Electron-hole liquid (EHL) conjecture rendering a mechanism of FLASH radiotherapy

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ABSTRACT

Purpose: FLASH radiotherapy (FLASH-RT), utilizing ultra-high dose rates (UHDR), orders of magnitude above those of conventional RT, is unique by its significantly reduced damage to healthy tissues (sparing effect) that do not compromise the anti-tumor effectiveness. The underlying physics of FLASH RT remains yet to be understood with multiple studies reporting the absence of FLASH effect. Here we address the FLASH enigma theoretically, using basic physics with a goal of describing the FLASH RT criteria and kinetics.

Methods: We consider radiation-induced generation of charge carriers, followed by that of free radicals, such as the hydroxyl (•OH) known for their distractive actions, either useful (killing the tumor cells) or detrimental (killing the healthy cells). We utilized analytical modeling techniques based on the standard kinetic equations with the Coulomb interactions. High concentration of charge carriers under UHDR results in transition from electron-hole gas phase (typical of conventional RT) to electron-hole liquid (EHL), forming strong diffusion barriers leading to their mobility arrest and sparing effects.

Results: The diffusivity drops by many orders of magnitude between the phases of gas and liquid; hence, the charge carriers remain almost frozen and free radical generation suppressed in the EHL. That sparing mechanism is limited to the healthy tissues which are structurally organized enough to avoid the high-rate electron-hole recombination and maintain EHL. In the disordered tumor structure, the high-rate recombination decreases electron-hole concentration below that of EHL thus keeping the radical generation strong enough for antitumor effectiveness.

Conclusions: Introducing the concept of EHL for ultra-high dose rates, we derived the equations for time-dependent charge carrier concentration, yielding criteria for the minimum dose and dose rate simultaneously required for transition to EHL and thus FLASH condition. Our results demonstrate the binding effect of EHL, the temporal dynamic of reactive secondary species, and the sparing effect.

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INTRODUCTION

A conventional radiotherapy (CONV-RT) typically requires multiple sessions, often spanning weeks, and relies on the classical radiobiology principles. Recently the focus has shifted to a dose rate modulation, unexpectedly providing a drastic increase in the therapeutic index with FLASH radiotherapy (FLASH-RT), leveraging average ultra-high dose rates (UHDR) of greater than 40 Gy/s, orders of magnitude higher than those of CONV-RT. A unique characteristic of FLASH-RT is that its significantly reduced damage to healthy tissues does not compromise the antitumor effectiveness of the treatment. The physics underlying that striking effect remains to be understood yet, after more than 60 years since the concept of FLASH-RT was introduced.[1]

METHODS AND MATERIALS

The FLASH problematic is presented via basic physics:

- We treat the FLASH enigma as originating in a two-phase system formed by the material of tumor embedded in a material of healthy tissues.
- The radiation generated charged particles (electrons and holes) participate in interactions creating reactive secondary species (RSS), such are free radicals, essential for destroying cancer cells or healthy cells.
- The tumor phase exhibits strong structural disorder (heterogeneity) as illustrated in Fig. 1.
- The disorder renders anomalously efficient electron-hole recombination and other related pathways allowing efficient energy relaxation. Such pathways exist due to random structural 'defects' (vacancies, dangling bonds, impurities, etc.; a-Si vs. c-Si in Fig. 1 (d) is a classical example). Those pathways make the tumor phase able to 'digest' all supplied electrons and holes without jamming and produce RSS at any dose rates.
- The healthy tissue is much less disordered not rendering efficient enough energy relaxation pathways. Therefore, under high dose rates, charge carriers accumulate forming **electron-hole liquid** (EHL). Our EHL is defined by the *classical* (not quantum) condition that energy of interaction between particles exceeds their kinetic energy. The relevance of classical description is guaranteed by a very strong interaction of electrons and holes with surrounding material making them 'hydrated' with effective masses on the order of atomic masses
- Our classical EHL behaves as most of the classical molecular liquids with diffusivities many orders of magnitude lower than that of their corresponding gas phases. It is important that EHL arrested diffusivity suppresses reactions between electrons and holes thus significantly slowing down RSS generation rates; hence, the sparing effect.

