Physics for Health in Europe

Overview of Session I

Radiobiology in Therapy and Space Science

Chairman: Marco Durante

Reporter/Rapporteur

Bleddyn Jones MD

[Prof. Clinical Radiation Biology],

Gray Institute for Radiation Oncology & Biology,
& Particle Therapy Cancer Research Institute, Oxford Physics, UK.

Initial Overview

- Health Physics is Healthy.
- Many promising theoretical models, projects & developments ‘on the ground’ especially Heidelberg Univ. Clinic.
- Wide scope for industrial + academic partnerships
- Targeting funding remains difficult - need simulations of health **impact** for new technologies [improved diagnostic rates, cure, quality of life, reduced or increased radiation exposure & malignant induction].
- Post-exposure modification of radiation damage relevant to therapy & space travel. Radioprotection applies to both but high dose effects should not be ignored such as accumulated dose for long duration travel for cells/spores (over light years).

Director-General: Introduction & Directive

Basic research, Innovation to applications:

Example: Paul Dirac - quadratic solution for electron mechanics implied two solutions: + and - for matter and anti-matter. Positrons now routinely used in Hospitals

- Encourage dialogue
- Find which technologies for which **problems**, given constraints?
- Discussion should not be institution centred
- INTENSIFY DIALOGUE…. brainstorming leading to ROAD MAP & PROGRESS.

D-G`s advice….think about it

- Excellent cooperation achieved in Physics, at CERN.
- Why not in Medical Applications?
- Countries have separate laws + requirements for practice + indemnity/legal codes…difficult for a Physician to practice in more than one country…., but precedents exist…π^- mesons (after Fowler & Perkins)

Oral presentations

- Physics meeting biology……new bio-agents increase efficiency of radiotherapy…reducing causes of radioresistance
- Initial DNA events in ion beam therapy….relative immobility of damaged sites …chromosomal events → low dose malignant induction, high dose cell kill.
- Space radiation: considerable overlap with particle therapy especially radioprotection, but more cyclical, repeated exposures over longer times to high doses + mixed low & high LET particles. **Weather.**
- MC-Fluka code applications in TPS, PET !

Oral presentations

- Experimental particle therapy facility at CERN...what is minimal requirement? Beyond accelerator advances, cells could be tested, but more RBE tissue animal experiments necessary.
- For **real benefits to humanity**, Ion Therapy at CERN (maybe under auspices of Univ. Geneva + EU)…..with ‘open access’.
- Heidelberg treatment planning ….biological dose distributions + assumptions made. Plans for TPS at INFN, Torino Italy with IBA (Brussels) extension of LEM.

Oral presentations

- Synchrotron micro-beam radiation for brain tumours: good tissue sparing, use of nano-particles discussed for several years but also some risk of carcinogenesis.
- Needs longer-term studies in larger animals to determine realistic late-effects…e.g. small linear areas of hypoplasia (reduced cell density along radiation tracks) may interact + ageing processes in humans…but better than we can achieve at present?
- ? Re-ionisation of cytotoxic platinum (from Pl covalently bound to proteins) is feasible during the synchrotron radiation, allowing further cell kill…if and only if ionised Pl diffuses to DNA…..this is a type of experiment that could be done at CERN + Grenoble.
- Capture for Pl needs to be studied further in proton and ion beam therapy also

