Webinar: MRI-guided FUS and therapies
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The quest to improve efficacy of endovascular neuro-interventions: focus on spatial precision of the blood brain barrier opening in a mouse model

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The quest to improve efficacy of endovascular neuro-interventions: focus on spatial precision of the blood brain barrier opening in a mouse model

Background. The brain is by far the most difficult target for drug delivery. Vast majority of systemically injected drugs do not reach therapeutic concentrations in the brain. As a consequence, virtually all promising drugs for brain diseases failed in clinical trials[1]. The main obstacles to the effective drug delivery to the brain have been the presence of the intact blood brain barrier (BBB), the vulnerability of brain tissue to ischemia and the devastating effects of even limited local injury[2]. Among the available drug delivery routes intra-arterial (IA) delivery stands out with several unique advantages including the generation of high tissue concentrations at a specific site, low systemic exposure and availability of techniques for reversible BBB opening[3, 4]. These obvious benefits have spurred clinical translation. Although IA drug delivery with BBBO has been used for decades in the treatment of brain tumors, the efficacy of therapies is still limited. To better understand obstacles and improve efficacy, we have systemically studied IA drug delivery in mice, exploiting the benefits of the guidance of magnetic resonance imaging (MRI) and intravital microscopy. Due to small size of cerebral vasculature, the prevalent approach for IA catheterization involves the complete blockade of CCA and the catheter is placed proximally within carotid arteries. This poses potential risks for hypoperfusion of the brain before IA drug delivery and inconsistency or ineffective perfusion of cerebral cortex from bolus injections into the common carotid artery (CCA).

Objective was to test the hypothesis that fully occlusive catheterization of the CCA and resulting re-routing of cerebral circulation restricts brain volume perfused by the catheter to deep brain structures. In contrast, less disruptive catheterization by accessing the external carotid artery (ECA) results in broader perfusion.

Methods. Male C57BL6 mice (10-12 weeks of age) were subjected to catheterization of ECA or CCA for injection into the internal carotid artery (ICA). Mice with IA catheter were placed in 9.4T MRI (Bruker) for image-guided neurointervention. Gadolinium (Gd) (1mM) was administered using infusion pump at the rate ranging between 150-500ul/min. Dynamic contrast-enhanced (DCE) and gradient-echo echo planar imaging (GE-EPI) sequences were used to dynamically assess brain perfusion territory. Mannitol (25%) was injected IA over 30 seconds at pre-determined speed to open the BBB and DCE with intra-venues (IV) bolus of Gd (0.1mmol/kg) being used to determine BBB integrity for calculation of vascular permeability constant (k-trans).

Results. IA delivery via CCA resulted in perfusion of restricted brain territory, primarily hippocampus and the thalamus. When catheter was placed in the ECA trans-catheter perfusion was directed to nearly entire hemisphere with significantly larger brain territory (p?0.05). Importantly ipsilateral cortex was consistently perfused. This spatially selective perfusion territory was in good agreement with brain region with open BBB following Mannitol injection. In none of the animals we did not observe hemorrhages or lasting neurological deficits.

Conclusions. We have shown that by selecting ECA vs. CCA it is possible to achieve more spatial selectivity in mice and that for targeting cerebral cortex ECA catheterization is a method of choice.

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Webinar: MRI-guided FUS and therapies
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Transcranial Focused Ultrasound Targeting Using Image Guidance and Array-Based Steering

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Objectives
Transcranial focused ultrasound (tFUS) can be used for a variety of applications including neuromodulation and blood brain barrier disruption. Accurate targeting is important to ensure the focus is in the targeting region prior to starting therapy. Optical tracking can be used to position the focus of the transducer at the target and a phased array transducer allows for electronic steering to correct tracking errors and skull induced shifts in the beam location. We established methods to target a phased array transducer in a nonhuman primate (NHP) brain using optical tracking and use the tracking information and MR acoustic radiation force imaging (MR-ARFI) to steer the focus to other nearby targets.

Methods
A custom backplate was built to attach an optical tracker to the back of a 128 element, 650kHz phased array transducer. An optically tracked hydrophone was used to establish the transformation from this tracker to the ultrasound coordinate system by sonicating a known grid of 27 points in a water tank and measuring the location of peak pressure. This transformation was tested in phantom and in vivo MR thermometry and MR-ARFI experiments and the translation aspect of this transformation was updated based on the observed error. Finally, this optical tracking and steering system was tested in vivo in a NHP by targeting the center of one hemisphere of the brain and using the optical tracking information and a single MR-ARFI image to steer to targets in the thalamus and insula.

Results
The fiducial registration error between known steering locations and measured pressure maxima was 0.26mm. Phantom testing and initial in vivo testing of the transform found a 6.6mm lateral bias and a 7.0mm axial bias in the transformation. This bias was used as an offset for an updated transformation. Registration of the transducer coordinate system to in vivo MR coordinate system in three MR-ARFI tests resulted in target registration errors of 1.0 mm, 3.6 mm, and 1.6 mm for an average error of 2.1 mm. Using the tracking information and a single MR-ARFI image at the geometric focus we were able to steer the focus such that the ARFI displacement region overlapped with targets in the thalamus and insula.

Conclusion
In this work we demonstrate a method to use optical tracking, MR-ARFI, and electronic steering to target and sonicate brain regions within a NHP. We registered the transducers coordinate system to MR images with optical tracking data. MR-ARFI is used to find the true geometric focus location after registration error and skull effects

and the focus is then electronically steered to the initial target or other nearby targets.

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Webinar: MRI-guided FUS and therapies
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Investigating the feasibility of targeting mesial temporal lobe structures using tcMRgFUS

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Objective
Despite years of development and clinical trials using less invasive methods, open surgical resection of the mesial temporal lobe remains the standard approach to medication refractory temporal lobe epilepsy (TLE). Although thermal brain ablation with transcranial MR guided focused ultrasound (tcMRgFUS) is FDA approved for essential tremor (ET) and Parkinson's disease (PD), its use in treating temporal lobe epilepsy has not been well explored likely because the target location for mesial temporal lobe (MTL) is out of the treatment envelope of currently FDA-approved tcMRgFUS systems.

Methods
In this study we performed 3D-finite difference acoustic simulations to assess the feasibility of targeting the MTL using the Neuro ExAblate (InSightc, Haifa, Israel) focused ultrasound system which is FDA approved. Furthermore, we validated the simulations ex-vivo on cadaveric skulls. Throughout the simulations, the use of lower power and longer sonication duration will be investigated to minimize skull heating, especially at the skull base. In addition, we developed an algorithm to block transducer elements to reduce skull heating.

Results
Our simulations suggest that 48-51°C rise in temperature can be easily obtained at the MTL target, resulting in a maximal temperature rise at the skull by <10°C from the baseline. Experimental results on cadaveric skulls are in close agreement with the simulations. Further reduction in skull heating is also possible through switching off the transducer elements that mostly contribute to skull heating without sacrificing the rise in temperature or significant change in the shape of the ultrasound beam at the MTL target. While future large scale clinical trials will provide information on the thermal dose required to create lesions in the MTL, it is quite likely that 100 min Cumulative Equivalent Minutes at 43 °C (CEM43) will be greater than that of lesions made when targeting the ventral intermediate nucleus for ET or globus pallidus for PD.

Conclusion
Overall, we have demonstrated through simulations that targeting the MTL for ablation using tcMRgFUS is possible with the currently approved clinical neuro system operating at 670 kHz. Furthermore, we have demonstrated experimentally that ablative temperatures can be obtained at the MTL target while avoiding excessive skull heating in cadaver skulls.

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Webinar: MRI-guided FUS and therapies
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Data-driven algorithms for pre and intraoperative planning of focal cryoablation of prostate cancer

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Objective: Focal cryoablation (FC) has been investigated as a minimally-invasive option for the management of low-risk organ-confined prostate cancer (PCa) and a salvage treatment option for post-radiation recurrence. Unlike radical treatments, FC aims to freeze and destroy only the lesion and the surrounding area using thin cryo-needles. FC is expected to reduce the risk of complications associated with the radical treatment, such as incontinence and impotence, while keeping acceptable oncological outcomes. Safe and effective cryoablation requires the deployment of the cryo-needles at optimal locations so that the lethal ablation zone created by the iceball fully encompasses the tumor with a certain ablation margin while preserving surrounding healthy tissues. Currently, physicians rely on pre and intraprocedural images and their own experience to define the best cryo-needle locations and to visually monitor the iceball formation using intraoperative images. However, predicting the final shape of the lethal ablation zone and monitoring the ablation margin in 3D are challenging tasks as it depends on patient-specific factors such as proximity to heat sources and thermal properties of the prostatic tissue. The lack of a computer-aided tool for planning and monitoring the ablation margin increases the risk of an unsuccessful ablation. This study explores different machine learning techniques for pre and intraoperative planning during focal cryoablation of prostate cancer.

