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TECHNICAL NOTE - PEDIATRICS

Robot-guided convection-enhanced delivery of carboplatin for advanced brainstem glioma

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Abstract
Background Patients with diffuse intrinsic pontine glioma (DIPG) have a poor prognosis with median survival reported as 9 months. The failure of systemic chemotherapy to improve prognosis may be due to inadequate penetration of the blood–brain barrier (BBB). Convection-enhanced delivery (CED) has the potential to improve outcomes by facilitating bypass of the BBB. We describe the first use of carboplatin for the treatment of advanced DIPG using a robot-guided catheter implantation technique.
Methods A 5-year-old boy presented with a pontine mass lesion. The tumor continued to progress despite radiotherapy. Using an in-house modification to neuroinspire stereotactic planning software (Renishaw Plc., Gloucestershire, UK), the tumor volume was calculated as 43.6 ml. A transfrontal trajectory for catheter implantation was planned facilitating the in-house manufacture of a recessed-step catheter. The catheter was implanted using a neuromate robot (Renishaw Plc., Gloucestershire, UK). The initial infusion of carboplatin (0.09 mg/ml) was commenced with real-time T2-weighted MRI, facilitating estimation of the volume of infusate distribution. Infusions were repeated on a total of 5 days.
Results The catheter implantation and infusions were well tolerated. A total volume of 49.8 ml was delivered over 5 days. T2-weighted MRI on completion of the final infusion demonstrated signal change through a total volume of 35.1 ml, representing 95 % of the targeted tumor volume. Follow-up at 4 weeks revealed clinical signs of improvement and increased T2 signal change throughout the volume of distribution. However, there was tumor progression in the regions outside the volume of distribution.
Conclusions This case demonstrates the feasibility of accurately and safely delivering small-diameter catheters to the brainstem using a robot-guided implantation procedure, and real-time MRI tracking of infusate distribution.

Keywords Convection-enhanced delivery · Carboplatin · Brainstem glioma · Robot-guided surgery

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Introduction

Brainstem gliomas constitute 10 % of all pediatric central nervous system tumors. The most common type of brainstem glioma (BSG) is identified as diffuse intrinsic pontine glioma (DIPG). Patients with DIPG have a poor prognosis—nearly 90 % of children are dead within 18 months of diagnosis and the median survival has been reported to be 9 months [7, 10, 18]. The mainstay of treatment has been radiotherapy, with a minority of patients undergoing open surgery or receiving chemotherapy. As a result of its location and diffuse nature, it has been clearly shown that surgical resection does not influence outcome [1, 6]. Attempts to increase delivery of radiotherapy utilizing hyperfractionation at total doses as high as 78 Gy have failed to show any benefit [13].

The place of chemotherapy remains disappointing in what has so far proven to be a chemoresistant tumor. The Société Française d'Oncologie Pédiatrique (SFOP) conducted two consecutive studies assessing chemotherapy in diffuse intrinsic BSG. In the first study, radiotherapy was followed 2 to 3 months later by a single course of high-dose chemotherapy followed by bone marrow transplantation. The regimen was a

combination of busulfan and thiotepa [3]. Thirty-six children were included and 25 completed the protocol. Only one patient was alive at 32 months. The second study assessed high-dose carboplatin (1,050 mg/m^2) in a phase II study followed by standard radiotherapy and concomitant carboplatin [9]. No response was observed in the high-dose carboplatin group comprising 37 patients.

The failure of systemically administered high-dose carboplatin to improve prognosis may be a result of inadequate penetration of the blood–brain barrier (BBB), resulting in sub-therapeutic concentrations within the tumor mass. In a study of the relationship between peak plasma and tumor concentrations of carboplatin in patients undergoing glioma resection, Whittle et al. demonstrated that the plasma concentration of carboplatin following intravenous administration peaked at 0.044 mg/ml, while the concentration of carboplatin in glioma tissue peaked at 0.013 mg/ml, well below the IC_{50} of carboplatin [20].

