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ALLEGRO



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ALLEGRO – Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy

Final Report

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Executive summary

The ALLEGRO Project was funded by EURATOM for two years to provide some initial answers and more importantly pointers for where the efforts should be put into new research. As well as helping with important decisions for radiotherapy, research into the normal tissue risk from radiotherapy has the potential to complement and contribute to current EURATOM initiatives in low-dose radiation risk research (e.g. DoReMi). The project has now completed the second year and has successfully finished each of the planned tasks.

The ALLEGRO consortium is made up of 13 partners from 8 European countries. The partners are leading research institutes, hospitals, and university medical departments, all active in the development of new radiotherapy modalities, or optimising current modalities.

The project was divided into seven work packages, four of which comprised research and technological development (RTD) tasks. These four work packages focussed respectively on:

1. measurement and modelling of the normal tissues doses from conventional and emerging radiotherapy;
2. assessment of the accuracy with which the normal tissue doses can be estimated for treatment planning optimisation and research purposes;
3. investigation of state of the art NTCP modelling and investigation of the suitability of NTCP models validated on conventional treatments to predict normal tissue risk from novel modalities;
4. investigation of the possibility of using existing clinical databases for deriving a dose-response model for the incidence of second cancer following radiotherapy.

A further work package provided an expert forum to review the results of the RTD tasks and to produce a series of reports defining the current state of the art, providing recommendations to the radiotherapy community on how the current knowledge can best be exploited to optimise radiotherapy treatment planning, and to give priorities and directions for the future normal tissue risk research effort.

Among the most important messages that come from the project are:

- A coordinated effort is required to generate and maintain clinical databases designed to facilitate research into both normal tissue complications and radiotherapy-induced second cancers, with sufficient patient treatment detail, follow-up, and compatibility to permit large multi-centre studies;

- NTCP models can provide valuable prediction of normal tissue risk, but should take account of confounding factors as well as dose parameters, and should be validated in each clinical application;
- More effort needs to be put into moving beyond the single-discipline epidemiological phenomenological approach to the incidence of radiation induced damage endpoints to a greater understanding of the underlying mechanisms
- There is a need to develop methods to optimise decision-making on multi-dimensional multi-timeframe risks, that takes account of short term and long term benefits to the patient as well as medical-ethical and medical-legal considerations.

Summary description of the project context and the main objectives.

Project context

Modern radiotherapy is a very successful cost-effective way of treating cancer. As the world population ages, there will be more and more cancer cases, and as many as 50% will be treated with radiotherapy. So as new and even more effective radiotherapy technologies are developed, it is becoming more important not just to cure the cancer, but to look after the quality of life and survival of the patient in the decades following the treatment. How can we optimise the treatments now in order to minimise the risk of long-term normal tissue damage or a second cancer 10 - 20 years later? Should we be worrying about small tissue volumes getting a high dose more than large volumes getting a low dose? Should we spend the money and use protons or carbon ions rather than photons because they are safer? The answer is that we really don't know yet.

The ALLEGRO Project has been funded by EURATOM for two years to provide some initial answers and more importantly pointers for where the efforts should be put into new research. As well as helping with important decisions for radiotherapy, research into the normal tissue risk from radiotherapy has the potential to complement and contribute to current EURATOM initiatives in low-dose radiation risk research (e.g. DoReMi). The project has now completed the second year and has successfully finished each of the planned tasks. We now know what we do and don't know about normal tissue risk, and we know what we must do to further our knowledge. It remains now to make sure the message gets to the right people who can act on the ALLEGRO recommendations.

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Project activities

The project was designed to cover every aspect of radiation damage to normal tissue from current and emerging treatment modalities. The first two RTD work packages investigated how well we know what dose normal tissues outside the treatment volume receive, and how accurately we can estimate these doses on individual patients. Most radiotherapy dosimetry is focused on accuracy within the treated volume. The dosimetry protocols, on which the prescribed dose is based, are designed to give an accuracy of the order of 0.5%, to a reference point. This calibration is transferred to the treatment planning system (TPS), which attempts to calculate the dose to the treatment volume with an accuracy of the order of 5%. But outside the treatment volume, the normal tissue dose is not nearly so well known. It is seldom measured, and the TPS is not optimised for accuracy in this region. The project addressed this uncertainty, both with out-of-field measurements, and with an investigation of the ability of a TPS and other software to calculate the doses to normal tissue for the purpose of risk assessment.

The next work package used powerful statistical methods to determine whether normal tissue complication probability (NTCP) models could be used with confidence to optimise individual treatments, and whether there were limits to the applicability. NTCP models are

not widely used clinically because the profession has not yet been persuaded that, for the work of implementing a model, there is a proven advantage in risk prediction for individual patients over the traditional “tolerance dose” constraints. The project sought to explore the state of the art of NTCP methodology and test how effective it could be. Another important question is: how well can a normal tissue risk predictor developed on one treatment modality (eg 3D CRT) predict the risks from another modality (eg, IMRT, IMPT) where the normal tissue dose distributions will be quite different? This question is crucial if this methodology is to be used to argue for the use of one modality being safer than another (especially if it is more expensive). This too was addressed in the work package.

A further work package tested the possibility of using existing clinical databases to derive the dose-dependence of the risk of second cancer following radiotherapy. Currently, the induction of a second cancer from the radiation received during therapy for the first is an established risk. It also seems a probability from the dose-response risk factors used in radiation protection, based on the atomic bomb survivor data. However, because of difficulty both with finding suitable data bases, and with reconstructing the doses received, so far there has been no way of determining with any accuracy the second cancer risk from a particular treatment. This work package used 4 different databases to investigate the problems involved and how to find a solution.

The results of each of these work packages were reviewed by experts from each of the participating institutions, together with a specially selected scientific advisory committee, to produce a series of focused documents defining the current state of knowledge and identifying all of the gaps that limit the confidence with which a clinician can predict the normal tissue response from a particular treatment on an individual patient.

The project is now completed. Each of the RTD work packages gave quite clear results, and the recommendations, both for the clinical application of the results, and for further research, have been written. A series of papers currently in preparation will be submitted to the radiotherapy clinical and research journals. A dedicated issue of the Green Journal (Radiotherapy and Oncology) is planned for 2012 to feature ALLEGRO papers. There will also be approaches made to EC and international bodies in order to promote the recommendations.

Description of the main S & T results/foregrounds

The ALLEGRO project was divided into seven work packages, four of which comprised research and technological development (RTD) tasks. These four work packages focussed respectively on:

1. measurement and modelling of the normal tissues doses from conventional and emerging radiotherapy;
2. assessment of the accuracy with which the normal tissue doses can be estimated for treatment planning optimisation and research purposes;
3. investigation of state of the art NTCP modelling and investigation of the suitability of NTCP models validated on conventional treatments to predict normal tissue risk from novel modalities
4. investigation of the possibility of using existing clinical databases for deriving a dose-response model for the incidence of second cancer following radiotherapy.

The activities and results from each of these tasks are summarised below.

Work package 2: measurement and modelling of the normal tissues doses

Out of field measurements

The aim of tasks 2.1-2.4 was to investigate experimentally the dose absorbed outside the treatment volume in radiation therapy with a particular effort in the characterization of the secondary neutron field and its contribution to the dose. The investigation included irradiations under treatment conditions using high-energy photons delivered with IMRT and ions (proton and carbon) modulated with passive and scanning techniques. Various experimental methods were applied in order to characterize the rather complex radiation fields which are generated by scattered primary radiation and secondary beam fragments including neutrons. The measurements were carried out for different systems and under different conditions, investigating both simple (water phantom) and complex (anthropomorphic phantom) geometries. The results provided an overview of all common radiation treatment modalities and the influence they have on the out-of-field dose profile. Furthermore the experiments were simulated with the Monte Carlo code PHITS for benchmark of the code for both ion and photon therapy.

The results collected with the simple and complex geometries indicated strongly that a treatment with photons is characterized by the highest out-of-field dose values independently of the distance from the target. For photon treatment, the photoneutron spectrum peaked around 1 MeV independently of the position and the yield decreased slowly with increasing distance to the volume directly irradiated. The neutron contribution to the absorbed dose appeared to be over one order of magnitude lower than the primary beam except in the out-of-field region at the surface, where the contribution of photons is negligible. Moreover, the out-of-field neutron fluence at the surface is constant independent of the distance from the field edge. This result proves that most of the neutrons are produced in the accelerator head rather than in the patient itself and that a shielding might be of great efficacy for reducing the patient exposure to unwanted radiation. (These results are in a paper to be submitted to Radiotherapy and Oncology.) A comparison of the neutron contribution to the lateral dose fall-off for

different machine types (Varian, Elekta, Siemens) suggested a significant difference between manufacturers: Elekta machines produce significantly less neutron dose than the other manufacturers. The measurements showed nearly no difference of neutron dose with regard to treatment technique (3D CRT, VMAT, IMRT).

Independent of the delivery technique, the dose produced by charged particles decreases to less than 1% of the target dose at 1.5 cm and less than 0.1% at 3 cm from the field edge. For photons, the corresponding dose levels are reached at about 4 and 25 cm, respectively. At the present stage, the comparison between passive and active modulations cannot bring to a final conclusion: the scanning technique proved to be optimal if coupled with carbon ions because it minimizes fragmentation along the beam line and does not affect significantly the lateral scattering unlike the case of protons, where the presence of the collimator seems to spare heavily the tissue surrounding the PTV. However, unlike protons carbon ions exhibit a significant dose tail behind the target which can cause severe problems for sensitive organs located there.

The overall agreement between the experimental dose profiles and the data simulated with PHITS is promising. The code can reproduce with fair accuracy the physical processes responsible for the behaviour of the lateral dose fall-off for both photons and ions. A further benchmark is necessary for a correct prediction of the secondary particle yield and energy spectrum, especially following photon irradiation.

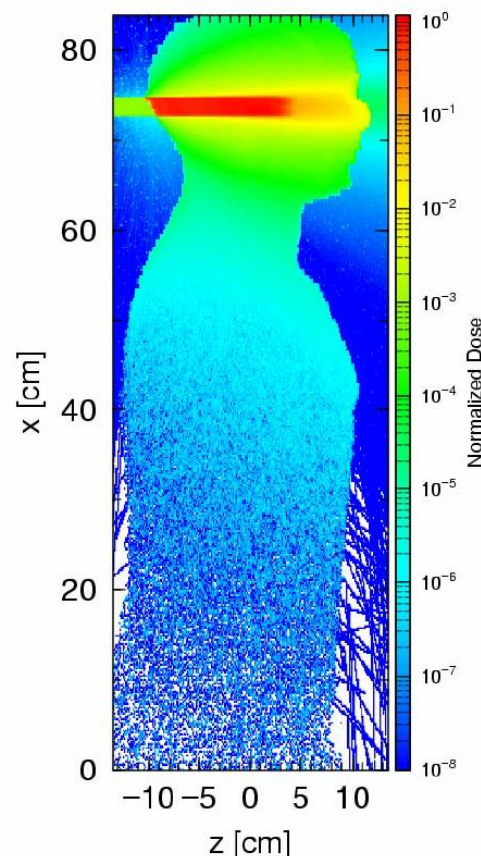


Fig.3.4.19 2D dose profile simulated by PHITS inside the Rando phantom irradiated with carbon ions at GSI.

