



# SCHOOL

## ESTRO Mobility Grant report: Decision tool for treatment of lung cancer with protons.

Institute / country visited: MD Anderson Cancer Center, Houston, Texas, US

### Background and aim of the visit

In theory, the beneficial beam characteristics of proton therapy could greatly improve the treatment outcomes for lung cancer patients. By reducing radiation doses to the normal tissue, treatment-induced toxicity could be avoided. However, it is not yet clear to what extent doses can be reduced nor what impact specific dose reductions will have on the induced toxicity.

As proton treatment is expensive and there is also limited capacity, not all lung-cancer patients can be treated with protons. This poses us the question: which patients will benefit the most from this innovative treatment? A reliable decision tool for proton therapy would thus have considerable value for clinical decision making.

The aim of my visit was to develop prediction models for lung-cancer treatment with proton therapy and integrate these into a clinical decision tool.

### Details of the scientific content of the visit

A dataset from a randomised trial was available. Stage III non-small-cell lung cancer (NSCLC) patients were randomised either to photon or to proton treatment. Results from the trial have already been published by the group at the MD Anderson Cancer Center<sup>1</sup>. The trial did not show any differences in toxicity between photon and proton treatment. A possible explanation for this might be that patients could only be randomised after comparison of the treatment plans for both modalities. If one of the plans was clearly superior, the patient was treated with that modality. Only if the treatment plans for both modalities were comparable were patients randomised. This might have excluded patients from randomisation who would have benefited most from proton treatment. Also, for proton treatment the passive scattering technique was used, which was basically comparable with 3D conformal photon therapy. Currently, the pencil-beam scanning technique has improved the quality of proton treatment greatly.

### Pneumonitis model

A previously published prediction model for radiation-induced dyspnea, which consists of WHO performance

status, forced expiratory volume in one second (FEV1), age, mean lung dose (MLD) and the patient's history of smoking, was validated through use with the trial cohort<sup>2</sup>. While the coefficients for most risk factors were comparable for the photon and the proton arms of the trial, the effect of smoking was estimated to be negative for the photon group (lower risk) and positive for the proton group (higher risk). As the number of events for pneumonitis was very low, firm conclusions could not be drawn.

In addition, the prognostic value of mitochondrial DNA (mtDNA) was investigated. Previously, the mtDNA from the patients included in this trial had been sequenced. Our hypothesis was that specific variants in the mtDNA could result in an oxidative phosphorylation system that functioned suboptimally. This could lead to more radiation-induced damage or a decreased repair capability. The model, based on mtDNA only, used a random forest algorithm and achieved a cross-validated area under the curve of 0.62. Incorporation of the MLD should improve the prediction accuracy. Also, clinical information will be added. This is an ongoing project.

### Lymphopenia model

As lymphocytes are very radiosensitive, the lymphocyte count usually decreases significantly during radiotherapy treatment. The risk and severity of lymphopenia is associated with patient and dosimetric characteristics. Immune dysfunction after radiotherapy has been linked to a decrease in survival rates and higher risks of disease recurrence<sup>3</sup>. With the introduction of immunotherapy into the standard-of-care treatment for lung cancer, it is of utmost importance that the immune system of the patient functions well. Otherwise, there is only very limited or no treatment benefit for the patient.

Therefore, a model to identify patients at risk of severe, prolonged lymphopenia after radiotherapy would be clinically very relevant. In addition, the differences between proton and photon therapy for risk, severity and duration of lymphopenia will be investigated.

### Proton centre

I had the opportunity to visit the MD Anderson proton centre, which has been operational since 2006. It consists of a synchrotron (70-250 MeV) and four treatment rooms, one of which is a fixed horizontal-beam treatment room, while the other three have moving gantries. Two gantry treatment

rooms and the fixed-beam treatment room have passive-scattering nozzles. The third gantry has a pencil-beam scanning nozzle for the delivery of intensity-modulated proton treatments (IMPT). The fixed horizontal beam is only used for prostate treatment (currently <10 patients per day). All other patients are treated with the beam-scanning system. The centre treats about 100 patients per day, of which 40% are head & neck cancer patients. The operational hours run from 4 AM until midnight. Between midnight and 4 AM, quality control is performed and some research activities are undertaken.

