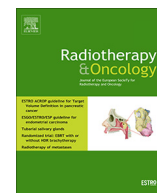


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Review Article

Proton therapy for selected low grade glioma patients in the Netherlands

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ABSTRACT

Proton therapy offers an attractive alternative to conventional photon-based radiotherapy in low grade glioma patients, delivering radiotherapy with equivalent efficacy to the tumour with less radiation exposure to the brain. In the Netherlands, patients with favourable prognosis based on tumour and patient characteristics can be offered proton therapy. Radiation-induced neurocognitive function decline is a major concern in these long surviving patients. Although level 1 evidence of superior clinical outcome with proton therapy is lacking, the Dutch National Health Care Institute concluded that there is scientific evidence to assume that proton therapy can have clinical benefit by reducing radiation-induced brain damage. Based on this decision, proton therapy is standard insured care for selected low grade glioma patients. Patients with other intracranial tumours can also qualify for proton therapy, based on the same criteria. In this paper, the evidence and considerations that led to this decision are summarised. Additionally, the eligibility criteria for proton therapy and the steps taken to obtain high-quality data on treatment outcome are discussed.

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Radiotherapy is an important treatment modality in the management of low grade glioma (LGG). The optimal timing of radiation treatment in the disease course is a dilemma in patients with minimal symptoms and favourable prognosis [1]. Early treatment can postpone tumour progression, a process that is otherwise continuously on going. Deferring treatment can postpone side effects, however, inevitably results in larger treatment volumes. Tumour progression and radiotherapy both adversely affect neurocognitive function (NCF). Whether tumour progression or radiation-induced late effects are more detrimental in the long term remains to be determined.

Proton therapy is an emerging radiotherapy modality that has become available in several countries over the last years, including

Abbreviations: LGG, low grade glioma; NCF, neuro-cognitive function; NTCP, normal tissue complication probability; RIBD, radiation-induced brain damage; IDH, isocitrate dehydrogenase; iADL, instrumental activities of daily living; MMSE, minimal mental state examination; MoCA, Montreal cognitive assessment; PTC, proton therapy centre.

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in the Netherlands since 2018. The implementation of proton therapy in clinical practise is more challenging than that of other technologies in radiotherapy. This is due to higher costs, limited availability, and lack of level 1 evidence showing superior clinical outcome [2]. In the Netherlands, the model-based approach is considered an alternative evidence-based methodology by health care authorities, to select patients for proton therapy [3]. Model-based selection entails, calculating the dose reductions that can be obtained in normal tissues with proton therapy, compared to the most optimal photon technique (plan comparison). Subsequently, normal tissue complication probability (NTCP) models are used to translate the dose differential into a toxicity risk reduction estimation (Δ NTCP) [4,5]. When the expected clinical outcome in terms of reduced toxicity is considered clinically relevant, a patient is eligible for proton therapy.

For LGG patients, proton therapy is an attractive alternative to conventional photon-based radiotherapy. Due to the physical properties of the proton beam, treatment can be delivered with significantly less radiation exposure (dose and volume effect) to the unaffected brain thus potentially limiting late radiation-induced side effects including NCF decline [6–8]. Despite its relevance, NCF is a difficult clinical endpoint to evaluate and quantify, and currently

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high-quality NTCP-models for NCF outcome, necessary to give clinical meaning to the superior dose distribution of protons, are lacking. As a consequence, the model-based approach for selecting patients with LGG for proton therapy is not yet achievable. There is, however, multifaceted evidence on radiation-induced brain damage (RIBD) from pre-clinical, radiological and clinical studies. An argument was made by the Dutch Radiation Oncology Society to allow an alternative approach to select patients with LGG and other intracranial tumours for proton therapy, and to define a new standard indication for these patients in addition to other approved standard indications such as paediatric patients and adult patients that require craniospinal axis irradiation.

In July 2019, the National Health Care Institute in the Netherlands concluded that there is scientific evidence to assume that proton therapy in LGG patients may have clinical benefit and advised the Ministry of Health to accept proton therapy as standard insured care for selected LGG patients. In this paper, the evidence and considerations that led to this decision are summarised. The focus in this paper lies specifically on WHO grade II LGG patients. However, patients with grade III anaplastic glioma's and other intracranial tumours can also qualify for proton therapy, based on the same criteria. The eligibility criteria for proton therapy and the steps taken to obtain high-quality data on treatment outcome, necessary to enable model-based selection in the future, are discussed.

