Case series

**Perfusion-guided endovascular super-selective intra-arterial infusion for treatment of malignant brain tumors**

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**ABSTRACT**

**Background** Survival for glioblastoma remains very poor despite decades of research, with a 5-year survival of only 5%. The technological improvements that have revolutionized treatment of ischemic stroke and brain aneurysms have great potential in providing more precise and selective delivery of cancer therapeutic agents to brain tumors.

**Methods** We describe for the first time the use of perfusion guidance to enhance the precision of endovascular super-selective intra-arterial (ESIA) infusions of mesenchymal stem cells loaded with Delta-24 (MSC-D24) in the treatment of glioblastoma (NCT 03896568).

**Results** MRI imaging, which best defines the location of the tumor, is co-registered and fused with the patient’s position using cone beam CT, resulting in optimal vessel selection and confirmation of targeted delivery through volumetric perfusion imaging.

**Conclusions** This technique of perfusion guided-ESIA injections (PG-ESIA) enhances our ability to perform targeted super-selective delivery of therapeutic agents for brain tumors.

**INTRODUCTION**

Over 290,000 new cases of primary brain tumors are diagnosed every year. Glioblastoma (GBM) is the most common and most aggressive. Survival for GBM remains very poor despite decades of research, with a 5-year survival of only 5%. The technological improvements that have revolutionized treatment of ischemic stroke and brain aneurysms have great potential in providing more precise and selective delivery of cancer therapeutic agents to brain tumors. Endovascular super-selective intra-arterial (ESIA) catheterization and infusion leads to over 100-fold increases in concentration of therapeutic agents in the brain compared with intravenous delivery.

**METHODS**

**General strategy**

MRI is ideal for defining the anatomic location of GBM, particularly the contrast-enhancing portion of the tumor, which histologically contains tumor cells and microvascular proliferation and often has a partially disrupted blood brain barrier (BBB). The contrast-enhancing portion of GBM is typically the desired target when delivering agents intra-arterially because of BBB disruption. During ESIA infusions, cerebral angiography is performed in order to help identify the vessels feeding the tumor, especially the enhancing portion. Traditionally, cerebral angiography defines the tumor based on the presence of a vascular blush, which is often not present or only faintly present in recurrent GBM cases after radiation and chemotherapy. As a result, we designed an optimal angiography-based infusion strategy that would benefit from fusing the preoperative MRI scan with real-time perfusion images from super-selective injection during angiography, we can precisely identify the vascular supply to brain tumors and facilitate ESIA infusion for brain tumor treatment.

We describe for the first time the use of perfusion guidance to enhance the precision of ESIA infusions using, as an example, infusion of MSC-D24 in the treatment of GBM (NCT 03896568). This technique of perfusion guided-ESIA injections (PG-ESIA) enhances our ability to perform targeted super-selective delivery of therapeutic agents for brain tumors.

**Preoperative MRI**

Prior to angiography MRI brain with contrast is obtained to accurately identify the contrast-enhancing portion of the tumor. In order to map the vascular supply to the contrast-enhancing portion of a GBM, the MR images are fused to the angiographic images. To optimally fuse the MRI data to the data acquired in the angiography suite, isotropic data with voxels of equal dimensions on each side should be obtained during the MRI acquisition. A variety of high resolution 1 mm images from super-selective injection during angiography, we can precisely identify the vascular supply to brain tumors and facilitate ESIA infusion for brain tumor treatment.
New devices and techniques

voxel three-dimensional (3D) ultra-fast spoiled gradient echo or 3D fast spine echo acquisition techniques are available across multiple vendors and all provide the necessary isotropic data. We include T1 post-contrast 3D BRAVO, brain volume imaging (General Electric, Milwaukee, Wisconsin, USA) as part of the protocol, which we have found to be optimal for multiplanar reformatting and fusion to the angiographic data. To perform the fusion we use syngo Fusion (Siemens Medical Solutions, Erlangen, Germany). Manual segmentation of the tumor volume from the MRI is performed and the 3D image of the tumor volume can be superimposed on real-time fluoroscopic images during the procedure. To save time during the procedure, segmentation of the tumor volume can be performed in advance.

