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Original Research Article

# Selection for proton radiotherapy of grade 1–3 glioma patients

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ABSTRACT

*Background:* For adult patients with grade 1–3 gliomas, identifying patients with an indication for proton therapy (PT) can be challenging due to sparse evidence supporting its benefits. In this study, we aimed to ensure national consensus and develop a decision support tool to aid clinicians in identifying patients with grade 1–3 gliomas eligible for PT.

*Methods:* Sixty-one historic patients referred for postoperative radiotherapy for glioma grade 1–3 were included in this study and had new photon therapy and PT plans calculated. These plans along with clinical parameters were presented to neurooncologists with experience in treating brain tumours. The patients were presented at three workshops (WSs), where each neurooncologist individually had to choose between photon and proton therapy. Important parameters were selected using cross validation. Multivariable logistic regression was used to predict the neurooncologists' treatment modality choice.

*Results:* At the three WSs 23, 24 and 19 randomly selected patients were presented. Seventy-five percent of the neurooncologists agreed for 14 patients (61%), 16 patients (67%) and 15 patients (79%) at WS1, WS2 and WS3. Age at radiotherapy and difference in mean dose (ΔDmean) to the residual brain were significant predictors of the choice of treatment modality, $p < 0.001$. Model coefficients were: $\beta_{age} = 0.07$ per year (95% confidence interval [CI] = 0.05–0.09), and $\beta_{\Delta dose} = -0.27$ per Gy (95% CI=-0.36–0.18).

*Conclusion:* Higher degree of agreement was reached. Age and ΔDmean to the residual brain significantly predicted the choice of radiation modality. We have developed a decision support model which may aid in the selection of patients with glioma grade 1–3 to PT.

## Introduction

Proton therapy (PT) is a promising radiotherapy option for brain tumour patients due to its physical properties, enabling reduction in normal tissue radiation dose while maintaining the dose to the tumour volume. In Denmark, a national health insurance system provides every citizen with the right and access to free treatment at hospitals including PT, if indicated. However, not all patients have a significant clinical benefit from receiving PT, thus identifying the right patients to receive proton or photon therapy (XT) is of great interest and will depend on many factors: diagnosis, prognosis, treatment side-effect, co-morbidity and others.

In Denmark and the Netherlands, a model-based approach is utilised for certain diagnoses, e.g. head-and-neck cancers. Here, patients are referred to PT based on a comparison of normal tissue complication probability (NTCP) models for given endpoints [1–4]. In the

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Netherlands, proton therapy is a standard insured care for selected patients with low-grade glioma (LGG) who have a good performance status and an expected survival of more than 10 years [5]. For these patients, the reduction of radiation-induced long term side effects and preservation of patients' neurocognitive function (NCF) will have a high priority. Aside from radiation necrosis, vision impairment and hearing loss, high level evidence data is not currently available about normal tissue complication in brain cancer patients. The data collected so far is based on small, heterogeneous populations, limited follow-up time and several different tools for testing patients' NCF. Other factors, such as the tumour itself including location, chemotherapy, antiepileptic drugs and surgery may also affect NCF [6]. Certain brain areas appear to be more sensitive to radiation, e.g. the low-dose bath to the left side of the brain has been correlated to poorer performance in NCF tests in a study of 17 LGG patients [7]. One of the models used in clinical practice to assess delayed verbal recall in relation to hippocampal dose, as developed by Gondi et al. [8] was based on a limited number of patients with different diagnoses who received variable dose prescriptions. However, the conclusions from this study could not be confirmed in the studies by Haldbo-Classen nor by Jaspers et al. [9–10], which involved larger groups of patients. This highlights the absence of consolidated evidence with respect to NCF and dose in the scientific community.

The treatment selection for LGG is therefore partly based on individual clinicians' judgement and interpretation of the incomplete available data and may become subjective. Danish patients with grade 1–3 gliomas are referred to a national plan comparison conference, where neurooncologists from all four referring centres treating patients with brain cancer meet. Based on the experience of the neuro-oncologists, dosimetric parameters, age and the patient history, a decision is made whether to recommend PT or XT. Therefore, this study aimed to organise national workshops to test the variability between trained neurooncologists, identify the most relevant clinical and dosimetric parameters and develop a logistic regression-based decision support tool to ensure national consensus when Danish neurooncologists refer grade 1–3 glioma patients to PT.

