Comparison of Segmentation Techniques Applied to MR Images of Convectively Delivered Gadolinium-labeled Liposomes in Monkey Brains

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INTRODUCTION

We are currently investigating convection enhanced delivery (CED) of liposomes as a method for administering chemotherapy to intracranial tumors[1,2]. With CED, a catheter placed in the brain creates a pressure gradient to push drugs into the interstitial space, bypassing the blood brain barrier. Liposomes can be used as vehicles to deliver therapeutic drugs or be labeled with molecules for visualization. The combination of the two delivery modalities leads to larger volumes distributed to discrete regions for a longer period of time. Previously, we demonstrated that it is possible to visualize distributed volumes of Gadolinium-filled liposomes on MR images[1,2,3]. Currently, we are exploring the accuracy of segmentation techniques for quantifying liposomal regions.

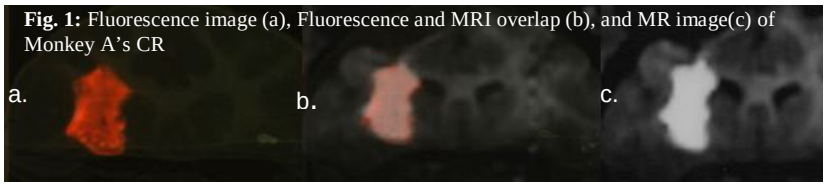

Fig. 1: Fluorescence image (a), Fluorescence and MRI overlap (b), and MR image(c) of Monkey A's CR

METHODS

Dynamic Imaging of Primates. As previously described, guide cannula were surgically inserted into various brain regions through the skulls of two normal rhesus macaques[4]. Targeted areas were the brain stem (BS), corona radiata (CR), and corpus collosum (CC) in monkey A; the right and left hippocampus (RHC and LHC) were infused in monkey B. Both monkeys were anesthetized and placed in a MR-compatible stereotactic frame. T1-weighted coronal SPGR images (flip angle 40° with TR/TE=28ms/8ms, slice = 1 mm, NEX = 4, matrix = 256x192, and FOV=16cm, 0.39mm^3 voxel volume) were captured with a 1.5T GE Signa scanner (Waukesha, WI) using a 5-inch circular surface coil placed on top of the skull. Baseline images were acquired prior to convection. Subsequently, liposomes encapsulating Gadoteridol (GD) and sulforhodamine B (SB) were distributed into the brain interstitium through catheters inserted into the guide cannula[1]. Images were continuously acquired throughout the duration of the infusion over a 1.5 to 2 hour time period. Following the procedure, the animals were immediately sacrificed, and the brains were harvested, cut into 3-6 mm coronal sections, and frozen with dry-ice cooled isopentane.

Data Analysis. Liposomal volumes were quantified from MR and histological images. Three methods were employed to segment MR images: Sobel edge masking (SEM), difference imaging (DI), and FMRIB's Automated Segmentation Tool (FAST)[5]. For SEM, background values were obtained from extracranial muscle near the infusion sites. The original MR images were filtered with a Sobel edge detection kernel using IDL (RSI, Boulder, CO). The edge maps were used to create masks of the liposomal distribution boundaries in the brain. After the original images were masked, the liposomal distribution was refined using a threshold that was based on the background values[1]. For DI, baseline images were subtracted from images acquired after the convection was completed. The volume was then segmented using a global threshold based on the standard deviation of the image. For FAST, images were segmented into cerebral spinal fluid, gray matter, white matter, and liposome classes using a hidden Markov random field model with an expectation-maximization algorithm[5]. For the histologic analysis, fluorescent images were taken of 40 µm thick section spaced 400 µm apart. The distribution of liposomes was quantified by hand using NIH image 1.62 (Bethesda, MD)[3]. Percent error was calculated as (MR volume – histological volume)/histological volume.

RESULTS

Visually, SB liposomes radiated to the same areas as GD liposomes (Figure 1)[2]. Table 1 summarizes the experiments conducted and their corresponding distributed volumes calculated from the various approaches. Regression lines for all three methods demonstrated that each was consistent with histology (two tailed t-test, P<0.005 for each). With respect to error, SEM had the lowest error for Monkey A, DI better segmented Monkey B, and FAST generally had the lowest error overall. SEM was susceptible to spatial variations. For example, Monkey A's images had sharp contrast and negligible chemical shift artifacts; conversely, Monkey B's images had diffuse contrast and noticeable chemical shift.

Table 1: Calculated Distributed Volumes

Subject	Region	Infused (µl)	Histology (µl)	SEM (µl)	SEM % err	DI (µl)	DI % err	FAST (µl)	FAST % err
A	BS	67	77.8	83	6.7%	61	-22%	55	-29%
	CR	99	240.7	259	7.6%	222	-7.8%	223	-7.4%
	PT	99	223.5	210	-6.0%	175	-22%	209	-6.5%
B	RHC	113.5	329	402	22%	323	-1.8%	343	4.3%
	LHC	113.5	359	454	27%	346	-3.6%	369	2.8%
Linear Regression w/Histology P-values				0.0029		0.0011		0.0001	

SEM performed better with Monkey A, since the edges were correctly mapped. The DI method was sensitive to noise. Monkey A's images had poorly matched SNR (infusion SNR/ baseline SNR = 1.7). However, Monkey B's images had comparable SNRs (infusion SNR/ baseline SNR = 1.1). DI resulted in more accurate volumes for Monkey B, because the noise was stable in the subtracted image. The FAST algorithm did not seem to be responsive to spatial variations or noise and generally estimated the histology volumes properly. However, the largest error emerged for the smallest histological volume with this method.

DISCUSSION

We have shown that a volume of convectively delivered GD liposomes can be accurately quantified using segmentation techniques. We utilized three different methods for measuring volumes on MR images, compared their output to histological volumes, and noted performance variations among them. The methods convincingly defined volumes, but each was affected by an inherent experimental characteristic: paramagnetic species chemical shift artifacts; noise fluctuations over the extended duration of the CED experiment, or small volumes of interest. Despite these issues, further processing could improve accuracy. Low-pass filtering may balance image variations which perturbed SEM and DI. FAST may be improved as well by revising boundary definitions for small volumes. More experiments are needed to confirm our findings.

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