Methods: We implemented a data-driven approach to predict the boundaries of the resultant iceball given a defined cryo-needle configuration. We used a voxel-wise model based on the square of the distances from each voxel to the thermal sources. This evaluation used retrospective data of patients, where 17-gauge cryo-needles were inserted transperineally using a guiding template. The model accuracy was evaluated by the Dice Similarity Coefficient (DSC) between the predicted and the actual iceballs. Additionally, we implemented a deep-learning algorithm to automatically segment the iceball boundaries in the intraprocedural image and allow for precise computation of the ablation margin in 3D. The visible iceballs on intraprocedural MR images were segmented using a convolutional neural network model based on the 3D U-Net. The model was trained using intraoperative MR images obtained during 46 MRI-guided FC procedures. Iceballs were manually segmented on 119 images consisting of 77 training, 21 validation, and 21 test images. The test images were used to compute the DSC between the manual and automatic segmentation.

Results: The preoperative prediction model achieved an average DSC of 0.76, which is comparable with recent works using bioheat modeling (DSC of 0.82). The automatic intraoperative iceball segmentation presented an average DSC of 0.84, which is also in line with previous studies of iceball segmentation.

Conclusion: This study presented promising preliminary results using artificial intelligence techniques to predict the iceball formation and segment it intraoperatively during focal cryoablation. We are currently integrating the proposed approaches into an open-source software for pre and intraoperative planning. Additionally, testing and validation on a larger prospective dataset are planned.

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Webinar: MRI-guided FUS and therapies
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Dual-tracked devices for efficient interventions utilizing multiple modalities: The MR-Tracked and Impedance-Tracked cardiac-arrythmia ablation example

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[Objectives] In multiple scenarios, optimal patient treatment can require interventions performed with guidance and/or imaging using two modalities or performed both within and outside an imaging modality. For these, it is desirable to have (a) interventional devices that are positionally located using two tracking methods ('dual-tracked'), with (b) one method being available in both environments, and (c) one method being geometrically linear and compatible with the imaging modality, and (d) there is a rapid means to alternate between methods and/or environments, without re-registration. An exemplary application is cardiac electrophysiological arrhythmia ablative therapy, where most devices operate best under X-ray fluoroscopy and Electro-Anatomic-Mapping (EAM) guidance, performed with electrical impedance tracking (IMT). However, Late Gadolinium Enhancement (LGE) MRI is required for selecting arrhythmia targets, for detecting chronic soft-tissue changes, while Long T1-weighted Long Inversion Time (TWILITE) is required for intra-procedurally monitoring thermal-lesion permanence after (500KHz) Radio-Frequency Ablation, but limited MR-conditional devices exist. This project utilized metallic-backbone MRI-conditional catheters and sheathes with both IMT and MR-Tracking (MRT) sensors on their shaft. A workstation was developed that accepts input from both tracking methods and performs accurate co-registration between the modalities, linearizing the fast (99 fps) but geometrically non-linear IMT tracking into the MRT (and MRI) linear coordinate frame. Phantom and swine interventions were performed on the MRI stretcher, utilizing linearized IMT-navigation and EAM outside the scanner, and MRI imaging and MRT/IMT tracking inside the scanner.

[Methods] Abbott developed 2.4mm diameter 1.1m long dual-tracked EP diagnostic/ablation catheters, and 6.1mm diameter 1.0m long deflectable sheathes with 3mm internal lumens that admit EP catheters. The devices use metallic-braided shafts that employ Miniature Balun technology for MRI-compatibility and have IMT electrodes and MRT micro-coils on their shafts. An RF-shielded systems cabinet with multiple sub-systems permitted performing MR-conditional IMT, EAM, and water-cooled RF Ablation within the Siemens 1.5T MRI environment without reducing MRI or MRT SNR. A custom plug-in module for 3D Slicer was developed to import, process and visualize IMT sensor locations together with their associated EGM traces, and MRT sensor locations from each device. During device navigation in water/Glycerol phantoms simulating abdominal intervention inside the MRI scanner, dual-tracked spatial locations were collected and IMT->MRT co-registered using a thin plate spline algorithm. Following co-registration, EAM could be performed using the registered IMT data either inside or outside the scanner.

[Results] Millimeter accuracy IMT->MRT registration was enabled using 0.15Hz low-pass filtering of the IMT data on the workstation. 15x15x90 mm3 Field of Views are linearized at once, with <2mm RMS error. Spatially-linear and accurate EAM mapping or RF Ablation can thereafter be performed both inside and outside the MRI scanner, accurately registered to a guiding MRI map (LGE, TWILITE). Subject transition between procedure-segments performed outside the MRI bore to within the MRI bore took <30 seconds and did not require re-registration.

[Conclusion] Interventions outside the scanner on the MRI table permit use of many conventional devices, while MRI or MRT inside the scanner provides unique inter-tissue contrasts. Dual-tracked MR-conditional devices support rapid transitions between these two domains.

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Webinar: MRI-guided FUS and therapies
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In vitro Evaluation of Full-length, MR-safe Interventional Passive Catheter Markers at 3T

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OBJECTIVES
MRI-guided intervention provides valuable functional information such as perfusion and diffusion that standard fluoroscopic guidance lacks. Recent studies have demonstrated utility in stroke treatment for multimodality X-ray and MR imaging suites. Yet, clinical adoption of MRI-guided intervention has lagged, and an absence of appropriate tooling could be a contributing factor. Prior work described a polymeric catheter featuring radiopaque markers doped with iron oxide nanoparticles (IONPs) as low-profile, MR-visible passive markers2,3. Here, we further investigate susceptibility artifacts in vitro at 0º and 90º with respect to B0. Marker separation was evaluated to identify a potential format for full-length visibility at 3.0T.

METHODS
Polymeric, 6.6 Fr guide catheter segments were built in a fabrication facility (Penumbra, Inc., Alameda, CA). Epoxy-based radiopaque ink was mixed with 9.1 wt% (w/w) iron(III) oxide (Fe_2O_3) nanoparticles of 20-40 nm diameter. Four circumferential marker bands ranging from 5 to 20 mm apart were applied in series starting 1 cm from the distal tip and cured at 20ºC.

15-cm segments submerged in copper sulfate solution ($CuSO_4$, 1-2 g/L) were oriented parallel (0°) and orthogonal (90°) with respect to B0. At 0°, images were acquired in coronal/sagittal slice orientations on a 3.0T MRI scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). At 90°, images were acquired in coronal/axial orientations to match image acquisition of 0°. Phase encoding direction was maintained parallel to the catheter major axes. T2-weighted turbo spin echo (TSE) and gradient echo (GRE) sequences were collected. Maximum artifact widths were evaluated per ASTM F2119-074, using ImageJ (http://imagej.nih.gov/ij).

RESULTS
Susceptibility artifacts induced by the IONP-doped markers are shown. 90° orientation produced worst-case artifacts in all sequences except the axial TSE. Furthermore, some artifacts could not be discerned at 90º. 20-mm separation yielded distinct artifacts without overlapping.

CONCLUSION
MR imaging demonstrated that the markers induced negative contrast at 3T in vitro. Previous studies have shown IONP concentration is tunable, enabling the ability to induce a larger artifact at the distal tip and smaller artifacts down the length of the catheter. Increased maximum artifact width was observed when catheters were aligned orthogonal to B0, but artifact size remained acceptable for use as a guide catheter. Furthermore, 20 mm marker separation could provide distinct artifacts during MRI-guided interventions, despite anatomic tortuosity. The phantom used in this study was shallow, which limited the ability to distinguish between real susceptibility artifacts and those arising from the solution-air interface. Hence, accuracy of the degree of increased artifact may warrant further testing and investigation. In the future, marker composition and separation can be tuned for other applications like intermediate or microcatheters. More data should be acquired using real-time imaging sequences to evaluate susceptibility artifacts during clinical use. This study simulated worst-case orientations in vitro; similar experiments should be conducted in vivo because native tissues and movement produce a continually changing imaging environment. Finally, while RF-induced heating and magnetically-induced torque are not anticipated to be an issue, characterization of device safety profiles should be performed per ASTM standards F2181 and F2213-1, respectively.

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Webinar: Imaging and sensing
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Prospective validation of diffusion-weighted MRI as a biomarker of tumor response and oncologic outcomes in head and neck cancer: Results from an observational biomarker pre-qualification study.

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Objectives: To determine diffusion-weighted imaging (DWI) MRI parameters associated with tumor response and oncologic outcomes in head and neck (HNC) patients treated with definitive radiation therapy (RT).

Methods: Eighty-six HNC patients enrolled in an active prospective imaging study at The University of Texas MD Anderson Cancer Center were included in the analysis. Patients had MRIs pre-, mid-, and post-RT completion. Inclusion criteria included adults with histologic evidence of malignant head and neck neoplasm indicated for curative-intent treatment with RT with/without chemotherapy, good performance status (ECOG score 0-2), and with no contraindications to MRI. Patients were scanned using a MAGNETOM Aera 1.5T MR scanner (Siemens Healthcare, Germany) with two large four-channel flex phased-array coils. We used fat-suppressed T2-weighted turbo spin echo sequences for tumor segmentation which were co-registered to respective DWIs for extraction of apparent diffusion coefficient (ADC) measurements. Treatment response was assessed at mid-RT and at 8-12 weeks post-RT using RECIST 1.1 criteria and was defined as: complete response (CR) vs. non-complete response (non-CR). Pre-RT ADC was correlated with RT response (CR vs. non-CR) at mid- and post-RT. The Mann-Whitney U test was used to compare ADC values between the mid-treatment CR group and the non-CR group. Recursive partitioning analysis (RPA) was performed to identify ADC threshold associated with relapse. Cox proportional hazards models were done for clinical vs. clinical and imaging parameters and internal validation was done using bootstrapping technique.

