Stimulated Raman histology and deep neural networks for near real-time intraoperative brain tumor diagnosis

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Background. Intraoperative diagnosis is essential for providing safe and effective surgical care of cancer patients. Current methods for intraoperative diagnosis preclude or limit the use of histology in surgical decision making. Dating back over a century, conventional techniques are time-consuming, labor- and resource-intensive and create a barrier between the surgeon and diagnostic histology images. Moreover, in many centers across the globe where cancer surgery is performed, pathology resources are not present to oversee a diagnostic laboratory or interpret often complex intraoperative cases. We present the culmination of a 10 year effort devoted to developing a complimentary pathway for intraoperative diagnosis, independent of traditional pathology laboratory. This pathway unites a powerful optical imaging method, called stimulated Raman histology (SRH), with convolutional neural networks (CNN) for near real-time automated brain tumor diagnosis.

Methods. SRH is an optical imaging method that provides rapid, label-free, sub-micron resolution, images of unprocessed fresh surgical specimens. We developed a bedside fiber-laser-based SRH imager ideally suited for intraoperative pathology. A tissue-to-diagnosis computer vision pipeline was developed that combines SRH and deep CNN for automated intraoperative histologic interpretation. A total of 1026 specimens from 441 patients undergoing brain tumor resection at the University of Michigan were imaged using clinical SRH and used to train the Inception-Resent-v2 CNN architecture. We redesigned the CNN to classify the 13 most common brain tumor subtypes, normal brain (grey and white matter), and nondiagnostic tissue. Over 2.6 million unique SRH patches were generated for model training and validation using a dense sliding window algorithm optimized for image classification and semantic segmentation. An inference algorithm was developed that maps a set of patches from a specimen to a single probability distribution over the diagnostic classes and allows for end-to-end training using backpropagation. Next, a multicenter, prospective, randomized, noninferiority clinical trial was designed for head-to-head comparison between SRH plus CNN interpretation versus the current standard of care, conventional H&E histology with board-certified pathologist's interpretation. Primary endpoint was patient-level multiclass overall diagnostic accuracy.

Results. Our SRH plus CNN pipeline was able to provide an intraoperative diagnosis in under 2.5 minutes, which is an order of magnitude faster than conventional H&E histology (~ 30 mins). A total of 204 patients were enrolled (minimum sample size, N = 190) with each of the 13 brain tumor subtypes represented from two tertiary health care centers, University of Michigan and Columbia University (external validation center). Our clinical trial results demonstrate that CNN-based diagnosis of SRH images was equivalent to pathologist-based interpretation of conventional histologic images (overall diagnostic accuracy, 94.6% vs. 95.5%, respectively). Importantly, the CNN correctly classified all 9 of the cases in which the pathologist's diagnosis was incorrect. Using hidden-layer activation maximization, we show that our CNN learned a hierarchy of interpretable (i.e. axonal density, chromatin structure, cytologic features, cellularity, etc) and class-specific SRH feature representations to diagnose the major subtypes of brain tumors. Moreover, our semantic segmentation method achieved a mean intersection over union value of 61.6 ± 28.6 for the ground truth diagnostic class, 86.0 ± 19.2 for tumor-infiltrated regions, and 91.1 ± 10.8 for normal brain regions within SRH specimens, thereby augmenting the surgeon's intraoperative assessment of SRH images in the context of CNN predictions.

Conclusion. In conclusion, we have demonstrated how combining bedside optical histology with deep learning can result in near real-time intraoperative brain tumor diagnosis. Our workflow provides a means of delivering expert-level intraoperative diagnosis where neuropathology resources are scarce and to improve diagnostic accuracy in resource-rich centers. While our computer vision system was validated in the context of neurosurgical oncology, many of the diagnostic features that are used to diagnose brain tumors are found in tumors derived elsewhere in the body. Consequently, we predict a similar workflow incorporating optical histology and deep learning could apply to dermatology, head and neck surgery, breast surgery, gynecology where intraoperative histology is equally central to providing optimal patient care. Importantly, our CNN-based workflow provides unparalleled access to microscopic tissue diagnosis at the bedside during surgery in near real-time, facilitating tumor margin sampling, enabling the study of regional histologic and molecular heterogeneity, minimizing the chances of misdiagnosis due to sampling error, and reducing the dangers of damaging key structures adjacent to lesional tissue.