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Original paper

A Pipeline for MRI-Guided dose painting by number radiation Therapy: GLIORAD – a phase I-II clinical trial in recurrent glioblastoma

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Highlights

- Development of a complete workflow for the application of the dose painting by number technique in a clinical setting.
- Use of the apparent diffusion coefficient derived from MRI-DWI imaging as biomarker for dose painting by number technique.
- Treatment of recurrent glioblastoma patient with dose painting by number technique.
- Assessment of plan quality and robustness in case of dose painting by number technique.

Abstract

Background/Objectives

The dose painting by number (DPBN) technique is a radiotherapy approach guided by imaging biomarkers. This paper investigates the physical/technical aspects addressed in a phase 1–2 study (GLIORAD, NCT04610229) employing the DPBN technique on patients affected by recurrent glioblastoma.

Methods

The DPBN approach was employed on 12 patients, converting the pixel-by-pixel Apparent Diffusion Coefficient map to a prescription dose ranging from 30 to 50Gy in 5 fractions. The DPBN maps were discretized in a patient-specific number of levels (DPBC), prescribing a different dose to each level. The agreement between the calculated dose distribution (TDD) and DPBC map was assessed. Plan quality and robustness against geometric uncertainties were evaluated. Patient-specific quality assurance was performed before treatment, and the agreement between measured and calculated doses was assessed with the γ metrics.

Results

A good agreement between DPBN and DPBC maps was observed with a median[range] of the quality factor introduced by Vanderstraeten of 0.067[0.038; 0.137]. In addition, the agreement between TDD and DPBC map was of 0.77[0.44; 0.93], indicating satisfactory conversion in deliverable dose distribution. All plans resulted to be deliverable with a median [range] of γ(10%) of 98.55% [88.3; 99.9] and robust against geometric uncertainties with a dose difference to the 99% of the volume < ±5% in 11/12 patients.

Conclusion

The workflow of DPBN approach for recurrent GBM was investigated.

The plan quality, robustness, and deliverability were reported and discussed, and the technical feasibility of the voxel-based DPBN approach in a standard clinical setting was demonstrated.

Introduction

Glioblastoma multiforme (GBM) is the most common malignant brain tumor occurring in adults [1]: the standard of care for patients with GBM is currently surgery followed by adjuvant chemotherapy with temozolomide combined with radiotherapy. Research studies have shown that more than 90% of all GBMs recur near the surgical cavity between 32–36weeks after surgery [2], [3]. To date, there are many therapeutic approaches for relapsed GBMs, although an optimal standard does not exist yet. Systemic therapy data from literature report an overall survival with chemotherapy of only 4–6months after relapse [3] while re-irradiation for relapsed GBMs has always been a controversial topic due to the risk of toxicity [4], [5].

Recently, Ciammella et. al. proposed a prospective experimental trial on dose-escalated stereotactic radiotherapy using an MRI voxel-based dose painting technique in patients affected by recurrent GBM [6]. Specifically, the dose painting technique involves the ability to create highly inhomogeneous dose distributions that allow selective irradiation of pathological areas at different risk of progression, identified by advanced imaging modalities, such as FDG-PET or MRI [7], [8]. From this concept, the term “dose painting by numbers” (DPBN) has evolved to distinguish that the dose prescription can be done on a voxel level and could potentially lead to a more effective radiation treatment than conventional treatment plans [9]. In particular, diffusion weighted imaging (DWI) can provide a quantitative measure of water diffusion through the apparent diffusion coefficient (ADC), an imaging biomarker directly derived by DWI [10]. Although the complex interactions between water and tissue microstructures have not been completely understood yet, in vitro and in animal models [11], [12], [13], [14] showed an inverse proportionality between tumor cellularity and the ADC values. More recently, this relation has also been confirmed in patient studies [15], [16], [17]. Starting from this evidence and considering that the cellular density is proportional to the number of clonogens, ADC value can be considered a surrogate of the cellularity and of the number of clonogens [18], [19] in brain tumors and the ADC maps could be used as a guide for dose redistribution so that the highest dose values would be delivered on volume with the lowest ADC values [18].

In a previous in silico work [20], the feasibility of the hypo-fractionated DPBN [21], [22], [23], [24], [25] approach guided by ADC maps on GBM recurrences with a Helical Tomotherapy was studied, with promising results on the treatment feasibility.

Considering the promising results reported in [20], a phase 1–2 study (GLIORAD, NCT04610229), which had as primary objective the evaluation of safety of GBM re-treatment using a dose painting process, was clinically conducted in our institution.

For this trial, the development of a workflow was required to permit an advanced integration of imaging techniques into the radiation treatment planning process.

This work aimed to study and report the application of the dose painting technique in a clinical setting, discussing and exploring the planning workflow, the delivery strategies, and the patient-specific QA related to this in-vivo prospective clinical trial.

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Section snippets

GLIORAD study design

The present study was approved by the Ethics Committee of the IRCCS-AUSL Reggio Emilia (approval number GLIORAD 15–18 approved on 16 September 2015, ClinicalTrials.gov ↗ identifier number: NCT04610229) and carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. In accordance with Italian legislation, written informed consent was obtained from all patients.

Twelve patients with relapsed GBM after standard surgery radio-chemotherapy treatment were enrolled …

Patient and plan characteristics

A total of 12 patients were enrolled and treated in this study and for each patient the workflow described in Fig. 1 was followed. All plans were generated considering the specific characteristics of each patient and were judged as clinically acceptable by expert radiation oncologists.

Median [range] of GTV volumes was 33.57 [7.00; 69.70]. The number of levels for target discretization had a median [range] value of 7 [4; 9]. In particular, the minimum level number corresponded to the minimum GTV …

Discussion

The idea of dose painting radiotherapy treatments is to escalate the dose to tumor volumes based on functional image data characteristics. In contrast with conventional radiotherapy, the DPBN approach provides a non-homogeneous solution in which the dose is voxel by voxel customized based on a specific quantitative biomarker.

In this study, the application of dose painting by numbers guided by the MRI ADC map was studied on a cohort of patients affected by recurrent GBM. In particular, we …

Conclusions

A phase 1–2 study was conducted on the possibility of DPBN approach for recurrent GBM patients. In this work, the workflow that permits the necessary integration between imaging techniques and radiotherapy planning process was described. The proposed method is independent from the TPS and can be generalized to any anatomical sites and imaging-related biomarker.

Plan quality, robustness and deliverability were reported and discussed, and the technical feasibility of voxel-based DPBN approach was …

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the IRCCS-AUSL di Reggio Emilia (approval number GLIORAD 15–18 approved on 16 September 2015, ClinicalTrials.gov ↗ identifier number: NCT04610229). …

Informed consent Statement

In accordance with Italian legislation, informed consent was obtained from all subjects involved in the study. …

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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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