Results: Eighty-one patients were included in this analysis. Median follow-up was 31 months. Pre-treatment ADC was not correlated with tumor response or oncologic outcomes ($P>0.05$). For patients with post-RT CR, there was a significant increase in mean ADC at mid-RT compared to baseline ((1.8 ± 0.29) × 10–3 mm2/s versus (1.37 ± 0.22) × 10–3 mm2/s, $p < 0.0001$), while patients with non-CR had no statistically significant increase ($p >0.05$). RPA identified GTV-P delta (?) ADCmean <7% at mid-RT as the most significant parameter associated with worse LC and RFS ($p=0.01$). Univariable and multivariable analysis of prognostic outcomes showed that GTV-P ?ADCmean at mid-RT ?7% was significantly associated with better LC and RFS. The addition of ?ADCmean significantly improved the c-indices of LC and RFS models compared with standard clinical variables (0.85 vs. 0.77 and 0.74 vs. 0.68 for LC and RFS, respectively, $p<0.0001$ for both).

Conclusion: ADC change at mid-RT is a strong predictor of oncologic outcomes in HNC patients. Patients with no significant increase of primary tumor site ADC at mid-RT relative to baseline values are at high risk of disease relapse. Multi-institutional data are needed for validation of our results.

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Webinar: Imaging and sensing
3:37 PM - 3:44 PM

The clinical impact of intraoperative margin assessment in breast cancer surgery using a novel pegulicianine fluorescence guided surgery system: A Prospective Single Arm Study

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OBJECTIVES. The objective of this study was to collect safety and efficacy data on pegulicianine fluorescence guided surgery (pFGS) for identifying residual cancer in the tumor bed of patients undergoing breast conserving surgery (BCS).

METHODS. This prospective, single arm, open-label feasibility study was conducted across 16 US sites. Female patients aged ?18 with newly diagnosed invasive or intraductal cancer undergoing BCS were injected intravenously with pegulicianine 4 ± 2 hours prior to surgery at a dose of 1.0 mg/kg. After completing standard of care (SOC) excision, pFGS imaging guided removal of areas suspicious for residual cancer.

RESULTS. 234 patients received pegulicianine and 230 completed pFGS imaging. One patient experienced anaphylaxis during the administration of pegulicianine, was treated, recovered without sequelae. pFGS guided additional excisions after complete SOC in 138 patients, which removed residual tumor from 26/138 (19%) of those patients. For 17/26 (65%) of these patients, the residual tumor was found by pFGS after negative SOC margins and would otherwise have been unaddressed by SOC. Positive margins after SOC BCS were identified in 38/230 (16.5%) patients, 23/38 (60.5%) of which had additional pFGS-guided shaves and 6/38 (15.8%) were converted to negative margins on final pathology. 3 additional patients might have avoided a second procedure; there was positive FGS in all orientations with positive margins, but pFGS-guided excisions were not taken based upon surgeon judgement. The overall final positive margin rate was 15% (35/230). The overall sensitivity, specificity, and negative predictive value of pFGS were 69.4%, 70.4% and 98.3% respectively.

CONCLUSION. The pFGS system guided intraoperative removal of residual tumor after SOC BCS in 19% of patients who underwent an additional margin excision for a positive pFGS signal. The safety profile of pegulicianine was consistent with other imaging agents used in BCS. These findings support further clinical assessment of pFGS in a prospective randomized trial (“INSITE”, NCT03686215).

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Webinar: Imaging and sensing
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Improved Color-Guided Depth Super-Resolution for Augmented Reality Guided Surgery

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Objectives: Though valuable in low quality cameras (Microsoft Kinect, HoloLens, etc.) and SLAM applications, current depth image super-resolution models have moderate rectification capabilities. Low resolution images typically possess two key problems: 1. the lack of accurate depth values (noise) and 2. the presence of holes in the images. especially with larger upsampling factors.

Methods: In this paper, we propose a deep learning-based, dual-input algorithm to improve upon depth image super-resolution in medical images, specifically for laparoscopic and handheld cameras. As is standard practice,the low resolution depth images are obtained through bicubic interpolation by a scale factor. Distinct from current computationally intensive models, the Color-Edge Guided Network (CEG-Net) restores depth image resolution with high resolution RBG assistance, combining patch extraction and a Canny Edge detection filter with two parallel streams. In addition, we propose a novel loss function derived from the structural similarity index metric (SSIM) and the commonly used Huber loss function.

Results: Our method has been evaluated on a large, general dataset composed of several RGB-depth image datasets including the Middlebury and RGB-D datasets. Additionally, the model has been evaluated on a medical dataset obtained with the Intel RealSense Depth camera. Finally, a surface reconstruction of a chest phantom was performed using a rectified depth image, yielding a finer detail output.

Conclusion: The results confirm the generalizability of the model and its applicability to both ordinary and medical datasets. Moreover, the results of the surface reconstruction are promising in the application of SLAM and augmented reality guided surgery.

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Webinar: Imaging and sensing
3:51 PM- 3:58 PM

Real-time Multimodal Optical Imaging and Risk Map Projection for Oral Cancer Detection and Biopsy Guidance

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Objectives
The Active Biopsy Guidance System (ABGS) and its associated software are designed to guide a clinician through widefield and high-resolution imaging to determine if and where a biopsy is needed for early detection of oral cancer and its precursors.

Methods
We use the ABGS, which consists of two optical subsystems controlled through a single user interface. The first system is a widefield camera and projector capable of white light and autofluorescence image acquisition and real time projection of visible risk maps on the tissue surface. The second system is a fiber-based fluorescence microscope that can directly image nuclear morphology. Custom software architecture fully integrates widefield autofluorescence imaging, high resolution imaging and real-time projection of cancer-risk maps.

Results

We demonstrate that risk maps generated from widefield autofluorescence images can be used to guide the placement of high resolution imaging of the oral epithelium; that multimodal imaging and robust probe tracking can be used to correlate high resolution information with anatomic location; and real time integration of multi-scale imaging can be used to generate a biopsy guidance map and project it onto the oral cavity.

Conclusions
Taken together, these results demonstrate the potential of the ABGS to integrate multiscale images and provide directly visible risk and guidance maps to help clinicians improve the early detection of oral cancer and its precursors.

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Webinar: Imaging and sensing
3:58 PM- 4:05 PM

Development of a radiolabeled peptide-drug conjugate for image-guided drug delivery

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Objectives: Temozolomide (TMZ) is a DNA damaging agent that produces high responses rates in neuroendocrine tumors (NETs) when the DNA repair enzyme, known as O6-methylguanine DNA methyltransferase (MGMT), is inactivated. When given at high-doses, TMZ therapy can exhaust MGMT activity and its associated resistance mechanisms, but also produces dose-limiting toxicities. Since nearly all NETs overexpress the somatostatin receptor subtype 2 (SSTR2), we hypothesized that a receptor-targeted TMZ analog could produce high intratumoral drug concentrations while avoiding systemic toxicity. Accordingly, we converted the clinically approved radiotracer 68Ga-DOTA-TOC into a radiolabeled peptide-drug conjugate (PDC) for SSTR2-targeted delivery of TMZ and report on the utility of the radioactive label for characterizing receptor-binding properties, pharmacokinetics, and tissue biodistribution.

Methods: The PDC was synthesized by (i) replacing DOTA with a multimodality chelator (MMC) to permit site-specific modification, (ii) attaching a modified TMZ analog to MMC, and (iii) conjugating the payload moiety to TOC on solid-phase. The product, tumor-targeted TMZ (ttTMZ), was labeled with 67/68Ga and evaluated using radioligand assays to determine SSTR2 binding, specificity, and internalization of the drug-receptor complex. To investigate SSTR2-targeting in vivo, positron emission tomography (PET) was performed 1 h after injection of 68Ga-ttTMZ in H69 xenografts in the presence and absence of a blocking agent. To further evaluate specificity and biodistribution at pharmacologically active drug concentrations, we performed a dose-escalation study with 67Ga-ttTMZ in (i) mice bilaterally implanted with HCT116-WT (SSTR2 negative) and HCT116-SSTR2 (transfected, high SSTR2) cells and (ii) mice implanted with IMR-32 cells (endogenous SSTR2). Resected tissues were weighed and gamma counting was performed to quantitatively measure drug biodistribution as injected activity per gram of tissue (%IA/g) at 3 h p.i.

