3. AXIS 3 : "MULTIMODALITY TARGETING IN ONCOLOGY, CIMULCAN PROGRAMME"

Steering committee: E. Lartigau, V. Grégoire, P. Véra

The "Anatomical and Functional Targeting" network, funded by INCa in 2005 to the tune of 1 million Euros over two years, focused on the contribution of functional positron emission tomography (PET) imaging in the biological targeting of head and neck cancer and lung cancer via intensity modulated radiotherapy. The project was coordinated by Vincent Grégoire (Université de Louvain, Brussels) and brought together teams from all CNO sites (Caen, Rouen, Amiens, Lille and Brussels). It provided an opportunity to examine the role of 3D imaging in oncology practice (medical, surgical and radiotherapy). In its 2007-2010 programme, the axis teams proposed to develop 2 central topics : anatomical and functional targeting, continuing in the line of the network's research, and technological targeting including the development of robot-aided treatment in radiotherapy then in surgery.

A. Key developments

Recent progress in functional PET imaging of the biological processes involved in the response to ionising radiation are opening up new prospects for defining target volume boundaries both before and during radiotherapy. More precise boundaries based on functional information as well as anatomical information may eventually lead to a more appropriate dose distribution and consequently increase the likelihood of tumour response and hence improve survival. However, there were still several questions that needed to be answered before this principle could be used routinely in clinical practice. How could the protocols for acquisition, reconstruction and segmentation of the PET images be improved? Which biological processes predictive of response to ionising radiation should be focused on? and is PET imaging sufficiently sensitive and specific to highlight subtle changes in these processes during treatment? Finally, would improved definition of target volume boundaries allow dose distribution to be adapted to the extent that it would increase tumour control and/or reduce the morbidity of treatments?

1. Anatomical targeting

1.1 Clinical trials

The purpose of anatomical targeting is to improve the quality of treatment and the detection and delineation of the macroscopic target, whilst keeping any harmful side effects to a minimum. Progress is being made thanks to cross-disciplinary lines of inquiry involving professionals from the fields of imaging, ballistics, physics and tumour metabolism. The research has involved the Rouen, Amiens, Lille and Brussels teams. It has focused primarily on the prognostic aspect of variations in metabolism during radiotherapy, defining target volumes in functional imaging and the inherent problems of respiratory-gated acquisition in PET imaging.

Using Fluoro-deoxy-glucose positron emission tomography (FDG-PET), simultaneous variations in cell metabolism, hypoxia and proliferation can be studied in cancer patients during radiotherapy. Respiratory gating increases the potential for detecting lesions and determining the displacement volume of moving tumours more accurately.

Five prospective projects have been organised :

RTEP1: *A study of changes in fluoro-2-deoxy-D-glucose (FDG) uptake measured in positron emission tomography (PET), in conjunction with respiratory gating in patients receiving radiotherapy or radiochemotherapy for primary lung cancer.*

RTEP2: *The prognostic value of fluoro-deoxy-glucose positron emission tomography (FDG-PET) during radiotherapy or radiochemotherapy in patients suffering from non small cell lung cancer.*

RTEP3: *The prognostic value of fluoro-deoxy-glucose positron emission tomography (FDG-PET) during concomitant radiotherapy and chemotherapy for cancer of the oesophagus.*

RTEP4: *A study of changes in uptake of fluoro-2-deoxy-D-glucose (FDG), fluoro-misonidazole (FMISO) and 3'deoxy-3-fluoro-thymidine (FLT) measured in positron emission tomography (PET) in patients before and during exclusive radiotherapy for primary lung cancer.*

VoSeRep: *The value of 18F-FDG PET-CT imaging in tumour volume determination in patients having undergone breast cancer surgery.*

The table below shows the progress of enrolment in February 2010.