3D space acquisition
Cone beam computed tomography (CBCT) is integral in planning IA injection and confirming the area of infusion. Unlike traditional CT with a thin fan beam from a high-dose x-ray source, CBCT uses a lower dose x-ray source which projects a cone of x-ray that is detected with the fluoroscopy image intensifier. The ability to obtain CBCT in the angiography suite with fluoroscopy allows us to precisely define the 3D location of the patient’s head within the angiography suite for 3D overlay and to obtain cross-sectional volumetric maps of the portion of brain infused by the microcatheter.

3D fusion and vessel selection
For tumors in the frontal and parietal lobes we acquire initial angiographic injections of the internal carotid artery and for temporal and occipital tumors we perform injections of the vertebral artery. Minimal additional time is needed to perform the 3D fusion. A single rotational 3D DSA (Siemens Medical Solutions, Erlangen, Germany) acquisition includes both a non-contrast mask CBCT and then an arterial phase post-contrast CBCT. On units that can spin both anteroposterior and lateral planes, the acquisition should only take 8–10 s for two rotations.
This single angiographic acquisition contains the information needed to automatically register and fuse the data from the brain MRI to the fluoroscopic images. In addition, this rotational angiographic acquisition creates a 3D rendering of the vascular tree. Since both the 3D vascular tree and the tumor volume can be directly superimposed in real time on the fluoroscopic image, it aids in the precise selection of potential target vessels for therapeutic infusion (figure 2). The vessels are fused to the MRI and the 3D representation of the tumor with a process that uses the non-contrast CBCT to perform the fusion with the MRI (figure 3). Once the appropriate branch is identified, the 3D DSA is then used for a 3D Roadmap (Siemens Medical Solutions) which overlays the 3D vascular tree on the fluoroscopic images to aid in vessel catheterization. After the vessel is catheterized, angiography can confirm the tumor blush. However, in many cases no visible tumor blush can be identified, which is very common in recurrent GBM. For those patients, selection of the dominant arterial pedicle for infusion is based on the vessel penetrating and supplying most of the tumor.

**Infusion area 3D acquisition and image fusion**

Once the microcatheter has been advanced to the potential tumor-supplying arterial pedicle based on the 3D fusion, we use a technique using the Neuro Parenchymal Blood Volume (Neuro PBV; Siemens Medical Solutions) to confirm the catheter is in a favorable location for tumor treatment. Previously, Neuro PBV has been used with IV contrast to estimate cerebral blood volume (CBV) in patients with ischemic stroke. Instead, we use the Neuro PBV following an IA contrast injection through the microcatheter. Similar to the previously described technique to assess CBV, the contrast enhanced CBCT is used to generate a colorized PBV map. However, the map obtained is not one of whole brain CBV but rather the area of brain parenchyma supplied by the catheterized arterial pedicle.

The injection parameters will depend on many variables including cardiac output and size of infusion area and contrast used. Our current injection rate is 1 mL/s for Visipaque 320 (GE Healthcare, Chicago, Illinois, USA) for 5 s. Acquisition is a 5 s rotation for the non-contrast CBCT followed by a 5 s rotation parenchymal phase CBCT with a 7 s x-ray acquisition delay after start of contrast injection to allow for parenchymal opacification. This results in an immediate volumetric map of the area that would be infused by the microcatheter. The non-contrast CBCT is used to fuse the MRI volume and the registration data are used to overlay the subtracted PBV CBCT. This fusion confirms that the tumor is within the area of infusion (figures 4 and 5). The entire process takes only several minutes at most and adds little additional time intra-procedurally over blind infusion in proximal vessels.

