Hadrontherapy with protons and carbon ions in France, research program and status of existing and projected clinical facilities

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спасибо

merci

Thank you
From radiotherapy to hadrontherapy

- first clinical radiotherapy in the world
  by Victor Despeignes (Lyon, July 1896)

- first proposal for the clinical use of hadrons
  by Robert Wilson (USA, 1946)

slowing-down properties of ions in tissues:
  - well-defined range
  - sharp Bragg peak
Bragg peak at the end of ion ranges in water
From low LET to high LET projectiles

- **Low LET projectiles**
  - photons, electrons
    - conventional radiotherapy
  - pions, **protons**
    - much better ballistics

- **High LET projectiles**
  - neutrons (via the production of recoil ions)
    - high Relative Biological effect (RBE > 1)
    - but … very poor ballistics
  - **Carbon ions**
    - good ballistics and high biological effects
Comparison between different modalities of tumour irradiation
Hadrontherapy in France

- **Neutrontherapy**: non-operational
  - Orléans centre
    - closed in 2008

- **Proton therapy**: in clinical activity
  - Orsay (CPO-Institut Curie, Paris)
    - open in 1994, 200 MeV p
    - new IBA cyclotron in 2009
  - Nice (MEDICYC- Centre Lacassagne)
    - open in 1994, 65 MeV p
    - for ocular cancers only

- **Ion therapy (carbon ions and protons)**
  - Lyon (ETOILE project, national clinical and research centre)
  - Caen (ARCHADE project, IBA prototype cyclotron, for R&D only)
Status of the *ETOILE* project

*Espace de Traitement Oncologique par Ions Légers dans le cadre Européen*

- **1997** project initiated at University of Lyon
  - oncologists (JP Gérard et al)
  - and physicists (JR et al)
- **1999** research program on hadrontherapy
  - funded, until 2013, by Region Rhône-Alpes and the City of Lyons
- **2003** first national recognition (Cancer Plan)
- **2005** first agreement by Health Ministry
Status of the *ETOILE* project

*Espace de Traitement Oncologique par Ions Légers dans le cadre Européen*

- **2007** creation of the Health Cooperation Groupment – GCS-ETOILE, directed by Prof Jacques BALOSSO
- **2007** opening of a Public-Private-Partnership offer – for the design, the construction, the maintenance and the technical management of the ETOILE center
- **2009** acquisition of a 12 000 sq.m.lot in Lyon
- **Feb 2010** positive evaluation of our clinical indications by the *High Autority for Health* (HAS)
- **July 2010**, final industrial offer
Description of the *ETOILE* project (1)

- **ETOILE: a public health need**
  - 3500 – 6000 patients require carbon ion therapy in France every year
    - ETOILE = 2000 patients per year (protons and C ions)
  - estimation confirmed by french HAS for our « consolidated indications »
  - treatment cost with carbon ions: 35 000€/patient, to be compared to
    - the average cost of cancer treatment in France
      - 24 000€/patient
    - the cost of innovative targeted therapies
      - 50 000€/patient
J. Balosso, P. Pommier et al

Total treatment cost of cancer per patient in France

- 2,500 €: Radiothérapie classique 3D (85% de la RTE)
- 4,500 €: Coût pharmaceutique 6 mois de FOLFOX ou FOLFIRI
- 6,400 €: Radiothérapie par IMRT ptumeurs ORL ou prostate
- 8,390 €: un traitement complet par Malthera
- 14,000 €: traitement minimum par Avastin durant 6 mois
- 15,660 €: coût moyen du traitement initial d'un cancer du sein
- 24,000 €: coût moyen du traitement en France
- 25,000 €: un an de traitement par Herceptin
- 35,400 €: intensification chimiothérapie avec autogreffe de CSP
- 50,000 €: un an de traitement par thérapie ciblée (Tarceva, Nexavar, Sutent...)
- 55,600 €: 2 ans de traitement par Gleevec
Description of the *ETOILE* project (2)