Biological effect of neutrons

Neutrons are produced by nuclear reactions of photons, protons and heavier ion beams when penetrating matter. The precise knowledge of their abundance and energy distribution is required for the estimation of their contribution to effects in healthy tissue in radiation therapy. The biological effects were analysed by means of a biophysical model, the Local Effect Model (LEM), which has been successfully implemented already in the framework of treatment planning for ion beam therapy.

Application of the LEM to neutron radiation requires the knowledge of the secondary charged particle spectra induced by neutrons as a function of the neutron energy. These spectra were determined using PHITS Monte Carlo simulations for monoenergetic neutron beams from 2.5 -70 MeV, covering the range of energies for which experimental data are reported in the literature.

Since the secondary charged particle spectra induced by neutrons represent a mixed radiation field, the LEM is applied using algorithms developed originally for application in treatment planning for ion beam tumour therapy. In a first step, the approach is validated by means of comparison to experimental data obtained with monoenergetic neutron radiation, where good agreement is observed. Good agreement is also observed in an example for comparison to *in-vivo* data; discrepancies at very low doses can be attributed in this case to low-dose hypersensitivity, which typically is only observed for the low-LET reference radiation.

Strategies for the application of the approach to broad neutron energy distributions are presented and are shown to represent the experimentally observed dependence of the RBE on the mean neutron energy in therapeutically relevant neutron beams.

Furthermore, it is demonstrated that the LEM can be applied also to complex biological endpoints like cell transformation. Therefore, an extension of the LEM is presented, which is based on the simultaneous calculation of cell killing and transformation induction as represented by two coupled linear-quadratic dose response curves. This approach is validated by comparison to experimental data for cell transformation after charged particle irradiation for a wide range of particle species and energies.

Finally, it is demonstrated that the LEM is also able to predict the general features of the dose response curves for cancer induction after neutron irradiation in animal models. Comparisons for lung cancer induction as well as leukaemia induction in mice show a good agreement with experimental data.

In conclusion, the LEM represents a useful tool for estimation of cell transformation *in-vitro* and secondary cancer induction *in-vivo* following exposure to neutrons. Although direct transfer of results from *in-vivo* studies to clinical cases will in general not be possible on the level of absolute risks, the model will be helpful in estimations of relative risks required for the ranking of different treatment options.

Concomitant dose from radiotherapy image-guidance

An extensive literature review was performed to discover the work performed on concomitant dose over the last 10 years. This was supplemented by also studying the literature on both out-of-field radiotherapy doses and second cancer. It was decided at an early stage in the project to estimate and measure doses to critical organs instead of using effective dose.

Contact was made with the group working on out-of-field radiotherapy doses to: a) confirm the sites of the body to be studied; b) the standard positions of critical structures within standard anthropomorphic phantoms. It was also decided that the most important concomitant doses to study were CBCT doses and Tomotherapy doses. Varian and Elekta (linac manufacturers) use kVCBCT; Tomotherapy uses MVCBCT. Some work was also done estimating the doses from kV radiography and MV portal imaging.

Anthropomorphic phantoms were used for both the pelvic and thoracic regions of the body, and the various critical structures close to the radiotherapy target volumes were identified in both phantoms. The doses from the various imaging techniques were measured at these sites. Doses to organs further from the target volume were estimated using the ImpaCT calculator. For portal imaging a special technique was used, making use of the treatment planning system at MVH, to determine doses at critical organs. Doses for kV radiography were estimated using published sources.

A comparison of dose from CBCT and Tomotherapy was made with typical radiotherapy out-of-beam measurements. It was seen that if total CBCT doses (based on daily imaging) were used:

1. The maximum concomitant dose (with daily imaging) approached about 50% of the total dose at organs close to the target volume for prostate treatments, but less than 30% for breast treatments.
2. Tomotherapy imaging doses were generally found to be less than those from conventional kV CBCT depending on the image quality selected. Individual user specified protocols can also reduce dose compared to manufacturers' default settings.
3. For the pelvis, MV portal imaging doses were found to be similar to kVCBCT doses, however, for the thorax kVCBCT doses are generally lower than those from portal imaging.
4. kV radiography doses were found to be typically a factor of at least 1/10 of kVCBCT dose.
5. for kV radiography on specialist equipment (such as Cyberknife) the dose increases because of the frequency with which imaging takes place during the individual fraction.

Dose to the foetus from electron intra-operative radiotherapy for breast cancer

The majority of pregnant women with early breast cancer are usually offered mastectomy instead of conservative surgery and conservative breast therapy (i.e. conservative surgery and whole breast radiotherapy). Conservative breast cancer treatment in pregnant women would require the delay in adjuvant radiotherapy until after delivery. Moreover, still some women decide to abort in order to receive a planned breast cancer therapy. Intra-operative radiotherapy (IORT) given during breast conservative surgery might reduce the dose to the uterus, compared to whole breast radiotherapy, and thereby it might constitute the breast conserving treatment for pregnant women.

Task 2.7 of ALLEGRO consisted of two parts: detailed physics measurements on a phantom under simulated treatment conditions, and in vivo measurements on (non-pregnant) patients during treatment.

Phantom measurements

An anthropomorphic Rando phantom was used to simulate patient treatments. Thermoluminescent dosimeters (TLD) were distributed through phantom slices from 15cm to 25cm in the cranio-caudal direction, from sternum to femora head, in order to measure the possible range of doses that could be received by a foetus at various stages of development. Measurements were taken using two different electron treatment machines (NOVAC-7 and LIAC), and compared with a conventional whole-breast photon treatment using a CLINAC-2100. In order to measure the protective effect from electron collimator scatter, measurements were also taken with and without lead aprons of various thicknesses over the abdomen.

The measurements gave a range of doses all less than 4mGy from the electron treatments, and this could be further reduced by more than a factor of 10 with the use of a 2mm Pb apron. By contrast the doses from conventional whole-breast photon treatment gave a potential dose to the foetus of the order of 100 times as great.

Clinical measurements

Measurements were taken on 5 patients using TLDs located on the skin in sub-diaphragmatic and supra-pubic positions, and using an applicator to measure intrauterine dose. The doses measured were all consistent with the phantom measurements and show that the intrauterine dose in the breast cancer patients undergoing IORT can be kept below 10 mGy. Initial indications are that IORT might be considered safe in the first pregnancy trimester, when the foetus is in the lower part of pelvic region. The results of this study will help patient counselling and, in consequence, might avoid unnecessary abortion or mastectomy in pregnant women diagnosed with breast cancer.

Work package 3: estimation of normal tissue doses for treatment planning optimisation and research purposes

Derivation and uncertainties of dose distributions in normal tissues from clinical treatments

The first part of this work package addresses the problem of extracting the information required (usually the dose-volume histogram, DVH) from clinical databases in order to implement different normal tissue complication (NTCP) probability models. An open source Matlab-based software tool was built to read different formats of DVH exports from different treatment planning systems (TPS). It can be found on SourceForge.net (<http://ntcpallegro.sourceforge.net/>). An extension of this software program relates doses to outcome in order to build own NTCP models (instead of using published parameter sets) or to validate NTCP models from literature with other institute's clinical data. Many problems, pitfalls and opportunities were found during the first modelling exercises and were helpful in Work Package 4 for the modelling of larger databases.

Another task in this work looks at the different sources of uncertainties that exist on dose estimates and corresponding calculation of NTCPs, focusing on two major uncertainties. First the calculation algorithm used in the TPS was analysed. A significant difference in probability of pneumonitis grade 2 in lung and breast patients was for instance observed when Pencil Beam (PB) plans were recalculated with AAA (a collapsed cone algorithm). The second source of uncertainty that was studied in depth was the positioning protocol used. We analysed the impact of uncorrected potential systematic setup errors in a prostate case and observed in extreme cases of antero-posterior shifts that NTCP was almost doubled for rectal

bleeding and bladder grade 2 toxicity, compared to the baseline NTCP value using the planning CT scan.

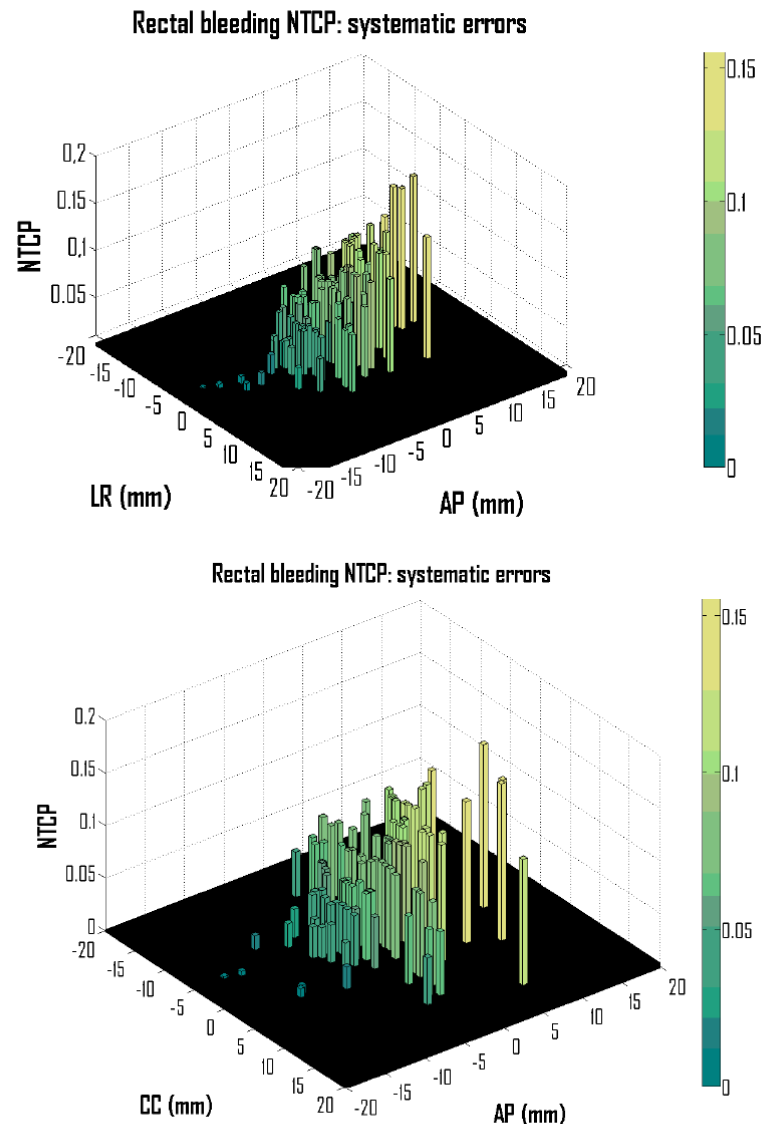


Figure 6 Impact of uncorrected systematic errors on rectal NTCP for a 3D-CRT plan to 70 Gy

Finally, the last part for this section concerned the applicability of NTCP models in the case of carbon ion treatments where the conclusion was that the resulting distribution of the RBE-weighted dose distribution reflects the expected dose distribution for photon radiation, leading to the same clinical effect under otherwise identical conditions (same fractionation, total time etc.). As such, all distributions, parameters etc. derived from the RBE-weighted dose distribution can be exactly handled as the corresponding values derived from photon fields. Therefore, classical NTCP calculations can be based directly on the DVHs as given by the treatment planning system as TRiP / SyngoPT

Performance of clinical treatment planning systems for estimating normal tissue dose

The first part of this section focuses on photon treatments. The performance of treatment planning systems using different dose calculation algorithms was studied. For this purpose, measurements were performed using Gafchromic film in a solid water phantom setup and using TLD-100 in an Alderson phantom. For both setups the TPS (designed primarily for the high-dose region) described very well the dose fall-off down to approximately 3% of the isocentric dose. At larger distances from the target the TPS (both AAA and PB algorithms) largely underestimates the dose and moreover does not provide any data beyond the limitation of the maximal field size (approximately 20 cm from the central axis).