		Tracers	Planned patients numbers	Patients enrolled	PET Scans per Patient	Nomber of PET Scans	Brussels	Lille	Rouen	Caen	Amiens
Lung	RTEP1	*FDG*	12	12	6	72			X		
	RTEP2	*FDG*	140	56	3	420			X		
	RTEP4	*FDG FLT FMISO*	5	5	6	30			X		
Œsophagus	RTEP3	*FDG*	100	18	2	200			X		
Breast	VoSeTep	*FDG*	30	0	1	30			X		
	Total		**287**	**91**	> 3	**752**			X		

Investigators

X Sponsors

Two of the studies have been completed and are in the process of being published (RTEP1 and RTEP4). The tracers used for this project were funded by CNO. The initial findings were presented at the Molecular Imaging in Radiation Oncology (MIRO) conference in Brussels in March 2010 (J Nucl Med 2010; Radiation & Oncololy,in press). The project should form the basis for a proposal for a nationwide hospital-based clinical research project (PHRC) in 2011 (RTEP5). The RTEP2 and RTEP3 studies are still in progress and due to the small number of recruits, new centres have been opened in France (Nancy, Nantes, Lyon, Marseille, Paris, Rennes). The VoSeTep trial was launched in February 2010.

1.2 Defining target volumes in radiotherapy

Targeting in radiotherapy requires the volumes of at-risk organs and the target tumour volume (or gross tumour volume, GTV) to be delineated. This is usually done using CT scan images. Functional PET imaging can then contribute further information for defining the GTV. The work of the Rouen group focused on i) delineation of volumes on CT images using belief functions, ii) delineation of tumour volume on PET images using an adaptive thresholding method and iii) fusion of information from both imaging modalities also using belief functions. For the segmentation of focal hypermetabolism points in PET, a generic adaptive thresholding algorithm was developed and published in 2009 [Vauclin, Phys Med Biol 2009]. It led to the improvement, evaluation and comparison of three thresholding methods proposed in the literature. This section of the programme received support from CNO in the form of funding for the purchase of an Aquilab processing platform. A partnership with Aquilab is currently underway, involving dissemination of the team's work as part of the European EuroStar project, in collaboration with teams from INSERM U703 (M. Vermandel, Lille), the University of Freiburg (Dr U. Nestle, Germany), and the UMANIA group (Italy).

Whilst the functional information supplied by PET images in an important factor in defining tumour lesions, PET is also characterised by weak spatial resolution and significant image noise, which makes accurate segmentation difficult. The teams belonging to this axis have developed various methods for segmenting /defining PET volumes. The Brussels team has developed a method based on the detection of gradient peaks in the images (watershed methodology). The Rouen team worked on existing algorithms to produce optimised versions, and the Lille team is proposing to use the MIP technique to obtain a 3D volume based on three 2D projections.

1.3 Factoring in breathing movements in Positron Emission Tomography

Because of the patient's breathing movements, uptake counts of the radiotracers used in PET imaging in thoracic and abdominal structures are spread out and as a result, the standardised uptake values (SUV) are altered. The aim of respiratory gated PET acquisition is to reduce motion-induced blurring by breaking down the movement sequence of the moving organs. Factoring in these movements could have significant consequences for diagnostics, therapeutic follow-up and/or target volume definition for radiotherapy based on the PET images. The team at Rouen assessed the impact of respiratory gating on the detectability of focal hypermetabolism points and on measurements of their volume and proved its value. Meanwhile, the Amiens team concluded that the solutions currently on offer from the manufacturers are not optimal and therefore proposed an original method for a respiratory-gated PET protocol using two strategies: selecting the PET signal by amplitude (Amiens team) and/or by frequency (Rouen team) [Daouk, Comput Meth Prog Biomed 2008; Fin, Eur J Nucl Med 2008]. This work led to a partnership with Siemens [3 'CIFRE' thesis split between Amiens and Rouen (CIFRE = *convention industrielle de formation par la recherche* – a research funding part-

nership between a company, a research facility and a young researcher].

A method for factoring in the movements during the image reconstruction process (MOSEM) has also been developed and applied to data acquired using a moving phantom and to data simulating a moving lesion in a patient. The results obtained are in the process of being published. This work is to be extended through a recently organised joint project with the Wolfson Medical Vision Laboratory at the University of Oxford.