A new proton treatment centre is being built. It will consist of a synchrotron and four scanning-beam systems and is expected to be operational in 2022.

In addition, I attended two scientific presentations

- Low-dose radiation in metastases enhances systemic tumour response
- Genetic predictors for immune checkpoint inhibitors.

## Results

### *Pneumonitis model*

A pneumonitis model, using mtDNA variants, was built (Figure 1). Stratification for MLD could improve the model, as well as adding clinical and patient characteristics. Further analysis is ongoing.

### *Lymphopenia model*

A descriptive analysis has been performed. Evolution of lymphopenia was investigated, and this showed a clear decrease during radiotherapy and different recovery patterns for individual patients (Figure 2). The statistical analysis is ongoing.

### *Cost-effectiveness model*

Data on costs were available only to a limited degree. Also, extended follow-up of patients was lacking as most patients returned to the referring hospital after treatment. The possibility to develop an accurate cost-effectiveness model should be investigated before proceeding with this subproject.

## References

1. Liao, Z., *et al.* Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* **36**, 1813–1822 (2018).

2. Dehing-oberije, C., *et al.* The importance of patient characteristics for the prediction of radiation-induced lung toxicity. *Radiother Oncol* **91**, 421–426 (2008).

3. Wang, X., Lu, J., Teng, F., & Yu, J. Lymphopenia association with accelerated hyperfractionation and its effects on limited-stage small cell lung cancer patients' clinical outcomes. *Ann Transl Med* **7**, 385–385 (2019).

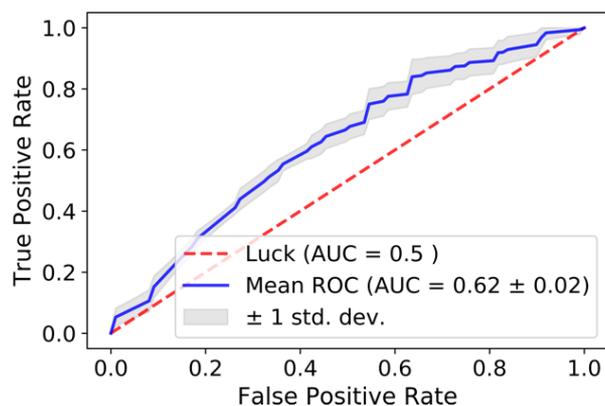


Figure 1. Prognostic value of mtDNA for pneumonitis >=grade 3

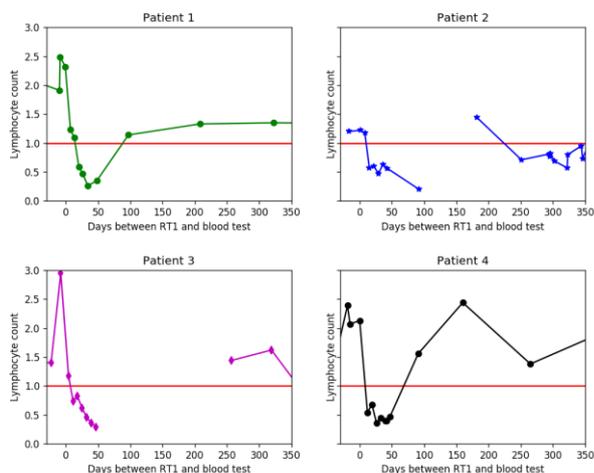


Figure 2. Lymphopenia evolution during and after (chemo) radiation. The horizontal red line indicates the lower level of normal lymphocyte count.



**Dr Cary Oberije**

Senior data scientist / statistics & epidemiology  
Department of Precision Medicine, University of Maastricht  
Maastricht, The Netherlands  
c.oberije@maastrichtuniversity.nl

