CIRRO

The Lundbeck Foundation Center for Interventional Research in Radiation Oncology

Halfway Report
May 2011

Contents

Executive summary

Radiotherapy is one of the most dominating means of cancer treatment and plays an increasingly important role in the loco-regional management of many cancer types. The aim of the Danish Center for Interventional Research in Radiation Oncology (CIRRO) is to establish individualized radiotherapy, which will lead to improved tumour control with fewer side effects for a large proportion of cancer patients. This project encompasses biological, clinical and technical studies, which will form the basis for clinical implementation of biology-guided adaptive radiotherapy.

A structure for interaction between the involved institutions, activities, and implementations has been developed. In collaboration with all Danish radiotherapy departments we have established work packages (WP) for translational research, and intervention protocols (IP) by which the clinical implementation of the various new methods in radiotherapy are being evaluated in phase I, II, and III protocols.

After successful grant applications in 2008, the centre started officially February 1, 2009 with a kick-off meeting for the 35 Danish experts and scientists involved in WPs and IPs. An academic coordinator was appointed March 2009, and the website www.cirro.dk was launched in April 2009. The scientific group has had two annual meeting in November 2009 and November 2010 with more than 60 scientists discussing ongoing and planned projects at a two-day meeting in Aarhus (see photo on front page). In August 2010 the first two-day meeting with the International Advisory Committee took place in Copenhagen.

The current report concerns the ongoing activities and results obtained after 28 months of operation.

The Lundbeck Foundation has supported CIRRO with a 30 mio. DKK grant. This has initiated substantial external funding from a number of public and private sources. Most of the budget for the Lundbeck Foundation grant has been allocated to PhD grants, fellowships and postdoc positions.

The CIRRO framework incorporates a total of 60 PhD projects (appendix 3), of which 11 are successfully completed by May 2011 (appendix 4). In addition, 47 senior scientists (post docs, fellows, consultants, associate professors, professors) are linked to the activities. For a complete list of the involved people, please see appendices 3 and 5 or www.cirro.dk.

CIRRO is currently involved in a total of 25 clinical intervention protocols, with a total of 1182 patients included so far (in Denmark). By May 2011, a total of 149 scientific papers have been published or accepted in peer reviewed international journals (appendix 1) and additional 24 papers are under review (appendix 2). CIRRO has been involved in the organization of three international meetings and two PhD courses in radiotherapy. More than 300 presentations (oral and posters) have been presented at international meetings.

We believe that the ongoing and planned research in CIRRO is progressing as expected at an international, highly competitive level, and we are confident that the centre will meet the high expectations and aims.

May 2011

Jens Overgaard
Director

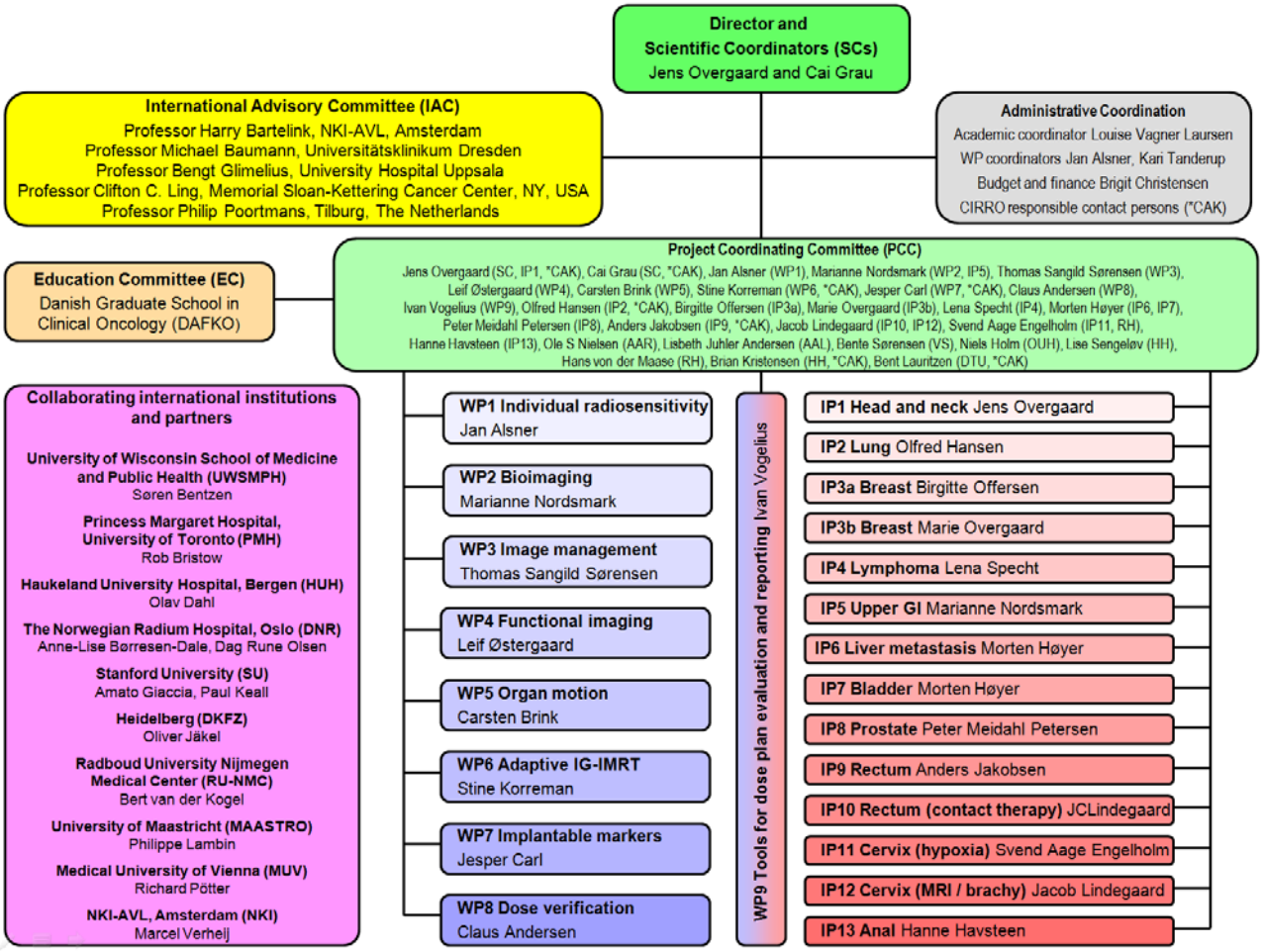
Cai Grau
Scientific Coordinator

Background and aim

Radiotherapy is one of the most dominating means of cancer treatment and plays an increasingly important role in the loco-regional management of many cancer types. The aim of the Danish Center for Interventional Research in Radiation Oncology (CIRRO) is to establish individualized radiotherapy, which will lead to better tumour control with fewer side effects for a large proportion of cancer patients. This project encompasses biological, clinical and technical studies, which will form the basis for clinical implementation of biology-guided adaptive radiotherapy.

Structure and organisation

The organizational structure presented in the original application has been implemented, with the formation of WPs, IPs, and a Project Coordinating Committee (PCC). An academic coordinator was appointed in March 2009. The administrative coordination has been strengthened by including CIRRO responsible contact persons from the participating centers. This reflected the need for smooth connection to the centers on a daily basis, which was not possible with the much larger PCC. The PCC has met so far three times and will continue to meet once a year. The International Advisory Committee (IAC) had their first meeting in August 2010.



Workpackages

The status of the pre-clinical and translational research conducted in the nine WPs is outlined in the sections below. *In brackets are given references to the milestones (M) mentioned in the original application. Numbers of papers published refer to the publication list given in Appendix 1.*

WP01 - Individual radiosensitivity

The biology of tumour response to radiotherapy is studied using preclinical models and large high quality clinical material. Techniques to quantify DNA, RNA and protein level are applied in order to identify factors that can form the basis for individualized therapeutic intervention. Tumour microenvironment conditions affecting response to radiotherapy such as oxygen concentration, metabolism, and blood supply can be very heterogeneous between individual patients. Our preclinical studies have established a novel marker (gene expression signature) for identifying hypoxia independently of pH. The hypoxia marker has been validated retrospectively, and by combining it with information on HPV status, it is possible to identify patients benefitting from a hypoxia-targeted therapy (M1.2). Other markers for characterizing tumour microenvironmental conditions are currently being developed. Late morbidity like radiation-induced fibrosis greatly influences the quality of life of long term survivors of radiotherapy. Ability to predict the risk of morbidity is important to individualize radiotherapy treatment. The risk of radiation-induced morbidity varies between individuals and has a genetic component. A preclinical model for radiation-induced fibrosis has been developed (M1.1). Furthermore a gene expression signature for predicting risk of radiation-induced fibrosis has been validated in an independent clinical dataset, and form part of the basis for ongoing genetic association studies (M1.2).

WP leader: Jan Alsner, Aarhus.

Papers published: 2, 5, 8, 12, 18, 21, 43, 53, 54, 57, 58, 62, 68, 80, 89, 91, 98, 102, 103, 108, 112, 120, 130, 143, 148.

WP02 - Bioimaging – from experimental tool to clinical applicability

Tumour hypoxia is common and adversely affects outcome since hypoxic cells are radio-resistant. PET tracers like ^{18}F-FAZA and ^{64}Cu-ATSM allow imaging of hypoxia which may assist individualized treatment that modifies or targets tumor hypoxia.

