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PII: S0150-9861(20)30131-0

DOI: https://doi.org/doi:10.1016/j.neurad.2020.02.005

Reference: NEURAD 895

To appear in: *Journal of Neuroradiology*

Please cite this article as: Szychot E, Youssef A, Ganeshan B, Endozo R, Hyare H, Gains J, Mankad K, Shankar A, Predicting Outcome In Childhood Diffuse Midline Gliomas Using Magnetic Resonance Imaging Based Texture Analysis, *Journal of Neuroradiology* (2020), doi: https://doi.org/10.1016/j.neurad.2020.02.005

PREDICTING OUTCOME IN CHILDHOOD DIFFUSE MIDLINE GLIOMAS USING MAGNETIC RESONANCE IMAGING BASED TEXTURE ANALYSIS

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ABSTRACT

BACKGROUND: Diffuse midline gliomas (DMG) are aggressive brain tumours, previously known as diffuse intrinsic pontine gliomas (DIPG), with 10% overall survival (OS) at 18 months. Predicting OS will help refine treatment strategy in this patient group. MRI based texture analysis (MRTA) is novel image analysis technique that provides objective information about spatial arrangement of MRI signal intensity (heterogeneity) and has potential to be imaging biomarker.

OBJECTIVES: To investigate MRTA in predicting OS in childhood DMG.

METHODS: Retrospective study of patients diagnosed with DMG, based on radiological features, treated at our institution 2007-2017. MRIs were acquired at diagnosis and 6 weeks after radiotherapy (54Gy in 30 fractions). MRTA was performed using commercial available TexRAD research software on T2W sequence and Apparent Diffusion Coefficient (ADC) maps encapsulating tumour in the largest single axial plane. MRTA comprised filtration-histogram technique using statistical and histogram metrics for quantification of texture. Kaplan-Meier survival analysis determined association of MRI texture parameters with OS.

RESULTS: 32 children 2-14 years (median 7 years) were included. MRTA was undertaken on T2W (n=32) and ADC (n=22). T2W-MRTA parameters were better at prognosticating than ADC-MRTA. Children with homogenous tumour texture, at medium scale on diagnostic T2W MRI, had worse prognosis (Mean of Positive Pixels (MPP): p=0.005, mean: p=0.009, SD: p=0.011, kurtosis: p=0.037, entropy: p=0.042). Best predictor MPP was able to stratify patients into poor and good prognostic groups with median survival of 7.5 months versus 17.5 months, respectively.

CONCLUSIONS: DMG with more homogeneous texture on diagnostic MRI is associated with worse prognosis. Texture parameter MPP is the most predictive marker of OS in childhood DMG.

Keywords: Children; diffuse midline glioma (DMG); diffuse intrinsic pontine gliomas (DIPG); magnetic resonance imaging (MRI); MRI based texture analysis (MRTA)

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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INTRODUCTION

Childhood diffuse midline gliomas most often form in the pons of the brainstem. These tumours, previously named diffuse intrinsic pontine gliomas (DIPG), account for 10 % of all childhood brain tumours and remain the biggest paediatric cancer killer [1]. Surgical resection is not feasible, because of the tumour location [2]. Irradiation therapy (RT) consisting of delivering 54 Gy during a 6-week period, has been the standard treatment alleviating symptoms [2, 3, 4, 5, 6]. The median overall survival of 9 months has not improved over the last 40 years despite multiple clinical trials. Less than 10% of children survive 2 years [1, 7, 8].