IMRT and VMAT(RA) prostate plans were also analyzed, this resulted in a decrease of peripheral dose with RA at distances beyond approximately 18 cm due to the higher MU efficiency of this technique (lower leakage term). Concomitant exposures (daily CBCT) were seen to be small but significant in the total peripheral dose to most tissues. Generally in the range of 5–10% of this dose.

The Peridose software was tested in the peripheral positions (both in prostate and breast post-mastectomy treatments) but it resulted in large overestimations of the measured dose values up to 250%.

The neutron doses were characterized using bubble detectors (BD and BD-PND) and turned out to be relatively low compared to the photon contribution for the 10 MV treatments under analysis (<5% of the total peripheral dose). Monte Carlo simulations were performed using the PHITS code. Both a Varian and Elekta machine were modelled and simulations were compared with depth dose and lateral dose profile measurements. Also a sensitivity study was performed to test the impact on peripheral dose of different components in the beamline.

A further part of the work analyzes the measurements performed at the scanning proton treatment facility at PSI. Comparison of TLD-700 measurements to the TPS calculations shows good agreement around the PTV (located in the head of phantom). An average deviation of 20 mGy per treatment Gy was observed.

Finally, the last part looked at the carbon ion treatment and planning system (GSI). The same setup for head and neck resulted in an agreement of measurements and calculations within 3% in the high-dose region. In the fragment region beyond the target region (behind the Bragg peak) however, the TLD measurements were underestimated by almost 20% by the calculations.

Work package 4: normal tissue complication probability (NTCP) modelling

NTCP model fitting and validation

This part of the project was set up to develop NTCP-models among patients with three different tumour sites, including head and neck cancer, lung cancer and prostate cancer. With the currently available data, it was not possible to develop NTCP-models in paediatric patients.

Traditional NTCP modelling methods, such as the LKB model, do not take into account other factors than dose volume histogram (DVH) parameters. In this work package, it was clearly shown that DVH parameters are indeed important. However, it was also shown that parameters other than DVH parameters are important and significantly influence the estimated risks on radiation-induced side effects (NTCP-values). This was particularly the case in head

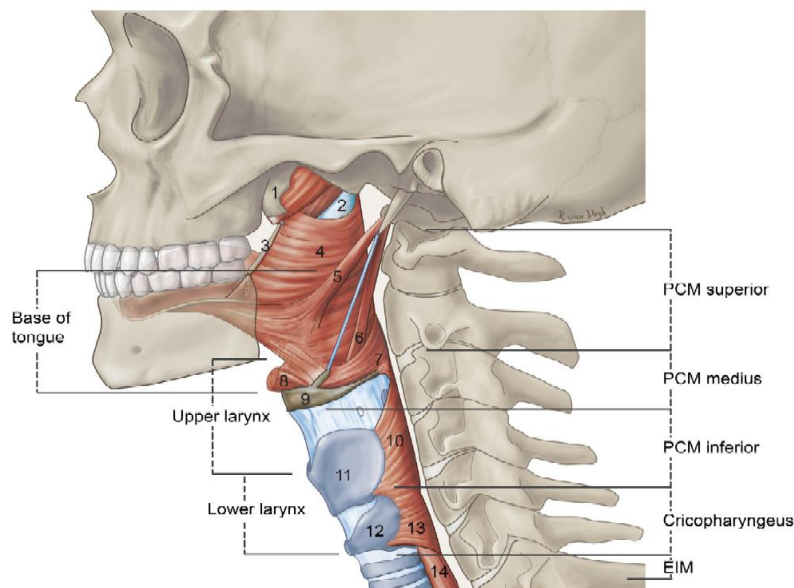
and neck cancer, in which besides DVH parameters, also age, baseline xerostomia, baseline swallowing dysfunction, the addition of chemotherapy and treatment technique were independent prognostic factors. Moreover, the performance of NTCP-models in terms of Area Under the Curve (AUC) significantly improved when these non-DVH parameters were added to the model. Similar results were found for radiation pneumonitis in lung cancer patients, in which age was also a critical factor significantly improving model performance when added to a model with the mean lung dose alone. In prostate cancer, previous abdominal surgery and cardiovascular co-morbid conditions turned out to be important.

The main message and recommendation from these findings is that when developing NTCP-models, advanced statistical learning methods are required to produce well powered models taking into account not only DVH-parameters but also other factors.

Another important message is that generalizing NTCP models from one population to another requires uniform guidelines with regard to the definition and delineation of relevant Organs at Risk (AOR). In this project, we clearly showed that differences between radiation-oncologists in OAR-contouring may lead to significant differences in the estimated NTCP-values in the same patient.

The results of the current project showed for some endpoints (e.g. xerostomia and swallowing dysfunction) that baseline function may be important. Many side effects, referred to as treatment-related side effects, are not necessarily related to radiation. E.g., swallowing dysfunction in head and neck cancer patients can also be due to tumour extension or other physical problems. Cross-sectional studies on NTCP model development do not normally take into account these baseline problems that may have a significant impact on the predictive power of NTCP-models. Therefore, clinical studies aiming at the development and external validation of NTCP models should be prospective, including baseline assessment of late toxicity, rather than retrospective and/or cross-sectional.

Figure 7: SWAORs delineated for the current project: pharyngeal constrictor muscles and related structures (1) processus pterygoideus (2) fascia pharyngobasilaris (3) raphe pterygomandibularis (4) PCM superior (5) styloglossus (6) stylopharyngeus (7) PCM medius (8) geniohyoideus (cut) (9) hyoid (1)



NTCP model validity in different treatment modalities

The main two objectives of this part of the project were: (1) to investigate if the 3D-CRT models described in D4.2 would also be applicable among patients treated with other techniques, such as intensity modulated radiotherapy (IMRT), and: (2) to investigate if emerging radiation delivery techniques such as protons would be able to further reduce the risk on radiation-induced side-effects.

This part of the project was done in head and neck cancer patients and in prostate cancer patients. Retrospectively, the available data on lung cancer and paediatric cancer patients were insufficient to validate the 3D-CRT based models in patients treated with IMRT.

An important finding was that not all 3D-CRT based models turned out to be sufficiently powerful among patients treated with IMRT. This was particularly the case for patient-rated xerostomia and sticky saliva. It should be stressed that the other 3D-CRT based NTCP models, including those on swallowing dysfunction and those developed in patients treated for prostate cancer, were also valid when treated with IMRT. The most important message and recommendation from these findings is that NTCP-models developed in patients treated with one technique are not necessarily valid among patients treated with another techniques and that external validation of NTCP-models should always be carried out when used in patients treated with a new technique.

In silico planning comparative studies were performed comparing standard IMRT (aiming at sparing the parotid glands only) with swallowing sparing IMRT (aiming at sparing the parotid glands and relevant swallowing structures) and swallowing sparing IMPT (aiming at sparing the parotid glands and relevant swallowing structures using spot-scanning protons). The results of the *in silico* planning comparative studies show that protons are significantly capable of reducing the relevant DVH-parameters resulting from the NTCP-modelling studies. In addition, when the results of these *in silico* planning comparative studies are integrated in NTCP-models, it is possible to estimate the potential benefit of these new radiation techniques in terms of NTCP-value reduction. In the current project, we can conclude that protons certainly have the potential to significantly reduce radiation-induced toxicity in head and neck cancer in the vast majority of patients. However, the actual results should be validated in well designed prospective clinical cohort studies. By using the 4-step methodology as described in the work package report, this could be done by sequential prospective cohort studies with standard follow up programs, instead of prospective randomized studies.

The link between biological mechanisms and NTCP models

The purpose of this task was to help with the development of better NTCP models that would be of more use to clinicians. It is important to consider in what ways an understanding of biological mechanisms of radiation injury can help achieving this objective.

In a top-down approach, for a number of complications induced by radiotherapy the clinical feature(s) which need to be reduced as much as possible were identified. In a second step, the experimental and clinical data were considered with the aims of identifying those gross anatomical structures and which dose distributions are leading to these complications. Finally, the pathogenic pathways and cellular and more specific anatomical and physiological parameters which have to be considered in this pathway and how the distribution of radiation

dose in time and the anatomical distribution of radiation dose within the organ at risk would influence the complication risk were determined.

Therefore, the following problems were addressed:

1. The clinically most relevant signs and symptoms of normal tissue complications in different organs (spinal chord lung, rectum, bladder, oropharynx and heart) were identified, i.e. those which cause the most significant impairment of quality of life of a patient who has been cured by radiotherapy. For each of those signs and symptoms, separate target structures, separate pathogenic mechanisms and separate NTCP models may have to be considered.
2. The probable pathogenic and pathophysiological mechanisms involved in the development, progression and compensation of the specific manifestations of those normal tissue complications were analysed. These mechanisms were shown to differ in their respective dependence on single cell radiation effects and on the interaction of cells and tissues within or between irradiated and non-irradiated parts of one or more organs.
3. The dependence of severity and of incidence of the different functional (physiological) and structural (anatomical, pathological) normal tissue effects on dose and dose distribution in clinical and experimental systems were analysed. It was demonstrated that volume-based criteria alone are adequate to model NTCP for many signs and symptoms. Other criteria of 3-D anatomical dose distribution have to be considered, resp. developed.