Low grade glioma

Prognosis and management

WHO grade II LGG is a brain tumour with moderate malignancy grade that manifests as a slow progressive disease. The majority of patients are young to middle aged adults, who are in a good clinical condition at the time of diagnosis [9]. Classification is based on histo-morphological and molecular features into oligodendroglioma and astrocytoma with or without mutated isocitrate dehydrogenase (IDH) [10]. The relevance of the traditional categorization of glioma into WHO grade II/low grade and WHO grade III/anaplastic for prognostication has moved to the background. The survival of oligodendroglioma and IDH mutated astrocytoma patients often exceeds 10 years [11].

The standard of care for WHO grade II LGG is maximum safe resection followed by radiotherapy and chemotherapy [12]. In favourable cases, a more conservative approach with careful clinical and radiological follow up is an accepted alternative strategy, deferring treatment and its side effects [1]. A potential downside of deferring radiotherapy is that this strategy inevitably leads to larger radiation treatment volumes and could therefore induce more side effects. The so called 'wait and scan strategy' is the focal point of the recently opened EORTC trial [clinicaltrials.gov identifier NCT03763422]. Omitting radiotherapy as first line treatment after surgery, using chemotherapy only, is under investigation in anaplastic oligodendroglioma [clinicaltrials.gov identifier NCT02444000].

Radiotherapy

Even-though the traditional discrimination between WHO grade II and III glioma has lost its importance in prognostication, in current radiotherapy practise the tumour grade remains relevant as this has consequences for the target volume definition as well as dose prescription. The recently updated Dutch radiotherapy consensus guidelines for WHO grade II LGG are identical for proton- and photon-based techniques. The target volume includes the visible tumour on MRI-FLAIR plus a 3D margin of 5 millimetres, adapted to anatomical barriers. The prescribed dose is 50.4 Gy_{RBE}, using conventional 1.8 Gy_{RBE} fractions, 5 times per week. Depend-

ing on location of the target volume, treatment plans are optimised on circumstantial radiation dose to the pituitary, cochlea, scalp, structures in the orbit, optic-chiasm and -nerves, brainstem and brain including the hippocampi [13]. Using daily image guidance, treatment is delivered robustly with 1–3 millimetre accuracy.

The physical properties of proton- and photon-based therapy are essentially different [14]. Where a photon beam can be manipulated in a two-dimensional fashion (perpendicular to the beam direction), the proton beam has finite range and therefore can be controlled in depth. As a result, photon and proton plans differ significantly in the intermediate to low dose range [6–8]. With proton therapy, dose to a large volume of brain, including the contralateral hemisphere and hippocampus, can be reduced to near-zero in most cases.

Although the effectiveness of photons and protons has not been directly compared, the available data do not suggest inferior outcome of protons on tumour control [15–17]. The circumstantial low to intermediate dose (≤ 30 Gy_{RBE}) in a large volume of the brain, typical of photon-based treatment plans, is not considered to have a noteworthy contribution to tumour control in glioma [18,19]. In brain tissue, proton therapy can have a higher biological effect at the distal edge of the beam. Imaging changes after proton therapy on MRI are more frequently seen than after photon therapy [20,21]. Since the prescribed dose for WHO grade II LGG is well under the tolerance dose of the brain, this is not a major concern in these patients. However, extra care is warranted when treating in eloquent regions such as the optic chiasm and brainstem, or to higher dose near or beyond the tolerance dose of the brain (≥ 54 Gy_{RBE}) as in anaplastic glioma [22].

Clinical outcome

The most common toxicities of radiotherapy for LGG patients in the acute phase include fatigue, worsening of focal neurological symptoms and hair loss, which usually resolve within a few months [1,23,24]. In the long term, irreversible adverse effects can develop. Endocrinopathies and decline in hearing function is relevant in patients exposed to significant radiation dose to the pituitary and/or cochlea [25]. NCF decline is considered to be a relevant late adverse effect, irrespective of tumour location [26]. Impairments in the NCF adversely affect quality of life, patient's independent functioning within society (instrumental activities of daily living (iADL)) and may have additional implications for the patient's proxies [27].

