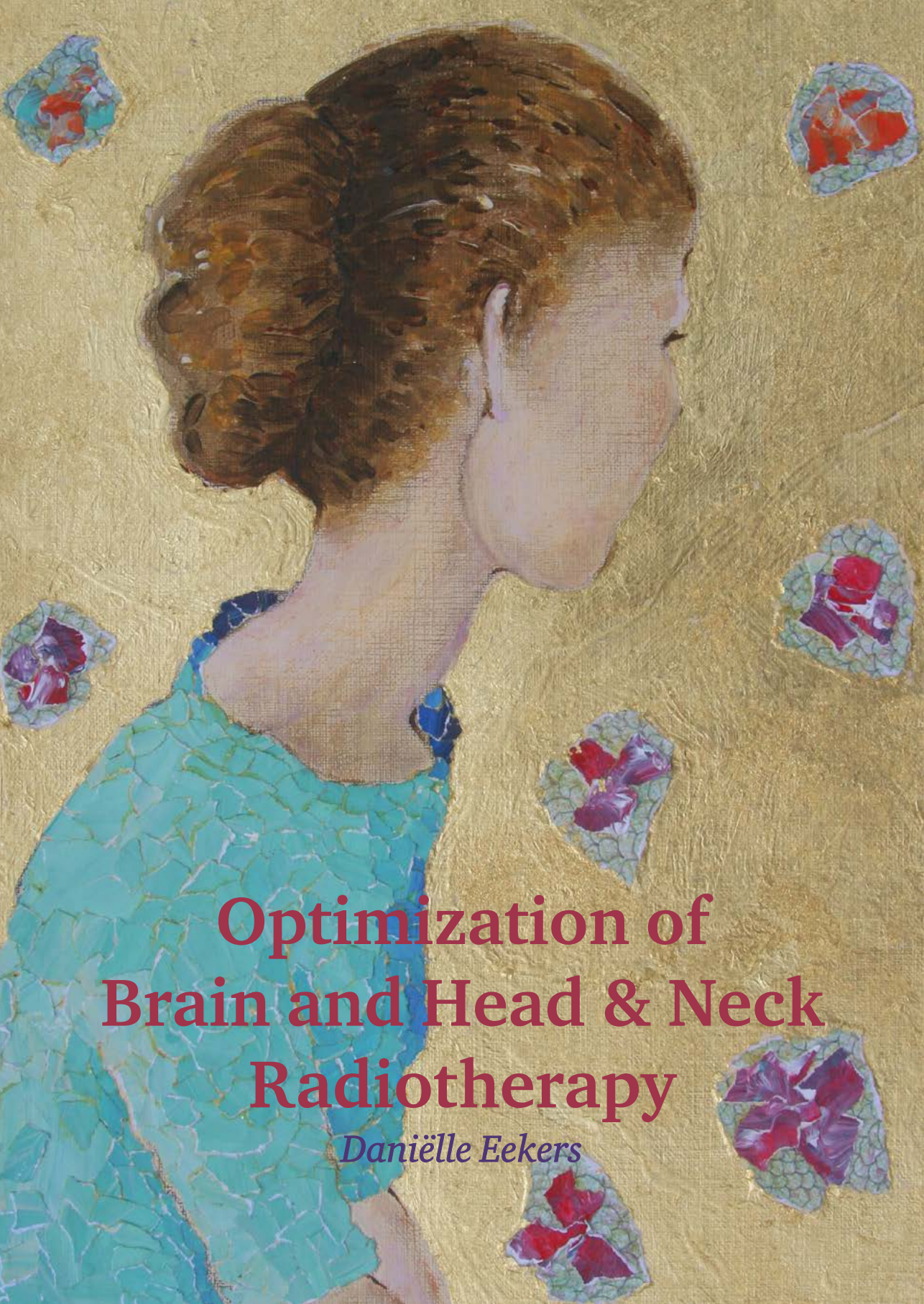

Optimization of Brain and Head & Neck Radiotherapy

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Cover: "Emma" by Pascal Eekers
Layout: Tiny Wouters Lenssen
Production: Datawyse Universitaire Pers Maastricht

ISBN: 978-94-6380-036-5

DOI: 10.17915/candat.2018.12.7

UNIVERSITAIRE PERS MAASTRICHT

Optimization of Brain and Head & Neck Radiotherapy

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 7 december 2018 om 10.00 uur

door

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Voor Imke, Karsten & Erik,
jullie geven de glans

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Chapter 1

General introduction

Introduction

Radiotherapy is one of the three pillars of anti-cancer therapy, besides surgery and systemic therapy. It uses ionising radiation to damage tumour cells by causing a plethora of effects, the most prominent being double strand breaks in the DNA of the cell. Most often, external beam radiotherapy, i.e., ionising irradiation applied from outside the body generated by a linear accelerator, is used. Thus, the ionising radiation needs to travel through the body to reach the tumour and will therefore damage not only tumour cells, but may also harm normal tissue cells, on its path. As opposed to tumour cells that are not properly equipped to recognise and repair the damages caused by radiation, healthy normal cells detect the damage and are able to repair it. A prerequisite for this is that the dose per fraction of radiation administered is to be kept reasonably low, e.g., 2 Gray (Gy), and consequently a full treatment is delivered over the course of several weeks. Nevertheless, not all healthy cells will survive, resulting in acute and long-term side effects of the so-called organs at risk (OAR). Most acute side effects recuperate in the period of weeks until three months after radiotherapy, however, the long-term side effects develop after months to years and are often irreversible. So, the aim of radiotherapy is to give a lethal dose to the tumour and to spare the surrounding OARs as much as possible in order to reduce the likelihood of acute and especially long-term side-effects.

Developments in radiotherapy

Since tumours have irregular shapes and are surrounded by healthy tissue, radiation technology needs to enable the radiation oncologists and physicists to view the tumour in three dimensions, to sculpt the beams to its shape, and to employ steep dose gradients sparing the OARs. By using multiple beams, the tumour is faced by the sum of these beams delivering a high dose to tumour, while the dose to the OARs in the tract of each beam is kept reasonably low. This technique is called 3D conformal radiotherapy (3D-CRT).

In the passing decade, radiotherapy has evolved from 3D-CRT to intensity-modulated radiation therapy (IMRT). In IMRT, one radiation beam is divided into multiple small beams, so-called beamlets. The intensity of these beamlets can be modulated over time in order to give an optimal dose distribution to the tumour and to spare the OARs. Over the last years, new rotational IMRT technologies have become available, such as volumetric modulated arc therapy (VMAT) and helical Tomotherapy (TOMO)[1-3]. VMAT and TOMO are a further development of IMRT, such that the linear accelerator rotates around the patient while the intensity of the radiation, the velocity of machine rotation

and the shape of the radiation field can vary during treatment. In most cases, while using VMAT, the machine is able to deliver the dose faster than when using IMRT, with a dose distribution that is often even more conformal to the tumour. VMAT can be delivered with standard gantry-based linear accelerators. Alternatively, it can be delivered using a linear accelerator combined with a computed tomography scanner (CT), rotating in a helix around the patient, the so-called TOMO system. In the previously described treatment modalities such as 3D-CRT, IMRT, VMAT and TOMO, high-energy photons are used to irradiate the tumour. Photons are packages of energy and as such have no mass or charge, delivering their dose to the tissue along the beam path by causing secondary electrons in the patient's body.

Still, it is inevitable that the OARs frequently receive a clinically significant dose with these techniques, especially when rotational photon-based [2,4]. In an attempt to reduce the dose to the OARs further, particle therapy (PT) is increasingly being introduced in clinical practice. Charged particles, such as carbon-ions and protons have a mass and are charged, which causes a different dose distribution in the patient. The particles have a low entry dose followed by an energy-dependent maximum dose delivery at the so-called Bragg peak with low to zero dose after the dose fall-off at the distal edge of the Bragg peak (see Figure 1.1). Particle therapy potentially leads to a superior sparing of the surrounding OARs compared to photons, a hypothesis that needs to be tested and confirmed in (*in silico*) clinical studies (*this thesis*). These studies can be designed as register studies, in a randomised fashion, or by model-based treatment selection.

Proton beam irradiation is delivered using a so-called cyclotron. In this cyclotron protons are accelerated outwards from the centre along a spiral path, in which they are held by a static magnetic field. In recent years, manufacturers of cyclotrons were able to reduce the size of these machines considerably and therefore increase the affordability of this relatively novel technique. Consequently, proton beam therapy is increasingly available throughout the world and prompts interest among physicians as well as health insurance companies regarding its therapeutic efficacy and possible toxicity reduction. There are currently two proton-beam delivery methods:
Passive scattered proton therapy (PSPT), and active proton therapy or pencil beam scanning (PBS). In PSPT, a modulator wheel placed in the beam path degrades the proton energy and spreads out the Bragg-peak (SOBP). Furthermore, individual patient- and beam-specific modifying devices, i.e. compensator and collimator, have to be designed to conform the dose to the target volume. In PBS, magnets are used to steer a small exiting pencil beam in horizontal and vertical direction, such that the target volume is 'painted' with dose. By adjusting the energy of the beam, the depth of the

Bragg-peak can be adjusted, creating a 3D dose volume with successive treatment layers to conform to the tumour. For PBS, no patient-specific-beam modulators are needed, however, its application to moving targets, such as lung tumours, is currently limited.

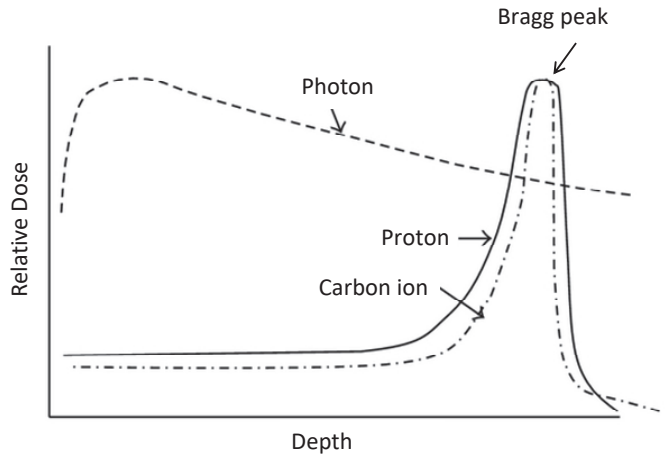

Figure 1.1 Relationship of depth and relative dose in photon (dashed line), proton (solid line) and carbon ion (dashed/dotted line) beams. Proton and carbon ion beams deposit the maximum dose in the so-called Bragg-peak.

Changing the beam intensity during treatment, thus resembling IMRT, is also possible in particle therapy: using protons this is called intensity-modulated proton therapy (IMPT) and using carbon ions, intensity-modulated ion therapy (IMIT). Due to the large impact of acute and late radiation-induced toxicities in patients with tumours originating from the brain or head-and-neck, these sites are of particular interest for the use of IMPT and IMIT.

Head and neck

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most prevalent cancer in the world and remains difficult to cure[1,5]. The treatment of the primary tumour and lymph nodes includes either primary surgical resection with or without postoperative RT or primary RT. RT can be combined with systemic treatment, depending on various patient and tumour characteristics.
Unfortunately, all treatment modalities applied with curative intent cause side effects. Surgery might cause temporary or permanent impaired speech, swallowing or

breathing impairment, endocrine dysfunction, or nerve damage (often facial nerve or accessory nerve). Radiotherapy as a part of organ preservation strategy in HNSCC may cause acute skin (redness, epidermolysis) and mucosal (mucositis) damage, xerostomia, taste loss, hypothyroidism, dysphagia, fibrosis, and fatigue or pain. Some of these side effects might recover in time and others remain after treatment.
The risk of local or regional recurrence after having undergone radio(chemo)therapy with or without surgery is still up to 30% despite many new treatment options[6-8]. In case of irresectable recurrent disease in the primary tumour or lymph nodes, one of the potentially curative treatment options is re-irradiation (re-RT), sometimes combined with systemic therapy. However, also after re-RT, the rates of severe grade 3 or 4 toxicity are high, with an incidence of up to 45% at 5 years, and only 1 in 3 patients surviving re-RT without recurrence and severe complications[9]. Reduction of this risk of radiation induced complications and improvement of the oncological outcome is needed[9-15].

Primary brain tumours / gliomas

Gliomas are the most common tumours of the central nervous system (CNS), with an annual incidence of 5.4 per 100.000 in Europe[16]. They can be classified according to the World Health Organization (WHO) grading system from grade I to IV[17]. Grade I is pathologically benign and grade IV the most malignant glioma, also called a glioblastoma. Low-grade glioma (LGG), classifying as WHO grade II, are diffusely infiltrative tumours and typically occur in younger adults (2nd-5th decade). Although most LGG show a protracted disease course, differences in survival rates have been identified. Molecular parameters, such as 1p19q co-deletions, isocitrate dehydrogenase (IDH) mutation, telomerase reverse transcriptase (TERT) promotor mutations, and epidermal growth factor receptor (EGFR) amplifications and mutations have been integrated in the WHO classification of CNS tumours revised in 2016, which helps to more accurately predict prognosis[18-20]. This integrated diagnosis of gliomas is now leading the neuro-oncology field towards multimodal treatment schedules capable of increasing overall survival of diffuse gliomas with an aggressive clinical behaviour[21,22]. Multimodal treatment schedules include neurosurgical resection if feasible and adjuvant treatment with radiation therapy as well as chemotherapy[22]. The surgical resection of a large part of the tumour (gross total resection) is not without risk and is in some cases performed while the patient is awake in order to preserve as much function as possible. There is a chance of bleeding, neurological deficits such as paralysis, cranial nerve palsy or vision loss depending on the location and infection.

Radiotherapy may cause headache, nausea, vomiting, fatigue and hair loss during treatment. The long-term the side effects of radiotherapy can include necrosis of healthy tissue (radio-necrosis) and cognitive decline. With increasing survival of LGG patients, therapy-induced toxicity, which subsequently decreases the quality of life of these patients, should be minimised[23].

Neurocognitive decline, which is marked by reduction of verbal memory, spatial processing, attention and novel problem-solving ability, is probably the most relevant (long-term) complication following (radio)therapy of the brain[24]. An important part of the limbic system, which is involved in emotions and the forming of memories, are the hippocampi, which play an important role in cognition[25]. Damage to the hippocampi, as is the case in Morbus Alzheimer, results in loss of short-term memory and disorientation. When both hippocampi are affected, even a total loss in the ability to create new memories may occur, called an anterograde amnesia. There is some evidence that besides the hippocampi, the cerebellum plays a role in neurocognitive function[26]. Traditionally, the cerebellum is known for its role in regulation and coordination in movement, posture and balance[26]. However, several clinical, anatomical and neuro-imaging studies have shown that the cerebellum, especially the cerebellum posterior, may also play a role in neurocognition[27-29].

Epilepsy

The most frequent symptom of patients with LGG is epilepsy in up to 65-90% of cases[30,31]. Having seizures causes a great emotional burden to a patient and decreases the quality of life significantly[32]. Epilepsy in general is one of the most common severe neurological disorders. The WHO has estimated that more than 50 million patients suffer from epilepsy worldwide[33-35]. Epileptic seizures are episodes of uncontrolled vigorous shaking as a result of excessive and abnormal neuronal activity in the cortex of the brain[36]. Epilepsy can be treated successfully with anti-epileptic drugs (AED) or in selected cases of AED-resistant patients, with surgery removing the epileptogenic focus. In patients with primary brain tumours, treating the tumour, e.g., with radiotherapy, has been shown to have a positive effect on the epilepsy[37].

Reduction in epilepsy frequency after treatment can be classified using the Engel classification from I-IV. Class I meaning that a patient is completely seizure free for at least 2 years, class II only rare seizure (≤ 2 seizures per year) remain, class III is considered worthwhile improvement and class IV meaning no significant improvement or even increase in seizure frequency.

Besides the fact that a certain epilepsy reduction can be achieved with radiotherapy in the presence of a tumour, patients with epileptic lesions *without* having a tumour can

also be treated with radiotherapy. These so-called non-neoplastic focal epileptic lesions (NNFE) are associated with focal seizures, which have a localised, well-circumscribed network of discharges and can be treated successfully with radiotherapy, besides receiving treatment with anti-epileptic drugs and resective surgery[38,39]. The success rate is around 50% (*this thesis*) whereas the postoperative seizure free outcome varies between 60-90% depending, among others, on the pathological substrate[40].
Radiotherapy as a non-invasive approach may be a good alternative to surgery when the epileptogenic region is located near the eloquent cortex or deeply sited brain areas and this region is too hazardous to resect[40,41]. Several publications have underlined the potential value of this alternative therapy in patients with drug-resistant epilepsy, although currently only few radiotherapy institutes in the world treat patients for epilepsy[40,42-44]. Having a feasible and non-invasive alternative for patients for whom surgery is no option is of great importance.

Challenges in radiotherapy

With all new developments in health care treating malignant or benign diseases, a tailor-made treatment selection for every individual patient is desperately needed. Therefore, it is crucial to find the evidence to support this decision-making, in particular between two treatment modalities with relevant differences in costs or toxicity profiles. Carefully performed randomised trials of two seemingly equal treatments could provide us with the evidence we need.
When considering proton therapy, however, randomised trials are increasingly difficult to perform mostly due to costs and availability. To deal with this dilemma, a new approach was introduced in the Netherlands, the so-called model-based approach[45]. This approach aims at selecting those patients most likely to benefit from a specific treatment, in this case proton beam therapy, using pre-treatment plan comparison and translating a dose distribution into anticipated clinical benefit using validated normal tissue complication probability (NTCP) models. The maturation and validation of NTCP models is strongly dependent on uniform delineation of the relevant OARs (*this thesis*). An NTCP model uses data on dose to OARs of previously treated patients and relates these to their reported toxicity. With such a model it is possible to estimate the individual patient's potential benefit of applying one treatment instead of another in terms of expected reduction of radiation-induced side effects, knowing the dose to a specific OAR[16,46-48]. Noteworthy, these NTCP models need to be validated and further developed using the outcome of clinical trials.

Further reduction of these therapy-induced side-effects should be one of the main goals of future research in radiotherapy. With all kinds of new technological developments, such as cheaper cyclotrons or magnetic resonance-integrated linear accelerators (MR-linac), we need a way to predict and compare the risk on side effects in order to select the right treatment modality, for the right patient. This is a necessity for photon as well as for particle therapy. There are many radiotherapy centres; in 2012 Europe had 1286 registered radiotherapy centres in the Directory of Radiotherapy Centres database[49]. Moreover, according to the particle therapy co-operative group (PTCOG) database, there are now 25 particle therapy facilities in Europe of which 11 are under construction. Until now, the neurological oncology community has not succeeded in collecting sufficient valid data to build a validated NTCP model for tumours of the central nervous system as opposed to the dysphagia and xerostomia NTCP models for the primary treatment of head and neck tumours (see Figure 1.2) [50-53].

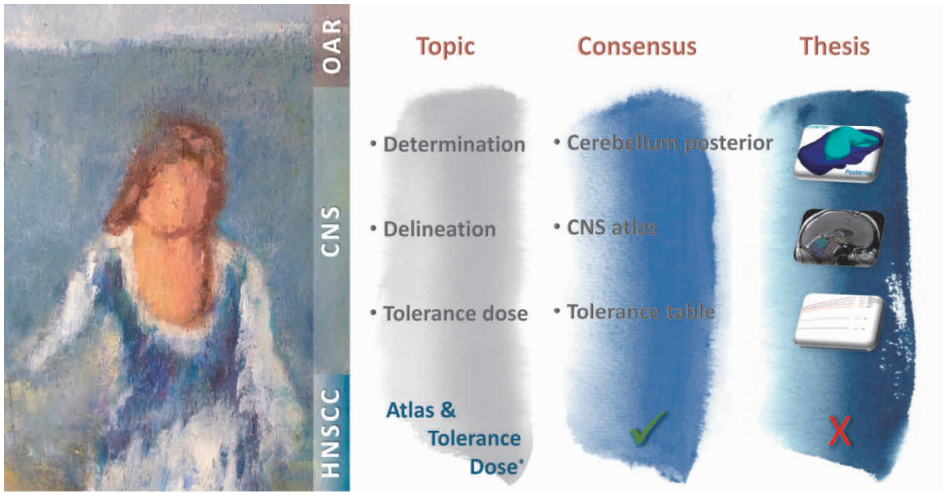

Figure 1.2 The central nervous system (CNS) and head and neck squamous cell carcinoma (HNSCC) status on consensus for organs at risk (OAR) determination, delineation and tolerance dose in relation to the outcome of this thesis. V = present in literature (*Brouwer *et al*.[54]). X = not a subject of this thesis. *Painting in private possession.*

Since brain tumours are rare and some side effects take years to develop, international cooperation and agreement is needed on 3 topics: first, on the identification of the relevant OARs; second, on the delineation of these OARs represented in an atlas; and third, on the tolerance dose of the identified OARs. Consensus on outcome reporting

measures, i.e., uniform follow-up timing, patient questionnaires and content of the follow-up, is mandatory as well[55-58]. In an attempt to reach these ideal conditions for comparison, a list of the OAR's distinct radiation-induced toxicities and the recommended dose constraints for conventionally fractionated radiotherapy is needed, for it has been a while since the recommendations by Emami et al.[59] and the QUANTEC series[60-63] were published. A solid data collection is also mandatory of all treated patients, including registration of the treatment modality (photon or particle), dose distribution and uniform registration of the side effects.
Recently, a taskforce from the European Society for Radiotherapy & Oncology (ESTRO) was established called the European Particle Therapy Network (EPTN). Within the EPTN, forces are joined to share knowledge and stimulate cooperation between the particle centres, for example on clinical trials in Work Package 1 (WP1).

Objective of this thesis

The overall objective of this doctoral thesis was to assess the value of proton beam therapy, in particular for re-irradiation in HNSCC and primary irradiation of LGG, see Figure 1.3. This included a comparative study on reducing the radiation dose to the OARs, and consensus on contouring of OARs and their tolerated dose constraints among European particle centres.
The first objective was addressed within the Radiation Oncology COllaborative Comparison (ROCOCO) initiative. ROCOCO is a consortium of various international centres conducting *in silico* photons and particles treatment plan comparisons[64-66]. To assess the potential gains due to the dosimetric characteristics of particle therapy for individual patients, two *in silico* treatment planning studies were conducted within this ROCOCO group (*this thesis*), one on a cohort of 25 HNSCC patients (clinicaltrial.gov ID: NCT 02242916), the other on 25 LGG patients (clinicaltrial.gov ID: NCT NCT02607397)[47].
The second objective was addressed within the EPTN. A group of expert radiation oncologists in the field of neuro-oncology discussed and reached agreement on which relevant OARs needed to be included in the delineation atlas, and on the tolerance dose of these OARs, in order to be able to uniformly gather data on dose-toxicity profiles in time *(this thesis)*[48,57,58]. Due to this uniformity, these data can be used in future joined efforts to generate and validate new CNS NTCP models for protons as well as photons.
The third objective was determining the role of radiotherapy in the treatment of drug-resistant non-neoplastic focal epilepsy in adults, being a possible indication for particle therapy in the future[67].

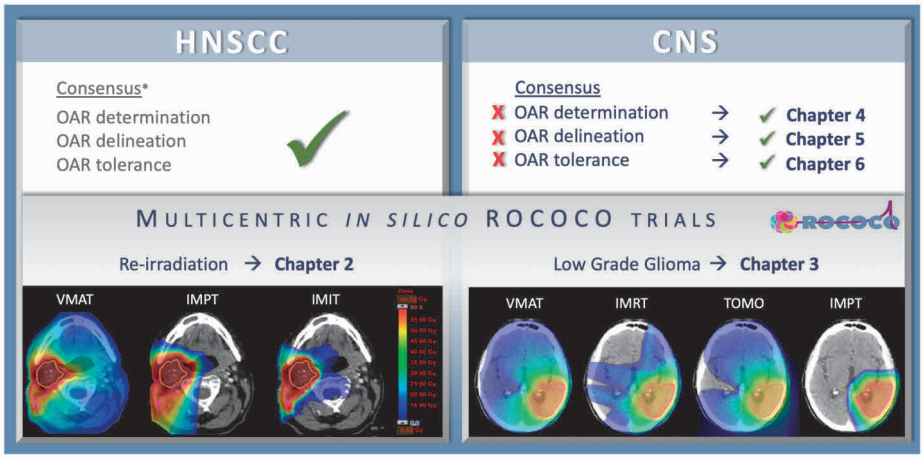

Figure 1.3 The outline of this thesis and the corresponding chapters. OAR = organ at risk, HNSCC = head and neck squamous cell carcinoma, CNS = central nervous system, * = Brouwer *et al.*[54] ,ROCOCO = Radiation Oncology COllaborative COmparison group. VMAT = volumetric modulated arc therapy, IMPT = intensity-modulated proton therapy, IMIT = intensity-modulated ion therapy, IMRT = intensity-modulated radiation therapy, TOMO = helical Tomotherapy.

Summary of the chapters

Chapter 2 reports on the results of the ROCOCO *in silico* trial comparing IMPT and IMIT with VMAT for re-irradiation of 25 head-and-neck cancer patients. The results showed a reduction in dose to all OARs using particle, in particular favouring carbon-ions[47,65].

Chapter 3 reports on the results of the ROCOCO *in silico* trial comparing IMPT, TOMO and IMRT with VMAT for irradiation of 25 low grade glioma patients. The study demonstrated that proton therapy was the most effective in reducing irradiated volumes at low and intermediate dose levels of contralateral OARs. Photons performed better in the high dose area resulting in a better target conformity[68].

Chapter 4 presents the posterior cerebellum as a possible, new organ at risk relevant for cognitive decline. This literature review summarises the available evidence on its role in cognition, which is in particular relevant for irradiation of head-and-neck cancer patients[69].

Chapter 5 reports on the EPTN consensus-based atlas for CT- and MR-based contouring in neuro-oncology. Relevant OARs in neuro-oncology and the corresponding delineation instructions are illustrated in a novel online atlas, harmonising current clinical practice[54,56].

Chapter 6 reports on the EPTN consensus regarding the radiation dose constraints for OARs in neuro-oncology based on the available literature. For the model-based comparison of photon and proton treatment plans as well as for prospective clinical trials, the use of these consented constraints is strongly encouraged[57,58].

Chapter 7 systematically reviews the available evidence on the efficacy of high precision radiotherapy for drug-resistant non-neoplastic focal epilepsy in adults. By incorporating the available response data from literature, a dose effect-model was fitted to describe a relationship between dose and the seizure frequency reduction defined as the radiotherapy-adapted Engel class[67].

In **Chapter 8** the results of this thesis are discussed and summarised. A Dutch and English summary and reports on the valorisation of this thesis is presented in **Chapter 9**.

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Chapter 2

Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric *in silico* ROCOCO trial

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Radiother Oncol. 2016;121(3):387-394

Abstract

Background and purpose

In this multicentric *in silico* trial we compared photon, proton, and carbon-ion radiotherapy plans for re-irradiation of patients with squamous cell carcinoma of the head and neck (HNSCC) regarding dose to tumour and doses to surrounding organs at risk (OARs).

Material and methods

Twenty-five HNSCC patients with a second new or recurrent cancer after previous irradiation (70 Gy) were included. Intensity-modulated proton therapy (IMPT) and ion therapy (IMIT) re-irradiation plans to a second subsequent dose of 70 Gy were compared to photon therapy delivered with volumetric modulated arc therapy (VMAT).

Results

When comparing IMIT and IMPT to VMAT, the mean dose to all investigated 22 OARs was significantly reduced for IMIT and to 15 out of 22 OARs (68%) using IMPT. The maximum dose to 2% volume (D_2) of the brainstem and spinal cord were significantly reduced using IMPT and IMIT compared to VMAT. The data are available on www.cancerdata.org.

Conclusions

In this ROCOCO *in silico* trial, a reduction in mean dose to OARs was achieved using particle therapy compared to photons in the re-irradiation of HNSCC. There was a dosimetric benefit favouring carbon-ions above proton therapy. These dose reductions may potentially translate into lower severe complication rates related to the re-irradiation.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most prevalent cancer in the world and is still considered difficult to cure[1,2]. In addition to the abuse of alcohol and/or tobacco, infection with human papilloma virus (HPV) is a risk factor.
Despite many new treatment options, the risk of local or regional recurrence for patients with HNSCC having undergone (chemo)radiotherapy or tri-modality treatment is still up to 30%[3-5]. Additionally, the estimated 5-year cumulative incidence of second new tumours was 13% in the radiotherapy group and 12% in the combined therapy group according to Bernier *et al*.[6].The treatment of locoregional recurrence of HNSCC consists of surgical resection with or without adjuvant (chemo)radiation or primary definitive (chemo)radiation, leading to an overall 5-year relative survival rate of 40-66% in selected patients[1].

In case of an unresectable recurrence, re-irradiation (re-RT) possibly combined with systemic therapy, is an alternative curative option. In the postoperative setting, re-RT should be considered if features in the pathology specimen, such a positive resection margin or extracapsular extension, indicate high risk of recurrence[7-10]. Long-term disease control and survival can be achieved in patients who receive re-RT as an adjunct to surgical resection. However, the rates of severe grade 3 or 4 toxicity after re-RT are high, with an incidence of approximately 45% at 5 years, and only approximately 1 in 3 patients survives re-RT without recurrence and severe complications[11]. Reduction of the risk of radiation-induced complications and improvement of the oncological outcome are needed[8,12-17].

In recent years, there has been enormous progress in radiotherapy techniques, moving from 3D conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), enabling highly conformal treatment with dose reductions to healthy tissue and surrounding organs at risk (OARs)[18,19]. Still the OARs and healthy tissues frequently receive a significant dose with 3D-CRT and IMRT[19,20].

Particle therapy (PT) is becoming increasingly available, which prompts interest among physicians as well as health insurance companies regarding its efficacy in HNSCC. To assess the potential gains of PT for individual patients in the re-irradiation setting, we conducted an *in silico* treatment planning study on a cohort of 25 HNSCC patients retrospectively retrieved from two Dutch radiotherapy departments. Data are available on www.cancerdata.org[21].

Methods

Study population

We retrospectively retrieved treatment plans of HNSCC patients stage I to IVB who had undergone (chemo)radiotherapy with curative intent (≥50 Gy, including at least lymph node levels II-IV) at Radboud University Medical Centre (UMC) or at MAASTRO clinic and who were subsequently (>1 year later) re-irradiated (with or without surgery and/or chemotherapy), with a relevant overlap of the target volume (clinicaltrial.gov ID: NCT 02242916).

Target volume and OAR definition

An individual neck support and head fixation was used in all patients. For treatment planning purposes, computed tomography (CT) images with intravenous contrast were used. The gross tumour volume (GTV) was delineated as the macroscopic tumour on the planning-CT fused with the hybrid fluorodeoxyglucose positron emission tomography (FDG-PET) and/or after rigid mutual-information-based registration with magnetic resonance imaging (MRI). The GTV and the clinical target volume (CTV) were delineated using local guidelines (RadboudUMC or MAASTRO clinic) based on Gregoire et al.[22-24]. The CTV was expanded to the planning target volume (PTV) taking into account the individual institutions' margin recipe: VMAT utilized 4 mm accounting for setup errors, intensity-modulated ion therapy (IMIT) employed 4 mm and intensity-modulated proton therapy (IMPT) 5 mm and 3 mm for the boost to the high risk PTV, to account for both setup and range uncertainties. The low risk volume, PTV with a prescribed dose of 54 Gy (PTV_{54Gy}), consisted of the tumour or tumour bed, the pathological lymph nodes and the elective lymph node levels. The high risk PTV planned to a total dose of 70 Gy (PTV_{70Gy}) was defined as the tumour or tumour bed and/or pathological lymph nodes. For all 25 patients included in this *in silico* study, the OARs were outlined by one dosimetrist (M.G.) and supervised by a radiation oncologist (D.E.) for the first and re-RT study set (see Table 2.1 for the list of OARs). Dental fillings and associated artefacts were delineated and the density was overridden to that of teeth or tissue, respectively, for dental fillings within the treatment beam were an exclusion criterion for PT. The use of any form of bolus to assure an accurate coverage of the target volume was permitted. There was no correction for the use of intravenous contrast.

Table 2.1 Dose constraints and priorities for organs at risk. The tolerance dose per OAR for the first and second treatment in Gy (E) with their planning priority.

		First treatment	Second treatment	
OAR	◯	Tolerance	Tolerance	Priority
Brain Stem	🔴	D_{max} 54 Gy	individual*	1
Spinal cord	🔴	D_{max} 50 Gy	individual*	1
Larynx	🟠	D_{max} 45 Gy	120 Gy**	1
Arytenoid	🟠	D_{max} 50 Gy	100 Gy**	1
Mandible	🟠	D_{max} 60 Gy	120 Gy**	1
Parotid glands (spared)	🟡	D_{mean} 26 Gy	no limit	2
Submandibular glands (spared)	🟡	D_{mean} 26 Gy	no limit	3
Swallowing muscle	🟢	D_{max} 50 Gy	no limit	4
Carotid artery	🟢	D_{max} 50 Gy	no limit	5
Jugular artery	🟢	D_{max} 50 Gy	no limit	5
Oral cavity	🟢	D_{mean} 26 Gy	no limit	5
Sternocleidomastoid muscle	🟢	D_{max} 60 Gy	no limit	5
Thyroid	🟢	D_{max} 60 Gy	no limit	5
Vertebrae	🟢	D_{max} 60 Gy	no limit	5

🔴 Dose limiting, exceeding this dose is not permitted
🟠 Only dose limiting if the OAR was not part of the CTV in the first and second treatment
🟡 Kept as low as possible if OAR was spared in the first treatment, not dose limiting
🟢 Goal limits, not dose limiting
* For each individual patient calculated assuming 30% recovery from first treatment
** Cumulative dose, the sum of the first and second treatment
OAR=organs at risk, D_{max}=maximum dose, D_{mean}= mean dose.

Treatment planning

The first treatment was considered a precondition in all patients, determining the remaining tolerance dose for the OARs, and therefore not described here. All subsequent paragraphs relate to the re-RT treatment plans. The PTV_{54Gy} was irradiated to a total dose of 54.25 Gy in 35 fractions of 1.55 Gy, the PTV_{70Gy} to 70 Gy in 35 fractions of 2 Gy using a simultaneous integrated boost (SIB) technique . In case no elective lymph nodes were included, 70 Gy was prescribed in 35 fractions of 2 Gy to PTV_{70Gy} (the tumour *or* pathological lymph node only).

All proton and photon treatment plans were calculated in centres that were already operating and had significant clinical experience treatment planning. The prescribed dose to the PTV_{70Gy} was set to 70 Gy of which 99% of the volume had to be covered by 95% of the dose for all modalities in order to enable a direct comparison. All plans were evaluated for robustness.

Dose constraints

For the OARs, the dose limits and priorities were defined in the protocol (Table 2.1). The dose-volume histograms (DVHs) of the original treatment plans were used to calculate the re-RT constraints for four OARs: the brainstem, spinal cord, mandible and larynx (including arytenoid). Since there was an interval of ≥1 year between first and second treatment, a 30% recovery was assumed for these four OARs[36-38]. The locations of the maximum dose (D_{max}) within an OAR in the first and secondary treatment plans were assumed to be the same, as a worst-case scenario, since the average overlap of the second treatment volume with the first treatment volume was determined to be 67%. No correction for fraction size was performed. Parotid and submandibular glands, if preserved in the first treatment, were attempted to be spared with second and third priority, respectively, without being dose limiting. For larynx, arytenoids and mandible, cumulative dose, which was the sum of the first and second treatment, was considered only dose limiting if the OAR was not part of the CTV in the first and second treatment (see Table 2.1). Attempts were made to minimize dose to the base of tongue, carotid arteries, jugular veins, oral cavity, sternocleidomastoid muscles, swallowing muscles, thyroid and vertebrae, but these structures were not dose limiting. For each re-RT plan, the mean dose (D_{mean}) was calculated per OAR as well as the near-maximum dose, defined as the highest dose to 2% of the volume (D_2), and the near-minimum dose defined as the lowest dose to 98% of the volume (D_{98})[39]. The mean integral dose (ID) was defined as the mean dose to the imaged part of the patient (body contour) minus CTV, also known as the residual volume at risk (RVR).

Photons

The original clinically applied re-RT treatment plans were created at RadboudUMC using Pinnacle (Pinnacle v8.2g Philips, WI) and at MAASTRO clinic using Varian (Eclipse™ v11.0 Varian Medical Systems, Palo Alto, CA). In order to account for improvements in photon plan techniques over the past years, the actual re-RT photon treatment plans were re-calculated employing state-of-the-art VMAT planning at MAASTRO clinic. With regard to VMAT, photons were considered to be innately robust relative to PT, therefore no explicit optimization techniques were incorporated into the VMAT plans as the PTV was assumed to be sufficient to produce a robust plan.

Protons

Proton re-treatment plans were calculated at University of Pennsylvania (UPENN) using IMPT for beam delivery with pencil beam scanning (PBS) (Eclipse™ v11.0 Varian Medical

Systems) using beam data modelled for IBA universal nozzle on a gantry (Ion Beam Applications, Louvain-la-Neuve, Belgium)[25]. Multi-field optimization (MFO) was used in the planning process as it produced superior OAR sparing compared to a single field uniform dose (SFO) approach[26]. To preserve small spots, UPENN utilised a universal bolus instead of a more conventional range shifter for the treatment of head and neck tumours[27]. A relative biological effectiveness (RBE) of 1.1 was used[28]. A typical field arrangement consisted of two posterior oblique beams or a posterior and posterior oblique beam, depending on target geometry. A lateral field was added or substituted for one posterior oblique when the D_{max} spinal cord constraint could not be met due to high dose target structures crossing the midline distal to the cord. PT is, with regard to IMPT, known to be intrinsically non-robust, therefore a PTV with a margin of 3 mm from the CTV was created with an additional 2 mm added to the planning optimization volume to account for range uncertainty. The 5 mm margin is a conservative value for head and neck assuming an overall uncertainty of 3.5% in conversion from Hounsfield Unit (HU) to relative proton stopping power and a range of approximately 15 cm[29,30]. The following margin definition in head and head-and-neck boost treatments was used: 3 mm transversal to the beam (on account of the residual patient positioning error, robotic table/imager uncertainties and beam steering) and 3 mm along the beam on account of the range uncertainties assuming HU calibration accuracy of 3% and beam range of ca. 10 cm[31,32].