## Materials and methods

### *Historic patient data*

Patient data from 71 adult patients with grade 1–3 gliomas (astrocytoma grade I-II and oligodendroglioma grade II-III) treated with XT in Denmark and seven patients treated with PT abroad from 2013 to 2018 was identified in the Danish Neuro-oncology Registry (DNOR) [11]. Clinical parameters collected were: age, diagnosis, type of surgery, and contrast enhancement on T1 weighted MRI, tumour location, tumour size, performance status, and neurological symptoms (Table 1 and supplementary Fig. S1). Only patients with a complete dataset, i.e. magnetic resonance imaging (MRI) and computed tomography (CT) scans, structure sets and sufficient clinical information were included in this study, resulting in the final dataset of 61 patients, 54 previously treated with XT and seven previously treated with PT (see Table 1).

### *New photon and proton therapy treatment plans*

Target volumes were copied from the clinical treatment plans, and the delineations of organs at risk (OAR) were adjusted according to Danish national guidelines [12]. New XT and PT treatment plans were generated for all patients. Details on the treatment planning are listed in the paper by Byskov et al. [13]. Briefly, the applied dose prescription in the present study was 50.4 Gy in 28 fractions for all patients to the planning and clinical target volume. PT plans were manually optimised in Eclipse TPS v13.7 (Varian Medical Systems, Inc., Palo Alto, CA, USA, Ver) by two medical physicists, JFK and CSB, and photon plans were optimised with Pinnacle Autoplan v16.2 (Philips Healthcare, Eindhoven, The Netherlands) by one medical physicist, CRH.

**Table 1**
Patient characteristics.

| | n | % |
|---|---|---|
| **Total patients** | 61 | 100 |
| **Age at RT (Years)**Median | 45 | |
| (IQR) | (34–59) | |
| **Diagnose** | | |
| Diffuse astrocytoma | 37 | 61 |
| Oligodendroglioma | 16 | 26 |
| Anaplastic astrocytoma | 4 | 7 |
| Pilocytic astrocytoma | 2 | 3 |
| Anaplastic oligodendroglioma | 2 | 3 |
| **Clinical target volume ($cm^3$)**Median | 189 | |
| (IQR) | (140–275) | |
| **Surgery** | | |
| Biopsy | 17 | 28 |
| Partial resection | 13 | 21 |
| Complete resection | 11 | 18 |
| NA | 20 | 33 |
| **Laterality** | | |
| Left | 35 | 57 |
| Right | 22 | 36 |
| Midline | 4 | 7 |
| **Location** | | |
| Frontal | 33 | 54 |
| Parietal | 11 | 18 |
| Temporal | 10 | 16 |
| Thalamus | 3 | 5 |
| Brainstem | 1 | 2 |
| Corpus callosum | 1 | 2 |
| Occipital | 1 | 2 |
| Basal ganglia | 1 | 2 |
| **Performance Status (WHO)** | | |
| 0 | 34 | 56 |
| 1 | 23 | 38 |
| 2 | 4 | 7 |

### *Workshop setup*

Three WSs were arranged where neurooncologists from the four referring Danish neurooncology centres and from the DCPT individually assigned each patient to XT or PT treatment based on the clinical parameters and the treatment plans. At least one neurooncologist with experience in treating glioma patients from each department (i.e. at least five neurooncologists) had to be present at all three WSs.

The neurooncologists had to choose the preferred treatment based on the available parameters only, thus not considering, e.g. patient address, time of onset etc (supplementary Fig. S1).

The first WS (WS1) was held in April 2019 (three months after the first patient was treated at DCPT), the second WS (WS2) was held in June 2021 and the last WS (WS3) in March 2022.