Most LGG patients will experience NCF decline over the course of their disease [28,29]. The cause is multifactorial, including the tumour itself, surgery, medical treatment (chemotherapy and anti-epileptic drugs) and radiotherapy [30–32]. The magnitude of contribution of the radiotherapy is currently not known [26]. Due to the many competing risk factors for NCF decline in LGG patients, radiation induced NCF decline is considered to be particularly relevant in the long term [33,34]. Complaints and impairments are systematically reported after photon radiotherapy, with worse outcomes with increasing brain dose and volume parameters as well as time intervals, indicating a chronic progressive clinical course [28,29,35–38]. The first study on NCF outcome after proton therapy had promising results, showing no NCF decline after 5 years [39].

Radiation-induced brain damage

Pathophysiology

RIBD is a complex process that includes multiple pathophysiological responses over time [40]. Within hours, radiation triggers a cascade of molecular and cellular processes which may result in cell loss within different cell lineages and brain regions [41]. Depending on the cells and regions involved, various pathophysio-

logical mechanisms come into play. Damage to the neural stem cells may interfere with neurogenesis [42,43]. Loss of oligodendrocyte progenitors leads to white matter injury and demyelination [44], and endothelial damage can result into (micro)vascular changes and disruption of the blood–brain barrier [45]. Additionally, radiation stress on mature neuronal cells alters dendritic morphology and synaptic function [46]. Alongside all of these processes, the brain can enter a potentially chronic neuro-inflammatory state with activation of microglia and astrocytes and infiltration of peripheral immune cells [47,48].

Imaging

Imaging is an important tool to detect and quantify RIBD in a patient over time. Radiation responses on molecular and cellular levels can result in anatomical and functional changes that can be visualised using MRI and PET based imaging [40,49]. Novel high-resolution techniques enable a more intricate and early evaluation of microstructural changes [50].

Anatomical changes in the grey matter that have been observed in the first year after radiotherapy include volume loss of the hippocampus [51,52], atrophy of the amygdala [53], and thinning of the cerebral cortex [54,55]. In the white matter, radiation-induced changes become apparent as either volume loss or white matter lesions that can be visualised on conventional MRI [56,57]. However, diffusion tensor imaging is a more sensitive MRI technique, which enables early detection of microstructural changes in the white matter [58–61]. White matter lesions may represent various pathophysiological processes including degeneration and cell loss, demyelination, astrogliosis and ischemic (micro)vasculopathy [62]. The grey matter and white matter display regional differences in radiation sensitivity [63–65]. Other anatomical changes that are seen after radiation include vasogenic brain oedema resulting from an increased blood–brain barrier permeability, and cerebral microbleeds due to structural damage to the microvasculature [50].

Functional changes can already be observed after radiation in the absence of any overt anatomic pathology. MRI spectroscopy is a functional imaging tool to detect and characterise alterations in metabolism. Neuronal damage can be signalled by changes in the chemical constituents. Within months after radiation treatment, signs of neuronal dysfunction can be observed [66,67]. Functional MRI and perfusion MRI measure neuronal activity indirectly through the measurement of changes in blood oxygenation and blood flow. Decreased neuronal activity can be found up to several months after radiotherapy in the higher dose regions [68,69]. Another interesting method to detect functional changes in the brain is by the use of PET imaging. Several PET tracers are already available for imaging of relevant processes involved in RIBD, including tracers for activated glial cells, cerebral blood flow, neuronal integrity, blood–brain barrier permeability, synaptic density, myelin density and various neuro-receptors and transporters [70–74]. So far, however, there is only limited data in the RIBD field [75].

Clinical course

The clinical presentation of RIBD is diverse, including both general and more specific symptoms and impairments [76]. The clinical course typically consists of an acute or early phase (during treatment, lasting up to 12 weeks post treatment) and a late-delayed phase (months to years after treatment). In the early phase general symptoms, including fatigue and somnolence resulting from brain oedema and transient demyelination, are the drivers of the clinical picture. The late-delayed phase is characterised by decline in NCF usually within multiple domains, showing a pro-

gressive worsening over time. Late radiation-induced NCF decline is a result of structural and functional brain damage, and the expressed clinical profile is dependent on the anatomical regions involved [77].