Formation of EHL can be visualized, following Fig. 3.

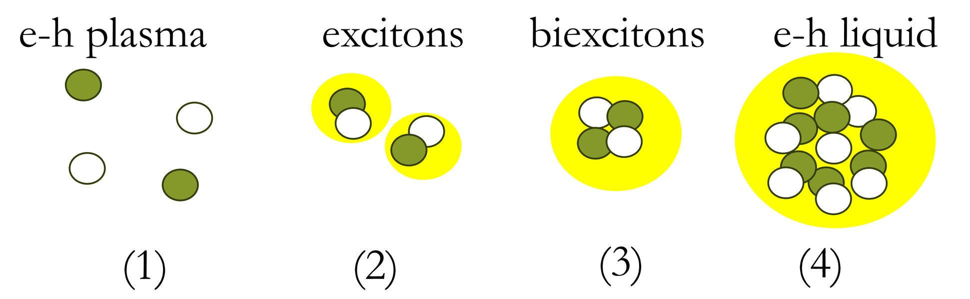

Fig. 3. Radiation induced ionization depending on dose rate and energy. Dark circles represent the electrons, white circles represent holes. From right to left: (1) plasma of weakly interacting electrons and holes generated with low dose rates high energy radiation; (b) excitons, i. e. coupled electron-hole pairs generated with higher dose rates and close to the absorption edge radiation; (3) biexcitons which are coupled pairs of excitons forming with increase of exciton concentration; (4) a droplet of electron hole liquid under high dose rate of well absorbed radiation.

We estimate the dose and dose rate criteria (both are required to be above the defined threshold) for formation of EHL as $D_{\min} \sim 10\text{Gy}$, $\dot{D} \sim 10-10^3$ Gy/s.

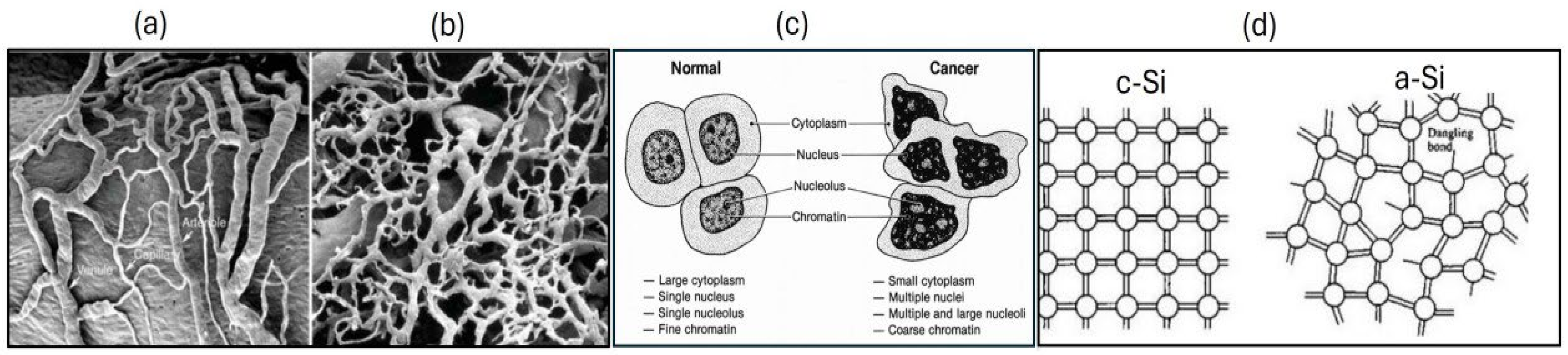

Fig. 1. Schematics of ordered vs. disordered counterpart structures. (a) Scanning electron microscopic imaging of polymer cast of normal microvasculature; (b) same for tumor microvasculature showing disorganization and lack of conventional hierarchy of blood vessels. (c) Cell structure in healthy vs. that of cancer tissue. (d) Crystalline (c-Si) vs. amorphous (a-Si)