Carbon ions

Carbon ion (C-ion) re-RT treatment plans were calculated at University of Marburg using a raster scanning technique with intensity-modulated ion therapy (IMIT) using Syngo PT Planning (Siemens Health Care Systems, Erlangen, Germany), which employed the local effect model (LEM1) for the biologically weighted dose computation[33,34]. The number of fields varied from 1 (in 1 case) to 3 (in 3 cases).The beam directions (using isocentric table rotations and gantry when deemed advantageous) were chosen individually for each case with two main considerations: avoidance of any unnecessary dose and evading strong density heterogeneities in the beam entrance channels[35]. Furthermore, beam directions traversing patient support and immobilization devices were avoided. For multiple beam setups reduced the under-dosages caused by potential range uncertainties, a uniform margin of 4 mm was applied with a tolerance of 2 mm, allowing the TPS to place additional raster spots outside the PTV as necessary, thus ensuring target coverage.

Plan robustness evaluation

All treatment plans (VMAT, IMPT, and IMIT) were assessed for robustness of the CTV coverage in their respective centres of origin. The robustness of the treatment plans was evaluated using worst-case scenario plan calculations with a ± 3 mm isocenter shift in x-, y-, and z-directions combined with a ±3.5% density shift (12 combinations per plan). The minimal dose to 95% and 98% of the CTV is given (D_{95} and D_{98}), respectively.

Storage of imaging datasets

The datasets was stored and exchanged through the secured collaborative MISTIR platform (www.mistir.info) hosted by MAASTRO clinic. Quality assurance procedures were applied to assess the necessity of corrections of transformations during treatment planning system (TPS) import and export[40].

Data evaluation and statistical analysis

Matlab software (The Math Works, Natick, MA) was used for statistical analysis. The dose matrices were scaled to the mean CTV_{70Gy} doses of 70 Gy (RBE equivalent) as this structure did not change between modalities. The dose metrics were extracted from the plan and statistically compared using two-tailed, signed-rank Wilcoxon tests to determine the significance of pairwise differences compared to VMAT (a p-value of <0.02 was considered significant, taking a Bonferroni correction into account).

Results

Twenty-five cases were included and in total 75 re-RT plans were analysed; one example is illustrated in Figure 2.1. All treatment modalities achieved a comparable dose to the CTV_{54Gy} and CTV_{70Gy} (Table 2.2). All plans were judged to be clinically applicable with worst-case scenario CTV robustness tests resulting in D_{98}=95.4±1.9% and D_{95}=97.9±1.4% for VMAT, D_{98}=94.6±2.8% and D_{95}=96.2±2.4% for IMPT, and D_{98}=93.1±3.0 and D_{95}=96.1±1.8 for IMIT (see Supplementary Table S2.1).

The average scaled values of the D_{mean} and D_2 for the OARs were compared between VMAT and IMPT/IMIT (Table 2.2, dose significance indicated with an asterisk). When comparing IMIT and IMPT to VMAT, the D_{mean} to all 22 OARs was statistically significantly reduced for IMIT and to 15 out of 22 OARs (68%) using IMPT (p<0.02) . The D_2 for the brainstem and spinal cord were statistically significantly reduced (p<0.02)

using IMPT and IMIT compared to VMAT. The integral dose was highest for VMAT (5.9 Gy), followed by IMPT (3.9 Gy) and IMIT (2.7 Gy).

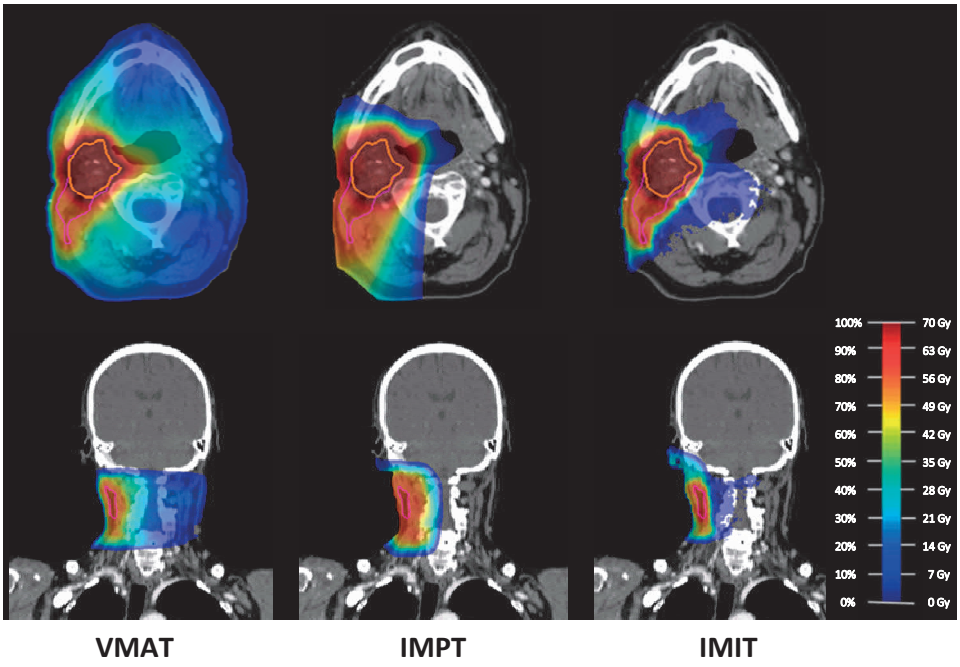

Figure 2.1 A set of re-irradiation treatment plans for a patient with a nodal recurrence of oropharynx carcinoma of the right tonsillar fossa, $rcT_0N_{2a}M_0$. In the VMAT (left column), IMPT (middle column) and IMIT (right column) plans, the CTV_{54Gy} (pink) and high-dose CTV_{70Gy} (orange). The dose-range is presented from high (red) to low (blue).

IMPT and IMIT proved to be superior to VMAT in sparing the contralateral located OARs. Depending on the OAR, this dose reduction was up to 85%-100% for the contralateral carotid artery and parotid gland, respectively, when using IMPT and 94%-99% for the contralateral carotid artery and parotid gland, respectively, when using IMIT. Conversely, IMPT increased the ipsilateral dose to the parotid gland (by 1%), carotid artery (by 2%) and submandibular gland (by 1%), albeit not to a clinically relevant level. The overall average D_{mean} and D_2 for all OARs and each treatment modality were plotted in Figure 2.2, showing that IMIT resulted in a lower D_{mean} in 100% of the cases and IMPT decreased the D_{mean} in 86% of the OARs compared to VMAT. For the D_2, the respective numbers were 100% and 59%.

Table 2.2 Mean doses (SD) of selected dosimetric parameters for organs at risk and target volume in Gy(E) for IMPT and IMIT compared to VMAT after scaling to the mean CTV_{70Gy} doses of 70 Gy; * is significant (p<0.02).

D_{mean} (Gy)	VMAT	IMPT	IMIT
Arytenoid ipsi & bilateral	34.5 (24.4)	27.3 (24.9)	20.6 (24.9)*
Arytenoid contralateral	17.6 (13.2)	2.3 (4.2)*	1.1 (0.9)*
Base of tongue	32.1 (19.4)	25.5 (23.3)	18.8 (21.7)*
Carotid ipsi- & bilateral	35.0 (17.1)	35.9 (19.4)	31.9 (19.8)*
Carotid contralateral	12.9 (8.4)	2.0 (4.5)*	0.83 (1.4)*
Body	5.9 (2.8)	3.9 (2.1)*	2.7 (1.5)*
Jugular ipsi- & bilateral	29.6 (20.2)	29.0 (22.5)	24.6 (22.8)*
Jugular contralateral	10.4 (6.6)	0.97 (3.0)*	0.57 (1.6)*
Larynx	34.1 (18.0)	27.2 (18.4)*	20.3 (17.5)*
Mandible	16.1 (12.7)	11.5 (11.5)*	8.2 (11.0)*
Oral cavity	14.9 (14.3)	9.0 (13.7)*	7.6 (14.6)*
Parotid ipsi- & bilateral	16.0 (15.2)	16.3 (16.6)	13.5 (14.5)*
Parotid contralateral	4.4 (2.1)	<0.01 (0.02)*	0.038 (0.13)*
Sterno cleido mastoid ipsi- & bilateral	31.2 (17.1)	30.9 (20.5)	26.3 (19.5)*
Sterno cleido mastoid contralateral	11.4 (6.8)	1.6 (3.0)*	0.64 (1.4)*
Submandibular gland ipsi- & bilateral	35.4 (20.0)	35.9 (20.2)	29.2 (18.5)*
Submandibular gland contralateral	16.3 (9.3)	0.64 (1.7)*	0.73 (1.2)*
Swallowing muscle total	31.9 (21.5)	25.1 (21.5)*	18.9 (21.1)*
Thyroid	30.9 (25.2)	29.8 (25.2)	25.9 (24.4)*
Vertebrae	18.1 (7.6)	10.8 (6.8)*	5.8 (4.2)*
CTV_{54Gy}	60.9 (2.7)	61.7 (2.7)*	61.3 (2.5)
CTV_{70Gy}	70.0 (<0.01)	70.0 (<0.01)	70.0 (<0.01)
D_2 (Gy)	VMAT	IMPT	IMIT
Brainstem	8.2 (7.9)	2.7 (5.3)*	1.3 (2.5)*
Spinal cord	16.6 (4.7)	6.7 (5.7)*	4.8 (3.2)*
V_{95} (%)	VMAT	IMPT	IMIT
CTV_{54Gy}	99.5 (0.6)	99.7 (0.4)	100.0 (0.02)*
CTV_{70Gy}	98.9 (2.5)	99.9 (0.3)	99.9 (0.2)

Dosimetric metrics of selected OARs per patient are plotted in Supplementary Figure S2.1 and S2.2. The maximum dose to the spinal cord (D_2), was significantly reduced (Table 2.2) for most patients using IMPT (96%) and for all patients using IMIT (100%) (Supplementary Figure S2.2). Regarding D_{mean} to the oral cavity and D_2 of the brainstem, IMIT decreased doses in all cases, compared to 88% and 96% of the cases when delivering IMPT. The D_2 of the Larynx and mandible showed less benefit for IMPT and IMIT (28% and 28%, and 50% and 76%, respectively). For all modalities, radiation doses to the spinal cord and brainstem remained below the constraints without the need to underdose the targets (Supplementary Figure S2.1). For the mandible 32% (VMAT), 36% (IMPT) and 28% (IMIT) of patients exceeded the cumulative dose of 120 Gy and the cumulative larynx constraint was not met in 78%, 83% and 83% of the patients, respectively.

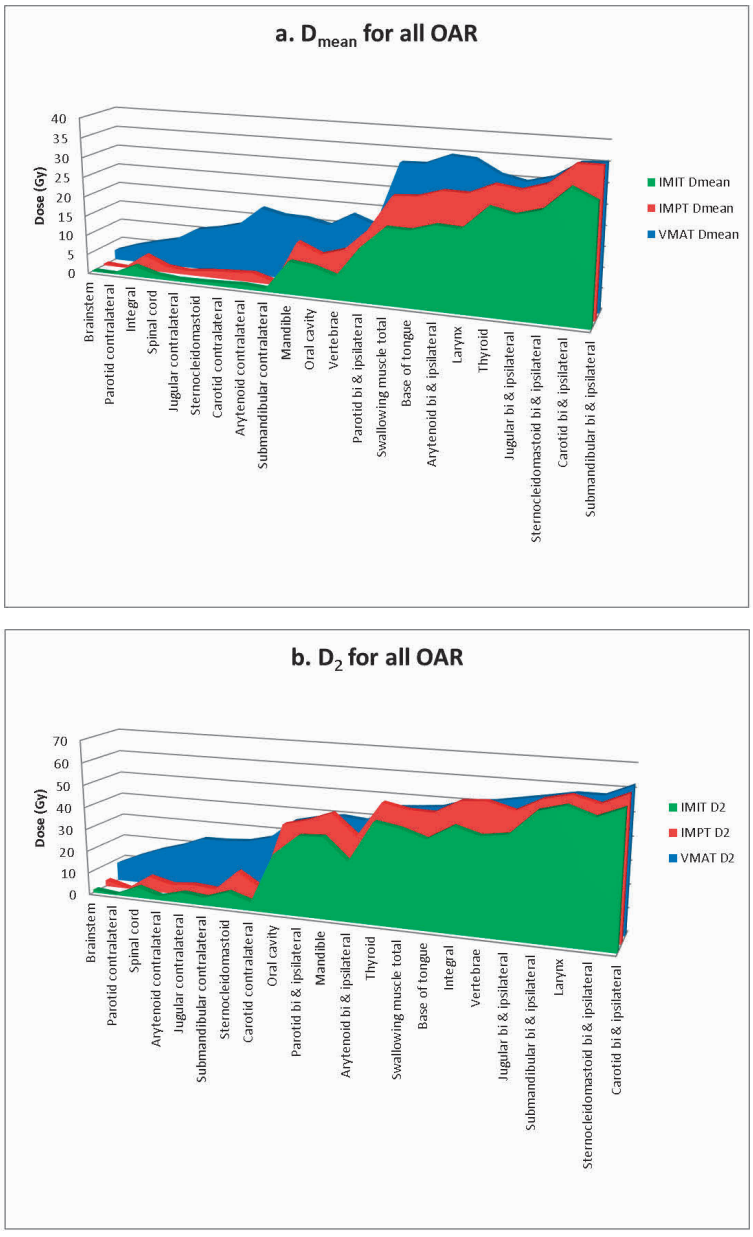

Figure 2.2 The overall average mean dose [$D_{mean;}$ a)] and maximum dose in Gy (equivalent) to 2% [D_2, b)] for all OARs is given for volumetric modulated arc therapy (VMAT, blue), intensity-modulated proton therapy (IMPT, red) and intensity-modulated ion therapy (IMIT, green).

The number of patients that benefit from IMPT and/or IMIT over VMAT was plotted in Figure 2.3. All individual patients benefitted from IMIT with regard to arytenoid, oral cavity, spinal cord, brain stem and integral dose, as opposed to 80%-100% of the patients for IMPT. The D_2 to the bony structures (mandible and vertebrae) decreased in a low percentage of patients using IMPT (28% and 16%) as compared to a high percentage of patients using IMIT (76% and 84%). Overall, in this population of re-irradiated HNSCC patients, PT generated a lower OAR dosage with an advantage of IMIT over IMPT compared to VMAT (84% and 60% respectively).

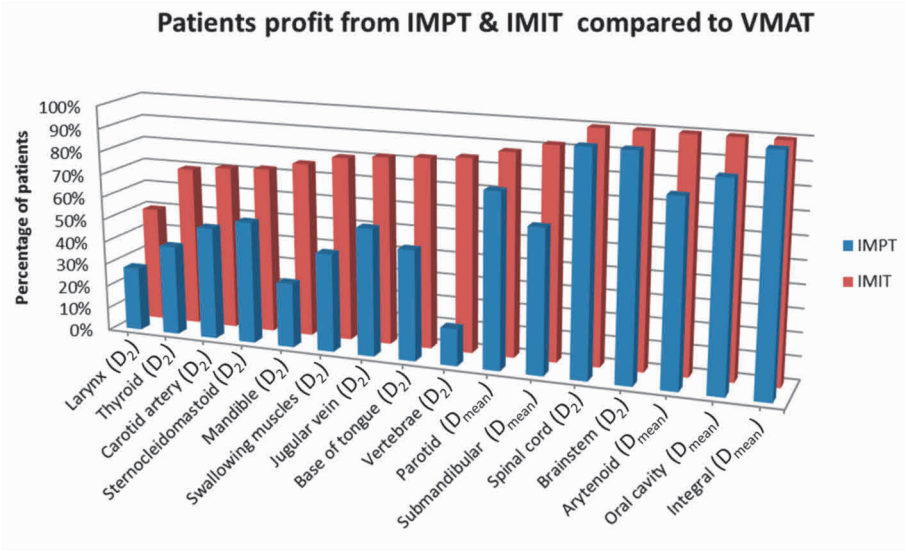

Figure 2.3 Percentage of patients receiving lower dose to the organs at risk when applying IMPT and/or IMIT compared to VMAT. The maximum dose received by 2% of that specific structure (D_2) and the mean dose (D_{mean}) both in Gy(E) are given.

Discussion

In this ROCOCO *in silico* clinical trial, through a comparison of state-of-the-art treatment plans prepared according to a strict clinical protocol, we have demonstrated, that re-RT of HNSCC patients using PT (IMPT and IMIT) can result in improved sparing of OAR when compared to photon therapy (VMAT). In most of the cases, this benefit was greater for the IMIT than for IMPT, which could be due to different beam characteristics such as sharper lateral penumbra or different spot size. While the clinical outcome data from randomized trials comparing proton *versus* carbon ion

treatment are not yet available, several treatment planning studies are in line with our findings suggesting advantages of carbon ions in terms of conformity, *i.e.*, dose to the normal tissue[41,42].

However, there are confounding factors that may have influenced our findings. In this ROCOCO study, the treatment plans of all the modalities were prepared independently complying with the internal protocols applied in the individual institute's routine clinical practice. Therefore, beyond the contouring and planning goal specifications, the treatment planning procedures themselves were not necessarily alike. As a result, differences may affect the numerical outcome reported here. For instance, the different PTV margins used by the three centres for the different treatment modalities may have caused an underestimation of the value of IMPT for re-irradiating HNSCC for the numerical comparison was unfavourable. These different PTV margins may have arisen from different choices regarding the range uncertainties (see Material and Methods). Even though beyond the scope of this publication a subsequent study with predefined strict margin may shed additional light on this matter.
Also the influence of different beam angles or optimization criteria cannot be excluded. For carbon ion plans, full beam direction flexibility afforded by the gantry was exploited in the beam setups when deemed advantageous. This decision was taken at the design stage of this *in silico* trial and had two main reasons. In clinical routine, each of the 10 carbon ion centres currently in operation has some, often (almost) unique, limitations that start to be overcome with additional degrees of freedom by couch roll and/or pitch (www.ptcog.ch). Moreover, there are on-going efforts aiming at making gantries more available. However, research to assess the actual benefit of gantry *versus* fixed nozzle is warranted.

Should we all change our strategy to carbon ions then in the setting of recurrent HNSCC eligible for radical re-irradiation? We know that there have been many years of experience in using proton beams in daily clinical practice[41]. However, for carbon ion beams there is only little experience, with only three papers describing clinical data on the treatment of HNSCC either as single modality or combined with photons/ protons[44-46].

In this study, IMPT and IMIT plans using multi-field optimization and active scanning delivery were investigated owing to their superior delivered dose conformity. Using passive-scattering proton therapy (PSPT) would have altered the results, e.g., Kase *et al*.[47] compared PSPT with IMPT in different primary tumour sites including nasal cavity and demonstrated that IMPT resulted in lower doses to OARs. In general, multi-field

optimization offers superior OAR sparing compared with PSPT or pencil beam plans optimized with uniform dose per field, and this benefit can be essential in the context of re-treatment[26,33].

Due to the sensitivity of pencil beam scanning proton plans to setup and range uncertainties as well as the degenerate optimal spot map solutions influenced by optimization algorithms which result in varying degrees of plan robustness, it is critical to examine robustness of PT plans[48]. On the other hand, optimization algorithms that explicitly incorporate robustness and can reduce uncertainties in IMPT and IMIT plans are likely to lead to less modulated fields, hence resembling SFO approach[49]. The influence of changing anatomy due to tumour regression and weight loss plays a more significant role in PT than in photon therapy which may necessitate the use of more frequent imaging or even adaptive planning strategies[50-54]. Furthermore, the presence of metal or/and associated artefacts within the treatment beam poses a problem in PT and is argued to be a patient exclusion criterion. Therefore, in our study, these artefacts were delineated and overridden to teeth and water densities, respectively, simulating their absence. This approach carries intrinsic uncertainties, which were assumed to be negligible with respect to influencing key dosimetric parameters. Richard *et al*.[55] found that in 110 oral cavity/oropharynx radiation treatment plans artefacts were identified in 74% obscuring the CTV in 95% of these cases. In a constructed head and neck phantom, they measured PTV baseline dose ranges of 98%-106% and in presence of metal amalgam 66%-111%. A potential solution may be exchanging metal fillings by composite before proton treatment planning to improve tumour visualization and dosimetry[55].

An individualised radiation oncology strategy based on multifactorial decision support systems would be of great help and is currently being developed for different tumour types[56-60]. In this ROCOCO trial, PT is beneficial for sparing OARs in all HNSCC patients who are candidates for re-RT. However, as long as particle therapy availability is limited and comes at significantly higher costs, finding the patient who is benefitting most is highly relevant to the treating physicians as well as health insurance companies[61]. Therefore, in the prospective Dutch model-based approach, a plan comparison is compulsory for all non-standard indications showing that a reduction in late toxicity computed from a dose difference will actually result in clinically significant lower normal tissue complication probability (NTCP)[63]. This potential benefit, however, must be proven in clinical studies since toxicity is of course dependent on type of tissue, previous dose, interval and co-morbidity (*e.g.,* vascular and metabolic comorbidity). In order to estimate this, a validated NTCP model for re-RT is needed. Developing such a re-RT-NTCP model will be difficult for it has to take into account various additional

parameters: *e.g.*, interval between treatments, repair capacity of the tissue as a function of dose given at first treatment and other treatments between radiations, concomitant systemic therapy (not taken into account in the current study).

In summary, the results of this *in silico* trial have demonstrated that PT can significantly reduce the dose to OARs whilst maintaining the prescription dose (assuming the planned dose is representative of the delivered dose); nevertheless, the exact magnitude of the clinical benefit is uncertain as a decrease in dose does not always translate into a clinically relevant decrease of toxicity risk. Proper development and validation of NTCP models for particle therapy is by no means trivial as there are many uncertainties to contend with, *e.g.*, treatment planning, treatment delivery, relative biological effects, tumour shrinkage, and patient co-morbidities. Rapid-learning approaches along with prospective cohort studies as well as (*in silico*) randomised controlled trials provide possible solutions in this regard[62].

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Supplemental materials

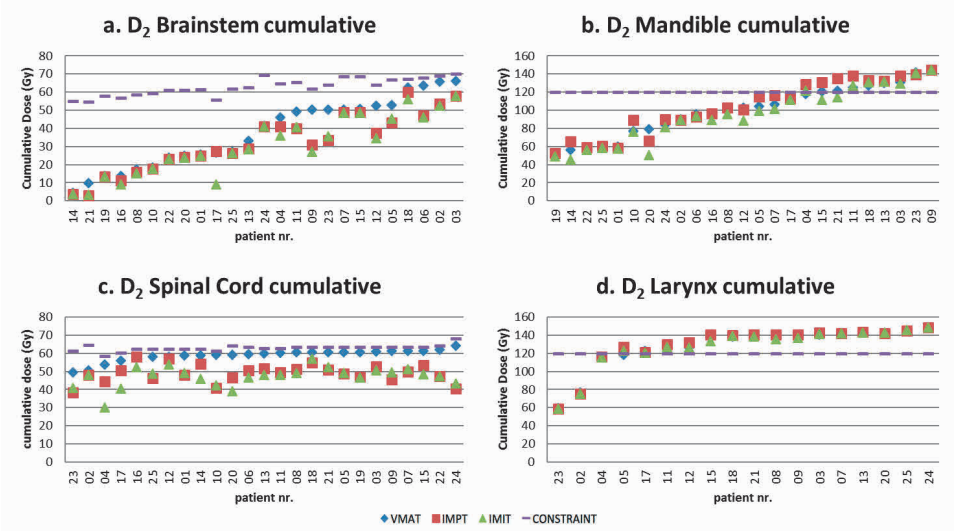

Figure S2.1 Dosimetric metrices cumulative for selected OARs per patient for VMAT, IMPT and IMIT treatment plans.
The dose (Gy) is depicted per patient for VMAT (diamond), IMPT (square) and IMIT (triangle) and is sorted for VMAT. The individually calculated dose constraint per patient is taking the first treatment into account (line): a) the maximum dose to 2% of the brainstem (D_2), b) the D_2 of the mandible, c) the D_2 of the spinal cord, d) the D_2 of the mandible, all in in Gy(equivalent).

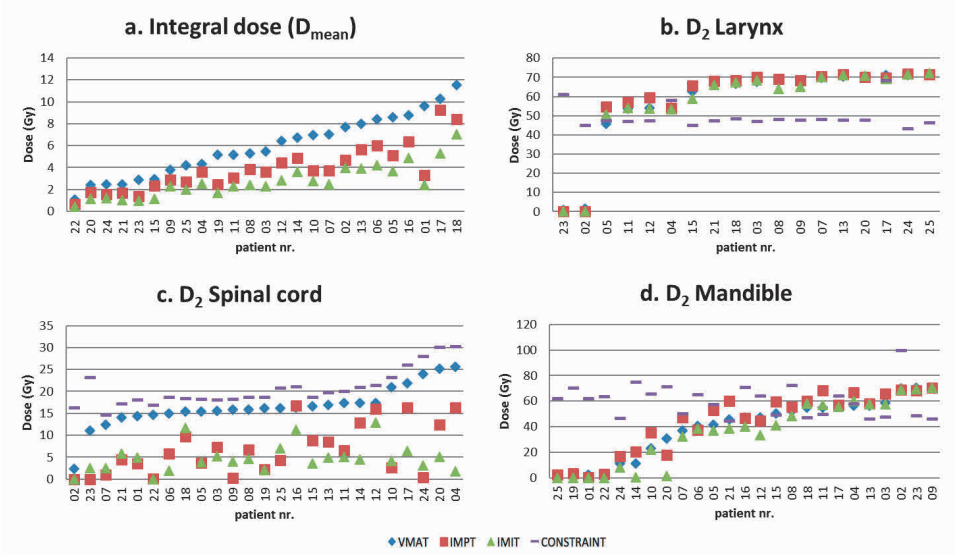

Figure S2.2 Dosimetric metrices for selected OARs per patient for VMAT, IMPT and IMIT treatment plans. The dose (Gy) is depicted per patient for VMAT (diamond), IMPT (square) and IMIT (triangle) is sorted for VMAT. The individually calculated dose constraint per patient is taking the first treatment into account (line): a) the integral Body dose (D_{mean}) minus the CTV, b) the maximum dose to 2% of the of the larynx (D_2), c) the maximum dose to 2% of the spinal cord (D_2) and d) the maximum dose to 2% of the mandible (D_2), all in Gy(E).

Table S2.1 Report of 'worst case' scenario of the 25 patients.

VMAT						IMIT						IMPT					
	Structure	*CTV*					*Structure*	*CTV*					*Structure*	*CTV*			
Patient No.	D_{95} (%)	D_{98} (%)	Direction	Magnitude (cm)	Density (%)	Patient No.	D_{95} (%)	D_{98} (%)	Direction	Magnitude (cm)	Density (%)	Patient No.	D_{95} (%)	D_{98} (%)	Direction	Magnitude (cm)	Density (%)
1	95,5	95,5	L	0,3	N/A	1	93,3	87,5	S	0,3	3,5	1	97,5	95,3	I	0,3	3,5
2	97,6	96,2	L	0,3	N/A	2	94,2	93,1	I	0,3	-3,5	2	96,7	93,6	P	0,3	3,5
3	100,3	96,6	S	0,3	N/A	3	95,0	92,8	R	0,3	3,5	3	95,6	93,8	L	0,3	3,5
4	96,6	94,7	L	0,3	N/A	4	95,6	94,3	L	0,3	-3,5	4	96,2	95,3	L	0,3	3,5
5	98,6	93,0	L	0,3	N/A	5	93,8	91,1	I	0,3	3,5	5	99,5	98,9	I	0,3	-3,5
6	96,3	92,6	P	0,3	N/A	6	94,7	92,2	I	0,3	3,5	6	97,2	95,3	P	0,3	-3,5
7	97,8	96,0	L	0,3	N/A	7	95,2	89,7	L	0,3	3,5	7	99,1	97,4	S	0,3	3,5
8	98,1	94,4	S	0,3	N/A	8	95,6	94,3	P	0,3	-3,5	8	98,4	96,4	P	0,3	3,5
9	98,8	96,9	L	0,3	N/A	9	95,6	88,0	S	0,3	3,5	9	95,2	94,4	R	0,3	3,5
10	100,3	98,4	L	0,3	N/A	10	98,1	96,0	S	0,3	-3,5	10	95,3	94,2	I	0,3	3,5
11	98,7	96,8	L	0,3	N/A	11	93,7	89,2	S	0,3	3,5	11	93,2	92,4	L	0,3	3,5
12	98,2	96,3	I	0,3	N/A	12	95,2	93,3	P	0,3	-3,5	12	96,6	94,1	A	0,3	-3,5
13	98,2	90,8	L	0,3	N/A	13	96,3	91,7	S	0,3	3,5	13	93,8	93,0	R	0,3	3,5
14	98,5	94,7	P	0,3	N/A	14	94,3	87,7	L	0,3	3,5	14	93,7	92,4	R	0,3	3,5
15	98,4	96,5	L	0,3	N/A	15	99,9	97,5	I	0,3	-3,5	15	98,8	96,5	I	0,3	3,5
16	99,6	97,8	L	0,3	N/A	16	96,6	95,1	I	0,3	-3,5	16	96,8	96,0	S	0,3	3,5
17	99,4	97,6	L	0,3	N/A	17	96,1	94,5	L	0,3	-3,5	17	95,2	94,0	L	0,3	3,5
18	98,3	96,5	S	0,3	N/A	18	95,6	90,6	S	0,3	3,5	18	96,5	95,8	L	0,3	3,5
19	97,9	97,9	L	0,3	N/A	19	97,2	95,5	I	0,3	-3,5	19	96,2	95,2	L	0,3	3,5
20	98,1	96,7	L	0,3	N/A	20	96,6	95,4	I	0,3	-3,5	20	101,6	101,1	R	0,3	3,5
21	94,7	94,7	S	0,3	N/A	21	99,4	97,4	I, A	0,3	-3,5	21	95,6	94,2	L	0,3	3,5
22	96,8	92,5	I	0,3	N/A	22	96,4	94,6	S	0,3	-3,5	22	97,8	95,9	L	0,3	3,5
23	98,2	93,9	L	0,3	N/A	23	98,3	96,4	I	0,3	-3,5	23	92,1	88,9	L	0,3	3,5
24	96,0	93,2	P	0,3	N/A	24	95,6	93,7	P	0,3	-3,5	24	91,7	87,5	R	0,3	3,5
25	95,7	95,7	L	0,3	N/A	25	99,1	96,9	I	0,3	3,5	25	94,0	92,8	P	0,3	-3,5
Mean.	97,9	95,4				Mean.	96,1	93,1				Mean.	96,2	94,6			
St.Dev.	1,4	1,9				St.Dev.	1,8	3,0				St.Dev.	2,4	2,8			

The D95 and D98 are reported as a % of the prescription dose. The direction is the direction of the 'worst case' scenario with a ± 3 mm isocenter shift in x-, y-, and z-directions of the patient combined with a ±3.5% range shift (A = Anterior, P = Posterior, L = Left, R = Right, S = Superior, I = Inferior). The magnitude of the robustness analysis displacement of the 'worst case' scenario is reported in (cm). The density is the % by which the density was scaled in the 'worst case' scenario (NB. Plus + or minus -). N/A = not available. The modality is the modality used (VMAT, IMPT, and IMIT).

Chapter 3

Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric *in silico* ROCOCO trial

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Acta Oncologica, 2018. In press

Abstract

Background and purpose

Patients with low-grade glioma (LGG) have a prolonged survival expectancy due to better discriminative tumor classification and multimodal treatment. Consequently, long-term treatment toxicity gains importance. Contemporary radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), Tomotherapy (TOMO) and intensity-modulated proton therapy (IMPT) enable high-dose irradiation of the target but they differ regarding delivered dose to organs at risk (OARs). The aim of this comparative *in silico* study was to determine these dosimetric differences in delivered doses.

Material and methods

Imaging datasets of twenty-five LGG patients having undergone postoperative radiotherapy were included. For each of these patients, *in silico* treatment plans to a total dose of 50.4 Gy to the target volume were generated for the four treatment modalities investigated (i.e., IMRT, VMAT, TOMO, IMPT). Resulting treatment plans were analyzed regarding dose to target and surrounding OARs comparing IMRT, TOMO and IMPT to VMAT.

Results

In total 100 treatment plans (4 per patient) were analyzed. Compared to VMAT the IMPT mean dose (D_{mean}) for 9 out of 10 (90%) OARs was statistically significantly ($p<0.02$) reduced, for TOMO this was true in 3/10 (30%) patients and for 1/10 (10%) patients for IMRT. IMPT was the prime modality reducing dose to the OARs followed by TOMO.

Discussion

The low dose volume to the majority of OARs was significantly reduced when using IMPT compared to VMAT. Whether this will lead to a significant reduction in neurocognitive decline and improved quality of life is to be determined in carefully designed future clinical trials.

Introduction

Gliomas are the most common tumors of the central nervous system (CNS), with an annual incidence of 5.4 per 100.000 in Europe[1]. Low-grade gliomas (LGG), classified as World Health Organization (WHO) grade 2, typically occur in younger adults (2nd-5th decade) and are diffusely infiltrative tumors. Most LGG show a protracted disease course; however, significant differences in survival rates have been identified. Consecutively, molecular parameters, such as 1p19q co-deletions, IDH mutation, TERT promotor mutations, and EGFR-amplifications and -mutations have found their way into the novel WHO classification of CNS tumors, revised in 2016[2-4]. This integrated diagnosis of gliomas is now leading the neuro-oncology field towards multimodal treatment schedules capable of increasing overall survival of diffuse gliomas with an aggressive clinical behavior[5,6]. Multimodal treatment schedules include neurosurgical resection if feasible and adjuvant treatment with radiation therapy as well as chemotherapy[6]. With increasing survival of LGG patients, therapy induced toxicity, such as neurocognitive decline caused by radiotherapy, which potentially decreases the quality of life of these patients, should be minimized[7]

There has been an impressive progress in recent photon-based radiotherapy techniques, moving from 3D conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and tomotherapy (TOMO), delivering high radiation dose to the target and low doses to surrounding organs at risk (OARs)[8]. Examples of this progress are the RTOG 0933 phase 2 clinical study on conformal hippocampus sparing whole brain radiotherapy showing a preservation of memory and quality of life, and the ongoing trial on hippocampus-sparing prophylactic cranial irradiation using VMAT, IMRT or TOMO (NCT01780675)[9].

As a result of their physical characteristics, protons deposit a low entry dose followed by maximum dose delivery the Bragg peak, and zero dose after the dose fall-off at the distal edge of the Bragg peak, resulting in a superior sparing surrounding OARs compared to photons. Conversely, the tumor control probability may be increased at maintained OAR dose or by exploiting the somewhat higher relative biological effectiveness[10-13]. Consequently, physicians, patients, and health insurance companies are interested in the role of proton therapy (PT), e.g., regarding its possible reduction of toxicity in LGG and head-and-neck cancer patients, amongst others.

To assess the potential dosimetric gains of intensity modulated proton therapy (IMPT) for individual LGG patients, we conducted an international multicenter *in silico* treatment planning study within the Radiation Oncology Collaborative Comparison (ROCOCO) group in a cohort of 25 LGG patients retrospectively retrieved from two Dutch radiotherapy departments[14-16].

Materials and methods

Study population

We retrospectively retrieved radiation treatment plans and underlying imaging data, *i.e.*, computed tomography (CT) and magnetic resonance imaging (MRI), of 25 WHO grade 2 LGG patients who had undergone radiation treatment (VMAT or IMRT) at the Radboud University Medical Centre (Radboudumc), Nijmegen (The Netherlands), or at the Department of Radiation Oncology of Maastricht University Medical Center (MAASTRO clinic), Maastricht (The Netherlands). These patients had previously undergone a gross total resection or biopsy depending on the localization of the tumor. No prior systemic therapy had been administered. This ROCOCO *in silico* trial was approved by the MAASTRO clinic institutional review board and was registered on clinicaltrial.gov ID: NCT NCT02607397. Data are available on www.cancerdata.org[17].

Target volume and OAR definition

An individual head support and thermoplastic mask was used in all patients. The gross tumor volume (GTV) was delineated as the resection cavity, encompassing any residual/recurrent macroscopic tumor on the planning-CT (2 or 3 mm slices) fused with the (pre- and post-surgical) MRI (T1-weighted with contrast agent and T2-weighted/FLAIR images) using image registration of Eclipse™ (v11.0 Varian Medical Systems, Palo Alto, CA). The clinical target volume (CTV) was defined by the treating radiation oncologist as the GTV with a 1 cm margin, corrected for anatomical boundaries, according the local guidelines at Radboudumc and MAASTRO clinic. For this *in silico* study, the CTV was distributed to the participating centers. Taking into account different photon techniques and the individual institution's margin recipes, the CTV was expanded to the planning target volume (PTV): linear accelerator (LINAC) based VMAT and IMRT utilized 2 mm accounting for setup errors, and helical tomotherapy based IMRT (TOMO) used a 3 mm margin based on the individual institution's clinically derived margins. Intensity-modulated proton therapy (IMPT) used a setup uncertainty of 2 mm and a range uncertainty of 3.5%. For all 25 patients included in this *in silico* study, the OARs were outlined by one dosimetrist (M.G.) and supervised by a radiation oncologist (D.E.) according the atlas by Eekers *et al.*[18] (see Table 3.1 for the list of OARs). A double-sided OAR was termed 'contralateral' when located at the contralateral hemisphere *and* not included in the CTV. Whenever the tumor was centrally located or both double-sided OARs were located within the CTV, this OAR was named 'bilateral'. Dental fillings and associated artifacts were delineated and the density was overridden to that of teeth or soft tissue, respectively. Dental fillings within

the treatment beam were an exclusion criterion for IMPT. There was no correction for the use of intravenous contrast during the planning-CT.

