

Development of clinical protocols in radiotherapy on human brain tumours	
Current designated sector:	Facility goes to:
ID17	ID17

1.1 SCIENTIFIC CASE

ID17 is fully dedicated to biomedical applications, and focussed on biomedical imaging and radiotherapy. The evolution of the imaging applications at ID17 is included in the UPBL5 and the present CDR concerns only radiotherapy.

Biomedical applications of synchrotron radiation have gone through a large increase in impetus and development in recent years, with very significant increases in both the user community and in the number of publications. Part of this drive can be attributed to the radiation therapy programmes aiming at studying and treating brain tumours. This kind of research is motivated by the fact that, despite considerable efforts in cancer therapies, brain tumours and gliomas in particular, are extremely resistant to present clinical treatments. Virtually no patients with high-grade glioma survive for more than a few years after diagnosis (Behin et al, 2003).

Over the last few years, in collaboration with different groups of users, the ID17 Biomedical beamline has pioneered innovative preclinical research in radiotherapy for targeting brain tumours. Two different techniques, namely the **Microbeam Radiation Therapy (MRT)** and the **Stereotactic Synchrotron Radiation Therapy (SSRT)** have been used, aiming at treating infants (MRT) or adults (SSRT). The two techniques are quite complementary: if the SSRT is focussed on curing adult brain tumors (glioma), MRT is well adapted to child tumors (brain stem, glioma, cerebellum) due to the extraordinary little or no damage to the growing tissue.

Following the advice from an international review panel of experts convened at the ESRF in 2005, the ESRF Management supported the move to clinical trials on humans in SSRT and on large animals in MRT.

MRT uses spatially fractionated X-ray beams (typically 25-50 μm wide and 200-400 μm spaced) delivered in extremely high doses (several hundreds of Grays) to treat aggressive brain tumours, for which no effective treatment exists. MRT, which necessitates low energies (100-300 keV), very high dose rates (>1000 Gy/s) and low diverging beam, is a technique that can be applied only at synchrotron sources (Laissue et al, 2007).

SSRT is a complementary research programme aiming at treating brain tumours, which has been developed at the ESRF. SSRT combines a ballistic effect to a dose enhancement by the presence of a high Z agent inserted in the tumour (Rousseau et al, 2009). The ballistic effect is obtained by irradiating the tumour from up to 9 different orientations (so that the normal tissues surrounding the tumour receive only a small fraction of X-ray dose), with an irradiation area defined by a collimator system. Quasi monochromatic beams of energies around 80 keV are used and the dose delivered in each orientation is in the order of 2 Gy (Prezado et al, 2009).

Preclinical MRT and SSRT experiments have provided the results to pave the way to clinical trials at the ESRF (See Paragraph 1.2).

Present status of MRT clinical trials programme on large animals

The construction of the MRT hutch, control cabin and renewal of the instrumentation has been completed in June 2008. The passive radiation protection (collimators to protect healthy tissues, gas filters to protect from low energy entering the irradiation hutch) and Patient Safety System (PASS) are being implemented. The PASS includes all active controls for radiation, instantaneous measurements of the dose and dose rate, patient position and velocity of movement and dosimetric tools; it will be completed and commissioned by 2009. A realistic goal is to start the first MRT clinical trials on large animals by the end of 2009/early 2010.

Present status of SSRT clinical trials programme

SSRT makes a good use of the instrumentation developed and built for the Angiography programme. Instruments specifically designed for SSRT include the accurate positioning of the patient's head and the addition of several safety components to ensure the full protection of the healthy tissues surrounding the tumour. As for the MRT, both the instantaneous dose and dose rate, and the Patient Positioning System (PPS, also called the "Medical chair") parameters (positions, velocities of displacement) are carefully monitored and controlled by the PASS. This PASS, specific for the SSRT, is currently being finalised and will be finally commissioned by Spring 2010. It will allow, in addition to the 2-D imaging (similar to the Angiography imaging), an irradiation mode at much lower vertical speeds for higher deposited doses, and a 3-D Computed tomography imaging mode. The entire patient's head positioning device and the collimator system are completed to date.

