Seeing more with less: virtual gadolinium-enhanced glioma imaging

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MRI is the main modality to diagnose and monitor the evolution and treatment of brain tumours. Radiological tumour grading relies on evidence of abnormal blood–brain barrier permeability, achieved by intravenous injection of gadolinium-based contrast agents (GBCA), leading to enhanced signal intensity on T1-weighted images. The current goal in glioma surgery is resection of the enhancing tumour parts and the response assessment in neuro-oncology (RANO) criteria for monitoring glioma treatment response heavily rely on the demonstration of recurring or enlarging enhancing tumour.[1]

The use of GBCA is being scrutinised because of the accumulation of gadolinium deposits in the brain, which have uncertain long-term consequences. Because of this uncertainty, restrictions are being imposed on the use of GBCA and their application is discouraged unless it is deemed completely necessary.[2] Additional drawbacks of repeated administration of GBCA are patient burden (intravenous injection and infrequent allergic reactions), prolongation of examination time, and the costs of the GBCA contrast agent itself. There is an urgent need for alternative image generation to mitigate these GBCA issues.

In *The Lancet Digital Health*, Chandrakanth Jayachandran Preetha and colleagues[4] used a Generative Adversarial Networks (GAN)[3]-based approach inspired by the pix2pix architecture[5] to generate images that are similar to GBCA-based approach. Routine unenhanced T1-weighted, T2-weighted, and FLAIR images were used to synthesise T1-subtraction images (showing the difference between unenhanced and GBCA-enhanced T1-weighted images). Along with the standard discriminator loss of GANs, both the mean absolute error and the structural similarity index measure (SSIM) between real and synthetic GBCA images contributed to the network optimisation function during training. The SSIM is a widely used similarity metric in the computer vision field and measures a combination of luminance, contrast, and spatial correspondence.

GAN-based synthetic contrast-enhanced T1-weighted images had a similarity of approximately 82% with those based on GBCA, and slightly, but significantly, outperformed a standard encoder-decoder network (U-Net) approach (81%). Compared with the GBCA scans, synthetic images underestimated tumour volume by a median of –7% (–0·48 cm^3) as derived using a previously published[6] segmentation approach (another convolutional neural network [CNN]) that was not specifically optimised for synthetic images. Although there was a significant association, Preetha and colleagues[4] show there is considerable random variation including volume overestimation and underestimation. Sørensen–Dice scores (evaluating pixel overlap of binary classified tumour presence or absence) were quite modest (median 0·28), although this score is partly affected by many small enhancing tumour volumes.

For the clinical validation tasks, the segmentation results were combined with T2-FLAIR volumes to classify tumour evolution when applying the RANO criteria,[1] effectively thresholding the results and removing some (potentially spurious) small increases or decreases. The mean time to progression was similar using GBCA-based and synthetic images, although 28% of patients were classified differently, with 15% showing progression using synthetic images and not with real GBCA data. For the important clinical outcome of overall survival, time to progression predictions using both approaches yielded similar hazard ratios in fully adjusted Cox regression models accounting for relevant covariates such as treatment and methylation status.

Strengths of the study included validation of the GAN approach in a realistic scenario, using trial data from more than 2000 patients treated across more than 200 institutions, suggesting that the GAN-based approach generalises across different MRI machines. Such a performance suggests that synthetic samples could act as a meaningful substitute for GBCA-based images in determining treatment effects (in a trial setting), even if not being perfect copies that are readily recognised by human observers. Whether they perform equally well in a diagnostic setting was not examined.

Future research may be needed to boost the performance of GAN-based synthetic images approach before we can dispose of the use of GBCA. Open questions include: what would be the best optimisation function to train a GAN and what is the best way to

evaluate the derived results? In the study by Preetha and colleagues,[4] the SSIM index is used both for training the GAN network and as one of the evaluation metrics, which could be suboptimal. Alternative CNN strategies might be able to produce more realistic images with increased usability in routine radiological practice. Conditional GANs, as used in this study, can learn hidden factors, which might be manipulated to modify the outcome of generated images through input of human experts, while assuring that the resulting images still produce similar segmentation performance.

The use of GBCA serves other purposes than demonstrating blood–brain barrier leakage. GBCA-based perfusion imaging is increasingly used to determine cerebral blood volume and perfusion, which are more relevant in determining glioma prognosis and can assess treatment effects such as radiation necrosis that also enhances vividly after GBCA administration. Alternative MRI pulse-sequences are being evaluated to provide similar information,[7] such as arterial spin-labelling and chemical-exchange saturation transfer imaging that can complement synthetic post-contrast T1-weighted images in a future glioma neuroimaging approach without GBCA administration.

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1 Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. *Neurotherapeutics* 2017; **14:** 307–20.

2 Runge VM. Critical questions regarding gadolinium deposition in the brain and body after injections of the gadolinium-based contrast agents, safety, and clinical recommendations in consideration of the EMA's pharmacovigilance and risk assessment committee recommendation for suspension of the marketing authorizations for 4 linear agents. *Invest Radiol* 2017; **52:** 317–23.

3 Goodfellow I, Pouget-Abadie J, Mirza M, et al. Generative adversarial nets. 2014. https://papers.nips.cc/paper/2014/file/5ca3e9b122f61f8f06494c97b1afccf3-Paper.pdf (accessed Aug 26, 2021).

4 Preetha CJ, Meredig H, Bugnara G, et al. Deep-learning based synthesis of post-contrast T1-weighted MRI for tumour response assessment in neuro-oncology: a multicentre, retrospective study. *Lancet Digit Health* 2021; published online Oct 20. https://doi.org/10.1016/S2589-7500(21)00219-3.

5 Isola P, Zhu JY, Zhou T, et al. Image-to-image translation with conditional adversarial networks. 2017. https://openaccess.thecvf.com/content_cvpr_2017/papers/Isola_Image-To-Image_Translation_With_CVPR_2017_paper.pdf (accessed Aug 26, 2021).

6 Kickingereder P, Isensee F, Tursunova I, et al. Automated quantitative tumour response assessment of MRI in neuro-oncology with artificial neural networks: a multicentre, retrospective study. *Lancet Oncol* 2019; **20:** 728–40.

7 Gonçalves FG, Chawla S, Mohan S. Emerging MRI techniques to redefine treatment response in patients with glioblastoma. *J Magn Reson Imaging* 2020; **52:** 978–97.