Dose prescription

For simplicity reasons, all doses are reported in Gy equivalents (GyE), taking into account the relative biological effectiveness (RBE) of 1 for photons and 1.1 for protons. The prescribed dose to the target was 50.4 Gy in 28 fractions of 1.8 Gy, such that at least 99% of the volume had to be covered by 95% of the dose ($V_{95\%}$=99%). All proton (IMPT) and photon (VMAT, IMRT, TOMO) treatment plans were generated in centers with significant clinical experience in treatment planning.

Dose constraints

The dose limits and priorities for the OARs were defined in the protocol of this *in silico* comparative study (see Table 3.1). The dose limits to the brainstem, brain, spinal cord, chiasm, optic nerves and retina were not to be exceeded. Attempts were made to minimize the dose to the other OARs without causing underdosage of the $PTV_{50.4Gy}$.

Table 3.1 Tolerance dose and planning priority per organ at risk in Gy(RBE).

OAR	○	Tolerance	Priority
Brain Stem	🔴	$D_{2\%}$ 54 Gy	1
Brain	🔴	$D_{2\%}$ 60 Gy	1
Spinal cord	🔴	$D_{2\%}$ 50 Gy	1
Chiasm & optic nerve	🔴	$D_{0.1cc}$ 55 Gy	1
Retina	🔴	$D_{0.1cc}$ 45 Gy	1
Cornea	🟠	$D_{0.1cc}$ 30 Gy	2
Lacrimal gland	🟠	D_{mean} 30 Gy	2
Cochlea	🟡	D_{mean} 45 Gy	3
Lens	🟢	$D_{0.1cc}$ 30 Gy	4
Hippocampus	🟢	D_{mean} 9 Gy	4
Pituitary gland	🟢	D_{mean} 45 Gy	4
Posterior cerebellum	🟢	D_{mean} ALARA	4

🔴 Dose limiting, exceeding this dose is not permitted
🟠 Only dose limiting if the OAR was not part of the CTV
🟡 Not dose limiting if the contralateral organ is preserved
🟢 Goal limits, not dose limiting

OAR=organ at risk, $D_{2\%}$= is the maximum dose to 2% of the volume of the OAR, D_{mean}= mean dose, $D_{0.1cc}$ is the maximum dose reported in case 2% is smaller than 0.1 cc. ALARA = as low as reasonably achievable.

Photon planning

The IMRT and VMAT treatment plans were created at MAASTRO clinic using Eclipse™ (v11.0 Varian Medical Systems, Palo Alto, CA). For VMAT plans, one or two 10 MV half- or whole arcs were used. For IMRT beam angle optimization was used for the optimal beam arrangement, using 4 to 7 beams of 10 MV each. The TOMO treatment plans were created at Radiotherapiegroep Deventer using Accuray Hi-Art Planning Station (v5.1.0.4, Accuray, Sunnyvale, CA). The photon plans using a PTV margin were considered to be innately robust relative to PT, assuming the PTV to be sufficient to produce a robust plan. A grid size of 2–3 mm was used for all modalities depending on the slice spacing of the dataset.

Proton planning

Proton treatment plans were calculated using RayStation (v4.65.99, RaySearch Laboratories AB, Stockholm, Sweden) using IMPT for beam delivery with pencil beam scanning (PBS). Treatment plans were created for each patient using a robust optimized plan with mostly two radiation beams. The air-gap used between the patient surface and the range shifter was 2 cm. The beam direction was chosen individually for every patient in order to spare the OARs and healthy brain tissue, and to avoid passing through air cavities. The minimum energy of the beam model used was 100 MeV with a spot size sigma ranging from 4 mm (220 MeV) to 8 mm (100 MeV) in the isocenter. These robust plans were generated optimizing the target coverage for the CTV, thus no PTV concept was used, including a setup uncertainty of 2 mm and a range uncertainty 3.5%, and considering 21 scenarios for the optimization process. A range shifter of approximately 7.5 cm water equivalent and a calculation grid of 3 mm were used in all cases.

Storage of imaging datasets

The datasets were stored and exchanged through the secured collaborative MISTIR platform hosted by MAASTRO clinic. Quality assurance procedures were applied to assess the necessity of corrections of potential transformations during import and export in the respective treatment planning systems[19].

Data evaluation and statistical analysis

For each treatment plan, the mean (D_{mean}) and maximum dose (D_{max}) as well as the near-maximum dose, defined as the highest dose to 2% of the volume ($D_{2\%}$) or to 0.1% ($D_{0.1cc}$) in case 2% was smaller than 2 cc, were calculated for each OAR and CTV[20]. The

mean dose to the imaged part of the patient (body contour) minus CTV was defined as the mean integral dose (ID).

For statistical analyses, an in-house developed script in Matlab (version 2017a, The MathWorks, Natick, MA) was used to extract dose-volume-histograms (DVH) metrics from the 3D dose distributions that were uploaded by the participating centers. To allow for a direct comparison between all treatment modalities, the doses to the CTV were considered as no PTV was used for protons. The doses were scaled such that 99% of the CTV received exactly 100% of the prescribed dose (50.4 Gy). Whenever needed, scaling was increased to be sure that the GTV was covered with at least 50.4 Gy. This was required in four patients with a factor between 0.98 and 1.16.

Considering the fact that VMAT was used for the actual treatment of the 25 LGG patients included in this study, it was considered the gold standard for the comparative analyses. The DVH metrics and doses to OARs were statistically compared using two-tailed, Wilcoxon signed-rank test to determine the significance of pairwise differences compared to VMAT. Accounting for multiple testing and applying a Bonferroni correction, a p-value <0.02 was considered statistically significant. The Van 't Riet[21] conformity number (0 to 1) was used to describe the conformity of the CTV coverage, with 1 indicating a perfect conformity.

To evaluate the TPS performance of robust IMPT planning, six random patients were evaluated with each having 26 scenarios for setup (2 mm) and density (3.5%) changes. Next, the $V_{95\%}$ of the CTV prescribed dose was calculated. To quantify the variability in the results, the Coefficients of Variation (CV=standard deviation over mean) were determined.

Results

In total 100 treatment plans for the twenty-five patients with LGG patients were calculated and analyzed. An example of the treatment plans for a patient is presented in Figure 3.1. The dose coverage of the $CTV_{50.4Gy}$ was statistically significantly better for TOMO than for VMAT (p=0.02; $V_{95\%}$ = 99.9%), overall the coverage was excellent for all modalities with the volume receiving 95% of the prescribed dose ($V_{95\%}$) of the $CTV_{50.4Gy}$ ranging from 99.7 to 100% (comparison to gold standard VMAT given in Table 3.2). The conformity expressed using the Van 't Riet[21] conformity number showed that VMAT plans had the highest conformity (0.74), followed by TOMO (0.72; p<0.02), IMRT (0.69; p<0.02), and IMPT (0.69; p<0.02; Table 3.2). In accordance with robust photon plans, the variability in robust planning for the six evaluated IMPT cases proved to be very limited with an average CV of 0.07% (range 0.05-0.12%; Supplementary Table S3.1).

The mean integral dose was significantly increased for TOMO (8.3 Gy; p<0.02) and IMRT (7.9 Gy, p<0.02) and decreased for IMPT (5.6Gy, p<0.02) compared to VMAT (7.8 Gy). Table 2 shows the average scaled values of the D_{mean} and $D_{2\%}$ for the OARs delivered by IMRT, TOMO and IMPT in comparison to VMAT; overall, the D_{mean} of the OARs statistically significantly differed from VMAT for IMRT, TOMO, and IMPT, being 1/10 (10%), 3/10 (30%), and 9/10 (90%), respectively. For the $D_{2\%}$, a statistically significant dose reduction was found in 3/12 (25%), 6/12 (50%) and 10/12 (83%) of the OARs, respectively. IMPT was the prime modality reducing dose to the OARs followed by TOMO. The pituitary gland was best spared by TOMO (Table 3.2).

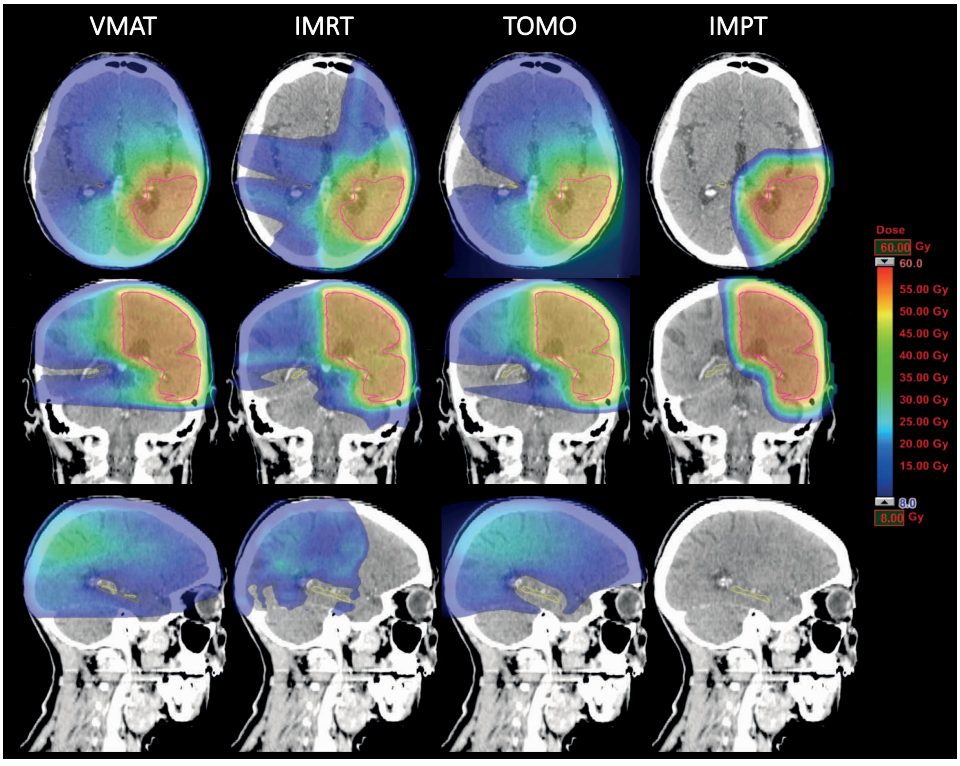

Figure 3.1 Example of a radiation treatment plans for a patient with a LGG parieto-occipitally in the left hemisphere. The CTV (pink), hippocampus (yellow) and dose distribution (ranging from low dose depicted in blue to high dose in red) are given for the VMAT (A), TOMO (B), IMRT (C) and IMPT (D) treatment plans, in the transverse (upper row), frontal (middle row) and sagittal (lower row) view. Of note is the large low-dose bath when using either of the photon techniques (A-C).

Table 3.2 Dose and coverage parameters per organ at risk or target volume per treatment modality (significance calculated in comparison to the gold standard VMAT).

Organ at risk	VMAT $D_{2\%}$	IMRT $D_{2\%}$	TOMO $D_{2\%}$	IMPT $D_{2\%}$
Brain	52.7 (1.1)	53.4 (1.7)*	52.7 (0.47)	52.4 (0.46)
Brainstem	40.7 (16.7)	40.5 (17.9)	39.5 (16.5)	39.2 (19.8)
Chiasm	37.7 (17.2)	36.4 (18.9)	33.7 (19.2)*	32.8 (22.5)*
Cornea ipsi & bilateral	13.8 (5.7)	14.1 (9.0)	12.1 (5.7)*	5.1 (7.0)*
Cornea contralateral	12.5 (4.8)	9.6 (5.4)*	11.0 (4.7)	1.3 (2.4)*
Lens ipsi & bilateral	5.2 (1.6)	6.9 (5.5)	4.4 (2.1)	1.4 (1.9)*
Lens contralateral	5.2 (1.5)	5.1 (2.9)	4.2 (1.8)	0.52 (1.3)*
Optic nerve ipsi & bilateral	31.6 (17.5)	30.7 (18.4)	27.4 (18.7)*	27.9 (22.8)
Optic nerve contralateral	26.4 (14.7)	21.5 (16.0)*	16.4 (12.9)*	16.0 (19.8)*
Retina ipsi & bilateral	17.6 (9.0)	18.0 (11.9)	14.0 (7.0)*	10.7 (12.2)*
Retina contralateral	14.6 (5.7)	10.9 (6.3)*	10.2 (4.2)*	1.8 (3.3)*
Spinal cord	3.0 (10.3)	3.8 (11.1)	3.1 (10.0)*	2.2 (10.5)*
Organ at risk / target volume	VMAT D_{mean}	IMRT D_{mean}	TOMO D_{mean}	IMPT D_{mean}
Cerebellum anterior	21.8 (15.8)	21.8 (16.2)	20.9 (14.4)	16.2 (15.8)*
Cerebellum posterior	7.1 (9.8)	8.5 (11.1)*	7.4 (9.4)	5.6 (9.2)*
Cochlea ipsi & bilateral	15.7 (17.0)	16.0 (16.7)	12.2 (12.9)*	19.7 (21.1)
Cochlea contralateral	7.4 (6.5)	5.8 (6.3)	4.0 (3.1)	0.015 (0.036)*
Hippocampus ipsi & bilateral	32.2 (17.8)	33.3 (17.4)	31.5 (18.6)	32.8 (19.6)
Hippocampus contralateral	10.4 (7.1)	10.8 (8.4)	7.6 (6.1)	2.2 (5.0)*
Hippocampus left & right	23.1 (10.4)	24.0 (10.9)	21.4 (10.5)	19.9 (10.5)*
Lacrimal gland ipsi & bilateral	12.3 (6.1)	10.8 (7.6)	8.0 (4.3)*	3.5 (4.7)*
Lacrimal gland contralateral	10.3 (4.3)	7.3 (4.1)*	5.8 (2.3)*	0.17 (0.47)*
Pituitary gland	24.0 (14.3)	23.0 (14.8)	13.0 (10.1)*	22.7 (19.7)
Integral dose to body	7.8 (3.5)	7.9 (3.6)	8.3 (3.6)*	5.6 (2.8)*
$CTV_{50.4Gy}$	52.0 (1.0)	52.4 (1.6)*	52.1 (0.37)	51.7 (0.36)
GTV	52.2 (1.0)	52.6 (1.6)*	52.6 (0.43)*	51.6 (0.35)*
Structure name	VMAT $V_{95\%}$	IMRT $V_{95\%}$	TOMO $V_{95\%}$	IMPT $V_{95\%}$
$CTV_{50.4Gy}$	99.8 (0.75)	99.7 (1.5)	99.9 (0.13)*	100.0 (0.019)

$D_{2\%}$ = Dose to 2% of the structure in Gy(RBE); D_{mean} = mean dose to organ at risk or target volume in Gy(RBE); $V_{95\%}$ = organ at risk / target volume receiving 95% of the dose; CN = conformity number; * = $p<0.02$.

The brain volume receiving a dose up to 30 Gy (V_{5Gy}-V_{30Gy}) was statistically significantly reduced using IMPT compared to VMAT (comparison of the percentage of hippocampus, posterior cerebellum, and brain to the gold standard VMAT is given in Table 3.3); the V_{5Gy} being 85 cc (SD 12 cc) for VMAT *versus* 49 cc (SD 16.3 cc) for IMPT and the V_{20Gy} 56 cc (SD 19 cc) *versus* 39 cc (SD 15 cc), respectively [see Figure 3.2 for 20 Gy(RBE) volume]. Besides for brain, the *low* dose volumes to the hippocampus (bilateral and contralateral) and posterior cerebellum were statistically significantly reduced using IMPT whereas the *high* dose volumes to hippocampus bi- and ipsilateral, posterior cerebellum and brain increased using IMPT compared to VMAT (Figure 3.3).

Table 3.3 Absolute percentage of the hippocampus, posterior cerebellum, and brain volumes receiving a dose between 5 and 50 Gy(RBE) presented per treatment modality (statistical comparison versus the gold standard being VMAT).

OAR V_x	VMAT % (SD)	IMRT % (SD)	TOMO % (SD)	IMPT % (SD)
Bi & ipsilateral hippocampus				
V_{5Gy}	90.2 (25.9)	92.1 (23.6)	85.1 (29.7)	78.8 (32.5)
V_{10Gy}	79.4 (34.8)	81.8 (31.9)	75.4 (38.5)	73.7 (37.6)
V_{15Gy}	72.6 (39.6)	73.5 (38.5)	68.1 (41.9)	70.2 (39.8)
V_{20Gy}	65.7 (41.3)	67.5 (39.7)	63.5 (43.3)	66.6 (41.0)
V_{25Gy}	59.5 (42.5)	62.5 (41.5)	59.3 (43.5)	63.2 (42.3)
V_{30Gy}	55.0 (43.7)	58.3 (42.4)	55.7 (43.7)	60.3 (43.3)
V_{35Gy}	50.7 (44.2)	52.9 (43.0)	51.3 (43.2)	57.7 (43.9)*
V_{40Gy}	46.5 (43.9)	48.0 (43.4)	45.8 (42.7)	54.6 (44.2)
V_{45Gy}	41.7 (42.8)	42.8 (42.5)	41.0 (42.4)	49.9 (43.9)*
V_{50Gy}	34.3 (40.9)	35.8 (41.9)	35.6 (40.5)	42.0 (42.0)*
Contralateral hippocampus				
V_{5Gy}	74.8 (39.3)	67.6 (44.5)	66.2 (35.9)	10.8 (22.3)*
V_{10Gy}	42.4 (42.5)	46.4 (44.5)	14.1 (22.7)*	6.2 (16.1)*
V_{15Gy}	21.4 (37.3)	24.5 (38.1)	6.5 (22.8)*	4.3 (13.1)*
V_{20Gy}	11.0 (26.8)	15.3 (33.1)	5.2 (22.3)*	3.1 (10.9)*
V_{25Gy}	4.3 (12.7)	10.3 (26.6)	3.9 (16.9)*	2.4 (9.3)*
V_{30Gy}	1.5 (5.6)	2.7 (7.9)	2.2 (9.5)*	1.9 (8.0)*
V_{35Gy}	1.0 (4.5)	1.0 (4.5)	1.5 (6.7)*	1.5 (6.6)*
V_{40Gy}	0.91 (4.0)	0.91 (4.0)	1.2 (5.3)*	1.2 (5.2)*
V_{45Gy}	0.8 (3.5)	0.83 (3.6)*	0.95 (4.1)*	0.9 (3.9)*
V_{50Gy}	0.6 (2.6)	0.72 (3.1)*	0.71 (3.1)*	0.44 (1.9)*
Cerebellum posterior				
V_{5Gy}	28.7 (32.1)	37.0 (35.8)*	31.9 (34.1)*	19.0 (23.4)
V_{10Gy}	19.0 (25.9)	24.2 (27.8)*	20.5 (27.3)	15.2 (21.7)
V_{15Gy}	13.0 (21.9)	16.2 (23.9)*	13.7 (22.0)	12.8 (20.5)
V_{20Gy}	9.6 (20.7)	12.1 (22.2)*	10.3 (20.6)	11.0 (19.4)
V_{25Gy}	7.9 (20.3)	9.8 (21.2)*	8.4 (19.8)	9.6 (18.4)*
V_{30Gy}	6.8 (19.4)	8.2 (20.4)*	6.9 (18.4)	8.3 (17.4)*
V_{35Gy}	5.8 (17.2)	7.1 (19.5)*	5.8 (16.6)	7.1 (16.4)*
V_{40Gy}	4.7 (14.6)	6.0 (18.0)	4.7 (14.5)	5.9 (15.2)*
V_{45Gy}	3.7 (12.1)	4.8 (15.2)	3.7 (12.2)	4.7 (13.3)*
V_{50Gy}	2.8 (9.8)	3.6 (12.4)	2.6 (8.9)*	2.8 (8.3)
Brain				
V_{5Gy}	84.7 (11.7)	83.2 (12.2)	85.9 (10.7)*	48.5 (16.3)*
V_{10Gy}	78.3 (13.8)	72.6 (15.5)*	78.9 (12.9)	44.2 (15.7)*
V_{15Gy}	67.6 (17.4)	62.7 (18.2)*	67.2 (16.6)	41.3 (15.2)*
V_{20Gy}	56.1 (18.9)	52.9 (19.8)	55.0 (17.1)	38.8 (14.7)*
V_{25Gy}	46.7 (18.6)	44.7 (18.7)	45.6 (16.4)	36.6 (14.2)*
V_{30Gy}	39.1 (17.1)	38.2 (16.8)	38.6 (15.0)	34.3 (13.5)*
V_{35Gy}	33.2 (15.0)	33.0 (14.6)	33.3 (13.7)	31.9 (12.8)
V_{40Gy}	28.6 (13.0)	28.9 (12.6)	29.2 (12.5)	29.4 (12.1)
V_{45Gy}	24.9 (11.2)	25.6 (11.1)*	25.6 (11.1)	26.2 (11.0)*
V_{50Gy}	20.7 (9.3)	21.8 (9.6)*	20.9 (9.5)	21.1 (9.0)

OAR = organ at risk; SD = standard deviation; V_{xGy} = the volume receiving x Gy(RBE); * = $p<0.02$.

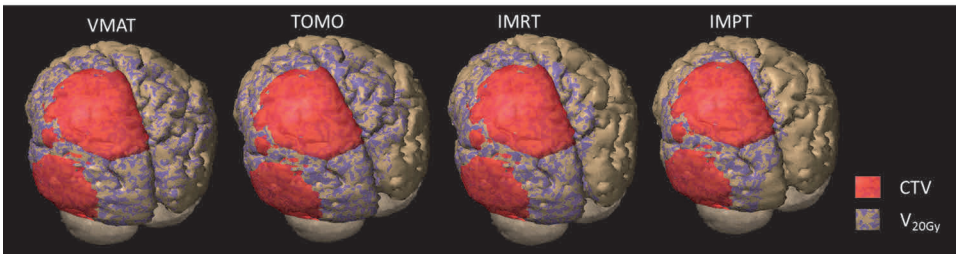

Figure 3.2 Three-dimensional representations of the cerebrum and cerebellum of a LGG patient highlighting the CTV in red and the 20 Gy isodose (purple/brown) of the different treatment techniques studied (VMAT, TOMO, IMRT and IMPT).

The mean $CTV_{50.4Gy}$ volume in the included 25 patients was 240 cc (SD 112 cc) with a range of 92-456 cc and a median of 171 cc. With increasing volume of the $CTV_{50.4Gy}$, the volume of irradiated brain tissue increased for all treatment modalities. Even the slopes for all photon modalities (VMAT, IMRT, TOMO) were identical to that of the IMPT plans. The dose given to a certain volume, *e.g.*, Brain $V_{10Gy,}$ was lower with IMPT than with photon-based treatment modalities, whereas the curves for Brain V_{40Gy} overlapped (Supplementary Figure S3.1).

Discussion

This ROCOCO study is the first to compare VMAT with IMRT, TOMO and IMPT in brain irradiation. IMPT was superior in sparing most OARs compared to VMAT and delivered the lowest integral dose. IMPT resulted in a significant dose reduction for structures related to cognition, such as non-target brain tissue, the hippocampus (bilateral and contralateral), and the posterior cerebellum. TOMO was the photon technique achieving the lowest dose to the OARs, while VMAT achieved the highest CI.

Thus far, there is limited experience comparing the different treatment techniques for LGG. Koca *et al*.[22] published an IMRT versus TOMO plan comparison of 20 glioblastoma patients showing TOMO to be superior to IMRT plans in sparing of OARs with slightly broader low dose ranges. Cao *et al*.[23] compared VMAT with TOMO for 10 body sites concluding comparable plan qualities of VMAT compared to TOMO in most of the cases. Skórska *et al*.[24] stated in their retrospective plan comparison of 15 brain tumor patients, that the advantage of TOMO was in the highly conformal uniform doses to the target volume, even though these could only be delivered in a coplanar mode.

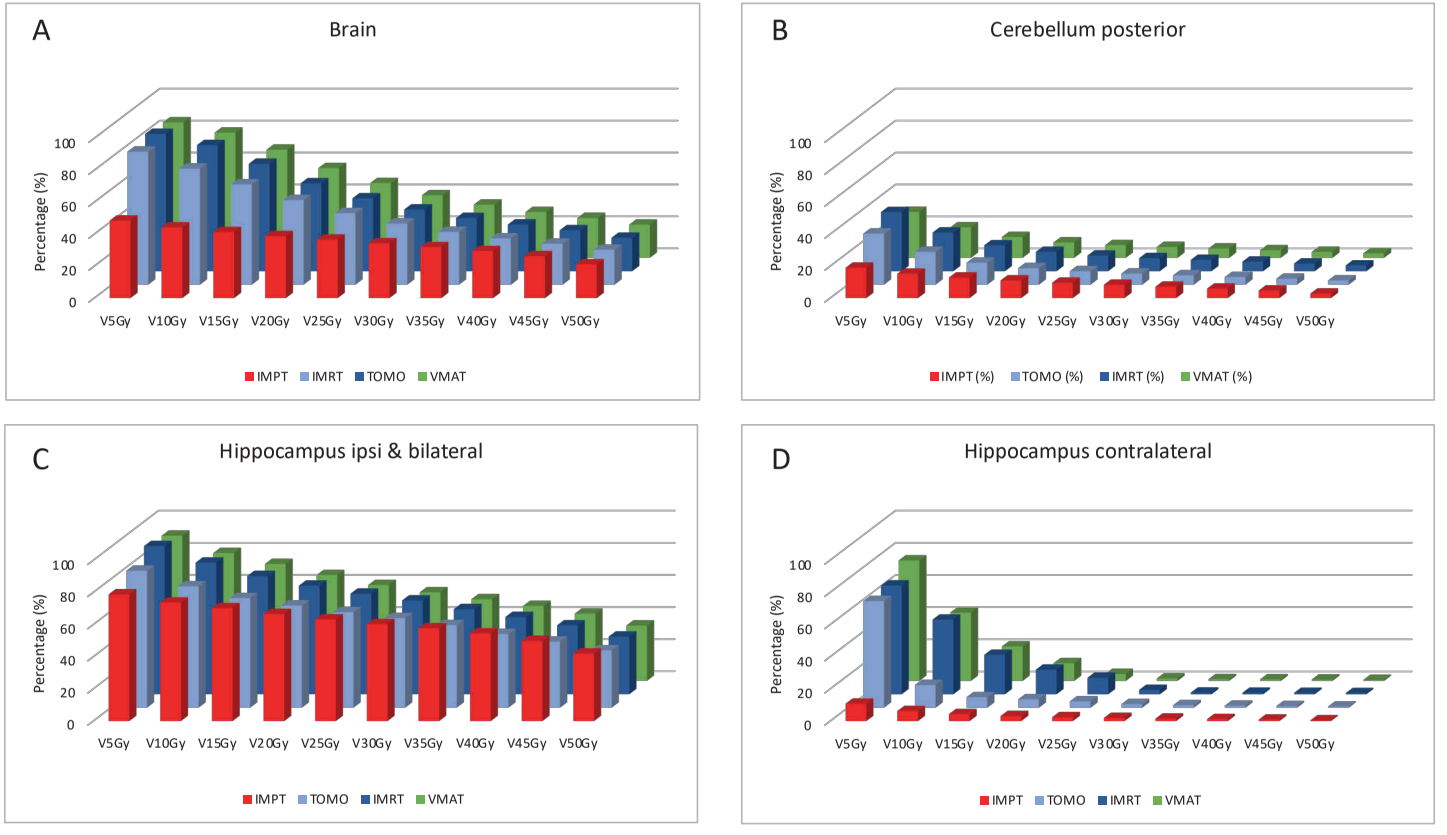

Figure 3.3 The percentage of organs at risk volume (related to cognition) receiving a radiation dose between 5 Gy and 50 Gy (V_{5Gy} to V_{50Gy}, respectively).

When comparing TOMO to coplanar (IMRT) and non-coplanar (ncIMRT) the median CI were best for TOMO and worst for IMRT. They reported that the largest reduction of D_{max} for lenses and D_{mean} for both eyes was achieved using ncIMRT. While D_{mean} for the optic chiasm and the ipsilateral optic nerve were best spared using TOMO, the contralateral optic nerve with ncIMRT[23].

Proton therapy has a dosimetric advantage due to its physical characteristics and is known to reduce the integral dose as was also seen in our *in silico* trial with a comparable coverage of the target volume and a lower dose to the OARs. Moreover, we found that in particular the dose to the contralaterally located OARs could be reduced. Thus far, publications on clinical experience treating LGG with proton therapy are scarce. Harrabi *et al*.[25] published the largest retrospective study on 74 LGG patients (median PTV volume 185 cc, range 12-710 cc) treated with proton therapy, generating a *non* state-of-the art conventional three-dimensional radiotherapy plan for plan comparison. The coverage of the target volume was comparable, also showing a reduction in maximal, mean, and integral doses to the OARs when using protons, especially in structures located contralaterally to the tumor. Other plan comparison studies concluded that proton therapy reduced the dose to surrounding normal tissues resulting in a significantly reduced whole-brain and -body irradiation[26-28].
In our study the pituitary gland could impressively be spared using TOMO due to the planning strategy in which all direct photon fluence passing the pituitary gland was abolished using the features of the TOMO binary multileaf collimator[29-31].

There are some shortcomings in our study, which may influence our results. First, all treatment plans were prepared in 3 different institutes, with their own routine and protocols besides the planning goals specifications which were prescribed by the study protocol. In line with international recommendations, e.g., the different PTV margins for each modality were determined locally based on local uncertainty data. However, this approach was chosen to include experts in their specific fields in this ROCOCO *in silico* study and, moreover, to reflect actual clinical practice. Second, one may debate about the required number of proton beams and their angles used in IMPT. There is an increasing awareness of the RBE uncertainty at the end of the Bragg peak, causing many proton centers to be cautious and avoiding overlapping spots at the end of the beam and using at least two beams[32].
Third, treatment uncertainties (setup, range and anatomical uncertainties) might significantly influence the difference between planned and delivered dose as was shown by Kraan *et al*.[33]. It could also be argued that a smaller grid size in IMPT could slightly increase the maximum target dose, but will probably have no effect on the

OARs as Rana *et al*.[34] reported in their study varying the grid size from 1mm to 3mm for IMPT techniques. They recommend using a grid size of 2.5-3mm for dose calculations with regard to the calculation time. Fourth, since there is currently no consensus on how to report robustness in a uniform manner, e.g. the suggestions of Liu *et al*.[35], we only performed a small evaluation using the CV, fully aware of the fact that no absolute limit of this value is known. Further analysis based on a voxel wise minimum and maximum are still under investigation.

Whether proton therapy is indicated in neuro-oncology and outweighs the increased costs is still a matter of debate since no randomized control trials are published demonstrating a clinical benefit of proton therapy. Combs[36] recently summarized and discussed the data on proton therapy for tumors of the CNS in comparison to modern photon therapy, showing that there are only few early data for low-grade glioma patients, underlining safety and low toxicity comparable to photons.

Will avoiding a low dose bath to the brain translate into a clinical benefit for the patient, especially regarding one of the most feared side effects: neurocognitive decline? This irreversible toxicity directly affects the patient's independence and wellbeing[37]. Variable mechanism can influence late cognitive toxicity to the brain related to radiotherapy such as vascular damage, demyelination and white matter changes as well as neurocognitive revalidation strategies[37-41]. Patients mostly exhibited overall stability in cognitive functioning after 5 years follow-up with, in some, more impairment on verbal measurements in tumors located in the left hemisphere and some on endocrine dysfunction. More data on late neurocognitive toxicity after PT as well as photon therapy is needed in relation to quality of life. Notably, the location of radiation dose deposition is considered important, defining type and level of radiation induced toxicity[42]. Moreover, it has to be considered that early side effects of proton and photon therapy for LGG are similar and transient, e.g., alopecia (81%), dermatitis (78%), fatigue (47%), and headache (40%), but bear the potential to adversely affect the patient's quality of life for several weeks[43,44]. Well-designed prospective studies including endpoints related to neurocognitive functioning and imaging are needed to determine the clinical relevance of low dose deposition to large CNS volumes.

In our study we did not correct for contrast enhancement. Iodine contrast agents (CA) used during CT imaging, lead to an increase of the Hounsfield units in tissue with increased CA uptake depending on the CA concentration. This causes errors in the approximation of the tissue composition and thus in the calculation of the proton ranges as described by Wertz *et al*.[45]. Consequently, this in theory leads to an exaggeration of the ion ranges during irradiation of 1.3 mm, for a tumor with a size of 5 cm. When OARs are close to the target volume this could be relevant[45]. Thus, the use of iodine contrast agent in a planning-CT to be used for proton therapy is highly

discouraged. If urgently required in clinical practice, though, two sequential CT scans may be obtained, with the native CT scan being the first.

In order to predict the benefit of dose reduction to OARs, normal tissue complication probability (NTCP) models are needed. For cognition, Gondi *et al*.[46] described a statistically significant correlation between the dose to 40% of both hippocampi ($D_{40\%}$) and cognitive decline in 18 patients with CNS tumors treated with stereotactic radiotherapy. This model needs validation in proton beam therapy and possible extension concerning the dose to each separate hippocampus, in particular when the ipsilateral hippocampus is part of the CTV.

Besides the hippocampi more regions in the brain related to neurocognition need to be identified, *e.g.*, the posterior cerebellum. In our recent review (Eekers et al.[47]), we illustrated that there is growing evidence from structural and functional imaging studies that the cerebellum plays an eminent role in neurocognition and that radiation to the posterior cerebellum has a negative effect on neurocognitive outcomes in long-term pediatric brain survivors, besides the multimodality approach.

Since there is the problem of equipoise, the chance of ever performing a randomized trial, besides the costs of such a trial, seems very low. In the Netherlands, the model-based approach has therefore been adopted by care givers and health insurance companies in order to provide an 'objective' tool to determine whether a patient is eligible for proton therapy[48]. In this model a 10% reduction in a grade 2 toxicity is needed using a validated (currently photon based) NTCP model. Unfortunately, there are currently no validated models for CNS. Therefore, uniform prospective collection of future toxicity data in a standardized way is urgently required for photon as well as proton therapy especially for low-dose-large-volume conditions. This will enable upfront assessment of a patient's likelihood to benefit from particle treatment. Uniform delineation and consensus on the tolerance on OARs are the first steps to achieve this besides a structured follow up including uniform neuro-cognitive tests[18,49]. This potentially improved quality of life ought to be outweighed against the additional costs of particles (protons, carbon ions) over technically advanced photon treatments. Changing the priorities as set in this study could alter outcome.

We conclude that IMPT can overall better spare organs than the other techniques, especially those OARs located contralateral to the target volume. In absence of NTCP models, an alternative approach, which will be implemented for supratentorial gliomas in The Netherlands, is to look at the reduction in mean dose to the brain and both hippocampi, excluding the CTV, achieved when using PT. However, the correlation of dose reduction to clinically relevant gain needs to be further investigated. Whether this will eventually lead to a significant improvement of quality of life needs to be determined in carefully designed future multicenter clinical studies.

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Supplemental material

Table S3.1 Robustness analysis of the CTV for six randomly chosen patients.

	$V_{95\%}$ of $CTV_{50.4Gy}$		
Patient	mean	SD	CV (%)
1	99,95	0,05	0,05%
2	99,97	0,03	0,03%
3	99,94	0,05	0,05%
4	99,80	0,12	0,12%
5	99,95	0,03	0,03%
6	99,85	0,11	0,11%
mean	99,91	0,07	**0,07%**
SD	0,07	0,04	0,04%

$V_{95\%}$ = volume of the PTV receiving 95% of the prescribed dose, $CTV_{50.4Gy}$ = clinical target volume with a prescribed dose of 50.4 Gy, SD = standard deviation, CV = Coefficients of Variation, i.e., standard deviation over mean.

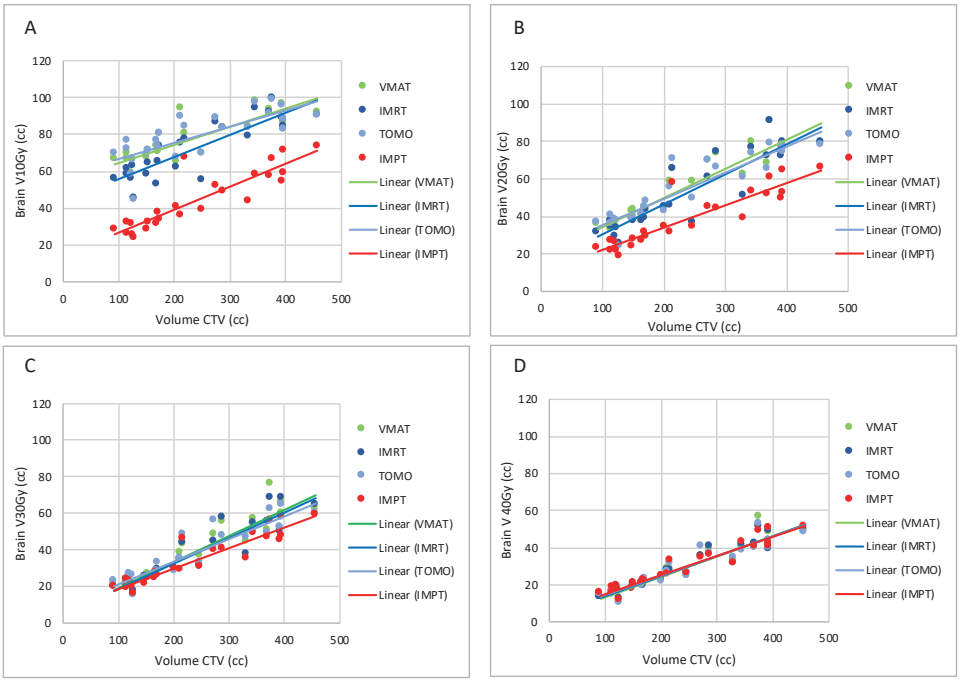

Figure S3.1 The volume irradiated brain (cc) per treatment modality (VMAT, IMRT, TOMO, IMPT) as a function of the CTV (cc) receiving a dose of (A) 10 Gy(RBE), (B) 20 Gy(RBE), (C) 30 Gy(RBE) and (D) 40 Gy(RBE); BrainV_{10Gy} to V_{40Gy}, respectively.