Clinical trials will be started only after the final release of a dedicated treatment planning system (developed by the CHU Grenoble together with DOSISOFT, an EU certified company) and having obtained the necessary authorisations for clinical trials released by the competent French Authorities. The aim is to **start clinical trials with human patients in 2010.**

ID17 MRT evolution

At the completion of the MRT clinical trials on large animals (2011) a decision whether moving to human clinical trials should be taken. One possible scenario is the following:

- An International expert panel convened by the ESRF Directors should review the results (as in 2005, see Section 1.2) and make the recommendation whether to move to clinical trials on humans.
- If this recommendation is positive, and the ESRF Directors decide to proceed, the next steps would be:
 - A local medical committee (CHU Grenoble) proposes a clinical protocol
 - Final decision taken by the Directors
 - Minor refurbishment of the MRT facility to allow for human studies.

In this scenario the following items should be foreseen:

- The patient positioning system for the treatment. It should allow orienting the tumour target and to scan it through the beam for delivering the prescribed radiation dose.
- The furnishing of an appropriated room next to the Experimental Hall (room 18.0.09) for the human patient preparation before the treatment. This room is presently assigned to ID17 and is a link between the Hall and the protected corridor leading to the MRT facility.

ID17 SSRT evolution

The scheduled clinical trials in SSRT foresee a sequence of protocols targeting first metastatic lesions, and then central nervous system primary tumours. Also different dose enhancement drugs are foreseen, first Iodine and then chemotherapeutic drugs. At the completion of each phase, a committee nominated by the French authorities will evaluate the success of the protocol.

After the completion of these protocols, which are already included in the medical proposal, it can be envisaged that new ones involving different and more sophisticated drugs capable to cross the blood brain barrier will be proposed by the medical team leading the trials. No additional instruments or investments are presently envisaged.

With regard to the present trials, all the hardware has been delivered or will be ordered in 2009; the following minor items related to patient and patient safety are foreseen for the period 2009-2010:

- Pending final indications and requirements of the French authorities, some dose and dose rate measurement devices (calibrated ion chamber, scattering monitors) will be needed.
- It may be necessary to purchase some small room-furniture and make minor renovation of the patient room (fluoroscopy room) in the satellite building.

Detectors

Before SSRT radiation treatment, the target will be imaged in tomography mode to quantify the contrast agent distribution and concentration. The permanently installed germanium detector will be used, being the only available large area (15 cm), fast and highly efficient detector. It is made from a monolithic P-doped Ge crystal electrically segmented into two rows of 432 parallel strips each. The Ge crystal is 2 mm thick, giving an efficiency of nearly 100 % at 33 keV and 45% at 99 keV. Each pixel is 300 μm wide, and the separation between two adjacent pixels is 50 μm , providing a final lateral pixel size in the images of 350 μm .

This detector is used since the opening of the ID17 beamline (1996). Therefore it is based on a 15 years old concept and electronics; spare items are not on the market anymore. Because aging effects are clearly appearing in particular on the electronics, this detector could not serve the beamline for more than a few years.

A higher resolution germanium detector (pitch ~50 μm) but with the remaining characteristics similar to the present one in terms of efficiency in a wide energy range (30-100 keV), detection area (150 mm), fast readout time (some μs), and linearity, is highly demanded for all in vivo applications (preclinical and clinical).

In parallel, a CCD-based detector with an entrance area allowing imaging with the full beam width (≥ 150 mm) and height (≥ 12 mm) would provide the users with an exceptional tool for performing imaging experiments on large size samples where resolution and acquisition speed are key factors (ABI, pharmaco-kinetic studies, palaeontology,...). The maximum width currently available is limited by a fibre-optic taper glued to the CCD chip, to 90 mm. The development of such a detector as an evolution of the FReLoN camera is within the technical capabilities of the ESRF Detectors Group. The expected resolution reaches $30 \times 30 \mu\text{m}^2$ (pixel size).

The role of the Biomedical Facility BMF

The success of a biomedical beamline, together with the active link with a medical community, who can lead, support and promote biomedical research, is strongly dependent on the availability of ancillary laboratories used for the preparation and analysis of biological samples after irradiation. For scientific, ethical and safety reasons, these laboratories have to be close to the experimental station and they are used not only during synchrotron radiation experimental sessions, but also for offline experiments (cell culture before and after irradiation, follow up of animals after treatment etc). Moreover, users' at other beamlines such as ID02, ID19, ID21 and ID22 require punctual access to the same kind of infrastructure and support.

