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CNS CANCER

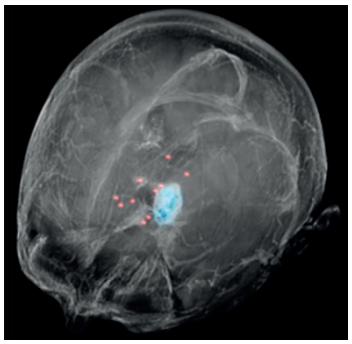
Visualizing secrets of glioma

Gliomas are inherently invasive, and accurate delineation of the diffuse boundary between tumour and normal brain tissues is not possible with current intraoperative imaging techniques, contributing to a local recurrence rate for high-grade gliomas of ~85%.

A new approach developed by Frederic Leblond, Kevin Petrecca and colleagues offers improved definition of cancer and normal tissues during surgery. The Raman spectroscopy modality distinguishes tissues based on their different molecular characteristics, which result in variable inelastic scattering of incident laser light and thus distinct spectral profiles. "This handheld Raman spectroscopy probe technique, coupled with our machine-learning tissue-classification algorithms, can detect brain cancer and, most importantly, invasive cancer cells on a background of normal brain, at cellular resolution," says Leblond.

Accuracy, sensitivity, and specificity of Raman spectroscopy classifications in 17 patients undergoing surgical resection were 92%, 93%, and 91%, respectively; false-negatives were observed only for tissues with a cancer-cell burden <15%, equating to <17 cancer cells per 0.0625 mm^2. Petrecca explains "these findings go far beyond what is detectable using MRI and intraoperative fluorescence detection technologies." He concludes, "this cancer-detection technology provides neurosurgeons with a real-time, intraoperative guide to detect brain cancer cells at cellular resolution, potentially enabling maximal resections, and thus improved outcomes."

In a different study, Sriram Venneti *et al.* addressed another challenge to delineation of glioma tumours: the high background uptake of ^{18}F-fluorodeoxyglucose (FDG) in the normal brain, which obscures tumour detection by FDG-PET. "Glutamine is a principle nutrient that cancer cells consume to generate the energy, lipids, proteins and nucleotides they need to survive and proliferate," Venneti explains. Thus, they leveraged this addiction in order to image tumour metabolism using a novel PET tracer, FGln (4-^{18}F-(2S,4R)-fluoroglutamine).



3D brain rendering showing the MRI-detected tumour volume (blue) and points (red) where Raman spectroscopy detected cancer cells invading normal brain beyond MRI enhancement. Image courtesy of Frederic Leblond and Kevin Petrecca.

In animal models, FGln uptake was high in glioma tissue with minimal uptake in the surrounding brain, in contrast to FDG uptake, enabling clear tumour delineation; moreover, FGln uptake in gliomas closely mirrored tumour response to chemoradiotherapy. Of note, FGln uptake was not increased in inflammatory lesions or after blood–brain barrier disruption.

In humans, FGln-PET accurately identified gliomas, including those with low MRI enhancement or low FDG uptake. "Aggressive tumours were metabolically more active, with high FGln uptake, whereas less aggressive gliomas showed lower glutamine uptake," states Venneti. "We plan on expanding our small clinical study to a larger cohort of patients with glioma and to assess the effectiveness of FGln in monitoring tumour response in patients undergoing treatment."

David Killock

Original articles Venneti, S. *et al*. Glutamine-based PET imaging facilitates enhanced metabolic evaluation of gliomas *in vivo*. *Sci. Transl. Med.* **7**, 274ra17 (2015) | Jermyn, M. *et al*. Intraoperative brain cancer detection with Raman spectroscopy in humans. *Sci. Transl. Med.* **7**, 274ra19 (2015)