Chapter 4

The posterior cerebellum, a new organ at risk?

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Clin Transl Radiat Oncol 2017;8:22-26

Abstract

Eekers et al.[1] have recently proposed a neuro-oncology atlas, which was co-authored by most centers associated in the European Proton Therapy Network (EPTN; Figure 4.1). With the introduction of new treatment techniques, such as integrated magnetic resonance imaging and linear accelerators (MR-linac) or particle therapy, the prediction of clinical efficacy of these more costly treatment modalities becomes more relevant. One of the side-effects of brain irradiation, being cognitive decline, is one of the toxicities most difficult to measure and predict. In order to validly compare different treatment modalities, 1) a uniform nomenclature of the organs at risk (OARs), 2) uniform atlas-based delineation [e.g., Eekers et al.[1]], 3) long-term follow-up data with standardized cognitive tests, 4) a large patient population, and 5) (thus derived) validated normal tissue complication probability (NTCP) models are mandatory.
Apart from the Gondi model[2], in which the role of the dose to 40% of both hippocampi (HC) proves to be significantly related to cognition in 18 patients, no similar models are available. So there is a strong need for more NTCP models, on HC, brain tissue and possible other relevant brain structures.In this review we summarize the available evidence on the role of the posterior cerebellum as a possible new organ at risk for cognition, which is deemed relevant for irradiation of brain and head and neck tumors.

Introduction

Survival rates of brain tumors, including gliomas have improved by the use of multimodality therapy, with advances in surgery, radiation therapy, chemotherapy and radiological technology prior to and throughout the treatment[3,4]. As survival rates increase, awareness of long-term complications due to therapy raises as well, for children as well as adults[5]. One of these (long-term) complications following (radio)therapy is neurocognitive decline, which is marked by reduction of verbal memory, spatial processing, attention and novel problem solving ability[6]. This decline has been shown in survivors of pediatric brain tumors, treated with multimodal treatment schedules, who have lower rates on high school graduation and employment relative to the overall population[7].

Traditionally, the cerebral hemispheres are considered the regions of the brain responsible for cognitive function, while the cerebellum is known for its role in regulation and coordination in movement, posture and balance[8]. However, several clinical, anatomical and neuro-imaging studies have shown that the cerebellum may also play a role in neurocognition[9-11]. The aim of this review was to summarize the available evidence on role of the cerebellum in cognition and on the effects of radiation dose on the cerebellum in regard to neurocognitive function. Potentially, this will lead to new NTCP models, such as the Gondi model[2], to predict neurocognitive outcomes related to radiation dose in different brain structures. Delineation guidelines for anatomical structures relevant in neuro-oncology have recently been proposed by Eekers et al.[1] (Figure 4.1).

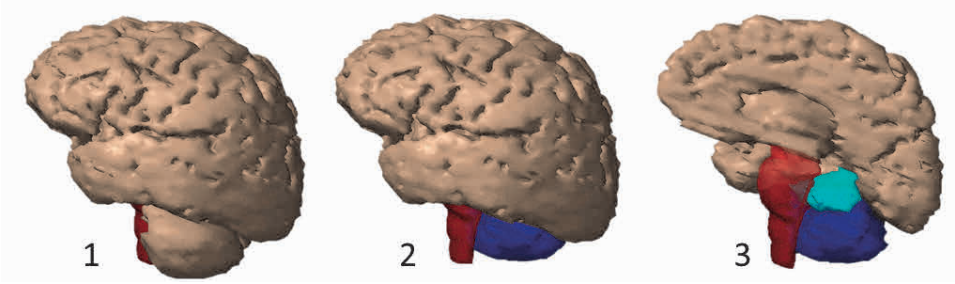

Figure 4.1 3D view of the Brain, brainstem, cerebellum posterior and anterior.
Lateral view of a 3D-reconstruction on CT of: 1. Total brain (brown) and brainstem (red). 2. Brain (brown), brainstem (red), cerebellum posterior* (dark blue). 3. Right brain (brown), brainstem (red), right cerebellum anterior* (light blue) and right cerebellum posterior* (dark blue). *In accordance to Atlas for Neuro-Oncology (Eekers *et al.*[1]).

Cognition and the cerebellum

Historical perspective

Until the 20th century, studies on cerebellar function primarily focused on motor function[12-14]. It is unclear why cerebellar involvement in cognition and language remained uninvestigated in that period, but this may be due to the subtlety of cognitive defects or the fact that motor function and cognitive function were investigated as two separate entities. In 1971 Prescott and Piaget[15] described that motor development is inherently connected to emotional and neurocognitive development. Children with motor development difficulties are often emotionally and cognitive challenged as well. Both development processes could be connected and cannot be studied separately. These new insights led to the theory that the cortex and cerebellum might be connected and that both regions may be involved in neurocognitive function. In 1978, Watson[16] was one of the first authors to suggest the possible role of the cerebellum in sensory processing, learning, affect and cognition. In current literature, evidence is mounting to support this suggestion, even though many questions remain unanswered.

Anatomy of the cerebellum

The cerebellum consists of two hemispheres divided by the vermis. Both hemispheres are organized into ten lobules. Traditionally, the cerebellum has been recognized as having three anterior-posterior divisions[10]: the primary fissure separates the anterior lobe (lobules I-V) from the posterior lobe (lobules VI-IX) and the posterolateral fissure separates the posterior lobe from the flocculonodular lobe (lobule X). Two other approaches to divide the cerebellum are based upon functional (F) or phylogenetic (P) criteria. The vestibulocerebellum (F) or archicerebellum (P) contains the flocculonodular lobe and immediately adjacent vermis. The spinocerebellum (F) or paleocerebellum (P) contains the vermis and intermediate parts of the vermis. The cerebro-cerebellum (F) or neocerebellum (P) contains the lateral parts of the hemispheres[10].

There are four deep nuclei in the cerebellum, the dentate, emboliform, globose, and fastigial, which receive and send information to the specific parts of the brain. Most afferent cerebral projections pass through the basal pontine nuclei and intermediate cerebellar peduncle, while most cerebello-cerebral efferent projections pass through dentate and ventral thalamic nuclei[17,18].

Cerebellum and the sensorimotor & associative cortex

In order to determine whether the cerebellum plays a role in cognition it is crucial to unravel whether there are anatomical connections between the cerebellum and regions of the brain with higher cognitive functions. As a matter of fact, multiple studies, including viral tract tracing methods and resting-state functional connectivity data, support the presence of reciprocal links between the cerebellum and the prefrontal and parietal association cortices via cerebello-thalamo-cortical and cortico-ponto-cerebellar loops[9-11,18-21]. These closed loop circuits provide topographically segregated connections between the cerebral cortex and the cerebellum[22,23]. Information from the primary motor cortex passes the caudal part of the brainstem and enters the anterior part of the cerebellum via pontocerebellar fibers through the intermediate peduncle. Information from associative cortices passes several points in the brain stem and enters the posterior part of the cerebellum via the intermediate peduncle[21]. In conclusion, the primary motor cortex is predominantly connected to the anterior part of the cerebellum, whereas the associative cortices are predominantly connected to the posterior part of the cerebellum[10].

Cerebellum activation in cognitive tasks

Activation of the cerebellum in cognitive tasks has been found in multiple functional imaging studies. It is present during language, working memory, visual spatial and executive functioning tasks. Each domain and its matching tests have different activation patterns. Language-related activity is focused in lateral and posterior cerebellar regions, while working memory and reading tasks activate bilateral regions of the cerebellar posterior lobe, mainly lobules VI and VII. Functional imaging of affective processing, executive functioning and spatial processing highlights lobules VI and VII of the posterior cerebellar lobe. One of the first studies to describe this connection was published by Kim *et al*.[24] in 1994. The authors used magnetic resonance imaging (MRI) to examine the activation of the dentate nucleus of the cerebellum in seven healthy human volunteers during their attempts to solve a puzzle. All seven adult participants showed more bilateral activation of the dentate nucleus during more challenging neurocognitive tasks. Later on, multiple imaging studies followed and found similar results[10]. In general, cerebellar activation during cognitive tasks is found in conjunction with activation of prefrontal and parietal regions, supporting the concept that the cerebellum is part of these functional networks[10,11].

Cerebellum and cognition

Clinical evidence for cognitive functioning of the cerebellum can, *e.g.*, be found in the clinical cerebellar cognitive affective syndrome (CCAS; Figure 4.2). CCAS is a condition, which leads to deficits in cognitive functioning resulting from cerebellar damage. This syndrome has been described in both children and adults. Affected domains are executive function, spatial cognition, working memory, language and affect[25,26]. Depending on the location of the lesion, CCAS can be present in the absence of cerebellar motor syndrome, which is a syndrome that affects motor functions. The lesions that are associated with CCAS are situated in the posterior lobe of the cerebellum. Schmahmann and Pandyat[19] were the first to describe this syndrome after studying 20 adults with cerebellar lesions due to either neoplasms, or vascular or traumatic damage. They all showed deficits in multiple cognitive domains as described above whilst maintaining semantic and episodic memory and consciousness. The latter deems cerebral damage as cause for these deficits unlikely. Lesions of the anterior lobe of the cerebellum produced only minor changes in executive and visual-spatial functions in contrary to the lesions in the posterior lobe. The constellation of deficits is suggestive of disruption in neural circuits connecting the cerebellum to prefrontal, posterior parietal, superior temporal, and limbic cortices[25,26].

Cuny *et al*.[27] recently published the cases of two siblings with small retrovermian arachnoid cysts. The 3-year-old children initially presented cerebellar signs and cognitive disorders with progressive worsening. Surgery was performed to relieve intracranial pressure in the posterior fossa. In both cases significant improvement was seen in the children's neurological and neuropsychological status during 3 years of follow-up.

Other clinical studies show specific neurocognitive domains can be affected by damage to specific regions of the cerebellum. It is reported that verbal expression impairments result from damage to the right cerebellar lobe, whereas spatial difficulties can arise from lesions in the left cerebellar lobe, damage to the midline vermis has been associated with deficits in social and affective processing[10,11,25,26].

Cerebellar volume and cognitive function

A large body of literature supports the hypothesis that cerebellar volume decreases with increasing age. It has been suggested that this has its effect on neurocognitive function as well. Hoogendam *et al*.[28] examined the correlation between cerebellar volume and neurocognitive function. They included 3745 individuals above the age of 45 years and found a minor non-significant relationship between larger cerebellar volume and better global cognition, executive function, information processing speed,

memory and motor speed. Their findings support the notion that the cerebellar volume has an influence on decline of cognition in aging but it is not the predominant structure. Likewise, Weier *et al*.[29] examined 28 pediatric-onset relapsing-remitting Multiple Sclerosis patients, comparing their cerebellar volumes to a control group and found that while the volumes did not differ between groups, posterior cerebellar lobe volume and infra-tentorial lesion volume accounted for extra variance on measures of information processing and vocabulary. Many other studies support these findings and underline the hypothesis that the cerebellum has a function in neurocognitive functioning[30].

Radiation to the cerebellum

One of the most interesting studies on radiation to the cerebellum was published by Merchant *et al*.[31], separately delineating the cerebellum and dividing it into a posterior and anterior part according to the article of Schmahmann *et al*.[32]. Seventy-eight children with low-grade glioma were included, prior treatment with chemotherapy was allowed in this study and there was no limit for the interval first surgery until irradiation (54-59.4 Gy), baseline and serial evaluations were performed to assess cognitive outcomes[31].

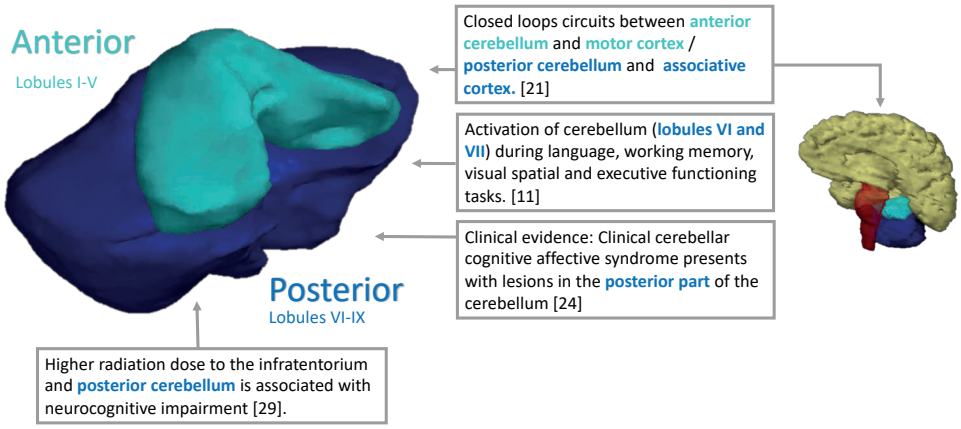

Figure 4.2 Role of cerebellum in cognition.

They found a statistically significant correlation between the radiation dose to the infratentorium and posterior cerebellum and neurocognitive impairment at several cognitive domains. To date, this is the only available study with separate dosimetric

data for the posterior cerebellum. Noteworthy, one of the limitations of that study was the absence of a control group. Rønning *et al*.[33] compared an only surgically treated pediatric patient cohort with astrocytoma (n=12) to a pediatric cohort with medulloblastoma (n=10), who had been treated with surgery followed by radio(chemo)therapy. Both the astrocytoma and medulloblastoma groups scored below the standard norms regarding motor speed, attention and executive function. The medulloblastoma group, however, performed worse than the astrocytoma group on the following neuropsychological measures: intelligence, motor function, speed processing, verbal and visual memory. Since the astrocytoma group was treated with surgery alone, cerebellar lesions were held responsible for neurocognitive decline. The fact that the medulloblastoma cohort was more affected may be explained by several factors including the underlying malignancy and the use of radiotherapy[33]. Gan *et al*.[34] assessed a group of ten adult patients treated with (intensity modulated) radio(chemo)therapy for squamous cell cancer of the head and neck. The authors delineated several brain structures separately, including temporal lobes and cerebellum, and performed neurocognitive function tests before and after treatment. The study population scored well on IQ but mean scores for all cognitive domains, except language and global cognitive function, were significantly lower than anticipated from the patients' IQ. Memory was the most severely affected cognitive domain. The patient with the lowest scores received a maximum dose of 36 Gy on the cerebellum and low radiation doses on the whole brain and hippocampi[34]. The studies of Merchant *et al*.[49] even demonstrated that radiation dose-volume-parameters remain the most clinically significant determinants of IQ outcomes and that further reduction in radiation dose to specific volumes of the brain should be pursued.

Beside radiation dose to the cerebellum, multiple modalities in the treatment of brain tumor patients can induce neurocognitive sequelae. These include the pre-treatment neurocognitive function, surgery and peri-operative complications, radiation dose and volume to the craniospinal axis, systemic or intrathecal application chemotherapy, implantation of a shunt for increased intracranial pressure, patient factors such as age, stress, fatigue and anxiety[33-49].

Conclusion & future perspectives

There is growing evidence from structural and functional imaging studies that the cerebellum plays an evident role in neurocognition (Figure 4.2). Radiation to the posterior fossa has shown to have a negative effect on neurocognitive outcomes in long-term pediatric brain survivors. In order to derive an NTCP model for the (posterior)

cerebellum, it is necessary to collect data on varying radiation doses to the (posterior and anterior) cerebellum and on prospectively assessing neurocognitive outcome.

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Chapter 5

The EPTN consensus-based atlas for CT- and MR-based contouring in Neuro-Oncology

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Radiother Oncol 2018;128(1):37-43

Abstract

Purpose

To create a digital, online atlas for organs at risk (OAR) delineation in neuro-oncology based on high-quality computed tomography (CT) and magnetic resonance (MR) imaging.

Methods

CT and 3 Tesla (3T) MR images (slice thickness 1 mm with intravenous contrast agent) were obtained from the same patient and subsequently fused. In addition, a 7T MR without intravenous contrast agent was obtained from a healthy volunteer. Based on discussions between experienced radiation oncologists, the clinically relevant organs at risk (OARs) to be included in the atlas for neuro-oncology were determined, excluding typical head and neck OARs previously published. The draft atlas was delineated by a senior radiation oncologist, 2 residents in radiation oncology, and a senior neuro-radiologist incorporating relevant available literature. The proposed atlas was then critically reviewed and discussed by European radiation oncologists until consensus was reached.

Results

The online atlas includes one CT-scan at two different window settings and one MR scan (3T) showing the OARs in axial, coronal and sagittal view. This manuscript presents the three-dimensional descriptions of the fifteen consensus OARs for neuro-oncology. Among these is a new OAR relevant for neuro-cognition, the posterior cerebellum (illustrated on 7T MR images).

Conclusion

In order to decrease inter- and intra-observer variability in delineating OARs relevant for neuro-oncology and thus derive consistent dosimetric data, we propose this atlas to be used in photon and particle therapy. The atlas is available online at www.cancerdata.org and will be updated whenever required.

Introduction

In order to evaluate the added value of new radiotherapy (RT) modalities and techniques, such as particle therapy and adaptive highly conformal photon RT, it is essential to be able to accurately predict the individual patient's benefit in term of radiation-induced side effects[1-3]. The maturation and validation of normal tissue complication probability (NTCP) models is strongly dependent on uniform delineation of the relevant organs at risk (OARs), and reducing the inter- and intra-observer and trial protocol variability between clinicians and radiotherapy departments is an important objective. In this context, Brouwer *et al*.[4] and Kong *et al*.[5] published atlases for OARs relevant for head and neck and lung tumors, respectively.

During the last decade, several papers have been published on the delineation of OARs relevant to neuro-oncology both for adults and children[4,6,7]. These atlases may differ in minor details, but also some major discrepancies might occur, for instance, variations in the upper limit of the brainstem. Discrepancies in a critical OAR may influence the dose distribution and thus compromise the coverage of the target volume[4,6].

Within the Dutch Platform for Neuro-Oncology and the ESTRO taskforce "European Particle Therapy Network (EPTN)" there was a need to generate an atlas, which identifies the relevant OARs for neuro-oncology and can be used both for daily practice as well as research purposes[8]. With the ever-growing insight into the influence of radiotherapy on neurological functions, it is essential that this atlas can be easily updated when indicated.

Selection of OARs

In order to avoid overlap with existing head and neck atlases, typical head and neck OARs, which were previously published, were excluded from this consensus atlas[4]. All OARs at present known to be relevant for radiation-induced toxicity in neuro-oncology were included, namely: brain, brainstem, cochlea, vestibulum & semicircular canals, cornea, lens, retina, lacrimal gland, optic nerve, chiasm, pituitary, hippocampus and skin. In case of paired organs, each organ separately (left and right), and the unity of the two were contoured.

For future development of NTCP models, three distinct parts for the brainstem were defined, and regarding cognition, the posterior cerebellum, a new OAR possibly involved was included, as was the separation of the hippocampus into anterior and posterior parts. For research purposes also the hypothalamus was included. Of note, no

validated dose response curve relationships have thus far been published for these separate parts of the brainstem, hippocampus and cerebellum.

Uniform nomenclature

To facilitate future comparison of the structures, the proposed nomenclature is in accordance with work by Santanam *et al*.[9] on standardizing naming convention in radiation oncology, illustrated with quotes between brackets behind every structure name, for example: retina *("Retina_R", "Retina_L" and "Retinas")*.

Delineation

The fifteen OARs introduced in several previous publications were delineated by the first author (DE)[4,6,7]. The anterior and posterior cerebellum were delineated by three authors (DE, LV, IC) using the high-resolution segment of the radiation treatment planning software (Eclipse™ v11.0 software, Varian, Palo Alto, CA). During a multi-disciplinary session, the senior radiation oncologist (DE), neuro-radiologist (AP), and two residents in radiation oncology (LV, IC) discussed the delineation of the OARs and came to consensus on a first draft atlas. This draft was then critically reviewed by Dutch and international experts in neuro-oncology and consensus on the final version of this atlas was reached.

Acquisition of CT and MR

CT images were acquired with intravenous contrast (Ultravist®, 150 ml of 300 mg Iodine per ml, 2 ml per sec, 5 min delay, slice thickness 1 mm, 50 cm field of view, 120 kV, 685 mAs) using window-width/window-level settings (WW/WL) of 120/40 and 120/1500 (SOMATOM Sensation 10, Siemens Healthcare, Erlangen, Germany) of the head of an adult male low grade glioma patient after first resection. Moreover, a three-dimensional spoiled gradient (3D-SPGR) axial 3T MR scan (1 mm slice thickness) scan of the same patient in standard axial, sagittal and coronal reconstruction, and an axial T2- and a gadolinium (Gadovist® 1.0 mmol/ml 0.1 ml/kg bodyweight) contrast-enhanced axial T1-weighted sequence were acquired, with sagittal and coronal reconstruction. Both CT and MR were obtained in the supine position with the head in a neutral position; immobilization devices routinely used in radiation therapy were used for CT

acquisition. Rigid MR-CT co-registration and delineation was performed using the Eclipse™ treatment planning system with the high-resolution segment.
For illustration purposes, 7T MR images of a healthy volunteer were acquired (Siemens Magnetom 7T) with a slice thickness of 0.7 mm using a 32-channel head coil (Nova Medical Inc., Wilmington, CA; Figure 5.1). The magnetization-prepared rapid gradient-echo (MP2RAGE) was selected for OAR delineation due to its superior soft tissue contrast (Figure 5.2). Scan parameters have previously been published by Compter *et al.*[10]. Vendor-based 3D distortion correction methods were applied.

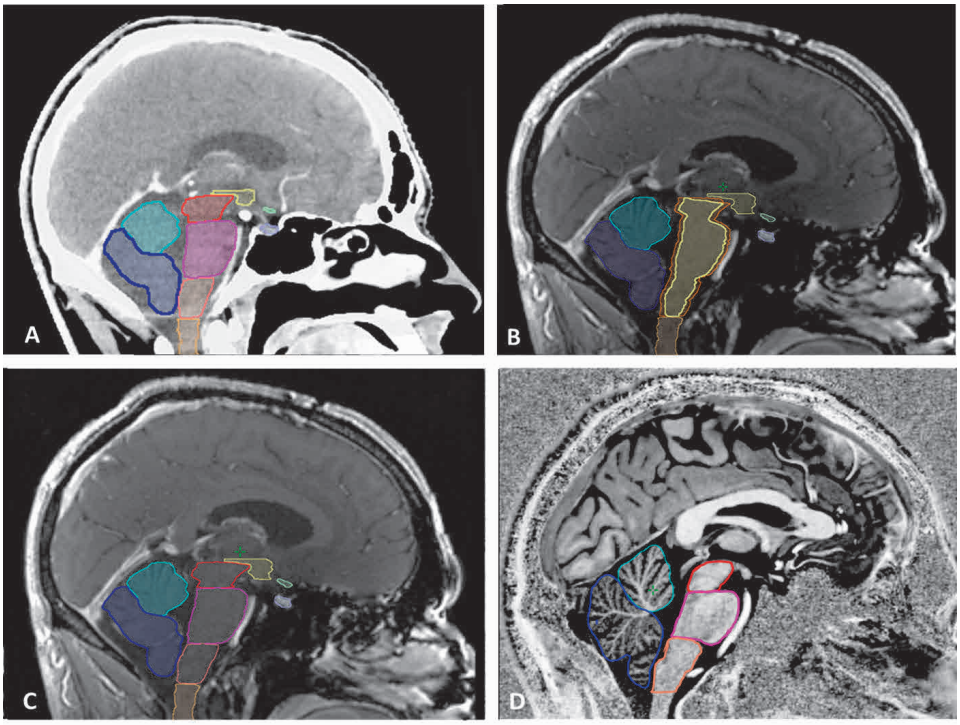

Figure 5.1 Sagittal (midline) view of the delineation
A: sagittal CT image (WL 140/40), B + C: sagittal 3 Tesla MRI (T1 with gadolinium), D: sagittal 7 Tesla MRI. Light blue = cerebellum anterior, dark blue = cerebellum posterior, red = midbrain, magenta = pons, pink = medulla oblongata, orange = spinal cord, light yellow = hypothalamus, green = chiasm, purple = pituitary, orange = brainstem surface, yellow = brainstem interior

Three-dimensional description of the OARs

Cornea ("Cornea_R", "Cornea_L" and "Corneas")
The cornea is located at the anterior segment of the eyeball consisting of the structures ventral to the vitreous humor, the iris, ciliary body, and lens[6]. Using a brush of 2-3 mm the cornea can easily be delineated on MR as well as CT.

Retina ("Retina_R", "Retina_L" and "Retinas")
The retina is a neurosensorial membrane of 2-3 mm thickness, located at the posterior part of the eyeball, posterior to the cornea and lens, and is the innermost of the three layers that form the wall of the eyeball (sclera, uvea/choroid and retina). Using a 3 mm brush, it can be delineated on MR as well as CT as a membrane covering the posterior 5/6 of the globe, extending nearly as far as the ciliary body. The anterior border of the retina is between the insertion of the medial rectus muscle and the lateral rectus muscle, posterior to the ciliary body. The optic nerve is excluded from this contour[4,6].

Lacrimal gland ("LacrimalGland L" , "LacrimalGland_R" and "LacrimalGlands")
The lacrimal gland is an almond shaped gland (18 mm craniocaudally, 15 mm axial length and 5mm axial width) located in the orbit superior-lateral to the eye, superior to the lateral rectus muscle and lateral to the superior rectus muscle. It can be delineated on CT using soft brain 120/40 or soft tissue 350/50 WW/WL settings[4,6,11].

Lens of the Eye ("Lens_R", "Lens_L" and "Lenses")
The lens (diameter up to 10 mm) is a clearly visible biconvex avascular structure, located between the vitreous humor and the iris and can easily be delineated on CT[6]. It should be taken into account that without instructing the patient, the position of the lens is not fixed and can vary during treatment.

Optic nerve ("OpticNerve_R", "OpticNerve_L" and "OpticNerves")
The optic nerve (2-5 mm thick) is delineated from the posterior edge of the eyeball, through the bony optic canal, where it narrows slightly, to the optic chiasm. Close to the optic chiasm, an MR scan (T1 weighted) is recommended for better delineation of the optic nerve. Contouring the optic nerve in continuity with the chiasm is crucial for dose reporting purposes, as dose gradients can be very steep with modern photon and proton techniques[4,12].

Optic chiasm ("Chiasm")

The optic chiasm (14 mm transverse, 8 mm antero-posterior and 2-5 mm thick) is located 1 cm superior to the pituitary gland, which has high signal on T1 MRI, and just anterior to the pituitary stalk (located above the sella turcica). The lateral border is the internal carotid artery. The chiasm is superiorly located in the antero-inferior part of the third ventricle, below the supra-optic recess and above the infundibular recess of the third ventricle, with the optic nerves in front and the divergence of the optic tracts behind. The anterior cerebral arteries and the anterior communicating artery are located ventral to the chiasm. A T1 weighted MR (axial, sagittal and coronal) is recommended for delineation of the optic chiasm[4,6].

Pituitary gland ("Pituitary")

The pituitary gland cannot be easily identified on axial CT, although the bony margins of the fossa are well shown. It is oval-shaped (craniocaudally up to 12mm) and lies in the sella turcica. Laterally, the pituitary gland is bordered by the cavernous sinuses, which are well visible with intravenous contrast agent, it is just inferior to the brain, and is connected to the hypothalamus by its pituitary stalk. The borders of the pituitary gland can be defined best in the sagittal view[4,5]. Alternatively, the inner part of the sella turcica can be used as a surrogate anatomical bony structure best identified using bone 1500/950 or soft tissue 350/50 WL/WW on CT.

Hypothalamus ("Hypothalamus_R, "Hypothalamus_L" and "Hypothalami")

The hypothalamus (2-4 cm^3) is a polygonal structure consisting of two separated volumes on each side of the third ventricle, delineated using MR-based anatomic landmarks representing surrogate boundaries for the hypothalamus itself. The superior boundaries are the axial slices containing the anterior and the posterior commissure. Inferiorly, the boundary consists of the base of the third ventricle or the visible edge of the cerebrospinal fluid (CSF) space within the suprasellar cistern, while posteriorly the contour reaches to the level of the interpeduncular fossa. The mammillary bodies should be included in the contour. The medial border consists of the third ventricle or the visible CSF space. Since the lateral border is not clearly visible, the contour was bounded laterally 3 mm from the third ventricle. Delineation on a T1 weighted MR is strongly recommended[13-16].

Hippocampus ("Hippocampus_P_R", "Hippocampus_P_L", "Hippocampus_A_R", "Hippocampus_A_L", and "Hippocampi")

The literature describes considerable age- and disease-specific variability in hippocampal size (range 2.8–4.0 cm^3) and location[7,17-19]. The hippocampus (HC) is

delineated as the grey matter medial to the medial boundary of the temporal horn of the lateral ventricle, bordered medially by the quadrigeminal cistern as described by Gondi *et al*.[7]. Blum *et al*.[20] suggest a separation of the HC into a posterior (corpus) and anterior (head) part using the lateral ventricle as dorsal border for the anterior hippocampus. In sagittal view, the head of the HC is separated from the body at the narrowing of the HC, with the uncus located dorsally[20,21]. Delineation on MR (T1 weighted) is essential.

Cochlea ("Cochlea_R", "Cochlea_L" and "Cochleas")
The cochlea is a spiral structure (up to 0.6 cm^3) located in a bony cavity in the petrous portion of the temporal bone, caudal to the semicircular canals, lateral to the internal auditory canal. Using a WW/WL setting of 120/1500 on CT images, its volume can be defined as a small cavity. The structures of the inner ear are well visible on MR (T2 weighted) images[4,6]. The semicircular canals should not be included.

Vestibular and semicircular canal ("VSCC_R", "VSCC_L", "VSCCs")
As the semicircular canals are a part of the bony labyrinth with the superior, posterior and lateral canals aligned in three planes, delineation is advised using the bone setting on CT images (WW/WL 120/1500). The semicircular canal is located laterally and cranially of the cochlea. The canals are also visible as small cavities on MR (T2 weighted)[6].

Brain Stem ("BrainStem", "Brainstem_surface", "Brainstem_interior" or "Midbrain", "Pons" and "Medulla Oblongata")
The brainstem is to be contoured on MR images and can be divided into three parts, from cranial to caudal, the midbrain, pons and medulla oblongata. The midbrain is defined from the nigral substance at the cerebral peduncle to the upper border of the pons. The pons is an oval shaped structure on sagittal views, which is easy to discriminate (see Figure 5.1C). The caudal limit of the medulla oblongata is the tip of the dens of C2 (*i.e.*, the odontoid peg), which is also the cranial border of the spinal cord; the cranial limit is the ponto-medullary junction[4,6,22]. For practical reason the cerebral aquaduct is included until it becomes the 4^{th} ventricle. The brainstem interior is the brainstem surface contour cropped by 2 mm (inner border). The brainstem surface is the brainstem excluding the brainstem interior[23,24]. These structures are contoured automatically (and checked thereafter) using a built-in delineation tool commonly found in treatment planning systems.

Brain ("Brain" and "Brain_Supratentorial")

The delineation of the brain includes the cerebellum, CSF and small brain vessels, and excludes the brainstem and large cerebellar vessels, such as the sigmoid sinus, transverse sinus and superior sagittal sinus (Figure 5.3C). For delineation purposes, CT in brain soft tissue 350/40 WW/WL-settings is recommended. Alternatively, the brain can be contoured automatically (and checked thereafter) using a built-in delineation tool commonly found in the majority of treatment planning systems[4,6,25]. In the middle cranial fossa the carotid canal and cavernous sinuses, most easily seen on contrast-enhanced T1 MRI, should not be included. The supratentorial brain equals the "Brain" excluding the cerebellum (see Section Cerebellum (''Cerebellum_P", ''Cerebellum_A" and ''Cerebellum")).

Cerebellum ("Cerebellum_P", "Cerebellum_A" and "Cerebellum")

The separation of the cerebellum into an anterior and posterior part is best seen on the sagittal T1 weighted MR (see Figure 5.1). The anterior cerebellum consists of the cranial part of the cerebellum including half of the medullary corpus. The posterior cerebellum consists of the caudal and posterior part of the cerebellum with a cranial border including the lower half of the medullary corpus. This part includes the flocculonodular lobe. The primary fissure, which is best seen on7-Tesla MR (see Figure 5.2), divides the anterior part from the posterior part of the cerebellum [26]. The lateral borders for both parts are the large vessels (the sigmoid sinus, transverse sinus and superior sagittal sinus) and CSF, which are both excluded.

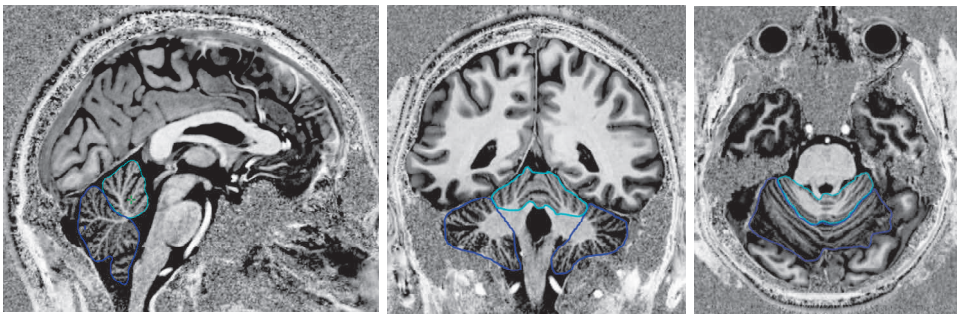

Figure 5.2 Sagittal (midline) view of cerebellum delineation on 7Tesla MRI
From left to right: 7 Tesla MRI, sagittal, coronal and transversal. Light blue = cerebellum anterior, dark blue = cerebellum posterior

Skin ("Skin")

The skin is the volume defined by the body contour (outer border) and the body contour cropped by 5 mm (inner border), both created on the CT. This structure is

contoured automatically (and checked thereafter) using a built-in delineation tool commonly found in treatment planning systems[4,6,25].

All mentioned OARs are delineated on CT and MR (see Figure 5.3) in an easy accessible delineation atlas at www.cancerdata.org.[27].

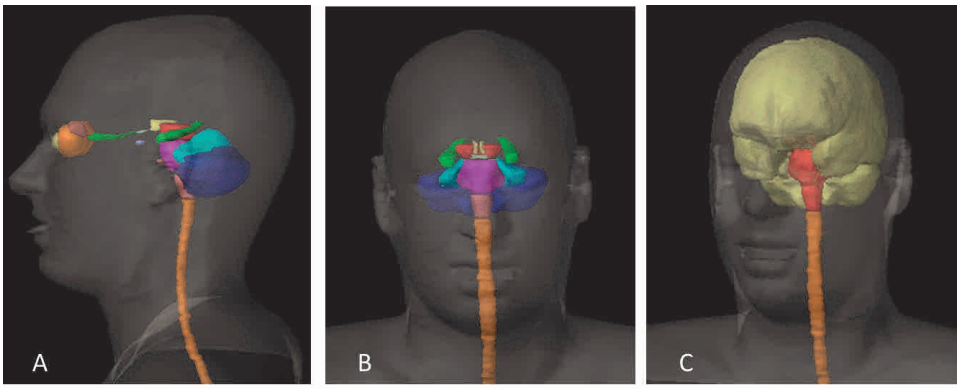

Figure 5.3 3D view of the OARs delineation on CT
A: From ventral to dorsal: yellow = cornea, orange = retina, brown = lacrimal gland, green = optic nerve, light green = chiasm, purple = pituitary, yellow (central) = hypothalamus, red = midbrain, green (central) = hippocampus anterior, dark green = hippocampus posterior, pink = cochlea, magenta = pons, pink = medulla oblongata, orange = spinal cord, light blue = cerebellum anterior, dark blue = cerebellum posterior. B: From cranial to caudal: yellow = hypothalamus, red = midbrain, light green = chiasm, green = hippocampus anterior, dark green = hippocampus posterior, magenta = pons, pink = medulla oblongata, Light blue = cerebellum anterior, dark blue = cerebellum posterior, orange = spinal cord. C: Yellow = brain, red = brainstem, orange= spinal cord.

Discussion

The presented atlas for contouring OARs involved in neuro-oncology aims at reducing the inter- and intra-observer delineation variability and thus enabling more consistent plan comparison. This is especially relevant when comparing different radiation treatment techniques and modalities, and for establishing detailed dose-response relationships and NTCP models for different OARs.
Toxicity to the optical system is a feared complication especially when it results in partial or total loss of vision or pain to the eye. Despite their small volume, a separate delineation of the different optical structures is crucial in order to derive dose-volume histograms and predict post-radiation toxicity. The optic chiasm is an anatomically

cross-shaped structure, as is depicted by Scoccianti *et al.* [6] and not round as presented in the atlas by Brouwer *et al.*[4]. Moreover, the chiasm should be contoured in continuity with both optic nerves in order to prevent high-dose deposits in un-delineated voxels. The retina is to be delineated separately from the vitreous body, since radiation induced retinopathy can be treated if observed in an early state. Consequently, correct dose calculation is of utmost relevance in order to refer a patient suffering from this radiation induced side-effect[28]. Separate delineation of the cornea is proposed since toxicity and tolerance dose differ from that of the retina[4,28,29]. Damage to the cornea, radiation keratitis, is painful and deteriorates sight. The mean radiation dose to the lacrimal gland is related to the development of a dry eye, which can be painful and render the eye susceptible to infections[28]. A cataract can develop at a rather low dose to the lens. This side-effect can be alleviated by surgical implantation of an artificial lens[28]. A normal lens is well seen because of its high protein content, whereas an artificial lens is difficult to see on CT or MR, but since it tolerates radiation dose, delineation is not required.

Hypo-pituitarism may take a long time to be diagnosed since its symptoms can be vague. Depending on the mean dose to the pituitary gland, an early referral to an endocrinologist can facilitate early initiation of treatment and thus prevent impaired quality of life[30,31]. In general, it is advised to delineate the entire sella content to be sure the whole pituitary is included rather than the central part only, excluding the suprasellar part of the infundibulum[4,6]. Even though there are no established dose constraints for the hypothalamus available yet, we believe that these data need to be collected in a prospective manner, in order to correlate levels of hormone production and regulation of metabolic processes with delivered radiation dose.