Basic biological questions that closely relates to the clinical studies described below are addressed in various animal models. Image contrast during hypoxia scans develop slowly which may compromise the hypoxia-specificity of simple single time-point scans. In accordance, we have previously shown that additional information may be derived from kinetic analysis of dynamic scans in tumor-bearing mice, but since decisive and accurate pharmacokinetic analysis requires repetitive blood samples these findings are now being confirmed and extended in rats. The tumor microenvironment is highly dynamic which in turn may compromise specialized treatment like IMRT, and we have therefore assessed the reproducibility of ^{18}F-FAZA-PET scans at baseline and during fractionated radiotherapy in a mouse tumor xenograft model, and we plan to include a second tumor model to generalize our findings. It still remains unclear to what extent hypoxia-PET can identify hypoxic tumours that will benefit from hypoxic intervention. Thus, we have carried out a study that assess the ability of ^{18}F-FAZA-PET to predict the efficacy of radiotherapy in tumour-bearing control mice or mice receiving hypoxia-targeting intervention (high oxygen-gas breathing), and a manuscript is being prepared. Finally, a ^{64}Cu-ATSM PET study in dogs with spontaneous tumours where PET images are compared to biopsy-based invasive analysis of hypoxia-regulated genes and the immunologically-detectable hypoxia probe pimonidazole has been finished and two manuscripts are currently being pre-

pared. Since the study revealed inconsistencies between the different hypoxia-measures we plan to do a head to head comparison between ^{64}Cu-ATSM and ^{18}F-FAZA PET in canine tumours.
Clinical ^{18}F-FAZA PET protocols in cancer of the head and neck (CIRRO-IP010109), rectum (CIRRO-IP090110) and uterine cervix (CIRRO-IP120111) have been activated.,. Since the clinical studies involve several PET centers and scanners, a project evaluating the inter-frame uncertainty margins for biological target definition has been initiated in collaboration with the Dept. of Radiation Therapy, Madison, USA. Finally, a protocol for cervix cancer (CIRRO-IP110110) that involves the use of ^{64}Cu-ATSM awaits for clinical approval of the tracer.
WP leader: Marianne Nordsmark, Aarhus.
Papers published: 7, 15, 30, 56, 110, 111, 126.

WP03 – Image management
The main objective of the studies is to develop reliable non-linear registration techniques to align all CT, MRI, and PET scans acquired during the course of treatment. The registrations can be used to develop the concept of adaptive radiotherapy treatment planning to account for changes in morphology and tumour biology encountered during a treatment course. We have developed a technique to obtain non-linear registration of cone-beam CT to planning CT (M 3.1). Likewise, registration tools from Varian have been evaluated clinically. An iterative registration technique guided by biomechanical physics has been developed as has a novel surface-based registration technique to estimate inter-fractional bladder motion : A valid registration of the bladder over multiple treatments makes it possible to compute the hot spot radiation more accurately and the goal is to allow higher doses in cases where the bladder incorrectly appears as a dose restricting organ due to overestimation of dose using crude addition of dose volume histograms (M3.3). A technical paper is published and the method is currently under clinical evaluation. Finally, an image sequence segmentation technique, which combines segmentation and registration in a joint framework, has been developed (supplement to M3.1).
WP leader: Thomas Sangild Sørensen, Aarhus.
Papers published: 60, 81, 128, 141.

WP04 – Functional imaging
Studies focus on functional imaging in preclinical and clinical settings for assessment of different characteristics of tumours and their microenvironment such as tumour volume, regional lymph node involvement, tumour biology, and response to radiotherapy.
High resolution imaging of oxygen levels, hypoxia, metabolism and targeted nano-particles is obtained by high-field (16.4T) MRI. Our work has so far led to the establishment of high-field ^{19}F MRI utilizing different ^{19}F labeled contrast agents (M4.1). Preliminary experiments show signal from hexafluorobenzene (oximetry) in murine tumours, and the method is being optimized. High field implementation of diffusion weighted imaging (DWI), dynamic contrast enhanced MRI (DCE-MRI) and susceptibility imaging with USPIO nano-particles has been established (M4.1). In vivo experiments in a novel and standardized murine angiogenesis model visualized progressive angiogenesis in agreement with histology. Targeted USPIO particles have been developed at Aarhus University, and the passive accumulation has been tested in murine tumours. Uptake dependence on particle size has been investigated in tumours and in the angiogenesis model, and dependence of particle core size has been investigated in tumours. Further targeted particles are under development. MRI perfusion and PET hypoxia comparison is being performed in human tumour xenografts and murine tumours following initial pilot studies .
Clinical implementation and optimization of DWI sequence has been performed in patients . Repetitive DWI MRI has been performed and analyzed in a cohort of patients (M4.2) to characterize correlation between

restricted diffusion regions and radiotherapy target volumes. A protocol for comparison of histopathology (biopsies) and functional imaging (DCE-MRI, DWI) in cervix cancer started enrolling patients by April 2011 (M4.2). Furthermore, DWI is used to assess the position of lymph nodes for improved definition of the elective radiotherapy target volume in cervix cancer by combining CT and MRI . Another protocol is planned to compare and evaluate the sensitivity and specificity of FDG-PET, DWI, and MRI with administration of the nano-particle contrast agent USPIO to make lymph node assessment in patients with operable rectal and gyneacological cancer. However, availability of the contrast agent USPIO is pending for clinical use and this work is consequently delayed.
WP leader: Leif Østergaard, Aarhus.
Papers published: 9, 29, 41, 42, 48, 59, 82, 83, 84, 105, 109.

WP05 – Organ motion - 4D imaging and treatment
Knowledge of tumour position is vital to the exact delivery of the prescribed radiation dose. Tumours move during a treatment course on different time scale going from second's e.g. breathing, minutes e.g. motion of flatulence and extending up to days e.g. weight loss. Technologies exist to monitor tumour position during the treatment course (4D imaging) and delivery techniques which account for these movements are available at a research stage. The objectives are to further develop 4D treatment techniques and to implement these in clinical routine practice. Currently there has been research performed within WP05 on all the above mentioned time scales.
Seconds
Although 4D imaging has the potential to reduce image artefacts due to motion in 3D CT scans, artefacts are still present in 4D images. A study on the influence on GTV definition due to image artefacts based on patient data from one 4D CT scanner has been performed. This study has been followed by a similar study on a number of 4D CT scanners by use of a motion phantom. A technique to optimise image quality by use of deformable image registration has been developed. This method reduced the image artefacts by a factor of two.High quality 4D CT is important in order to reduce the treated volume. However, for large respiration motion it can be beneficial to track the tumour motion e.g. by use of a dynamic MLC. Research activities within WP05 includes the first demonstration of image-based tracking during intensity modulated arc therapy (IMAT) and the first in vivo DMLC tracking of a mammal (using pigs, in collaboration with WP07).
Minutes
Tracking of seeds during treatment is of interest not only due to the respiration, but also due to motion of flatulence and bladder filling. There has been a large research activity in WP05 on the possibility to track seeds inside a patient during radiotherapy based on Cone Beam CT. It has been shown that it is possible to track different types of seeds on-line both in liver and prostate. The tracking of the seeds can be used either as a tracking signal or to interrupt the treatment if the detected position is outside predefined levels.
Days
Change in anatomy during the treatment course has an influence on the delivered dose. Studies on the influence of change in dose to critical structures due to e.g. weight loss have been performed. Very recent research activity in WP05 is related to the possibility to extract toxicity information from CBCT performed during the treatment course. It is shown that a relationship between dose and density changes in the healthy lung tissue exists and can be observed during the treatment course. Currently the relation between the density signal and clinical outcome is ongoing. If such a relation is established this could open for biological adaptive radiation therapy by use of CBCT images.
WP leader: Carsten Brink, Odense.
Papers published: 16, 36, 38, 61, 69, 70, 71, 72, 73, 74, 75, 95, 106, 129, 131, 133, 134, 135.

WP06 – Adaptive image-guided modulated radiotherapy

Both tumour and normal tissues undergo significant changes in size, shape, and position during a treatment course. A way to improve individualized radiotherapy is by adapting treatment plans with regard to the anatomical changes based on in-room imaging strategies. The "plan-of-the-day" scenario where replanning of treatment occurs on a daily basis is pursued. In-room imaging mainly refers to on-board cone-beam CT scanning which has a poorer soft tissue contrast than the planning fan beam CT scan. Therefore methods enabling use of CBCT scans to adapt treatment plans are needed. In one project delineation in CBCT has been successfully approached through propagation of structures from CT to CBCT scans. With improvement in diagnostic image properties for CBCT image reconstruction this lead to good agreement in key dose-volume parameters between CT- and CBCT-based planning in a humanoid phantom. Finally, in a series of head and neck cancer patients good agreement between clinically relevant dose-volume histogram parameters for CT and CBCT scans was demonstrated (M6.1). Time-resolved diode dosimetry utility has been compared for dynamic arc radiotherapy for several commercial dosimetric systems (M6.1). Target and organs at risk (OAR) dose limits are studied by combining CT and CBCT scans for adaptive planning (M6.2). Studies on Monte Carlo simulations/full dose measurements by use of gel dosimetry have been performed for volumetric arc treatment (M6.2), and investigations have been carried out for balancing dose limits to organs at risk and target for non-small cell lung cancer patients (M6.2). Studies on optimization for optimal cost-effectiveness and integration with volumetric arc therapies are ongoing for various cancer sites, and studies of inter-fractional motion of the three involved targets for different IGRT positioning strategies have been performed for prostate IGRT. (M6.3). Studies have been commenced and first results reached for individualized head and neck cancer volumetric arc treatment planned with functional imaging and heterogeneous dose distributions (dose painting). Phantom studies of the influence of fiducial markers in diffusion weighted MRI have been performed, serving as the first step towards probability-based planning for temporal/spatial uncertainties in biological images (M6.3).