- **ETOILE benefits of regional, national and european dynamics and funds**
  
  **Regional**
  
  - the Regional Council of Rhône-Alpes and the Lyon urban Community support investments up to 17M€ and research up to 4M€

  **National**
  
  - ETOILE was supported by three successive ministers of health; 10M€ investment and 1M€/year funding of GCS ETOILE

  **European FP7**
  
  - since 2002, ETOILE participates to the hadrontherapy consortium *ENLIGHT* based at CERN. With the successive programs (*PARTNER, ULICE, ENVISION*, …)
    
    - we have in particular been able to finance more than 25 thesis and postdoctoral positions
Description of the *ETOILE* project (3)

- **ETOILE** is at the center of a dense national network of research and development
  - Since 1999 a regional network for hadrontherapy research (*PRRH*) has been driven by University Lyon1 and continuously supported by *Région Rhône Alpes*
  - The Regional Program of Research in Hadrontherapy is strongly coupled with other national research structures
    - The cancer cluster **CLARA** (Canceropole Lyon Auvergne Rhône Alpes)
    - The **IN2P3-CNRS** research groupment **MI2B** (Instruments and methods for biomedical imaging)
• ETOILE will be also an open platform for hadrontherapy *R&D*
  – In addition to the 3 treatment rooms, a room with beam equipments specially devoted to R&D will be implanted
  – *Laboratories* dedicated to hadrontherapy will be implanted inside the ETOILE center building
  – This set of facilities, will be managed by a permanent *technical staff* able to assist external teams in their experiments.
Regional Program of Research in Hadrontherapy

- a program driven for ten years by a hundred of researchers linked to ETOILE
- coordinated by Prof. J-M Moreau and J.R.
Thematics of PRRH

– Medical project (J.Balosso and P.Pommier)
– Medico-economy and epidemiology (P.Pommier)
– In-silico modelling of treatments (B.Ribba)
– Basic data acquisition, irradiation control (D.Dauvergne)
– Hadronbiology (C.Rodriguez, M.Beuve and N.Foray)
– Simulation of dose deposition (D.Sarrut and N.Freud)
– Movement and deformation of tumours (B.Shariat)
– Study of a cryogenic ion gantry (in coll. with CEA)
The medical project (1)

- **Organization of equitable recruitment of patients with the highest medical benefit**
  - Literature study + groups of medical experts
    - elective indications for photons/protons/carbon ions
  - **consolidated indications** for C ions, 800-1000 french cases/year (validated by HAS = to be reimbursed by the social security system)
    - Adenoid cystic carcinoma (head and skull base)
    - Melanoma mucosa (head and neck)
    - Chordoma (skull base and spine)
    - Chondrosarcoma (axial skeleton)
    - Soft tissue sarcoma
  - **prospective indications**, more than 3000 french cases / year, (to be financed in the framework of clinical research programs)
P. Pommier et al

**Procedure**

1. **Step 1 →**
   - Biological and physical basic criteria to apply Hantrotherapy

2. **Step 2 →**
   - Local Working Groups: Screening of all topographies and histologies to identify a priori any potential indication for Hantrotherapy

3. **Step 3 ↓**
   - “Evidence based medicine” approach: screening of all relevant literature to extract the present state of the art outcome of selected pathologies

4. **Step 4 →**
   - “Epidemiological landscape”: search of national French collection of cancer registry (FRANCIM) and “One day survey” in French radiation oncology departments

5. **Step 5 →**
   - International experts evaluation and validation
     - By end of 2006
     - Indications double hierarchy = priority table
       - 1) according to the frequency
       - 2) according to the expected medical benefit

6. **Step 6 ↑**
   - Rational choice of indications to organise the recruitment through international multicentric prospective clinical trials

   - For 2006
   - During 2006 to 2008

   - A portfolio of multicentric clinical trials

   - Spread of medical literature
     - by
       - localisation

   - Increasing incidence
   - Increasing medical benefit

   - The priority table
The medical project (2)