Hearing preservation after radiotherapy is known to be related to dose to the cochlea[32-34]. There is agreement in the literature on its delineation, most optimally done on a CT scan with thin slices using a bone WW/WL-setting considering its location in the mastoid bone[4,6]. Since dizziness is a side-effect occasionally reported after radiotherapy it was decided to delineate the semicircular canals as well, using the same WW/WL-settings as for the cochlea, although future data are needed to establish a validated dose constraint.

Recent literature has shown some dose response relationship between the hippocampus and cognition as described by Gondi *et al.*[34] using the absolute radiation dose to 40% of both hippocampi (D40%). We firmly encourage delineating the hippocampi separately and into anterior and posterior parts, since the left hippocampus is known to be dominant in most patients (including left-handed patients) for verbal memory, and the right hippocampus for non-verbal memory also known as

visual memory. Moreover, the posterior parts of the hippocampi are more related to memory than the anterior parts[35-39].

The brain is often automatically delineated and for practical reasons the included small vessels are left in the contour since editing the contour would be too time consuming. There are dose constraints for brain tissue, especially on high doses related to temporal lobe radionecrosis in head and neck cancer patients[40-45]. Regarding neuro-cognition, some publications on paediatric patients have shown a correlation between low dose radiation to the supra-tentorial brain and cognitive decline[46,47]. Further data are needed to transfer this knowledge to adult patients. Data on whole brain radiotherapy and prophylactic cranial irradiation have hinted at the negative effect of low dose on cognition[48-55]. However, there still is a strong need for an adult NTCP model on brain tissue and cognition.

Symptomatic brainstem necrosis is a feared, but rare complication following radiotherapy to the brain[56,57]. It was decided to contour the brainstem in three anatomically distinct parts, because some hypothesize that specific volumes within the brainstem are more sensitive to radiation than others. In particle beam therapy, the anterior surface and center of the brainstem are delineated separately since a higher tolerance at the surface of the brainstem has been observed[23,24]. This should be subject to further research for both photon and particle radiotherapy.

The delineation of the cerebellum is also added as a possible new OAR for research purposes, since there are data suggesting a relationship between the posterior cerebellum and cognition[58]. Cantelmi *et al.*[59] states that recognition of the important cognitive contributions of the cerebellum might lead to improved cognitive outcome and quality of life. This definitely needs further research into a possible dose response relationship and tolerance dose, which is only possible when agreement is reached in the delineation, as proposed based on Schmahmann *et al.*[26,56,59].

For radiation treatment planning purposes, the skin is added as an OAR since alopecia and erythema are disturbing side-effects. Using the skin structure enables lowering the dose during treatment planning, which is of particular importance in proton therapy with its relatively high entry dose[60].

A limitation of the atlas is the fact that the three dimensional angulation possibilities in a radiation treatment planning systems are often limited and patients are mostly not aligned perfectly in the midline. This is why the atlas was based on a random CT/MR-dataset of an imperfectly aligned patient, resembling routine clinical practice. The atlas includes transversal, coronal and sagittal views to assist the delineation process. A second potential limitation of this atlas is that we had to limit the number of OARs proposed for otherwise the atlas would have been impracticable and thus not used in routine clinical practice. Future research should unravel the role of additional OARs and

the NTCP value for: Eustachian tube, circle of Willis, optic tract, frontal & temporal lobe, anterior eye chambers, macula, mammillary bodies, spinal canal and cerebrospinal space. Thirdly, this atlas does not summarize the available literature on dose constraints for the contoured organs at risk; this enormous effort will be a separate project of the EPTN. Finally, even though this atlas was contoured on a 3T MR scan, it can be easily transferred to 1.5T MR images.

Uniform contouring of structures in the central nervous system, both in photon and particle therapy, is considered important for: 1) the generalization of normal tissue dose constraints, 2) establishment or update of NTCP models taking into account new radiation treatment techniques, and 3) for comparative multicenter clinical studies on radiotherapy in patients with primary brain tumors. Besides uniform contouring, consensus on OAR dose constraints is also required for implementing and improving NTCP models. A separate article on dose constraints for the given OARs, again consented by the EPTN, is currently being prepared.

Conclusion

In order to decrease variability in delineating OARs involved in neuro-oncology and to allow the generation of consistent dosimetric data, we propose an atlas for neuro-oncology including some new OARs in order to give an anatomical basis for the development of international acknowledged constraints and volumes. This will enable the community to amplify existing and new NTCP models such that more accurate prediction, and possibly prevention, of long-term radiation toxicity comes within reach. The atlas is available online on www.cancerdata.org and will be updated whenever required.

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Chapter 6

Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus

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Radiother Oncol 2018;128(1):26-36

Abstract

Purpose

For unbiased comparison of different radiation modalities and techniques, consensus on delineation of radiation sensitive organs at risk (OARs) and on their dose constraints is warranted. Following the publication of a digital, online atlas for OAR delineation in neuro-oncology by the same group, we assessed the brain OAR-dose constraints in a follow-up study.

Methods

We performed a comprehensive search to identify the current papers on OAR dose constraints for normofractionated photon and particle therapy in PubMed, Ovid Medline, Cochrane Library, Embase and Web of Science. Moreover, the included articles' reference lists were cross-checked for potential studies that met the inclusion criteria. Consensus was reached among 20 radiation oncology experts in the field of neuro-oncology.

Results

For the OARs published in the neuro-oncology literature, we summarized the available literature and recommended dose constraints associated with certain levels of normal tissue complication probability (NTCP) according to the recent ICRU recommendations. For those OARs with lacking or insufficient NTCP data, a proposal for effective and efficient data collection is given.

Conclusion

The use of the European Particle Therapy Network-consensus OAR dose constraints summarized in this article is recommended for the model-based approach comparing photon and proton beam irradiation as well as for prospective clinical trials including novel radiation techniques and/or modalities.

Introduction

The field of radiotherapy is rapidly evolving with new techniques, *e.g.*, MR-linac, and beam modalities, *i.e.*, protons and carbon ions, entering the scene of image-guided high precision treatment. These innovations aim at increasing the tumour control probability (TCP) while maintaining or reducing the normal tissue complication probability (NTCP). For comparison of the latter, ideally, consensus on (1) the delineation of the organs at risk (OARs), on (2) the tolerable radiation dose to be administered to the OARs, and on (3) the outcome reporting measure, *i.e.*, uniform follow-up timing, patient questionnaires and content of the follow-up, should exist.

Regarding the first pre-requisite, Eekers *et al*.[1,2] recently published a digital, online atlas for OAR delineation in neuro-oncology on behalf of the task group "European Particle Therapy Network" (EPTN) of ESTRO. Addressing the second required condition, it has been a while since the recommendations by Emami *et al*.[3] and the QUANTEC series[4-7] were published. In an attempt to reach the ideal conditions for comparison, we therefore summarize the OAR's distinct radiation induced toxicities and the recommended dose constraints for conventionally fractionated radiotherapy.
Moreover, we identified gaps of knowledge that need to be filled, preferably in a prospective multi-centre effort, to fully exploit the potential of highly conformal radiotherapy. Of note, this summary of the literature does explicitly not cover hypofractionated / ablative regimens, carbon ion radiotherapy, re-irradiation, or paediatric data.

Materials and methods

For each of the OAR described in the EPTN delineation consensus paper a dose constraint was sought for and the available data summarized[1]. Published manuscripts were identified through a PubMed search using combinations of ("radiotherapy" or "radiation therapy" or "radiation-induced") and "xerophthalmia"; "dry eye syndrome"; "keratoconjunctivitis"; "retinopathy"; "cataracts"; "optic neuropathy"; "vision loss"; "hemianopsia"; "hearing loss"; "tinnitus"; "vertigo"; "hypopituitarism"; "neurocognition"; "radionecrosis"; "Temporal lobe necrosis"; "brain stem toxicity"; "hippocampus"; "cerebellum"; "alopecia". Those manuscripts available in English or French, containing data on adult patients obtained from primary conventionally fractionated photon and proton radiotherapy, and describing a dose-toxicity relationship were included in this recommendation. Papers on re-irradiation,

hypofractionation, carbon ion therapy and stereotactic ablative radiotherapy were omitted.

Relevant papers were summarized and put into Supplementary Tables (6.1-6.10)

The relevant quantitative analyses of normal tissue effect in the clinic (QUANTEC) papers were used for reference when applicable as was the paper by Emami *et al*.[3-7].

The literature was then reviewed by 20 Radiation Oncology experts in the field of neuro oncology and a consensus was reached as depicted in Table 6.1 (see Figure 6.1). The units of all dose constraints are given in Gy regardless of the reported unit in the analysed data. Doses were recalculated to equivalent dose in 2 Gy-fractions (EQD2) using the formula:

$$EQD_2 = \frac{D\left(d + \alpha/\beta\right)}{\left(2 + \alpha/\beta\right)}$$ with D: the total dose and d: the dose per fraction.

Table 6.1

Organ	α/β (Gy)	Dose constraint EQD2	Toxicity
Brain[7,87-90]	2	V_{60Gy} ≤3 cc	Symptomatic brain necrosis
Brainstem[52,93-101]	2	Surface $D_{0.03cc}$ ≤60 Gy Interior $D_{0.03cc}$ ≤54 Gy	Permanent cranial neuropathy or necrosis
Chiasm & Optic nerve[23,48-54]	2	$D_{0.03cc}$ ≤55 Gy	Optic neuropathy
Cochlea[57-60,64-66]	3	D_{mean} ≤45Gy D_{mean} ≤32 Gy	Hearing loss Tinnitus
Cornea[13,21]	3	$D_{0.03cc}$ ≤50 Gy	Erosion/ulceration
Hippocampus[108,109]	2	$D_{40\,\%}$ ≤7.3 Gy	Memory loss
Lacrimal gland[9,11,14-16]	3	D_{mean} ≤25 Gy	Keratoconjunctivitis sicca
Lens[36,37]	1	$D_{0.03cc}$ ≤10 Gy	Cataract
Pituitary[66,76,79,80]	2	D_{mean} ≤45 Gy D_{mean} ≤20 Gy	Panhypopituitarism Growth hormone deficiency
Retina[13,23,26,31]	3	$D_{0.03cc}$ ≤45 Gy	Loss of vision
Skin[114]	2	$D_{0.03cc}$ ≤25 Gy	Permanent alopecia

EQD2 = equivalent dose in 2 Gy per fraction; $D_{3\ cc}$ = dose to 3 cc of structure/organ; $D_{0.03\ cc}$ = near maximum dose to 0.3 cc of structure/organ; D_{mean} = mean dose; $D_{40\%}$ = mean dose to 40% of the volume of both hippocampi.

Results

Orbital structures

Radiotherapy of central nervous system (CNS) tumours often results in intentional or incidental irradiation of the different orbital structures. This gives rise to a wide variety of acute and late toxicities ranging from transient erythema of the peri-orbital skin to

permanent blindness. The complex anatomy and physiology of the eye make it a challenging task to give a full and detailed description of all toxicities, and literature on many of them is scarce.

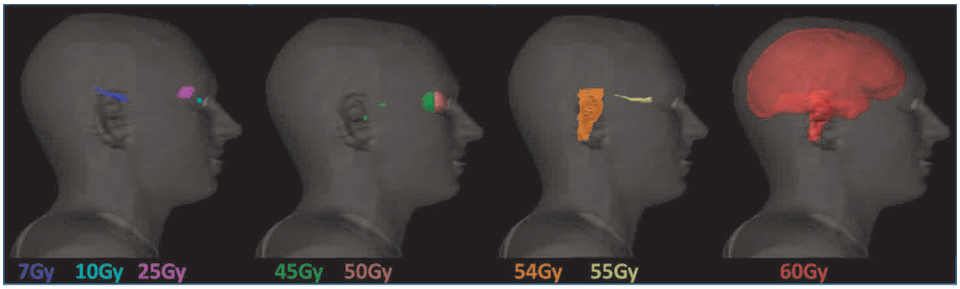

Figure 6.1 A 3D representation of the OARs and the recommended corresponding dose constraints[1]: hippocampus (purple), lenses (light blue), lacrima gland (magenta), pituitary (green), cochlea (green), cornea (pink), brainstem interior (orange), chiasm (yellow), optic nerve (yellow), brainstem surface (red), brian (red). All doses are given as maximum dose to 0.03 cc of the OAR volume ($D_{0.03cc}$), except for the dose to hippocampus, which is the $D_{40\%}$, and the pituitary gland and cochlea, which are mean doses (D_{mean}).

Lacrimal gland

The lacrimal gland system includes the main lacrimal gland, accessory lacrimal glands and the lacrimal duct system. This system is crucial for the production of tears, however, other structures, such as Meibomian glands or the conjunctival goblet cells also contribute to the production of an adequate tear film. Radiation injury to any of these structures might result in xerophthalmia or the so-called dry eye syndrome (DES) and the exact contribution of the individual components is difficult to establish[8-10]. DES typically develops between 1 month and 3 years after irradiation, depending on the total dose and fractionation[9,11].

In the common terminology criteria for adverse events (CTCAE) version 4.0 three grades of xerophthalmia are identified ranging from mild symptoms up to a decrease in visual acuity (<20/40); limiting self-care activities of daily life (ADL)[12]. DES can lead to damage of the conjunctival and corneal epithelium (*keratoconjunctivitis sicca*), which causes pain, foreign body sensation, photophobia, corneal ulceration, and even perforation[13].

Several retrospective series have demonstrated that the risk of atrophy and fibrosis of the lacrimal gland increases sharply with the delivered dose (Supplementary Table S6.1)[9,11,14-16]. Although the exact clinical endpoints in these series are not always clearly defined, they agree on a sigmoidal dose-response curve for DES with a negligible risk at

absolute maximum doses (D_{max}) <30 Gy, with a steeply increasing risk >40 Gy and a 100% rate of severe dry eye with D_{max} >57-60 Gy[17,18].
The EPTN consensus group therefore proposes that if possible, the mean dose (D_{mean}) to the lacrimal gland should not exceed 25 Gy for a risk for DES (> grade 1) less than 5%. No data was found on an α/β ratio for the lacrimal gland and late dry eye syndrome, therefore we suggest to assume an α/β ratio of 3 Gy for late toxicity similar to that of the parotid gland[19].

Cornea

The cornea's main functions are refraction of the light and protection, and even slight alterations of its shape can result in decreased visual acuity. Corneal complications may arise secondary to the loss of the tear film (*keratitis sicca*) or resulting from direct injury to the corneal surface epithelium and the deeper layers of the cornea. Direct radiation induced changes originate from the disruption of the mitotic activity in these layers and do not arise from the avascular cornea.
In CTCAE v4.0 keratitis is defined as a disorder characterized by an inflammation of the cornea with severity ranging from mild inflammation to perforation and complete blindness[12].
Even though accurate dose-volume parameters are scarce, a dose-toxicity relationship has been described in several retrospective series[13,18,20,21]. In one retrospective analysis corneal complications were evaluated after orbital radiotherapy for lacrimal gland malignancies[21]. In this series patients were treated up to cumulative doses of 50-60 Gy to the entire orbit. All patients developed an acute radiation keratoconjunctivitis, 54% of the patients had chronic corneal epithelial defects and 13% developed a corneal perforation. These perforations generally occurred within 3 years of radiotherapy. While there are several limitations to this analysis, it confirms that high dose radiotherapy can have serious consequences on the ocular surface (see Supplementary Table S6.2). We therefore propose $D_{0.03cc}$ to the cornea not to exceed 50 Gy if the orbit is not part of the target volume. Again, we propose an α/β ratio of 3Gy for late toxicity in absence of solid data.

Retina

The retina is the third and inner coating of the eye and is essential in visual perception. In embryogenesis both the retina and the optic nerve originate from the diencephalon and should therefore be considered as part of the central nervous system.
Retinopathy is characterized by slowly progressive microangiopathic decompensation with a focal loss of capillary endothelial cells and pericytes[18]. Clinically, radiation

retinopathy includes microaneurysms, cotton wool pots, capillary dilation, telangiectasia and capillary closure, all histopathologically resembling diabetic retinopathy[22,23]. The latency period is typically between 6 months and 3 years, although longer periods have been described[18,24-26]. The CTCAE v4.0 defines retinopathy using 4 grades ranging from asymptomatic up to grade 4 blindness (20/200 or worse) in the affected eye[12]. The pathogenesis of radiation induced retinopathy is dependent on the total dose, the fraction size, number of fractions, concurrent chemotherapy and coexisting morbidity, *e.g.*, diabetes, hypertension[23,27-29]. A selected number of studies reported on the dose-toxicity relationship for retinopathy and are depicted in Supplementary Table S6.3[13,26,30,31].

The risk of retinopathy increases steeply with D_{max} exceeding 45-50Gy in 5 weeks. Emami *et al*.[3] estimated the 5% severe complication rate in 5 years (TD5/5) of the retina, *i.e.*, visual loss, to be 45 Gy and the 50% severe complication rate at 5 years (TD50/5) to be 65 Gy.

We therefore propose the $D_{0.03cc}$ to the retina to be kept below 45 Gy. Again, we propose an α/β ratio of 3 Gy for late toxicity in absence of solid data[19].

Lens of the eye

The lens is a biconvex structure in the eye that helps to refract light. Any stimulus causing posterior migration and proliferation of the lens epithelial cells reduces the lens clarity, causing a cataract, and often results in some degree of visual loss[32]. The CTCAE v4.0 distinguishes 4 grades of cataract based on visual acuity ranging from asymptomatic (grade 1) to complete blindness (20/200 or worse) in the affected eye (grade 4)[12].

Irradiating the lens can lead to cataract formation. The initial insult consists of damage to the germinative zone of the lens epithelium, which leads to extensive cell death, compensatory mitosis, and the generation of the so-called 'Wedl' cells[18,27,32-35]. The severity and delay until onset of radiation-induced cataracts is dose-dependent, however, the accurate threshold is poorly understood. Several retrospective studies have investigated the occurrence of cataract after irradiation[36,37] (Supplementary Table S6.4).

While Emami *et al*.[3] estimated the TD5/5 of the lens to be 10 Gy and the TD50/5 to be 18Gy, other series have demonstrated that even lower doses can result in the occurrence of cataract[38,39]. Recently, the International Commission on Radiological Protection (ICRP) defined 0.5 Gy as the new threshold dose for lens opacities, which is based on the data from population based studies in diagnostic imaging and occupational exposure[40,41].

Based on these data, the EPTN consensus panel suggests the dose to the lens to be kept as low as reasonably achievable (ALARA) and should not surpass $D_{0.03cc}$ of 10 Gy. Conversely, as replacement of a damaged lens is a relatively harmless procedure nowadays, target volume coverage should not be compromised in an attempt to spare the lenses. Since the limited data on an α/β ratio for the lens suggests values of 0.76-1.2 Gy, we propose to use an α/β ratio of 1 Gy for late toxicity[19,42,43].

Optic Nerve

First described in 1956, radiation induced optic neuropathy (RION) is a rare yet disabling condition with a potentially devastating impact on the vision of the affected eye[44]. The pathogenesis of RION is not fully understood, but it is often considered to be delayed radionecrosis in the CNS and thus the effect of radiation on the optic nerve appears to be both vascular and neuropathic in nature[23,32,45,46]. It usually presents with painless, rapid visual loss and can occur between 3 months and 8 years after treatment, with a peak between 1-1.5 years[45,47]. It is graded according to the CTCAE v4.0 as grade 1 being asymptomatic, grade 2 limiting vision of the affected eye (20/40 or better), grade 3 limiting vision in the affected eye (worse than 20/40) but better than 20/200 or grade 4, blindness which is 20/200 or worse in the affected eye[12].
Complication data for RION have been reported for photons and protons, and following irradiation for several indications. A selected group of studies is depicted in Supplementary Table S6.5 [23,48-54]. Emami *et al*.[3] suggested a TD5/5 of 50 Gy and a TD50/5 of 65 Gy. However, in the QUANTEC analysis this was deemed inaccurate after review of the literature concluding that the incidence of RION was unusual for a D_{max}<55 Gy using conventional fractionation[5]. The incidence of RION increased between 55-60 Gy (3-7%) and was substantial (>7-20%) for D_{max}>60 Gy, although it should be noted that in some studies even at these high doses no clinically significant RION was observed. For particles most investigators also confirmed that the incidence of RION was low for a D_{max}<54 Gy (RBE).
Within the EPTN group we therefore support the use of $D_{0.03} \leq 55$ Gy for the optic nerve and suggest to use an α/β ratio of 2Gy for late toxicity[19].

Optic chiasm

In the optic chiasm, the optic nerve fibers from the nasal sides of each retina cross to the opposite side of the brain. Toxicity of the optic chiasm is graded similarly as in RION. However, instead of unilateral visual loss, it typically presents as a bitemporal hemianopsia or even total blindness. As pathophysiology is similar to RION, the same principles apply, and we suggest to use the same constraint, *i.e.*, $D_{0.03cc} \leq 55$ Gy and α/β

ratio of 2 Gy[19]. Specific caution should be taken in patients, in whom the optic chiasm has been manipulated, *e.g.*, during neurosurgery.

Inner Ear

The inner ear, also called labyrinth of the ear, is that part of the ear that contains the organs responsible for hearing (cochlea) and balance (vestibule and semi-circular canal). The bony labyrinth is divided into three sections: the vestibule, the semi-circular canals and the cochlea. Each section of the bony labyrinth contains perilymph and a part of the membranous labyrinth. The vestibule contains the utriculus and sacculus, the semi-circular canals contain a semi-circular duct, and the cochlea contains the cochlear duct.

Cochlea

Sensorineural hearing loss (SNHL) is the most important radiotherapy-induced complication of the inner ear, with up to 44% of patients reporting hearing loss after radiotherapy when one of the radiation beams passes the inner ear[55,56]. Consistently throughout the literature, the high frequencies appear to be more affected than lower frequencies, and this is dose-dependent[56-60].

Hearing loss can be graded according to the CTCAE v4.0[12]. While early hearing loss during conventionally fractionated radiotherapy is usually transient and commonly due to serous otitis media, true SNHL classically occurs with a latency period of 1.5-5 years after radiotherapy and is irreversible[55,57,61,62]. Histopathologically it results from loss of cochlear primary sensory cells and/or damage to the spiral ganglion or cochlear nerve[63].

The relationship between the dose to the cochlea and SNHL has been extensively investigated. Emami *et al*.[3] identified a TD 5/5 of 60 Gy and TD 50/5 of 70 Gy for sensorineural or vestibular damage. However, based on more recent dose volume data the QUANTEC consensus paper suggested the D_{mean} to the cochlea ≤45 Gy or even more conservatively ≤35 Gy[57-60,64,65].

The recent publication by De Marzi *et al*.[66], who investigated 140 patients treated with photon and proton therapy for base of skull tumours, reported on a dose-response model for the inner ear. After qualitative correlation of D_{mean} with auditory toxicity (scored as grade 1-2 hearing loss, based on CTCAE v4.0), no significant cut-off value could be determined. Considering the size of the organ, they calculated the generalized equivalent uniform dose and found it to be a predictive factor for late complications. For the cochlea and inner ear, a tolerance uniform dose delivered to the whole organ for 50% complication rate (TD 50) of 56 Gy (95%CI 53.6-58.5) and 53.6 Gy (95%CI

51.8-55.4 Gy) was reported with slope of the response curve at TD50 (γ50) of 2.8 for both and an a-value of 1.2 and 0.1, respectively. These values are in the same range as the QUANTEC data.
The EPTN consensus panel proposes the D_{mean} to the cochlea to be kept to ≤45 Gy. Since, there is no clear threshold dose for hearing loss after radiotherapy, the ALARA principle applies. Again, we propose an α/β ratio of 3 Gy for late toxicity in absence of solid data.

Besides SNHL, tinnitus is also a potential side effect from ionizing radiotherapy. CTCAE v4.0 defines tinnitus as a disorder characterized by a perception of noise or ringing in the ears, and has 3 grades, based on the impact of the tinnitus on the activities of daily life[12]. Limited data are available on the effect of dose on the occurrence of tinnitus and it is probably under-reported. As a result, there is no QUANTEC guideline for the cochlea to avoid tinnitus. Lee *et al.*[67] investigated the incidence of tinnitus after intensity modulated radiation therapy (IMRT) for head and neck cancer patients and noticed that 11.6% of developed grade>2 tinnitus, consistent with other reports in the literature[68,69]. Based on a logistic and Lyman-Kutcher NTCP model derived from their results, D_{mean} to the cochlea should be kept <32 Gy in order to keep the incidence of grade>2 tinnitus <20% using IMRT[67]. External validation of this model is thus far lacking. In the absence of data, we suggest to use a traditional α/β ratio of 3 Gy for late toxicity[19].

Vestibulum and semi-circular canal

Vestibular toxicity can be graded according to the CTCAE v4.0 as vertigo or more generally as a vestibular disorder[12], even though occasionally acute nausea following radiotherapy is reported instead.
There is very little data concerning vestibular toxicity related to radiotherapy. Gabriele *et al*.[70] investigated the vestibular function in 25 head and neck cancer patients. Eleven of these patients showed vestibular abnormalities on electronystagmography, but only three reported vertigo. More recently Lee *et al*.[71] analysed 49 consecutive nasopharyngeal carcinoma patients treated with radiotherapy alone, of whom six reported nausea and no patient dizziness or vertigo. Using multivariate analysis, the authors identified a correlation between the volume of the vestibules receiving 40 Gy (V_{40Gy}) and incidence of nausea. Again, external validation is awaited. Prospective collection of dose-volume data and accurate toxicity scoring is mandatory to identify dose-volume parameters in the nearby future. As such, EPTN cannot recommend any dose-constraint threshold for this OAR.

Pituitary gland/hypothalamus

The pituitary gland is an endocrine gland essential for the regulation of many physiological processes including growth, thyroid gland function, reproduction, and lactation. It is closely linked to the hypothalamus through the pituitary stalk. Dysfunction of this hypothalamic-pituitary axis is a common problem after radiotherapy of both brain and head and neck tumours and is associated with significant morbidity and even mortality[72-76]. Adequate management of radiation induced hypopituitarism is essential to optimize outcomes and improve quality of life in these patients[77]. The CTCAE v4.0 identifies several endocrine disorders, which may be associated with hypopituitarism, although clinically it can present with a large variety of non-specific symptoms and should always be in the differential diagnosis in the follow-up of patients treated with radiotherapy for head and neck or brain tumours[12]. Despite its high incidence, little information on the correlation between dose and dysfunction of the hypothalamic pituitary axis is available[74,78]. Relevant studies are depicted in Supplementary Table S6.6[66,76,79,80].

In children, Merchant *et al*.[81] described the decline in growth hormone (GH) levels after cranial radiotherapy by an exponential equation dependent on the radiation dose to the hypothalamus and the follow-up time interval, which was confirmed by Agha *et al*.[76] in an adult population. GH deficiency may occur after low doses (D_{mean}<40 Gy) especially in patients whose hypothalamopituitary axis (HPA) was impaired by the presence of a tumour and/or previous surgery[78,82,83]. Deficiency of all anterior-pituitary hormones occurs mainly after high dose irradiation (D_{mean}>60 Gy) in nasopharyngeal carcinoma or base of skull tumour patients (see Supplementary Table S6.6)[79,80,84]. There is a steep increase in the incidence of endocrinopathy at a D_{mean} or minimum dose (D_{min}) of 40-50 Gy. Only one study attempted to model the NTCP for the pituitary gland using the equivalent uniform dose and found a TD50 of approx. 60.5 Gy (95%CI: 59.1-62 Gy)[66].

Some preclinical studies suggest there may be a differential radiosensitivity between the hypothalamus and the pituitary gland[85]. One study by Pai *et al*.[80] found that doses below 20 Gy (RBE) to the hypothalamus were associated with endocrinopathies, while this association was only found for a D_{min} above 50 Gy(RBE) for the pituitary gland. Noteworthy, target volumes of most patients included in this analysis were located in the clivus and strict dose constraints were imposed on the optic chiasm resulting in a steep dose gradient between pituitary gland and hypothalamus. Larger dose variation and patient populations will be necessary to distinguish the individual contribution of each of these structures to HPA dysfunction. Until further data is available we propose to use the same dose constraint to both these structures.

The EPTN consensus panel proposes a D_{mean}<45 Gy to the pituitary gland in the prevention of panhypopituitarism. Of course, if clinical context demands, higher doses may be justified. However, even at low doses deficiency of one of the hormonal axes might occur and a rigid endocrinological follow-up needs to be put in place, as adequate hormone replacement therapy is available and needs to be prescribed. Specific care is to be taken in patients treated for pituitary tumours or after surgery to this area, in which cases, lower tolerance doses should be employed[77,78]. There is currently no valuable data on the tolerance doses of the hypothalamus. As such, EPTN cannot recommend any dose-constraint threshold for the hypothalamus at this stage. Prospective and standardized reporting of dose and toxicity might help us to overcome this. In addition, there is no clear data on the α/β ratio of the pituitary gland or hypothalamus for the endpoint hypopituitarism, therefore we suggest to use an α/β ratio of 2 Gy for late toxicity.

Brain

Damage to the CNS is of considerable concern in the radiation treatment of brain tumours. However, evaluating cerebral toxicity is extremely difficult as we only begin to understand the intricate interplay between the different substructures in physiological conditions, let alone in pathological conditions. In this review two main long-term adverse effects will be evaluated mainly radionecrosis and neurocognition.

Brain

Despite its complexity, dose constraints to the brain and cerebrum are uniformly applied to the entire cerebral parenchyma without distinction between cortex, white matter and nuclei. Concerning radionecrosis, Emami *et al*.[3] reported a TD5/5 of 60 Gy, 50 Gy and 45 Gy and a TD50/5 of 75 Gy, 65 Gy and 60 Gy if 1/3, 2/3 or the entire brain, respectively, was irradiated up to that dose. These values appear to be too conservative in the 3D era, as the QUANTEC project found a dose response relationship in the brain: the incidence of radionecrosis increases from 3% with a D_{max}<60 Gy, to 5% at D_{max}=72 Gy, and to 10% when D_{max}=90 Gy, using an α/β=3 Gy[4,86]. Following the QUANTEC data, several papers reported on the dose-volume relationship for temporal lobe necrosis using both photons and protons[87-90]. They all highlight the importance of the volume receiving a certain dose in the occurrence of brain necrosis. The results are depicted in Supplementary Table S6.7.

Based on these data, the EPTN consensus panel proposes to V_{60Gy}<3 cc in EQD2. The α/β ratio for brain tissue is 2 Gy for radionecrosis[19].

Aside from radionecrosis, radiation induced white matter damage can also cause serious neurocognitive disturbances[91]. However, to our knowledge there is no clear dose-volume data available allowing us to selectively spare a specific part of the supratentorial brain. As such we cannot recommend any dose constraint threshold for brain and neurocognition, and thus the ALARA principle applies.

Brainstem

The brainstem consists of the medulla oblongata, pons and midbrain. It plays a crucial role as a relay between the body, the cerebellum and cerebrum, it gives rise to nine functions. Damage to the brainstem is therefore a severe and potentially lethal complication and can present as a wide spectrum of clinical features depending on the location and the extent of the damage[92]. This of course has important implications for the dose constraints; unlike for several other OARs, no long-term toxicity should occur at the level of the brain stem. There are several recommendations based on the available literature and there seems to be a clear distinction between the dose constraints used for photons and protons[6,92]. An overview of some selected reports on planning constraints and toxicity are depicted in Supplementary Table S6.8[52,93-101].

Historically, Emami *et al*.[3] defined the TD5/5 for necrosis of the brainstem as 50 Gy, 53 Gy and 60 Gy to the entire, 2/3 and 1/3 of the volume of the brainstem, respectively, and the TD50/5 of the entire brainstem was estimated at 65 Gy[102]. However, these values appear to be overly conservative considering the data available from recent retrospective analysis. It appears that the entire brainstem may be treated to 54 Gy using conventional fractionation with limited risk of severe or permanent neurological effects, while small volumes of the brainstem may even be irradiated to D_{max}=59 Gy. The risk appears to increase markedly for D_{max}>64 Gy[6,103].

The consensus panel therefore suggests $D_{0.03cc}$ <54 Gy in EQD2, in particular to the interior to the brainstem. Whenever institutions opt to use higher doses, we propose that $D_{0.03cc}$ of the brainstem surface should be kept <60 Gy EQD2, which correlates with the absolute dose of 64Gy RBE used in the proton literature for base of skull[97-101]. For both, the brain and brainstem, we assume an α/β ratio of 2 Gy for late CNS toxicity[19].

Hippocampus

One of the most elusive long-term toxicities related to radiotherapy of the brain is neurocognitive decline and memory impairment. It has become exceedingly important in the debate surrounding the use of more complex and expensive radiotherapy techniques, even though the exact pathophysiology is complex and poorly understood[104-106]. In the time of the QUANTEC project there was insufficient evidence

to support the claim that partial brain radiotherapy in 2 Gy fractions causes neurocognitive decline[7]. This was partly due to insufficient outcome measurements as well as the lack of detailed brain dose-volume data. However, over the last decade there is a growing insight in the mechanisms behind neurocognitive disability after radiotherapy, particularly in respect to the hippocampi, which are instrumental in learning, memory and neurogenesis[104,107]. The seminal article by Gondi *et al*.[108] compared a control group with a historical group of patients treated for benign tumours or low grade gliomas. They found that if the $D_{40\%}$ of the bilateral hippocampi exceeded 7.3 Gy this was associated with a decrease in the WMS-WL delayed recall test at 18 months. Many studies are currently underway, investigating hippocampal avoidance in several clinical settings, however, we are still awaiting results. Imaging studies have revealed that doses exceeding 40 Gy resulted in a significant atrophy of the hippocampus (see Supplementary Table S6.8)[109].
Based on these data it is somewhat preliminary to propose dose constraints to the hippocampus. If possible, the dose to the hippocampi should be kept ALARA and preferably the $D_{40\%}$ of both hippocampi combined should be kept below 7.3 Gy. Again, an α/β ratio of 2 Gy for late CNS toxicity.

Cerebellum

Classically, the cerebellum is known for its role in the regulation and coordination of movement posture and balance. Radionecrosis could thus have an important influence on these factors. For this outcome there is currently no data suggesting a different radiosensitivity of the cerebellar cortex or white matter, and thus the same constraints as those used in the brain are proposed.
Interestingly there is more and more evidence that the cerebellum is also involved in cognitive functions[110]. In paediatric patients with infratentorial ependymoma one report found a correlation between the infratentorial radiation dose and neurocognitive decline[111]. However, in adults this evidence is lacking and so to date no clear dose constraints can be defined for the anterior and posterior cerebellum.

Skin

Radiation to the scalp can give rise to several toxicities. Since the skin itself is rarely part of the target volume in primary brain tumours, temporary and permanent alopecia is the most important late toxicity after radiotherapy. Temporary alopecia can occur after very low doses, while permanent alopecia requires relatively higher doses to the skin[112,113]. Lawenda *et al*.[114] performed an depth dose response analysis on permanent alopecia at >12 months in patients treated with photons for a primary CNS tumour.

After multivariate analysis, only the follicle dose was significantly correlated to permanent alopecia. In the dose-response relationship the TD_{50} was estimated at 43 Gy EQD2 (95%CI 33-52) with a γ50 slope of 0.9 (95% CI 0.3-1.4). Using this dose-response relationship, a follicle dose of 25 Gy is associated with <20% risk of permanent alopecia grade≥3. In order to avoid this side effect a reduction of the dose to the hair follicles should be attempted.
The EPTN therefore suggests the $D_{0.03cc}$ of the skin should be kept <25 Gy to avoid permanent focal alopecia and consequently the V_{25Gy} to the skin should be kept ALARA. The suggested α/β ratio for the skin is 2 Gy[19,114].

Discussion

Despite the increasing number of patients treated with radiotherapy for brain tumours, scarce precise information is available on the relationship between dose and toxicity of the central nervous system. In the past several efforts have already been undertaken to try and summarize the available evidence on the tolerance of normal tissues[3,4,102]. However, several relevant OARs, such as the lacrimal gland, the cornea, the vestibulum and semi-circular canals, the HPA, hippocampus, cerebellum and skin were not discussed in these papers. In addition, the increasing availability of highly conformal photon and proton therapy, the widespread use of image-guided and adaptive radiotherapy enable the radiotherapy community to deliver high doses to the target volume and selectively spare certain organs at risk. While dosimetrically these techniques might produce 'better' treatment plans, they do not always translate into clinical reality. In order to justify the use of these expensive treatments and make an accurate estimation of the benefit of one technique over the other, an objective estimation of the normal tissue complication rate is crucial[115,116]. Such a model-based approach allows us to compare different treatment strategies and select patients who will most likely benefit from a certain technique based on the difference in NTCP models between two techniques. These NTCP models need to incorporate both dosimetric and clinical factors and provide us with objective data on the superiority of one technique over the other[4,102,117]. However, the construction of these models requires an large amount of uniformly scored patient data. Consequently, for all OAR and toxicities described in the manuscript, such a multifactorial NTCP model is not available.
Therefore, one of the key goals of the EPTN is to try and set-up a framework for international cooperation within the radiotherapy community, which allows the introduction of a uniform, consensus-based means for data collection. In a first

consensus paper, relevant OARs in neuro-oncology were selected and delineation guidelines were given[1]. This manuscript aimed to review the available evidence on the dose-toxicity relationship for the previously defined OAR. While we succeeded in producing a consensus table on dose constraints (see Table 6.1), there are several shortcomings of the data presented here.