At WS1, 11 neurooncologists were present. Of these, seven were from the referring centres in Denmark, and four were from DCPT. Twenty-three cases were reviewed at this WS. At WS2, 10 neurooncologists were present, six from the referring centres and five from DCPT. Here, 19 new cases were reviewed, and five cases from the first WS to evaluate the level of scoring consistency. At WS3, eight neurooncologists were present, six from the referring centres and two from DCPT. At this WS 19 cases were reviewed. An arbitrary agreement threshold was set as at least 75% of the neurooncologists agreeing on the referral decision at each WS.

### *Data analysis for decision support tool*

To predict the neurooncologists' treatment modality choice, a multivariable logistic regression model was developed. Tested input parameters (predictors) were: age, diagnosis, type of surgery, contrast enhancement on T1 weighted MRI, tumour location, tumour size, performance status, neurological symptoms, difference between photon and proton (Δ) $D_{mean}$ of residual brain (brain – CTV – brainstem),

$\Delta D_{mean}$ of hippocampus L, hippocampus R and pituitary.

To avoid overfitting, the parameter selection process was done through 5-fold cross-validation best-subset, where all parameter combinations were tested in four folds and validated in the last fold. For each model the fitting error was estimated. From this, the optimal model was selected (full model), and the reduced model, with a similar performance, was selected. Logistic regression with the features from the reduced model was fitted to the data and the model accuracy was evaluated in the independent test set from WS3 using the area under the Receiver-Operating-Characteristics (ROC) curve analysis.

Differences between the two scorings of five selected patients from WS1 and WS2 were tested with Student's paired T-test and a p-value $<$ 0.05 was considered significant.

## Results

### *Treatment modality selection*

At WS1, at least 75% of neurooncologists agreed on the treatment modality for 58% of the patients (Fig. 1). Of these, four were selected for XT and 10 for PT. At WS2, the number was 67%, where only one patient was selected for XT, and 15 were selected for PT. At WS3, clinicians agreed in 79% of cases where two were selected for XT and 13 patients for PT. Two patient cases are shown in Fig. 2 where neurooncologists disagreed and reached total agreement, respectively. No statistically significant difference in the treatment modality selection was seen for the five patients who were scored at both WS1 and WS2 ($p = 0.2$).

### *Feature selection*

Best subset analysis resulted in a full model with six relevant parameters (age at RT, performance status, neurological symptoms, residual brain $\Delta D_{mean}$, left hippocampus $\Delta D_{mean}$, pituitary $\Delta D_{mean}$) while the simplest model resulted in a two-parameter model. The model features in the reduced model were age at RT and residual brain $\Delta D_{mean}$ ($p < 0.001$) and these were used in a logistic regression model (Fig. 3). Model coefficients were: $\beta_{age} = 0.07$ per year (95% confidence interval [CI] = 0.05–0.09), and $\beta_{\Delta dose} = -0.27$ per Gy (95% CI=-0.36–0.18). The odds ratio (OR) for a $\Delta D_{mean}$ of 10 Gy and a decrease in age of 10 years was 2.06 for a patient of age 45 years and a $\Delta D_{mean}$ to the healthy brain of 17.3 Gy.

### *Model validation*

The model was validated on the patients from the final workshop (n = 19). The validation resulted in an accuracy of 0.84. The area under the curve was 0.87. The calibration plot between workshop and model results is shown in Fig. 4.

## Discussion

As a national centre, it is of utmost importance to ensure equal access to highly specialised PT for all glioma patients, regardless of their place of residence in the country. For this reason, we defined strict selection criteria for brain tumour patients who will need RT. These criteria included age, WHO performance status and cognitive functioning, tumour histology, tumour markers (i.e. IDH1) and differences in dose-volume parameters in comparative treatment planning. Differences in dose-volume criteria are often decisive for the outcome of the selection process and despite their objectiveness they may not always have the highest relevance for this process. We therefore wished to test the neurooncologists preferences, allowing them to include objective as well as subjective criteria and weights of criteria.