1.4 Developing new tracers

In a joint project with the Institute of Fine Organic Chemistry in Rouen (UMR 6014 IRCOF), and with the LCHOF unit in particular (Prof. Marsais), the Rouen team developed an F-Mizonidazole derivative (F-R-Mizo) as a hypoxia tracer. The research was published in 2009 [Bohn et al., Nucl Med Biol 2009]. The microPET images were obtained by the Brussels team led by Prof. Gregoire. The team demonstrated the feasibility of fluor 18 labelling in a partially aqueous medium of new compounds containing a nitroimidazole group. The labelling can be carried out very quickly (under 5 minutes) with excellent radiochemical yield (> 90%). The stability of the final product was studied and optimised. The team also developed the tracer ^{99m}Tc-RGD, which shows an affinity for newly formed vessels during tumour angiogenesis. This tracer is currently being tested in breast and teratoma models [Aide, Eur J Nucl Med 2010] before being entered into clinical trials (work with Centre François Baclesse, Caen).

2. Technological targeting

There are two branches to these developments:

→ An assessment of the medical value of an innovative new robot radiotherapy machine supplied by the industry, the CyberKnife, installed in Lille in 2007 (see Original Projects).

→ The development of new technological approaches in robotic radiotherapy. The Lille teams have launched a technological innovation programme aimed at developing robot-aided treatment in radiotherapy (CI-ROB) and then in surgery. A project investigating ultrasound-guided robotic implantation of iodine seeds for prostate brachytherapy with real-time dosimetry was set up in mid-2008 with the École Polytechnique Universitaire de Lille and the robotics research team at LAGIS. A jointly supervised PhD (*doctorat*) on this subject, co-funded by the Nord-Pas de Calais region and the Oscar Lambret centre, received financial support from Cancéropôle Nord-Ouest in 2009.

B. Original Projects

1. Quality control of Positron Emission Tomography (PET) scanners

The group's work in this field focused primarily on validating a phantom developed by the Lille team. The quality control protocol (preparation of the phantom and image acquisition) was drawn up in consultation to ensure it was compatible with the ward structures. By running this procedure weekly, gradual changes in signal or malfunctioning of the equipment can be detected. The phantom can also be used for comparing acquisition protocols on a given machine or comparing different machines in the case of multicentre trials (Vermandel et al. Med Phys, 2008 ; European patent application 2008 EP 1923000: PET quality control phantom).

2. Factoring in breathing movements in Positron Emission Tomography

The Amiens team devised an original method for a respiratory-gated PET protocol using two strategies: 1) compensation by selecting certain data according to the 'respiratory state' (i.e. the position of the tissue at a given time), and 2) correction, by using all the data, reorganised according to the respiratory state:

➲ Compensating for respiratory motion

The team developed an original CT-based method, generating a single PET volume in which the PET data selection corresponds to a given tissue position. The workability of the corresponding acquisition protocol was evaluated both experimentally and clinically. This research was described in several publications and presentations in 2007 and 2008. Two clinical trials were organised, with the collaboration of the gastrointestinal and abdominal surgery, respiratory medicine and anatomical pathology and cytology departments at Amiens university hospital (CHU d'Amiens) to compare the sensitivity and specificity of this new approach with standard imaging in liver stages and lung stages. The preliminary results from the RespiTEP trial were published in 2009 and appear to demonstrate enhanced sensitivity. They now need to be confirmed by the anatomical pathology analyses.

➲ Correcting respiratory movements

The team at Amiens has developed an original semi-experimental tomographic algorithm (OSEM-DR). The algorithm was developed and tested on reconstructions with no movement, then applied to data simulating respiratory movements. The OSEM-DR technique significantly reduces image noise and improves contrast and quantification in relation to the geometric algorithm usually incorporated into clinical systems [Daouk, Acta Radiologica 2009; Fin, Comput Meth Prog Biomed 2009].