Accurate response assessment in clinical trials, before the start and during early treatment, is crucial to optimise therapy based on predicted outcome. Therefore, over the last decade different MRI biomarkers, such as apparent diffusion coefficient (ADC) values, tumour volume, and relative cerebral blood flow, have been extensively studied to evaluate the response of diffuse midline gliomas of the pons (DMG) to therapy [1, 9, 10]. Although

conventional magnetic resonance imaging (MRI) plays an essential role in diagnosing diffuse midline gliomas, none of the MRI parameters have value in predicting patients' survival [11]. Additionally, neuro-radiological criteria, such as McDonald, the World Health Organisation (WHO), the Response Evaluation Criteria in Solid Tumours (RECIST) or the Response Assessment in Neuro-Oncology (RANO) available in the literature to diagnose tumour progression, have not been validated in children [1, 12, 13]. The imaging challenge together with the short natural history of the disease hinder the evaluation of efficacy of possible novel therapies. The perspective of novel therapies for childhood diffuse midline glioma requires reliable means to evaluate tumour response, ideally early during treatment.

A considerable amount of work has recently been done on magnetic resonance imaging texture analysis (MRTA) as a tool to quantify tumour heterogeneity [14, 15]. Filtration-histogram based MRTA renders quantitative information about tumour texture features that are imperceptible to human visual assessment, such as distribution of pixel signal intensity values within the tumour [16]. In general, MRTA assesses the distribution of gray-levels within an image to obtain texture features that quantify intra-lesional heterogeneity [17]. Imaging tumour heterogeneity via MRTA could be a non-invasive tool that can enhance clinical care management by enabling the personalization of treatment plans based on predicted outcome. To date, there are no reports investigating whether MRTA in DMG can be used as an imaging biomarker. The purpose of this study was to evaluate the role of MR image texture analysis (MRTA) in predicting the outcome of childhood diffuse midline gliomas of the pons (DMG) in response to radiotherapy through correlation of MRTA parameters with overall survival (OS).

MATERIALS AND METHODS

Patients

Approval for this study was obtained from the Institutional Review Board (IRB no Radiology 2405). Informed consent from children and their parents/guardians was waived for this retrospective study of anonymized imaging data.

We searched the neuro-oncology database to identify children diagnosed with diffuse midline glioma of the pons (DMG) based on clinical and radiological criteria, and treated with radiotherapy at the University College London Hospital NHS Foundation Trust (UCLH). The search covered the time period from January 2007 to January 2017.

Pantients enrolled into BIOMEDE (Biological Medicine for Diffuse Intrinsic Pontine Glioma Eradication trial) were excluded from the study to ensure our cohort of patients received similar treatment. All patients were treated with cranial radiotherapy of 54 Gy in 30 fractions (1.8 Gy

per fraction) delivered over a period of 6 weeks, and in a few cases, with adjuvant chemotherapy (Temozolamide).

The true progression was determined retrospectively based on the combined radiological findings, patients' clinical status, and the date of death. Radiological appearances of tumour progression were established using The Response Assessment in Neuro-Oncology (RANO) criteria [1, 13].

MRI imaging

MRI was performed at 2 distinct time points: at diagnosis before treatment and 6 weeks following radiation therapy. The availability of those MRI images for review was mandatory to be included in the study. The diagnosis was established based on radiological criteria by an experienced paediatric neuro-radiologist with more than 5 years of experience. DMG was defined as a T1-hypo (or -iso) intense and T2-hyperintense tumour involving at least 50% of the pons (11).

MRI imaging acquisition

Children were examined on different scanners but with a standard brain imaging acquisition protocol consisting of Axial T2-WI, Coronal FLAIR, DWI/ADC at b-values 0, 500 and 1000, pre and post contrast T1-WI acquired in axial, coronal and sagittal planes. For the purpose of our analysis b- values 0 and 1000 were used.

MR texture analysis

MRTA was performed using a commercially available research software, TexRAD (Feedback Medical Ltd., Cambridge UK - www.fbkmed.com) [18]. For each DMG patient a freehand region of interest (ROI) was manually drawn by a radiologist on a single axial slice around the largest cross-section area of the tumour on T2 and ADC.
MRTA used in our study was based on a previously published method that employed a filtration-histogram technique [14, 15, 19, 20, 21, 22].