WP leader: Stine Korreman, Copenhagen.

Papers published: 1, 17, 19, 22, 23, 28, 34, 37, 52, 87, 90, 93, 104, 117, 122, 127, 142, 146.

WP07 - Implantable markers for Image guided radiotherapy

The ability to deliver radiation dose accurately requires that the target is easily localized in the patient. Studies in this work package aim at developing and investigating three different fiducial markers: a Ni-Ti memory shape stent, X-ray contrast media lipiodol, and a radiofrequency MR marker coil. The current status is that a clinical feasibility study using the Ni-Ti stent as a fiducial marker in prostate cancer radiotherapy has completed and the first results demonstrating low frequencies in late toxicity in both bladder and rectum have been published (M7.3). A semi-automatic method using mutual information and a rigid co-registration of planning CT and MR image sets has been demonstrated to give good results in image sets from ten different patients on a qualitative basis. Co-registration combined with auto-segmentation of the prostate will be the subject of further studies. A theoretical planning study has been looking into the possibility of sparing the urethra if radiation dose in external beam therapy is to be increased. The preliminary results estimate that if IMRT techniques are used the dose to the urethra may be lower than the intended target dose. Clinical protocols for retrospective and prospective follow-up studies have been developed and both studies are recruiting patients. A first pre-clinical animal study of a prototype for a lung stent revealed that further development of the instrumentation was needed. A second preclinical animal study using technologically more advanced instrumentation has been completed and the new instrumentation was demonstrated to overcome the previous problems. Twenty three stents were inserted in 10 animals and no stent migrated. The study also investigated the possibility to apply apnoeic respiration as an alternative to compensate motion in lung cancer radiotherapy. Significant motion however was seen in several animals

during apnoeic respiration – possibly caused by incomplete muscle relaxation. *In vivo* treatment using MLC tracking was attempted as well. In eleven of fifteen beams tracking was successful. The study revealed that very poor contrast of the stent was seen in the high voltage portal images used for tracking. The stent either has to be optimized for high voltage or kilo voltage images should be used instead. Currently, virtual bronchoscope methods to estimate the expected optimal position of the stent relative to a given tumour in the lung are being developed. Also automatic image analysis to score acute and late adverse effects from lung radiation is being developed. It is assumed that the lung stent method combined with electromagnetic bronchoscope navigation is ready for a human feasibility test. Protocol for LMS approval is expected to be ready in 2012 (M7.2). Protocols and new phantoms have been developed and are used in two new studies. These studies are evaluating the accuracy and precision for use of the fiducial marker in the lung, including reconstruction errors in respiration resolution scans (4D CT and 4D PET).
A clinical protocol (CIRRO-IP070109 - Image guided tumour boost of localized unifocal c. vesica urinaria) for using lipiodol as a fiducial marker in bladder cancer is currently active and data from the first patients have been analyzed. The results demonstrate so far that lipiodol can successfully be injected into the bladder mucosa and subsequently visualized on CT and CBCT as a fiducial marker (M7.1).
WP leader: Jesper Carl, Aalborg.
Papers published: 31, 44, 100, 116.

WP08 - Dose verification
Development and use of new dose verification procedures will improve safety and precision of individualized radiotherapy. Novel techniques have been developed within the fields of dosimetry and Monte Carlo calculations.
A new dose verification protocol using time resolved online *in vivo* dosimetry in brachytherapy of cervical cancer patients was developed and evaluated in five patients. The work suggested that improved dose verification can be achieved using time-resolved luminescence dosimetry directly in the tumour region . The instrumentation and the data processing algorithm were improved further. For example, the instrumentation is now insensitive to errors induced by irradiation of the optical fiber cable attached to the *in vivo* dosimeter. Furthermore, a new so-called saturated radioluminescence protocol was developed. This protocol features a large dynamic range (from a few mGy to above 50 Gy) and is more suitable for use in a clinical environment than what has been used previously. Extensive phantom tests simulating treatment errors of brachytherapy patients was carried out. The study involved both cervical and prostate patients, pulsed and high-dose brachytherapy, and different applicators (needles and tandem/ring applicators). The study demonstrated the ability of the system to accurately identify treatment errors introduced under controlled conditions.
A complete workflow has been established at Herlev which allows for automatic Monte Carlo calculation of treatment plans for dynamic radiotherapy such as IMRT and Rapid Arc. The study has further underlined the inaccuracies introduced when conventional treatment planning systems are used for dose calculations in geometries involving large density variations . Significant progress has been made towards converting patient CT data to accurate Monte Carlo compatible density and media matrices. Experimental studies on reference dosimetry were undertaken and a conjunction of experimental techniques and Monte Carlo computations have been carried out, in particular addressing the measurement problems encountered with small field MV photon dosimetry. Both small alanine detectors and a novel dosimetry system based on minute organic plastic scintillators have been used.

Investigation of the characteristics of the solid state dosimeter PRESAGE™ has been performed followed by a publication of the temperature dependence on dose response and an accepted manuscript with saturation measurements. Further investigations of the characteristics of PRESAGE™ are ongoing.
The production of gel dosimeters has been initiated and the gels are currently used investigating the conventional dose read-out method for 3D dosimeters, MRI, with the relatively new method, optical CT, the latter is installed in Aarhus. A new high resolution 1D optical scanner has been build and is currently being tested. In addition the use of 3D dosimetry to verify complex radiation delivery with tumor tracking has been performed.
WP leader: Claus Andersen, DTU.
Papers published: 3, 4, 6, 24, 25, 26, 27, 32, 40, 44, 47, 49, 76, 78, 96, 113, 118, 119, 123, 124, 138, 139, 147, 149.

WP09 – Tools for dose plan evaluation and reporting
The main objective is to develop feasible and effective tools for reporting and analyzing radiotherapy planning, delivery, and outcome data. The ultimate aim is to develop a national database containing 3D/4D treatment data and outcome for all patients undergoing radiotherapy in Denmark. An analysis of existing tools for dose plans reporting resulted in the choice of a Conquest DICOM-RT database for dose plan archiving. User rights and access control is improved through a supplementary web-based interface, which have been designed for this purpose. Secure communications is achieved through an external partner, MedCom. Odense University Hospital, Vejle Hospital, Rigshospitalet and Århus University Hospital have verified full connectivity. The Danish Data Protection Agency has approved the data collection (protocol no. 2008-58-0035). Some performance and stability issues discovered during use are currently being addressed and the scalability of the database is being investigated. Radiotherapy dose plans from the clinical protocols in breast cancer, CIRRO-IP030109 and CIRRO-IP030209, are at present being stored in the database. Furthermore, a collaboration between Vejle and Aarhus University Hospital regarding retrospective investigation of lung cancer treatments is using the database for information sharing. Additional funding has been applied for from the Danish Council of Independent Research with the purpose of scaling the database to allow storing of routine data and to automate data collection to improve compliance.
WP leader: Ivan Vogelius, Copenhagen.

Intervention protocols

The aim of the clinical intervention protocols is to test the biological and technical developments in phase I, II and III clinical multicenter trials on a national scale.

By May 2011 a total of 25 protocols were active or planned. A total of 1182 patients have been included in 22 protocols (two of which are closed). One protocol, which is running internationally, is approved and ready to include patients in Denmark (CIRRO-IP050109). Another two protocols (CIRRO-IP100109 and CIRRO-IP110110) have not yet been initiated – one due to technical difficulties with the equipment and the other due to a pending permission to use the Cu-ATSM tracer in patients. For details about the intervention protocols please see the figure 1 below and appendix 6.

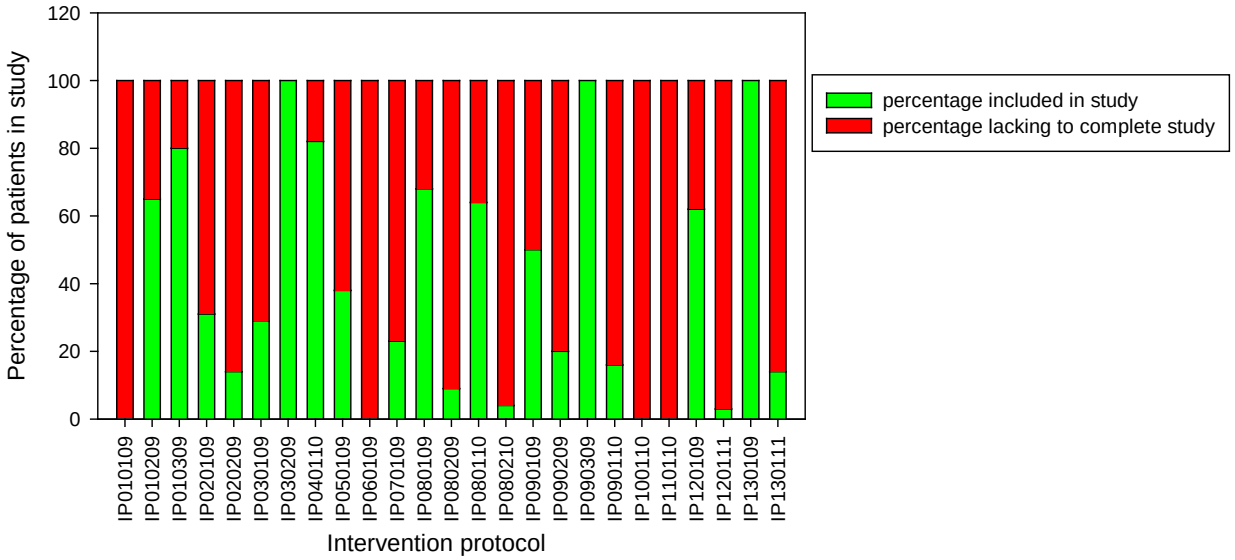


Figure 1. Status of patient accrual in CIRRO intervention protocols. Green: percentage of patients included in study. Red: percentage of patients needed to complete study. For actual numbers of patients see appendix 6.