Results: ttTMZ was efficiently produced with (radio)chemical purity >90%. Cell-based experiments showed that the specific binding of 67Ga-ttTMZ was similar to 67Ga-DOTA-TOC and correlated with SSTR2 expression. In HCT116-SSTR2 cells that highly overexpress SSTR2, 14.8±4.8% of 67Ga-ttTMZ and 17.0±4.2% of 67Ga-DOTA-TOC were taken up by cells. Markedly less accumulation was observed in cell lines with lower SSTR2 expression. SSTR2 selectivity was further demonstrated in blocking studies where tracer binding was reduced by nearly 90% when co-incubated with octreotide. Acid-washing experiments demonstrated internalization of 67Ga-ttTMZ after receptor-binding, indicating retention of agonist properties following chemical modification. PET imaging in H69 xenografts showed a notable accumulation of 68Ga-ttTMZ in tumors, which was reduced by 1.2-fold in blocking studies. Similar SSTR2 selectivity was seen in the dual implant model as shown by >5-fold higher uptake in the SSTR2-positive tumors. The tissue distribution profile of 67Ga-ttTMZ was analogous

to 68Ga-DOTA-TOC: high tumor uptake, rapid elimination through the kidneys, and low signal in normal tissues. This pattern was also observed in dose escalation studies and demonstrates the preferential uptake of ttTMZ in tumors in a therapeutic setting.

Conclusion: We developed a novel drug conjugate that selectively delivers TMZ to SSTR2-expressing cells. Direct radiolabeling of ttTMZ via the MMC enhanced agent characterization by enabling quantification of binding in cells and non-invasive imaging of agent biodistribution in animal models that eventually guides optimization strategies.

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Webinar: Imaging and sensing
4:05 PM- 4:12 PM

Multimodality guidance for breast-conserving cancer surgery using real-time navigated mass spectrometry

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OBJECTIVES: For early-stage breast cancer, the recommended treatment includes breast-conserving surgery (BCS) to remove the tumor while conserving normal tissue for improved cosmesis. In current practice, positive margin rates have stagnated around 30%, requiring repeat surgeries to ensure that the cancer is completely removed. To facilitate intraoperative margin assessment, we propose a multimodality surgical guidance system integrating rapid evaporative ionization mass spectrometry (REIMS) data with real-time navigation based on electromagnetic (EM) tracking and intraoperative ultrasound (US) imaging. The overarching aim of this system is to reduce positive margin rates for BCS and improve conservation of healthy tissue compared to the current standard-of-care.

METHODS: REIMS has been proposed as an intraoperative tool based on its ability to profile and classify tissues in real-time using pre-built spectral databases and machine-learning to analyze the metabolites in the electrosurgical plume produced by the cautery tool. Although REIMS can indicate the presence of cancerous tissue, it does not provide spatial information that would allow surgeons to navigate back to this location and remove additional tissue, necessitating the integration with guidance technologies.

As a proof-of-concept, REIMS was used intraoperatively during thirteen surgeries to analyze and retrospectively classify the tissue dissected with an EM-tracked cautery. During these procedures, a localization wire with an EM sensor was placed into the tumor as a marker and the tumor was contoured using tracked US images, creating a 3D model. We have previously shown in a study of 40 patients that use of the navigation system during BCS results in the removal of less normal breast tissue without compromising positive margin rates; however, its use is limited to the US-visible tumor region.

The REIMS data was temporally synchronized with the navigation system, allowing computation of the spatial origin of the signals. In the current study, we trained and cross-validated a tissue classifier based on ex vivo REIMS spectra from pathology-validated normal breast (N=118) and invasive breast cancer (N=36) then retrospectively tested our model on the intraoperative REIMS data. Spectra classified as ‘tumor’ were mapped onto a display of the tumor region and compared with the pathology report.

RESULTS: Ex vivo spectra from cancerous tissue was characterized by a distinctly-elevated ratio of

glycerophospholipids-to-triglycerides. The tissue classifier demonstrated 90% accuracy on cross-validation. Preliminary assessment of the combined REIMS and navigation data has shown the complementary nature of these data types. Three specimens showed positive margins on the post-operative reports. Navigated REIMS detected tumor-breaches in two of these cases, showing agreement with the pathology report in the 3D location. In the third case, tumor encroachment was detected on navigation; however, with REIMS one spectrum was suspicious but could not be classified due an absence of reference compound in the spectrum.

CONCLUSION: Preliminary results show that an integrated multimodality guidance system combining real-time REIMS with navigation technologies is feasible in the operating room for BCS to provide intraoperative margin assessment. Future studies will expand on this clinical validation, as well as the incorporation of deep-learning tools for data interpretation and to improve clinical workflows.

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Webinar: Imaging and sensing
4:12 PM - 4:19 PM

Targeted Multicolor In Vivo Imaging Over 1000 nm Enabled by Nonamethine Cyanines

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Recent progress has shown that using wavelengths between 1000 and 2000 nm, referred to as the Shortwave-Infrared range (SWIR), can enable in vivo imaging at depths and resolution not possible with conventional optical wavelengths such as visible (<700nm) and near infrared (NIR, 700-1000 nm). However, a critical bottleneck in this field is access to biologically compatible and targeted fluorescent probes that operate in this range with high absorption coefficients, well-separated absorbance maxima and efficient emission in the SWIR region – properties critical especially for targeted in vivo multiplexing experiments. The objective of this study was to generate and investigate novel SWIR bioconjugatable compounds for performing fluorescence guided surgery (FGS) in multicolor in tumor mice, with negligible crosstalk between the channels.

Enabled by a rational design process, persulfonated indocyanine dyes (FNIR-872 and FNIR1072) were generated with absorbance maxima at 872 and 1072 nm through catechol- and aryl-ring fusion, respectively, onto the nonamethine scaffold.

Both dyes were successfully conjugated to a monoclonal IgG2 therapeutic antibody (Panitumumab, against the epidermal growth factor receptor (EGFR) overexpressed in multiple cancers) or to a glucan molecule such as dextran, commonly used in microscopy experiments for vasculature imaging. Both conjugates were tested in breast tumor mouse models (MDA-MB-468) in combination with the heptamethine dye indocyanine green (ICG).

These chemical and biological studies were supported by complementary advances in a custom-built SWIR imaging setup and software package for multicolor real-time imaging in vivo that incorporates different NIR laser excitation sources specific for each of dyes (?ex = 785 nm for heptamethine cyanine dyes, ?ex = 892 nm for FNIR-872 and ?ex = 968 nm for FNIR-1072), as well as a 1300 nm LED for reflectance imaging. Lasers and LEDs were sequentially triggered and we used long-pass emission filters (>1050nm) which detect the emission tail of these dyes (excitation multiplexing).

In vitro analysis of these FNIR dyes demonstrated that they have significant emission in the SWIR range (>1000 nm) and red-shifted absorbance maxima compared to the clinically employed heptamethine indocyanines, ICG and IR-800CW. Multiplexed three- colors in vivo imaging using monoclonal antibody Panitumumab- and dextran- conjugates with FNIR-872 or FNIR-1072 in breast tumor model illustrate the benefits of concurrent labeling of the tumor as well as the macro and micro vasculature in the surroundings. Moreover, these conjugates were multiplexed against ICG dye for labeling in parallel lymphatic vessels, while the reflection channel was used for room light visualization of the surface of the mouse.

Here we report the development of two novel bioconjugatable indocyanines derived dyes suitable for targeted-SWIR- FGS in multicolor in combination with existing heptamethine indocyanines. The high acquisition speed allowed us to precisely perform fluorescence guided resection of tumor mass and associated lymph-node in tumor mice. These molecules in combination with the multi-color real time visualization software tools we have developed will have applications in diverse preclinical and clinical contexts where multiplexed information of targeted biological structures is needed. Results have been published in nature method journal (doi: 10.1038/s41592-022-01394-6)

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Webinar: Imaging and sensing
4:19 PM - 4:26 PM

Interpretable computer aided margin assessment in navigated iKnife surgeries

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Objectives: Difficulties associated with detection of cancer in surgical margins can result in incomplete tumor resection that implies the need for revision surgeries. The navigated iKnife is an intraoperative mass spectrometry modality that provides surgeons with real-time metabolite signatures of tissues corresponding to the excision location. Reinforcement of iKnife with artificial intelligence in a computer aided intervention scheme creates an intraoperative margin assessment tool that improves patient outcome. Deployment of deep models for clinical decision making should not only provide accurate prediction but also insights on how the decisions are made. We are proposing a new approach for representation, visualization, and analysis of surgical mass spectrometry data for interpretable margin assessment.

Methods: A local mass spectrometry dataset was collected ex-vivo from lumpectomy cases at our tertiary clinical center under supervision of a senior pathologist. After standard preprocessing pipeline, each mass spectrum was converted to a multi-level hierarchical graph where each graph node contained peaks from an overlapping sub-band of the spectrum. A deep graph neural network is then designed and trained to output the predicted tissue label, as well as the spectrum attention map that leads to this prediction. The performance of the proposed method was compared with several baseline models.

Results: In a 4-fold cross validation experiment, an average cancer classification AUC of 95.6% was achieved, outperforming baseline models statistically significantly. Distinguishable distributions of attention patterns were revealed in the proposed visualization. The cancerous and normal burns gather more attention in the lower and higher spectral sub-bands respectively, which agrees with previous findings in metabolomics literature. Prospective exploration of spectral attention patterns for different cancer grades reveals the correlation between the model attention and cancer progression, which further proved the legitimacy of the proposed framework.

Conclusion: Intraoperative navigated iKnife provides surgeons with metabolic signatures of the cauterized tissue, along with the spatial information of the cauterization location. Interpretable deep models are critical components in turning the navigated iKnife into an intraoperative margin assessment tool that facilitates surgical decision-making. The proposed framework for representation, visualization and analysis of mass spectrometry data is a perfect fit for this goal due to its high classification accuracy and interpretability of the outcome.