Contrast enhanced spoiled gradient echo (SPGR) sequence was selected to extract and enhance texture features at different sizes corresponding to the different spatial scale filters (SSFs) within the tumour ROI. During filtration step objects of a particular size corresponding to fine (SSF=2mm), medium (SSF=3-5mm) and coarse (SSF=6mm) texture scales were extracted and enhanced. SSF values below 2 were not taken to account as these are inclined to represent image noise (no biologically useful information). Filtration step was followed by quantification of texture using statistical and histogram metrics comprised of mean intensity, standard-deviation (SD), entropy, mean of positive pixels (MPP), skewness and kurtosis. A CT texture analysis study using the filtration-histogram method highlighted what the filtration-histogram

based texture analysis actually means and how the quantification reflects different components of heterogeneity (namely - feature or object size, density and concentration) in an objective manner as perceived by a radiologist in a subjective manner [21]. An illustration of the MRTA is presented in Graphical abstract. The analysis was performed by a clinical researcher with more than 5 years of experience in using this method on radiographic imaging.

Follow-up

Patients were followed up every 2 months after completing radiotherapy unless clinically indicated. Overall survival was defined as the time between the date of diagnostic MR examination and the date of death caused by disease or censored at the date of last contact.

Statistical analysis

The ability of MR texture parameters to predict overall survival was assessed using univariate Kaplan-Meier survival curves. Survival curves for patients above and below each threshold (optimised and median value for each texture parameter) were constructed to display the proportion of those alive at any given time. Differences between survival curves were evaluated using a non-parametric log-rank test, with a p-value of less than 0.05 considered to indicate a significant difference. All statistical tests were performed using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Mac, Armonk, NY: IBM Corp).

RESULTS

Participants

36 children aged from 2 to 14 years (median 7 years) were identified. Two patients were excluded due to a non-diffuse midline glioma of the pons based on histological diagnosis and two patients had corrupted imaging data.

Thirty-two patients had available T2-weighted (T2W) MRI sequences, and 22 had ADC maps for both time points and were eligible for MRTA.

Univariate Kaplan-Meier survival analysis

The median survival of the patients was 9.6 (95% CI : 7.6-11.6) months. Thirty one of 32 patients died within 56 months of their diagnostic MRI examination. The shortest survival time was 1.6 months. A number of MR texture parameters (mean, SD, entropy, MPP, Skewness and Kurtosis) across the different SSFs were significant predictors of overall survival. MRTA on T2W was better at predicting the outcome of children with DMG than MRTA on ADC maps. Furthermore, MRTA assessment on the diagnostic (baseline) MRI images was better at prognosticating than on the scans at 6 weeks following radiotherapy. Particularly texture quantified at medium texture scales at 3-5mm were most significant predictors of overall

survival, where children with a more homogenous tumour texture (as reflected by a lower mean, SD, entropy, MPP and higher kurtosis) at medium scale on baseline T2W MRI, had worse prognosis (mean < 141.165, p=0.009; SD < 319.05, p=0.011; entropy < 7.505, p=0.042; best was mean of positive pixels (MPP) < 305.16499 p=0.005; kurtosis >=0.545, p=0.037 - Figure 1).

Median survival of children with homogenous tumour texture (medium texture, MPP), i.e. poor prognostic group was 7.5 months compared to children with more heterogenous tumour texture, i.e. good prognostic group was 17.5 months.

Figure 2 demonstrates the technique and illustrates the MRTA results for a DMG patient with poor and one with good prognosis based on the texture parameters (Figure 2).

DISCUSSION

In our retrospective study we demonstrated that MR image texture analysis (MRTA) has predictive value in relation to survival of children with diffuse midline gliomas of the pons (DMG), previously known as DIPG. To date, there has been no research carried out to assess whether texture analysis of MRI in these tumours can potentially be used as an imaging biomarker for predicting the outcome.

In our study, DMG with more homogeneous texture on diagnostic MRI was associated with worse prognosis. The median survival was 7.5 months in the poor prognostic group and 17.5 months in the good prognostic group as identified by MRTA, which is keeping with the literature on DMG [23, 24, 25, 26]. Recent studies in adult patients with glioblastoma have also demonstrated that texture analysis based on MR and PET images contained prognostic information [27, 28].