However, convection-enhanced delivery (CED) of carboplatin has proven effective in pre-clinical models of brainstem glioma. Degen at al. used CED to administer carboplatin into a rat brainstem malignant glioma model and found that this resulted in long-term survival compared to the control group, which received systemically administered chemotherapy [5].

CED describes continuous infusion of agents through neurosurgically placed microcatheters [2]. This method has several potential advantages over conventional drug delivery methods as CED facilitates highly accurate anatomical targeting, delivery of higher (therapeutic) drug concentrations throughout clinically relevant volumes of brain tissue or tumor, and reduces the risk of systemic side effects. CED offers particular advantages for the treatment of DIPG because this type of tumor is rarely amenable to surgical resection.

In this case report, we describe the first use of carboplatin for the treatment of advanced brainstem glioma using robot-guided catheter implantation and real-time MRI tracking of infusate distribution.

Methods

History

A 5-year-old boy presented with a 1-month history of unsteady gait, intermittent diplopia, and swallowing difficulty. Contrast magnetic resonance imaging (MRI) revealed a large mass lesion expanding the pons and midbrain with patchy areas of enhancement extending superiorly along the right cerebral peduncle and consistent with a diagnosis of diffuse intrinsic pontine glioma. He was commenced on oral dexamethasone and then treated with a 6-week course of radiotherapy, resulting in stabilization of his neurological condition for approximately 3 months. After this time, he developed progressive left-sided weakness and dysphagia requiring increases in his dexamethasone dose.

At 9 months after diagnosis, the patient's clinical status deteriorated as he developed dysphasia, progressively worsening trismus, dysphagia, and lethargy. Following review by the pediatric neuro-oncology multidisciplinary team and approval from our Institutional Review Board, a decision was made to proceed with convection-enhanced delivery of carboplatin.

Pre-operative planning

MR imaging under general anesthetic was undertaken to facilitate pre-operative stereotactic planning (field strength 3 T, Philips Achieva TX, Philips Healthcare, The Netherlands) 1 week prior to surgery. This imaging confirmed a significant increase in tumor size with extension of the tumor along the left cerebral peduncle and patchy areas of necrosis. Using an in-house modification to neuroinspire stereotactic planning software (Renishaw Plc, Wotton-under-Edge, Gloucestershire, UK) the total tumor volume was calculated as 43.6 ml, including 6.8 ml of necrotic areas. A left transfrontal trajectory for catheter implantation was planned (Fig. 1a–d) facilitating the in-house manufacture of a bespoke catheter with a winged hub (Fig. 2a). The catheter was manufactured from polyether ether ketone (PEEK) with an outer diameter (OD) of 0.6 mm, which was bonded onto a fused-silica cannula with a laser-cut tip (OD 0.23 mm). The catheter was designed to be implanted through a 1-mm OD carbothane guide-tube, a procedure modeled on the technique used by our research group for MRI-directed electrode implantation for deep-brain stimulation [14].

A decision was made not to perform a biopsy prior to catheter implantation, in order to minimize surgical risk. The rapid clinical and radiological progression of the tumor following radiotherapy was sufficient evidence of a high-grade tumor.

Surgical procedure

On the day of surgery, the patient was anesthetized and placed in a Leksell frame. A pre-operative CT angiogram was performed and co-registered with the post-contrast T1-weighted planning MRI scan to facilitate output of stereotactic co-ordinates to a neuromate neurosurgical robot (Renishaw) (Fig. 2b). A 3-cm left frontal curvilinear scalp incision was made and the periosteum retracted. The robot was driven to the entry position on the skull, and using custom-made hand drills, a multi-featured burr hole made into which the guide-tube hub would push fit. The dura was pierced and a 1-mm guide-rod inserted to a point 24 mm proximal to the target within the tumor. The guide-tube was then implanted on a 0.6-mm guide-rod to maintain trajectory. The catheter was tunneled out

