary from 0.1~20,000 Gy/min, D_0 =2~50 Gy
- T = 60 seconds for human adult, and T = 5~10 seconds for mice
- Various A% and B% for different scenarios

Slide 16

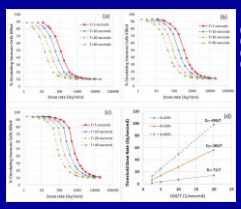
Effect of dose rate

- Irradiation at a particular condition (A% = 50%, B% = 10%, T = 60s) with D_0 = 30 Gy (similar as to one lung).
- Percentage of circulating immune cells killed reduced from 95% to 10%.



Slide 17

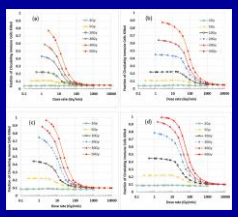
Effects of T and A%



(a) A%=20%
(b) A%=50%
(c) A%=80%
(d) Threshold FLASH dose rate dependence on T

Slide 18

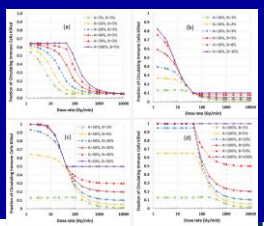
Effect of Dose



(a) A% = 10%
B% = 5%
(b) A% = 50%
B% = 5%
(c) A% = 20%
B% = 10%
(d) A% = 50%
B% = 10%

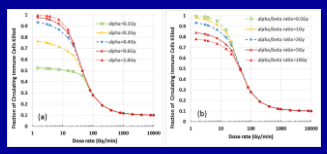
Slide 19

At various A% and B%



Slide 20

At various α and β values



Slide 21

Summary

- Simulation and experimental studies suggest that oxygen depletion is unlikely to be the mechanism for FLASH effect
- Simulation and experimental studies suggest that recombination is likely to be responsible for observed normal structure sparing effect in FLASH radiation. However, there might be no clinical benefit for this effect because recombination may also occur for tumors
- A simulation study suggests that FLASH RT may spare immune cells in circulating blood. However, experimental studies are needed to verify the result
- Although it was reported that immune system may play a role in repair of normal tissue damage and RT-induced lymphopenia is associated with tumor control and survival, further studies are needed to prove FLASH-induced immune sparing is related to the FLASH effect