Several factors inhibit the opportunity to perform high-quality clinical studies necessary to increase our understanding of the clinical impact of RIBD [78,79]. No neurocognitive test has been developed for frequent repetitive evaluations, available tests are not adapted for use in neuro-oncological patients, and test batteries require specialised experts and are time-consuming for patient and caregiver. Finally, there is no systematic way to objectively quantify and grade the severity of neurocognitive impairments.

NCF decline occurs systematically after partial and whole brain radiation for primary and secondary brain tumours [26,33,80], as well as patients with head and neck tumours [81]. Advanced radiotherapy techniques with overall less radiation exposure to the brain (dose and volume reduction) compared to more conventional techniques improve neurocognitive outcome. This has been shown for photon techniques in patients with brain metastases and low grade brain tumours [80,82], as well as proton versus photon techniques in paediatric brain tumour patients [83,84]. The hippocampi are a relevant subvolume of the brain for NCF endpoints. Selective sparing of radiation dose to the hippocampi in whole brain radiation for brain metastases results in better preservation of memory function [85,86]. And several other studies in low grade and paediatric brain tumour patients report on dose–effect relationships in the brain [87–89]. Even though these studies are conducted in a variety of patient groups, and no high-quality NTCP model has been developed yet, these studies confirm the proof of principle that less radiation dose to the brain leads to better NCF outcome in brain tumour patients.

Dutch eligibility criteria for proton therapy in LGG and other intracranial tumours

We can conclude that radiation to the brain can induce damage through the initiation of several pathophysiological processes. This RIBD results in clinically meaningful NCF decline and is a major concern in patients with favourable long-term prognosis that require radiotherapy early in their disease course. Proton therapy offers the opportunity to significantly reduce the radiation exposure to the brain (dose and volume reduction) without compromising on efficacy. It is plausible that this reduction in radiation exposure to the brain will lead to better clinical outcome of treatment in terms of toxicity. The patients that are expected to benefit most from proton therapy have a long prognosis and good clinical performance before start of therapy.

In the Netherlands, the most favourable LGG patients with an indication for radiotherapy are eligible for proton therapy. Eligibility criteria are: (1) good prognosis, defined as an expected 10-year survival of 50% or higher; (2) good clinical and neurocognitive status prior to radiotherapy, defined as a Karnofsky performance status of 80 or higher and iADL independent function; (3) dose benefit of proton therapy over photon therapy, defined as more than 5% dose reduction to the supratentorial brain and/or both hippocampi outside the target volume. This last criterion serves as a quality check, to assure that no patients are treated with proton therapy that would have better dosimetrics with (stereotactic) photon therapy. Due to the typical size and lateralisation of the treatment volumes in LGG patients, this parameter does not contribute much to LGG patient selection and is more relevant for other intracranial tumours with more central location and/or small target volume. An illustrative LGG case is presented in Fig. 1.

Patients with anaplastic glioma, who fulfil all the above-mentioned criteria, are eligible as well. However, the higher dose prescribed for these tumours and consequential toxicities that