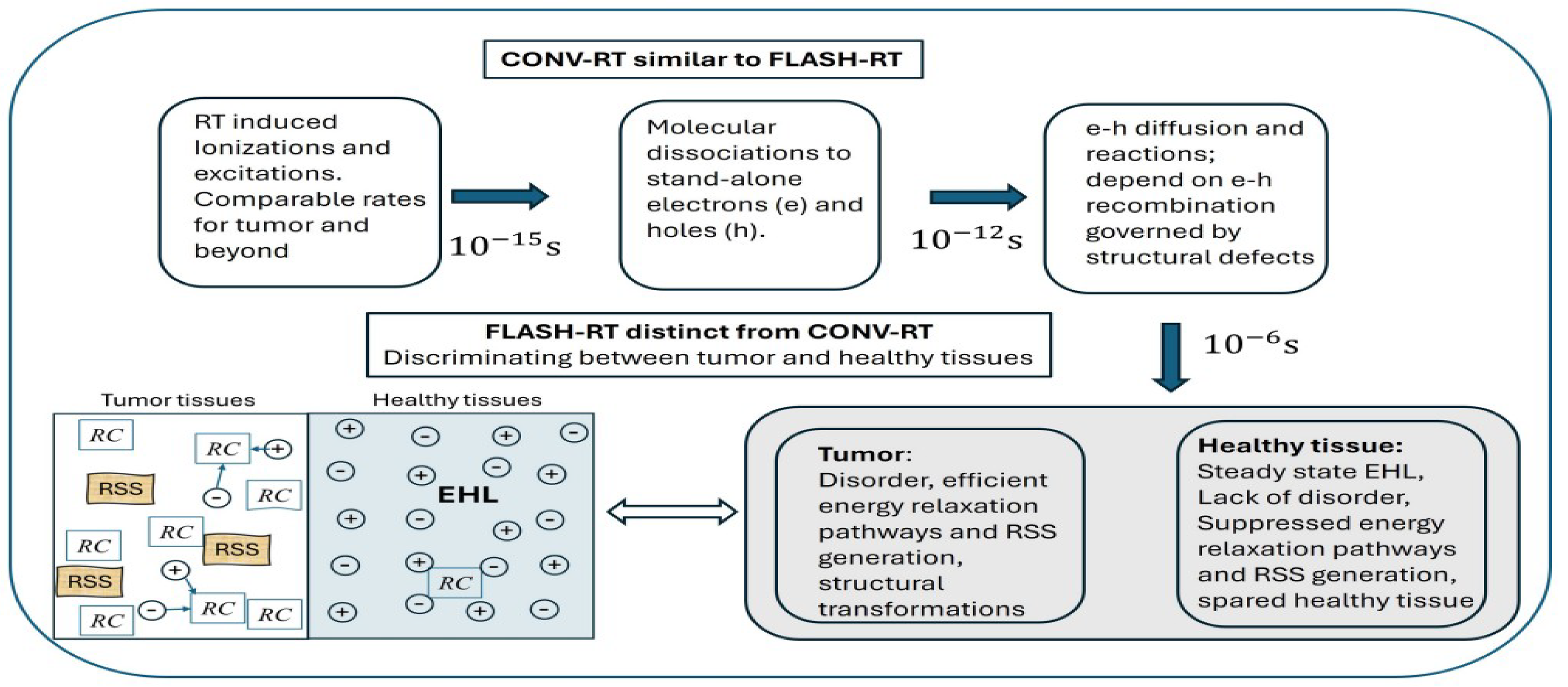

Fig. 2. The top row boxes present processes found with both CONV-RT and FLASH-RT. The bottom row discriminates between CONV-RT (left) and FLASH-RT (right). The insert figure in the left bottom corner illustrates the electronic processes under irradiation in the tumor (left) and healthy tissues (right) regions. Arrows show e-h recombination processes, RC stands for recombination centers (defects). + and – denote holes and electrons, respectively.