It would be desirable to base NTCP modelling on objective symptoms which can be measured, such as lung density, pO₂ in the blood, saliva flow, compliance of the bladder or the rectum. However, the clinical complications reported by the patients show often a poor relationship to those results of measured tissue changes, indicating that at present the understanding of which set of biological responses in the end constitute patient-reported complications is still poor. Since the quality of life after cure has been achieved is the overriding criterion for clinically useful NTCP models, the subjective judgement of the patient has to be given priority in the evaluation of signs and symptoms of normal tissue complications. This usually would require well designed structured interviews or questionnaires.

Currently most models are based on DVHs instead of a full 3-D dose distribution in NTCP modelling which assumes that “location” is not a parameter, i.e. that all radiation effects are uniform. The results of clinical and of experimental studies in animals, in which various organs received high precision partial organ irradiation have demonstrated that this assumption is not generally valid.

The biological mechanisms potentially involved in the pathogenesis of normal tissue complications of radiotherapy can be classified as either

1. Single cell effects such as “cell death”, sterilisation of stem cells, inhibition of proliferation. These effects are probably all caused by radiation-induced DNA damage, in particular double strand breaks and subsequent chromosomal damage. They are local effects and follow steady, non-threshold dose response relationships, usually adequately described by the linear-quadratic model which also describes the results of fractionation experiments well. Few of the analysed signs and symptoms of late normal tissue damage follow this pathogenic pathway.

2. Tissue effects which depend on the interaction between different cells and cell populations within organs or between organs such as inflammation or differentiation. Cell differentiation is the progressive restriction of the developmental potential and the increasing specialisation of function which leads to the formation of specialised cells in tissues and organs. The demonstration of a strong involvement of regulatory factors in radiation-induced differentiation proves that radiation-induced differentiation is the result of multiple interactions and thus cannot be described as single cell effect.
3. The most obvious sign of early normal tissue radiation damage is inflammation, characterised by erythema and oedema. Early inflammation occurs in all normal tissues after high radiation doses. Chronic inflammation, on the other hand, is one of the key signs of late normal tissue damage in most organs and tissues. Whereas early inflammation appears to be directly induced by radiation damage to endothelial cells or radiation-induced hypoplasia, chronic inflammation is initiated and propagated by the late radiation damage to other tissue components as a secondary inflammatory response to impaired tissue function. The key target cells for the induction and propagation of the inflammatory process are endothelial cells and macrophages. Both mechanisms, differentiation and inflammation are secondary consequences of radiation damage to target cells or target structures and usually involve activation of a network of signalling molecules such as cytokines. Thus the dependence of effect on dose, fractionation and dose heterogeneity is unlikely to follow directly that of single cells. Moreover, the effects are not limited to the irradiated cells and tissues. Dose and volume thresholds are likely.
4. Effects which result from alterations of tissue structure such as vascular injury. The most important of those effects is micro-vascular damage which can lead to atrophy, Another characteristic late radiation effect in most tissues is the development of telangiectasia which tend to cause overt haemorrhage (e.g. in the rectum) or distinct haemorrhage (e.g. in the brain leading to stroke). These effects are loco-regional and restricted to areas of volumes which received a dose in excess of a threshold dose which appears to be >30 Gy. The pathogenic pathway leading to reduced capillary density, ischaemia and atrophy starts with radiation-induced changes in the capillary endothelial cells which may begin as a single cell effect. The further development of damage is dominated by an orchestrated process in the entire tissue which may take decades in human organs to lead to the characteristic features of late normal tissue damage after radiotherapy. Whereas capillary density reduction and telangiectasia occur throughout the tissue volume that is exposed to supra-threshold doses, are the functional and clinical consequences dependent on the volume and particularly on the specific physiology of the affected part of the organs.
5. Other, less well defined functional changes such as alterations in neuromuscular function that are particularly important in the pathogenesis of radiation effects in the gastro-intestinal system and the urinary tract. The most commonly recorded effects are changes in muscular tone and rhythmic contraction activity. Some of these are triggered by the autonomous or the intrinsic nerve plexus, others are directly induced in smooth muscles. They are not single cell effects but depend on complex inter-cellular and inter-tissue communication by highly specific molecular signals and electrophysiological impulses. Some data suggest a dependence on irradiated volume, although the main characteristic is that the consequence of these mechanisms is the response of the entire organ and not of the particular irradiated organ volume alone. Little data exist on the dose and dose fractionation dependence.

This differentiation between underlying mechanisms is important since these different classes of effects are likely to differ with regard to the shape of the dose response relationship: some may have a clear threshold, others may have a steady increase with dose. Also the fractionation effect and the time factor may differ, and in particular, the effects relating to volume irradiated are different for the different classes of mechanisms. There is urgent need for experimental studies on the biological mechanisms involved in the development of different complications in the same organ using suitable animal models as well as in-depth clinical investigations using refined functional imaging techniques.

Work package 5: second cancers following radiotherapy

Cohort studies on large populations of long-term cancer survivors have demonstrated that definitive, curative radiotherapy is associated with a significant risk of radiation-induced second cancers. For the common, adult-onset cancers this risk is in the order of ~1% absolute risk at the time of treatment, for those patients who survived more than 5 years, this risk increases to several percent. The size of the risk is different for different types of primary cancer and increases with decreasing age of the patient at the time of primary treatment. The types of second cancer also vary depending on age, sex and follow-up time. The risk of second cancers is increased both close to the target volume, i.e. in the part of the body which receives >10 Gy as well as at larger distance from the target volume, i.e. in the low dose volume which receives <1 Gy total dose. More and more, radiotherapists become concerned about the possible long-term consequences of these low radiation dose exposures of their patients. The more successful radiotherapy is becoming with curing cancer patients and offering them a normal life expectancy, the larger will be the population of cancer survivors who have received significant total body low dose radiation exposures and may develop treatment-induced second cancers.

The main concern of treatment planning in radiotherapy today is the reduction of moderate and severe signs and symptoms of late normal tissue damage. However, many new treatment techniques, which are expected to reduce the risk of severe normal tissue complications, lead to a larger body volume which is irradiated with doses of <2Gy. The latter, however, have been demonstrated to lead to a small but significant risk of radiation-induced cancer.

Clinical follow-up studies after curative radiotherapy suggested that for the same dose to the planning target volume (PTV), different treatment techniques are not only associated with different late normal tissue complications but also different rates of second cancers. This demonstrates that the inevitable risk of treatment-related second cancers could be reduced but optimising the dose distribution outside the PTV. This requires, however, knowledge on the dependence of second cancer risk on dose and anatomical dose distribution in the different organs at risk.

The methods proposed by ICRP for risk estimation are based on mean organ doses which, however, are not suitable for the particular situation of radiotherapy, as has been repeatedly stressed by ICRP by stating that these methods and the recommended effective doses and their associated risk should never be used in radiotherapy risk estimation. It has been demonstrated that this methods results in risk estimates which are orders of magnitude false. ICRP rather recommends the use of risk factors and risk estimation procedures derived directly from clinical studies. The cohort studies which have been widely discussed by radiation oncologists are suitable to estimate the existence and the overall size of the risk, which is in the same order of magnitude for adult-onset patients as the risk of severe normal

tissue complications and even higher in juvenile and paediatric patients treated for cancer using radiotherapy. However, the method of cohort studies does not provide the information needed to identify the dependence of risk on dose and anatomical dose distribution within the organs at risk. This crucial information required for the further optimisation of cancer treatment is most likely derived from case-control studies which relate the odds ratio to parameters of individual dose distribution. On the basis of these considerations, the aim of WP5 was to explore the possibility to perform such case-control studies on four large cohorts to cancer survivors. The data should eventually be used as a basis for biological models of the dose-response relationship of tumour induction by ionising radiation.

WP5 used existing clinical databases to investigate the relationship between 3-dimensional radiation dose distribution from radiation therapy and the occurrence of second cancers. With this, WP5 aimed at identification of the feasibility and optimal requirements for research databases to extract suitable data; exploitation of the results of dose assessments in WP2 to refine dose estimates, particularly outside the moderate/high-dose volume available in the data, analyses of dose-dependence and latent times of second tumours in relation to the position of the initial radiotherapy volume and the site in the organ or tissue where the second tumour originated, and draft mathematical models to develop optimization criteria for treatment planning to include minimizing the risk of radiotherapy-induced second cancers.

Second cancers in the single institution series in Ulm.

The single institutional clinical database in Ulm covers the time from 1981 to 2007. It includes about 22000 patients, about 12000 survivors > 1 year, and 61000 observation years. Nearly 500 cases of potentially radiogenic 2nd cancers were identified (339 female, 154 male). In a Kaplan-Meier plot, the incidence rate was nearly constant at ~1% per year for the patients at risk. Six out of seven leading 2nd-cancer entities namely colorectal, lung, head-and-neck, upper-GI-tract, pelvic-gynaecologic, and prostate cancer had similar incidence-rates. Only the rate for breast cancer was significantly higher. 32% of all 2nd cancers were breast cancer (table 1) and 80% of these were contra-lateral breast cancer. This high incidence may relate to predisposition: not only BRCA but numerous other confounders of breast cancer have been described, none of which were recorded in our database.

Irrespective of the (im)precision of dosimetry, a higher dose will definitely occur at the inner quadrants of the contra-lateral breast compared with the outer quadrants. If this higher dose establishes an increased risk, then the spatial distribution of single-quadrant breast cancers would be altered in radiogenic 2nd breast cancer compared to the spontaneous 1st disease. However, in the patients who eventually developed contra-lateral breast cancer, no such redistribution could be demonstrated from the data.

A broad dose gradient was connected with colorectal 2nd cancer after 1st breast, 1st pelvic-gynaecologic or 1st prostate cancer. In the latter two entities, numerous 2nd cancers were in-field", so that planning software (Varian Eclipse) could be used for dosimetry, thus improving the precision. A case-control analysis with 33 cases and 99 matched controls was conducted, but at the level of gross average doses, there was no significant difference between 2nd tumour sites and corresponding control sites ($p = 0.19$ for 1st breast, $p = 0.30$ for 1st pelvic-gynaecologic and $p = 0.94$ for 1st prostate cancer).

Second primary lung cancers among patients with breast cancer in the Danish Cancer Registry

The study was a cancer-registry based cohort study. The cohort includes all Danish women operated for early breast cancer and treated according to the 1982 through 2007 DBCG guidelines in the period 1982-2008. Second primary breast cancer was not considered as an outcome in this study since registration in the Danish Cancer Registry has not been consistent over the years. Therefore, it would be difficult to distinguish between a recurrence of the initial breast cancer and a new primary second breast cancer. We further only included the first second primary cancer in women diagnosed with two or more cancers in order to avoid the additional effect of any treatment given.