This is the reason why in this upgrade programme significant weight is given also to the development of these facilities which give a decisive contribution of maintaining the biomedical research at ID17 at the cutting edge.

The evolution of the Biomedical Facility

In order to keep the biomedical science at the state of the art, the BMF has to evolve in the direction of satisfying as much as possible the new user requirements.

- With regards to cell and molecular biology, for more efficient and safer work, the present two laboratories L1 (molecular biology) and L2 (cell laboratories), heavily used for on-line and off-line experiments (usually weeks before and after a single experiment) should be separated.
- There is a constant increase of using immuno-depressed rodents for in vivo tumour model studies and some species of transgenic animals. Both are very fragile and must be separated from others, for sanitary and safety reasons and to fulfil legal requirements. These requests cannot be presently satisfied for lack of space in the animal house.
- The work at the animal house covers 365 days/year, and there is a need of automating some recurrent heavy works like cage washing.

These projects call for a small expansion of the biomedical facility which could be combined with the building works related to the UPBL5.

1.2 PROJECT HISTORY

The present CDR is an evolution of the CDR “CPR” (“Development of Clinical Protocols in Radiotherapy” Purple Book page A111).

Since their start, the final goal of both the SSRT and the MRT scientific programmes has been that of performing clinical trials at the ESRF. Several international panel consultation, workshops and presentations to the Directors have been produced in the past years to define needs, and the pathway to go towards the clinical trials. The milestones are summarised below:

- The experience gained by the team (both technical and in terms of patient safety) with the successful completion of the coronary angiography clinical trials (2000-2003) together with the possible reuse of most of the instrumentations, guarantees a smooth and relatively cheap implementation of the SSRT clinical trials.
- The International Radiotherapy Expert Panel report (October 3-4, 2005) has highlighted the high scientific and medical profile of the radiotherapy research, and has favourably evaluated the opportunity to move to clinical trials for both MRT and SSRT. It gave specific scientific, technical and ethical recommendations on the subject.
- The Beamline Review Panel report (November 2005) has confirmed the recommendations of the International panel and made the final recommendation to the Directors to initiate the necessary steps to clinics. These included the construction of a wider white beam hutch for MRT and the implementation of necessary infrastructures for SSRT clinical trials.
- The presentations at the SYRAD workshop (“SYRAD: New prospects for brain tumour radiotherapy: Synchrotron light and Microbeam Radiation Therapy”, >100 attendees) organised by the ID17 teams at the ESRF (June 2008) has confirmed and developed the scientific and medical expectations from SSRT and MRT clinical trials (this latter on large animal patients first).

Operatively, the ESRF has proceeded with the following steps:

- The construction of a new hutch for MRT with an appropriate patient safety system to proceed with clinical trials in large animals has been decided and financed (December 2006).
- The implementation of the SSRT clinical trials on human beings at ID17 has been decided and financed (December 2006).
- A medical physicist has been recruited as second ID17 scientist (October 2007) with the mission to provide the necessary expertise for the clinical trials implementation (medical requirements, dosimetry, simulations etc.).
- The ESRF has renewed a contract with the CHU Grenoble, the INSERM and the UJF Grenoble focussed on SSRT clinical trials (five year contract, ending on January 1st 2012).

1.3 BASIC TECHNICAL CONSIDERATIONS

Microbeam Radiation Therapy

For MRT Clinical Trials on human patients, the facility still has to be developed in two different directions:

1. Human Patient Positioning System (PPS).

Technically this is the most demanding instrument to be developed. Two options are possible: a) either to build a PPS based on the “kappa” geometry similar to the existing MRT goniometer but with increased dimensions, or b) to build a more conventional cartesian goniometer similar to the “Medical chair”.

a) *Kappa geometry.* The design would be a scaled version of the current sample positioning system to adapt the dimensions to support a seat for a patient, and also to provide the necessary stiffness to cope with the particularly tight specifications in terms of maximum wobble and speed linearity for the vertical motion of the patient during an irradiation scan. The Canadian Light Source is currently developing such a Kappa-geometry goniometer with adequate dimensions for human patients, which is based on commercial rotation tables in order to lower the total cost.