In this study, we have developed a decision support tool, which can be easily implemented in the clinic and help in daily decision-making when choosing which patients with grade 1–3 gliomas may be referred to PT. Our model provides an evaluation of the patients based on Danish expert opinions. The model is now implemented in Eclipse as a Scripting application programming interface at DCPT [14] and can be used for national plan comparison conferences, provided that both an XT

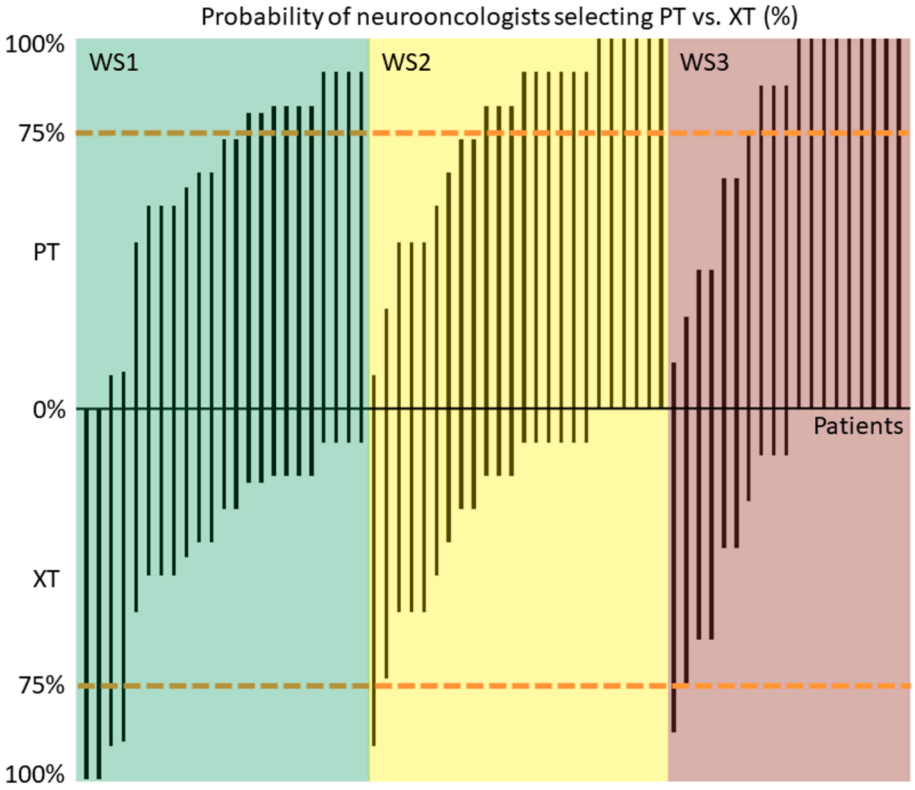


**Fig. 1.** Probability of neurooncologists selecting proton therapy (PT) or photon therapy (XT) for each patient at workshop (WS) 1, 2 and 3.