Some topics covered in posters include

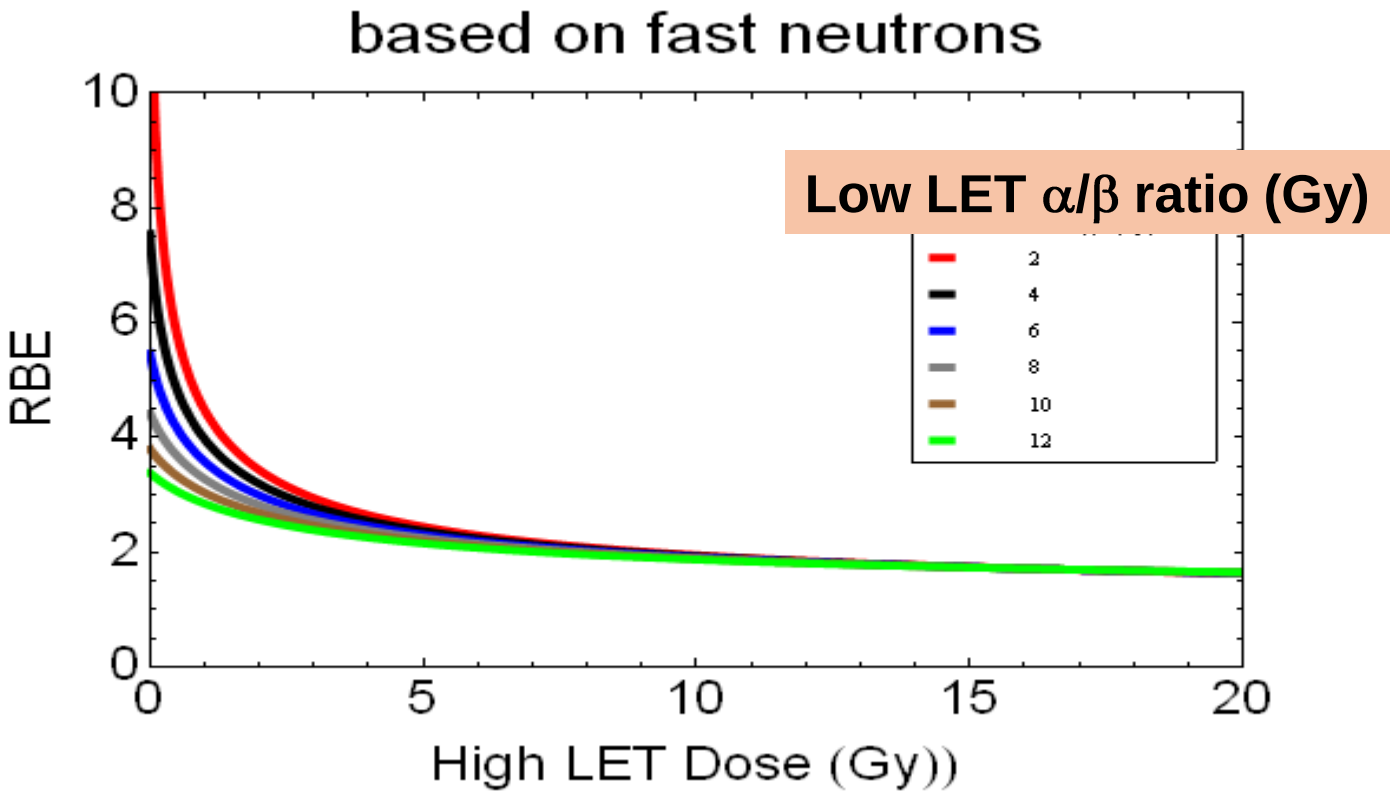
- Amorphous track models…..better access to codes by forming a library
- M-C simulation methods….many applications
- RBE prediction….by theory…many unknowns; all models provisional [Newton].
- Vibration patterns in DNA….resonances? [Some chromosomes more susceptible than others?]
- Red blood cell membrane damage as surrogate for radiation exposure levels at low dose.
- Anti-protons….'event size' is large but peak RBE is excellent….could be used as boost….one visit to CERN?
- Radiation collagen cross links causing scaring in cardiac tissues…are they repairable, or digestible is next question?

What remains to be done?

- Better RBE prediction ..refinement of models, + robust linkage to α/β of reference radiation.
- RBE at higher doses (lower surviving fractions)….necessary for larger fraction sizes…..LEM based on low dose so needs extension.
- Animal data testing…with robust numbers…for late tissue effects.
- Better malignant induction probabilities (MIP) in treatment planning? Because high LET is more carcinogenic per cell, so minimise beam tissue-traversion distances.
- Gantry requirements: cost versus better dose distributions + total tissue traversion…relating to MIP.
- Ultra high dose rates –will consume oxygen faster than replacement diffusion.
- Verification of dose position with better accuracy.

LEM & RBE

- At present LEM underestimates RBE...accuracy ~10 - 25%; most work done in CHO-V79 cells with high α/β ratio.
- Implication 1: if RBE is then higher in more slowly growing tumour and high dose confined to tumour….will get extra tumour RBE effect & excellent control
- Implication 2: if RBE is higher in critical normal tissue, then dose planning constraints need to be very demanding……achievable with C^{6+} in most applications.
- With increased dose per fraction these may change…..as in Japanses lung experience