Axis	Repeatability Accuracy	Resolution	Speed	Range	Motor Type	Stage Type	Encoder (on axis)
Z_{SCAN}	50 μm	5 μm	5-200 mm/s Speed Stability <1% required.	700 mm	Servo	trans	Y/incr
Y_{TRANS}	50 μm	5 μm	20 mm/s	+/- 50 mm	Stepper 2/4 phase	trans	Y/incr
ω	1 mrad	1 mrad	3.14 rad/s (180°/s)	2π (360°)	direct drive	Rot	Y/incr
κ	1 mrad	1 mrad	0.2 rad/s (10°/s)	2π (360°)	Stepper 2/4 phase	Rot	Y/incr
ϕ	1 mrad	1 mrad	0.2 rad/s (10°/s)	2π (360°)	Stepper 2/4 phase	Rot	Y/incr
X_{POS}	5 μm	5 μm	2 mm/s	+/- 50 mm	Stepper 2/4 phase	trans	Y/incr
Y_{POS}	5 μm	5 μm	2 mm/s	+/- 50 mm	Stepper 2/4 phase	trans	Y/incr
Z_{POS}	5 μm	5 μm	2 mm/s	+/- 25 mm	Stepper 2/4 phase	trans	Y/incr

Table 1.5.1. Summarised specifications for a Kappa-based Patient Positioning System for MRT.

b) *Cartesian geometry.* The human patient would be supported on a stiff structure comprising only linear translations moving in an orthogonal Cartesian system of coordinates. There would be only one large rotation stage allowing a rotation around the vertical axis. The advantages are obviously an easier control of the patient position (there is no need for a coordinate change by software), a larger stiffness, and an easier implementation of the PASS resulting from an easier positioning. However, since the design cannot be based on commercial units, the final cost will be more important, and the study and construction time will increase. The assembly will also be much less compact.

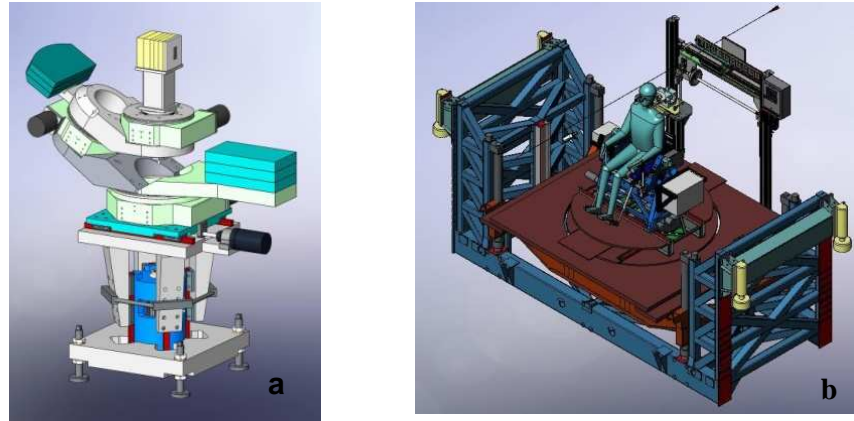


Figure 1.5.1 a) Present Kappa goniometer used in MRT. b) Present patient positioning system for SSRT (“patient chair”).

2. Patient room for MRT.

The room 18-0-09 is currently used as a buffer room between the outside of the building and the access corridor to the MRT area. In a first step, it will be upgraded into a temporary housing area for the large animals (refurbishment to be completed by the end of 2009), and when MRT clinical trials on human beings are started, it will be transformed into a patient room to accommodate the patient arriving to the ESRF just before the treatment. It should be equipped with a bed, a sink and possibly a toilet. In addition, the loading/unloading area for the ambulance bringing the patient to the ESRF should be covered with a light roof as shown (in pink) on Fig. 1.5.2..

