Proton and heavy ion radiotherapy: Effect of LET

As a low LET particle traverses a DNA molecule, ionizations are far apart and double strand breaks are rare.

With high LET particles, ionizations are closer together and double strand breaks are more common.
Effect of LET on cell survival curves

Cell sensitivity increases as LET increases.

The increase in sensitivity is represented by the RBE:

\[
RBE = \frac{\text{dose of } ^{60}\text{Co radiation}}{\text{dose of different LET radiation}}
\]

to produce the same biological effect.
Factors which influence the RBE

- RBE depends upon:
  - radiation quality (LET)
  - radiation dose
  - dose/fraction
  - dose rate
  - biological system or endpoint
The RBE is low for high doses (=1.5)
The RBE is high for low doses (=3.0)
The RBE is high for low doses/fraction (=2.6)
Effect of dose and dose/fraction on the RBE

- At low doses (and low doses/fraction), the RBE will be higher since there is more repair at low doses and this favors the standard $^{60}$Co radiation
  - the numerator in the RBE equation increases as dose decreases

- A similar effect is seen with low dose-rate irradiation
RBE dependence on the type of cell irradiated

- In general, cells which exhibit large shoulders in their survival curves will have high RBEs.
- Conversely, cells with little, if any, shoulder will have low RBEs.
- But there are exceptions due to the different interaction mechanisms between low- and high-LET radiations e.g. cell-cycle effect.
Variation of RBE and OER with LET

As LET increases:

RBE increases

and OER decreases
Influence of LET on cell-cycle effect

- For high-LET radiations the cell-cycle effect is less than with low LET radiations
  - cancer cells or late reacting normal tissue cells trapped in resistant phases of the cell cycle will be less protected when treated with high-LET radiations
Why high-LET radiotherapy?

- **Physical benefits**
  - *the Bragg peak*
  - *reduced penumbra*

- **Radiobiological benefits**
  - *reduced effect of hypoxia*
  - *reduced cell cycle effect*
Why protons?

- The major reason is physical
  - the Bragg peak
Depth-dose characteristics of high-energy protons

The depth of the Bragg peak can be adjusted by changing beam energy

(Jones, 2006)
The Bragg peak

- Depth can be changed by varying the energy
- Too narrow for all but very small lesions
- Can be widened by mixing beams of several energies using a range filter (diluted Bragg peak)
Variable range shifter

The number of slabs of the range shifter are varied to modulate the energy of the beam reaching the patient in order to produce the spread out Bragg peak.

The patient specific compensator is designed to shape the distal extent of the high dose region.
Spreading out the proton Bragg peak

By using 12 slabs of range shifter in this example it is possible to produce a spread out Bragg peak of uniform intensity from 15 to 40 mm in depth.
Biological benefits within the spread out Bragg peak

- Because the spread out Bragg peak contains protons from the low-LET plateau region, the average LET is not very high
  - biological benefits such as reduced effects of oxygen and the cell cycle will be greatly reduced
Proton treatment for macular degeneration using the Bragg peak

For beams that do not need to be spread out, the LET of the protons remains high.

Biological benefits of high LET radiations are maintained.

Moyes et al, Medical Physics 26, 777, 1999
Partial breast irradiation using the spread-out Bragg peak
Target volume DVHs for this breast treatment by different modalities

Weber, 2006
Heart DVHs for this patient

CONVENTIONAL
IMRT - PLAN A
IMRT - PLAN B
PROTONS

Weber, 2006
Ipsilateral lung DVHs for this patient

CONVENTIONAL
IMRT - PLAN A
IMRT - PLAN B
PROTONS

Weber, 2006
Comparisons of protons, IMRT, and conventional photons for breast treatments

<table>
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<tr>
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IMRT vs. protons

Comparative dose distributions for (a) IMRT and (b) protons for a recurrent sarcoma in a 12-year-old boy (Jones, 2006)
Proton beam treating an intracranial lesion
Comparison of protons and IMRT

Lomax, et al, Radiotherapy and Oncology 51, 257, 1999
In intensity modulated proton therapy, a narrow proton pencil beam is scanned magnetically over the target volume, while both the energy and the intensity of the beam are modulated.
Intensity Modulated Proton Therapy (IMPT)

Figure 1: IMPT treatment plan for a head & neck case: uniform dose distribution on the target is achieved by superposition of inhomogeneous distribution delivered by proton beams from different directions.