First, as is clear from this review, the vast majority of dose constraints rely on the reports from retrospective, single centre studies. Furthermore, in most of the cases no accurate dose-volume analysis could be done as the majority of patients within each series is treated for a variety of primary tumours with a variety of doses and fractionation schedules, using old radiotherapy techniques, and without uniform contouring of the OARs. We can therefore only estimate the dose delivered to a certain OAR. Also, in the majority of cases absolute doses are reported, with little to no information on the exact fractionation, making it impossible to recalculate the doses to EQD2. For the consensus table we aimed to define all D_{max} constraints in EQD2, using the linear quadratic formula, this allows us to recalculate the dose depending on the number of fractions (Figure 6.2)[118]. Of note, this conversion using the linear quadratic formula does not apply to D_{mean} dose constraints. Instead, the mean dose to the OAR and its standard deviation is required for this conversion, and therefore, we cannot provide these technique-dependent values[119,120]. In keeping with the ICRU 83 and 91 reports we avoided using the maximum absorbed dose at a single calculation point (D_{max}) for the constraint table[121,122]. However, for larger OARs such as the brain and brainstem, the classical $D_{2\%}$ might result in a relatively large volume exceeding the tolerance dose. We therefore opted to use the $D_{0.03cc}$ as this approximates the D_{max} used in the majority of the literature, since this depends less on the treatment planning system and scanner parameters used, and thus provides a more realistic calculation of the delivered dose. Only dose parameters related with specific toxicities were included in the consensus table, however, for planning purposes it is obvious that more than one dose-volume parameter should be included in the optimization process (as objectives or constraints) to ensure the optimal plan is generated.

Second, when setting dose constraints we assume a dose volume effect for the structures, and set a threshold below which the odds of a certain toxicity are reasonable. The outcome of this exercise depends highly on the severity of the toxicity and at what cost the dose is pushed below a certain threshold. Conversely, it is obvious that RT related toxicity is a more complex and multifactorial process where genetic disposition, co-morbidities, dosimetric and clinical factors all play an important role in explaining why some patients experience excess toxicity at low doses and others can be treated up to high doses without any toxicity[117]. This interplay is impossible to grasp in a single parameter and, again, requires more complex models, which incorporate

clinical, genetic, and dosimetric factors into a multifactorial NTCP model which allows for an individual patient-based risk assessment.

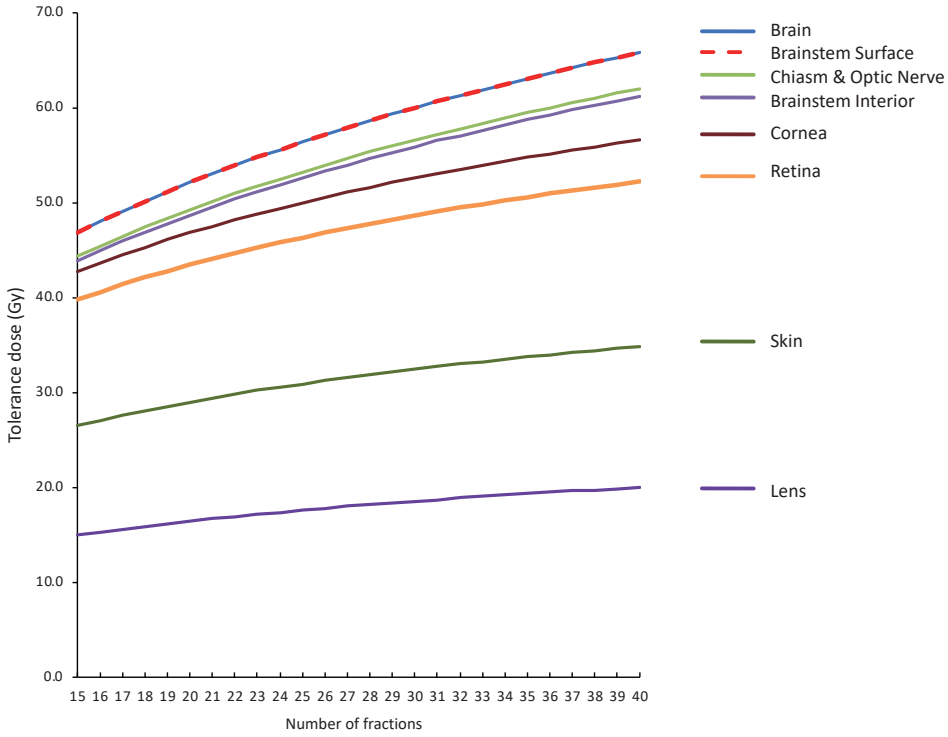

Figure 6.2 Tolerance dose versus total number of fractions. The Tolerance dose is calculated using the EPTN consensus dose constraints and a/b versus the total number of fractions. On the X-axis the total number of fractions is given and on the Y-axis the corresponding physical tolerance dose (Gy); for all OAR the $D_{0.03cc}$ (= dose to 0.03 cc of the organ/structure) except for the brain (D_{3cc} = dose to 3 cc of the brain).

Third, toxicity was not uniformly scored in all series. In the review several toxicity scoring mechanisms have been used, with the RTOG/EORTC Late Effects Normal Tissue Task Force subjective, objective, management, and analytic (LENT/SOMA) score and CTCAE being the most prominently used[12,123]. Uniform scoring of toxicity is of utmost importance when constructing a prospective database. Throughout the manuscript, we promote the use of the CTCAE scoring system as it is widely accepted and applicable and allows for a more detailed scoring of the severity of toxicity compared to the LENT/SOMA evaluation. Aside from the physician scored toxicity, patient reported

outcome (PRO) scoring systems should also be implemented, in the prospective data collection as several studies have demonstrated that there is severe discrepancy between patients and physician reported toxicities and that generally physicians tend to underreport the presence and severity of treatment related toxicities[124,125].

Fourth, it is very important to realize that there is an interplay between different structures when looking at toxicity. For example, while DES and corneal damage are described separately, in reality they are very closely interlinked. This interplay, however, is not taken into account when proposing a single dose constraint for the lacrimal gland. The problem becomes even more complex when looking at a toxicity which is multifactorial in principle such as neurocognition[108,110,126]. While the hippocampus was among the first structures to be related to neurocognitive decline, and is instrumental in learning and memory, it is not the only structure responsible for good cognitive functioning. The prefrontal cortex, the cerebellum and the hypothalamus all play an important role in the higher cognitive function of the brain[106,110,126,127]. To what extent radiation induced damage to these structures impairs their function is far less understood. With increasing practice to spare the hippocampus, the relative importance of these or other structures will become increasingly important.

Therefore, it is important that the summary constraint table in this manuscript is not to be considered as an endpoint. As radiation techniques evolve, treatment changes and survival improves, relevant toxicities will also evolve. While some toxicities were initially of great importance and dose limiting, they can become less frequent and other toxicities gain the upper hand. An example for this is optic neuropathy. While frequently reported in older papers, there have been no relevant papers on this toxicity using conventionally fractionated radiotherapy since the QUANTEC report[5]. This can partly be explained by the combination of clear dose constraints with the ability to effectively reduce the dose to the optic nerve using conformal radiotherapy techniques.

The true value of this manuscript lies in the fact that it provides a consensus on the dose constraints for relevant OARs in the treatment of brain tumours among experts in the field. Of note, it is only a consensus, with all the shortcomings described above. Together with the delineation guidelines by Eekers *et al*.[1], however, it is a starting point for uniform OAR delineation and dose prescription. If we succeed in setting up a standardized follow-up with prospective scoring of toxicity it provides a basic framework within which a large number of patients are treated and followed uniformly and thus can be used to develop and validate multifactorial NTCP models.

Fifth, all constraints in Table 6.1 are reported in EQD2 unless otherwise reported. To facilitate conversion we suggested an α/β ratio based on the best available evidence found, while it should be noted that there is considerable uncertainty regarding these

ratios[19,128]. In principle, the dose constraints are useful for both photon and proton radiotherapy provided that a conversion factor of 1.1 for conventional fractionation is used to account for the difference in RBE[129]. However, at the very distal edge of the Bragg peak, the linear energy transfer is higher, resulting in an increased RBE[130]. This is of concern as the distal edge of the Bragg peak is often very close or even overlapping with the dose-limiting OAR and might result in unexpectedly high toxicity or abnormal imaging changes[131-133]. Therefore, close observation of all these patients remains crucial.

Finally, the set of dose constraints aims to provide assistance to the physician and physicist/dosimetrist in the difficult task of coming up with the optimal plan for each patient, balancing out tumour control and potential toxicity with regard to the age, co-morbidities and life expectancy of the patient. From this review it should be obvious that they are not absolute values and the risks and benefits of each treatment should be thoroughly discussed with the patient.

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Table S6.1 Lacrimal gland.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Lacrimal gland Dose**	Incidence***	α/β ratio
Parsons et al.[9]	Extracranial head and neck tumors including entire orbit	Photon	33	various ≤2Gy OD or BID	ND	Severe DES	<30Gy 30-40 Gy 40-45 Gy >57 Gy	0% 25% 50% 100%	ND
Bhandare et al.[11]	Extracranial head and neck tumors	Photon	78	various ≤2Gy OD or BID	ND	Severe DES: RTOG grade 3 or 4 or CTCAE grade 2 and 3	<35 Gy 35-39,9 Gy 45-49.99 Gy 60-64,99 Gy ≥ 65Gy	0% 6% 50% 90% 100%	ND
Bessel et al.[14]	Lymphoma of the conjuctiva and orbit	Photon	112	2Gy	ND	Late dry eye	<30 Gy 30-39 Gy 40-49 Gy	0% 5% 23%	ND
Letschert et al.[15]	Orbital non hodgkin's lymphoma	Photon	30	2Gy	ND (21-57 Gy)	Severe DES	30 Gy 40 GY	0% 41%	ND
Batth et al.[16]	Tumours of the nasal cavity and paranasal sinuses	Photon	40	median 2 Gy (1.8-2.1 Gy)	Median 60Gy (30.6-70 Gy)	RTOG Grade 2+ late toxicity	(D_{mean}) 1-4.99 Gy 5-14.99 Gy 15-24.99 Gy 25-34.99 Gy ≥35 Gy	0% (0/17) 13% (1/8) 29% (2/7) 60% (3/5) 100% (2/2)	ND

Table S6.2 Cornea

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Cornea Dose**	Incidence***	α/β ratio
Nakissa et al.[13]	Tumours of paranasal sinuses	Photon	30	(1.8-2.5 Gy)	ND (34-86 Gy)	Punctate keratitis Edema Chronic ulceration/ perforation	30-50 Gy 40-50 Gy >60 Gy	ND	ND
Gore et al.[21]	Primary epithelial malignancies of the lacrimal gland, some with corneal shielding	Photon	76	(1.8-2.0 Gy)	ND (50-60 Gy)	Punctate keratitis Chronic defects Corneal perforation	50-60 Gy 50-60 Gy 50-60 Gy	100% 54% 13%	ND

Table S6.3 Retina.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Retina Dose**	Incidence***	α/β ratio
Nakissa et al.[13]	Paranasal sinus cancer	Photon	30	(1.8-2.5 Gy)	ND (34-86 Gy)	Detectable damage Decreased or loss of vision	>45 Gy 65-75 Gy	100% 13%	ND
Parsons et al.[23]	Head and neck tumours	Photon	68 eyes	2 Gy OD 1.2 Gy BID	ND (50-72 Gy)	Vision loss	D_{min} 50% retina <45 Gy D_{min} 50% retina 45-49,99 D_{min} 50% retina 50-54,99 D_{min} 50% retina 55-59.99 D_{min} 50% retina 60-64.99 Gy D_{min} 50% retina ≥65 Gy	0% 56% 33% 75% 88% 100%	ND
Takeda et al.[26]	Advanced nasal and paranasal cancer some received concurrent chemotherapy	Photon	43 eyes	various, ND	ND	Retinopathy	D_{max} eyeball < 50Gy D_{max} eyeball ≥ 50Gy	0% 44%	ND
Evans et al.[31]	Macular degeneration Cochrane database review	ND	1154	ND	ND	Radiation retinopathy	7-24 Gy	0%	ND

Table S6.4 Lens.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Lens Dose**	Incidence***	α/β ratio
Henk et al.[36]	Orbital lymphoma or pseudotumor	Photon	40	(0.2-3 Gy)	ND <5 Gy germinitative zone	Lens opacities	Estimated dose at germinative zone <5Gy ≥ 16,5Gy	0% 100%	ND
Deeg et al.[37]	TBI for Hematological malignancies	Photon	277	ND	ND	Cataracts	No TBI 10 Gy SD TBI 2-2.25Gy MF	17% (16/96) 55% (58/105) 16% (12/76)	ND

Table S6.5 Optic nerve.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Optical nerve Dose**	Incidence***	α/β ratio
Parsons et al.[23]	Head and neck cancer	Photon	131 (215 optic nerves)	<1.9 Gy ≥1,9 Gy ≥1,9 Gy ≥1,9 Gy <1.9 Gy ≥1,9 Gy	ND	Visual acuity < 20/100	D_{max} <65 Gy D_{max}<65 D_{max}65-69.99 Gy D_{max}65-69.99 Gy D_{max}≥70Gy D_{max}≥70 Gy	0% (0/97) 33% (5/15) 8% (2/24) 40% (4/10) 10% (3/31) 22% (2/9)	ND
Jiang et al.[48]	Cancer of the nasal cavity and Paranasal sinus	Photon	219	ND, various	ND	Acuity <20/100	D_{max} <50 Gy 50-60 Gy 61-78 Gy	0% 3% 34%	ND
Goldsmith et al.[49]	Postoperative meningioma	Photon	49	ND	ND	Radiation optic neuropathy	D_{mean} 53,6 Gy (45-59.4 Gy)	2% (1/49)	ND
Martel et al.[50]	Paranasal sinus tumour	Photon	20 40 optic nerves	1.8 Gy	ND (50.4-70 Gy)	All complications No complications	D_{max} 63,1 Gy (47.5-75.5 Gy) D_{max} 56.8 Gy (0-80.5 Gy)	15% (6/40) 85% (34/40)	ND
Flickinger et al.[51]	Craniopharyngioma	Photon	21	median 1.8 Gy (1.6-2.8 Gy)	60Gy (51.3–70 Gy)	Optic neuropathy	FS 1.8 Gy >61,5Gy	10% (2/21)	ND
Hoppe et al.[52]	Unresectable carcinoma of the paranasal sinuses +/- chemotherapy	Photon	39	2 Gy	70 Gy (48-72)	Grade 3 + RTOG scoring	D_{max}>77 Gy	3% (1/39)	ND
Mackley et al.[53]	Pituitary adenoma	Photon	34	ND (1.6-2.1 Gy)	ND (45-49.3 Gy)	Vision loss	ND	3% (1/34)	ND
Bhandare et al.[54]	Head and neck carcinoma +/- chemotherapy	Photon	273	ND various OD and BID	ND	RION	D_{min} 1/3 optic nerve: <50 Gy 50 to 59.99 60 to 69.99 ≥ 70 Gy	 0% (0/73) 10% (4/41) 10% (9/91) 16% (11/68)	ND

Table S6.6 Pituitary gland / hypothalamus.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Pituitary Dose**	Incidence***	α/β ratio
De marzi et al.[66]	Chondroma or chondrosarcoma of the skull base	Proton & Photon	103	ND	ND	No complications	gEUD D_{mean} 50.5 Gy (±19 Gy)	56% (58/103)	ND
						Complications	gEUD D_{mean} 65Gy (± 5Gy)	44% (45/103)	
Agha et al.[76]	primary nonpituitary brain tumor.	Photon	56	ND, various	ND	hypopituitarism (any degree)	BED 71 Gy (59-80)	43% (23/53)	3
						No hypopituitarism	BED 43 Gy (34-58)	57% (30/53)	
Bhandare et al.[79]	Head and Neck carcinoma	Photon	312	ND, various	ND	Clinical hypopituitarism	D_{mean} <39,99 Gy	4% (1/28)	ND
							D_{mean} 40-49.99 Gy	10 % (5/48)	
							D_{mean} 50-59.99 Gy	14 % (10/74)	
							D_{mean} 60-69.99 Gy	17 % (22/126)	
							D_{mean} >70	17 % (6/36)	
Pai et al.[80]	Base of skull tumors	Proton & Photon	107	ND, various	ND	Endocrinopathy	PG: D_{min}< 50 CGE HT: D_{max} < 50 CGE	28%	ND
							PG: D_{min} < 50 CGE HT D_{max} ≥ 50 CGE	50%	
							PG D_{min} ≥ 50 CGE HT D_{max} ≥ 50 CGE	65%	
						Hyperprolactinemia	D_{max}<70 CGE	5 yr 65%	
						Hypythyroidism		5 yr 26%	
						Hypoadrenalism		5 yr 8%	
						Hypogonadism		5 yr 12%	
						Hyperprolactinemia	D_{max} ≥70CGE to PG	5 yr 80%	
						Hypythyroidism		5 yr 32%	
						Hypoadrenalism		5 yr 34%	
						Hypogonadism		5 yr 75%	

Table S6.7 Brain.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Brain Dose**	Incidence***	α/β ratio
Lawrence et al.[7]	Nasopharyngeal cancer, brain metastases and glioma (review)	Photon	11-621 (125 mean)	1.2-4.2 Gy (2.1 Gy mean)	30-79 Gy (D_{mean} 60.5 Gy)	Radionecrosis brain	BED 120 Gy 100-140) BED 150 Gy (140-170)	5% 10%	2.9
Su et al.[87]	nasopharyngeal carcinoma	Photon	870	2.3 Gy	68 Gy	Temporal lobe necrosis at 5 year	D_{max} 64–68 Gy D_{1cc} 52–58 Gy	< 5% < 5%	ND
Zhou et al.[88]	Nasopharyngeal carcinoma	Photon	86	2.2 Gy	66-70.4 Gy D_{mean} 61.7 Gy	Temporal lobe necrosis < 5cc	V_{45Gy} <15.1 cc	PPV 57% NPV 96%	ND
Mc Donald et al.[89]	Chondroma, chondrosarcoma of the skull base adenoid cystic carcinoma or sinonasal malignancies	Proton	66	1.8-2 Gy	62-79.2 Gy	Temporal lobe necrosis in 3 years	V_{60Gy}>5.5 cc V_{70Gy}>1.7 cc	15% 15%	ND
Pehlivan et al.[90]	Chondroma or chondrosarcoma of the skull base	Proton	62	ND (2.2-2.7)	63-74 Gy (D_{mean} 71.7 Gy)	Brain necrosis Non Grade1 Grade 3 Temporal lobe necrosis	 $D_{0.02cc}$ RBE 71 Gy (64-76 Gy) $D_{0.02cc}$ RBE 74 Gy (69-79 Gy) $D_{0.02cc}$ RBE 76 Gy (74-78 Gy) D_{3cc} ≥ RBE 64 Gy D_{2cc} ≥ RBE 68 Gy D_{1cc} ≥ RBE 72 Gy $D_{0.5cc}$≥ RBE 73 Gy	 0% 8% 3% 86% 86% 86% 86%	ND

Table S6.8 Brainstem.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Brainstem Dose**	Incidence***	α/β ratio
Hoppe et al.[52]	Nasal and paranasal cavity	Photon	85	ND	ND	ND	D_{max} <50Gy	0%	ND
Jian et al.[93]	Nasopharynx	Photon	48	ND	ND	ND	D_{max} 60Gy <5cc D_{max} 65Gy<3cc	0%	ND
Uy et al.[94]	Meningeoma	Photon	40	ND	ND	ND	D_{max} 55.6 Gy D_{mean} 30 Gy	3% (1/40)	ND
Schoenfeld et al.[95]	Head and neck cancer	Photon	100	ND	ND		V_{55Gy} <0.1 cc	0%	ND
Zheng et al.[96]	Nasopharynx	Photon	208	ND	D_{max} 54Gy D_{mean} 28,79 Gy	Grade 2	D_{max} <56 Gy	0.5% (1/208)	ND
Weber et al.[97]	Chondroma or chondrosarcoma of the skull base	Proton	222	ND	ND	ND	Surface BS ≤ 63 CGE[#] Center BS ≤ 54 CGE[#]	0%	ND
Nishimura et al.[98]	Olfactory neuroblastoma	Proton	14	ND	ND	ND	Surface BS < 64 CGE Center BS <53 CGE	0%	ND
Noël et al.[99]	Chondroma or chondrosarcoma of the skull base and cervical spine	Photon Proton	100		ND	ND	D_{max} anterior BS ≤ 64 CGE D_{max} mid BS ≤55 CGE	0%	ND
Debus et al.[100,101]	Chondroma or chondrosarcoma of the skull base	Photon Proton	367	ND	D_{max} BS ≥60 CGE	ND	Surface BS ≤ 64 CGE Center BS ≤53 CGE	5% (17/367)	ND

Table S6.9 Hippocampus.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Hippocampus Dose**	Incidence***	α/β ratio
Gondi et al.[108]	Benign or low grade glioma	Photon	18	ND	ND	(WMS-WL) delayed recall test	$D_{40\%}$ of bilateral HC >7.3Gy	OR 19.3 (p = 0.04)	2
Seibert et al.[109]	Glioma/meningioma	Photon	52	ND	ND	Volume change of HC at 1 year	D_{mean} >40 Gy D_{mean} <10 Gy	6% 1%	2

Table S6.10 Skin.

Reference	Population	RT	Number patients	Fraction size (range)*	Total dose (range)	Toxicity	Skin Dose**	Incidence***	α/β ratio
Lawenda et al.[114]	Primary central nervous system tumors	photons	26	ND	ND	Grade 3 or 4 alopecia >12 months	25 Gy	<20%	2

Chapter 7

Evidence on the efficacy of primary radiosurgery or stereotactic radiotherapy for resistant non-neoplastic focal epilepsy in adults: a systematic review

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Seizure 2018;55:83-92

Abstract

Purpose

Although the majority of adult epilepsy patients respond well to the current antiepileptic drug treatment, 20-40% of them are drug-resistant. In these patients, resective epilepsy surgery is a curative treatment option, for which, however, only a limited number of patients is eligible. The purpose is to summarize the outcome of radiotherapy for drug-resistant non-neoplastic focal epilepsy and to elucidate its efficacy for seizure outcome and long-term toxicity in adults.

Method

A systematic literature search was performed in Pubmed, Ovid Medline, Cochrane library, Embase and Web of Science. The methodological quality was evaluated using an adapted QUADAS checklist.

Results

Sixteen out of 170 initially identified studies were included in this systematic literature study (n=170 patients). Twelve of the 16 studies described a positive effect of radiotherapy on seizure frequency reduction, with 98 of the patients (on average 58%, range 25%-95%) reporting no or rare seizures (defined as radiotherapy-adapted Engel class [RAEC] I and II. In total, 20% (34 patients) of the patients needed subsequent surgery due to radionecrosis, cysts formation, edema, and intracranial hypertension or remaining seizures. A dose-effect model was fitted to the available response data in an attempt to derive a relationship between prescribed dose and RAEC frequency.

Conclusions

Radiotherapy is a possible non-invasive treatment option for patients with drug-resistant focal non-neoplastic epilepsy. This systematic review showed that there is only level 4 evidence of primary radiotherapy reducing seizure frequency in adult patients. Prospective randomized trials are needed to determine its exact value compared to other treatment approaches.

Introduction

Epilepsy is one of the most common severe neurological disorders. The World Health Organization has estimated that more than 50 million patients suffer from epilepsy worldwide[1-3].

According to the International League Against Epilepsy several types of epilepsy exist[4,5]. In this review we focus on non-neoplastic focal epileptic lesions (NNFE), associated with focal seizures, which have a localized, well-circumscribed network of discharges[6].

Non-neoplastic lesions, that have been described by the European Epilepsy Brain Bank consortium as the pathological substrate of focal seizures include, in descending order of frequency, hippocampal sclerosis (36.4%), long-term epilepsy-associated tumors (23.6%), malformations of cortical development (19.8%), vascular malformations (6.1%) and glial scars (4.8%) as well as no lesion (7.7%)[7]. The most frequent non-neoplastic lesions of drug-resistant focal epilepsies, constituting about 80% of all resective epilepsy surgery cases, are hippocampal sclerosis and malformations of cortical development besides long-term epilepsy-associated tumors[7]. In the group of low-grade epilepsy associated tumors, some of these tumors can, although very rare, dedifferentiate into high-grade neoplastic subforms[8-10]. This is one reason why we focus on hippocampal sclerosis and malformations of cortical development in this review. A second reason is that almost all well-documented clinical series of focal epilepsy and radiosurgery include patients with tumors. Since the beginning of the 21st century, studies are emerging describing non-space-occupying lesions, mainly hippocampal sclerosis, with long-term follow-up[11-15]. Only very recently, studies on the radiosurgical treatment of periventricular heterotopias and focal cortical dysplasias have been published, although with a short follow-up period of the treated patients[16,17].

The type and origin of epilepsy determines the prognosis and the efficacy of the treatment. Currently, the two most frequently used therapeutic options include antiepileptic drug (AED) therapy and resective epilepsy surgery. Still resective epilepsy surgery is underused globally and patients tend to be referred with a long delay[18,19]. Noteworthy, postoperative seizure free outcome varies between 60-90% depending, among others, on the pathological substrate[20].

The third, less frequently used therapeutic option is radiation therapy (RT). This non-invasive approach may be superior to surgery when the epileptogenic region is located near the eloquent cortex or deeply sited brain areas. In theory, RT may achieve a better neurotransmitter equilibrium than resective epilepsy surgery, and thus result in better neuropsychological outcome despite the late response effects[20,21]. Stereotactic RT (SRT) is a high-precision three-dimensional external beam radiation therapy technique directing beams to a well-defined target, relying on detailed imaging and precise

treatment set-up to deliver the radiation dose while sparing the surrounding normal tissue. By using multiple fractions (so-called fractionated) SRT, the dose is delivered in multiple sessions over a longer period of time, instead of a single-session large dose, also referred to as stereotactic radiosurgery (SRS). Fractionated SRT has been proven to be superior to SRS when considering tolerance dose of normal brain tissue and cranial nerves and thus higher (radio-)biologically equivalent doses can safely be delivered using the former[22].

Since long-term side effects of RT may comprise the induction of secondary tumors and growth delay in children, we focused on adult patients in this review. So far, several publications have underlined the potential value of RT in patients with drug-resistant epilepsy[18-20,23]. To date, however, no systematic review has been published on the efficacy of RT in adults patients with drug-resistant FNNE, excluding bias effects of previous resection. Therefore, this systematic review summarizes the available evidence for efficacy (no or rare seizures in Engel class I&II patients[24]) and treatment-related side effects in patients with focal drug-resistant epilepsy undergoing RT.

Materials and methods

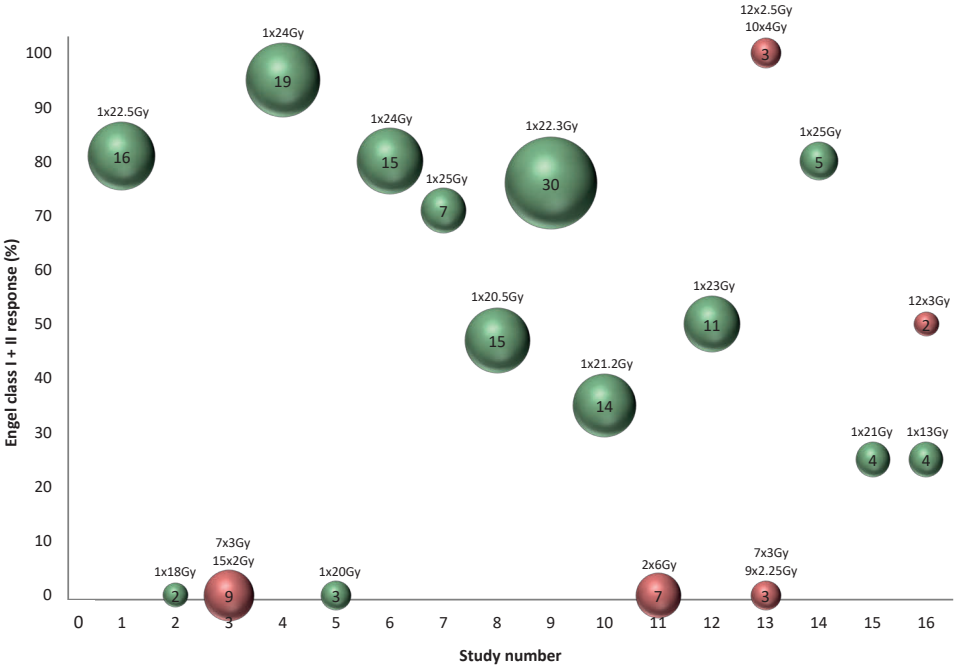
Research protocol

To develop the research protocol and identify the scope of the review, we followed a structured approach to identify the patient population, interventions, comparators, outcomes, and study design (PICOS criteria). [25] As ILAE-terminology on epilepsy recently changed (Fisher 2017), search terms for epilepsy were “focal” and ”localization related”. The research question was defined as: what is the level of evidence on the efficacy of primary RT for drug-resistant FNNE in adults? For this, therapeutic benefit was defined as seizure frequency reduction using the modestly adapted Engel classification. We adapted only the Engel class III, which was defined as an improvement of epilepsy frequency with more than 75% (Figure 7.1). Therapy-induced complications were defined as late radiation damage. The research protocol contained a comprehensive search strategy and screening criteria for abstracts, titles and full text articles.

Eligibility criteria, search strategy and study selection

A comprehensive search was performed to identify the current papers in PubMed (National Center for Biotechnology Information, NCBI), Ovid Medline, Cochrane library, Embase and Web of Science. PubMed was used as the primary data source; Ovid

Medline, Cochrane library, Embase and Web of Science were used to extract additionally available articles (Supplementary Table S7.1 and S7.2). These search strategies were frequently performed with the last search in May, 2017. To finalize the systematic literature search all included articles' reference lists were crossed-checked (citation tracking) on potential relevant studies that met the inclusion criteria.



RAEC	Definition [20]	Corresponding ILAE classification [5]
Class I	Seizure free	1
Class II	Rarely seizures	2
Class III	Improved more than 75%	3 & 4
Class IV	No significant improvement	5 & 6

Figure 7.1 Percentage patients with Engel class I+II. Top: The percentage of patients with Radiotherapy adapted Engel classification (RAEC) I+II for the 16 studies. On the horizontal axis, the study numbers is given (corresponding to Table 7.1), while on the vertical axis the percentage of patients is plotted. The numbers given in, and the size of the respective bubble indicate the number of patients included in each study. The green colour indicates a single fraction, while red highlights multiple fractions. The prescribed dose (number of fractions times the mean fraction dose) is given above each bubble. Bottom: The Radiotherapy adapted Engel classification (RTAEC) used to define response to radiation treatment translated to International League Against Epilepsy (ILAE) classification.

After literature collection, completed abstracts and titles were first assessed on identical records and duplicate findings were removed from the search. In addition,

identical patient cohorts were only entered once, comprising the study with most information on patient characteristics, seizure outcome and the longest follow-up period. Abstracts and full text articles were assessed using inclusion criteria and exclusion criteria (Supplementary Table S7.3). Two investigators (EP and DE) established the research protocol and independently performed the literature searches. A third independent reviewer (ET) was consulted if no agreement was reached amongst the two investigators.

Data collection

Data collection was performed with the use of a well-defined questionnaire in Microsoft Excel (Supplementary Table S7.4). Unfortunately, we were unable to perform a meta-analysis for controls since studies were not designed with control groups.

Data quality assessment and risk of bias within studies

To assess the methodological quality of the included studies the QUADAS-2 checklist was intended to be used.[24] However, most domains (patient selection, index test, reference standard and flow and timing) of the QUADAS checklist were not applicable to our research.[24] Mainly the index test, which in our study would have been a control group, was not described in the studies included in this review. Therefore, it was decided to use a modified version of the QUADAS checklist to assess the risk of bias and applicability to the research question of all included articles. In this way the individual quality of each included study was evaluated (Supplementary Table S7.5). For all studies information on in- and exclusion criteria, loss to follow-up, follow-up time, definition of outcome measure and exposure to radiotherapy was scored.

Dose-response model

Dose response was tested with Kendall's tau correlation[17]. The biological effective dose (BED) is commonly used for isoeffective dose calculations when comparing differing fractionation schedules, i.e. fraction dose and number of fractions. After converting the physical dose to BED using an α/β of 10 Gy (BED_{10}), a logistic probability density function (logit model) was fitted by the least-square method:

$$P(D) = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$$

where D = BED_{10}, D_{50} is the BED_{10} at 50% response, and γ_{50} is the normalized slope at D_{50}. The 95% confidence intervals (95% CI) were determined by bootstrapping.

Results

Data extraction and bias assessment

Study selection

The study selection process complying with the PRISMA statement[25] is illustrated in Figure 7.2. Sixteen out of 170 initially identified studies were included in this systematic literature study (n=170 patients).

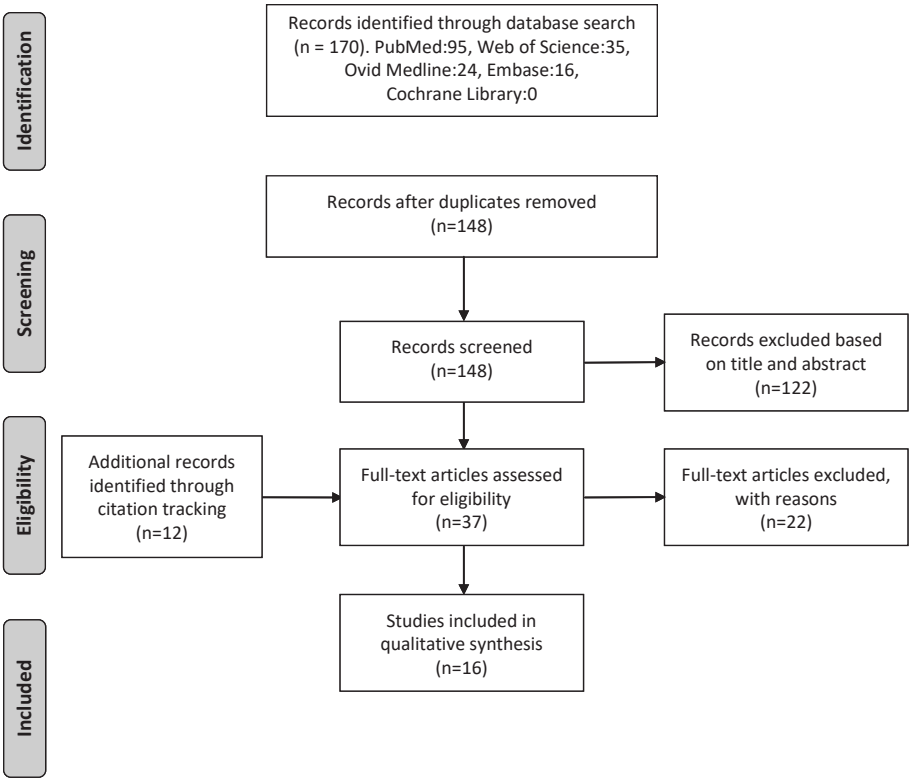


Figure 7.2 PRISMA flow diagram[11].

Risk of bias within studies

A summary of the parameters that we used to identify the risk of bias is found in Supplementary Table S7.4. Nine out of 16 studies explicitly described inclusion criteria that were carefully selected and enabled comparisons between study populations.

However, exclusion criteria were not well defined in most publications and by comparing the seizure frequency before and after therapy, the patient was used as his/her own control. None of the studies used control groups. Therefore, selection bias could not be identified. In addition, information on the cohorts from which the study populations were drawn was not given, which hampered comparisons. A final risk of bias was the fact that the definitions of the post-treatment seizure outcome measures were not in accordance with the Engel classification in seven of the included studies, but sufficient information was provided to enable the transformation to the radiotherapy-adapted Engel class (RAEC). RAEC I was defined as seizure free, II as rarely seizures, III as an improvement of more than 75% and class IV as no significant improvement (see Figure 7.1).

Patient selection in individual studies

The most important information from each included study is presented as a framework for conclusions. In the study by Régis *et al*.[11], patient number 11 and 18 were identical to the patients in the study by Rheims *et al*.[26]. For reason of longer follow-up, these patients were analyzed in the latter study only. In addition, two patients discussed in the study by Usami *et al*.[27] were identical to patients in the article of Kawai *et al*.[28]. Since more details about the patient characteristics were available in the article of Kawai *et al*.[28] these two patients were analyzed there. In the studies by Kawamura *et al*.[29], Usami *et al*.[27], Barbaro *et al*.[12], Regis *et al*.[11], Srikijvilaikul *et al*.[30], and Rheims *et al*.[26] some patients underwent surgery or died before the end of the follow-up time. Since only Srikijavilaikul *et al*.[30] documented in detail which specific patients underwent surgery or died, these patients could not be excluded from the systematic review in the other studies. Therefore, the effect of RT on the outcome of seizures could not be undoubtedly shown in these three included studies, posing a possible bias in treatment outcome.

Data analysis

Study characteristics

Table 7.1 shows the RT parameters of the included studies. Detailed information on the study characteristics is shown in Table 7.2. Long-term toxicity is summarized in Table 7.3. Noteworthy, the number of patients questioned regarding their subjective radiation-induced side effects is unknown for they were objectively visualized by magnetic resonance imaging.

Table 7.1 Outcome Engel classification of included studies and radiotherapy parameters.