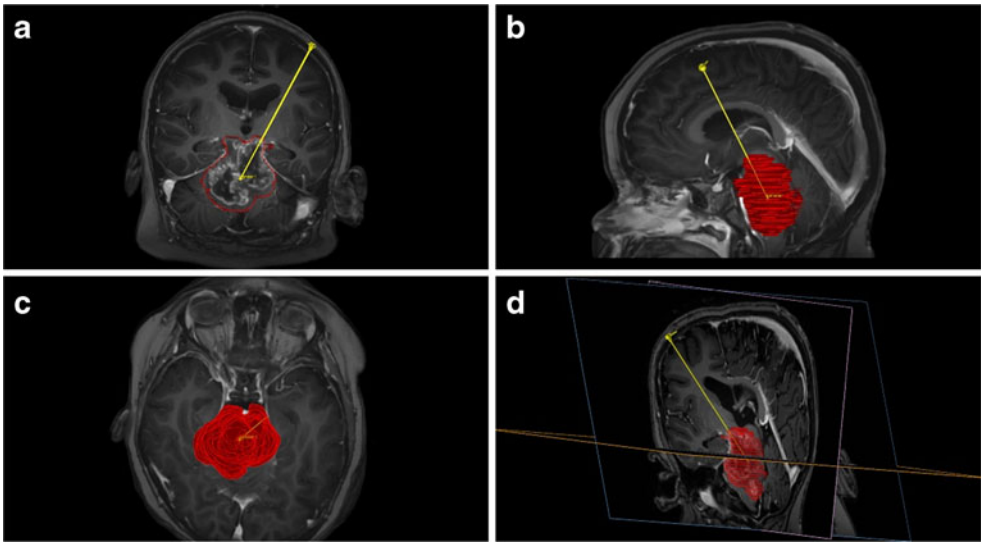

Fig. 1 Trajectory (**a**), sagittal (**b**), axial (**c**) and multi-planar views (**d**) of the tumor using an in-house modification to neuroinspire stereotactic planning software. This software facilitated analysis of tumor volume (*shown in red*) and planning of a left transfrontal catheter trajectory (*yellow*)

through a separate stab incision in the scalp and connected to a custom-made in-line gas and bacterial filter. The catheter was attached to an infusion pump (B Braun, Melsungen, Germany) and primed with artificial cerebrospinal fluid (Torbay Pharmaceutical Manufacturing Unit, Torbay, UK). The fused-silica catheter was then implanted via the guide-tube with 3 mm of fused silica retained within the guide-tube and 24 mm extending beyond the guide-tube tip, thus creating a "recessed-step" within the distal guide-tube (Fig. 2c). The winged hub of the catheter was turned 90° at the skull and secured with 5-mm titanium screws. The distance from skull surface to catheter tip was 105 mm. The skin incision was closed in layers and the externalized catheter tubing secured in a loop on the scalp (Fig. 2d).

Infusions of carboplatin

While under general anesthesia, the child was transferred to the 3-T MRI scanner. The externalized catheter was attached to a 6-m extension line to allow infusions to be performed from a syringe driver (B Braun) outside of the scan room. Infusions of carboplatin diluted in artificial cerebrospinal fluid to a concentration of 0.09 mg/ml were commenced using the following infusion regime:

> 0.5 μl/min for 10 min, 1 μl/min for 5 min, 2.5 μl/min for 5 min, 5 μl/min for 5 min, 7.5 μl/min until completion.

Serial real-time T2-weighted MRI scans were performed in order to allow areas of hyperintense signal change to be used as a proxy measure for drug distribution as previously described [8, 17]. The volume of distribution was estimated to be 2.06 ml after infusion of 0.52 ml of carboplatin, resulting in an approximate volume of infusion (Vi) to distribution (Vd) ratio of 4. Based on this Vi:Vd ratio, the volume of infusion required to fill the full tumor volume (excluding necrotic areas) was estimated to be approximately 9 ml. Once the Vi:Vd ratio was established, the child was recovered from anesthesia and monitored in a high-dependency area until completion of the infusion. The total infusion time was 20 h. Infusions of carboplatin were performed on three consecutive days in order to maintain exposure to the cytotoxic chemotherapy for at least 72 h. A total volume of 26.6 ml was infused into the tumor over 3 days.