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Webinar: Surgery
3:30 PM - 3:37 PM

NousNav: Democratizing Access to Neuronavigation

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[Objectives] It is estimated that 13.8 million patients per year require neurosurgical interventions worldwide. Surgically treatable disorders and diseases affecting the brain and central nervous system therefore have a significant impact on health worldwide. Of that nearly fourteen million patients needing neurosurgical interventions every year, it is estimated that 82% arise in low- and middle-income countries. In these lower resources settings, current commercial neuronavigation solutions are inaccessible. Building a low-cost neuronavigation system to democratize access to these tools could thus have a significant impact on global health. Making neuronavigation accessible everywhere is what we strive to achieve with the proposed NousNav system.

[Design] Our goal is to design a complete open-source system, with both hardware specifications and a software implementation, that could be built and reproduced by any team in any region as an alternative to current commercial offerings where they are not affordable. To achieve this goal, we set the following specific requirements for the devised system: 1-to be fully available under permissive open-source licenses; 2-to rely only on low-cost, readily available, off-the-shelf components or components that can be locally manufactured in low-resource settings; 3-to use reusable components as much as possible, rather than single-use consumables; 4-to be easy to use for non-technical users; 5-to be as data-agnostic as possible; 6-to be as rugged and robust as possible; 7-to be as modular as possible.

[Implementation] We designed and built an initial prototype of NousNav hardware and software to show the feasibility of fulfilling our design requirements. Sourcing all hardware required to build the prototype costs under 6k USD. The software is a custom 3D Slicer application that was built using the SlicerCustomApp template and uses functionalities from SlicerIGT. The PLUS library and OpenIGTLink library and protocol are used for communication between the tracker and the computer. A custom interface was designed and built to achieve the requirements outlined in the Design section above, i.e., that it should be operable by the surgeon and be compatible with OR constraints. The interface is simple, intuitive and uncluttered so that it can easily be navigated intraoperatively, viewed from a distance, and doesn't need to be run by a technical user, thus alleviating the need for a technician to be present. The workflow is minimal but complete with a logical progression between steps. Emphasis is placed on image visibility in a dark OR setting. The large font size and contrasted colour scheme help make the system easy to use intraoperatively. Text can be read from afar and colours make important information salient to the user.

[Conclusion] Our first prototype of NousNav demonstrates that our goal of designing and building an open-source low-cost neuronavigation system is feasible. Even at this initial prototype stage, NousNav already reaches most of the set design objectives. However, additional improvements are needed to reach the remaining ones: reduce use of consumables, support a broader range of input data, support intraoperative interaction under sterile conditions and further improve robustness and ruggedness of both software and hardware.

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Webinar: Surgery
3:37 PM - 3:44 PM

Neurosurgical Guidance at Cortical Level: Concepts and Preliminary Results

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[Objective] A craniotomy is the removal of a part of the skull to allow surgeons to have access to the brain and treat tumors. When accessing the brain, a tissue deformation occurs and can negatively influence the surgical procedure outcome. In this work, we present a novel Augmented Reality neurosurgical system to superimpose pre-operative 3D meshes derived from MRI onto a view of the brain surface acquired during surgery.

[Methods] Our method uses cortical vessels as main features to drive a rigid then non-rigid 3D/2D registration. We first use a feature extractor network to produce probability maps that are fed to a pose estimator network to infer the 6-DoF rigid pose. Then, to account for brain deformation, we add a non- rigid refinement step formulated as a Shape-from-Template problem using physics-based constraints that helps propagate the deformation to sub-cortical level and update tumor location.

[Results] We tested our method retrospectively on 6 clinical datasets and obtained low pose error, and showed using synthetic dataset that considerable brain shift compensation and low TRE can be achieved at cortical and sub-cortical levels.

[Conclusion] The results show that our solution achieved accuracy below the actual clinical errors demonstrating the feasibility of practical use of our system. This work shows that we can provide coherent Augmented Reality visualization of 3D cortical vessels observed through the craniotomy using a single camera view and that cortical vessels provide strong features for performing both rigid and non-rigid registration.

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BWH Radiology Department Research Pilot Grant Award
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Webinar: Surgery
3:44 PM - 3:51 PM

Resection Progress Mapping For Real-time Residual Tumor Identification and Brain Shift Estimation

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Introduction
Extent of resection in low and high-grade gliomas is strongly correlated with prognosis and is a major modifiable determinant of survival. Challenges to gross total resection arise from difficulties in distinguishing tumor tissue from peritumoral eloquent parenchyma and from brain shift. Surgical adjuncts such as intraoperative MRI (iMRI), intraoperative ultrasound (iUS) and fluorescence imaging can augment the surgeon's ability to minimize unintentional residual tumor, but introduce their own limitations. We propose a method to provide the surgeon with direct feedback on the progression of resection and identify potential residual by mapping time-stamped tool-tip positions of navigated instruments.

Objective
We demonstrated the application of resection progress mapping in 18 phantom experiments as well as 37 hemispheric glioma patients to showcase its ability to identify potential residual as well as to flag brain shift.

Method
We simulated resection on 18 brain phantoms with tracked neurosurgical tools such as the CUSA (Cavitron Ultrasound Aspiration device), bipolar forceps, the suction tip and standard navigation pointers. Tracking data was streamed from a Brainlab neuronavigation system to a custom module in 3D Slicer using OpenIGTLink. Models of the resection cavity were generated in real-time using time-stamped tool-tip positions and displayed both as 2D map overlays and 3D models. We also temporally color-coded the tracking results to illustrate the sequence of resection. The system was subsequently translated to the Advanced Multimodality Image Guided Operating Suite (AMIGO) in 37 hemispheric glioma cases to assess its utility by comparing the residual tumor burden predicted by our method with iMRI.

Results
In 18 phantom experiments, the resection maps generated from our workflow were evaluated using the metrics - coverage and overlap. Coverage was defined by how well the resection map covered the resection cavity segmented on intra-procedural imaging. Overlap was defined by how well the resection map overlapped the segmented resection cavity. We achieved a coverage of 97.5% and an overlap of 94.7%. In the 37 hemispheric glioma cases, 70% were found to have residual tumor on intraop MRI. After excluding cases with inadequate sampling density, our technique estimated the existence and location of residual tumor in 93% of cases. In a subset of these cases, we reliably predicted the extent of residual tumor as well.

Conclusion
We developed a resection tracking system with sub-millimeter sampling resolution in real-time and with the highest reported sampling rate, that can direct the surgeon's attention to the location of residual tumor as well as flag brain shift. From the perspective of global neurosurgery, our method shows potential in providing an alternative to iMRI for resource-limited settings. The temporally color-coded resection process can serve as a tool for teaching resection strategies. While the focus of our work pertained to the resection of gliomas, this technique can be extrapolated to multiple skull base approaches, resection of epileptic foci and other hemispheric tumors.

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Webinar: Surgery
3:51 PM- 3:58 PM

Image-guided Instrument Adapter Array-assisted Cavitron Ultrasonic Surgical Aspirator^CUSA Resection of a Right Temporal Glioblastoma – A Technical Case Report

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Introduction:
Image-guided instrument adapter array-assisted (IAAA) resection has been presented as a useful tool in the resection of gliomas. In this report, we present a case where an IAAA cavitron ultrasonic surgical aspirator (CUSA) was used to achieve gross total resection of a right temporal glioblastoma.

Case Report:
A 72-year-old, left-handed male on Rivaroxaban for Factor V Leiden deficiency was diagnosed with an

incidental right temporal tumor that had heterogenous moderate enhancement of the posterior portion on preoperative magnetic resonance imaging (MRI). He underwent Image-guided IAAA CUSA excision of his tumor with modeling of the resection cavity using resection progress mapping in 3D Slicer. An area that appeared normal under the surgical microscope and displayed absence of resection coverage by IAAA CUSA resection cavity mapping, was discovered to be tumor on intraoperative MRI, subsequent resection, and pathology. The patient did not have any new neurologic deficits postoperatively.

Conclusion:
The surgical utility of IAAA CUSA coupled with 3D Slicer resection tracking was highlighted. Improvements in IAAA device ergonomics and balance, line of sight to arrays, and tracking algorithm integration into the microscope may further improve the utility of this surgical technique.

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Webinar: Surgery
3:58 PM- 4:05 PM

Image-guided Ommaya reservoir placement for leptomeningeal metastasis in the Philippines: a case series and scoping review

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Background. Leptomeningeal metastasis is a severe disease with poor prognosis and limited therapeutic options. With maximal therapy, overall survival is several months and if therapy is not given, survival times are within weeks after diagnosis. Intra-Ommaya chemotherapy is an effective treatment for these patients and is preferred over a lumbar puncture in terms of drug distribution and complication rates. Image-guided catheter placement is superior to the free-hand technique not only in placement accuracy but also in proximal catheter failure rates.

Objectives. The objective of this study is to show the safety and feasibility of image-guided placement of an intraventricular catheter and intra-Ommaya methotrexate chemotherapy in Filipino patients with leptomeningeal metastasis. A secondary objective is to present an economic evaluation of the procedure and to perform a scoping review of the literature to determine the use of the technique in low- to middle- income countries.