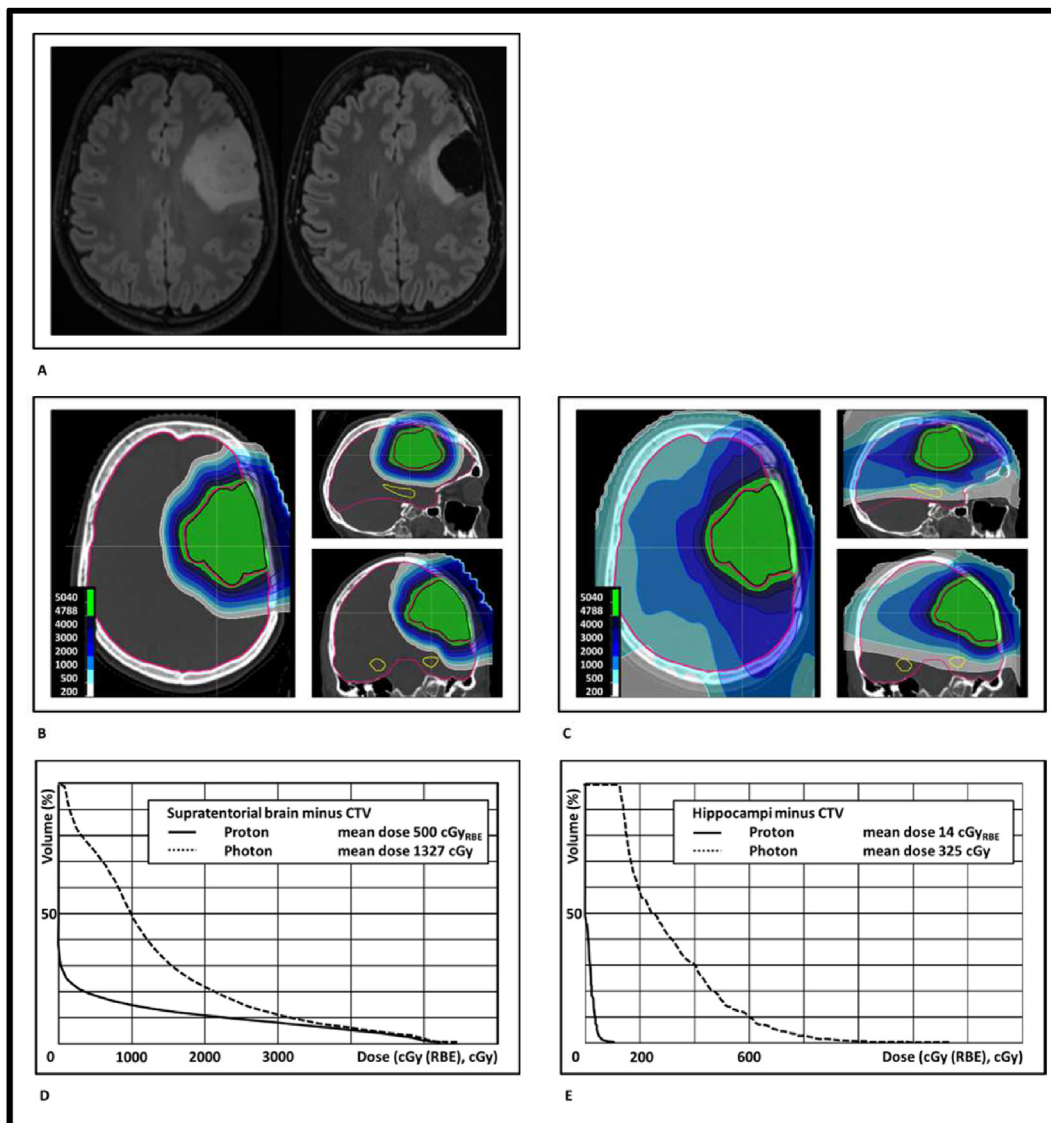


Fig. 1. Illustration of a typical LGG case selected for proton therapy in the Netherlands. (A) 38 year old woman, presentation with epilepsy only and a left frontal tumour on FLAIR MRI (left). Using an advanced neurosurgical technique (awake craniotomy) maximum safe sub-total resection was performed, FLAIR MRI (right). Post-operatively the patient remained in a good clinical condition (Karnofsky score 90) without any neurological deficits and good neurocognitive performance (iADL independent functioning). Pathological examination of the tumour showed an oligodendroglioma WHO grade II, with complete co-deletion of 1p and 19q and IDH 1/2 mutation. The estimated 10 year survival with adjuvant radiotherapy and chemotherapy is 80% [11]. This patient is at risk for radiation-induced NCF decline. (B and C) The dose distribution using a 2 field, intensity modulated, proton technique (B), and a volumetric intensity modulated arc photon technique (C) is shown. Both plans are optimised on supratentorial brain (pink) and hippocampi (yellow) dose, assuring adequate robust dose to the CTV (black). With the photon technique there is an inevitable low - intermediate dose bath to a large volume of brain. With the proton technique a large volume of brain receives zero dose. (D and E) The dose difference in the supratentorial brain minus CTV (D) and both hippocampi minus CTV (E) using protons instead of photons is 62% (8.27 Gy) and 96% (3.11 Gy) respectively. This dose reduction is accepted as being clinically relevant.

could potentially be more substantial with proton therapy [21,22], should be weighted as well. Other tumour entities in or around the brain with similar or better prognosis than LGG, are also eligible for proton therapy, provided that the dose to the brain with photon treatment becomes relevant (i.e. small targets are preferably treated with stereotactic techniques).