- **Medical Organisation of the Recruitment for Carbon Ion Radiotherapy (OMéRRIC))**
  - ETOILE’s capacity, 26,000 sessions (p+ C)/year
  - in the routine mode, 6,000 proton sessions (less than 250 patients) for 20,000 carbon sessions (1,500 patients)
- **Preparation of the clinical trials**
- **Set-up of national, european and world wide networks**
  - **ULICE** *(Union of Light Ion Centers in Europe)*
Medico-economical simulations

- Three integrated medico-economical models
  - Patient recruitment, Treatment cost and cost-effectiveness, Operating process
    - from 4 inputs (epidemiology, indications, protocols and treatment centers)
- The results were used for the tendering process, for exemple, in the optimisation of
  - the patient recruitment, from a new epidemiologic study (EpiHadron)
  - the number of treatment rooms and their equipment (rotating gantry ?)
  - the patient scheduling and trajectory in the ETOILE building

Coll.: Centre Léon Bérard, Univ. Lyon, St Etienne, Clermont-Ferrand, European network ULICE
In silico modeling and experimentation of hadrontherapy therapeutic effects

A transfer to hadrontherapy of the « in silico » modeling principles used for medicaments development

• A tool
  – to help patient selection
  – to optimize treatment delivery

• A model at three levels
  – cell level: search for predictive biomarkers of cell survival
    • microarray data on +/- radioresistant cells
  – tissue level: dynamics of tumour growth
    • in vivo animal experiments
  – body level: relation tumour growth / patient survival
    • from japanese and german databases of patients

Coll. Univ. Lyon1, E N S Lyon, INRIA, INSERM
B. Ribba et al
Basic data acquisition and irradiation control (1)

3D dose distributions receive a large contribution from **nuclear fragmentation events**
- to be included in the Treatment Planning Systems
- to be controlled by *in situ imaging* during patient irradiation

**Fragmentation data for carbon projectiles**
- data and theories are not accurate enough
  - for carbon incident energies <150 MeV/u
- two experimental programs to measure energy/angle distributions of all fragments in biological targets
  - a national collaboration at GANIL-Caen (95 MeV/u $^{12}$C)
    - by IN2P3 teams (*Caen-Lyon-Strasbourg*)
  - a European collaboration at GSI-Darmstadt (150-400 MeV/u)
    - by teams from INFN-Italy, GSI-Germany, CEA and IN2P3-France
Basic data acquisition and irradiation control (2)

- **In situ and on line dose imaging**
  - detection of radiations / particles linked to the fragmentation events can be used
    - **prompt gamma rays**
      - development of a high efficiency Compton camera
        *IPNLyon, INSALyon, Univ Lyon and Aix-Marseille, ENVISION*
    - **light fragments (protons, …)**
      - development of a proton tracking detector
        *IPNLyon, Univ. Lyon, CNRS MI2B, ENLIGHT*
    - **two photon annihilation of positrons emitted by \(^{11}\text{C},^{15}\text{O},^{10}\text{C}\)**
      - development of an in-beam TOF-PET camera
        *IPNLyon, Univ.Lyon and Clermont- Ferrand, CNRS MI2B, ENLIGHT*
Prompt gamma camera

Multi-detector prototype (C. Ray et al)
Prompt gamma yield, for C ions in PMMA

\[ \text{Number gamma / ion} \]

\[ \text{Depth (mm)} \]

GSI  

\[ ^{12}\text{C @ 305 MeV/u} \]

Bragg peak

E. Testa et al (PTCOG 48)
Proton vertex imaging (P. Henriquet et al)
Radiobiological effects of C ions (1)

1. Molecular and cellular mechanisms of radioresistance: search for biomarkers
   - experiments with photons and C ions
     - show the role of Cancer Stem Cells in the local recurrence after photon or C irradiations
     - show the role of p53 and ceramide on failures in DNA repair, apoptosis and mitotic catastrophes
   - simulations of oxidative stress / anti-oxidant defense
     - show that O2- and H2O- radicals play a major role in the reduction of the oxygen-effect with ions
     - evidence the role of glutathione (anti-oxidant) in the radioprotection of ADN (radioresistence of tumours)
2. Improving treatment protocols (TPS)