Methods. This is a descriptive study of six consecutive patients with leptomeningeal metastasis who underwent image-guided placement of a ventricular catheter and Ommaya reservoir at a single institution in the Philippines. A scoping review of the literature about leptomeningeal metastasis treatment was performed.

Results. Six patients with small ventricles and evidence of leptomeningeal metastasis underwent image-guided placement of a ventricular catheter using the BrainLab VarioGuide system. There were no note of ventricular catheter malposition, failure, or infection during a course of 53 consecutive injections of intra-Ommaya methotrexate therapy. Leptomeningeal enhancement resolved in three patients (50%). Complications include oral ulcers in 4 patients and cough, difficulty breathing, dysphagia, and mucositis in 3 patients. The median asymptomatic interval is 4.0 days (95% CI of 3.7 to 4.3 days). Overall survival after image-guided placement was 6.6 months (95% CI of 4.3 to 9.0 months). The average cost of surgery with neuronavigation and intraventricular methotrexate is $5000 and $250, respectively. A search was performed using the terms “intraventricular”, “leptomeningeal”, and “metastasis”. Randomized controlled trials, observational cohorts, case series and case reports from different countries were published from 1976 to 2022. Only 3.8% (4/105) of the studies were performed in low- to middle- income countries.

Conclusion. Image-guided ventricular catheter placement and intra-Ommaya methotrexate chemotherapy is a

safe procedure for patients with leptomeningeal metastasis.

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Webinar: Surgery
4:05 PM- 4:12 PM

Progression-free and Overall Survival of Adult Patients with High-Grade Gliomas undergoing Image-Guided Surgery: A Network Meta-analysis utilizing Individual Patient Survival Data

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Introduction. Randomized controlled trials, systematic reviews and network meta-analyses have compared the effectiveness of image-guided surgery (IGS) in the treatment of high-grade gliomas (HGGs) with extent of resection (EOR) as their primary outcome. Progression-free survival (PFS) and overall survival (OS) are reported in these reviews but time-to-event data are not compared consistently due to the different styles of analyzing survival data. The goal of this study is to compare the types of IGS based on their effects on PFS and OS.

Methods. A search was performed on PubMed, Cochrane, and Google Scholar for studies comparing at least two of the following: standard surgery (SS), conventional neuronavigation (NN), 5-amino-levulenic acid (5-ALA), intraoperative MRI (ioMRI), and intraoperative ultrasound (ioUS). The primary outcomes for this study were PFS and OS. Individual patient survival data were digitally extracted using WebPlotDigitizer. Comparative analysis and ranking of the different IGS treatments will be performed using the Frequentist network analysis (NMA) and Cox-proportional hazards (CPH) regression models.

Results. The median PFS of 557 patients was 6.139 months (95%CI of 5.618,6.660). The median OS of 258 patients was 17.572 months (95%CI 15.828,19.316), respectively. A Frequentist NMA model for PFS showed a significantly better mean survival time (months) of ioMRI (MD=3.23; 95%CI 0.89,5.56) and for 5-ALA (MD=1.18; 95%CI 0.30,2.06) compared to NN (reference intervention). The NMA for PFS suggested a ranking of ioMRI, 5-ALA, and NN (from best to worst). CPH regression for PFS showed that NN (OR=2.65; 95%CI 1.573,2.980; p<.001) and 5-ALA (OR=1.460; 95%CI 0.982,2.172; p=.062) had poorer PFS compared to ioMRI. OS was not significantly different between the IGS types (p>.236).

Conclusions. The suggested ranking of treatment effectiveness is 1) ioMRI, 2) 5-ALA, and 3) NN (best to worst). An individual patient data meta-analysis (IPD-MA) is recommended to better elucidate the treatment effectiveness and independent factors affecting IGS treatment strategies.

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Webinar: Surgery
4:12 PM - 4:19 PM

Non-invasive robotic tumor bed inspection in breast conserving surgery

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INTRODUCTION: Delineating tumor margins during breast conserving surgery is a challenging task due to the high mobility and deformation of breast tissue. After resection of the primary tumor in these procedures, there is often cancer left behind on the tumor bed. We hypothesize that inspecting the tumor bed to identify and localize

potential residual cancer cells can help mitigate this challenge. Towards this idea, we demonstrate an open-source testbed that combines imaging, artificial intelligence (AI) and cooperative robotics to achieve such a system. We focus on implementing a non-invasive imaging approach that relies on a combination of optical and acoustic inputs to help characterize the surface layer of tissue on the tumor bed while also providing depth information about the tissue being imaged. For tumor bed inspection, this is necessary to identify residual cancer cells, and how far they penetrate the surrounding anatomy without causing any unnecessary, additional healthy tissue loss. In this study, we focus on the software and hardware tools used to achieve this testbed for prototyping as well as initial results from preliminary imaging studies on animal tissue.

METHODS: This system for tumor bed inspection requires parallel flow of multiple imaging inputs that are spatially registered using robotics and temporally synched. To achieve this, we make use of 3D Slicer for visualization and navigation, as well as SlicerIGT (http://www.slicerigt.org/wp/) to stream imaging inputs. Signal processing and data fusion can then be done with AI tools in SlicerAIGT (https://github.com/SlicerIGT/aigt) which enables direct communication between AI models and imaging inputs in 3D Slicer. To demonstrate the technical viability and function of this testbed, we investigate the use of a combined temporally enhanced ultrasound (TeUS) imaging [1] and broadband spectroscopy to detect tissue heterogeneity in animal models. Tissue phantoms, made up of heterogeneous tissue are imaged with throughput broadband spectroscopy and ultrasound. Following this acquisition, the absorption of broadband light is computed to characterize the surface tissue optically. Additionally, the TeUS signals from the tissue are used to classify pixels in the US images according to their tissue type with a simple support vector machine (SVM).

RESULTS: Using this test bed, we were able to successfully demonstrate a tumor bed inspection system that deploys combined optical and acoustic imaging with machine learning for tissue recognition. More specifically, the absorption curve for each broadband acquisition showed distinct separability for every tissue phantom and our trained SVM could successfully classify 82% of the ultrasound pixels in the TeUS images according to their tissue type.

CONCLUSIONS: These preliminary results demonstrate the viability of this imaging approach and testbed for robotic tumor bed inspection in addition to the potential usage of combined optical and acoustic imaging for non-invasive tissue recognition. To achieve this, we are currently working on using this imaging system as the input for the cooperative robotic control scheme.

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Webinar: Surgery
4:19 PM - 4:26 PM

A surgical planning software for DIEP flap breast reconstruction using a depth camera

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[Objectives]
DIEP flap breast reconstruction uses tissue from the abdomen to shape the new breast. It is a challenging procedure to ensure symmetry of the reconstructed breasts. Further, accurately estimating the amount of harvested tissue from the abdomen is difficult and prone to qualitative judgement of the surgeon. Improper reconstruction of the breast can lead to asymmetry of the breasts, further resulting in detrimental quality of health, depression and anxiety for breast cancer patients. The objective of this abstract is to develop novel imaging algorithms to enable accurate reconstruction of the breast to ensure symmetry and, in turn, good quality

of life.

[Methods]
We have developed a 3D Slicer module coupled with a depth camera to plan the reconstruction of the breast post-mastectomy. An Intel RealSense depth camera is used to scan the healthy breast of the patient. The depth and RGB videos are then co-registered. A mosaic of the mirror image of the breast is obtained using a novel Simultaneous Localization and Mapping (SLAM) method. After cropping the mosaic to only keep the region of interest, a mesh model is generated for 3D printing a mold for intraoperatively shaping the DIEP flap. The process from entering patient information to exporting the different files generated is separated into distinct steps to provide an easy-to-use and intuitive software interface for the user.

[Results]
The repeatability and accuracy measurement of the 3D surface reconstruction method showed average errors under 1.46mm. The breasts of the patients with different skin tones and shapes were successfully scanned and reconstructed in the software.

[Conclusion]
Our 3D surface reconstruction system offers an inexpensive and effective way of planning the flap shape for breast reconstruction. It also provides a straightforward way to quantify breast volume and shape to guide the DIEP flap harvest from the patient's abdomen.

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Webinar: Surgery
4:26 PM - 4:33 PM

Locating tumor classifications in breast cancer surgery

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[Objectives]: Lumpectomies are performed in early-stage breast cancer to remove tumors. Mass spectrometry systems (such as the iKnife) have been used to differentiate tumor from healthy tissue [1]. In comparison to other techniques, a system with real-time spatial tracking and tissue classification would address critical problems surrounding breast-conserving surgery [2]. This system would enable the surgeon to navigate back to locations where residual tumour needs to be excised but doing so has two challenges. First, the iKnife has a variable time-delay, dependent on factors related to the surgical set-up. Second, we must determine when surgeons are making incisions to locate where iKnife classifications originated. Our objective is to calculate the time-delay and determine when surgeons are making incisions, in recorded surgery and in real-time.