After a 4-day break in treatment, the fused-silica catheter and external filter were exchanged for a new system under a short general anesthetic. Infusions of carboplatin were recommenced at a concentration of 0.18 mg/ml at a maximum infusion rate of 10 μl/min, and repeated on two consecutive days. Infusion volumes, times, and maximum flow rates are shown in Table 1. On completion of the final infusion, a T2-weighted MRI scan was performed in order to allow volumetric analysis of signal change as a proxy measure of the final infusate distribution. The volume of T2 signal change was measured as 35.1 ml, suggesting drug distribution throughout approximately 95 % of the targeted tumor volume (Fig. 3a, b). There was no evidence of reflux along the guide-tube on T2-weighted MR imaging.

The microcatheter implantation procedure and infusions of carboplatin were well tolerated, and not associated with any reduction in conscious level. During the infusions, the patient experienced a transient worsening in neurological status with worsening of his trismus and swallowing difficulty. These changes were reversible on cessation of the third infusion, and his neurological status returned to baseline over the following 24 h. The catheter was removed on day 12 and replaced with a stylet. The guide-tube remained in situ to facilitate further catheter implantations without the need for application of a stereotactic frame or robot-guidance. The patient was discharged home on day 14.

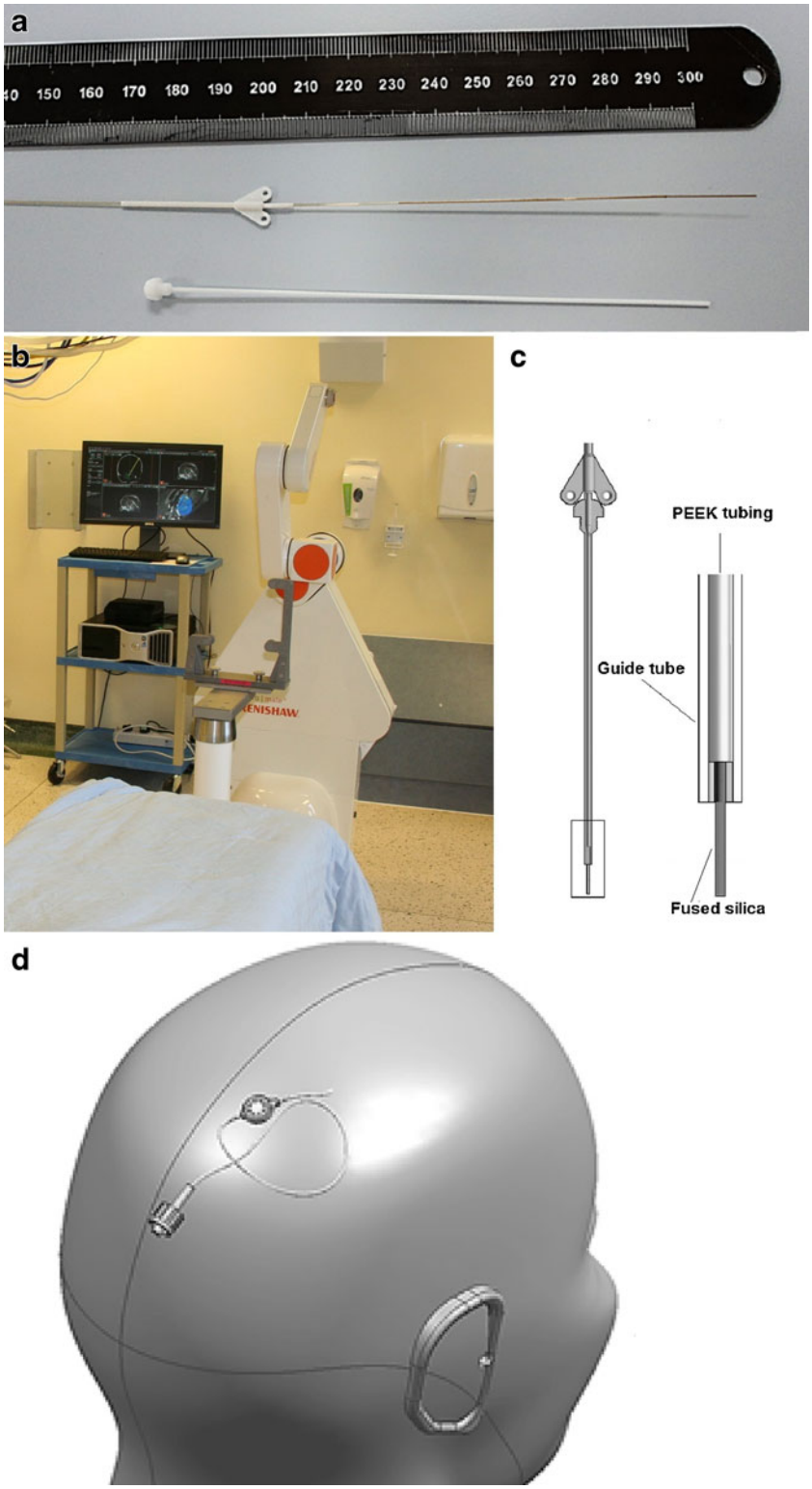

Fig. 2 Pre-operative trajectory planning facilitated the in-house manufacture of a bespoke catheter composed of PEEK bonded onto fused silica and with a winged hub section (**a**). In-house software was used to output stereotactic co-ordinates to the neuromate robot used for guide-tube and catheter implantation (**b**). On