- The **LEM model** (GSI), currently used for C ion TPS, was revisited
  - from experimental arguments
    » need for calibration of free parameters
  - from conceptual arguments
    » introduction of non-local effects

  **an alternative model is now under construction**

- An experimental program is running to measure the effect of ion dose rate on cell survival
  - and its consequences on the duration of irradiation sessions
3. Understanding and prevention of the radiosensitivity of normal tissues

- immunofluorescence was used to evidence unrepaired DNA double-strengthen breaks and then side effects in hadrontherapy of brain

- the role played by specific proteins was measured

propositions to improve radioprotection during the treatment of brain tumours are in progress

Coll. Univ. Lyon 1 (Lyon-Sud Hospital, IPNL, LIRIS), INSERM, GANIL-Caen, GSI-Darmstadt, CAL-Nice, ENLIGHT
Simulation of dose deposition for treatment planning (1)

Need for realistic simulation tools for TPS
dose distributions and secondary particles

- **Medical realism**
  - anatomical complexity (from 3D or 4D CT scans)
  - biological complexity (RBE = f(particle, energy, LET, tissue))

- **Physical realism**
  - Monte Carlo simulations (realistic but far too slow) ?
  - deterministic methods (fast but not realistic enough) ?

- **Inverse planning strategies**
  - for the optimisation of irradiation parameters: beam direction, number of beams, Bragg peak position, fluence values
Simulation of dose deposition for treatment planning (2)

- **Acceleration of simulations by**
  - **Particle transport optimisation** (*Geant4/GATE*)
    - *modeling and experimental validation of fragmentation and secondary emission of p, n, prompt gamma, …*
  - **Hybrid algorithms**
    - Monte Carlo production of secondary particles
    - deterministic transport of these particles (ray casting)
  - **Massively parallel computing**
    - on local clusters or on computing grids

_Coll.: Univ Lyon1 (CREATIS, IPNLyon), INSA-Lyon, IN2P3-MI2B Geant4-GATE, ENVISION_
Treatment of moving organs (1)

Predictive evolution of tumour and organs at risk

- position, shape and density
- due to breathing (lung cancer), blood flow, ...

1. Image processing (non-invasive methods)

- Development of processing tools
  - for the accurate reconstruction of a (3D+T) breathing image of the patient, from *in situ* Cone-Beam (2D+T) projections

- Extension of the method
  - to fluoroscopy images taken at different viewing angles and from external chest video cameras
2. **Biomechanical modeling** of respiration
   
   - breathing is a chaotic motion
     - due to the **independent action of chest muscles and diaphragm**
   
   - development of a full biomechanical model
     - including rib cage (intercostal muscles), soft tissues (around skeleton), diaphragm and **pleura**
     - correlates exchanged **air flows** to ribs and diaphragm movements
     - correlates the external movements of the **skin** (external sensors) to the internal movement (of the tumour)

*Coll.: Univ Lyon1 (LIRIS, CREATIS), ENVISION*
Biomechanical model for human respiration (B. Shariat et al)
Conclusions on hadrotherapy in France

• **Clinical protontherapy** is available, since 1994, at Paris (CPO) and Nice (Medicyc)

• **Clinical carbon ion therapy** will be available at the opening of the ETOILE center in Lyon

• **Advanced research programs** on hadrotherapy are developed
  – around the ETOILE project
  – by CNRS-IN2P3 (MI2B research groupment)
  – and strongly coupled to the ENLIGHT european network

• **Facilities for hadrotherapy R&D** will be available
  – at Caen (Archade, IBA-C400 cyclotron)
  – at Lyon (ETOILE research plateform)
спасибо

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Thank you
Part of the PRRH-ETOILE research group