Publications

By May 2011 a total of 149 papers have been published or accepted for publication. 24 papers are currently under review. See appendices 1 and 2 for a complete list of publications.
More than 300 oral presentations and posters have been presented at international conferences.

PhD projects

A total of 60 PhD projects (49 ongoing and 11 completed) are linked to the activities (WP or IP) in CIRRO. CIRRO PhD students are all affiliated with DAFKO (Danish Graduate School in Clinical Oncology). Together with DAFKO, CIRRO has organized two one-week PhD courses in radiation oncology.

Meetings and seminars

In addition to funding scientific projects CIRRO has organised, sponsored or supported a number of activities.

A **kick-off meeting** was organized at Koldkærgård Conference Center in Aarhus February 17-18 2009 with 35 participants. The focus was to present and discuss the planned activities of the centre.

Two annual CIRRO meetings have been held (November 2009 and November 2010), also at Koldkærgård Conference Center in Aarhus. Both annual meetings have had around 65 participants and the ongoing and future activities in the center were presented and discussed.

In conjunction with the annual meetings, CIRRO has in collaboration with the Danish Graduate School in Clinical Oncology (DAFKO) organized **two PhD courses**. The first was a basic course on biology, imaging and technology in radiation oncology held in November 2009 and the second was a course in advanced radiotherapy held in November 2010. Around 30 students attended each course.

The international Tumour Microenvironment Workshop in Toronto, May 2-5 2010 was sponsored and co-organized by CIRRO, which was also represented with nine oral presentations. Other co-organizers included two research centers similar to CIRRO, namely the German "Center for Radiation Research in Oncology (OncoRay)" and the Canadian center "Spatio-Temporal Targeting and Amplification of Radiation Response (STTARR)".

CIRRO was co-organizer of the **Acta Oncologica symposium BiGART2010** (Biology Guided Adaptive Radiotherapy) in Aarhus, May 26-28 2010. This international meeting had a strong international faculty and attracted more than 140 participants, of which 58 were affiliated with CIRRO. The proceedings of the meeting are published as a special issue of Acta Oncologica.

CIRRO co-organized the **4th Danish workshop for Proton and Heavy-Ion Dosimetry** in Aahus, November 16-18, 2009.

Other activities include a seminar in radiation injuries in the pelvic region (April 8, 2010), a WP09 user meeting (April 19, 2010) and meetings with CIRRO responsible contact persons (CAK) from the participating departments (four per year). A national meeting/workshop with the purpose of harmonizing lung toxicity follow up and scoring systems has been organized in Odense in August 2011.

International Advisory Committee

An international advisory committee has been established to get direct outside expert input on CIRRO network activities. In August 2010, a two-day meeting with the advisory members was organized at Schæffergården in Copenhagen. The CIRRO center vision and structure as well as selected projects were presented. On the basis of the presentations and the 2010 Scientific Report, the advisory committee reported on the progress of the research center. The full report can be seen in appendix 7.

The main conclusions from the meeting were:

- CIRRO is a unique national research center engaging all radiotherapy departments in Denmark
- Research in work packages is progressing well and according to plan with very carefully thought out ideas and realistic work programs
- Most of the described clinical trials have been activated and a few more trials have been added
- The translational research is of very high quality and several translational research activities have been added to the ongoing clinical projects
- The CIRRO project brings Denmark in an internationally very competitive position in new developments in cancer research

The advisory committee had three main advices for future developments: 1) CIRRO should enhance incorporation of the strong translational activities e.g. functional imaging, genetic analyses, and use of fiducial markers, into existing clinical trials and new clinical projects; 2) CIRRO should work on strategies for exchanging young investigators between laboratories worldwide; and 3) the national central dose plan bank (WP09) is unique, and should be extended beyond quality assurance of CIRRO trials.

CIRRO has reacted to the suggestions in several ways. Implementation of own translational research was the main theme at the annual CIRRO meeting in 2010, and e.g. the recently started protocol IMAP (CIRRO-IP120111) was developed based on translational research performed in CIRRO. Exchange of knowledge has been strengthened by an extensive travel support program. Within the first year, 45 scientists have obtained a travel grant. Finally, a vision to extend WP09 to encompass a radiotherapy dose plan databank for all Danish patients treated with radiotherapy has been launched. The initial work in WP09 has made it clear that a national database, collecting dose plans from all clinical protocols (and in the future all radiotherapy treatments), is a possibility. Together with the four major Danish Multidisciplinary Cancer Groups (breast, lung, prostate, head and neck) CIRRO has applied for funding for this large new project from the Danish Council for Independent Research.

Homepage

CIRRO launched the homepage www.cirro.dk in April 2009. The website is our preferred platform of information both for members of CIRRO and the public. The website gives an overview of the research activities within the center as well as listing news, publications, events etc. All CIRRO members are expected to register and create a public profile at the homepage. Per May 2011, the homepage has 106 registered users.

Economy

The Lundbeck Foundation is the main contributor to the budget of the CIRRO center with 30 mio. DKK. Substantial external funding has been obtained from institutional support to permanent staff, establishment of new research positions and external grants from a large number of private and public sources. Among major co-sponsors are:

- The Danish Council for Strategic Research (Programme on Health, Food, and Welfare)
- Danish Council for Independent Research
- The Danish Cancer Society
- Varian Medical Systems
- Elekta

- Aarhus University Hospital
- Aarhus University
- University of Southern Denmark
- Danish Technical University
- Copenhagen University

The grant from the Lundbeck Foundation is allocated mainly to salary for scientific personnel. The funds are allocated primarily to projects initiated in 2009 or 2010, since the aim is to have all funded projects completed and published before the end of the project in 2014.

CIRRO is also funding travel expenses. So far 45 CIRRO affiliated scientists have obtained support for participation in courses, conferences, seminars as well as longer and shorter exchange visits to international collaborators.

As mentioned above, funding to expand the dose plan databank in WP09 has been applied for.

Concluding remarks

We believe that the ongoing and planned research in CIRRO is progressing as expected at an international, highly competitive level, and we are confident that the centre will meet the high expectations and aims.

Appendix 1: List of scientific publications, per May 2011

2009

1. Aarup LR, Nahum AE, Zacharatou C, Juhler-Nøttrup T, Knöös T, Nyström H, Specht L, Wieslander E, Korreman SS. The effect of different lung densities on the accuracy of various radiotherapy dose calculation methods: implications for tumour coverage. Radiother Oncol. 91: 405-14, 2009.
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6. Bassler N, Holzscheiter M. Calculated LET Spectrum from Antiproton Beams Stopping in Water. Acta Oncol. 48: 223-226, 2009.
7. Busk M, Horsman MR, Jakobsen S, Hansen KV, Bussink J, van der Kogel A, Overgaard J. Can hypoxia-PET map hypoxic cell density heterogeneity accurately in an animal tumor model at a clinically obtainable image contrast? Radiother Oncol. 92: 429-36, 2009.
8. Eriksen JG, Overgaard M. Late onset of skin toxicity induced by EGFr-inhibitors. Radiother Oncol. 90: 280-281, 2009.
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133. Poulsen PR, Carl J, Nielsen MS, Nielsen J, Thomsen JB, Jensen HK, Kjærgaard B, Zepernick PR, Worm E, Fledelius W, Cho B, Sawant A, Ruan D, Keall PJ. MV image-based dynamic MLC tracking of a NiTi stent in pig lungs on a linear accelerator. Int J Rad Onc Biol Phys. 2011 (in press).
134. Poulsen PR, Fledelius W, Keall PJ, Weiss E, Lu J, Brackbill E, and Hugo GD. A method for robust segmentation of arbitrarily shaped radiopaque structures in cone-beam CT projections. Med. Phys. 38: 2151-2156, 2011.
135. Ravkilde T, Keall PJ, Højbjerre K, Fledelius W, Worm E, and Poulsen PR. Geometric accuracy of DMLC tracking with an implantable wired electromagnetic transponder. Acta Oncol. 2011 (in press)
136. Rosenschöld PM, Engelholm S, Ohlhues L, Law I, Vogelius IR, Engelholm SA. Photon and proton therapy planning comparison for malignant glioma based on CT, FDG-PET, DTI-MRI and fiber tracking. Acta Oncol. 2011 (in press).
137. Rylander S, Thörnqvist S, Haack S, Pedersen EM and Muren LP. Intensity profile based measurement of prostate gold marker impact on 1.5T and 3.0T diffusion-weighted MR images. Acta Oncol. 2011 (in press).
138. Skyt PS, Balling P, Petersen JB, Yates ES and Muren LP. Temperature dependence of the dose response for a solid-state radiochromic dosimeter. Med Phys. 2011 (in press).
139. Sørensen BS, Overgaard J, Bassler N. In vitro RBE-LET dependence for multiple particle types. Acta Oncol. 2011 (in press)
140. Sørensen BS, Vestergaard A, Overgaard J, Præstegaard LH. Dependence of cell survival on instantaneous dose rate of a linear Accelerator. Radiother Oncol (in press).
141. Thor M, Petersen JBB, Bentzen L, Høyer M and Muren LP. Deformable image registration for contour propagation from CT to CBCT in radiotherapy of prostate cancer. Acta Oncol. 2011 (in press).
142. Thörnqvist S, Bentzen LN, Hysing LB, Petersen JBB and Muren LP. Plan robustness in simultaneous integrated boost radiotherapy of prostate and lymph nodes for different image-guidance and delivery techniques. Acta Oncol . 2011 (in press).
143. Toustrup K, Sørensen BS, Nordsmark M, Busk M, Lassen P, Wiuf C, Alsner J, Overgaard J. Gene classifier predicts for hypoxic modification of radiotherapy in head and neck cancer. Cancer Res. 2011 (in press).
144. Vogelius IR, Bentzen SM, Maraldo MV, Petersen PM, Specht L. Risk factors for radiation induced hypothyroidism: A literature based meta-analysis. Cancer 2011 (in press)
145. Vogelius IR, Westerly DC, Aznar MC, Cannon GM, Korreman SS, Mackie TR, Mehta MP, Bentzen SM.Estimated radiation pneumonitis risk after photon versus proton therapy alone or combined with chemotherapy for lung cancer. Acta Oncol. 2011 (in press)