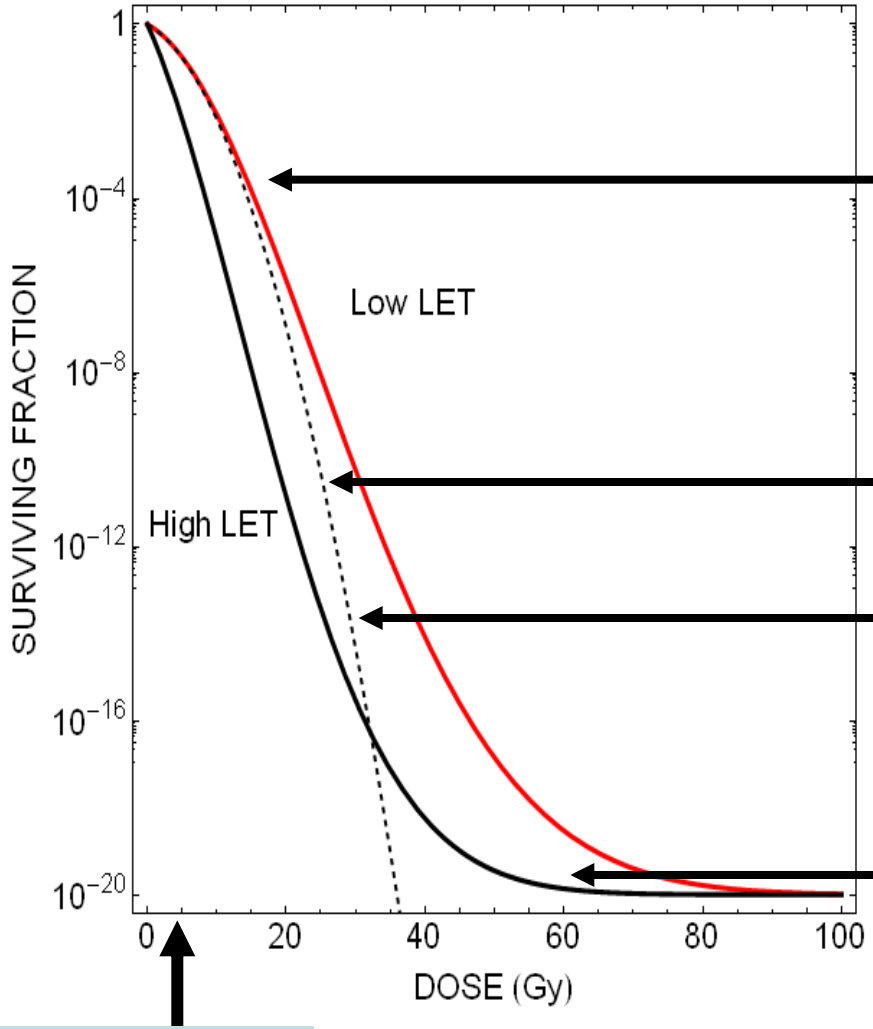


RBE variation mainly found at low dose per fraction, with greater range in late-reacting tissues (low α/β ratio).

Note: most high-LET assays done using low α/β ratio endpoints using short term assays using rapidly dividing cell systems such as Chinese Hamster Ovary- V79 hybrid cells (respond like brown and green lines).

More experimental work

- Animal models (in-bred systems) show very steep dose responses for spinal cord paralysis. Dose-response gradient cannot be same as human.
- Human data… more heterogeneity ….of radiosensitivities, epigenetics, other simultaneous pathologies, vascular disease and lifestyle influences (smoking, diet etc).



Limit of *in-vitro* testing range

Range required for tumour cure

Unmodified LQ model

Range for sending cells/spores in space for a long single fraction of high LET at low dose rate with no repair, but allowing solar flare and other fluctuating dose rates

Whole body lethal dose

Radio-surgery mentioned: comparing particles with surgery for cancer

- Particle therapy is comparable with ‘key-hole’ surgery ?
- Keyhole was proven in randomised trials to be cost–effective, by reducing hospital admission times….which persuaded Governments to adopt rapidly.
- Same standard needs to be applied in particle therapy.

Interactions with molecular based treatments

- Repair inhibitors….? Repair promoters…?
- Re-oxygenating anti-proliferative drugs…. McKenna showed examples using several signal transduction inhibitor drugs……if these work, then lower LET particles may be sufficient - protons, helium may be as good as carbon & neon,
- Neo-adjuvant priming of tumour…drugs to cause shrinkage, re-oxygenation, improved treatment geometry might allow far higher dose to be given with safety
- Testing of concept in clinic at European Ion Beam centres?

Weakness of CPT: image dependency

- Non-image-dependent therapies should interact constructively; chemotherapies + radiation.
- Some drugs potentiate high LET particle therapy …those which selectively increase β parameter, α increases > β at high LET. [TEMOZAR/TEMODAL]
- After surgery? Particles must have role after surgery, when no 'visible' tumour, but target is a **volume** with moderate to high risk of recurrence.

BUT,

- **Diagnostic resolution improvements will benefit particle therapy, and confirm beam positions, aid early diagnosis and help provide more 'ideal' patients for particle therapy**

Choices …need to be researched

- Particle type: protons, helium, neon, oxygen, carbon ions.
- Some particles might be preferred on their physical basis e.g. He ions in head, neck, near brain and spinal cord, according to local anatomy.
- What molecular-based treatment to include…..and when during treatment?
- Comparative trials; mixtures of each + molecular approaches….reducing radioresistance & hypoxia?

Summary

- Europe has good range of research in radiobiology….but from past experience of fast neutrons, needs careful & totally comprehensive approach at highest scientific level.
- Applied radiobiology is complex and includes physics, medicine, biology and computing; with 3-D tissue anatomy + reliable Δ RBE with dose in different tissue types…..not trivial.
- CERN could be provider of definitive solutions…but would need partnerships + comprehensive facilities (cellular+animal imaging + analysis of human irradiations…for Europe & perhaps worldwide??
- Suggest feedback to marco.silari@cern.ch