PriMera Scientific
Medicine and Public Health
Volume 6 Issue 5 May 2025
ISSN: 2833-5627

Recent Developments in Molecular Radiation Biology Can Improve Radiation Oncology

Type: Short Communication
Received: February 26, 2025
Published: May 03, 2025

Citation:
Anders Brahme. "Recent Developments in Molecular Radiation Biology Can Improve Radiation Oncology". PriMera Scientific Medicine and Public Health 6.5 (2025): 19-20.

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I will use this opportunity to inform about recent radiation biology developments that can significantly improve curative radiation oncology. Interestingly, while developing an improved cell survival formulation better applicable for normal tissue responses [1, 2] we found that most normal issues that have a wild type TP53 gene are also linked to Low Dose Hyper-Sensitivity (LDHS [3-5]). Because about ½ Gy or 18 DSBs are needed to start full DNA repair capability in the cell by starting non-homologous end joining and homologous recombination by phosphorylation of p53 at the serine 15 and 20 sites [3, 6, 7]. This LDHS in normal tissues is an effect of the cellular cancer avoidance system developed to induce Low Dose Apoptosis (LDA) to avoid misrepair before the DNA repair system is fully functional. Instead, after a single low dose irradiation the caspase 3, that performed the apoptosis, will remarkably remember the cell loss and induce a compensatory accelerated repopulation of the missed cell to recover homeostasis [8]! This is in contrast to most tumors that commonly are associated with a mutant p53 that instead often is associated with a Low Dose Radiation Resistant (LDRR [3]) phenotype and therefore generally are rather radiation resistant at low doses generally without LDA. This mechanism makes most tumors more difficult to treat at low doses making effective IMRT the method of choice for curative treatments. However, the LDHS of most normal tissues implies that as soon as we need to go above about 0.5 Gy to treat the underlying tumor it is better to continue up to about 2 Gy (as in classical parallel opposed treatments [6]) since now we have full repair induced and we should use the thereby induced radiation resistance to increase the dose to the tumor using IMRT. In fact the optimal radiation tolerance of most normal tissues is in the range 1.8-2.3 Gy/Fraction as was established through the last 80 years of radiation therapy [9]. However, using IMRT the tumor dose should be much higher now, than the classical parallel opposed beam ≈2 Gy/Fr, since we now generally know we face a LDRR tumor that need higher doses per fraction for cure, as the increasingly popular ultra-hypo-fractionation schedules propose [3, 10-13]. The 2 Gy/Fr to normal tissues at risk fractionation schedule was proposed already 1999 [14] and it is really the best way to describe the tumor boost and the resultant dose per fraction increase in the tumor to reach about ≈3-4 Gy to avoid too massive cell kill in large tumors. A total tumor dose reduction of about ≈10 Gy is achievable by this type of tumor boost as described recently [3, 4, 7].

A further way to improve normal tissue recovery during fractionated radiation therapy is to also increase the dose on Friday and Monday as the 72 h weekend DNA repair is then used at its best. Such a schedule is making homologous recombination repair about 50% recovered, whereas non-homologous end joining recovers sufficiently already in the normal 24 hrs. between fractions. A further im-

provement is obtained by lower doses Tuesday and Thursday and high dose also on Wednesdays as discussed in some detail recently [3, 4]. By this approach a total increase in complication free cure of the treatment of 10-12 % was estimated! There are a number of further improvements possible as suggested in the associated references that I may come back to in a second editorial!

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