[Methods]: The iKnife's time delay was measured by video recording tissue incisions and corresponding iKnife classifications. In recorded surgery, a surgical incision was estimated to be when the cautery tip was within 25 mm of the tumor's center. This is where a positive margin is most likely, near the tumor boundary. A custom python script was used to calculate the distance (mm), time (s), and speed (mm/s) of each incision. Positive classifications from the iKnife were adjusted to surgical incisions using the time delay.

A surgical incision is when the cautery is activated and touching tissue, called the energy event. The cautery can be in 5 states: off, cut-mode-in-air, cut-mode-touching-tissue (energy event), coagulate-mode-in-air, and coagulate-mode-touching-tissue (energy event). To automatically detect these states, we attached current sensors cautery's electrodes, digitized the current with an oscilloscope, and streamed data into 3D Slicer [3, 4]. We

performed ex-vivo and in-vivo tissue testing. A Support Vector Machine (SVM) was trained on various amplitude and frequency-based features of the voltage signals. Integration of voltage data, training the SVM, and classifying the cautery state intraoperatively in real-time was built within an open-source 3D Slicer module (GitHub repository: https://github.com/SlicerIGT.git).

[Results]: The average time delay was 2.84 s with a standard deviation of 0.42 s. The average incision velocity was 21 mm/s. The system accurately classifies cautery states, with an SVM classification accuracy of 100%. The iKnife and oscilloscope classification is completed at a rate of 1Hz and 10Hz, respectively.

[Conclusions]: Our study locates iKnife classifications in recorded breast cancer surgery. Accurately classifying cautery states will allow us to locate iKnife classifications in real-time. By performing majority voting on the cautery classifications during an iKnife classification, we may be able to reduce the model error in detecting the cautery state. Detecting the cautery state enables the analysis of mass spectra differences due to cautery mode. In the future, we will use four inputs to isolate a surgical incision: cautery energy state, low cautery velocity, short cautery distance-to-tumor, and a chromatogram signal. Using these methods, we hope to improve our ability to locate positive iKnife classifications. Doing will likely present clinically sufficient indicator for the need to adjust excision boundaries intraoperatively. This will be explored in future studies.

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Webinar: Medical Robotics
3:30 PM - 3:37 PM

An Ultra-Thin Steerable Transnasal Endoscope to Replace Exploratory Middle Ear Surgeries

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Objectives:
The objective of this project is to create a new low-cost, needle-sized steerable endoscope that makes it possible to survey and diagnose middle ear disease using a minimally-invasive trans-Eustachian tube approach, sparing patients from invasive surgery. Clinical significance comes from the 84,000 surgeries per year (in the USA alone) performed on patients who suffer from a middle ear disease called cholesteatoma that requires exploratory surgery for diagnosis, which is currently achieved surgically by lifting the eardrum to expose the middle ear space. Surgery is currently the only definitive way to diagnose these patients. Worse yet, a second surgery is performed to check for recurrence a year later – even though 67% of patients will be disease free at that time. We seek to replace surgical inspection with a simple endoscopy, facilitated by our new ultra-thin steerable endoscope passed through the Eustachian tube. Our central hypothesis is that our new trans-tubal endoscopic approach can achieve diagnostic visualization of the middle ear equivalent to that provided by surgery today. This has the potential to spare many patients from the pain and complications associated with surgery, by replacing it with a simple endoscopy done through the nose.

Methods:
To accomplish the objectives, we will harness elastic interactions in asymmetrically stiff, thin-walled tubes to create a steerable endoscope that is (1) small enough to pass through the Eustachian tube, while (2) carrying a tiny camera and optical illumination fibers within its own central lumen. The small diameter of the Eustachian tube precludes the use of bulky standard endoscope steering mechanisms. Instead, we harness stiffness asymmetry encoded into the material properties of two tubes that are attached at their tips, thereby transforming small axial motions applied at the endoscope handle into dexterous local bending at the endoscope tip. The result is an inexpensive, needle-sized, disposable, steerable endoscope for trans-tubal visualization of the middle ear.

Our approach in Aim 1 is to use laser micromanufacturing and catheter-inspired design processes to fabricate a clinic-ready steerable endoscope tip with integrated imaging and illumination. CT imaging of the middle ear will be used to optimize the design of the tubes and the resulting shape of the device during middle ear navigation. Aim 2 incorporates rigorous quality and human factors-based design enhancements, preparing our device for FDA 510(k) clearance review immediately at the end of Phase II. Aim 3 focuses on statistically powered experiments to evaluate our hypothesis that our new steerable aiming tip will enable middle ear inspection and cholesteatoma diagnoses to be performed using a non-surgical, trans-Eustachian tube approach, with equal diagnostic-quality visual coverage compared to the surgical standard-of-care. Success in validating these hypotheses will strongly motivate future Phase III activities (supported by private capital after the conclusion of this Phase II SBIR) where we complete the FDA 510(k) clearance process and launch our device on the market.

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Webinar: Medical Robotics
3:37 PM - 3:44 PM

On Surgical Planning based on Patient-Specific CTR Design for Percutaneous Nephrolithotomy

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[Objectives]: Percutaneous nephrolithotomy (PCNL) is considered a first choice minimally invasive procedure for treating kidney stones larger than 2 cm. It yields higher stone-free rates than other minimally invasive techniques and is employed when extracorporeal shock wave lithotripsy or uteroscopy are deemed infeasible or undesirable for some reason. Using this technique, surgeons must determine skin and kidney puncture locations to create a tract through which a scope is inserted for gaining access to the stones. Traditional PCNL tools, however, present limited maneuverability, may require multiple punctures and often lead to excessive torquing of the instruments which can damage the kidney parenchyma and thus increase the risk of hemorrhage. In this work, we propose an approach for determining surgical plans and patient-specific designs of flexible concentric tube robots (CTR) for treating complex calculi through a single incision port with the aim of reducing complications associated with PCNL.

[Methods]: We have developed a general framework comprising a nested optimization-driven scheme for determining a single-tract percutaneous and renal access as well as the design of customizable CTRs tailored specifically for each individual patient undergoing PCNL. Based upon preoperative CT scans digitally segmented on 3D Slicer, we propose a minimum volume coverage ellipsoidal approximation to the kidney stones and utilize it to introduce the concept of ``main directions'' of the kidney stone presentations. This concept is leveraged to capture the end goal of maximizing the reachability of the anatomically constrained CTR along the most important directions a surgeon must navigate during the stone treatment process.

[Results]: We have applied the optimization algorithm on clinical data of seven patients who underwent PCNL at the Brigham and Women's Hospital under an institutional review board (IRB) approved protocol. The simulation results were obtained by running all seven cases in parallel on an Intel i5-7500, 3.40GHz Linux based machine for 4 hours and 47 minutes. In order to investigate the kinematic capability of the surgical plan and the optimized CTR design in each clinical case, the manipulator was steered along the main directions of the stones whereby the distribution of the position error at the calyx, across all cases, was such that a 5mm error threshold fell below the 75th percentile, as desired in this type of medical intervention.

[Conclusion]: In this work, we have developed and assessed an optimization-driven approach for surgical planning based on patient-specific CTR designs for use in percutaneous neprolithotomy. As illustrated by the seven clinical cases investigated in this work, we believe that this patient-specific approach can help reduce the clinical complications associated with PCNL for a wide variety of stone presentations of different complexities.

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Webinar: Medical Robotics
3:44 PM - 3:51 PM

C-am fluoroscopy-guided Pose Estimation and Path Planning of Surgical Robots

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Objectives: Pose estimation of robots during interventional procedures continues to be a challenging task. In minimally invasive surgery for mitral valve repair, catheters are often used for placement of clip that latches on to a mitral valve leaflet to treat leaky valves and minimize backflow or regurgitation. Fluoroscopic guidance is used for the placement of clips and tracking the placement of clips through the procedure is useful. Steerable guidewires are also becoming increasingly popular for MIS. Furthermore, this fluoroscopy can be used to determine the path that steerable guidewires can follow in vasculatures.

Methods/Design: We use 350 images acquired from a GE OEC 9800 C-arm where a robot that is designed for mitral valve surgery is actuated into various positions and orientations for clip delivery. This is done to determine a data-based algorithm to determine the pose of the robot. Since the robot has torsional and bending capabilities, the estimated pose should be comprised of both parts. A convolutional neural network architecture based on the ResNet-50 design is used to train semantic segmentation algorithms that classify the pixels in the fluoroscopic image as part of the torsional distal springs, proximal springs, or clip. Then, an equivalent ellipse algorithm is used to determine the bending angle, whereas an SVM based on HoGs is used to estimate the angular orientation of the robot. For path-planning for steerable guidewires, an approach for determining the optimal path for steerable guidewires to follow is constructed. From fluoroscopic images of a steerable COAST guidewire in phantom vasculatures, the workspace of the robot is found through a flood-fill algorithm. Then, the user-defined start and endpoints for a path are used to construct an optimal path using the constraints for these steerable guidewires using a modified hybrid A-star algorithm. The constraints of the guidewire are that the motions can be of straight or constant curvature paths, and those are the constraints for the modified hybrid A star algorithm.