RESULTS AND DISCUSSION

We derived the equations for time-dependent charge carrier and free radical (reactive secondary species, or RSS) concentration n. Here $\mathcal{M}$ is the Madelung constant (typically ~2 varying between different structures), k_B is the Boltzmann's constant and T is the absolute temperature; and g is the EHL charge generation rate.

$$\frac{dn}{dt} = -\frac{n}{\tau_0}\exp\left[-\frac{\mathfrak{M}e^2}{\kappa k_B T}\left(\frac{4\pi n}{3}\right)^{1/3}\right] + g$$

RSS concentration R(t) generated by charge carriers overcoming the EHL binding is given in Fig. 4.

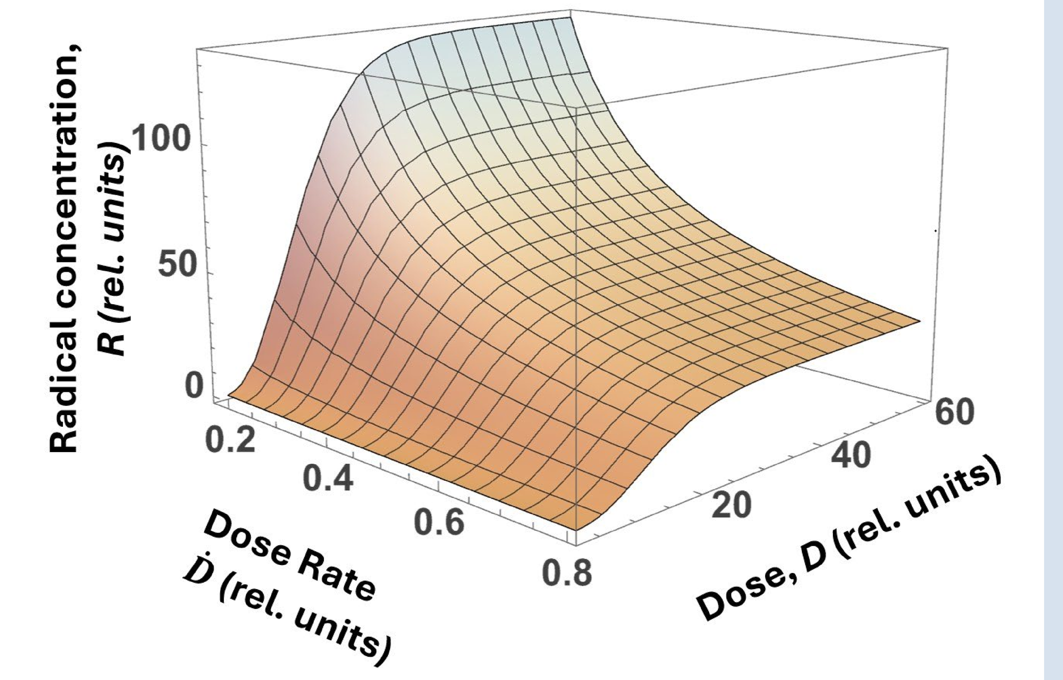

Fig. 4. A calculated sketch of sparing effect showing how RT created modifications decrease with the dose rate for fixed recombination parameters representing normal tissue

Overall, our work introduces the concept of EHL attributing sparing of healthy tissues to suppressed chemical reactivity of charge carriers due to EHL binding. Phenomenologically our mechanism of sparing correlates with the "free radical hypothesis"8 and hypothetical scavenger effects, according to which some undefined processes diminish the concentration of free radicals. Our hypothesis attributes such processes to the EHL binding under UHDR radiation.

CONCLUSIONS

(1) What is understood. Why FLASH exists. Why it has low value thresholds for both the doses and dose rates. A degree of irreproducibility can be explained by ill-controlled impurities, affecting the EHL conditions.
(2) What is not understood. The quantitative temporal kinetic of tumor evolution under FLASH-RT.
(3) Possible experimental verifications. Electric conduction and optical properties under UHDR; verification of criteria for dose and dose rate to achieve FLASH effect; doping effects on EHL, which would destroy or enhance the FLASH effect; temperature dependence of the FLASH effect; calorimetric verification of EHL formation (as a phase transition). Establishing the existence of EHL in sub-organismal and water-based substances.

REFERENCES

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