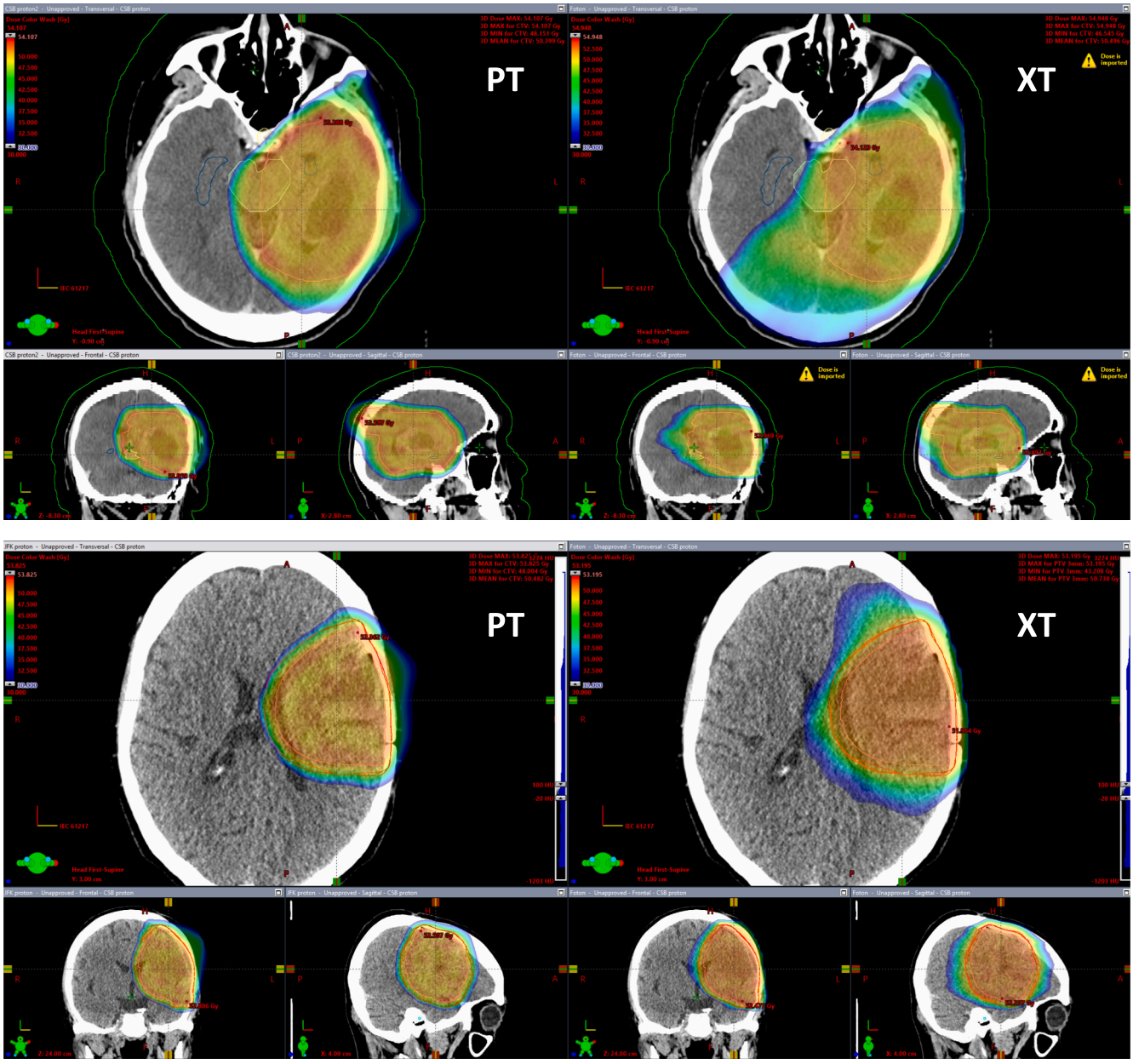


**Fig. 2.** Example of a case where neurooncologists disagreed on the choice of treatment modality (top). At the first workshop, 55% chose proton therapy for this patient who was 60 years old at RT. Bottom: An example where total agreement was reached among neurooncologists and all chose proton therapy. This patient was 38 years old at RT. PT: Proton therapy, XT: Photon therapy.

and a PT plan have been optimised. The plan comparison conference may even be unnecessary for cases where the model would predict PT or XT with a 75% probability or more, resulting in less time spent on the decision process. Also, if dose prediction models are used to predict the dose to the residual brain based on tumour size and position, this could alleviate the time and resource consumption taking place before the patient referral decision. The most significant variables in the decision making process were age, corresponding to life expectancy, and difference in mean dose to the healthy brain which may play a role for the degree of treatment side effects. These parameters were also found to be important for Swedish patients with LGG referred to PT as described in the paper by Ek et al. [15]

There are some limitations to the design of the present study. First of all, for the neurooncologists to make truly individual selections during the WSs, they should have had no interactions at all with each other. The fact that national plan comparison conferences were ongoing throughout this project has indeed given rise to some bias. At the conferences, certain criteria were set up in the selection process, e.g. a dose reduction of $>$ 20% in the volume of the healthy brain receiving 30 Gy ($V_{30}$) for patients more than 45 years old would result in PT (Supplementary Table S1). These criteria undoubtedly played a role in the WSs.

In this project we have tried to include the most relevant clinical parameters for selecting treatment modality. The parameters were extracted from DNOR [11]. However, during the WSs we found some of the parameters to be erroneous. For these parameters to be adequate for the neurooncologists in their selection process, they should have been externally validated before the WSs.