Towards model-based selection

The development of NCF-based NTCP models in LGG patients is a laborious but essential effort to move forward. Being able to predict the impact of radiotherapy can not only support patient selection for proton therapy (or other technological radiotherapy innovations) but will also help decision making during treatment planning and may even give some direction on choosing the optimal timing of radiotherapy.

Implementation of structural evaluation of NCF in routine clinical practise is challenging. Subjective evaluations using PROMs are not correlated to objective evaluations [90]. Short screening tools such as the Minimal Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) have a low sensitivity for detection of NCF impairments in LGG [91]. Therefore a battery of neuropsychological tests, covering multiple NCF domains, is recommended to evaluate NCF [78,92]. Since there is a potential bias when re-testing a patient, the timing of these evaluations should be planned strategically and not too frequent. At this moment the applicability of the CTCAE [93] is limited for grading any NCF-based endpoint. Evaluation of iADL along with NCF might prove to be useful, to grade the severity of NCF impairments and give more clinical meaning to these endpoints.

The brain volumes that need to be looked into include supratentorial brain, infratentorial brain or cerebellum, brainstem and specific subvolumes of the brain such as the hippocampi [13,89]. Other volumes that might be of interest include brain areas that can be assigned to a specific NCF-based endpoint, as well as specific white matter tracts or brain nuclei and cortex [94]. However, the brain is the most intricate, complex organ of the human body: the brain does not contain independent functional units [95]; functional brain areas can change over time (plasticity) [96]; and the communication within the brain through neuronal networks is a phenomenon that we are only just beginning to understand [97].

LGG is a relatively rare disease, and collaboration within the radiation oncology society is necessary to obtain large datasets needed for model development and validation. In the Netherlands we expect to treat at least 100 LGG patients per year with proton therapy, for whom all relevant patient, tumour and treatment characteristics are registered. Prospective evaluation of NCF with a standardised neuropsychological test battery (including the Hopkins Verbal Learning Test, Trail Making Test part A&B and Controlled Oral Word Association test), as well as fatigue and iADL evaluations are mandatory for patients receiving proton therapy and strongly advised for patients receiving photon therapy or wait and scan approach. Patients are evaluated at start of treatment and every 2.5 years thereafter. A large variability in dosimetrics of brain and substructures of the brain is expected since the selection criterion for dose advantage with protons has a low threshold of 5%, which is easily met for LGG patients. This variability will facilitate the assessment of dose effect relationships in the brain and substructures of the brain. The first analysis of the collected data is planned after the first 100 patients have had their 5 year follow-up evaluations [clinicaltrials.gov identifier expected soon]. A national electronic infrastructure to share and manage the data is being created. Where-as these mandatory clinical evaluations are already implemented in the Netherlands, similar efforts are currently ongoing within the European Particle Therapy Network as well.

Discussion

This paper specifically describes the Dutch approach for selecting LGG patients for proton therapy. Since the financial, political and health care landscape is unique to every country, the purpose of this paper is not to dictate but merely to inform practitioners about the Dutch policy. At present, there are three Proton Therapy Centre's (PTCs) in the Netherlands, all are affiliated to large academic radiation oncology departments. The geographic distribution is in such a way, that proton therapy is easily accessible to almost all patients without the need for on-site accommodation. The extra treatment delivery costs of proton therapy are financed through an obligatory social medical insurance system.

In patients with favourable LGG and expected long survival, radiation-induced NCF decline is of major concern. Since the main goal in treating these patients is not only to optimise survival but also to minimise toxicity and preserve quality of life, several radiation technique innovations have been implemented over the years with the aim of reducing dose to the brain and specifically the hippocampi as a relevant substructure of the brain for NCF endpoints. Innovations that are now considered standard of care include: more complex and conformal techniques (intensity modulated and stereotactic techniques), image guided delivery of treatment, and MRI guided target definition. Proton therapy is the next step in this technical evolution of radiotherapy, combining high conformity of prescribed dose to the target with avoidance of circumstantial intermediate to low dose to large volumes of brain. Most technical innovations in radiotherapy are implemented with

out results from RCTs based on the As Low As Reasonably Achievable (ALARA)-principle. However, considering the magnitude of costs involved and the influence on patients and caregivers, it makes sense that for proton therapy different requirements for clinical implementation apply.

