Application of Hadron Beams in Cancer Radiotherapy

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NORMAL TISSUE
Differentiated cell layer

CELL INITIATION
Dividing cell in basal layer
Basal lamina
Capillary

DYSPLASIA
An initiating event creates a mutation in one of the basal cells

More mutations occurred. The initiated cell has gained proliferative advantages. Rapidly dividing cells begin to accumulate within the epithelium.

BENIGN TUMOUR
More changes within the proliferative cell line leads to full tumour development.

MALIGNANT TUMOUR
The tumor breaks through the basal lamina. The cells are irregularly shaped and the cell line is immortal. They have an increased mobility and invasiveness.

METASTASIS
Cancer cells break through the wall of a lymphatic vessel or blood capillary. They can now migrate throughout the body and potentially seed new tumours.

SCHEMATIC DEVELOPMENT OF NEOPLASTIC DISEASE
The basic modern approaches to cancer therapy are:

- surgery,
- radiotherapy,
- chemotherapy and immunotherapy.

Radiotherapy, applied alone or in combination with other techniques, is of basic importance in cancer treatment.

Over 50% of all cancer patients are nowadays treated with ionising radiation. This results from the major advances in the technology of clinical equipment made in the last decades (medical accelerators, radioactive source technology, diagnostic equipment, imaging techniques, computer technology).
The basic techniques of modern radiotherapy are:

- **teleradiotherapy**,  
- **brachytherapy**,  
- **systemic radiotherapy** (radioisotope therapy).

**Selectron brachytherapy unit (Cs-137)**

**Medical accelerator**  
(4-23 MV photons & 4-23 MeV electrons)
The aim of radiotherapy is to achieve the best (conformal) distribution of delivered dose over the target volume (tumour volume) independently of its shape, in order to protect the surrounding healthy tissues and critical volumes.
The technique of irradiation affects the width of the „therapeutic window”

Tumour Control Probability
Normal Tissue Complications
Cure = TCP (1 – NTCP)

Two opposing beams

CONFORMAL TECHNIQUE
Four beams

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de
Intensity Modulated RadioTherapy (IMRT) offers new possibilities of dose conformation.
In a typical external radiotherapy beam treatment, a total dose of about 60 Gy is applied to the tumour volume in 30 fractions of 2 Gy given each weekday.

Assuming that about $\frac{1}{2}$ of the number of cells exposed to 2 Gy survive, a fraction of about $\left(\frac{1}{2}\right)^{30} \approx 10^{-10}$ survives after a dose of 60 Gy.

There are some $10^{10}$ cells in 1 cm$^3$ of tissue.
Radiotherapy is designed to cause cell death in the target (tumour) volume while sparing healthy tissues and critical organs.
The Cell Survival Curve
(cell cultures *in vitro*)

Note that „high-LET“ (i.e. densely ionising radiation, such as neutrons or heavy ions) are more effective cell killers per dose – as given by Relative Biological Effectiveness (RBE)

Survival curve formulae:
\[ \alpha D + \beta D^2 \]
\[ m - \text{target} \]
The Oxygen Effect

Cells deprived of oxygen (anoxic or hypoxic) are generally more resistant to photon radiation than are aerobic (oxygenated) cells. Thus, neighbouring healthy tissues are more likely to be damaged than tumour cells which proliferate rapidly and may lack oxygen supply. From analysis of survival curves the Oxygen Enhancement Ratio (OER) may be found.

**FIGURE 6.12** These images show a section from a rodent tumor illustrating chronic hypoxic cells. The animal was treated with the 2-nitroimidazole hypoxia detection agent EF5 24 hours preceding surgical removal of the tumor. **A:** Photomicrograph of the tumor section illustrating the tumor stroma, viable tumor cells, and necrotic tumor core. **B:** The same tumor section demonstrating the presence of chronically hypoxic tumor cells that stain positive with EF5 (white rim) adjacent to the necrotic core. (Courtesy of Dr. Sydney Evans.)
The standard procedures of radiotherapy

- Clinical workout, therapy decision
- Choice of patient immobilisation technique
- Diagnostic & topographic imaging
- Tumour localisation
- Computer Therapy Planning
- Patient setup
- Patient irradiation
- Treatment verification & Evidence
Patient Immobilisation

Since the patient has to be repeatedly irradiated (typically 30 times when 2-Gy fractions are delivered), his/her body should not move during irradiation and his/her positioning should be repeatable with an accuracy of 0.5-3 mm, depending on site irradiated.