implantation of the catheter, a 3-mm section of fused silica was retained within the distal end of the guide-tube thus creating a recessed-step (**c**). A diagrammatic representation of the externalized catheter tubing and in-line gas and bacterial filter on the head is shown (**d**)

Results

Clinical and radiological follow-up

The patient was re-admitted 1 month after completion of the infusions for clinical review and MR imaging. He demonstrated increased alertness and interaction with his family and showed some improvement in left arm function. He had also tolerated a reduction in steroid dosage from 2 mg dexamethasone twice daily to 0.8 mg twice daily, something that was not possible prior to treatment. However, there was evidence of worsening axial stability

Table 1 Schedule of infusions

Day	Carboplatin concentration (mg/ml)	Maximum infusion rate (μl/min)	Infusion volume (ml)	Infusion time (h)
1	0.09	7.5	8.73	20
2	0.09	7.5	8.98	20
3	0.09	7.5	8.92	20
8	0.18	7.5	8.96	20
9	0.18	10	14.2	24

and he continued to suffer with intermittent trismus, dysphasia, and dysphagia. Follow-up T2-weighted MR imaging revealed areas of increased signal change throughout the volume of infusate distribution. Although the histological nature of these high signal areas could not be confirmed, the appearances may have represented the early stages of tumor necrosis (Fig. 4a–f). However, post-contrast T1-weighted imaging confirmed tumor progression in the inferior and anterior regions of the tumor. The areas of tumor progression were outside of the volume of T2 signal change visualized on completion of the infusions.

Unfortunately, the child died 2 months following completion of treatment after suffering a rapid deterioration in neurological status with reduced conscious level, and developing signs and symptoms suggestive of aspiration pneumonia.