Study number	Study authors year	Type of epilepsy	Outcome Engel class	Outcome other than Engel	Mean dose (range)	Dose prescription (isodose)	Treatment Technique	Volume treated (cm3)	Surgical intervention
1	Regis et al, 2000	MTLE	I 81%, III 13%, IV 6%		1 x 22.5 Gy (20-25)	50%	GK	6.8 (6.5-7.0)	no
2	Kawai et al, 2001	MTLE, HSC	IV 100%	No significant improvement (2)	1 x 18 Gy	50%	GK	7.5 (6.2-8.7)	yes
3	Grabenbauer et al, 2002	TLE	III 9%, IV 91%	Reduction after RT: 9% (1), 10% (1), 17% (1), 24% (1), 27% (1), 29% (1), 34% (1), 37% (1), 52% (1), 54% (1), 70% (1), 77% (1)	7 x 3 = 21 Gy 15 x 2 = 30 Gy	90-95%	LINAC	8.2 (5.1-16.0)	yes
4	Regis et al, 2004	MTLE	I 67%, II 28%, III 5%		1 x 24 Gy (23-25)	50%	GK	7,3	no
5	Srikijvilaikul et al, 2004	MTLE	IV 100%		1 x 20 Gy	50%	GK	7.3 (6.1-8.7)	no
6	Bartolomei et al, 2008	MTLE	I 60%, II 20%, III 13%, IV 7%		1 x 24 Gy (23-25)	50%	GK	5.5-9.0	no
7	Hoggard et al, 2008	MTS	I 50%, II 12.5%, III 37.5%		1 x 25 Gy	50%	GK	6,2	yes
8	Rheims et al, 2008	TLE	I 7%, II 40%, III 13%, IV 40%	ILAE I (1), II(6), IV(2) V6()	1 x 18, 20 or 24 Gy	50%	GK	6,9	yes
9	Barbaro et al, 2009	MTLE	High dose: I 76%, II 5%, III 3%, IV 16%. Low dose: I 59%, II 5%, III 18%, IV 18		1 x 22.3 (20-24)	50%	GK	6.5 (5.5-7.5)	yes
10	Vojtech et al, 2009	MTLE	I 7%, II 28%, III 36%, IV 29%		1 x 21.2 Gy (18-25)	50%	GK	6.8 (5.2-8.9)	yes
11	Liang et al, 2010	TLE	III 57%, IV 43%	50% reduction (2), 30% reduction (1), no reduction (2), aggravation (2)	2 x 6 = 12 Gy	85%	LINAC	MTL: 1.1 (1.0-1.2,) LTL: 3.2 (2.8-3.5)	no

Table 7.1 (continued)

Study number	Study authors year	Type of epilepsy	Outcome Engel class	Outcome other than Engel	Mean dose (range)	Dose prescription (isodose)	Treatment Technique	Volume treated (cm3)	Surgical intervention
12	Kawamura et al, 2012	MTLE	I 50%, III 25%, IV 25%		1 x 23 Gy (20-25)	50%	GK	10.6 (4.8-17.1)	yes
13	Rauch et al, 2012	TLE (5), ETLE (1)	I 33%, II 17%, IV 50%	Reduction after RT: 24% (1), 38% (1), 60% (1), 86% (1), 100% (2)	7 x 4 = 21Gy 12 x 2.5 = 30Gy	95%	LINAC	47 (10-69)	no
14	Usami et al, 2012	MTLE	I 40%, II 40%, 20% loss to FU	40% seizure free, 40% significantly decreased	1 x 25 Gy	50%	GK	9.9 (7.8-12.3)	yes
15	Chen et al, 2014	TLE (2) PLE (1), FLE (1)	I 25%, IV 75%		1 x 21 Gy (20-24)	50%	GK	7.3 (6.5-7.5)	yes
16	Boström et al, 2016	FCD	I 33%, III 17%, IV 50%	ILAE I (2), IV(1), VI (3)	1 x 13Gy or 1 x 15Gy 12 x 3 Gy or	100%	LINAC	SRS: 1.74 (0.7-4.3) FSRT: 3.84 (3.4-4.3)	no

ND = not defined, MTLE = mesial temporal lobe epilepsy, TLE = temporal lobe epilepsy, PLE = parietal lobe epilepsy, FLE = frontal lobe epilepsy, ETLE = extra temporal lobe epilepsy, MTS = mesial temporal sclerosis, HSC = hippocampal sclerosis, FCD = focal cortical dysplasia, GK = gamma knife, LINAC = linear accelerator. SRS = stereotactic radiotherapy, FSRS = fractionated stereotactic radiotherapy, surgical intervention yes, an intervention after radiation therapy was indicated, no: no surgical intervention after radiation therapy.

Table 7.2 Study and patient characteristics of included studies.

Study authors year	Design	Mean age in years	No of patients	Timeframe			
Regis et al, 2000	PS	ND (ND)	16	ND	AC, head and ant half of hipp body, ant part PG	24 (6-72) m	ND
Kawai et al, 2001	PS	26.5 (31-22)	2	ND	AM, hipp head and body, most of PG and EC	ND (16-30) m	MRI, SPECT, interictal FDG-PET,NE
Grabenbauer et al, 2002	PS	37.5 (17-61)	9	ND	Identical to the theoretical extent of surgical resection in TLE	18 (18) m	NE, sphenoidal electrodes, MRI, MEG, SPECT, PET
Regis et al, 2004	PS	33.6 (20-46)	19	1996-2000	Ant PR, EA, RS, head and ant part hipp, AAC	24 (ND) m	Foramen ovale electrodes, MRI, NE en QoL
Srikijvilaikul et al, 2004	RS	40.4 (19-57)	3	1999-2001	Ant hipp, AM, PG	20 (18-22) m	MRI, MRS, PET intracarotid sodium amytal test
Bartolomei et al, 2008	PS	35.8 (22-46)	15	1995-1998	Ant part PR, EA, RS, head and ant part hipp, AAC	96 (72-120) m	NE, MRI, foramen ovale recording
Hoggard et al, 2008	RS	38 (ND)	8	1998-2000	AM, head and anterior half hipp, anterior half PG	42 (24-53) m	MRI
Rheims et al, 2008	RS	38.5 (16-66)	15	1994-2004	Ant part PR, EA, RS, head hipp, ant part hipp body, AAC	60 (31-112) m	Physical examination, MRI, FDG-PET
Barbaro et al, 2009	PS	34.1 (ND)	30	ND	AM, ant hipp, PG	36 (ND) m	MRI, EEG, video EEG, NE, Wada tests
Vojtech et al, 2009	RS	33.4 (ND)	14	1995-1999	MTL, AM, hipp, PG	64 (ND) m	MRI, intracarotid amytal test
Liang et al, 2010	RS	21 (14-38)	7	2003-2005	AC, hipp, ant part PG	50 (40-63) m	FDG-PET, MRI, FLAIR, NE
Kawamura et al, 2012	PS	51.5 (41-65)	11	1997-2000	Ant hipp, AM, PG	> 108 (ND) m	MRI, SPECT, PET, NE
Rauch et al, 2012	RS	52 (27-74)	6	1996-2009	RTL, LTL, central	125 (24-168) m	MRI, MEG, NE
Usami K et al, 2012	PS	38.8 (22-66)	5	1996-1999	AM, hipp head and body, most of PG and EC	ND (12-120) m	CT, MRI, SPECT, FDG-PET
Chen et al, 2014	RS	31.6 (19-39)	4	1998-2000	Temporal, parietal, frontal lobe	150 (144-168) m	MRI
Boström et al, 2016	PS	28,3 (20-42)	6	2013-2014	precentral gyrus, insular cortex, primary visual cortex, right fornix	16 (6-27) m	MRI, NE, SPECT, PET, MAP

PS = prospective, RS = retrospective, ND = not defined, ant = anterior, hipp = hippocampus, PG = parahippocampal gyrus, EC = entorhinal cortex, AM = amyg- dala, AC = amygdaloid complex, EA = entorhinal area, PR = parahippocampal region, RS = rhinal sulcus, AAC = amygdalofugal part of the amygdaloid complex, RTL = right temporal lobe, LTL = left temporal lobe, MTL = medial temporal lobe, TLE = temporal lobe epilepsy, NE = neuropsychological evaluation, QoL = assessment of quality of life, HVL = Hopkins verbal learning test, MRI = magnetic resonance imaging, EEG = electroencephalography, SPECT = single photon emission computed tomography, PET = positron emission tomography, CT = computed tomography, FDG PET = fludeoxyglucose positron emission tomography, MEG = magneto encephalography, MRS = magnetic resonance spectroscopy, FLAIR = fluid attenuation inversion recovery, MAP = Morphometric Analysis Program.

Table 7.3 Reported toxicity of included studies.

Study authors year	Trancient side effects	Permanent toxicity	Post RT resection	MRI
Regis et al, 2000	19% headache, nausea and/or vomitting (DM)§	19% visual field deficit (asymptomatic)	0%	ND
Kawai et al, 2001	ND	ND	100% ©	No changes on MRI
Grabenbauer et al, 2002	25% local alopecia, 25% headache + nausea (DM)§	22% memory deficit, 33% verbal deficit	100% ©	ND
Regis et al, 2004	62% headache, nausea and/or vomitting (DM) §	50% visual field deficits (asymptomatic)	0%	MRI changes after 1 year on T2, disappeared after 2 years
Srikijvilaikul et al, 2004	None	ND (100% died as result of seizure)	0%	MRI changes hyper intense on T2
Bartolomei et al, 2008	60% headache (DM) §	59% visual field deficit (asymptomatic)	0%	Asymptomatic cyst in RTL
Hoggard et al, 2008	25% headache, nausea, vomitting and/or dysphasia (DM) §	ND	12.5% ©	100% Edema after 6-12 months
Rheims et al, 2008	53% headache (DM) §	13% visual field deficit (asymptomatic)	20% ©	Peak in MRI signal changes after 9-24 months
Barbaro et al, 2009	70% headache §	50% visual deficits (asymptomatic accept for *), 25% verbal learning impairment	7%	T2 en T1 constrast enhancement related to new headache
Vojtech et al, 2009	60% headache, nausea and/or vomitting (DM) §	14% visual field deficit (asymptomatic)	50% ©	64% Edema
Liang et al, 2010	29% headache, nausea	14% incomplete aphasia, 14% dystaxia, 29% visual field deficit (asymptomatic)	0%	ND
Kawamura et al, 2012	9% headache, nausea and/or vomitting (DM) §	9% RN recover after necrotomy, 9% cognitive impairment with hemiparesis recover after resection cyst, (9% died as result of seizure)	36% (18% ©)	RN, hematomas in LTL, cyst RTL and LTL
Rauch et al, 2012	headache and/or nausea, malaise, alopecia	45% neurocognitive verbal decline	0%	ND
Usami et al, 2012	20% headache (DM) §	40% RN recover after necrotomy (14% died as resuly of seizure)	40%	Edema, hydrocephalus, RN, cyst formation after 10 years
Chen et al, 2014	ND	100% RN recover after necrotomy	100%	Cystic lesion in the LPL, cystic lesion in RTL after 12 years, 100% RN
Boström et al, 2016	none	none	none	No changes on MRI

ND = not defined, RN = radio necrosis, LPL = left parietal lobe, RTL = right temporal lobe, LTL = left temporal lobe, MRI = magnetic resonance imaging, DM = treated with dexamethasone, x = increased intracranial pressure/intracranial hypertension caused by edema, © = resection because of epileptic activity, * = one patient with papilledema and enlarging blind spots, despite DM the patient received a temporal lobectomy.

Radiation therapy dose schedules and prescription

The included studies used a wide range of dose schedules, from single fractions prescribing 13-25 Gy as marginal dose to 2, 7, 12 and 15 fractions of 6, 3, 4, 2.5, 3 and 2 Gy, respectively, prescribed to the 95% isodose (Table 7.1). The maximum dose in the target volume was only reported in the study of Rauch *et al*.[31]

Treatment effect on seizure outcome

As measure of efficacy of RT, the RAEC system was used in this systematic review. Most studies (n=9) used the Engel classification system, five studies did not use any of the classification systems but provided sufficient information on seizure outcome, and two studies indicated the seizure outcome with ILAE classification. To be able to compare study outcome, the investigators independently assessed these seven studies and transformed the seizure outcome to RAEC (Figure 7.1).[16,26-28,30-33] RAEC I and II were subsequently combined since these classes are both assumed to give a beneficial effect after treatment (class I no seizures; class II rare seizures; Figure 7.1)[24]. Twelve of the 16 studies reported a positive effect of RT on the seizure outcome defined by the total percentage of RAEC I and II patients, ranging from 25%-95% per study, with an overall average of 57% (98 patients). In the two smallest studies (two and three patients, respectively), RT had no favorable effect on the seizure outcome (class IV), although treatment was delivered with similar techniques, dose per fraction and target volumes compared to the other studies.[28,30,31]

Dose-response relationship in FNNE

RT was found to exhibit a dose effect in the RAEC I+II cohorts (r=0.69, $p \leq 0.001$). The model parameter values obtained were: D_{50} = 69.03 [95% CI: 64.4−74.1] Gy and γ_{50} = 2.16 [95% CI: 1.21−6.6]. The fitted dose-response graph is illustrated in Figure 7.3. As can be gathered from the graph, a BED_{10} of 69−80 Gy is required for an RAEC I+II response in 50−75% of the patients. Furthermore, this figure suggests that higher response rates can be obtained at a lower BED_{10} for multi-fraction schemes than for single-fraction schemes.

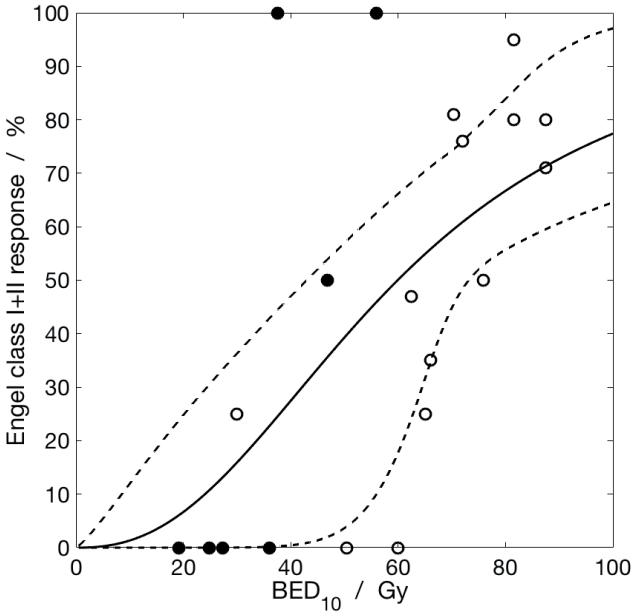


Figure 7.3 Dose response analyses. Engel class I + II rate as function of the biological effective dose using an α/β of 10 Gy (BED_{10}), with fitted logistic probability density function (solid lines) superimposed over data points from single-fraction (open circles) and multi-fraction (closed circles) treatment schemes depicted in Figure 1. The 95% confidence intervals (dashed line) were determined by bootstrapping.

Long-term toxicity

MRI changes

All studies reported on long-term toxicity after treatment with RT, of which 10 studies included imaging information on structural/anatomical MRI (Table 7.3). The first changes on MRI scans were observed after 6 months whereas they also occurred 10 years following RT.[28] Hyperintense regions on the T2-weighted MRI scans were first detected after 6 months (peak 9-24 months) and tended to disappear after a few years, whereas four studies described cystic lesions several years after treatment which needed resection.[11-14,27,29,30,32,34,35]

Surgical intervention

Overall, 20% (34 patients; range 7-100%) of the patients in nine of the 16 studies underwent subsequent surgery.[12-14,26-29,32,34,35] In six of these studies resection was performed because of persisting seizures, mostly within a 2 years follow up period, in

those patients in whom AEDs could not control the epilepsy.[26,28,29,32,34,36] In all studies, in which MRI was performed, the symptoms that were described by the patient were corresponding to an alteration visible on MRI scans. In three studies treating with SRS (21, 23 and 25 Gy), radionecrosis was reported to have occurred requiring subsequent surgery 7-12 years following treatment.[13,27,29] In one study, one patient underwent surgery without any abnormalities seen on MRI.[12] Noteworthy, following fractionated treatment schedules, no patient required surgical resection or developed radionecrosis.

Neurocognitive functioning

Some of the studies reported on cognitive functions. Grabenbauer *et al*.[32] treated nine patients with temporal lobe epilepsy and found post-treatment memory deficit in 2/9 (22%) and verbal deficit in 3/9 (33%) patients. In the second study from Rauch *et al*.[31], verbal decline was found in 45% of the treated patients for temporal lobe epilepsy and extratemporal lobe epilepsy. Quigg *et al*.[37] published the neuropsychological outcome of the article by Barbaro *et al*.[12], in which they concluded that there was no difference from baseline regarding language, verbal memory, cognitive efficiency and mental flexibility, nor mood. Conversely, QOL scores improved at 24 and 36 months, with those patients attaining seizure remission by month 24 accounting for the majority of the improvement. Regis *et al*.[11] observed no neuropsychological deterioration 2 years after treatment, reporting the quality of life being significantly better than that before surgery. Vojtěch *et al*.[36] published their neuropsychological results in a separate article in 2015, in which they reported no significant changes in memory or intelligence at two years after radiosurgery[38]. The effect on daily functioning has not been stated. As Taphoorn *et al*.[39] described, AED itself are more strongly associated with cognitive deficits than RT.

Miscellaneous side-effects

Headache, nausea and/or vomiting related to increased intracranial pressure and edema on MRI, were reported in 12/16 studies and easily treated with corticosteroids. The moment of onset and duration of these complaints was not described in detail.[11-13,26,27,29,31,32-36] Visual field deficits, *i.e.,* quadrantanopia and hemianopia, were reported in 6/16 studies with an incidence of 14-59%.[11-14,33,36] Strikingly, quadrantanopia was also found in the study of Liang *et al.*[33] after administration of 2 fractions of 6 Gy, a total dose not generally considered to cause visual deficits.

Discussion

The optimum treatment for mesial temporal lobe epilepsy would be eliminating seizures with low risk, yet sparing the hippocampal function and surrounding brain. When *no neoplastic lesion* is present it was hypothesized by Régis *et al*.[23] that single fraction stereotactic radiation therapy is inducing changes in the functioning of the neural tissue, by inducing remodeling of the glial environment, and is leading to the modulation of function while preserving basic processing. Chang *et al.*[15] proposed progression of vascular injury and tissue necrosis following radiotherapy to be associated with a remission of seizures. Barbaro *et al*.[12] randomized patients by dose; they demonstrated that the higher dose arm had better outcomes (within statistical power limits). This same effect was found in other small series underlining the tendency of higher doses to have a better antiepileptic effect than lower doses[40-43]. Maesawa *et al*.[44] showed in a rat model, that SRS controlled epilepsy accompanied by stabilization of memory compared with untreated epileptic rats without causing subsequent behavioral impairment, for high (60 Gy) as well as low dose (30 Gy), supporting the hypothesis that even this relatively lower dose RT could be effective. The lowest listed radiosurgical single dose is 13 Gy as a marginal dose (see Figure 7.1).

Also outside of the mesial temporal structures, crucial for a successful seizure outcome after resective epilepsy surgery or SRS is to define and precisely delineate the seizure onset zone (SOZ) or the so-called focal epileptic generator. There is a worldwide growing tendency to consider the potential epileptogenic network as important as the focal lesion on MRI. As clearly illustrated by Ladino et al.[45] and Stefan et al.[46], heterotopia associated seizures can arise from the heterotopia alone (= focus) but can also be generated from overlying and surrounding cortex, another distant heterotopic nodule or even a dual pathology lesion, like hippocampal sclerosis (= network theory). Before definitive treatment, open resection or SRS, is advised to the patient strong evidence must be collected whether the MRI focus or the network generates the seizures in this particular patient, e.g. by invasive electrode implantation.

Summary of evidence

This systematic review gives an overview of the available literature on the efficacy of primary RT for FNNE in adults. Due to the lack of case-control studies, the results of this study only provide level 4 evidence indicating that RT may be a therapeutic option to reduce the seizure frequency for NNFE in adults.[47] When considering the low level of evidence there is an inevitable ceiling effect because the absence of “control” groups is nearly inherent in surgical studies since the demands of equipoise would not allow

design of studies with a non-treatment arm in most US and European studies. For example the study of Wiebe *et al*.[48] randomizing open surgery to a wait-list, could not be performed in the US, and concerns over sudden unexpected death in epilepsy (SUDEP) in control arms prevents any non-treatment/wait-list designs.

In most of the studies it was not described whether AED treatment was reduced or discontinued and in those reporting on it, AED intake remained identical as prior to RT. Only two studies showed no improvement of seizure control after RT.[28,30] A reason for this may be that RT is able to reduce the seizure frequency, but a vast number of the reported patients were not completely seizure free after RT thus requesting surgery. Furthermore, the long-term toxicity (*e.g.*, cystic lesions) of RT may be another reason for the high rate of surgical interventions after primary RT. Interestingly, two studies investigated the cost effectiveness and found that surgery and Gamma Knife for hippocampal sclerosis were both safe and effective, but the surgical resection led to better results in freedom of epilepsy, (93% *versus* 54%) and a reduction of cost.[49,50]

Limitations of the study

Our study has some limitations. First of all, the only randomized study was retrievable in abstract-form only and attempts receiving a manuscript in preparation from the authors failed. Consequently, the work has not been peer-reviewed and thereupon modified yet, which hampers the resulting strength of our work. Although we checked in detail with available data, there is always the potential of patient overlap to occur between multicenter studies. In addition, control groups were not reported in the majority of studies, thereby limiting the strength of the study's design. Furthermore, studies described the primary outcome parameter differently using ILAE and pure description *versus* the Engel classification. Therefore the two reviewers (EP and DE) translated the seizure outcome of the corresponding studies to the RAEC to be able to compare the different studies on outcome. In the published studies the former ILAE classification on seizures and on epilepsies was used. Recently Fisher[5] published the new ILAE classification renaming and specifying types of focal seizures and a few new generalized seizures, based on earlier clarification of terms used to name seizures.[6] For this review, we assumed that the new term "focal epilepsy" is equivalent to the former term "localization related epilepsy".

Moreover, only 1 out of 16 studies reported information on the patient's quality of life. It is important that future research will include quality of life questionnaires in the design. Seizure outcome and long-term toxicity should be weighed against quality of life. In addition, two studies did not define their follow-up time. Nevertheless, we have

decided to include these studies since important information about the efficacy of RT in epileptic patients was described[27,28].

No conclusions can be drawn on the effect of fractionation compared to single-fraction on treatment outcome and toxicity due to limited amount of available fractionated studies.

In our dose response analyses we assumed the Linear-Quadratic (LQ) model to be correct in determining the 2Gy-per-fraction equivalent dose (BED_{10}) for fraction doses up to 24 Gy. Brown *et al*.[51] concludes that the LQ model is reasonably predictive of *in vitro* and *in vivo* normal tissue dose response relations in the dose per fraction range of 1.8 to 20 Gy and that it is currently not possible to identify an alternative high-dose model that performs better than the LQ for predicting cell killing. Even the lowest dose schedule showed a moderate result defined as Engel class I-III of 57%.[33] Side-effects were similar in this study except for cyst formation, which was not seen. In order to derive a possible future fractionation schedule, we derived a dose-effect relationship, however, the definition of the (correct) target volume based on reported outcome (epilepsy frequency) is mandatory though still lacking. We agree with Régis *et al*.[52] suggesting that further basic research is needed for better understanding the influence of dose, volume, target topography and dose distribution homogeneity on the molecular effect in treating epilepsy. In addition, some recent studies hypothesize that the effect of RT should not be qualified as a destruction of the glial environment but as a modulation of the neural tissue. In particular in FNNE, this would be of interest[12,20,23].

Radiobiology

The majority of treatments for epilepsy have been with SRS due to technical factors, mainly related to the requirements for immobilization of the patient's head and the availability of targeting systems. Although SRS has been shown to reduce seizure frequency in various forms of epilepsies, its mechanism of action remains unclear. Different mechanisms have been postulated as the basis of an anti-epileptic effect of SRS, such as the destruction of the epileptic focus and its pathways of spread by necrotizing SRS doses, or suppression of the epileptic activity as a neuromodulation effect at non-necrotizing doses[53,54]. There is no knowledge about fractionation effects for control of non-lesional epilepsy. From a radiobiological point of view, it is not clear whether SRS can better achieve the therapeutic goal than fractionated SRT with lower doses per fraction. Traditionally, the therapeutic effect of SRS is to destroy a small volume of brain tissue by radionecrosis, which results from vascular endothelial cell damage causing occlusion of small arterial vessels. There is growing interest that the same therapeutic effect may also be achieved by lower, fractionated doses of radiation,

not inducing necrosis but having a neuromodulatory effect with possibly the same therapeutic and less unwanted effects. Studies are underway to investigate the threshold doses to achieve such neuromodulation[53,55]. Since there are no conclusive data on the value of the α/β of epileptogenic lesions, we assumed the α/β to be the same as for proliferating tissue like in brain metastasis or tumor tissue. It remains unknown whether the use of the α/β value of non-neoplastic tissue or even normal brain tissue would be more adequate. Although changing the value of α/β will change the absolute BED values, it hardly changes the relative positions of the data points in the dose response curve. Furthermore, this does not change the conclusion that the response correlates with BED. However, the difference in BED between single and multi-fraction schedules will increase: an α/β of 2.2 Gy instead of 10 Gy will cause a shift of the data points from the single-fraction schedules further to the right in relation to the multi-fraction schedules. This suggests the response is sensitive to fractionation, and a fractionated scheme would be favorable over a single-fraction scheme.

Suggestions for future research

This systematic review gives rise to the following suggestions for future research on RT for FNNE. First, more information on the quality of life of epileptic patients is compulsory (with information about AED reduction after treatment). Although seizures are not completely controlled after treatment, patients may benefit from seizure reduction, which is sometimes already a relief. Second, neurocognitive testing should be standard in studies on seizure frequency to gain knowledge on the effect of RT on the neurocognitive functioning. Thirdly, the definition of the (correct) target volume based on reported outcome (epilepsy frequency) is mandatory though still lacking. Functional MRI may augment defining this target volume. Fourth, little information is known about LINAC-based fractionated (stereotactic) radiotherapy and only four out of 16 studies that were included in this review used this technique. Hence, the effect of fractionation could not be assessed in detail. Therefore, the next step in assessing radiotherapy for FNNE is to improve the therapeutic ratio by reducing toxicity, which currently has a high incidence and is often the cause of resection after several years of follow-up. Bearing in mind the superior normal-tissue tolerance when employing a fractionated SRT scheme, future clinical trials may for example use 32−38 fractions of 1.8 Gy to obtain such response frequencies. The radiation techniques currently available allow for accurate dose delivery to a small volume of brain tissue. The first step to improve the therapeutic ratio would be to use lower total doses to similar volumes (*e.g.*, by fractionation) in order to avoid healthy tissue destruction under iso-effect conditions. Once such doses have been shown to be equally effective, the

radiosurgical use of charged particle beams with protons or carbon ions may further enhance the therapeutic ratio, based on their lower integral dose, lower risk of side effects and enhanced biological effectiveness.[54-56] After improvement of the therapeutic ratio, prospective randomized-controlled trials to define the value of radiotherapy compared to anti-epileptic drugs, surgery, and other invasive approaches are urgently required.

Conclusions

Radiotherapy is a possible treatment option for focal epilepsy even though its present role in the management of drug-resistant epilepsy is limited. So far, no valid studies have been published to assess the efficacy of radiotherapy for drug-resistant FNNE in adults with a sufficiently high level of evidence. Since randomized control studies are lacking, existing evidence is mainly limited to case series. Hence, there is an urgent need for prospective randomized-controlled trials to define its value compared to anti-epileptic drugs, surgery, and other invasive approaches. Further research is needed to establish agreement on target volume definition and to determine the optimal dose prescription in order to improve the current results of radiotherapy.

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Supplemental material

Table S7.1 Medical subjects headings per database.

Database	Medical Subject Headings (MeSH terms)
Pubmed	epilepsy AND radiotherapy AND seizures AND control groups AND radiotherapy dosage AND maximum tolerated dose AND radiation effects
Ovid Medline	radiotherapy AND epilepsy AND seizure control
The Cochraine Library	radiotherapy AND epilepsy AND seizure control
Embase	radiotherapy AND radiation AND epilepsy AND seizure control
Web of Science	radiotherapy AND radiation AND epilepsy AND seizure control

Table S7.2 Search history PubMed.

Search items
((("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields]) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms])) AND (Outcome[All Fields] OR (("seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields])))) AND (("radiotherapy dosage"[MeSH Terms] OR ("radiotherapy"[All Fields] AND "dosage"[All Fields]) OR "radiotherapy dosage"[All Fields]) OR ("maximum tolerated dose"[MeSH Terms] OR ("maximum"[All Fields] AND "tolerated"[All Fields] AND "dose"[All Fields]) OR "maximum tolerated dose"[All Fields]) OR ("radiation effects"[Subheading] OR ("radiation"[All Fields] AND "effects"[All Fields]) OR "radiation effects"[All Fields] OR "radiation effects"[MeSH Terms] OR ("radiation"[All Fields] AND "effects"[All Fields])))

Table S7.3 In and exclusion criteria.

Inclusion criteria	Exclusion criteria
√ Studies published after 1990	√ Animal studies
√ English-written	√ Pediatric patient population (<18 years of age)
√ Minimum follow-up time of 12 months after radiotherapy available	√ Case reports
	√ Prior resection
√ Seizure frequency reduction outcome available	√ Possible neoplastic causes of epilepsy (including arteriovenous malformations, hamartoma, cavernoma and neoplasms)
√ Patients older than 18 years with focal drug-resistant epilepsy	
√ Information on medication reduction available and information on dose prescription	√ Bias caused by patient selection linked to outcome or toxicity
√ Treatment technique and toxicity of radiotherapy available	√ Non-English
	√ Articles that were not accessible and could not be provided by the corresponding author

Table S7.4 *Excel questionnaire.*

Article	Patient selection	Treatment	Outcome	Toxicity	Search
Authors	Study design	Number of patients treated	Mean time follow-up (months)	Long-term toxicity	Seizure outcome classification
Year of publication	Type of epilepsy	Treatment period	Range follow-up time	Symptomatic complication treatment	Database
Title	Prior surgery	Number of fractions	Seizure outcome (Engel/ILAE class)	Magnetic resonance imaging (MRI)	Date
	Age	Total dose (Gy)	Remission after radiotherapy class I	Period after radiotherapy (mean)	
	Gender	Dose prescription (isodose)	Time until class I was reached	All-cause mortality	
	Location of target volume	Maximum dose (Gy)	Medication free after 2 years		
		Dose to organs at risk			
		Treatment technique			
		Antiepileptic drugs reduction post radiotherapy			
		Volume treated (cm^3)			
		Image modality used for target volume definition			

Table S7.5 Bias assessment within studies.

Study authors year	Inclusion criteria	Exclusion criteria	Control group	Loss to follow-up	Follow up (mean months)	Definition of outcome measure	Exposure radiotherapy
Regis et al, 2000	-	-	-	+	+	+	+
Kawai et al, 2001	-	-	-	+	-	+/-	+
Grabenbauer et al, 2002	+	+	-	+	+	+/-	+
Regis et al, 2004	+	+	-	+	+	+	+
Srikijvilaikul et al, 2004	+	+	-	+	-	+	+
Bartolomei et al, 2008	+	+	-	+	+	+	+
Hoggard et al, 2008	+	+	-	+	+	+	+
Rheims et al, 2008	+	-	-	+	+	+/-	+
Barbaro et al, 2009	+	+	-	+/-	+	+	+
Vojtech et al, 2009	-	-	-	+	+	+	+
Liang et al, 2010	+	-	-	+	+	+/-	+
Kawamura et al, 2012	+	-	-	+	+	+	+
Rauch et al, 2012	-	-	-	+	+	+/-	+
Usami et al, 2012	-	-	-	+/-	-	+/-	+
Chen et al, 2014	-	-	-	+	+	+	+
Boström et al, 2016	+	+	-	+	+	+	+

In-and exclusion criteria +: well defined criteria, +/-: not explicitly defined but can be extracted from the text, -: not defined. Control group -: when no control groups were described. Loss to follow-up: +: when it was explicitly described why patients were loss to follow-up or there was no loss of follow up, +/-: when a patient was loss to follow-up but not defined why. Follow-up: +: when time was explicitly described. _: when time was not described. Outcome: +: when outcome was defined according to the Engel classification, +/-: when outcome was defined according to a classification other than Engel. Exposure radiotherapy: +: when fraction, fraction dose, dose prescription and treatment technique were explicitly described.

Chapter 8

General discussion

Discussion

The overall aim of this thesis was to optimize radiotherapy of primary tumors of the brain and head-and-neck, specifically by assessing the therapeutic value of particle therapy (PT).
When treating a tumor with radiotherapy, a reasonable balance is needed between tumor control probability (TCP) and normal tissue complication probability (NTCP). In this thesis, we mainly investigated potential improvements in NTCP models. Since these NTCP models already existed for the primary treatment of HNSCC, I particularly focused on tumors and organs at risk (OARs) of the central nervous system (CNS)[1-4]. This included determining the clinically relevant OARs of the CNS, uniforming their delineation by introducing a CNS atlas, and reporting on a consensus on tolerance dose. These elements are indispensable for the development of NTCP models needed for an optimal plan comparison between different treatment modalities such as photon and particle therapy. This is especially true when costs or availability limit one of the treatment options, as is the case in the Netherlands were only 3% of all radiotherapy patients are eligible for proton therapy within the coming years.

Due to the limited resources and in order to accelerate the generation of clinical evidence, the Dutch model based approach was introduced. This approach consists of 4 steps[5,6]. The first step is the selection of validated, photon-based NTCP models from literature by experts in the field. The second step is the prediction of the individual patient's NTCP values for a certain toxicity taking the baseline toxicity into account. When a certain threshold is exceeded, a plan comparison between photon and proton therapy is indicated. Step 3 is individual patient selection by determining the delta NTCP of the two treatment plans, indicating the predicted gain by reducing toxicity. Within the Netherlands there is an agreement to use the common terminology criteria for adverse events version 4 (CTCAE-4). Since CTCAE-4 grade 1 toxicity gives no permanent damage, only grade 2 to 4 are taken into account. Grade 2, 3 and 4 toxicities require a delta NTCP of 10%, 5% and 2%, respectively, to favor the treatment with proton beam therapy. The fourth step is the validation or modification of the existing, photon-based NTCP models, on the basis of the observed toxicity following proton beam therapy[5,6].

In the current absence of validated NTCP models for CNS and HNSCC re-irradiation, a dosimetric plan comparison was conducted in two ROCOCO trials. These data can assist in decision-making which treatment modality is expected to be the most favorable for an individual patient in reducing the side effects caused by radiotherapy. However, the

development of these desired NTCP models itself was no subject of this thesis and this needs to be investigated in future research. These NTCP models will not only focus on dose-response relationships for treatment related toxicity, but ideally these will also take patient characteristics and other treatment modalities such as systemic treatments into account. By this the NTCP models could assist in developing decision support systems and shared decision tools, which enable not only the doctor but also the patient to make a well balanced choice between surgery, systemic therapy or various options of radiotherapy[7-11]. This principle also applies for nonmalignant diseases, for example epilepsy. Currently, there is growing interest in treating this disease with high-conformal radiation techniques, e.g., proton beams. Until now it is unknown what dose is required to treat foci of epilepsy. Therefore, there is a need for a radiation dose response model in epilepsy. For a validated dose response model future clinical trials are needed to validate the data retrieved from retrospective studies.

Plan comparison HNSCC & CNS

Through comparison of state of the art treatment plans in the ROCOCO trial for re-RT of HNSCC and low grade glioma (LGG) we demonstrated that particle therapy (PT) improves the sparing of most OARs, with evident reduction of the integral dose[12,13]. Carbon ions were superior to protons in most cases in the ROCOCO re-RT HNSCC trial, which can be explained by the different beam characteristics such as a sharper penumbra of carbon ions as also demonstrated in several other planning studies[14,15]. Unfortunately, no randomised trials have yet been performed confirming a superior clinical benefit for carbon ions above protons in reducing the dose to the OARs[12]. This is likely due to limited access and increased costs of any of the two modalities compared to photon-based treatment. Tomotherapy (TOMO) was found to be superior to volumetric modulated arc therapy (VMAT) in sparing OARs in the ROCOCO LGG trial, most striking the centrally located OARs such as the pituitary gland[13]. This is in agreement with Koca *et al*.[16] showing TOMO to be superior to intensity-modulated radiotherapy (IMRT) in sparing OAR in a plan comparison of 20 glioblastoma patients.
A high dose conformity index to the clinical target volume was achieved by using VMAT in the LGG trial, followed by TOMO and IMRT[13]. This lower conformity index of particle therapy was most likely caused by the necessity of robust treatment planning in particle therapy. Resulting in a good coverage maintenance while no tolerance doses are exceeded. Despite a variety of setup changed during treatment. Creating an area of higher dose around the clinical target volume (CTV) exceeding slightly the planning target volume (PTV) used in photon planning such as VMAT, IMRT and TOMO. Particle therapy is more sensitive to density changes than photon therapy. Making robust

optimization necessary to account for possible positioning errors. Causing a slightly different path length for the proton beam causing relevant dose differences.
Weight loss, mucous filling of the air-filled sinuses or tumor regression will also influence the dose distribution and require repeated imaging and recalculation of the treatment plan, most profound in HNSCC patients[17-21]. This leads to one of the limitations of this *in silico* study being the fact that density changes, caused by these anatomical changes during therapy, were not taken into account. This possibly influences the outcome and might in daily practice require regularly new computed tomography (CT) and treatment plan adaptation during the course of treatment. This may possible influence the NTCP for that particular OAR after calculating the cumulative dose distribution.
Another limitation not taken into account in the ROCOCO study even though possibly influencing the plan comparison is the presence of metal artefacts, such as dental fillings and crowns, within the particle beam. In our ROCOCO study these metal filling, including the streak artefacts on the planning-CT caused by them, were delineated and replaced by water densities since they were considered of small influence on the dosimetric outcome of this comparative trial. In a phantom study of Richards *et al*.[22], the baseline proton dose ranges of 98-106% around the planning target volume (PTV) resulted in 66-111% coverage in the presence of metal fillings. In daily practice it is strongly advised to avoid metal in the line of the proton beam. If this cannot be avoided, it should be considered to remove, if possible, this metal[23].
A third factor confounding the results is that in these ROCOCO studies treatment plans were generated in different institutes having, besides the study protocol, their own clinical practice and internal protocols. Therefore, the treatment planning procedures may not necessary be the same possibly causing an altered numerical outcome, for example, due to the slightly different PTV margins, determined by each participating department. Likewise, the influence of the beam angles and the number of beams cannot be excluded. In our ROCOCO trials we found that in particular the contralateral OARs benefit from particle therapy. There are some publications confirming this observation. The largest being the retrospective study from Harrabi *et al*.[24] in which 74 LGG patients were treated with proton therapy. The delivered proton treatment plan were compared to generated *non* state of the art conventional three-dimensional radiotherapy plans showing comparable coverage of the target volume and reduction of the dose especially in the contralateral OARs.
After both ROCOCO trails it remains unclear if the reported reductions in dose to the OARs will result in a reduction of clinical relevant side effects. This will need to be proven in future research. This is in particular true for the ROCOCO LGG trial in which the cerebellum posterior is incorporated as a possible new CNS OAR[26].