(From the German Cancer Research Centre)
Intensity and energy modulation with protons
Iterative DVH modification for this patient
Proton IMPT vs. photon IMRT for prostate cancer

Proton IMRT for a rhabdomyosarcoma

Example of an intensity-modulated proton therapy plan with sparing of the lacrimal gland for a 12-year-old boy with an orbital rhabdomyosarcoma initially infiltrating the surrounding soft tissue

Timmermann, 2006

Monterrey, December 2009
Why heavy ions?

- **Physical advantages:**
  - Bragg peak
  - Adjustable Bragg peak depth
  - Sharp beam edges (small penumbra)

- **Biological advantages:**
  - Potentially low OER, reduced cell-cycle effect
Why heavy ions work
Carbon ion Bragg peaks
Carbon ions vs. protons

Bragg peaks with heavy ions are much narrower than those for protons and the dose in the plateau region is lower.

Figure 5. Depth dose curves for proton and carbon beams. The solid curve represents a Bragg peak of 160 MeV protons characteristic for the Harvard Cyclotron (HCL) in Boston. The dashed curve shows the much narrower Bragg peak of a 260 MeV/u carbon ion beam measured at GSI (Courtesy of O. Jäkel).
Biological effectiveness within the spread out Bragg peak

- Compared with protons, the Bragg peak for heavy ions is much higher and the radiation within the Bragg peak has a much higher LET.
- Consequently, when the Bragg peak is spread out, much of the biological benefit is retained.
Changes of RBE with depth for spread-out Bragg peaks

Within the spread out Bragg peak, LET (and RBE) will be highest at the distal end of the beam where there is less plateau region contamination.

To get a uniform biologically effective dose throughout the target volume, the physical dose must be higher at the proximal side of the beam.
400 MeV C-ion Bragg peak diluted using 6-step Lucite range shifter
Heavy ion therapy

A schematic diagram of a synchrotron treatment center (Jones, 2006)
Active raster scan system for C ions at GSI, Darmstadt, Germany

Instead of a shaped collimator beams can be shaped by active raster scanning.

The energy of the beam can be continuously adjusted, thus avoiding the need for a physical range shifter.
Scattering of heavy ions

- Multiple scattering is reduced considerably as the size of the particle increases
  - *this reduces the penumbra*
Penumbra decreases as atomic number increases

Kempe, 2007
Physical and biological advantages of different types of radiotherapy
Heavy ions

Disadvantages:
- Very large
- Very expensive
Benefit vs. Cost

Schematic of benefit versus cost achieved with technical advances in radiation therapy. kV, kilovoltage x-rays; MV, megavoltage x-rays; 3-D CRT, 3-D conformal radiation therapy; SIMAT, simplified intensity-modulated arc therapy (forward planned); IMAT, intensity-modulated arc therapy (inverse planned); IMRT, intensity-modulated radiation therapy; Hi LET, High LET charged particle radiation therapy; Hi LET IMRT, High LET charged particle intensity-modulated radiation therapy.
Summary: applications and relative costs of different modalities

<table>
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<tr>
<th>Particle</th>
<th>Tumor Characteristics</th>
<th>Energy deposition</th>
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## Particle therapy facilities worldwide

<table>
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<th>PARTICLE</th>
<th>MAX. CLINICAL ENERGY (MeV)</th>
<th>BEAM DIRECTION</th>
<th>START OF TREATMENT</th>
<th>TOTAL PATIENTS TREATED</th>
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Over 60,000 proton and 5,000 carbon ion patients treated

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<tr>
<th>WHO, WHERE</th>
<th>COUNTRY</th>
<th>PARTICLE</th>
<th>MAX. CLINICAL ENERGY (MeV)</th>
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Monterrey, December 2009
Proton and heavy ion radiotherapy: Summary

- The Bragg peak provides significant dose distribution advantages
- Because the Bragg peak is so narrow it needs to be spread out
- The average LET in the proton spread out Bragg peak is too low for any biological benefit
- With heavy ions the biological benefit is retained
- Heavy ion radiotherapy machines are very expensive

Monterrey, December 2009