Immobilisation of patient’s head with respect to treatment chair (proton beam eye therapy)

Individual vacuum couch with positioning frame (for prostate treatment)
Optical system for verifying patient positioning

3D surface scanning (Laser-based, LCD based)

Advantage: Anatomical information

Challenge: Not yet real-time (1-2 seconds / image)
Problem – movement of target volume
Respiratory movement of the target volume in the lung - (a study of 3D Carbon RT)

Approximation: All fields delivered simultaneously

E Rietzel
Application of different imaging techniques (CT, MRI, PET) provides the diagnosis and enables the target volume to be determined.
Determination of tumour volume

From a sequence of tomography scans (CT + MRI) it is possible to determine the target volumes, critical volumes and patient topography for therapy planning purposes.

Computer radiotherapy planning – optimising the placement of photon beams required to model the spatial distribution of dose

projections:
„beam’s eye view” (BEV)       geometrical projection

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de
Computer radiotherapy planning – viewing and optimising the 3D dose distribution

Dose distribution in the target volume and in critical volumes

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de
Verification of the irradiation fields (dynamic MLC)

A sequence of fluence maps is shown for five photon beams providing the optimum individual treatment plan for the prostate.
The future medical linear accelerator?

Key features:

+ “true” 3D mobility,
+ Pencil beam (6MV) conformality
+ DRR patient positioning
+ On-line organ tracking
? Dose delivery algorithm
? „true” IMRT
? „true” 3D Radiotherapy planning….

Is this the standard against which Hadron RT should compete?
What new elements are introduced by Hadron Radiotherapy?

- conformity of dose (well-defined range, charged particles)
- Bragg Peak at distal end of ion range
- RBE (Relative Biological Effectiveness) > 1
- OER (Oxygen Enhancement Ratio) ~ 1
Conformity of dose (well-defined range, charged particles)

**Ion Beams („high-LET”)**

- Bragg Peak: C12 (GSI) – Proton (HCL)
  - 150 MeV p
  - 250 MeV C12

**Conventional Radiotherapy („low-LET”)**

- 6 MV photons
- Co-60

Note: no effect of Bragg peak in ion tracks!

Ion tracks in nuclear emulsion

RBE?

Electron Beams

(4-20 MeV)

Percent dose-depth distributions
RBE (Relative Biological Effectiveness) > 1
OER (Oxygen Enhancement Ratio) ~ 1

How does cell survival depend on ion LET (-dE/dX)?

Survival of V79 cells in vitro vs. LET of a Carbon-12 beam:
Aerated cells
Anoxic cells

**RBE (Relative Biological Effectiveness) > 1**

**Fractionation** is less effective for high-LET RT, but RBE may then be higher

**Figure 7.3** Typical survival curves for mammalian cells exposed to x-rays and fast neutrons. **A:** Single doses. The survival curve for x-rays has a large initial shoulder; for fast neutrons, the initial shoulder is smaller and the final slope steeper. Because the survival curves have different shapes, the relative biologic effectiveness (RBE) does not have a unique value but varies with dose, getting larger as the size of the dose is reduced. **B:** Fractionated doses. The effect of giving doses of x-rays or fast neutrons in four equal fractions to produce the same level of survival as in A. The shoulder of the survival curves is reexpressed after each dose fraction; the fact that the shoulder is larger for x-rays than for neutrons results in an enlarged RBE for fractionated treatments.

**Conclusion:** Fewer fractions needed in heavy-ion radiotherapy.....

High-LET survival & RBE can be modelled
Entrance dose  Bragg Peak dose

Bragg Peak: C12 (GSI) - Proton (HCL)

Relative Dose

Depth in Water (cm)
The CSDA range of all ion beams is $R = 26.0$ cm, in water

<table>
<thead>
<tr>
<th>Ion</th>
<th>Z</th>
<th>A</th>
<th>$E_{in}$ MeV/A</th>
<th>$\beta_{in}$</th>
<th>LET($Z, \beta_{in}$) keV/$\mu$</th>
<th>Fluence/1Gy $10^7$ ions cm$^2$</th>
<th>$\sigma_z$ mm</th>
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<td>Li</td>
<td>3</td>
<td>7</td>
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<td>0.5982</td>
<td>3.666</td>
<td>17.05</td>
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<td>B</td>
<td>5</td>
<td>11</td>
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<td>0.6710</td>
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<td>0.7067</td>
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<td>5.668</td>
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<tr>
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<td>0.7265</td>
<td>14.328</td>
<td>4.362</td>
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<tr>
<td>O</td>
<td>8</td>
<td>16</td>
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<td>0.7434</td>
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DEPTH DISTRIBUTIONS OF LET, SURVIVAL AND RBE$_S$