Organs at risk for treatment of CNS tumors

Determination

Due to the use of multimodality therapy, the survival rates increase for LGG patients, raising awareness to the long-term side effects of which neurocognitive decline is one of the most feared ones due to its direct influence on the patient's quality of life[26]. Apart from the paper by Gondi *et al.*[27], it is still unclear what OARs cause this cognitive decline and at which radiation dose. Gondi *et al*.[27] described a NTCP model based on the dose to 40% of both hippocampi, which significantly correlated with cognitive decline in 18 patients. The cerebral hemispheres are considered responsible for cognitive function, whereas the cerebellum is known for its role in regulating and coordinating movement, balance and posture[28]. In this thesis, through a review of the available literature, the possible role of the cerebellum in cognition is described. Schmahmann *et al.*[29] suggested the division of the cerebellum in an anterior and posterior part. Merchant *et al*.[30] was the first to delineate the anterior and posterior part separately according to this, in his pediatric LGG study. They evaluated 78 children with LGG treated with radiotherapy with or without prior chemotherapy. A significant relationship was found between neurocognitive impairment and the radiation dose to the posterior cerebellum[30]. Gan *et al*.[31] studied 10 adult head and neck cancer patients treated with radiation therapy and showed that memory was the most severely affected cognitive domain. The one patient most affected received a maximum dose to the cerebellum of 36 Gy with a low dose to the whole brain and hippocampi. To date these data still need to be confirmed in a prospective study. In order to do so, agreement is needed in how to delineate the posterior and anterior part of the cerebellum[32,33].

Besides previously described cognitive impairment, other relevant toxicity require delineation of other OARs e.g. for vision, hearing, endocrine and brainstem function. An uniform delineation of the related OARs such as optical nerve, chiasm, cochlea, pituitary and brainstem is mandatory.

Delineation

Reduction of the inter- and intra-observer variability for delineation of OARs (and target-volumes) in radiation oncology is greatly depending on the use of guidelines for delineation[34]. This guidelines can be offered by an atlas. In daily practice and even more indispensable in conducting clinical trials, the conformation to a region specific delineation atlas is crucial in comparing dose to the delineated structures. In head and neck cancer, Brouwer *et al*.[35] composed a consensus guideline delineation atlas in

cooperation with DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG for this purpose. Also for thoracic radiotherapy an OAR atlas is available provided by Kong *et al.*[36] In accordance, Vinod *et al*.[37] concluded in their review of 56 studies, which evaluated delineation, that the inter-observer variability in delineation of the target volume and OARs can be reduced with the use of guidelines, provision of auto contours and teaching including the use of multimodality imaging, which was considered useful in certain tumor sites such as CNS. Conversely, a recent study of Bartel *et al*.[38] demonstrated a large inter-observer variation of hippocampus delineation in a hippocampus avoidance study. They evaluated the delineation of 10 hippocampi by 4 radiation oncologists, 2 radiation technicians and one neuro-radiologist, all from different institutions, using the EORTC hippocampal contouring atlas by Gondi *et al*.[39]. Concluding that even with the use of an atlas the delineation variability remains large. Illustrating that the upload and approval of the OARs delineation should be part of the quality assurance procedures of clinical trials.

In order to create uniform CNS delineation, the first step was to agree upon which OARs are relevant for CNS radiation, excluding the specific head and neck OARs as defined in the Brouwer atlas[34]. OARs deemed relevant for radiation-induced toxicity in neuro oncology and to be included in the new CNS delineation atlas were: brain, brainstem, chiasm, cochlea, cornea, lacrimal gland, hippocampus, lens, optic nerve, pituitary, retina, skin and vestibulum & semicircular canals. The second step was defining the borders of those specific OARs based on their anatomy on CT and magnetic resonance (MR) imaging. The third step was the development of an online available CT and MR based contouring atlas. The fourth and last crucial step to ensure wide spread use of the atlas was reaching a consensus on all previously mentioned steps within the European Particle Therapy Network (EPTN)[32,33].

For efficient digital comparison of different radiation modalities a uniform nomenclature based on standardizing naming convention in radiation oncology by Santanam *et al.*[40] was used.

A potential limitation of this atlas is the limitation of OARs. Anterior eye chambers, cerebrospinal space, circle of Willis, Eustachian tube, frontal & temporal lobe, optic tract, macula, mammillary bodies and spinal canal are possible relevant OARs for which future research might show its relevance. Even though, due to practicality and resources, the international panel of experts decided to adhere to the OARs in the current atlas and to extend the set if shown relevant in the future. Since the atlas is available online it will be updated when indicated for these or other future relevant OARs[32].

Tolerance dose

After uniform CNS delineation using a CT and MR based CNS atlas, a consensus on the dose constraints of these OARs is mandatory[33]. A comprehensive search of the current literature on the aforementioned OARs on dose constraints was performed[41]. For each of these OARs the available data were summarized and a dose constraint was determined in consensus with 20 Radiation Oncology experts in the field of neuro oncology within the EPTN. All dose constraints and corresponding α/β values were reported in Gy. The doses were recalculated to equivalent dose in 2 Gy-fractions (EQD2).

Damage to a serial OARs, e.g., the optic nerve, chiasm, cornea, retina, lens, skin and brainstem, will lead to toxicity after damage of only a sub-volume of this OAR. For these OARs a volume constraint was added as a near maximum value. Only for the serial OARs the tolerance dose versus the total number of fractions was recalculated based on the consensus constraints for serial OARs, using the linear quadratic formula[41]. These values were defined as near maximum EQD2 values.

Parallel OARs being cochlea, hippocampus, lacrimal gland and pituitary, will lose their function depending on the mean dose to the whole structure. For the parallel OARs no tolerance dose per fraction was calculated since according to Perko *et al*.[43] and Hoffmann *et al*.[44] these are comprised of the treatment plan's dose and its standard deviation, which are patient- and technique- dependent.

A confounding factor of this study is that the consensus tolerance doses could only be based on the scarce information found in literature on the dose and toxicity relationship for most of the OARs described in the neuro delineation atlas. Some possible relevant OARs such as the vestibulum and semi-circular canals, hypothalamus and the cerebellum could not be included in this consensus document, because the required data are still lacking. In order to pursue consenting a dose, these data and an accurate delineation is most relevant in order to collect data and related toxicity in the future.

Radiotherapy for non-neoplastic Epilepsy

In the previous studies effort was made to assist in developing NTCP models in the central nervous system. Similar to an NTCP model predicting the possibility of toxicity, a TCP model predicts the possibility on treatment response, in oncology this is equivalent to tumor response. In a disease without a tumor, i.e., non-neoplastic epilepsy, there is also a need for a dose-response model.

In order to find evidence on the effectiveness of radiotherapy in drug-resistant non-neoplastic focal epilepsy in adults and to fit the dose-effect model, we conducted a

systematic literature search. Sixteen studies out of 170 initially identified studies on drug-resistant non-neoplastic focal epilepsy in adults were included, including in total 170 patients[45]. A positive effect of radiotherapy on the seizure frequency was seen in 12 of the 16 studies, showing and average reduction in 58% of the patients, meaning no or rare seizures defined as radiotherapy-adapted Engel class (RAEC) I and II. Despite the positive effect of radiotherapy, 20% of the patients still needed surgery afterwards due to toxicity or remaining seizures. The toxicity requiring surgery included radionecrosis, cysts formation, edema and intracranial hypertension.

With the available data a dose-effect model was fitted between the prescribed dose and the seizure reduction score. This study showed that radiotherapy is a good alternative treatment in drug resistant non-neoplastic focal epilepsy in adults, although further research is needed to determine its role compared to other treatment modalities such as MR–focused ultrasound and laser interstitial thermal therapy, which were not subject of our study[46].

The major shortcoming of that review is the fact that the Rose trial[47] could not be incorporated since it was published after the publication of our review. In the Rose trial, stereotactic radiosurgery to a dose of 24 Gy was randomized to anterior temporal lobe lobectomy for patients with drug resistant unilateral temporal lobe epilepsy[47]. After 36 months, 74% of patients treated with stereotactic radiosurgery were seizure free versus 85% of the patient after an anterior temporal lobe resection. An important observation in the Rose trial confirmed within our 6 reviewed studies, is the time to response, being 3-6 months after surgery compared to 24 months after radiotherapy[45,47]. There was no significant difference in quality of life in epilepsy (QOLIE) between the two groups in the Rose trial confirming our conclusion that radiotherapy seems a good alternative to respective surgery in drug-resistant epilepsy.

Future perspectives

Particle therapy, such as proton therapy is not a new treatment. The first patient was treated in 1954 and subsequently over 60.000 patients have been treated worldwide[48]. Still, solid evidence of equivalence or superiority of particle therapy is lacking. Level I evidence would include a randomized trial, comparing particle therapy to state of the art photon radiotherapy. In the last decade, it has been proven difficult to perform such a randomized trial. Costs are a crucial factor, since health insurance companies are reluctant to reimburse a treatment without convincing evidence, making this lack of evidence-discussion a vicious circle. Even if a randomized trial is conducted, e.g. the LGG trial (clinicaltrial.gov NCT03180502) open for inclusion since 2017 with cognition being the primary endpoint, it will take years before results become available and

radiation treatment techniques will have developed, still raising doubt on the clinical results and thus leaving us one step behind.
For eye melanoma, chordoma and chondrosarcoma, there is mature evidence of high local control rates and low toxicity, which is very difficult to achieve with photon therapy due to the required high dose and the proximity of the target to critical OARs. For paediatric tumours, there is a broad acceptance of particle therapy by the general public and health insurance companies due to the striking reduction of the integral dose, which can be achieved using particle therapy, resulting in a putative reduction of secondary tumour induction. As Schneider *et al*.[50] stated in his review, radiation induced secondary cancers can be the price of success if the primary cancer is cured or at least controlled.

As of early 2018 particle therapy has become available for daily patient care in The Netherlands. It is expected that within the next 4-6 years up to 3% of all patients referred for radiotherapy can be treated with proton therapy. Since resources are scarce and costs high (roughly estimated to be 3 times higher compared to photon therapy), a good patient selection is therefore warranted.
Thanks to the impressive national collaboration between all radiotherapy department throughout The Netherlands, a solid model based approach was adopted, enabling the doctors to select only the right patient for proton therapy[5]. In this model a plan comparison is required for the non-standard indications. Standard indication are paediatric tumours, chordoma & chondrosarcoma and eye tumours. Recently, craniospinal axis irradiation and primary brain tumours with a 10 year overall survival expectancy of more than 50%, excluding all brain tumours eligible for stereotactic radiotherapy, were added to the standard indications.
The health insurance companies agreed to this approach, under the condition that within the next decade data are provided supporting the hypothesis that in a selected patient group, proton therapy is superior to photon therapy. Only if good patient selection is performed and all Dutch radiotherapy departments work closely together, The Netherlands might be able to show the gain of proton therapy compared to photon therapy. This principal is essentially different from earlier attempts to introduce particle therapy. Some particle centres even had to face bankruptcy in the past. Some causative factors being the huge investments, patient referral lagging behind and non-substantial reimbursement. Leading to the increasing need to accept patients able to pay for the treatment themselves and not necessary the most likely to benefit from particle therapy.
In this thesis we showed that particle therapy has dosimetric advantages over photon therapy in HNSCC re-irradiation and LGG, but there is still a need to confirm these in

silico treatment planning studies with real clinical data (see Figure 8.1). In order to prevent large costly trials, upfront patient selection is needed and for that validated NTCP models are mandatory. This is not only needed for proton therapy but it will also be of great value in photon treatment. Accurate NTCP models enable the radiation oncologist to predict for each and every patient as precisely as possible the change of a certain toxicity, giving certain patient characteristics. In order to achieve this goal future research is needed, especially in patient specific factors. Whether these factors arise from genetic profiles, imaging (radiomics), blood samples, co-morbidity or are as simple as age or gender, a lot of work still has to be done for each OAR.

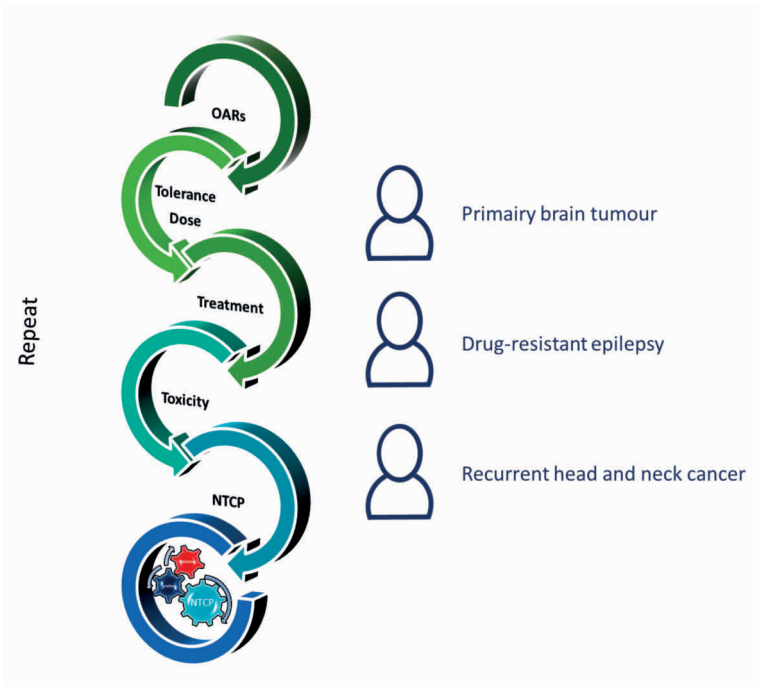

Figure 8.1 Repetitive cycle subject of this thesis optimizing brain and head & neck radiotherapy illustrating the need for clinical data. NTCP = normal tissue complication probability model. Wheel shapes red = proton radiotherapy, dark blue = photon radiotherapy, light blue = NTCP model.

Since the amount of data required due to all different variables, good cooperation with the particle centres, as well as all photon facilities is needed resulting eventually in a shared goal; the best treatment available for our patients. The EPTN is such an initiative in which radiation oncologist from particle centres all over Europe work together harmonise, gather and analyse data.

In this thesis a consensus within the CNS experts of the EPTN was reached in order to facilitate combining data in the future by agreeing to delineate OARs in a uniform way and take the same tolerance does into account during treatment planning. Even if there is only limited evidence for a certain tolerance dose, a uniform threshold enables us to collect data to accept or reject the threshold in time. Due to increasing interest in particle therapy and evolving technology, the size and costs of a cyclotron keeps declining resulting in smaller proton facilities most of them combined with photon radiotherapy, making this treatment in future more accessible to all patients in Europe. As a result of these smaller proton facilities, it becomes even more essential to work together to get the data needed to improve patient selection by improving NTCP models including molecular markers and imaging. Elaborating a cooperation such as the ROCOCO initiative in with international parties work together. This underlines the need for rapid collecting/pooling and exchanging of international research data in the field of radiotherapy as suggested by Skripcak *et al*.[49]. They describe the challenges that have to be addressed such as utilisation of standards, data quality and privacy concerns, data ownership, rights to publish, data pooling architecture and storage[49]. Recently the Dutch Cancer Society Koningin Wilhelmina Fonds (KWF) awarded a grant of €1.5 million to Maastro clinic, a radiotherapy depertment at Maastricht and University Medical Centre Groningen (UMCG). They will set up a research infrastructure for proton therapy (PROTRAIT), working closely together with Holland Particle Therapy Center (HPTC) and all the other university medical centres.
We are now in a unique situation of expansion of the number of proton facilities throughout Europe and not enough radiation oncologists with long-term proton experience to work in them. Since most of the current experienced radiation oncologist received only limited education on particle therapy, there is an immense need for collaboration and sharing of knowledge with the experienced centres. Standardizing the follow up within the EPTN with regard to imaging, blood samples and research as well as daily patient care could be an important first step. Working together on a large scale by organizing educational sessions, internships, sharing our data safely open access and reporting our outcome on a large scale will become even more important than ever, to make particle therapy a part of the radiation oncologist wide pallet of treatment options.

With increasing survival rates after cancer treatment due to the combined efforts of doctors and researchers all over the world, an increasing number of survivors are subject to experience radiation induced long-term side effects[50]. Radiation induced secondary cancer is one of them, of special interest in those patients with a pathologically benign disease, such as meningioma or epilepsy, or with pediatric tumors

treated with radiotherapy. With the increasing use of IMRT and VMAT techniques a low dose bath is administered to a large volume, not exceeding any tolerance dose[51,52]. Combined with patient related factors, e.g., age, gender, treatment of primary cancer (systemic treatment) and genetic disorders, second cancers associated with radiation are most often seen in proximity of the irradiated area and after a long latency period, on average between 10 and 20 years[52]. The integral dose from particle therapy is beneficially on average 2-3 times lower than from photon therapy[54]. On the contrary nuclear interaction of protons create neutrons mainly within the patient, assuming pencil beam scanning as is the standard in The Netherlands, which induces a low dose everywhere in the patient. When passive scatter technique is used even more neutrons are produced. Which parameters will prove to correlate the best with secondary tumour induction is yet undetermined and needs to be subject to further research.

Another long term side effect of interest is neurocognitive decline with a long latency period up to 12 years[55,56]. In the search for OARs related to cognition we suggested the posterior cerebellum as a possible new OAR in this thesis [25]. Since the cerebellum receives unintentional low dose in patients treated for HNSCC, this is the ideal patient group to prospectively evaluate neurocognitive functioning before and after radiotherapy with standardized cognitive testing. More cognition related structures besides hippocampi or posterior cerebellum need to be determined. With the proposal of our atlas for neuro-oncology, the workload for the technician and radiation oncologist further increases. Future auto segmentation based on this consensus atlas will help to speed this process. This should be strived for my academic centres and companies specialised in image analysis. Future new structures possibly related to cognition need to be identified and integrated in the atlas, ensuring uniform delineation and dose registration. It will remain difficult to determine which OAR is the most dominant factor and needs to be spared as much as possible, especially if those OARs are located adjacent to each other receiving comparable dose during treatment.
Radiation is not the only factor influencing cognition, systemic therapy, surgery, medication and also patient factors, e.g., stress, anxiety and fatigue can cause cognitive decline. Another problem with the development of a NTCP model for cognition is the standardization of cognitive testing. There are several domains to be tested and in an individual patient the most relevant tests would be selected depending on patient related factors, e.g., tumour location, specific post-operative deficits and age. In order to collect data for future NTCP models, cognitive testing and imaging should also be performed in a standardized way. Within the EPTN, subgroup working on standardisation of neuro-oncology is now preparing a consensus paper on the follow up

of all to the aforementioned selected OARs and their related toxicity after radiotherapy including cognitive testing and imaging.

In this era of increasing number of patients treated with proton radiotherapy and growing follow up time, there is some concern about potential proton specific side effects, which clearly need further attention. Using particles the potential to induce a biological effect in cells, also called the relative biological effectiveness (RBE) is assumed to be larger; the RBE for carbon ions, protons and photons being of 3.0, 1.1 and 1.0 respectively. In the review of Lühr *et al*.[57] studies are presented suggesting that the RBE of protons might be higher than 1.1, possibly varying on the position relative to the Bragg-peak, characterized by an increased linear energy transfer (LET). In daily practice this RBE of 1.1 is used for proton radiotherapy, according to the recommendation of the ICRU 78. Carefully illustrated by Lühr *et al*.[57] pre-clinical studies consider the RBE a complex function of radiation dose, LET, cell type, endpoint etc. showing a cell survival from 1.1 at the spread out Bragg-peak (SOBP) entrance to even 4-6 in the distal fall off at 2Gy per fraction[57,58]. They rightfully suggest 4 approaches to enhance proton therapy and deliver safe treatments. Step 1 being the awareness of RBE uncertainties during plan evaluation, step 2 mitigate the RBE effect by modification of beam positioning, step 3 generate clinical data by analysing patient outcome data and step 4 initiation of clinical relevant *in vivo* RBE studies[57]. On top of that, we suggest a fifth step: incorporating these data into proton treatment planning systems. This process should be accelerated in close collaboration with the clinicians and radiobiologists involved in the EPTN network as well as vendors of proton treatment planning systems.

The relevance of registration and reduction of side effects is also illustrated by the toxicity observation in our epilepsy review showing permanent toxicity, such as radionecrosis, cognitive and (asymptomatic) visual field deficit. Since there are no conclusive data on the α/β, quantifying for fractionation sensitivity of tissues, e.g. epileptogenic lesions, future research should include fractionated radiotherapy schedules in order to investigate whether this leads to a reduction in toxicity compared to a single fraction, maintaining the reduction of seizure frequency. In an attempt to further reduce the toxicity of this pathologically benign disease, a randomized or at least a prospective registry study is indicated investigating the role of proton versus photon radiotherapy.

In conclusion there is still work to be done, to gain in depth knowledge of the full potential of particle radiotherapy, whether this concerns possible reduction of side

effects, increased tumour control or variable RBE. Through further elaboration of current collaborations throughout the radiotherapy community together with all our colleagues within the medical field, there is a unique possibility to alter the side effects of our patients like a proton: positive!

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Valorisation

Valorisation

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.

Summary

Summary

The aim of this thesis is to further optimise radiation therapy of Brain and Head & Neck by reducing the dose to the healthy surrounding tissue, so called organs at risk (OARs), leading to a reduction in side effects

The first objective of this doctoral thesis was to assess the value of proton therapy in reducing the dose to the OARs, in particular for re-irradiation in head and neck squamous cell carcinoma and primary irradiation of low-grade glioma. **Chapters 2 and 3** report on two *in silico* trials conducted within the international Radiation Oncology Collaborative Comparison (ROCOCO) consortium, comparing different radiotherapy modalities including proton therapy, to assess the potential gains for individual patients due to the dosimetric characteristics of particle therapy. The first trial compared intensity-modulated proton therapy (IMPT) and carbon-ion therapy (IMIT) with the golden standard volumetric modulated arc therapy (VMAT) when re-irradiating patients with head and neck squamous cell carcinoma. The second trial compared intensity-modulated radiation therapy (IMRT), IMPT and helical tomotherapy (TOMO) with the golden standard VMAT in patients with a low-grade glioma. Both trials demonstrated that particle therapy can significantly reduce the dose to OARs whilst maintaining the prescription dose. Whether this translates into a clinically relevant benefit, is the subject of future research. In order to predict such a benefit, normal tissue complication probability (NTCP) models are needed. Validated NTCP models are currently lacking for head and neck re-irradiation as well as for the primary treatment of the central nervous system (CNS).
In **Chapter 4**, the posterior cerebellum is introduced as a new, potentially relevant OAR for the future development of an NTCP model that is focused on cognition, based on the growing evidence from structural and functional imaging studies that the cerebellum plays a role in neurocognition.

Delineation of the relevant OARs on computed tomography (CT) and magnetic resonance imaging (MRI) is needed to optimise the treatment plan before administering the corresponding dose to the patient. This manual delineation is a time-consuming process and a well-known source of error within the planning process, due to inter- and intra-observer variability[1].

Reducing this CNS OAR delineation variability is the second objective of this thesis, as described in **Chapter 5.** An international group of expert radiation oncologists in the field of neuro-oncology reached agreement on the European Particle Therapy Network

(EPTN) consensus-based CNS delineation atlas, in order to decrease the variation in CNS delineation. This CNS atlas is presented online (www.cancerdata.org) and encompasses delineation instructions for 15 CNS OARs, including the posterior cerebellum. It includes one CT-scan at two different brightness and contrast settings and two MR scans (3 and 7 Tesla) showing the OARs in three directions (axial, coronal and sagittal view). In **Chapter 6**, an EPTN consensus-based normal tissue tolerance table, including all currently known and deemed relevant CNS OARs, reports the tolerance dose in equivalent dose (EQD2), which enables a uniform comparison of different treatment modalities in the future (www.cancerdata.org). The use of the consensus-based EPTN CNS atlas and tolerance table is recommended for the Dutch model-based approach comparing photon and proton beam irradiation as well as for future prospective clinical trials including novel radiation techniques and/or modalities[2].

The third objective of this thesis was determining the role of radiotherapy in the treatment of epilepsy. **Chapter 7** contains a systematic review about the evidence on the efficacy of primary radiosurgery or stereotactic radiotherapy for drug-resistant non-neoplastic focal epilepsy in adults. After treatment, an average of 58% of the patients reported no or rare seizures (defined as radiotherapy-adapted Engel class [RAEC] I and II). A dose-effect model was fitted to the available response data to derive a relationship between prescribed dose and RAEC frequency of this, in the Netherlands, new indication for radiotherapy. In **Chapter 8**, the results of the previous mentioned chapters of this thesis are being discussed and future perspectives are presented. Additional research needs to be conducted to gain further knowledge to fully understand the potential of particle therapy. Thanks to solid collaborations throughout the radiotherapy community and beyond, with all our colleagues in the medical field, there is a unique possibility to further optimise the treatment of Brain and Head & Neck together.

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Samenvatting

Het doel van dit proefschrift is de verdere optimalisatie van de radiotherapeutische behandeling van aandoeningen in hersenen en hoofd & hals door de dosis te verlagen in het gezonde omringende weefsel, de zogenaamde risico-organen (OAR's), wat leidt tot een vermindering van bijwerkingen.

Het eerste doel van dit proefschrift was het beoordelen van de waarde van protontherapie bij het verlagen van de dosis in de OAR's, in het bijzonder voor hernieuwde bestraling bij plaveiselcelcarcinoom van hoofd & hals en de primaire bestraling van laaggradige gliomen in de hersenen. **Hoofdstukken 2** en **3** rapporteren over twee *in silico*-onderzoeken die zijn uitgevoerd binnen het internationale Radiation Oncology Collaborative Comparison (ROCOCO) consortium, waarbij verschillende radiotherapie modaliteiten, waaronder protonentherapie, worden vergeleken om de potentiële voordelen voor individuele patiënten te bepalen vanwege de dosimetrische kenmerken van deeltjestherapie. Het eerste onderzoek vergeleek intensiteit gemoduleerde protonentherapie (IMPT) en koolstof-ionentherapie (IMIT) met de gouden standaard, zijnde volumetrisch gemoduleerde boogtherapie (VMAT) bij het opnieuw bestralen van patiënten met plaveiselcelcarcinoom van hoofd & hals. In het tweede onderzoek werden intensiteit gemoduleerde bestralingstherapie (IMRT), IMPT en helical tomotherapy (TOMO) vergeleken met de gouden standaard VMAT bij patiënten met een laaggradig glioom. Beide onderzoeken toonden aan dat deeltjes therapie de dosis aanzienlijk kan verlagen in de OAR's terwijl de voorgeschreven dosis op de tumor gehandhaafd blijft. Of dit zich vertaalt in een klinisch relevant voordeel, is onderwerp van verder onderzoek. Om een dergelijk voordeel te voorspellen, zijn modellen nodig die de kans op complicaties aan gezond weefsel voorspellen (NTCP-modellen). Gevalideerde NTCP-modellen ontbreken momenteel voor hernieuwde bestraling van hoofd & hals en voor de primaire behandeling van het centrale zenuwstelsel (CZS).

In **Hoofdstuk 4** wordt het achterste deel van de kleine hersenen (posterior cerebellum) geïntroduceerd als een nieuw, potentieel relevant OAR voor de toekomstige ontwikkeling van een NTCP-model dat gericht is op cognitie. Er is groeiend bewijs op basis van structurele en functionele beeldvormingsstudies dat het posterieure cerebellum een rol speelt bij neurocognitie.

De delineatie van de relevante OAR's op computertomografie (CT) en magnetische resonantie beeldvorming (MRI) is nodig om het behandelplan te optimaliseren voordat de overeenkomstige dosis aan de patiënt wordt toegediend. Deze handmatige delineatie is een tijdrovend proces en een bekende bron van fouten binnen het planningsproces, vanwege inter- en intra-waarnemer variabiliteit[1].

Het reduceren van deze CNS OAR-delineatie variabiliteit is de tweede doelstelling van dit proefschrift, zoals beschreven in **Hoofdstuk 5**. Een internationale groep van deskundige Radiotherapeut Oncologen op het gebied van neuro-oncologie bereikten overeenstemming over de European Particle Therapy Network (EPTN) consensus-gebaseerde CNS-delineatie atlas, om de variatie in CNS-delineatie te verminderen. Deze CNS-atlas wordt online gepresenteerd (www.cancerdata.org) en omvat de delineatie-instructies voor 15 CNS OAR's, inclusief het posterior cerebellum. Het bevat één CT-scan met twee verschillende helderheid en contrast instellingen en twee MR-scans met verschillende veldsterkten (3 en 7 Tesla) die de OAR's in drie richtingen weergeven (axiaal, coronaal en sagittaal). **Hoofdstuk 6** rapporteert een EPTN-consensus tolerantie tabel voor normale weefsels met inbegrip van alle momenteel bekende en relevant geachte CNS OAR's en hun tolerantiedosis in equivalente dosis (EQD2) waardoor een uniforme vergelijking van verschillende behandelmodaliteiten in de toekomst mogelijk is geworden (www.cancerdata.org). Het gebruik van de consensus gebaseerde EPTN CNS-atlas en tolerantietabel wordt aanbevolen voor de Nederlandse model gebaseerde benadering ("model-based approach") waarbij fotonen- en protonen bestraling wordt vergeleken, evenals voor toekomstige prospectieve klinische onderzoeken met inbegrip van nieuwe stralingstechnieken en / of -modaliteiten[2].

De derde doelstelling van dit proefschrift was het bepalen van de rol van radiotherapie bij de behandeling van epilepsie. **Hoofdstuk 7** bevat een systematische review van het bewijsmateriaal over de werkzaamheid van primaire radiochirurgie of stereotactische radiotherapie voor niet-neoplastische focale epilepsie bij volwassenen die resistente zijn tegen geneesmiddelen. Na behandeling rapporteerde gemiddeld 58% van deze patiënten geen of zeldzame epilepsieaanvallen (gedefinieerd als radiotherapie-aangepaste Engel-klasse [RAEC] I en II). Een dosis-effectmodel werd gemaakt gebaseerd op deze uit de literatuur beschikbare gegevens waarbij een verband gelegd wordt tussen de voorgeschreven dosis en de epilepsie (RAEC) frequentie, voor deze in Nederland nieuwe radiotherapie indicatie. In **hoofdstuk 8** worden de resultaten van de eerdergenoemde hoofdstukken van dit proefschrift besproken en worden toekomstperspectieven gepresenteerd. Bijkomend onderzoek moet worden uitgevoerd om meer kennis te verkrijgen om het potentieel van deeltjestherapie volledig te

begrijpen. Dankzij solide samenwerkingsverbanden in de gehele radiotherapie gemeenschap en daarbuiten, met al onze collega's van andere vakgebieden, is er een unieke mogelijkheid om de behandeling van hersenen en hoofd & hals samen verder te optimaliseren.

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Dankwoord

Dankwoord

Het succesvol afronden van een proefschrift doe je niet alleen. Hieronder de mensen waar mijn speciale dank naar uit gaat.

Prof. dr. Philippe Lambin (promotor), voor het zien van de passie in mij en de kans en vrijheid die je me hebt gegeven me op wetenschappelijk gebied verder te ontwikkelen.

Prof. dr. Dirk de Ruysscher (promotor), voor je rustige vertrouwen in mij en het zien en aanspreken van mijn talenten. Onze samenwerking op wetenschappelijk gebied stopt gelukkig niet met het afronden van mijn promotie.

Prof. dr. dr. Esther Troost (promotor), voor het overbrengen van de kunst van het schrijven, je perfectie, enthousiasme, eerlijkheid en vriendschap. Jij verstaat de kunst een ander te laten excelleren.

Dr. Frank Hoebers (co-promotor), voor je vakkennis op het gebied van de hoofd hals oncologie en je blijvende interesse en stimulering tijdens mijn promotie.

Prof. dr. ir. Frank Verhaegen (voorzitter leescommissie), voor je tomeloze energie, gedrevenheid, humor en enorme kennis van ons mooie vak welke je moeiteloos deelt met jong en oud.

Corona leden (dr Jacoline Bromberg, dr. Albert Colon, prof. dr. Klaus Herfarth, prof. dr. Martin Klein, prof. dr. Maarten Lambrecht, prof. dr. Yasin Temel, dr. ir. Gloria Vilches-Freixas, prof. dr. ir. Frank Verhaegen, prof. dr. Joachim Wildberger), voor de prettige samenwerking nu en in de toekomst, met de optimale kruisbestuiving tussen onze vakgebieden.

Prof. dr. Klaus Herfarth (leescommissie), für Ihre Gastfreundschaft und Offenheit beim Teilen Ihrer jahrelangen Erfahrung in der Partikeltherapie in Heidelberg (HIT).

Dr. Ann Hoeben, voor je vriendschap, inzicht en gedrevenheid. Je passie is inspirerend voor iedereen om je heen.

Dr. Linda Jacobi (A.A. Postma), voor je positief kritische hulp en de humor waarmee dit gepaard ging, waarvoor je altijd weer tijd wist vrij te maken.

Dr. Albert Colon, dr. ir. Aswin Hoffmann, drs. Esther Pijnappel & dr. Olaf Schijns, voor jullie enthousiasme en professionele gedrevenheid om samen te zoeken naar alternatieve behandelingen om de epilepsiepatiënt verder te helpen. Mooi dat onze prettige samenwerking zo tijdloos is gebleken.

ROCOCO members (Andre M, Ann H, Charles N, Erik R, Esther T, Filippo A, Frank H, Geert J, Hans K, Lieke V, Macarena C-M, Marlies G, Maura K, Peter A, Philipppe L, Raquel DF, Robert Jan S, Sean W, Timothy S, Tobias F, Urszula J, Yvonne K), for investing your energy, ideas and time in this impressing international project nourished by Erik Roelofs, resulting in at least 4 PhDs!

EPTN CNS members, for all your enthusiasm and professional willingness to work together as a solid team of experts in the field of neuro-oncology.

Neuro-oncologie research team (Ann H, Ans S, Inge C, Jan B, Jaap Z, Karin T, Kasper R, Linda A, Linda J, Maikel V, Marc V, Martijn B, Mieke G, Monique A, Olaf S, Onno T, Piet vd E, Rob J), voor het laten zien wat een team samen kan bereiken.

Maastro medewerkers, voor de fijne samenwerking. In het bijzonder, team 4 voor het onderlinge respect, de humor en natuurlijk de heerlijke taarten en Mariëlle & Natascha voor de enthousiaste en professionele secretariële ondersteuning.

Inge, Lieke & Maikel, voor jullie enthousiasme; het doet me plezier jullie PhD-traject te mogen begeleiden.

Marie-Cécile & Anja, voor jullie vriendschap en de gezellige lunches in en rondom ons geliefde Vijlen.

Protongirls (Judith, Karolien & Stephanie), voor de proton typische sfeer (positief), gezellige etentjes & bakjes koffie/thee.

Paranimfen (Debby en Andrea), voor jullie jarenlange vriendschap. Jullie liefde, humor en openheid geeft mij steeds weer positieve energie.

Schoonouders (Luiksje en Jan), voor het herkennen en stimuleren van mijn liefde voor tuinieren en het verrijken van ons gezin met onze lieve viervoeters Rocky en ?

Zussen (Patricia en Pascal), voor jullie lieve bemoedigende woorden, interesse en relativeringsvermogen. Patricia ook bedankt voor je altijd weer nuttige inhoudelijke feedback als gewaardeerd collega en Pascal voor het delen van je artistieke talent door het maken van de prachtige kaft “Emma”.

Ouders (Mariet en Albert), voor jullie liefde en onuitputtelijk steun naast de stimulering om op eigen benen te staan en een eigen onderbouwde mening te vormen en deze respectvol te uiten. Jullie zijn de beste fanclub die een dochter zich maar wensen kan.

Kinderen (Karsten en Imke), voor jullie liefdevolle knuffels; samen met papa geven jullie de glans aan mijn leven. Karsten bedankt voor je fantastische humor, je altijd weer verrassende kennis en het samen Rocky uitlaten. Imke bedankt voor je zonnige lach, je heerlijke kookkunsten, het samen zwemmen, shoppen, vakanties plannen en binge-watchen.

En als laatste en belangrijkste ondersteunende factor in het behalen van mijn PhD: **Erik**. We hebben de afgelopen jaren vaak ook met veel plezier als collega’s aan de keukentafel gezeten om onze research ideeën bij elkaar te toetsen en vorm te geven. Je bent een uitzonderlijk lieve en zorgzame vader en partner. Wat bof ik toch dat ik samen met jou door het leven mag gaan.

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List of publications

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Curriculum Vitae

D.B.P. (Daniëlle) Eekers, was born on March 1970 in Almelo, The Netherlands, and grew up together with her two sisters Patricia and Pascal in Nijverdal where she completed her secondary education (VWO). In 1996, she obtained her medical degree cum laude at the University of Groningen. Due to the radiotherapy treatment of her close friend, she developed a strong interest in Radiation Oncology. She therefore started her specialisation in Radiotherapy at the RTIL in Heerlen, later called MAASTRO CLINIC. After finishing her education in Maastricht as a Radiation Oncologist, she further specialised in Neuro-Oncology while working as a staff member at the Verbeeten Institute (BVI) in Tilburg. Thanks to her scientific interest, especially in particle therapy, she joined the MAASTRO CLINIC team again in 2012 and started combining her work as a Radiation Oncologist with working on her thesis within the ROCOCO (Radiation Oncology Collaborative Comparison) project. In this multicentric cooperation, she worked closely together with experienced Particle Centres around the world. She now combines working at MAASTRO CLINIC with working at the South-East Netherlands Proton Center (ZON-PTC). Using her experience as board member of the Dutch Radiotherapy Neuro-Oncology Platform (LPRNO) and member of the Dutch Platform for Proton Therapy (LPPT) and the European Particle Therapy Network (EPTN) and other national and international organisations (e.g. NVRO, ESTRO-BTG, LWNO, DBTR, EANO, AWEC) she strives for consensus on standardisation and uniform data collection to allow for optimal selection and personalisation of patient treatments. She will continue focussing her research on particle therapy within the neuro-oncology, with special interest in cognition and epilepsy. She is happily married with Erik Roelofs. They have two great children: Karsten & Imke.