146. Vogelius IS, Westerly DC, Cannon GM, Mackie TR, Mehta MP, Sugie C, Bentzen SM. Intensity-Modulated Radiotherapy Might Increase Pneumonitis Risk Relative to Three-Dimensional Conformal Radiotherapy in Patients Receiving Combined Chemotherapy and Radiotherapy: A Modeling Study of Dose Dumping. Int J Radiat Oncol Biol Phys. 2011 (in press).
147. Waldeland E, Helt-Hansen J, Malinen E. Characterization of lithium formate EPR dosimeters for high dose applications - Comparison with alanine Radiation Measurements. 46: 213-218, 2011.
148. Wiechec E, Wiuf C, Overgaard J, Hansen LL. High Resolution Melting (HRM) analysis for mutation screening of RGSL1, RGS16 and RGS8 in breast cancer. Cancer Epidemiol Biomarkers Prev. 20: 397-407, 2011.
149. Yates ES, Balling P, Petersen JB, Nesarizadeh M, Skyt P, Bassler N, Kaiser F-J, and Muren LP Characterization of the optical properties and stability of PRESAGE following irradiation with photons and carbon ions. Acta Oncol. 2011 (in press).

Appendix 2: Submitted manuscripts

1. Appelt AL, Vogelius IR. A method to adjust radiation dose-response relationships for clinical risk factors.
2. Bertelsen A, Lorenzen EL, and Brink C. Validation of an accelerator control system from Elekta facilitating continuously variable dose rate for VMAT.
3. Christensen BO, Overgaard J, Kettner LO, Damsgaard TE. Long-term evaluation of postmastecomy breast reconstruction with the TRAM flap.
4. Christensen BO, Overgaard J, Vorum H, Honore B, Damsgaard TE. A proteomic analysis of the effect of radiation therapy on wound healing in women reconstructed with the TRAM flap.
5. Elstrøm UV, Petersen JBB, Muren LP and Grau C. Improving head and neck cone-beam CT Hounsfield Unit accuracy using site-specific calibration and reconstruction methods.
6. Emmertsen K, and Laurberg S. Low Anterior Resection Syndrome Score. Development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer.
7. Hansen AE, Kristensen AT, Law I, McEvoy F, Engelholm SA. Multimodality functional imaging of spontaneous canine tumors using 64Cu-ATSM and 18FDG PET/CT and dynamic contrast enhanced perfusion CT.
8. Hansen DC, Lühr A, Herrmann R, Sobolevsky N, and Bassler N. Recent Improvements in the SHIELD-HIT Code.
9. Hennessy BT, Faratian D, Ju Z, Agarwal R, Lluch A, Carey MS, Myhre S, Lee J-S, Gonzalez-Angulo AM, Coombes KR, Overgaard J, Alsner J, Broaddus R, Deng L, Sørlie T, Sahin A, Valero V, Harrison DJ, Børresen-Dale A-L, Mills GB. Proteomic Predictors of Outcome After Adjuvant Anti-Hormonal Therapy for Hormone Receptor-Positive Breast Cancer.
10. Herrmann, R, Greilich, S, Grzanka, L, and Bassler, N. Amorphous-track predictions in 'libamtrack' for alanine relative effectiveness in ion beams.
11. Høyer M, Swaminath A, Bydder S, Lock M, Romero AM, Kavanagh B, Goodman K, O'Kunieff P, Dawson LA. Radiotherapy for Liver Metastases: a Review of Evidence.
12. Kyndi M, Tramm T, Sørensen FB, Knudsen H, Alsner J, Overgaard J. Validation of BCL-2, E-cadherin, EGFR, p53, Ki-67, and EMMPRIN applied to tissue microarrays in breast cancer.
13. Laursen LV, Elstrøm UV, Vestergaard A, Muren LP, Petersen JB, Lindegaard JC, Grau C, and Tanderup K. Residual rotational set-up errors after daily cone-beam CT image guided radiotherapy of locally advanced cervical cancer.
14. Maraldo MV, Brodin NPVogelius IR, Aznar M, af Rosenschöld PM, and Specht L. Risk of developing cardiovascular disease after involved node radiotherapy vs. mantle field for Hodgkin Lymphoma.
15. Mortensen HR, Overgaard J, Specht L, Overgaard M, Johansen J, Evensen J, Andersen LJ, Andersen E and Grau C. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7 trial with accelerated radiotherapy for head and neck cancer.
16. Ottosson RO and Behrens CF. CTCask; a new algorithm for conversion of CT numbers to tissue parameters for Monte Carlo dose calculations applying DICOM RS knowledge.
17. Søndergaard J, Holmberg M, Jacobsen AR, Muren LP, Grau C and Høyer M. Morbidity profiles following conformal vs intensity-modulated radiotherapy for urinary bladder cancer.
18. Thor M, Apte A, Deasy J and Muren LP. Incorporating statistical simulations of actual delivered dose to improve prediction of post-radiotherapy rectal morbidity.

19. Toustrup K, Sørensen BS, Lassen P, Alsner J, Wiuf C, Overgaard J. Gene expression classifier predicts for hypoxic modification of radiotherapy with nimorazole in squamous cell carcinomas the head and neck.
20. Tramm T, Hennig G, Kyndi M, Acht T, Alsner J, Sørensen FB, Overgaard J. Robust gene expression analysis from whole slide formalin fixed, paraffin-embedded breast cancer tissue sections.
21. Vogelius IR and Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis.
22. Wiechec E, Overgaard J, Hansen LL. Allelic imbalance, DNA copy number variations and chromosomal breakpoints affecting the putative tumour suppressor gene, RGS8 at 1q25.3 in breast cancer.
23. Wiechec E, Overgaard J, Kjeldsen E, Hansen LL. Evaluation of 1q25.3 copy number in breast cancer by three diagnostic tools (AI, MLPA, FISH).
24. Wojdacz TK, Thestrup BB, Cold S, Overgaard J, Hansen LL. No difference in the frequency of constitutional locus specific methylation in peripheral blood DNA of women diagnosed with breast cancer and age matched controls.