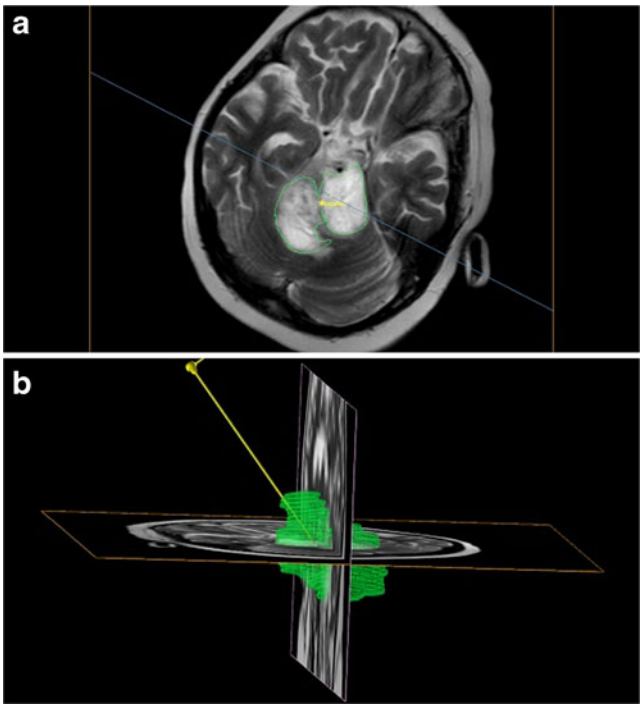

Fig. 3 Axial (**a**) and multi-planar (**b**) T2-weighted MR images on completion of the final infusion. Hyperintense signal change was used as a measure of infusate distribution within the tumor (*shown in green*). The volume of T2 signal change represented 95 % of the targeted tumor volume

Discussion

Despite advances in radiation therapy and chemotherapy, the prognosis for patients with high-grade brainstem glioma remains poor. Systemic administration of chemotherapy has proven disappointing in clinical trials, which may be a consequence of inadequate penetration of the blood–brain barrier. Convection-enhanced delivery has the potential to facilitate drug delivery to brainstem tumors more effectively by bypassing the BBB. However, a number of technical challenges have emerged in recent CED trials, which have hindered the progression of this novel treatment strategy. The major barriers to effective clinical translation include reflux of infusate, which results in sub-therapeutic drug concentration within the target structure and off-target side-effects, and poor drug distribution within the target volume [12, 15, 16].

The causes of drug reflux are multifactorial and include large-diameter catheters [4], tissue trauma on catheter implantation [19], and the use of high infusion rates [4]. However, in order to distribute therapeutic agents homogenously through large and clinically relevant tumor volumes, the flow rate must be high enough to establish a pressure gradient at the tip of the catheter in order to exploit bulk flow rather than diffusion. The drug must also be infused at a sufficiently high rate to compete with dynamic extracellular fluid clearance, particularly through the perivascular spaces, which act as peristaltic pumps [11].

In this case, we were able to safely and accurately deliver a microcatheter with a 0.23-mm outer diameter to an intratumoral target at a depth of 105 mm from the skull surface. By employing a stable robot-guided platform for catheter implantation, our intention was to minimize tissue trauma on guide-tube and catheter implantation, thus reducing the risk of reflux. The novel recessed-step feature (manuscript in preparation) may also have contributed to the achievement of reflux-free infusions by creating an effective seal at the interface between the guide-tube tip and surrounding brain. We believe that the combination of a robot-guided implantation method and recessed-step catheter design allowed us to achieve high-volume, high-flow-rate infusions without reflux.

