# Project: Reduction of risk of long-term complications of radiotherapy for lymphomas.

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Other participants:
Ivan Vogelius, physicist, Rigshospitalet, University of Copenhagen (responsible for calculations of normal tissue complication probabilities (NTCP) and second cancer (SC) risk, and for evaluation and comparison of different NTCP/SC algorithms; responsible for calculations of proton dose plans)
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Deborah Schut, dose planner, Rigshospitalet, University of Copenhagen (contouring of some normal structures, calculations of dose plans (extended fields, involved node fields))
One ph.d. student (physician, funding will be applied for separately)
Possible collaborators from other centres.

## *Contents*



## *1. Background*

Patients with malignant lymphoma, in particular Hodgkin lymphoma, were previously treated with very large radiation fields (extended field radiotherapy, EFRT), leading to irradiation of large volumes of normal tissues. Serious long-term sequelae on normal tissues of these treatments have become evident within the past 10-15 years (1,2,3,4,5,6,7,8,9,10). An excess risk of death from second cancers and cardiovascular disease is particularly serious, but other, less serious but still significant, long term side effects, e.g. reduced pulmonary function, neck muscle atrophy, hypothyroidism, xerostomia, are also important for patients' quality of life. These long term side effects of radiotherapy for lymphomas have led to great scepticism regarding the use of radiotherapy for lymphomas.

However, randomized trials and a recent meta-analysis (11) have shown, that combined modality treatment with chemotherapy followed by radiotherapy for patients with early stage Hodgkin lymphoma yields superior results compared with chemotherapy alone, not only with regard to relapse free survival but also with regard to overall survival. Radiotherapy remains the single most effective treatment modality for most types of lymphoma, and the inclusion of radiotherapy in the treatment strategy is essential for achieving the optimal outcome.

Research during the past 10-15 years, some of it by the PI of this project, has led to very significant reductions in the irradiated volume in lymphoma patients down to involved field radiotherapy (IFRT) and more recently even down to involved node radiotherapy (INRT) (12,13,14). The volume of normal tissue being irradiated has therefore been reduced drastically. Consequently, the risk of long term complications has been reduced, too, but the magnitude of this reduction is not known. In order to enable optimal use of radiotherapy for lymphomas it is of paramount importance to obtain precise estimates of the risks of long-term normal tissue complication probabilities with these reduced treatment fields. These estimates will be included in the evaluation of different treatment strategies, and will enable the inclusion of radiotherapy in modern lymphoma treatment on a rational basis.

Furthermore, the implementation of even more advanced radiotherapy technology in order to further decrease irradiation to normal tissues is particularly important in this group of patients, as many of them are young and most of them are cured, thus leading to a large number of long-term survivors. Radiotherapy with protons offers the possibility to further reduce irradiation to normal tissues compared to photon therapy (15). Whether proton therapy will offer significant improvements with regard to long term complications in lymphoma patients is, however, not known.

## *2. Purpose*

To estimate the risk of long-term complications from modern, involved node radiotherapy for Hodgkin lymphoma in comparison the risk seen in patient cohorts treated 20-30 years ago with extended field radiotherapy, from whom our present estimates of the long-term risk of complications after radiotherapy for Hodgin lymphoma stem.

*Hypothesis: the risk of long-term complications from modern limited radiotherapy fields are very much smaller than the risk of long-term complications which was seen after extended field radiotherapy in the past.*

To estimate the further reduction of the risk of long-term complications with even more advanced technology, e.g., intensity modulated radiotherapy (IMRT), respiratory adaptation, and proton therapy.

*Hypothesis: use of very advanced technologies for radiotherapy of Hodgkin lymphoma will offer further significant reductions in the risk of long-term complications.*

Estimates of the reduction in risk of long term complications with the use of involved node radiotherapy, and of the further reductions with advanced technologies, will be used to develop realistic risk estimates for use in decision making with regard to the optimal treatment for patients with Hodgkin lymphoma.

*Hypothesis: Robust estimates of the risk of long term complications after radiotherapy for Hodgkin lymphoma can be achieved from detailed, 3-dimensional dose plans, and from mathematical modelling using dose-response data from the extended-field radiotherapy era.*

# *3. Material and Methods*

## 3.1 Retrospective study

For all patients with early stage supradiaphragmatic classical Hodgkin lymphoma (HL) treated at Rigshospitalet during 2006-2009 (about 50 patients) planning CT-scans will be used. Collaboration from other centres which have used the INRT technique for the treatment of Hodgkin lymphoma is possible, and will be presented within the Danish Hodgkin Group (where the PI is chairman). Pre- and post-chemotherapy lymphoma volumes have already been contoured on these scans, all pre-chemotherapy volumes have been contoured using PET/CT-scans. All relevant normal tissues will also be contoured, i.e. lungs, heart, left and right coronary arteries, left and right carotid arteries, thyroid, esophagus, breasts, salivary glands and neck muscles. For each patient, treatment plans for EFRT (i.e. mantle field), INRT with conventional technique (usually AP-PA), INRT with IMRT, and involved node proton therapy (INPT) will be made and irradiated volumes of the relevant normal tissues will be compared on dose-volume histograms (DVH).

