Pre-clinical radiotherapy

Propositions

Pre-clinical radiotherapy: from imaging to dose

Ana Vaniqui

1. Pre-clinical research platforms can provide a cost-effective experimental pipeline for timely validation of new treatment modalities or interpretation of clinical experience on large cohorts. (*Valorisation addendum*)

2. The abiding debate over which [dose-reporting] quantity to favour is foreseen to linger while it is not clear which quantity correlates better with the biological effects of ionizing irradiation: pre-clinical radiotherapy might represent an ideal platform for measurement-based studies to settle this fundamental question. (*this thesis*)

3. The following challenges are closely connected: imaging requires sub-millimetre resolution, affects dosimetry and is affected by motion. Pre-clinically mimicking clinical scenarios require lower energies to avoid large beam penumbras and dose (re-)buildup regions which also affect dosimetry and might yield different treatment outcomes if dose calculations do not consider medium heterogeneities. (*this thesis*)

4. It is necessary to consider anatomical and physiological characteristics during clinical to pre-clinical translation, or vice-versa. Although margins are sometimes extrapolated from clinical experience, they might not be representative for small animal disease models. (*this thesis*)

5. Beyond the dose-reporting quantities currently employed, and besides their proportional relationship with biological effects, radiotherapy treatments and fundamental radiation knowledge could benefit from a quantity more tightly related to RBE, e.g. cell death probability, biological endpoint or treatment outcome, rather than radiation dose.

6. Ion therapy in vivo studies could be useful for different radiobiological hypotheses, e.g. RBE dependence on fractionation, differential immune effects with respect to photon beams or, more generally, biological dependence on high LET.

7. Preclinical and clinical research should work as a cycle "considering the biology which needs to be represented in the model, tailoring the physics of the irradiation as close to the human situation as possible and acknowledging the limitations that cannot be overcome". *Koontz et al (2017)*

8. Radiation therapy evolved as an empirical art, not an exact science. Clinical innovation and experience have consistently been followed by attempts to explain the underlying biology. Fractionation was introduced, not because of an appreciation of the nuances of radiobiology, but because the technological limitations of the early therapy machines meant that any treatments had to be given using interrupted regimens. *The Royal College of Radiologists, BFCo(06)1, (2006)*

9. I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me. *Isaac Newton*

10. A poet once said, 'The whole universe is in a glass of wine.' We will probably never know in what sense he meant it, for poets do not write to be understood. But it is true that if we look at a glass of wine closely enough we see the entire universe. There are the things of physics: the twisting liquid which evaporates depending on the wind and weather, the reflection in the glass; and our imagination adds atoms. The glass is a distillation of the earth's rocks, and in its composition we see the secrets of the universe's age, and the evolution of stars. (...) There in wine is found the great generalization; all life is fermentation. (...) If our small minds, for some convenience, divide this glass of wine, this universe, into parts – physics, biology, geology, astronomy, psychology, and so on – remember that nature does not know it! So let us put it all back together, not forgetting ultimately what it is for. Let it give us one more final pleasure; drink it and forget it all! *Richard P. Feynman*