Potentially radiotherapy induced cancer sites were selected as follows: salivary glands, thyroid gland, esophagus, lung, pleura, bone and soft tissues, pharynx, larynx, stomach, liver, gallbladder heart and mediastinum, pancreas and colon. The risk of developing a second primary cancer was estimated by the standardized incidence ratio (SIR). The cohort included 46,176 one-year survivors, 23,627 (51%) women were treated with postoperative radiotherapy and 22,549 (49%) did not receive any radiotherapy. The median latency in years from initial breast cancer treatment to the development of a second primary cancer was the same for the two groups with 6 years among the irradiated women vs. 7 years among the non-irradiated women. By the end of 2008 with a median follow-up of 6 years (range 1-26), 2,595 second primary cancers had occurred, including 1,148 potentially radiotherapy induced second cancers. From the total number of second cancers 283 cases of ill-defined and unspecified cancers were subtracted; 130 cases among the irradiated women and 153 cases among the non-irradiated women.

The standardized incidence ratio (SIR) for potentially radiotherapy induced sites was 1.2 (95% CI 1.1-1.3) among the irradiated women and 1.0 (95% 0.9-1.1) among the non-irradiated women. The risk though for developing a potentially radiotherapy induced second solid cancer increased over time among the irradiated women. SIR for these sites increased from 0.8 (95% CI 0.7-1.0) 1-4 years after treatment to 1.9 (95% CI 1.4-2.4) +15 years after treatment among the irradiated women. In absolute numbers lung cancer was the most frequent second cancer with an increase of SIR of >4 at +20 years after treatment among the irradiated women compared to the general female Danish population.

In the original study design a case-control study, with 3 controls for each case, was planned. A total of 448 cases of potentially radiotherapy induced cancers were found among the irradiated women. In the case-control study with a 1:3 distribution 1,344 controls needed to be found. For the controls a CT scan or an x-ray had to be found in order to determine the exact anatomical location for dose determination as for the site of the primary breast cancer in the corresponding case. Since most patients in this project were treated before 3D CT scans were standard protocol in the treatment planning most patients did not have an accessible CT scan. Furthermore most patients used as controls did not have an x-ray or CT scan done prior to their breast cancer operation. Hence, it was not possible to retrieve the images needed in the controls in order to conduct a case-control study.

Second cancers from the Dresden cancer registry

The case-control study was based on the departmental (RadOnc) database and the Dresden Clinical Cancer Registry (DCR) in patients with any first gynaecological cancer treated with radiotherapy. The analysis was initiated to compare radiation doses at the second cancer site in the cases to the doses in the same site in the controls that did not develop the second cancer.

Based on both RadOnc and DCR, a total of 51 index cases could be identified for which dose reconstruction could be performed. For patients where the second tumour occurred at a distance of >5 cm from the initial treatment field (“distant” tumours”), the software PERIDOSE was applied. At a closer distance to the high dose treatment area, dose reconstruction was performed with the treatment planning system. A total of 202 controls were identified. For this, all paper files of potential controls (ca. 900) had to be checked, some of which were missing in the archive. For very old or very young cases, only few controls matched with age. The most frequent criterion for exclusion, however, was that the follow-up time of the controls was shorter than the latency time of their cases. No significant or systematic difference in the dose between cases and their controls was detected. The data retrieved are insufficient as a basis for identification of a dose-dependence for the induction of second primary tumours or for modelling second cancer induction.

Second cancer following breast cancer treatment in the institutional data base of the European Institute of Oncology in Milan.

This study was based on the institutional database 19,000 early breast cancer patients treated with EBRT and/or IORT between 1996 and 2007 at the European Institute of Oncology (IEO), Milan, Italy. The study aimed at a comparison of RT doses in the second cancer site in the index patients that developed second malignancy to the RT doses in the same site in the control case patient that did not develop the second cancer.

Altogether 256 second cancer were reported, 195 occurred in the patients treated with RT and this subgroup was considered as subject of this analysis. Ninety three out of 195 second cancer patients were excluded: 87 patients because RT was performed in different institutions and 6 because RT data were missing. The remaining 102 cases included 77 second cancers observed after post-operative EBRT and 25 second cancers observed after IORT. For each of the index cases, 5 controls were selected from the institutional database of breast cancer patients treated with RT, independent of RT techniques. After all, only 6 index cases were feasible for the analysis, in which proper dose reconstruction could be performed. Five index cases were matched with 3 control patients (15 control patients) and 1 index case was matched with 2 control patients only. The doses in second primary site in the index cases and the same anatomical site in the control cases were very low and similar.

The limitations of the study are related to its retrospective character. The treatment plans in electronic form were not available (Only paper treatment sheets and simulation films could be requested from the clinical archive). The simulation CT scans of the patients included exclusively the thorax. Short follow-up after the primary treatment of breast cancer further reduced the number of available cases.

Strategy for modelling cancer risk from calculated organ doses.

It was planned to use the results from task groups 5.1-5.4 for obtaining organ specific dose-response estimates. Unfortunately only task 5.1 could present reliable data usable for such estimates. From with data from task 5.1 it was possible to perform a case-control analysis for secondary Oesophagus and colorectal cancer.

The cases and controls were grouped into 4 dose groups. The mean age at exposure and the mean attained age were determined for each dose group. ODDS ratio was calculated for each dose group and normalised to the lowest dose level (0-1Gy). The ODDs ratio was calculated by applying the temporal time patterns from the A-bomb survivors for colorectal and oesophageal cancer. Excess absolute risk was fitted based on a mechanistic model for cancer induction including fractionation. It was assumed that EAR in the lowest dose category was predicted by the A-bomb survivor data.

The analysis resulted in a predicted dose-response relationship with maximum tumour induction at 1-5 Gy. The uncertainty of the shape of the dose response curves results from low case numbers and dosimetric inaccuracy, the latter related to poor documentation of tumour position (including unavoidable organ motion), and shortcomings of the PeriDose software. Despite these uncertainties, a linear or purely exponential character of the true curve appears unlikely and even at high doses the EAR remains above zero.

Work package 6: review of the results and recommendations

Clinical recommendations

Based on a review of the methodology and results of the QUANTEC project (Quantitative Analyses of Normal Tissue Effects in the Clinic) and of the results of our own work packages the ALLEGRO consortium draw the conclusion that individual patient data on pre-treatment status, treatment details, outcome, and in the future also on biological data are necessary to allow the analysis of the impact of specific parameters e.g. dose, dose-volume or confounders on the risk of individual patients.

Results of ALLEGRO also indicate that useful information on dose-volume parameters with consideration of clinical co-factors may be obtained from highly condensed minimal data sets such DVH from individual patients if these are linked to reliable baseline and outcome parameters. More informative results, however, may be obtained from spatially resolved full 3D dose distribution datasets.

Including data on the risk of radiation induced secondary cancers into today's treatment planning optimization process currently remains very difficult, e.g. due to treatment techniques which are no longer in place today. Therefore conclusions on reducing the risk of secondary cancers need to remain general and need mostly to address avenues for further research to obtain more reliable evidence in the future. Here long-term follow-up times and large databases with minimal datasets including basic dosimetric data allowing approximating the dose at the site of the secondary tumour are an issue. Furthermore, future research should include more simplified methodologies for assessing the patient neutron dosimetry and dose distribution in general.

The use of more conformal radiation techniques and technologies, e.g. particle therapy, only makes sense if all other steps of the treatment planning and application chain are optimized

and potential advantages need to be demonstrated in well-designed prospective clinical investigations.

Multidimensional and time course specific relative risk assessment is a newly emerging field of basic research which holds substantial promise for further improving outcome of radiotherapy, thereby increasing health and quality of life of the European citizens.

Recommendations for paediatric radiotherapy

For decades paediatric oncologists and paediatric radiation oncologists have spent considerable resources and intellectual energy to refine the treatment of paediatric malignancies in a collaborative effort through the conduct of clinical trials. A significantly higher percentage of paediatric patients are entered into clinical trials compared to the adult population. Modern, 3D radiation therapy and treatment planning are ubiquitously available since the mid 90's, i.e. for at least the last 15 years. 3D-treatment planning permits organ specific dose volume analysis in proximity or in distance to the treated tumour. Yet, in the past and at present there is a significant disconnect between the concerns for radiation related side effects with its present ability to determine organ specific dosages and the almost universal lack of collecting prospectively organ specific dose volume related data. Except possibly single institution studies, even most recent major multi-centric studies only collect basic rudimentary data which will in the future not permit a more detailed risk analysis and determination of a dose-volume-age dependent threshold of long-term side effects.

With few notable exceptions European multi-institution-based late effects efforts (for example "British Cancer Survivor Study") are presently dominated by the United States based efforts of the "Childhood Cancer Survivor Study" organization. This includes late effects analysis and recreation of distant dose distribution by anthropomorphic model analysis of previously and actually delivered treatments.

European efforts should focus on creating a European, multi-institutional, centralized database for paediatric radiotherapy. Present efforts to collect radiotherapy data are insufficient and ill-defined to collect appropriate data. An initial task force should be created with the mandate to create a template and define a standard for data collection appropriate to capture modern therapy based dose distributions; this presently simply does not exist.

NTCP Models:

European efforts should focus on supporting the development of paediatric normal organ NTCP models. The present NTCP models in paediatric patients are insufficiently defined. They are single institution efforts only. At present there is no standardized, accepted NTCP model developed within the European Union. Only few normal organs are studied thus far. The mandate of an initial task force should be to create appropriate NTCP models, and to incorporate models into database collection in order to facilitate validation.

Radiobiology:

European efforts should focus on supporting translational radiobiology to understand the effects of partial organ dose deposition on the anatomic and physiologic development of normal organs as well as the risks of second malignant neoplasm induction (SMN induction). We have limited or no knowledge on the effects of partial organ irradiation in children given the fact that modern RT leads to sharp dose gradients within normal tissues. The mandate of an initial task force would be to study effects of partial dose deposition and varying dose rates

within normal organs in-vitro, in-silico and in-vivo (= for organs close to the radiation target). In addition a study should be conducted to better understand the low-dose effects on induction of second malignant neoplasms (= for organs distant to radiation target).

The special case of particle therapy:

All issues outlined above apply also in general to particle therapy. Particle specific issues are related to the “variable” of RBE (Relative Biologic Effectiveness), which is particle dependent, dose rate dependent etc. Particle therapy specific is the issue of neutron production and its effects on induction of second malignant neoplasm. Particle therapy in Europe is presently in a transitional phase from research-based facilities to wide spread clinical use through hospital-based particle therapy facilities. There is a window of opportunity to unify efforts early on before the general tendency of isolated, single institution efforts take their natural course and will de facto prevent or significantly delay potential collaborative efforts. European-wide efforts by unified particle therapy community could be an example for radiotherapy in general.

The fact cannot be over emphasized that present data acquisitions will by and large not provide answers in the future due to lack of detailed data collection. However, in particular in particle therapy, all present and future centres routinely collect organ-specific dose-volume histogram data. The choice is either to create resources to prospectively collect these data now, or to decide to postpone allocation of resources for a later time, at likely significantly higher costs.