3. Technological targeting

The technological addition of the CyberKnife robot installed in Lille in 2007 provided the opportunity to organise clinical trials to assess the medical value of this new radiotherapy tool. The healthcare consortium comprising the Oscar Lambret Centre and Lille University Hospital is one of the 3 sites (with Nancy and Nice) authorised to use the CyberKnife robot within the framework of Cancéropôle Nord-Ouest. Funding was obtained for two hospital-based clinical research projects (PHRCs) in this area :

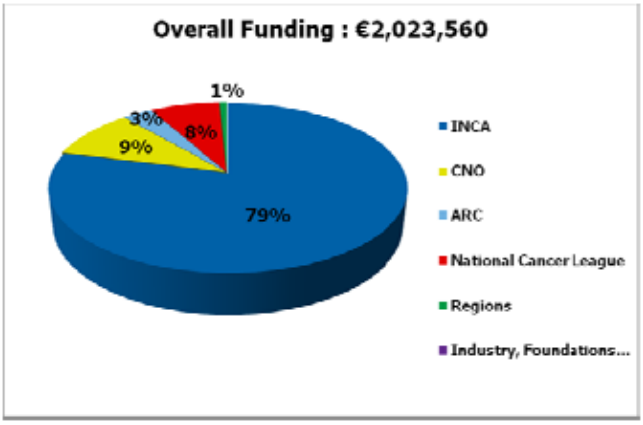
- **PHRC 2008**: Stereotactic irradiation of hepatocellular carcinomas: CyberKnife Northwest phase II project. Sponsor: Centre Oscar Lambret; Chief Investigator**:** Dr X. Mirabel.
- **PHRC 2009**: Adjuvant stereotactic irradiation of intermediate prognosis prostate cancer: CyberKnife Northwest phase II project. Sponsor: Centre Oscar Lambret; Chief Investigator: Pr E. Lartigau.

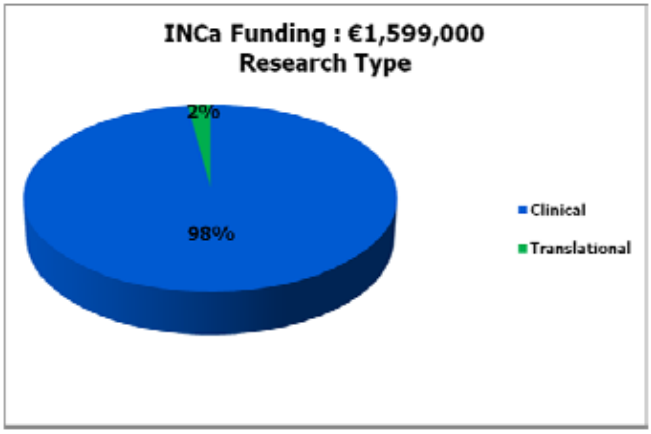
C. Networking and events

The teams belonging to CNO's radiotherapy network met twice a year for working seminars in 2007 (19th February and 29th June) and 2008 (29th March and 2nd June) and the first "Functional imaging and intensity-modulated radiotherapy" workshop, entitled "What imaging to use for what target?", organised by the axis teams in Lille in December 2008, provided an opportunity to present the work carried out within the network to the scientific community *(see programme in appendix 7).* In 2009, the teams met several times (in person on 24 June 2009 and by telephone) to prepare their response to the call for proposals under the 7th European framework programme for research & development. This allowed them to refocus their work in the context of a new project following from the initial network - the MOVE project - covering the field of innovative photon radiotherapy techniques. The project did not receive funding as part of this call for proposals, but the parties involved met regularly in 2010 by telephone and in person on 4 June, to discuss the implementation of the project.

AXIS 3 :

"MULTIMODALITY TARGETING IN ONCOLOGY, CIMULCAN PROGRAMME"





10 projects were funded for the period 2007-2010 by the various organisations funding cancer research in France, broken down as follows:

- INCa (*Institut national du cancer* – National Cancer Institute): 4 projects, including 3 PHRCs (hospital-based clinical research programme) and 1 training programme for doctors in translational research *(see appendix 4).*
- ARC (*Association pour la Recherche sur le Cancer* – Cancer Research Association): 11 projects and 1 research grant (doctorate or post-doctorate).
- Haute Normandie, Basse Normandie, Nord and Picardie Regional cancer leagues: 5 projects.

This axis will have had 31 publications based on these research projects to its credit between 2007 and 2010 *(see appendix 5).*

Half of the support provided by CNO for axis 3 consisted of support for emerging projects, which enabled the tracers to be funded for the clinical trials and the launching of the MOVE project. The other half of its support went towards personnel costs (1 year's funding for a doctorate student on the robot-aided treatment) and equipment costs (purchase of an Aquilab treatment station).