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Review Article

On the Optimal Choice of Radiation Modality: Maximizing Light Ion Fractionation and Flash effects

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Abstract

All radiation types produce δ -rays ≈1 keV that can impart MGy doses to 10 nm size volumes of DNA. These events can produce severe **Dual Double Strand Breaks (DDSB)** at the periphery of nucleosomes in single events particularly in heterochromatic DNA. These DDSBs are the most common multiply damaged sites and their probabilities are determining the biological **effectiveness and therapeutic responses** of different beams. The recent understanding that most normal tissues with intact TP53 genes generally are low-dose hypersensitive (LDHS) and **low-dose apoptotic (LDA)**, implies that the well-known universal clinical fractionation window at ≈ 2 Gy/Fr defines the optimal tolerance level of normal tissues and not the optimal tumor dose per fraction using IMRT. Interestingly, practically all cancer cells are linked to genomic instability in some DNA repair, cell cycle or growth control genes like TP53 that is affected in 50% of all tumors. Unfortunately, this often gives tumor cells a **low dose radiation resistant phenotype (LDRR).**

The clinical fractionation window is due to the low-dose and LET initiation of full DNA repair capability after ≈1⁄2 Gy, and we should use this acquired repair advantage and consequent induced radiation resistance in normal tissues to its full extent up to ≈2.3 Gy where the **high dose apoptosis (HDA)** may start.

Understanding Quantum Biological Cure implies that light ions should truly have the lowest possible LET in normal tissues to retain the classical low LET fractionation window and have a high LET only in the gross tumor region. Furthermore, carbon and heavier ion treatments may ideally require that the last ≈10+ GyE being delivered by **low LET (electrons or photons)** to minimize normal tissue damage get a steep dose response and maximize complication free cure. In fact, the microscopic heterogeneity of heavier ions suggest the use of the lightest ions with a low LET in normal tissues allowing **quantum biology optimized molecular radiation therapy** with **He-Li-B** ions. This results in negligible increase in therapeutic effect in normal tissues and highest possible tumor apoptosis, senescence and cell kill in the tumor! Carbon and heavier ions should therefore be delivered with a **10-15 GyE low LET roundup** to really **maximize their complication free cure**! In fact, it is conceptually wrong to try to eliminate the last few tumor clonogens by ion beams with severe cold spots in the tumor region. Ion therapy is only useful during the first 50 GyE when there is still hundreds or more of viable tumor cells left in the target volume!

The principle of Flash is due to a **high dose inverse dose rate effect** in the tumor due to **Repair Protein Panic (RPP)** and a **dual gantry** arm design is proposed for significantly increased tumor responses not least using ion beam **Ultra Fractionation** and high dose biologically optimized IMRT-Flash++ or **Super Flash** where dual simultaneous beams collaborate only in the tumor volume.

Keywords: TP53 damage sensors and modification sites; TP53 mutations; LDRR tumors; light ion radiation therapy; therapy optimization; multiply damaged sites; dual nucleosomal double-strand breaks; low-dose hyper-sensitivity; low- dose apoptosis; optimal daily - weekly fractionation; quantum biology optimized molecular radiation therapy; Ion Beam Ultra fractionation; Super Flash; IMRT-Flash++ dual gantry

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