Obtaining level 1 evidence in LGG is challenging, due to the low incidence and long-term overall survival of patients that may exceed 10–15 years after completion of treatment. Studies typically have long running times and by the time results are published, there is a likelihood of significant policy changes that may hamper the interpretation of the data. In addition, radiotherapy specific conclusions from clinical studies are impeded because technical developments move into clinical practise rapidly. The techniques used in clinical studies will therefore be regarded as out-dated at the time definitive results become available. Whether we will be able to obtain level 1 evidence on proton therapy through a RCT in LGG is questionable. In the Netherlands, it was concluded that a RCT *photons versus protons* in LGG was not feasible for several reasons: (1) the primary endpoint should be NCF, since differences in NCF after radiotherapy are not expected to be significant within the first years after treatment, a long follow-up time is necessary; (2) low patient numbers and several significant confounding factors will imply a long accrual time; (3) a large budget is needed, since the finances for proton therapy (being the experimental arm) will not be covered by medical insurance; and (4) concerns about the caregivers and patients motivation to contribute or participate: whether there is true clinical equipoise can be debated. However, at least one randomised phase II trial is currently open in the United States [clinicaltrials.gov identifier NCT03180502], and another randomised trial is being initiated in the United Kingdom [98]. The progress and results of these studies are followed with great interest.

Model-based selection is an alternative scientific approach for implementation of proton therapy, accepted in the Netherlands by health care authorities [4,5]. Unfortunately, the model-based approach is not achievable in LGG patients, since the essential data to quantify the effect of dose reduction on the brain or relevant brain substructures such as the hippocampi is either lacking or of poor quality. Also the often quoted hippocampus model by Gondi [89] did not pass the minimal quality requirements for model-based selection [5]. Within the Netherlands Society for Radiation Oncology, there was a preference for introducing proton therapy as a standard radiation option for selected LGG patients: an empirical approach. This does not imply that every eligible LGG patient should be treated with proton therapy. The national indication protocol for proton therapy is merely a tool for a careful clinical implementation of proton therapy and making proton therapy an insured treatment option for eligible patients. However, there will be patients that prefer to be treated closer to home, without referral to a PTC. Whether or not the patient is referred for proton therapy is a typical example of shared decision making between the radiation oncologist and patient in the local treatment centre.

Finally, the clinical introduction of proton therapy for LGG patients in the Netherlands should be considered an academic approach. The current data on radiation induced NCF impairments in LGG patients consists of low-certainty evidence and the magnitude of the radiotherapy impact is uncertain. It is a challenge to investigate, in this young research niche, the true value of proton therapy. However, each PTC is affiliated to at least one large academic radiation oncology department and it is mandatory to prospectively evaluate NCF by a standard neuropsychological test battery in every patient that receives proton therapy. This centralization and intensification of care will be the foundation for many research projects, both local and (inter)national. The focus will be on developing NTCP models for NCF outcome after radiotherapy,

to enable model-based selection for proton therapy in LGG patients in the future.

In conclusion, well-selected patients with LGG and other intracranial tumours have favourable prognosis, with overall survival rates extending beyond 10 years. A significant subset of patients is treated with radiotherapy early in the disease course, and late radiation-induced NCF effects are of major concern. There is convincing evidence that radiation to the brain impairs NCF. It is plausible that reducing radiation dose to the brain by using proton therapy is clinically relevant in selected patients. Since there are multiple factors in LGG patients affecting NCF outcome, radiation effects are not expected to become detectable and clinically relevant within the first years after treatment.

Proton therapy is an approved radiotherapy option for selected LGG patients by health care authorities in the Netherlands. In the coming years collaborative efforts will be made within the Netherlands Society of Radiation Oncology to prospectively evaluate and register NCF outcome data with the intention to develop NCF-based NTCP models to enable model-based selection in the future.

Conflict of interest

None.

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