Appendix 3: CIRRO affiliated PhD projects and students

1. Appelt, Ane: Evaluation of dose plan quality with focus on prediction of side-effects following radiotherapy of lung and rectum [Evaluering af dosisplankvalitet med fokus på prædiktion af bivirkninger ved strålebehandling af lunge og rectum]. University of Southern Denmark (enrolled 2010).
2. Bertelsen, Anders: Volumetric Modulated Arc Therapy (VMAT®) - advantages and disadvantages. University of Southern Denmark (enrolled 2008)
3. Bjerre, Troels: Automated image-based procedures for radio-therapy treatment evaluation and daily dose re-planning. Danish Technical University (enrolled 2010)
4. Bøje, Charlotte: The importance of comorbidity for the outcome of radiotherapy for head and neck cancer. Aarhus University (enrolled 2009)
5. Christensen, Bekka A.O: Postmastectomy breast reconstruction. Evaluation of factors influencing early and long-term outcome. Aarhus University, project completed 2011.
6. Christoffersen, Christian: Motion compensated image reconstruction. Aarhus University (enrolled 2010)
7. D'Andrea, Filippo: Genetic or microenvironmental origin of radioresistance in sarcoma Studies in mesenchymal cancer stem cells derived soft tissue sarcoma model. Aarhus University (enrolled 2007)
8. Dieperink, Karin: A new everyday life – rehabilitation and mastering late effects of radiotherapy for prostate cancer [En ny hverdag - Rehabilitering og mestring af senfølger efter kurativ strålebehandling for prostatacancer]. University of Southern Denmark (enrolled 2009)
9. Due, Anne Kirkebjerg: Imaging and tumour definition in IMRT of head and neck cancer [Billeddannelse og tumordefinition ved IMRT af hoved-halscancer]. Copenhagen University (enrolled 2009)
10. Elstrøm, Ulrik Vindelev: Image-guided adaptive radiotherapy of head and neck cancer. Aarhus University, project completed 2011.
11. Emmertsen, Katrine: Influence of neoadjuvant radiotherapy on bowel, urinary and sexual function after treatment for rectal cancer. Aarhus University (enrolled 2008)
12. Gottlieb, Karina Lindberg: Investigation of respiration induced intra- and inter-fractional tumour motion using a standard Cone Beam CT. University of Southern Denmark (enrolled 2009)
13. Grantzau, Trine: Risk of second primary cancer among Danish women with breast cancer treated with postoperative radiotherapy. Aarhus University (enrolled 2010).
14. Haack, Søren: Diffusion Weighted MRI for Radiotherapy Planning. Aarhus University (enrolled 2009)
15. Hansen, Anders Elias: Characterization, regulation and the role ofhypoxia and markers of hypoxia to radiotherapy of canine soft tissue sarcomas *a spontaneous model of human disease. Copenhagen University (enrolled 2009)
16. Hansen, Henrik: Introduction of 64Cu-ATSM as hypoxia tracer in cervical cancer patients – a feasibility study [Feasibility studium med henblik på indtroduktion af 64Cu-ATSM som hypoksi tracer hos patienter med cervixcancer]. Copenhagen University (enrolled 2010).
17. Hassan, Mohammed: Preliminary Results, Quality Assurance and Biological Studies of Head and Neck Cancer Patients undergoing Accelerated Radiotherapy with or without Nimorazole in a Randomized Multicenter Trial. Aarhus University (enrolled 2010).
18. Havelund, Birgitte Mayland: Clinical aspects of hypoxia-inducible factors in colorectal cancer [Kliniske aspekter af hypoksi-inducible faktorer ved colorectal cancer]. University of Southern Denmark (enrolled 2009).

19. Herrmann, Rochus: Investigation of dosimetric and radiobiological models for particle therapy. Aarhus University (enrolled 2009)
20. Hoff, Camilla: Importance of Hemoglobin Concentration and its Modification for the Outcome of Head and Neck Cancer Patients treated with Radiotherapy. Aarhus University (enrolled 2007)
21. Kaiser, Franz-Joachim: Novel Dosimetry Methods in Heavy Charged Particle Beams. Aarhus University (enrolled 2010)
22. Kallehauge, Jesper: Functional Imaging for Individualized Adaptive Radiotherapy in Locally Advanced Cervical Cancer. Aarhus University (enrolled 2010)
23. Kertzscher, Gustavo: Real-time radiation dosimetry for improved patient safety in brachy therapy. Danish Technical University (enrolled 2010).
24. Korsager, Anne Sofie: Evaluation of autosegmentation strategies in hybrid medical imaging. Aalborg University (enrolled 2011)
25. Lassen, P. The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. Aarhus University, project completed 2010.
26. Laurberg, Tinne: A study on age-dependent tumorbiological characteristics among low-risk breast cancer patients. [Et studie af aldersafhængige tumorbiologiske kararkteristika blandt lavrisikopatienter med brystkræft]. Aarhus University (enrolled 2011).
27. Laustsen, Søren R: Functional magnetic ressonanse scans in patients with brain tumors. [Funktionel magnetisk resonans scanninger hos patienter med hjernetumor]. Aarhus University (enrolled 2011).
28. Lønbro, Simon: Resistance training and dietary supplements as intervention for regaining muscle mass following radiotherapy in head and neck cancer patients. Aarhus University (enrolled 2009)
29. Lyngholm, Christina: Breast Conserving Therapy (BCT) Cosmetic outcome and longterm adverse reactions in the DBCG 89-protocol. Aarhus University (enrolled 2009)
30. Mohamed, Sandy: Image guided radiotherapy in cervical cancer. Aarhus University (enrolled 2011).
31. Møller, Søren: Clinical applications of O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET in patients with gliomas. Copenhagen University (enrolled 2010)
32. Mortensen, Hanne Rahbek: Reduction of dysphagia-related morbidity in head and neck radiotherapy. Aarhus University (enrolled 2010)
33. Mortensen, Lise Saksø: 4D biological imaging of hypoxia in human tumours. Aarhus University (enrolled 2008)
34. Nawroth, Isabel: Intervention studies for Radiation-induced fibrosis (RIF) using RNA interference. Aarhus University. Project completed 2011.
35. Nielsen, Martin Skovmos: Precision and accuracy in Image Guided RT. Impact of NiTi stent for lung cancer patients. Aalborg University (enrolled 2010)
36. Nielsen, Mette Bak: Role of extensive surgery with or without interstitial brachytherapy in advanced primary or locally recurrent rectal cancer. Aarhus University (enrolled 2009)
37. Nielsen, Tine Bjørn: Organ motion - 4D imaging and treatment. University of Southern Denmark (enrolled 2009)
38. Noe, KØ. Deformable Image Registration for Use in Radiotherapy. Aarhus University, project completed 2009.
39. Nygaard, Ditte Eklund: Modelling of positional tumour variations in 4D [Modellering af positionelle tumor-variationer i 4D] Copenhagen University (enrolled 2009)
40. Ottosson, Rickard: Monte Carlo based treatment plans for radiotherapy: Evaluation and optimization of modern treatment planning and treatment techniques. Danish Technical University (enrolled 2010)
41. Pagh, Anja: Aarhus University (enrolled 2010)

42. Petersen, Stine Elleberg: Morbidity in patients with prostate cancer treated with radiation therapy. Aarhus University (enrolled 2010)
43. Ravkilde, Thomas: Dose delivery for moving targets with and without tracking. Aarhus University (enrolled 2011)
44. Rønjom, Marianne Fenn: Radiation-induced hypothyroidism in head-and-neck cancer. University of Southern Denmark (enrolled 2011)
45. Sander, Lotte: Side effects following use of a Ni Ti stent as a marker in radiotherapy of prostate cancer [Bivirkninger efter brug af Nikkel Titanium stent som markør ved intenderet kurativ strålebehandling for prostatacancer]. Aalborg University (enrolled 2010)
46. Schytte, Tine: Clinical advantages and disadvanteges of optimized radiation therapy and planning as a respiratory guided planning and rotation IMRT in conjunction with altered radiation dose and the addition of radiation potentiating drugs [Kliniske fordele og ulemper ved optimeret stråleplanlægning og terapi som respirations vejledt planlægning og rotations IMRT sammenholdt med ændret stråledosis og tillæg af stråleforstærkende medicin]. University of Southern Denmark (enrolled 2009)
47. Serup-Hansen, Eva: Tumourmarkers and the predictive value of MRI and PET-CT scans in concomitant chemoradiotherapy of anal cancer [Tumormarkører og den prædiktive værdi af serielle MR og PET-CT scanninger ved konkomitant kemostrålebehandling af analcancer]. Copenhagen University (enrolled 2010)
48. Skyt, Peter Sandegaard: Three-dimensional dosimetry in radiotherapy using new polymer materials and optical tomography. Aarhus University (enrolled 2009)
49. Søndergaard, Jimmi: Image guided tumour boost of localized unifocal c. vesica urinaria [Billedvejledt tumorboost af lokaliseret unifokal c. vesica urinaria: Et fase I/II project]. Aarhus University, project completed 2011
50. Sørensen, BS: Influence of tumour microenvironmental factors on endogenous markers of hypoxia. Aarhus University, project completed 2009.
51. Sveistrup, Joen: Radiotherapy treatment of prostatecancer – Effect, sideeffects, and ability to function [Strålebehandling af prostatacancer - Effekt, bivirkninger og funktionsevne]. Copenhagen University (enrolled 2010)
52. Thor, Maria: Prediction of adverse effects in pelvic radiotherapy incorporating normal tissue position and biology patterns. Aarhus University (enrolled 2010)
53. Thörnqvist, Sara: Robust treatment planning to account for variations in target position and function for RT of locally advanced prostate cancer. Aarhus University (enrolled 2009)
54. Thorsen, Lise: Impact of adjuvant radiotherapy to the internal mammary lymph nodes in the treatment of early lymph node metastasizing breast cancer. Aarhus University (enrolled 2010)
55. Toustrup, Kasper: Tumour Microenvironment, Hypoxia and Gene Expression Signatures in Squamous Cell Carcinomas of the Head and Neck. Aarhus University (enrolled 2007)
56. Tramm, Trine: Gene expression analysis on RNA extracted from archival paraffin-embedded tissue from a cohort of breast cancers. Aarhus University (enrolled 2007)
57. Wiechec, Emilia. Characterization of new breast cancer susceptibility genes with impact on prognosis and design of novel anticancer therapies. Aarhus University, project completed 2010.
58. Wojdacz, Tomasz. Methylation Sensitive High Resolution Melting (MS-HRM) - development and application in cancer research and diagnostics. Aarhus University, project completed 2010.
59. Worm, Esben: Liver tumour motion during radiotherapy. Aarhus University (enrolled 2010)
60. Wright, Pauliina: Development and modelling of image-guided adaptive radiotherapy strategies for bladder cancer. Aarhus University, project completed 2010.