Clinical guidelines for PT dose planning were updated according to improved planning strategies during the project. The final WS was held three years after DCPT started treating patients, and a RapidPlan® model was implemented and available for all PT plans at this WS. This

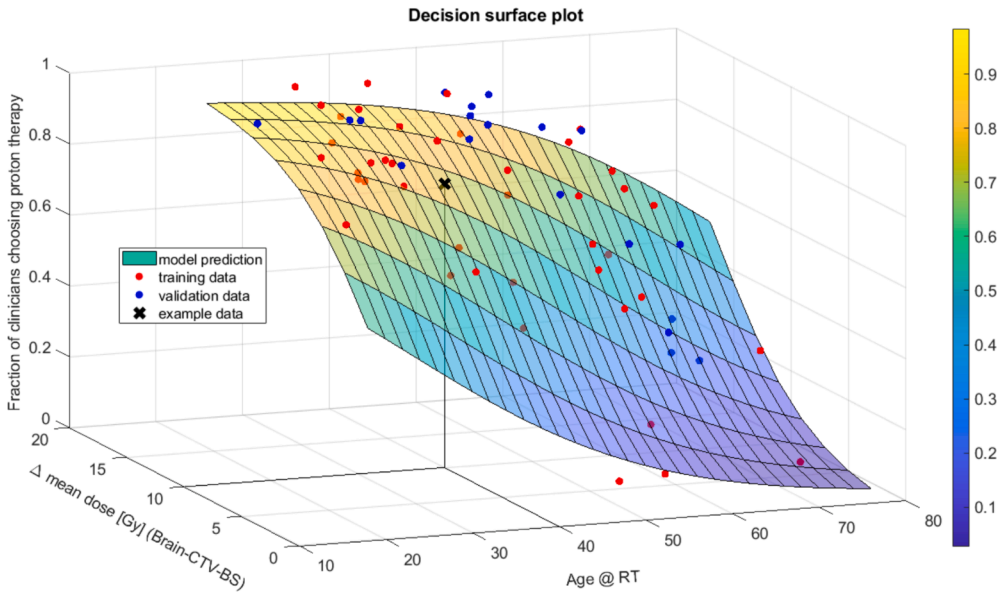


**Fig. 3.** Decision surface plot with two predictor variables; age at radiotherapy and difference in mean dose to the residual brain (Brain-CTV-brainstem). Both are predictors for the fraction of oncologists choosing proton therapy. The red dots are each individual patient in the training data. Blue dots are patient validation data points. The **X** is an example of a 40-year-old patient with a 10 Gy reduction in dose to the residual brain with proton therapy. According to our decision surface, approximately 70% of oncologists would prefer proton therapy for this patient.