**Infusion area volume analysis**

The MRI and PBV map can be exported to MIM 6.0 (MIM Software, Beachwood, Ohio, USA) to calculate the precise volume of the infused area. This software platform is commonly used by radiation oncology, nuclear medicine, and interventional radiology. MIM allows for automatic fusion of the PBV to the MRI volume without significant manual correction. It uses a landmark-based deformation algorithm that registers each volume to a standard template for fusion. As MIM is commonly used on positron emission tomography (PET) data, it will perform fusion without the non-contrast CBCT source data. The software also performs rapid semi-automated segmentation of the infused area. The PET Edge (MIM Software) gradient-based segmentation tool is very effective in rapidly defining the area of...
infusion from the PBV map. 3D sculpting tools can be used to refine the edges.

Illustrative cases

Illustrative case 1
A patient in their 40s who presented with left occipital recurrent GBM (figure 6A) underwent MSC-D24 infusion ($2 \times 10^7$ cells in 20 mL) through the left posterior cerebral artery (PCA) (figure 6B) as part of a phase I clinical trial (NCT 03896568). The perfusion location and volume from the microcatheter in the PCA were shown (figure 7).

Illustrative case 2
A patient in their 30s who presented with left frontal recurrent glioblastoma (figure 8A) underwent MSC-D24 infusion ($2 \times 10^7$ cells in 20 mL) through the left middle cerebral artery (MCA) (figure 8B) pre-frontal branch as part of a phase I clinical trial (NCT 03896568). The perfusion location and volume from the microcatheter in the MCA were shown (figure 9).
outside the liver has been extremely limited. Recently, a canine model demonstrated successful selective arterio microcatheter delivery of Y90 with up to 69% size reduction seen in canine brain tumors.3

The process for radio-embolization of liver tumors involves conventional catheter angiography for treatment planning weeks in advance. During planning, a surrogate radiopharmaceutical, Tc-MMA, is delivered to verify uptake in tumor, to determine the amount of uptake in normal liver and to perform dosimetry planning. More precise doses for IA radio-embolization therapies have been shown to have improved outcomes for liver tumors.12 13 Precise dosimetry will likely be important for any clinical trials of Y90 infusion in patients with GBM.

While the precise volume of tissue infused is not currently a concern for MSC-D24 as it can replicate outside the area of infusion and should not affect normal brain since it only replicates in glioma cells, radio-embolization requires precise treatment volumes to ensure both effective therapy and to minimize toxicity. However, in general, traditional methods of calculating the therapeutic dose based on weight and body surface area are not applicable to IA therapies. For instance, Gobin et al have proposed that the IA retinoblastoma chemotherapy dose should be based on eye size, not body size.14 Dose escalation studies for IA drug efficacy and toxicity may need to be based on tumor size and volume of brain that is being infused rather than simply the patient’s weight or body surface area for more predictable outcomes.

The limits of this approach are that the precise perfusion volume cannot be predicted pre-procedurally without selective intracranial catheterization. While a separate diagnostic angiogram for mapping is common for liver radio-embolization, it may not be reasonable for GBM therapy given the higher risks of intracranial catheterization. Potentially, our technique of using intra-procedural CBCT perfusion maps could also predict the uptake in tumor to normal brain and total treatment volume in a single session, similar to techniques described in single session hepatic radio-embolization to avoid two separate catheterizations.15

Our experience suggests that future trials of IA infusion for treatment of malignant brain tumors should be guided by fusion of pre-procedural brain MRI to intra-procedural CBCT to ensure the most optimal microcatheterization is performed. Brain MRI should be fused to microcatheter perfusion maps both to document the volume of tumor that is infused and to minimize non-target infusion in potentially dangerous territories.

CONCLUSION
Endovascular neurosurgical oncology is a field poised for rapid application and growth. Safe ESIA infusions for brain tumors have been made possible by advancements in microcatheter technologies. These infusions will be guided by similar advances in imaging that were not previously available to the neurointerventionalist. Volumetric acquisitions of the 3D intracranial vascular anatomy have become common. These data can be easily fused to the MRI demonstrating the exact vessels supplying brain tumors. Our report shows that perfusion volume maps generated from microcatheter infusion previously developed for stroke and liver tumor radio-embolization can be used for precise intracranial ESIA delivery of therapeutics to GBM by fusing them with the preoperative MRI using existing software tools.

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