We have only begun to develop the tools to analyze the past. Standards and models are urgently needed. Although prospective data collection in general meets the highest standards of data collection and provides highest statistical power, the significant draw-back will be that late effects occur late, i.e. children require usually a minimum follow-up of 3-5 years, a mean follow-up of approx. 10 years and induction of SMN estimates require a mean follow-up of probably 10-15 years. Alternatively, treatment planning and treatment delivery based on 3D-treatment plans is available for approximately 15 years. A significant series of clinical studies within the European Community have been completed and long term follow-up with documentation of late adverse events and second malignant neoplasm induction are available or about to be available in the next years. A thought should be given to a project to retrospectively “mine” the treatment plans, create dose volume histograms of organs that are already part of the treatment plan and correlate those with late events. This alternative method would be able to provide essential data within several years and facilitate the development of NTCP modelling. In addition, it would provide very important data that will influence treatment considerations now instead of in 15 years time.

As it relates to particle therapy, the specific issue of neutron production and its energy dependent, dose dependent and dose rate dependent effects on SMN induction of various normal tissues close or distant to the treated target, should be addressed in a separate project. Proton therapy has been embraced as a superior alternative to photon therapy by the paediatric oncology community and will be increasingly implemented in Europe as new centres become operational. Since literally every proton centre has pledged its commitment to paediatric proton radiation oncology, it can be anticipated that in the future possibly the majority of children treated with radiation therapy will be referred to proton centres. This tendency is already present in the US and is likely to continue. Therefore, to understand the neutron production issue will become increasingly important, if not already now, then in the mid-term future.

Recommendations to manufacturers

This report gives and explains ten recommendations to manufacturers of radiotherapy equipment (particle therapy facilities, medical electron linear accelerators, devices for image guided radiation therapy and treatment planning systems). The aim of these recommendations, based on the status of the current technology in clinical radiotherapy and furthermore, on data and results generated by the ALLEGRO project, follows the overall objective of ALLEGRO to initiate a process of improving the quantitative understanding of the size and the consequences of therapy-related normal tissue doses and of reducing this dose and its effects. Thus, the seven device-related recommendations on treatment facilities (particle therapy units and conventional medical electron accelerators as well as imaging equipment) can contribute to normal tissue dose reductions. The three recommendations on treatment planning systems primarily support the ALLEGRO objective on investigations of the magnitude and distribution of radiation doses and spectral fluences in normal tissues. This knowledge is a precondition for gathering clinical data of high quality as a basis for the development of valid radiobiological models of normal tissue damage and second cancer induction. The recommendations have been given according to their needs in terms of the objectives formulated by ALLEGRO and the authors did not restrict themselves to such recommendations which can be clinically implemented immediately. Therefore, the recommendations cover a wide time scale and complexity for realization. As examples, the given recommendations on optimizing the photon production and head shielding in linear accelerators or on optimized collimator designs for passively scattered proton beams may reach the clinic within a few years, whereas setting improved data and operational standards for treatment planning systems is expected to become only realistic, if this concern is widely supported by the community of radiation oncologists and medical physicists and an intensive discussion on this issue can be successfully initiated with TPS developers.

Future research recommendations for normal tissue dosimetry

Out-of-field dosimetry

Out-of-field dosimetry is a complex matter and covers a number of specializations (i.e. diagnostic radiation, megavoltage radiation, neutron dosimetry and charged particle dosimetry). A common ground and language needs to be established for all of these. One of the major hurdles is the use of confusing language to denote, the dose and the biological effects thereof.

Neutron Dosimetry

The contribution of neutrons to the whole body dose appears to be quite large in a number of classical treatments. If historic data is to be used to refine the available risk models, there should be adequate quantification of this dose. Measurement of neutron doses is by no means a trivial task. Many of the detectors have a limited energy response range and some of the devices are too unwieldy to use in clinical settings. To provide clinically relevant information the proposal is to validate methodologies to calculate neutron contributions, be it through monte carlo simulation or alternatively deterministic calculative means.

Monte Carlo simulations

A proposal is to use Monte Carlo simulations to provide the necessary data from patient treatments. However, as was shown in this project, it is not enough to have a good monte carlo dose deposition modality. The correct implementation for the specific treatment machine used is of utmost importance to obtain accurate results. Therefore, optimization needs to be performed for out-of-field dose instead of in-field. In addition, stochastic methods like Monte Carlo suffer from inaccuracies for low dose contributions. They therefore need to be adapted to perform better in low dose regions by using variance reduction techniques. Most current codes have been optimized to provide accurate prediction in high dose volumes like the treated volume. Furthermore, not all codes provide data on neutron contributions.

Biological effects

The use of a concept like RBE causes confusion to many of the practitioners and the public. The concept of RBE denotes the same biological effect for a given modality as the effect obtained from the same dose by a reference modality (usually, photon irradiation from ^{60}Co or a 250kVp source) the same dose delivered using a different modality. This looks like a straightforward concept, however the biological effect envisaged can be different depending on the what biological effect is looked at. This means that the same dose using the same modality can have a host of different RBE's. To wit if one is interested in therapeutic efficacy, short term complications, long term complications, or the generation of secondary tumours. In all cases the physical dose is the same but the effects can be vastly different. It can also occur that the RBE depends on the dose delivered as well as the dose rate. Biological effects need to be more standardized, RBE seems to be a bad way of dealing with these issues as it depends on particle, energy and dose. Future research should focus on generating a framework where a more adequate quantification of biological effects as a function of dose (or maybe even some other quantity) is introduced and validated.

Secondary tumour risks

The risk models for secondary tumours are currently not well-established. Two major questions remain low and high dose responses. The most well-known is the question of a threshold dose. The current consensus is that for the purpose of radiation protection there is no threshold, which clearly is the most conservative measure. The high dose response is also not well known, some models suggest a constant tumour induction after reaching a given dose level, while others predict a decrease in tumour induction with higher doses. The data currently used in these risk assessments is flawed in that the data available at these dose levels is limited as well as inaccurate with regard to the dose absorbed. In patients that underwent radiation therapy the doses delivered to parts of the patient provide the correct levels to refine the available models. Secondary tumour risk models can benefit from a more in-depth analysis from low doses due to medical treatments, to do this it will be necessary to provide adequate reconstruction of the dose deposited in this case. In short, secondary tumour risk models need to be re-evaluated using correct dosimetry of the out-of-field dose and medical data is the only way to provide sufficient data on the risk models. However, as can be gleaned from workpackage 5 only a large scale effort can gather sufficient data to eliminate the current uncertainty.

Newer charged particle modalities

From the data presented here, there is an indication that the use of charged particle treatment, reduces the out-of-field doses by an order of magnitude compared to classical treatments and two orders of magnitude compared to more complex photon treatments (IMRT, VMAT). If and when the risk models are incorporated in the choice what treatment modality is to be used it becomes clear that the use of protons (be it passive or scanning) or heavier charged particles gain a clear advantage. In the case of the latter treatment it is not yet clear how the changed biological effectiveness of the radiation will affect the risk models. This project has also shown that it is possible to incorporate such models in treatment planning but the validation thereof is still elusive. As the data in this project shows, it is clear that when late effects are a deciding factor then there is an increased probability that these newer modalities will become mainstream sooner than later.

Recommendations for research into the underlying biological mechanisms of normal tissue complications

The development of improved NTCP models should be based on the following principles that has be derived from the analysis of clinical and experimental data:

1. Improved NTCP models should be sign and symptom specific rather than organ specific.
2. This means that some organs or anatomical sites may be included in multiple NTCP models for different complications.
3. The optimisation of treatment plans requires the careful balance of the impact of different signs and symptoms on the quality of life of the patient which goes far beyond the present severity scoring systems and requires the development of novel “cost functions”.
4. Only in rare situations is the entire organ the OAR that needs to be delineated. Different signs and symptoms require the delineations of different structures or sub-volumes at risk
5. The dependence of severity of signs and symptoms within one organ on treatment-related factors (e.g. dose, dose per fraction, overall treatment time and dose inhomogeneity in the critical sub-volumes) are likely to be vary between signs and symptoms within one organ since underlying radiobiological mechanisms are different.
6. There is urgent need for experimental studies on the biological mechanisms involved in the development of different complications in the same organ using suitable animal models as well as in-depth clinical investigations using refined functional imaging techniques.

Recommendations for research into the development and application normal tissue complication (NTCP) models

The current project showed that NTCP-models with high predictive power include prognostic factors related to radiation dose distributions as well as demographic, patient-rated and other treatment-related variables. Therefore, studies aiming at developing NTCP-models should take into account dose distribution parameters as well as patient-related, demographic and other treatment-related parameters. Moreover, to select the most relevant prognostic factors, advanced statistical variable selection methods are required. In addition, proper statistical modelling requires well powered studies with sufficient numbers of subjects included.

Endpoints for NTCP modelling should be chosen carefully and candidate prognostic factors for each specific endpoint should be selected based on clinical, dosimetric and radiobiological considerations. It is essential to determine the specificity of the endpoints related to organs at risk. Many endpoints are not specifically induced by radiation but may be related to pre-existing co-morbid diseases. Therefore, clinical studies aiming at developing or validating NTCP models should always be prospective and should include baseline assessments of the endpoints of that study.

NTCP-models developed in patients treated with a certain radiation delivery technique should be validated among patients treated with a new radiation technique, in particular when the distribution of the prognostic factors that are included in the NTCP-model is different.

Recommendations for research into the dose-risk relationship for second cancers

Direct carcinogenic effects of ionising radiation are known, but need further, molecular clarification (e.g. sensitive pts.). This must include in-vitro-, animal-, and clinical studies.

Indirect tumour induction through (hyper-proliferative) late “deterministic” sequelae of radiation exposure are known, e.g. for large intestine and bladder. Their risk in other tissues requires investigation. Dose-volume effects must be studied (e.g. risk of minimal, but very high-dose volumes in brachytherapy, which requires animal as well as clinical studies).

Mechanistic and clinical data are required to improve/validate risk models for second tumours in radiation oncology.

Effects of chemotherapy/biologicals in combination with irradiation need to be investigated.