Moreover, normal tissue complication probabilities (NTCP) will be calculated using the most common models of NTCP for each organ and endpoint in question. As part of the study a critical review of the different NTCP algorithms will be carried out along with a review of possible clinical co-factors modulating radiation response. A sensitivity test on the choice of model and parameter set will be performed when appropriate, as it is often not possible to distinguish the models statistically based on available clinical data.
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Estimates of the risk of second cancers in different organs will be calculated for EFRT, INRT, and INPT, respectively, and the estimates will be compared in order to provide a realistic estimate of the reduction in risk with modern advanced highly conformal treatment (INRT and INPT) compared to the risk after the now obsolete EFRT, which was used in the studies demonstrating the highly significantly increased risk of second cancers after radiotherapy for HL in the past.

Estimates of the risk of cardiac sequelae and the risk of long term complications from other organs, e.g. lungs, esophagus, thyroid, carotid arteries, and neck muscles, will be made. Again, comparisons will be made between EFRT, INRT (conventional), INRT with IMRT, and INPT with regard to risks of the relevant long-term complications, calculated with the different algorithms developed for the estimation of the risk of long-term complications from radiotherapy in different organs and regarding the different relevant endpoints.

These analyses will lead to estimations of the risk of long-term sequelae of modern radiotherapy for lymphomas, and comparisons with the risks that have been demonstrated for the now abandoned EFRT, which are the risks that have led to the pervading scepticism of radiotherapy for lymphomas.

A pilot project on the first three patients has been carried out, and results have been striking, showing highly significant reductions in dose and irradiated normal tissue volume.

## 3.2 Prospective study

A prospective study in patients needing mediastinal irradiation for lymphomas (Hodgkin lymphoma or other types of lymphomas), testing the value of respiratory adaptation during radiotherapy, has recently started accruing patients at Rigshospitalet. Data from the past indicate that a significant part of the lungs may be spared toxic doses of radiotherapy by this method (16,17,18). Patients entered into the protocol have a pre-chemotherapy PET/CT scan, both in free breathing and in inspiration breath hold. After chemotherapy the patients have a planning CT-scan for their radiotherapy planning, again both in free breathing and in inspiration breath hold. The corresponding pre- and post-chemotherapy scans are fused and target volumes are contoured on the post-chemotherapy planning CT-scans, making optimal use of the information form the pre-chemotherapy PET/CT-scans. Dose plans are calculated for treatment in free breathing and for treatment in inspiration breath hold. The plans are compared with respect to normal tissue dose and volume, and the best plan is chosen for treatment.

Patients with Hodgkin lymphoma in this study will be analyzed further. All the relevant normal structures, lungs, heart, coronary arteries, oesophagus, will be contoured, and the dose, volume and estimated risk of long term complications in these organs will be calculated. These analyses will lead to an estimate of the benefit of respiratory adaptation of radiotherapy for mediastinal radiotherapy for Hodgkin lymphoma with regard to long-term complications of treatment.

## 3.3 Methods of analysis

Contouring and dose planning will be carried out using the Eclipse software from Varian Medical Systems. Intensity modulated proton dose plans will be calculated using the spot-scanning technique.

NTCP calculations will be carried out using the following models:

- the Lyman model with a generalized equivalent uniform dose (19,20)
- the relative seriality model (21)
- the critical volume model (22,23)

Statistical comparisons of the estimated complication probabilities when using the different radiation delivery techniques will be carried out using descriptive tabulations and the non-parametric bootstrap resampling method.

The risk of SC will be estimated using linear, plateau and bell shaped dose response models (24), and an analysis on sensitivity towards the choice of model will be performed. Statistical comparisons between the different treatment delivery techniques with respect to risk of SC will be carried out using descriptive tabulations and bootstrap resampling.

Comparisons of dose and volume data for the different normal structures will be carried out using descriptive tabulations and non-parametric statistical tests.

Comparisons of the risk of long term complications in the different normal structures with the different radiotherapy methods and with different algorithms for NTCP calculation will also be carried out using descriptive tabulations and non-parametric statistical tests.

## *4 Ethical considerations*

The retrospective study is entirely done on already existing data. Approval will be sought from the Data Protection Committee. No further approvals are necessary. The study does not have any ethical problems.

The prospective study is approved by the Ethics Committee of the Capital Region. All patients give informed consent before entering the study. The study is also approved by the Data Protection Committee. The study is ongoing, and no further approvals are necessary.

## *5 Conclusions and future perspectives*

The results of this project will provide evidence for future guidelines and treatment policies with regard to the use of radiotherapy in the treatment of Hodgkin lymphoma, and indirectly also for the use of radiotherapy in the treatment of other types of lymphomas, in particular the high-grade lymphomas which are treated with combined modality treatment.

The project will provide evidence of the benefit, if any, of modern advanced radiotherapy technologies, such as IMRT, respiratory adaptation, and proton therapy. It will therefore provide evidence to guide in the acquisition and implementation of these technologies.

The project will also provide a critical analysis of the different algorithms for calculation of NTCPs, the assumptions underlying the different methods, the parameters taken into account in the algorithms, and insofar as this is possible the agreement between the calculated probabilities and the risks seen in patient populations treated previously.

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