Maastricht University

Optimization of Brain and Head & Neck Radiotherapy

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Valorisation

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Since the introduction of radiotherapy for the treatment of cancer, more than hundred years ago, doctors have been trying to report treatments results as systematically and precisely as possible in order to learn about tumour as well as healthy tissue response to radiotherapy. The ultimate goal of radiotherapy is to eradicate the tumour without any lasting toxicity. In order to achieve this ambitious goal, several approaches are possible.

One approach being subject of this thesis is reduction of the actual dose to the healthy tissue surrounding the tumour also known as the organs at risk (OARs). This reduction of dose can be achieved by using state of the art irradiation techniques such as intensity-modulated radiotherapy (IMRT) in which the intensity of the dose within the beam can be modulated resulting in an adequate dose to the tumour and an as low as possible dose to the OARs. Thanks to evolving technical possibilities, there are several ways to use IMRT in benefit of the patient, for example volumetric modulated arc technique (VMAT) and helical tomotherapy (TOMO). Another way to reduce dose to the OARs is using particle therapy instead of photon therapy, in which charged particles, for example protons and carbon ions, are used for irradiation. Due to specific characteristics of these particles the dose to surrounding healthy tissue can be reduced in some patients. Whether this reduction in dose to the OARs is clinically relevant has to be proven in time. Since proton therapy is becoming more and more available, although still on a small scale, the need for optimal patient selection becomes warranted since only a limited number of patients can be treated in such facilities.

There are also extra costs involved with particle therapy compared to photon radiotherapy. This is why *in silico* studies are the logical first step to investigate whether a dosimetric advantage is achievable and effective. In **Chapter 2 and 3** head and neck and low-grade glioma patients are included the two separate *in silico* trials conducted within the Radiation Oncology Collaborative Comparison (ROCOCO) consortium. These studies demonstrated the benefit of particle therapy through simulation instead of actual treatment.

Thanks to these *in silico* trials, we know there is a dosimetric advantage for particle therapy, but it remains unsure whether this translates into a clinical benefit. To this end, an accurate prediction of the effect of radiation on various tissues is essential, such as the prediction of tumour response related to the delivered dose, also known as the tumour control probability (TCP). For many tumours, a higher dose is related to a better local control. This of course needs to be weighed against the inevitable exposure of the surrounding healthy tissue to radiation causing side effects, known as the normal

tissue complication probability (NTCP). Both TCP and NTCP are dependent on various patient-related factors of which some are not yet identified, especially in case of re-irradiation, but also for central nervous system (CNS) side effects, specifically. When TCP and NTCP are known for each type of tissue (tumour and healthy tissue) a well-balanced treatment choice can be made based on the risk of side effects versus the possibility of achieving local control of the tumour per treatment modality.

Many different radiation centres started collecting dosimetric and toxicity data decades ago. Surprisingly, despite these great efforts in the past, there is still a desperate need for validated TCP and NTCP models, especially in the field of neuro-oncology. One of the reasons the collected data did not result in proper validation of such prediction models is because they lack uniformity of the actual collected data. It is therefore of great importance that the relevant CNS anatomical structures are identified and uniformly delineated in order to uniformly report the received dose related to registered side effects. For this a consensus-based delineation atlas, which includes all (potentially) relevant OARs, is needed. This thesis provides in this need by producing a European Particle Therapy Network (EPTN) consensus-based Neuro-Oncology Atlas including the posterior cerebellum **(Chapter 4 and 5)** as a new potentially relevant OAR. This neuro-oncology atlas will enable photon and particle radiotherapy centres within Europe and beyond to uniformly report on dose related toxicity for each specific OAR. Since manual delineation of OARs is one of the most time consuming task in radiotherapy planning and subject to inter- and intra-observer variability, there is a great interest in developing an automated delineation atlas. The CNS atlas presented in this thesis will serve as a base for this, e.g. for the Danish head and neck group (DAHANCA) and Danish brain oncology group (DNOG).

When there is agreement on the relevant OARs and the structure names and delineation thereof, the next important issue is agreement on the dose each OAR tolerates without long-term toxicity, based on available literature. This agreement is important since the literature on tolerance dose is scarce, causing room for individual interpretation. This results in treatment plans being based on different, by radiation oncologists accepted doses in the OAR obstructing accurate treatment modality comparison. The latter is needed to upfront select the best treatment option for each individual patient. This thesis provides in this need by reaching this agreement by producing an EPTN consensus CNS Tolerance Table **(Chapter 6)**. Both the CNS Delineation Atlas as well as the Tolerance Dose table are now incorporated into daily practice guidelines, as well as in trial protocols within and outside of the EPTN.

This year, the first patient was treated with proton therapy in The Netherlands and health insurance companies together with the government and experts in the field of

radiotherapy will continue to work together to improve patient selection by collecting actual toxicity data in a mutual database. Collecting these data in a uniform matter will be the next challenging step. Especially for neuro oncology, were cognitive decline after radiotherapy is of great importance, uniform cognitive testing is needed, for example. As a result of chapter 4, 5 and 6, an EPTN expert group is now continuing previous work by producing a consensus on this toxicity registration. This will eventually result in the possibility to uniformly combine CNS dosimetric and toxicity data from all different centres throughout the world, enabling efficient cooperation between experts to produce and validate the needed NTCP models within the coming years.

Another good example of cooperation leading to optimal treatment results is the treatment of epilepsy. Epilepsy in general is one of the most common severe neurological disorders. It is a disease in which patients have unexpected seizures making participation in daily family life and working processes challenging, which can have severe economic consequences. If the epilepsy is resistant to anti-epileptic drugs, resection of the epileptogenic region is an invasive treatment option for only a small group of patients. Currently, there is a need for non-invasive alternative treatments, especially for those patients not eligible for radical surgery. **Chapter 7** shows that radiotherapy is such an alternative treatment for epilepsy. Due to the excellent collaboration between the neurologist, neurosurgeon, neuro-radiologist and -radiotherapist within the southern part of The Netherlands, and having the best radiotherapy techniques, the next logical step will be offering radiotherapy to a selected group of epilepsy patient in Maastricht for the first time in the Netherlands.