Depth distributions of ion LET, cell survival and RBE$_S$ for V79 and AA cells in a beam of $^{12}$C ions of initial energy 385.2 MeV/amu, delivering an entrance dose of 1.0 Gy.
Depth distributions of ion LET, cell survival and RBE$_S$ for V79 and AA cells in a beam of $^{12}$C ions of initial energy 385.2 MeV/amu, delivering an entrance dose of 1.0 Gy.
Depth distributions of ion LET, cell survival and RBES for V79 and AA cells in a beam of $^{12}$C ions of initial energy 385.2 MeV/amu, delivering entrance dose 0.25, 0.5 and 1.0 Gy.
DEPTH DISTRIBUTIONS OF $RBE_S$ (V79 CELLS) FOR LIGHT ION BEAMS (is Carbon-12 the best ion for hadron radiotherapy?)

RBE$_S$- depth dependences of V79 cells over the last 1 cm of residual ion ranges, for light ion beams of range 26 cm, delivering an entrance dose of 1 Gy. Aerobic V79 cells are represented by parameters fitted to the data of Furusawa et al. (2000)

(is Carbon-12 the best ion for hadron radiotherapy?)
Protons – Bragg peak or Straggling?

200 MeV Protons

Stopping Power

Straggling

\( \frac{1}{\rho} \frac{dE}{dx} \) [MeV cm\(^2\)/g]

Depth in water [cm]
Elements of a Hadron Radiotherapy Installation

- accelerator (H, C, 250 MeV/u, variable energy, beam sweeping?)
- beam transport system
- Gantry (isocentric patient irradiation)
- PET imaging
Spread-out Bragg peak (SOBP)

- „passive” method
- „active” method
Spreading out the Bragg peak using absorption filters
Spreading out the Bragg peak using absorption filters

Figure 3-2 Ridge Filter

Figure 3-3 Bolus

Figure 3-4 Final collimator
Compensation Filters (detail)
Principle of the Active Beam (GSI Darmstadt)

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de
Comparison of treatment techniques
Transversal cuts through the biologically effective dose distribution planned for a medial tumor of the base of the skull using two nearly opposing fields. Dose values in this color-wash presentations are: dark gray > 0.1% to < 10%; blue < 50%, green < 60%, yellow < 80%, dark yellow < 90%, red >= 90%. The PTV is indicated by red contours, the OARs by yellow (optical chiasm) and green (brain stem, myelon) contours (GSI Darmstadt).

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
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Springer Electronic Media
http://www.springer.de
HIMAC – NIRS, Japan
Patient chair and X-ray computer tomograph for CTs in seated position at HIMAC
Gantry (PSI Villigen)
Proton radiotherapy of eye melanoma
THE PROTON RADIOTHERAPY OF EYE MELANOMA PROJECT
at the Institute of Nuclear Physics (IFJ PAN) in Krakow

Milestones (June 2006):
- 55 MeV beam extracted
- decision to fund project positive inwestycji
- beam measurements (Bragg peak)
- initial measurements of spread-out Bragg peak (SOBP)
- beam control electronics assembled
THE ENLIGHT PROJECT
European Network for Research in Light-Ion Radiotherapy

Network began within the 5th EU Framework Programme, with the following members:

ESTRO (European Society for Therapeutic Radiology and Oncology)
EORTC (European Organisation for Research in the Treatment of Cancer)
ETOILE (Espace de Traitement Oncologique par ions Legers – Lyon (France))
Karolinska Institutet – Stockholm (Sweden)
GHIP (German Heavy-Ion Project) GSI-Darmstadt & Heidelberg University (Germany)
Virgen Hospital – Macarena (Spain)
MED-AUSTRON – Wiener Neustadt (Austria)
TERA Foundation – Milan (Italy)
CERN – Geneve (Switzerland)
WILL WE HAVE A HADRON RADIOTHERAPY FACILITY IN POLAND?

**ENLIGHT and the European projects**
- GSI project for the University of Heidelberg Clinics
- TERA project for CNAO in Pavia
- Med-Austron for Wiener Neustadt (partner of PIMMS since 1996)
- ETOILE in Lyon
- Nordic Centre in Stockholm

Modular PIMMS accelerator (CERN) for European ENLIGHT hadron RT installations