Results/Findings: The accuracy of semantic segmentation using the neural net architectures was determined to be about 77% for the clip, 60% for the distal spring, and 81% for the proximal spring. Using these segmentations, a series of bending experiments were performed using the robot with an electromagnetic tracker to find the accuracy of the bending angle calculation, and the mean error was 7.7°. The torsional angle detection accuracy for classifying the angle into 5 ranges was 76%. For the steerable guidewire navigation, the COAST guidewire robot was traversed along several paths in vascular phantoms that were generated using the modified hybrid A star path-planning algorithm. The accuracy of the final tip position as compared to the intended position was within 4mm for all the trials, with an average error of 2.01 mm.

Conclusions/Implications: Fluoroscopic imaging can potentially be used to track the pose of medical robots such as the mitral valve robot during interventional procedures, and the same imaging modality can be used to compute optimal paths for steerable guidewires such as the COAST guidewire to traverse vasculatures.

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Webinar: Medical Robotics
3:51 PM- 3:58 PM

Dynamic Modelling and Control of a Robotic Intracardiac Echo Catheter

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[Objectives] Currently, the treatment of atrial fibrillation with intracardiac echo (ICE) guidance is tedious and requires simultaneous manipulation of the ablation and ICE catheters. The objective of this work is to develop a robotic ICE catheter, dynamic model and control algorithm to robustly control the ICE catheter inside a beating heart.

[Methods] We have modified the Sensei Robot (Hansen Medical, Inc.) to an open architecture robot with full access to the nine revolute and translation joints. The Sensei robot was connected to a Delta Tau motion controller and each motor was driven by a Maxon linear amplifier. A Siemens Acuson ICE catheter was disassembled and tendons controlling the distal tip of the ICE catheter were connected to the Sensei robot. Further, we have developed a model for the robotic ICE catheter based on the Cosserat rod theory that relies on strain parametrization while accounting for the actuator motions, motor and tendon frictions, and the external loads along the catheter body which arise during the cardiac procedure. Parameter estimation of the dynamic model was performed using weight release experiments. Optimal control design (LQR and H-infinity) was simulated to regulate the dynamics of the catheter's tip position.

[Results] The parameters of the catheter were consistent for differing weights and catheters. Preliminary simulation results demonstrate an accurate and robust control of the distal end of the catheter. Experimental validation using an EM sensor feedback and tendons actuation for closed-loop control is currently underway.

[Conclusion] The simulation results show that our approach can robustly regulate the dynamics of the robotic ICE catheter in the presence of uncertainties and disturbances within the beating heart environment.

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Webinar: Medical Robotics
3:58 PM- 4:05 PM

Preclinical Evaluation of a Marker-less, Real-time, Augmented Reality Guidance System for Robot Assisted Radical Prostatectomy

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Background and Objectives

Robot-assisted laparoscopic radical prostatectomy (RALRP) is a surgery in which entire cancerous prostate is removed. Because prostate cancer is not visible with standard endoscopic equipment, in many cases cancer is left behind. Augmented reality (AR) during surgery can mitigate incomplete cancer removal by overlaying the anatomical boundaries segmented from medical imaging data onto the camera image. Therefore, many AR guidance systems have been proposed for robot-assisted surgery [1][2]. Although useful, two major problems in these systems are the use of external calibration objects [1] and a manual alignment step [2]; these interfere with the surgical workflow and thus present a hindrance in the adoption of AR. Therefore, we present the first such AR guidance system for RALRP that transforms the medical imaging data from the transrectal ultrasound (TRUS) coordinate system to the camera image coordinate system without using any external calibration markers before or during surgery. Only surgical instrument visible in the camera is utilized for calibration without changing the surgical workflow significantly. Therefore, the current work has following objectives: 1 - To present a single step, marker-less, joint camera and hand-eye calibration step to reduce the total number of intra-operative calibrations. 2 - To perform an overall system evaluation on real and simulation set up by calculating overall mean re-projection errors (MRE) and overall system error (SE) from TRUS to Camera Image frame.

Methods

Our guidance system requires two transformations: TRUS to robot, TRUS_T_DV, and camera projection matrix, M (i.e., the transformation from endoscope to camera image frame). TRUS_T_DV is estimated by the marker-less method proposed in Mohareri et al., 2015 [3]. M is estimated by selecting corresponding 3D-2D data points in the endoscope and the image coordinate frame, respectively, by using a CAD model of the surgical instrument and a preoperative camera intrinsic matrix with an assumption of a projective camera. The parameters are estimated using Levenberg–Marquardt algorithm. Overall errors (MRE and SE) are reported using simulated and real data using a water bath. We show that M can be re-estimated if the focus is changed during surgery.

Results

Using simulated data, we received an overall MRE in the range of 11.69–13.32 pixels for monoscopic and stereo left and right cameras. For the water bath experiment, the overall MRE is in the range of 26.04–30.59 pixels for monoscopic and stereo cameras. The overall system error from TRUS to camera world frame is 4.05 mm.
Conclusion We demonstrate a markerless AR guidance system for RALRP that does not need calibration markers and thus has the capability to re-estimate the camera projection matrix if it changes during surgery, e.g., due to a focus change.

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Webinar: Medical Robotics
4:05 PM- 4:12 PM

A Literature Study on Needle Insertion Mechanical Factors Affecting Prostate Core Biopsy Sample Quality

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[Objectives] The examination of the prostate biopsy procedure is essential in the optimization of the diagnostic pathway of such a prevalent affliction as prostate cancer among men worldwide. With the core needle biopsy being the standard of care for the diagnosis of prostate cancer cases, the ability to obtain quality core samples is directly related to patient treatment and diagnostic reliability. Needle deflection and dynamic tissue deformation are two chief sources of unrepresentative samples outside of human error. The objective of this review was to analyze trends in the literature and comprise a comprehensive analysis.

[Methods] To assess how these factors affect overall histological sample quality, and what variables influence deflection and deformation, an exploratory systematic review of related literature and clinical trials was developed. A literature search using keywords [(core prostate) OR (prostate)] AND [(biopsy) OR (needle)] AND [(histological) OR (fragmentation) OR (deflection) OR (deformation)] AND [(factors) OR (rate) OR (quality)] was conducted. The resulting articles were analyzed for relevance of factors influencing histological sample quality and selected on a basis of inclusion and exclusion criteria.

[Results] The results highlighted the velocity of needle insertion into the soft tissue as a variable affecting dynamic deformation, including compression and manipulation of the prostate, and the geometry of the beveled biopsy needle tip combined with the application of a biopsy template impacting the deviation of the needle from the linear target. The impact of the application of an external template continues to be variable, limiting potential target locations with fixed guide clearance while introducing an additional component of friction, but fundamentally improving accuracy and precision. Friction forces also significantly influence the final product as related to these factors, shown by the inverse relationship between insertion velocity and friction stress and its effect on deformation through kinetic and viscous energies.

[Conclusion] This literature study clarifies the sensitive aspects of the biopsy procedure and provide for a basis to discuss the improvements to the system and its external influencers to improve overall patient care. This invites further studies to expand on core prostate biopsies by manipulating various factors with the intention of advancing the procedure.

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Webinar: Medical Robotics
4:12 PM - 4:19 PM

A Calibration Framework for Enabling Image-Guided Robotic Surgery with the da Vinci Xi Surgical System via Integrated Stereovision and Joint Kinematics

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[Objective] With widespread deployment of robotic surgical systems, the key hardware components of image guided surgery (IGS) are readily available to surgical teams, but are rarely used to their full potential in clinical practice. Fusion of preoperative imaging with intraoperative video has been demonstrated for a variety of

minimally-invasive robotic procedures, where typically segmented tomography is manually warped to match the surgical view1,2. In this work we demonstrate an efficient calibration framework that will enable automated nonrigid alignment using high quality anatomical surface observations that are derived from stereo reconstruction and fully-registered to the surgical field through the robot kinematic chain.

[Methods] We develop a five-frame tracking topology (Fig. 1a) and describe procedures for estimating each transform in the chain. Initial in vitro validation is performed by imaging a custom renal phantom model with the da Vinci Xi surgical system (Fig. 1b). Observed surface patches are reconstructed from stereo pairs using a modification of PSM Net3 fine-tuned with endoscopic images from the SCARED dataset4. The resulting point clouds are expressed in a common global frame, and the resulting mosaic is compared to the segmented phantom CT.

[Results] To estimate the transform from reconstructed surface to endoscope tip, eleven kinematically-derived endoscope tip positions are registered to optically-tracked ground truth with residual RMS and angular errors of 1.36mm and 1.01°. Using the optimized tip transform, the robot to tracker transformation is estimated from five additional endoscope poses, resulting in 0.84mm RMS error in reprojected calibration features. Disparity maps are produced from nine stereoscopic phantom observations with an average computation time of ~800ms per map. Overall RMS error between the mosaiced point clouds and ground truth CT is less than 1mm.

[Conclusion] This phantom evaluation of the proposed calibration framework extends work by Ferguson, et al.5 on the da Vinci Si system, demonstrating the feasibility of stereovision-based surface capture with the newer Xi robot at millimeter-level registration accuracy. This result will enable development of near real-time image guidance in procedures including robot-assisted partial nephrectomy and trans-oral robotic surgery. This approach features minimal setup and delivers rapid online disparity computation, producing registered surface point clouds that can drive iterative guidance updates through nonrigid warping of preoperative tomography.

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