Recommendations on the requirements for databases to support normal tissue risk research

Detailed and structured follow-up information on the effects of irradiation on normal tissues and on the induction of secondary cancers is necessary to further improve the quality of radiotherapy. Currently there are many clinical databases potentially available. However, all these databases suffer from substantial shortcomings. For example data sets with limited follow-up are prone to miss important information in particular if relatively rare events such as cancer induction are studied. In addition such slow evolving data usually are obtained over several generations of radiation treatment equipment and therapeutic approaches. This hampers gravely the retrieval of correct scientific information, which then prospectively can be utilized in the interest of minimizing risks in the European population. These obstacles can only be overcome by high quantity and high quality prospective databases. Such data repositories are also mandatory for future state of the art individualized risk reduction based on molecular markers. A de-centralized or a centralized scenario for multi-institutional and/or multi-national databases is conceivable. In the ALLEGRO consortium most of the investigators concluded that de-centralized databases are more likely to be successful. Demands for such databases include: compatibility, storage of baseline data, all treatment and follow-up data, linked to biobank and modern technologies allowing multicentre retrieval and analysis. These efforts need to be accompanied by the development of the necessary legal framework by national and European policy makers. A group of acknowledged European experts should be established to provide a framework ensuring scientific validity and compatibility of databases. Manufacturers should be motivated to support these endeavours.

In the following the 10 most important conclusions and recommendations from the ALLEGRO project, which are crucial for valid databases for research into normal tissue damage and induction of secondary cancers, are summarized.

1. Long term follow-up must be considered an essential part of quality control measures. Therefore strategies have to be generated to motivate follow-up, maybe through an adequate reimbursement of the routine costs.
2. National and European policy makers must develop the necessary legal framework which allows retrieval of anonymized patient-related data for research into radiation protection.
3. Databases must be powerful, i.e. large enough to address the relevant questions. Thus data from national or even multinational networks need to be jointly analyzed.
4. Databases need to record individual patient data.
5. Strong efforts must be made to profit as much as possible from the data already existing through the pooling of prospective and retrospective clinical data sets.
6. Similar structures and contents for databases are needed. Data must be retrievable also after long times.
7. A recognised expert group must provide short pragmatic reports on minimal requirements. Required “minimal data sets” needed from every patient and regulations for data formats should be specified. This ensures data quality and guarantees uniformity and compatibility.
8. Appropriate endpoints for scientific analysis need to be defined. Feedback loops to the minimal dataset definitions are necessary.
9. Efforts to create such database structures must be started as soon as possible. The efforts should accompanied by regular test runs to identify problems which in the long term hamper high quality scientific analysis.
10. Manufacturers must be motivated to support modern databases fulfilling these requirements without additional work and costs for the departments.

Further information on the recommendations

For more details on the ALLEGRO Project recommendations please refer to the website (see below) where the full text of each report will be available.

Expected results and impact of the ALLEGRO Project

The ultimate purpose of the ALLEGRO project is to be able to take medium and long term normal tissue harm into account in making radiotherapy treatment decisions. It is essential to be able to predict medium and long term effects in order to plan treatments and evaluate the competing new technologies.

The impact of the project falls into three categories:

- 1 To establish and define the current state of knowledge of normal tissue risks following radiotherapy.
- 2 To provide practical advice to the radiotherapy community as to how the state of knowledge can best be used to reduce normal tissue risks in current clinical radiotherapy practice and radiotherapy technology;
3. To use the perspective gained from the project to define more clearly the key areas and topics where research and development should be supported in the immediate and near future.

Current state of knowledge

Damage to normal tissue was recognised as a serious problem right from the beginnings of radiotherapy in the early 20th century, and ever since there has been a continuing research effort. The discoveries of the harmful effects have led to improvements in treatment techniques, which in turn have led to new research into the reduced yet nevertheless present tissue damage. The normal tissue risk research has played a vital role in the evolution of radiotherapy technology and practice, but ironically the success in improving the safety of radiotherapy has created challenges for the research community. The greatest challenge is to model and predict the normal tissue-sparing quality of a new technique or modality, based on data from recent treatments with short follow-up or obsolete modalities with longer follow-up.

The ALLEGRO project has shown that for the near future, knowledge of the (absolute) normal tissue risks from radiotherapy must be derived from human clinical data. While the understanding of the basic processes and biological mechanisms underlying both normal tissue complications and second cancer induction are an essential component of the development of predictive risk models, the causal chain from the initial radiation damage to the final macroscopic endpoint is so complex that current systems biology approaches can not address the problem of quantitative risk estimation. Rather, the current most successful normal tissue risk models have been created using a knowledge of the biological mechanisms to identify the critical dose parameters, and confounding parameters, followed by the use of powerful statistical methods to validate the models on clinical data. The impact on both the clinical and research communities should be to focus research and development efforts in the directions that are most likely to benefit radiotherapy patients.

Practical advice to the radiotherapy community

The ALLEGRO project has been useful in clarifying several issues that have been concerning the radiotherapy community and confirming where other issues still are not clear. One of the questions has been whether to implement sophisticated NTCP models into routine planning on individual patients, or whether to stay with experience-based tolerance dose limits. The project has shown clearly that there are considerable benefits for patients from NTCP models,

but there are caveats as well: the implementation must be informed by local clinical experience, and the range of applicability is very specific.

For second cancers, it is clear that it is not possible to estimate individual risks yet, but that the overall risk from the induction of a cancer following radiotherapy appears to be similar to the risk of serious long-term normal tissue complications. So a “prudent avoidance” approach of reducing normal tissue exposure everywhere (including high, medium, and low dose exposures) if this is possible without reducing the treatment effectiveness is probably worth the effort.

Clear evidence as presented by ALLEGRO should provide an impetus for changing standards of clinical practice.

Areas and topics for future research and development

Every task in ALLEGRO after just 2 years could define further work that would fruitfully add to the results. However, the benefit of the comprehensive design of the project structure was to be able to identify the recurrent themes in where the greatest needs were.

The strongest message was that estimates of normal tissue risks are derived from clinical data, and so the quality and uncertainty in the estimates are determined by the quality and size of the data bases. The greatest limiting factor in research particularly into the incidence of second cancers is the availability of large homogenous set of clinical data with long-term follow-up. There are quite specific recommendations on what should be done to address this, discussed below.

The other indication is that more effort needs to be put into moving beyond the single-discipline epidemiological phenomenological approach to the incidence of radiation induced damage endpoints to a greater understanding of the underlying mechanisms. But rather than starting at the microscopic level of molecular biology, genomics, proteomics, etc, the most fruitful approach should be to begin with an analysis of the biology of the endpoints, then work “from the top down” to help unravel the mechanisms that can be related to the influencing factors of dose-volume distributions, pre-existing health conditions, concurrent treatments, etc.

The recommendations have been set out in a series of reports covering all of the relevant categories of research. With appropriate dissemination these should significantly help in directing the research efforts along the most promising lines.

Dissemination activities

The most effective mode for dissemination of the ALLEGRO findings in this area is through the major specialist scientific publications and conferences. By the end of the project a total of 9 papers had already been published or accepted for publication. A further 22 papers were in preparation, and there had been 28 presentations and 18 posters at major scientific conferences. (See list of publications below.)

ALLEGRO has been fortunate in having the primary European organisation for the advancement of radiotherapy practice, research, and education (ESTRO) as a consortium partner to facilitate dissemination for the project. There were dedicated ALLEGRO sessions in the annual conferences in 2010 and 2011 (ESTRO 29 in Barcelona 12-16 September 2010

and ESTRO Anniversary 8-12 May 2011). The ESTRO official journal (Radiotherapy and Oncology, the “Green Journal”) is planning a feature issue for ALLEGRO, many of the papers have already been either accepted or published in this journal.

The ALLEGRO website (<http://www.allegroproject.org/>) will be a major point of dissemination following the completion of the project. A list of all ALLEGRO publications and links to any freely downloadable papers.

As well as the usual scientific publications and presentations, there will be other more targeted dissemination activities following the end of the project. One of the recurring themes in the project has been the need for better, more complete, more accessible, and more compatible clinical databases that are structured to facilitate research. As has been highlighted already, a recognised expert group needs to formulate a prescribed database content and structure to be universally adopted to allow multi-institutional studies to take place. Representatives of such groups will be approached to set up meetings with ALLEGRO representatives to take this proposal forward.

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Appendix: Publication status at 16 January 2012

Work package 1

Published and accepted for publication

Ottolenghi A, Facchetti A, Smyth V, Trott KR, The ALLEGRO Project gets underway. ESTRO Quarterly Newsletter # 71 Spring 2009 Pages 46-47

Andrea Ottolenghi, Vere Smyth and Klaus R. Trott, The risks to healthy tissues from the use of existing and emerging techniques for radiation therapy, Radiat Prot Dosimetry. 2011 Feb;143(2-4):533-5

Submitted and in preparation

Andrea Ottolenghi, Klaus Trott, Vere Smyth, Normal tissue risk from radiotherapy: the ALLEGRO Session at the ESTRO Anniversary conference, London 9 May 2011, Submitted for publication in ESTRO Quarterly Newsletter

Posters

Ottolenghi A, Facchetti A, Smyth V, Trott KR, ALLEGRO: Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy. ESTRO 10th Biennial Conference, Maastricht, The Netherlands, 30 August – 3 September 2009.

Work package 2

Submitted and in preparation

1. R. Kaderka¹, D. Schardt¹, M. Durante¹ and C. La Tessa¹ Out-of-field dose measurements in a water phantom using different radiotherapy modalities' To be submitted to Radiotherapy and Oncology
2. C. La Tessa¹, T. Berger², R.Kaderka¹, D. Schardt¹, C. Körner², J. Licher², U. Ramm³, N. Matsufuji⁴, C. Vallhagen Dahlgren⁴, E. Grusell⁴, T. Lomax⁵, G. Reitz² and M. Durante¹ Out-of-field dose studies with an anthropomorphic phantom. I. Comparison of X-rays and particle therapy treatments. To be submitted to Radiotherapy and Oncology
3. C. La Tessa¹, T. Berger², R. Kaderka¹, D. Schardt¹, C. Körner², G. Martino¹, N. Matsufuji⁴, W. Yamashita⁴, S. Burmeister⁵, G. Reitz² and M. Durante¹ Out-of-field dose studies with an anthropomorphic phantom. II. Radiation quality measurements. To be submitted to Radiotherapy and Oncology
4. Shah A, Aird E, Shekhdar J, Contribution to normal tissue dose from concomitant radiation for two common kV-CBCT systems and one MVCT system used in radiotherapy; submitted to Radiotherapy & Oncology (Special edition 2011)
5. Rondi E, Jereczek-Fossa BA, Orecchia R, Luraschi R, Cattani F, Pedrolì G, Cambria R., et al. Intrauterine dose in the breast cancer patients undergoing intraoperative radiotherapy: phantom study. - prepared for publication in Radiotherapy & Oncology

Posters

1. C. La Tessa, D. Schardt, R. Kaderka, M. Durante, "Out-of-field dose contribution of secondary particles: comparison between measurements and Monte Carlo simulations", Heavy Ion Symposium, Cologne, Germany, 2009.
2. R. Kaderka, D.Schardt, M. Durante, C. La Tessa "Out-of-field dose measurements in a water phantom using different radiotherapy modalities", PTCOG 50 2011, Philadelphia, US

3. R. Orecchia., V. Galimberti , BA Jereczek-Fossa, E. Rondi , R. Lazzari, A. Cecconi, MC Leonardi, C. Fodor , R. Luraschi , A. Morra, C. Chifu ,P. Baratella, M. Sargenti, V. Zanagnolo, D. Franchi, F. Cattani, G. Pedroli, U. Veronesi. PROSPECTIVE STUDY ON IN VIVO DOSIMETRY OF PELVIC SKIN AND INTRAUTERINE DOSE IN THE PATIENTS UNDERGOING INTRAOPERATIVE RADIOTHERAPY FOR BREAST CANCER: preliminary results of the ALLEGRO EAEC project [FP7/2007-2013] under grant agreement n° 231965. Poster at XXI National Congress of the Italian Association of Radiation Oncology (AIRO), Genoa 19th-22nd Nov, 2012. Published in Tumori Suppl.