Appendix 4: Dissertations by CIRRO affiliated students

PhD degree

1. Elstrøm, UV. Image-guided adaptive radiotherapy of head and neck cancer. PhD Thesis, Faculty of Health Sciences, Aarhus University. To be defended June 17, 2011.
2. Lassen, P. The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. PhD Thesis, Faculty of Health Sciences, Aarhus University. Defended June 18 2010.
3. Nawroth, I. Intervention of radiation-induced skin fibrosis by RNA interference. PhD Thesis, Faculty of Science, Aarhus University. Defended May 19 2011.
4. Noe, KØ. Deformable Image Registration for Use in Radiotherapy. PhD Thesis, Faculty of Science, Aarhus University. Defended October 1 2009.
5. Søndergaard, J. Intensity-modulated image guided radiotherapy of bladder cancer: Clinical implementation and early outcome. PhD Thesis, Faculty of Health Sciences, Aarhus University. Defended April 1, 2011.
6. Sørensen, BS. Influence of tumour microenvironmental factors on endogenous markers of hypoxia. PhD Thesis, Faculty of Health Sciences, Aarhus University. Defended November 6 2009.
7. Wiechec, E. Characterization of new breast cancer susceptibility genes with impact on prognosis and design of novel anticancer therapies. PhD Thesis, Faculty of Health Sciences, Aarhus University. Defended May 28 2010.
8. Wojdacz, TK. Methylation Sensitive High Resolution Melting (MS-HRM) - development and application in cancer research and diagnostics. PhD Thesis, Faculty of Health Sciences, Aarhus University. Defended June 4 2010.
9. Wright, P. Development and modelling of image-guided adaptive radiotherapy strategies for bladder cancer. PhD Thesis, Faculty of Health Sciences, Aarhus University. Defended October 26, 2010.
10. Christensen, B. Postmastectomy breast reconstruction. Evaluation of factors influencing early and long-term outcome. PhD Thesis, Faculty of Health Sciences, Aarhus University. To be defended June 14, 2011.
11. Toustrup, K. Development of a hypoxia targeted gene expression classifier in squamous cell carcinomas of the head and neck. PhD Thesis, Faculty of Health Sciences, Aarhus University. To be defended August 18, 2011.

Masters degree

1. Kofoed, T. Image quality of 4DCT scans. Master's Thesis, Niels Bohr Institute, University of Copenhagen. May 2009.

Appendix 5: CIRRO affiliated senior scientists

1. Alsner, Jan. Associate professor, AUH. WP01 leader. WP coordinator.
2. Andersen Claus. Associate professor, Risø-DTU. WP08 leader.
3. Andreassen, Nicolaj. MD PhD, AUH.
4. Bangsgaard, Jens-Peter. Medical physicist, RH. CAK.
5. Bassler, Niels. Associate professor, AU.
6. Behrens, Claus. Physicist PhD, Herlev.
7. Bentzen, Lise. MD PhD, AUH.
8. Brink, Carsten. Associate professor, OUH. WP05 leader.
9. Busk, Morten. Senior scientist PhD, AUH
10. Carl, Jesper. Chief physicist, Aalborg. WP07 leader, CAK
11. Engelholm, Svend Aage. Professor MD, RH. IP11 coordinator.
12. Eriksen, Jesper Grau. MD PhD, OUH
13. Fledelius, Walther. Postdoc, AUH
14. Grau, Cai. Professor MD, AUH. Scientific coordinator. CAK
15. Hansen, Olfred. MD PhD, OUH. IP02 coordinator. CAK
16. Havsteen, Hanne. MD PhD, Herlev. IP13 coordinator
17. Helt-Hansen, Jakob. Senior scientist, Risø-DTU
18. Horsman, Mike. Associate Professor, AUH.
19. Høyer, Morten. Associate professor MD, AUH. IP06 and IP08 coordinator.
20. Jakobsen, Anders. Professor MD, Vejle. IP09 coordinator. CAK
21. Johansen, Jørgen. MD PhD, OUH
22. Korreman, Stine. Director of Physics Research, RH. WP06 leader. CAK.
23. Kristensen, Brian. Chief physicist, Herlev. CAK
24. Larsen, Rasmus. Professor, DTU.
25. Lauritzen, Bent. Head of programme, Risø-DTU. CAK
26. Laursen, Louise Vagner. Academic coordinator, postdoc. AUH
27. Lindegaard, Jacob. Associate professor MD, AUH. IP10 and IP 12 coordinator.
28. Lühr, Armin. Postdoc, AU.
29. Muren, Ludvig. Associate professor, AUH
30. Nielsen, Thomas. Postdoc, AUH
31. Nordsmark, Marianne. MD PhD, AUH. WP02 leader and IP05 coordinator.
32. Nørrevang, Ole. Chief physicist, AUH
33. Offersen, Birgitte. MD PhD, AUH. IP03 coordinator.
34. Østergaard, Leif. Professor, AUH. WP04 leader.
35. Overgaard, Jens. Professor MD, AUH. Director. IP01 coordinator
36. Overgaard, Marie. MD, AUH. IP03 coordinator.
37. Pedersen, Erik Morre. MD PhD, AUH
38. Petersen, Jørgen. Senior scientist PhD, AUH.
39. Petersen, Peter Meidahl. MD PhD, RH. IP08 leader.
40. Poulsen, Per Rugaard. Associate Professor, AUH.
41. Skogholt, Peter. Medical physicist, Vejle Sygehus.
42. Sørensen, Brita Singers. Postdoc, AUH.
43. Sørensen, Thomas Sangild. Associate professor, AU. WP03 leader.
44. Specht, Lena. Professor MD, RH. IP04 coordinator.
45. Tanderup, Kari. Associate Professor, AUH. WP coordinator.
46. Vogelius, Ivan. Postdoc, RH. WP09 leader.
47. Wojdacz, Tomasz. Postdoc, AU.

Appendix 6: Status for Intervention Protocols

The detailed status of the Intervention Protocols is listed below:

- **CIRRO-IP010109 – Identification of tumour hypoxia by ^{18}F-FAZA PET scanning in patients with operable head and neck carcinoma** [Bestemmelse af tumor hypoksi med 18F-FAZA Positron Emissions Tomografi i tumorer hos patienter med operabel hoved-hals karcinom (DAHANCA 23)] PI: Lise Saksø Mortensen, AUH. Status: Activation expected fall 2011.
- **CIRRO-IP010209 – Prognostic value of ^{18}F-FAZA PET scans following primary radiotherapy in patients with head and neck carcinoma** [Den prognostiske værdi af 18F-FAZA Positron Emissions Tomografi hos patienter med hoved-hals karcinom efter primær strålebehandling (DAHANCA 24)] PI: Lise Saksø Mortensen, AUH. Status: Protocol active. 26 patients accrued. Participating departments: Aarhus, Odense.
- **CIRRO-IP010309 – Resistance training and dietary supplements as intervention for regaining muscle mass following radiotherapy in head and neck cancer patients** [Styrketræning kombineret med kosttilskud som intervention til genopbygning af muskelmasse efter strålebehandling for hoved-hals cancer (DAHANCA 25A and B)]
  PI: Simon Lønbro, AU. Status: DAHANCA 25A, protocol closed, 30 patients accrued. DAHANCA 25B, protocol active. Participating departments: Aarhus, Odense, Herlev.
- **CIRRO-IP020109 - NARLAL - Navelbine And Radiotherapy in Locally Advanced Lung cancer** PI: Olfred Hansen, OUH. Status: Protocol active. 35 patients accrued. Participating departments: Odense, Aarhus, Aalborg, Vejle, Herlev, Rigshospitalet.
- **CIRRO-IP020209 - TARLAL - Tarceva And Radiotherapy in Locally Advanced Lung cancer** PI: Olfred Hansen, OUH. Status: Protocol active. 8 patients accrued. Participating departments: Odense, Aarhus, Vejle.
- **CIRRO-IP030109 – A randomized trial of Partial Breast Irradiation (PBI) in node-negative early breast cancer.**
  PI: Birgitte Offersen, AUH. Status: Protocol active. 181 patients accrued. Participating departments: Aarhus, Aalborg, Vejle, Odense, Rigshospitalet, Herlev.
- **CIRRO-IP030209 - Hypofractionated adjuvant radiotherapy in node-negative early breast cancer** PI: Marie Overgaard, AUH. Status: Protocol active. 489 patients accrued. Participating departments: Aarhus, Aalborg, Vejle, Odense.
- **CIRRO-IP040110 - Reduction of risk of long-term complications of radiotherapy for lymphomas.** PI: Lena Specht, RH. Status: Protocol active. 70 patients accrued. Participating departments: Rigshospitalet
- **CIRRO-IP050109 - CRITICS-study: ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach.**
  PI: Marianne Nordsmark, AUH. Status: Protocol active. No patients accrued in Denmark yet. 301 patients accrued internationally.