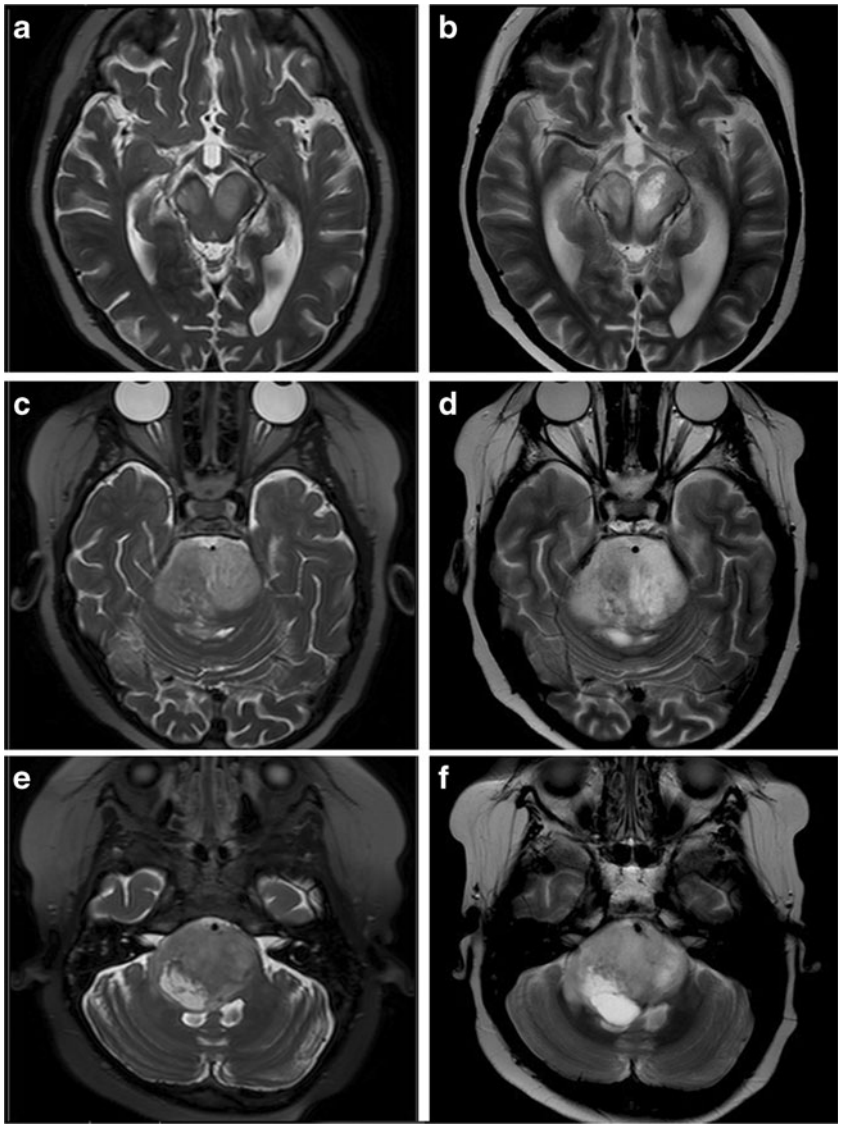

Fig. 4 Comparison of T2-weighted MR imaging prior to treatment (**a**, **c**, **e**) and corresponding images at 4 weeks post-infusion (**b**, **d**, **f**) revealed areas of increased hyperintensity within the left cerebral peduncle, as well as within the mid and lower pons. However, there was evidence of continued tumor progression at the inferior and anterior aspects of the tumor, which were outside the volume of T2 signal change on cessation of the infusions

The use of T2-weighted MR imaging for volume of distribution analysis has been described in previous clinical studies [17], and it has been reported that the volume of T2 signal change significantly underestimates the true volume of drug distribution [8]. In this case, we used serial real-time T2-weighted MRI scans to estimate the Vi:Vd ratio thus allowing us to estimate the total volume of infusion required to achieve drug distribution throughout the target tumor volume. On completion of the final infusion of carboplatin, the volume of T2 signal change was measured as 35.1 ml, representing 95 % of the targeted tumor volume. The areas of tumor progression on follow-up imaging were outside of this volume suggesting inadequate drug delivery to the peripheral areas of tumor. We would therefore advocate the use of multiple catheter trajectories for the future treatment of advanced and very large brainstem tumors.

This case demonstrates the feasibility of accurately and safely delivering very small diameter catheters to deep targets within the brainstem using a robot-guided catheter implantation procedure. Large-volume infusions were well tolerated at flow rates as high as 10 μl/min, without evidence of reflux. Based on T2-weighted MR imaging, infusate distribution was achieved throughout the majority of the tumor volume, and we are hopeful that this treatment strategy could favorably impact the prognosis of patients with smaller tumors treated at earlier stages of the disease process. It is our intention to use the experience gained in this case to develop a robust protocol for a phase 1 clinical trial of convection-enhanced delivery of carboplatin for progressive brainstem glioma.

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Conflicts of interest N. Barua is a consultant clinical advisor to Renishaw Plc. S. Gill is Renishaw's clinical director.

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