Work package 3

Published and accepted for publication

1. Lievens Y, Nulens A, Mousa AG, Defraene G, De Wever W, Stroobants S and Van den Heuvel F. Intensity modulated radiotherapy for locally advanced non-small-cell lung cancer. *Int J Rad Onc Biol Phys*, 80(1), 306-313 (2011).
2. Erven K, Petillion S, Weltens C, Van den Heuvel F, Defraene G, Van Limbergen E and Van den Bogaert W. Conformal Locoregional Breast Irradiation with an Oblique Parasternal Photon Field Technique. *Medical Dosimetry*, 36 (1), 28-34 (2011).
3. Xu CJ, van der Schaaf A, Schilstra C, Langendijk JA, van't Veld AA. Impact of statistical learning methods on the predictive power of multivariate Normal Tissue Complication Probability models. Accepted by *Int J Radiation Oncology Biol Phys*.
4. van der Schaaf A , Xu CJ , van't Veld AA, Langendijk JA, Schilstra C. Multivariate Modelling of Complications with Data Driven Variable Selection: Guarding Against Overfitting and Effects of Data Set Size. Accepted by *Radiotherapy and Oncology*

Submitted and in preparation

1. Van den Heuvel F, Defraene G, Crijs W. Determining out-of-field contributions for IMRT and VMAT using Gafchromic film. To be submitted to *Radiotherapy and Oncology*.
2. Van den Heuvel F, Defraene G, Crijs W. A high dynamic range technique for Gafchromic films. To be submitted to *Medical Physics*.

Work package 4

Published and accepted for publication

1. G Defraene, L Van den Bergh, A Al-Mamgani et al., The benefits of including clinical factors in rectal normal tissue complication probability modeling after radiotherapy for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics*: accepted for publication.
2. van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue-sparing: A systematic review of literature. *Oncologist* 2011;16(3):366-377.
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(D-N°:6.6) – ALLEGRO – Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy: Final Report

Dissemination level :PU

Date of issue of this report : 15/06/2011

Development of NTCP models for head and neck cancer patients treated with 3 dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. *Radiother Oncol* 2011 May 30 [epub ahead of print].

6. Beetz I, Schilstra C, van Luijk P, Christianen ME, Doornaert P, Bijl HP, Chouvalova O, van den Heuvel ER, Steenbakkens RJ, Langendijk JA. External validation of three dimensional conformal radiotherapy based NTCP models for patient-rated xerostomia and sticky saliva among patients treated with intensity modulated radiotherapy. *Radiother Oncol*. 2011 Dec 12. [Epub ahead of print].
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Submitted and in preparation

1. van de Water TA, Lomax AJ, Bijl HP, Schilstra C, Hug EB, Langendijk JA. Sparing the salivary glands with protons in oropharyngeal cancer: benefits of 6-beam split-field intensity-modulated proton therapy (IMPT) versus 3-beam IMPT. Submitted to *Int J Radiat Oncol Biol Phys*.
2. van der Laan HP, Christianen MEMC, Bijl HP, Schilstra C, Langendijk JA,. The potential benefit of swallowing sparing intensity modulated radiotherapy to reduce swallowing dysfunction: an in silico planning comparative study. Ready for submission.
3. van der Schaaf A , Xu CJ , van't Veld AA, Langendijk JA, Schilstra C. Sampling Fluctuations of Data Driven Variable Selection in Multivariate NTCP Modelling. Submitted to *Radiotherapy and Oncology*
4. Ivo Beetz, Cornelis Schilstra, Patricia Doornaert, Henk P. Bijl, Olga Chouvalova, C.R. Leemans, G.H. de Bock M.E.M.C. Christianen,, B.F.A.M. van der Laan, Vissink A, Roel J.H.M. Steenbakkens Johannes A Langendijk, Development of NTCP models for head and neck cancer patients treated with intensity modulated radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. To be submitted to *Radiotherapy and Oncology*

Abstracts posters

1. Schilstra C, van der Schaaf A, Langendijk JA, van't Veld AA. Selection of the optimal prior for Bayesian NTCP calculation (ESTRO Biennial Meeting, Maastricht, 31 augustus 2009). *Radiother Oncol* 2009; 92 (suppl. 1): S37.
2. van de Water TA, Lomax T, Bijl HP, Schilstra C, Hug E, Langendijk JA. Sparing the salivary glands with scanned protons in head and neck radiotherapy: Benefits of 6-field Intensity Modulated Proton Therapy (IMPT) as compared to 3-field IMPT. *PTCOG 2009 Heidelberg (12-06-2009)*.
3. Langendijk JA, Christianen MEMC, Bijl HP, Beetz I, Chouvalova O, Doornaert P, Rietveld DHF, Steenbakkens RHJM, Oosting SF, Leemans CR, van der Laan BFAM, Roodenburg JL, Verdonck-de Leeuw IM, Schilstra C. A predictive model for feeding tube dependency after curative radiotherapy or chemoradiation in head and neck cancer. 3rd ICHNO (Barcelona, 25 february 2011). *Radiother Oncol* 2011; 98 (suppl 1): S14.
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6. Christianen MEMC, Bijl HP, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, Doornaert P, Rietveld DHF, Leemans CR, Rinkel RNP, van der Laan BFAM, Verdonck-de Leeuw IM, Langendijk JA. Een predictief model voor dysphagia 6 maanden na (chemo)radiotherapie bij hoofdhalshals kanker. 1^{ste} Jonge Onderzoekersdag NWHHT (Amsterdam, 22 september 2010).
7. Christianen MEMC, Bijl HP, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, Doornaert P, Rietveld DHF, Leemans CR, Rinkel RNPM, van der Laan BFAM, Verdonck-de Leeuw IM, Langendijk JA. A predictive model for dysphagia 6 months after (chemo)radiotherapy in head and neck cancer patients; results of a prospective multicenter cohort study. ESTRO 10 (Barcelona, 12-16 september 2010). Radiother Oncol 2010; 96 (suppl.1): S83. Young Scientist Poster Session.
8. van de Water TA, Lomax AJ, Bijl HP, Schilstra C, Hug EB, Langendijk JA. Intensity-modulated proton therapy with a reduced spot size improves salivary gland-sparing in oropharynx cancer. Submitted to Biennial 11th ESTRO on Physics and Radiation Technology (Londen, 8-12 May, 2011).
9. van Herpt H, van de Water T, van der Laan HP, Schilstra C, van der Hulst P, Langendijk JA, van 't Veld. Impact of systematic alignment errors in spot-scanned intensity-modulated proton therapy for head and neck cancer. Submitted to Biennial 11th ESTRO on Physics and Radiation Technology (London, 8-12 May, 2011).
10. van der Laan HP, van de Water TA, van Herpt HE, Christianen ME, Bijl HP, Schilstra C, Langendijk JA, on behalf of the ROCOCO Group. Dysphagia reduction with optimized photon and proton intensity-modulated radiotherapy for head and neck cancer patients. Submitted to Biennial 11th ESTRO on Physics and Radiation Technology (London, 8-12 May, 2011).
11. Schilstra C, van der Laan HP, Christianen ME, Bijl HP, Langendijk JA. Specifically optimized IMRT reduces the predicted probability of dysphagia in head and neck cancer. Submitted to Biennial 11th ESTRO on Physics and Radiation Technology (London, 8-12 May, 2011).
12. Langendijk JA. The assessment of the potential benefit of new radiation techniques using prospective standardized follow up programs. PREVENT meeting (Brussels, 20 March 2011). Oral presentation. Radiother Oncol 2011; 98 (suppl 2): S8.
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Work package 5

Published and accepted for publication

1. B. Welte, P. Suhr, D. Bottke, D. Bartkowiak, W Dörr, KR Trott, T. Wiegel: Second Malignancies in High-Dose Areas of Previous Tumor Radiotherapy. Strahlenther Onkol. 2010;186:174-79.
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3. Newhauser WD, Durante M., Assessing the risk of second malignancies after modern radiotherapy. Nat Rev Cancer. 2011 Jun;11(6):438-48.
4. Detlef Bartkowiak, Nicole Humble, Peter Suhr, Juliane Hagg, Katharina Mair, Bernd Polivka, Uwe Schneider, Dirk Bottke, Thomas Wiegel. Second cancer after radiotherapy, 1981 – 2007. Accepted for publication in Radiotherapy and Oncology.

In preparation

1. Uwe Schneider, Marcin Sumila, Judith Robotka, Günther Gruber, Andreas Mack, Jürgen Besserer. Dose-response relationship for breast cancer induction at radiotherapy dose, submitted to Radiation Oncology

2. Uwe Schneider, Marcin Sumila, Judith Robotka. Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy, submitted to Theoretical Biology and Medical Modelling
3. Roger Hälgl, Jürgen Besserer, Uwe Schneider. Out of field and imaging dose from IGRT, to be submitted
4. Roger Hälgl, Jürgen Besserer, Uwe Schneider. Out of field photon and neutron dose from 3D-CRT, IMRT, RA and proton therapy, to be submitted
5. Trine Grantzau, Lene Mellekjær, Jens Overgaard: Second primary cancer among Danish women with early breast cancer treated with postoperative radiotherapy; an ALLEGRO project. To be submitted

Posters and presentations

1. R. Orecchia , E.Rondi, R. Luraschi , BA. Jerezek-Fossa , A. Cecconi , MC. Leonardi, N .Rotmensch, E. Botteri, C. Fodor, A. Morra , R. Lazzari ,AM.Ferrari, F. Cattani, 3G.Pedroli, 2V. Galimberti, 2, A. Luini, 2,5P. Veronesi, W. Doerr , N. Humble , U. Veronesi Second cancer following breast cancer treatment: pilot study. Case-control study on a database including the data of 19,000 early breast cancer patients treated between 1996 and 2007. Results of the ALLEGRO EAEC project [FP7/2007-2013] under grant agreement n° 231965. Presented at the XXI National Congress of the Italian Association of Radiation Oncology (AIRO), Genoa 19th-22nd Nov, 2012. Published in Tumori Suppl.