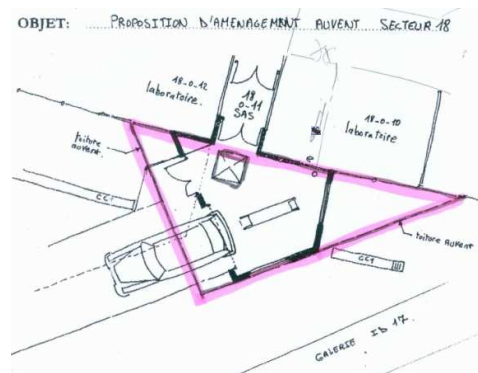


Figure 1.5.2: The location of the patient room for MRT clinical trials.

Stereotactic Synchrotron Radiation Therapy

The development of the SSRT programme hardware is close to completion. However, two small hardware projects still need to be financed:

1. The purchase of some dose and dose rate measurement devices (mainly calibrated ion chambers) should be envisaged after the final recommendations of the French authorities for patient protection (foreseen by beginning 2010). All items are from catalogue and undergo certified calibration.

2. The Patient room used for the Angiography programme (17-1-02) is currently used as an office for the INSERM staff. It has to revert into a patient room to accommodate the patient before and in between the different treatment phases. The medical equipment will be provided by the CHU, free-of-charge, but we have to foresee a redecorating (painting of the walls and door). Same works should be foreseen for the experimental hutch and the Fluoroscopy room in which the patient will transit.

Refurbishment of the germanium detector

The basic requests for a new two lines detector are the following:

- Pixel size ~ 50 μm
- Large area (150 mm, i.e. 3000 pixels per line)
- Line distance ~ 10 mm (for dual energy imaging)
- High efficiency in the range 30-100 keV to avoid increasing dose to the sample
- Large dynamic range (16 bits or more) (to allow for tomography of highly absorbing samples)
- Low noise and fast readout (for in vivo applications).

As suggested by the Detectors Group, the development of a new Ge-detector for ID17 could be associated to those for UPBL11, which has also requested a Ge-strip detector with same pitch and ASIC readout chips and backend DAQ.

High resolution, high speed, large width CCD-based detector

The developments in progress at the ESRF Detectors Group open the door to a CCD-based detector including a 4000 x 4000 pixels chip ("E2V" type), and a flat optics taper cut in a 180 mm diameter fibre-optic taper. The expected detector would be have a sensitive area of 180 mm width and 12 mm height, forming a matrix of 6000 x 340 pixels with a pixel size of about 30 x 30 μm^2 [Figure 1.5.2.6], operable in various binning modes. The scintillator would be interchangeable (different materials, thicknesses) to cope with the variable requirements for the in vivo and in vitro experiments (energies below 50 keV, high detector efficiency in the first case to limit the total X-ray dose deposited; energies above 80 keV, higher resolution and not strong requirements on efficiency in the latter case).

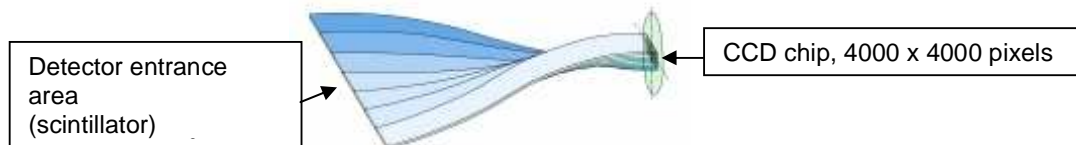


Figure 1.5.3: Fibre optics image guide principle, acting as a funnel for visible light.

Storage ring current increase to 300 mA

The main optics components installed in the ID17 optics hutch (primary slits, attenuators, shutter + photon absorber) were originally designed to accept the heat load generated by the ID17 wiggler at closed gap, and for a current in the storage ring equal to 100 mA. In 1997 a partial upgrade of these components was performed (by respecting the limits imposed by the small space available in the

existing vacuum vessel) to accept 200 mA. In order to accept the additional heat load corresponding to 300 mA without deformation of the slit defining edges, and while keeping an acceptable safety margin before reaching the melting temperatures of the filters and photon absorbers, these components must be completely re-studied and re-built. The vacuum vessels, their pumping systems and their supports must also be re-built.

Operating the beamline at larger wiggler gaps could help reducing the heat load on the components, but the beam spectrum would shift towards the lower energies, thus reducing the dose rates available at energies ≥ 60 keV which are of prime importance for the radiotherapy programme. This is therefore not acceptable.

1.4 REFERENCES

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