A mean of positive pixels, MPP, was the best predictive marker of overall survival (OS) in our cohort of childhood DMG (p=0.005). This parameter, in addition to mean, SD, entropy, and kurtosis have previously shown to be useful discriminators between low and high-grade gliomas in adult patients [14]. Therefore, MR image texture analysis fulfills many criteria for a radiological biomarker, characterized as a "measurable and quantifiable biological parameter" [21]. MRTA is a non-invasive technique that determines quantitative information about tumour microstructure, which is difficult to discriminate by the human visual system. It uses a conventional imaging data without the need for extra sequences and can be applied to different scanners and field strengths. Moreover, programming skills are not required to use this technique as MRTA is managed by carrying out a manual tumour segmentation applying workstation-integrated software [21].

Image texture analysis studies in adult glioma have proven its ability in assisting diagnosis of malignant glioma and possibly assessing treatment effect [19, 29, 30, 31]. Miles et al. further demonstrated what filtration-histogram based texture analysis actually means in terms of the different components of heterogeneity and how it is associated to visually perceptible images features [21].

There were some limitations to our study. This retrospective study analysis has not been validated by other centres. Although our preliminary results highlighted the potential for MRTA to act as a prognostic marker for children with DMG, further validation is required. The validation of DMG tumour texture as an image biomarker should incorporate the assessment of reproducibility involving a larger cohort at a multi-center level. Previous studies have demonstrated good reproducibility for filtration-histogram based MRTA using test-retest technique [32, 33].

Secondly, contour of the tumour was drawn on a single axial slice. Although the multi-slice delineation would be a better representation of the whole tumour, it is not practical in clinical settings due to a time consuming process. However, Ng et al. reported that a considerable cross-section tumour region is representative and provides results comparable to the whole tumour analysis [19, 34].

We were not able to conclude prognostic significance of tumour MR image texture analysis in the response assessment scans following treatment with radiotherapy. Due to limited number of patients, whose tumour size increased after radiotherapy, we were unable to evaluate the role of MRTA assessment in differentiation between pseudo-progression and true progression. We also found it difficult to ascertain the effect of corticosteroids on radiological response. We are planning to explore this further in future studies involving a larger cohort.

Before 2017 DMG biopsy was not standard of care at our institution. Therefore, we performed analysis of a refined cohort of patients, who matched the approved clinical and radiological criteria for inclusion into clinical trials for DMG prior to the era of biopsy. The criteria included: enlargement of the pons with diffuse T2 signal change occupying > 50% of the volume and presence of symptoms of ataxia, cranial nerve palsies or long tract signs [11]. All of our patients met these criteria.

Our study had only a few patients with histology and molecular data available to evaluate its prognostic potential. Although stereotactic brainstem biopsy is often performed safely, there remains the potential for significant risk to the patient [35, 36]. Furthermore, a repeated biopsy to study the treatment effect will not be acceptable. This only emphasizes the potential future

role of surrogate markers such as image based texture analysis. Moving forward, the performance of texture analysis will need to be assessed by using randomized clinical trials and future research combining MRTA assessment with molecular profiling of a larger cohort of DMG patients.

Diffuse midline gliomas of the pons (DMG) are enigmatic tumours, with the lowest survival rates of all paediatric glial tumours, where further therapeutic gains are urgently needed in addition to standard radiotherapy [1, 10]. In order to improve the outcome of children with DMG we need to focus on not only developing new agents but also the means to measure their effect and select patients for whom these advances will be the most beneficial.

CONCLUSIONS

In conclusion, our study provides the preliminary evidence that MRTA, a software platform, has a potential value for computer-aided analysis of DMG tumour texture, which can act as a marker of survival for patients.

CONFLICT OF INTEREST STATEMENT

None declared.

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