- **CIRRO-IP060109** - **RAS-trial: Radiofrequency ablation versus stereotactic body radiation therapy for colorectal liver metastases: A randomized trial.**
  PI: Morten Høyer, AUH. Status: Protocol active. 1 patient accrued in Denmark. Participating departments: Aarhus, Odense.
- **CIRRO-IP070109 – Image guided tumour boost of localized unifocal c. vesica urinaria** [Billedvejledt tumorboost af lokaliseret unifokal c. vesica urinaria: Et fase I/II project].
  PI: Jimmi Søndergaard, AUH. Status: Protocol active. 7 patients accrued. Participating departments: Aarhus, Herlev,.
- **CIRRO-IP080109 - Hypo-RT-PC: Study on hypofractionated radiotherapy in intermediary risk prostate cancer patients** [Fase III studie om hypofraktioneret stråleterapi til patienter med prostatacancer i intermediær risikogruppe].
  PI: Morten Høyer, AUH. Status: Protocol active. 10 patients accrued in Aarhus (400 internationally). Participating departments in Denmark: Aarhus.
- **CIRRO-IP080209 - PROPEL A+B Pelvine lymph node irradiation with concomitant boost to the prostate in high risk prostate cancer patients** [Pelvin lymfeknudebestråling med samtidigt boost til prostata for prostatakræftpatienter i høj-risikogruppe: Et fase I/II studium].
  PI: Lise Bentzen, AUH. Status: Protocol active. 7 patients accrued in Aarhus. Participating departments: Aarhus. Aalborg and Odense expected to start within a month.
- **CIRRO-IP080110 – A new everyday life – Rehabilitation and mastering late effects of radiotherapy for prostate cancer** [En ny hverdag - Rehabilitering og mestring af senfølger efter kurativ strålebehandling for prostatacancer].
  PI: Karin Dieperink, OUH. Status: Protocol active. 102 patients accrued. Participating departments: Odense
- **CIRRO-IP080210 – RADICALS - Radiotherapy and Androgen Deprivation in Combination after Local Surgery** [Radioterapi og androgen deprivation i kombination efter prostatektomi]
  PI: Peter Meidahl Petersen, RH. Status: Protocol active. 4 patients accrued at RH. Participating departments: RH. OUH, Herlev, Aarhus, and Vejle expected to follow soon.
- **CIRRO-IP090109 - Watchful Waiting in rectal cancer: A prospective observational study of rectal cancer patients after concomitant chemoradiotherapy** [Watchful waiting: Et prospektivt observationsstudie af patienter med cancer recti efter concomitant strålebehandling og kemoterapi].
  PI: Anders Jakobsen, Vejle. Status: Protocol active. 15 patients accrued. Participating departments: Vejle (treating patients from other departments also)
- **CIRRO-IP090209 – Contrast enhanced transrectal ultrasound scanning of rectal cancer patients** [Kontrast forstærket transrektal ultralydskanning af patienter med rektal cancer].
  PI: Anders Jakobsen, Vejle. Status: Protocol active. 6 patients accrued. Participating departments: Vejle (treating patients from other departments also)
- **CIRRO-IP090309 – Consecutive rectoscopies in connection with pre-operative chemo-radiotherapy of rectal tumours** [Konsekutive rektoskopier foretaget i forbindelse med præoperativ kemostråleterapi af rektum tumorer på Vejle Sygehus].

PI: Anders Jakobsen, Vejle. Status: Protocol closed. 100 patients accrued. Participating departments: Vejle (treating patients from other departments also)

- **CIRRO-IP090110 – Predictive value of 18F-FAZA-PET/CT in neoadjuvant radiotherapy of patients with locally advanced cancer recti [Den prædiktive værdi af 18F-FAZA-PET/CT ved neoadjuverende strålebehandling til patienter med lokal avanceret c. recti].**
  PI: Birgitte Mayland Havelund, Vejle. Status: Protocol active. 8 pt. Participating departments: Vejle.
- **CIRRO-IP100110 – Observational study on contact X-ray and transanal endoscopic microsurgery in curative treatment of rectal cancer (CONTEM).**
  PI: Jacob Lindegaard, AUH. Status: Activation expected fall 2011.
- **CIRRO-IP110110 – Feasibility study for the purpose of introducing hyoxia tracers in patients with cervical cancer** [Feasibility studium med henblik på introduktion af hypoksi tracer hos patienter med cervixcancer].
  PI: Henrik Hansen, RH. Status: Protocol not yet initiated. Clinical use of Cu-ATSM PET tracer is pending.
- **CIRRO-IP120109 - EMBRACE: An International Study on MRI-guided Brachytherapy in Locally Advanced Cervical Cancer.**
  PI: Jacob Lindegaard, AUH. Status: Protocol active. 52 patients accrued in Aarhus (370 in total). Participating departments in Denmark: Aarhus.
- **CIRRO-IP120111 – IMAP: Repetitive Functional Imaging & Mapping Biopsies in Locally Advanced Cervical Cancer.**
  PI: Jacob Lindegaard, AUH. Status: Protocol active. 2 patients accrued. Participating departments: Aarhus (others are expected to follow).
- **CIRRO-IP130109 – IMANAL: PET-CT scans and MRI in anal cancer patients** [PET-CT skanning og MR ved analcancer].
  PI: Hanne Havsteen, Herlev. Status: Protocol closed. 22 patients accrued. Participating departments: Herlev.
- **CIRRO-IP130111 - ^{18}F-FMISO-PET, ^{18}F-FDG-PET/CT, DWI-MR, and DCE-MR scans as predictor of response on chemo-radiotherapy of patients with anal cancer** [^{18}F-FMISO-PET, ^{18}F-FDG-PET/CT, DWI-MR og DCE-MR scanninger som prædiktorer for respons på kemoterapi/radioterapi af patienter med analcancer].
  PI: Eva Serup-Hansen, Herlev. Status: Protocol active. 7 patients accrued. Participating departments: Herlev.

Appendix 7: International Advisory Committee Report

CIRRO IAC report August 2010

General comment
The Lundbeck Foundation Center for Interventional Research in Radiation Oncology (CIRRO) forms a very important and well coordinated research project in cancer care focusing on radiotherapy. As such it is a unique research project which is an example for the rest of the world. Of special relevance is the ambition to engage the entire Danish radiotherapy network. Within CIRRO there is an excellent opportunity for interaction between basic, translational, and clinical research which brings together modern biology, physics, and medicine. The latter will have a major spin-off for the quality of health care in Denmark and elsewhere. The first signs of further advancement of the quality of the radiotherapy treatment in Denmark are already visible, as for example illustrated at the recent BiGART meeting in Aarhus. Overall, the CIRRO project brings Denmark in an internationally very competitive position in new developments in cancer research.

- **Scientific relevance of project**

  Radiotherapy is a mainstay of modern cancer treatment that likely will further increase in importance in the future. Already now it is applied in half of the cancer patients contributing to the cure and/or palliation of cancer patients. This project deals with central aspects of the radiotherapy process. Only systematic research as performed in the CIRRO project is in the position to advance science and patient outcome in this field.
- **Scientific method, expected data quality and project design**

  The strength of this project is the optimal use of the special expertise available in the participating centers. The design of the different work packages is performed jointly by a group of experts which results in very thoroughly thought through ideas and realistic work programs. Many of the projects build on ongoing clinical trials performed by Danish cooperative groups and add new and highly relevant aspects of translational research in different fields. Already now some parts of the translational research are incorporated in the ongoing trials, which will result in better quality of the treatments and guarantee very reliable data coming out of these trials. The attempt to involve most if not all Danish centers in patient recruitment is of great importance as is the strive to engage also centers in other countries. Formal contacts with prestigious research groups outside Denmark have been established. However, attempts to exchange young investigators between laboratories worldwide have not yet been entirely successful and strategies to achieve this should be encouraged.
- **Organizational structure and management**

  Both leading investigators have a large expertise in running this type of projects and are well equipped to make this CIRRO project a success. They are both critical and positively

stimulate the participants and demonstrate excellent coordinating activities. The structure itself builds on and further extends existing collaboration between Danish cancer centers and research groups including the multi disciplinary trial groups. Some of them have a longstanding proven high activity whereas others are more recently initiated. It appears as if CIRRO has been instrumental in initiating their work. The PhD projects performed in the work packages are well coordinated and are integrated in the Danish graduate school in clinical oncology (DAFKO). The projects make optimal use of the funding supplied by the Lundbeck Foundation by fully exploiting the resources including heavy investments available in medical departments, biology and physics laboratories. There are regular meetings and a well established internal evaluation process of the projects. The website increases visibility and allows evaluation of the progress made within the CIRRO work packages.

- **Initiation of project and accomplishments in the first year and a half**

  It appears that all projects in the nine work packages have been initiated and based upon the annual report and presentations they all appear to be running well. Most of the described clinical trials have also been activated and in addition a few more trials have been added. We recognized that several translational research activities have been added to the ongoing clinical projects but at the same time we noticed that such activities could be added even to a greater extent. It could be an advice for CIRRO to enhance incorporation of the strong translational activities e.g. functional imaging, genetic analyses, and use of fiducial markers, into existing clinical trials and new clinical projects. Another advice for CIRRO would be to analyze as soon as possible the results of translational studies performed with retrospective material for the design of future interventional clinical trials. Accomplishments in terms of scientific output are, considering the short time period of CIRRO, fully in line with ambitious expectations.

- **Advice for the future**

  For the coming 3½ years it is suggested to take into account the strength of the basic and translational research of the Danish cancer centers to incorporate this into newly designed clinical trials. This will also be of help to guarantee successful continuation of the CIRRO at the end of the 5 year funding period. Another suggestion is to intensify the communication between the basic and translational researchers and the clinicians involved in the clinical trials. In this way new and innovative trials where radiation is incorporated can be created.

Copenhagen, August 26-27, 2010.
Harry Bartelink
Michael Baumann
Bengt Glimelius
Philip Poortmans