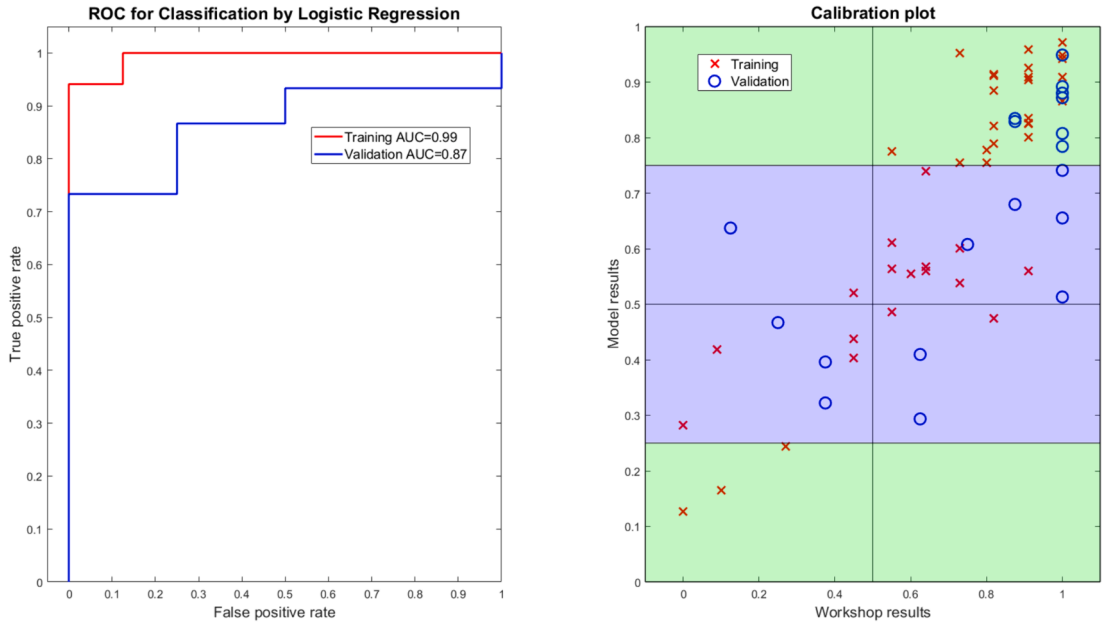


**Fig. 4.** Left: Receiver operating characteristics (ROC) curve for training and validation of the decision support model. Area under the ROC curve was 0.99 for training and 0.87 for validation. Right: Calibration plot between workshop data and model results. Points in the lower left and upper right quadrant are predicted correctly by our model. The light green areas correspond to a model threshold of 25% and 75%, above where the model would predict all patients correctly.

resulted in more optimal PT plans towards the end of the project and may also have influenced the neurooncologists decisions. Also, a 2 mm setup uncertainty was used instead of 3 mm in the treatment plans for WS3, which will also have influenced the dose distribution. This may explain the trend that clinicians agreed more towards the end of the project (Fig. 1). Furthermore, at the time of WS1, treatment at DCPT was still in the start-up phase, and clinicians were perhaps more reluctant to proton therapy. At the end of the project and at the final WS, many patients had been discussed at the national plan comparison conferences, and a more general consensus about which patients to refer to PT may have been reached.

Unfortunately, not all of the neurooncologists could attend all WSs. However, the group of six neurooncologists who attended all WSs are also neurooncologists from each referring centre in Denmark and thus represented the group of neurooncologists who usually attends the national plan comparison conferences.

The decision of treatment modality will, of course, never be based upon age and reduction in dose alone. The neurooncologist will always consider several clinical parameters, the patient's history, etc. Furthermore, patients' wishes may also influence the decision. The development of high-quality NTCP models would be an important improvement in the treatment modality selection for this group of patients, however,

this would require phase III clinical trial data which is not currently available. Medico-economical models are not taken into consideration in the selection of Danish patients due to the national health insurance system. In future Danish cases, very young patients and patients with either limited or a very large dosimetric benefit of PT compared to XT can be omitted from the national plan comparison conference, saving valuable time in the daily clinical workflow. From our results in this study, eight of 19 patients (42%) were selected correctly based on age and reduction in healthy brain $D_{mean}$ if a model threshold of 75% agreement is set (Fig. 4). In future work we will validate the model on patients at the national plan comparison conferences also including other brain tumour diagnoses and dose prescriptions.

In conclusion, we have determined the most important parameters used by neurooncologists in the decision-making when referring grade 1–3 glioma patients for proton therapy in Denmark. We have developed a decision support tool to aid in this process and have successfully conducted national workshops to ensure a broad national consensus in the referral process.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve the scientific writing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## CRediT authorship contribution statement

**C.S. Byskov:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration, Funding acquisition. **A. Muhic:** Resources. **R.H. Dahlrot:** Resources. **C.A. Haslund:** Resources. **T.L. Guldberg:** Resources. **M. Høyer:** Resources. **P.W. Nyström:** Resources. **L. Dysager:** Resources. **S. Hansen:** Resources. **L. Haldbo-Classen:** Resources. **A.K. Trip:** Resources. **Y. Lassen-Ramshad:** Resources. **B. Weber:** Resources. **S. Lukacova:** Resources. **C.R. Hansen:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Supervision, Funding acquisition. **J.F. Kallehauge:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Supervision, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100836.

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