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Molecular-Guided Surgery: Molecules, Devices, and Applications III

Brian W. Pogue

Sylvain Gioux

Editors

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Molecular-Guided Surgery III: Review of the conference

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ABSTRACT

The Molecular Guided Surgery III conference grew in attendance yet again in this third year, and the number of invited and contributed talks grew as well. This year the focus of the meeting shifted a bit more towards technology goals, standards, FDA approvals, and society guidance. As in previous years, the goal is to foster interaction of basic scientists, translational scientists, companies and practicing surgeons towards the purpose of molecular guided surgery. The presentations started with Advanced Molecular Imaging Methods, then Imaging Systems, then Contrast Agents, and then to Clinical Translation and Applications. The conference ended with an invited review talk from the FDA, and a discussion panel focused around devices, standards, calibration, and differences between academic clinical trials and company developed device performance. This year there was also an additional joint symposium with the Optical Methods for Tumor Treatment and Detection conference, on the Monday morning focused on the topic of Optical and Ionizing Radiation Interactions for Diagnosis and Therapy.

1.0 INTRODUCTION

The third version of this conference was designed macroscopically to be quite similar to the previous two, although there was a strategic focus to steer it towards discussion around technical aspects of systems with the end goal of reaching some review thoughts on standards, tissue phantoms, and consensus around academic system approaches that learn from the industrially developed methods and also feedback some society guidance towards standards that are informed by the known challenges of imaging light remitted from tissue. The format of sessions was largely the same, but strategic invited speakers helped shape the sessions and especially on the 2nd day, focus the discussion around the variety of systems and their performance and measures of performance, and then towards standards, phantoms and FDA regulatory processes. Each day had room for both invited and contributed talks, and the discussion panel was curtailed at 1 hour to allow for ample time to visit the poster session.

The conference format was extended though this year with a Monday session on Optical and Ionizing interaction to explore this as a future topic or conference, with some key invited speakers who have been pioneering this emerging field. This was done jointly with the Optical Methods for Tumor Treatment and Detection conference, chaired by Tayyaba Hasan (Harvard) and David Kessel (Wayne State U.).

2.0 METHODS: MOLECULES & TOOLS

2.1 *Advanced Molecular Imaging Methods*

The conference has always started with a technology focus, and this year the focus on scatter based imaging systems was again the kick off of the meeting. Darren Roblyer (Boston University) reviewed a range of advanced miniaturized technologies for continuous wave (CW) spectroscopy of tissue, combined with frequency domain (FD) spectroscopy, with the goal of making a combined hybrid instrument similar to the ACRIN tested DOSI system from UC Irvine. This invited talk reviewed the latest plans to utilize printed circuit technologies for sources and detectors in CW as well as small RF systems for FD measurement of quantitative tissue metabolism. The talk then transitioned into work on spatial frequency domain imaging (SFDI) as well. Next invited speaker David Cuccia (Modulated Imaging Inc.) reviewed the history and current status of SFDI methods and the research and clinical applications that Modulated Imaging has been focusing on. The RS system has been used by many laboratories in IRB approved clinical trials, and now the Modulated Imaging Ox-Imaging CSTM system has recently received US Food and Drug Agency 510(k) clearance for premarket approval, paving the way for its sale as an imaging system for measuring S₀O₂ in tissue as a

measure of tissue health in patients with potentially compromised circulation, such as the limbs of diabetic patients. Next Sang Hoon Chong presented the work at University of Pennsylvania on SFDI fluorescence imaging and Jessica Ramella-Roman (Florida International U.) presented a more developed device for combined polarization, SFDI imaging of skin lesions. The session ended with David McClatchy from Dartmouth talking about their work on high frequency SFDI imaging of lumpectomy specimens in a system that combines surface optical spectroscopy with x-ray tomography, to detect potential cancer on the margins of the resected specimen.

The second session of Advanced Molecular Imaging Methods focused on different technologies, starting with Bernard Choi (UC Irvine and Beckman Laser Center) reviewing the status of laser special imaging systems that are commercially available and in early phase clinical trials, to image blood flow non-invasively. The use of fluorescence lifetime sampling of tissue to classify tissue as likely benign or malignant was reviewed by Laura Marcu (UC Davis). B Pogue presented for Jonathan Elliott (Dartmouth) on the use of multi-tracer imaging studies in glioma tumors, for tracers used to guide resection, and the ex vivo analysis with fluorescence imaging of sections as compared to immunohistochemistry staining of the molecular features. The session was completed by Nikolas Dimitriadis (Fraunhofer-institut für Produktionstechnik und Automatisierung, Germany) who presented on temporal multiplexing for multispectral fluorescence imaging in an operative setting.

2.2 Imaging Systems

The imaging systems section of the conference was started on with a focus on fluorescence standards by Ute Resch-Genger (Bundesanstalt für Materialforschung und -prüfung, Germany) who presented a review of fluorescence standards that have been developed by her institute in collaboration with industry partners, and how these are developed and then translated out into practice. Maritoni Litorja (US National Institute of Standards & Technology) then presented work on use of tissue phantoms developed at NIST to standardize the responsivity of different systems, and how this might lead towards more homogeneity of response between centers in the same clinical trial or to simply compare data across institutions. Rudolf Verdaasdonk (Vrije Univ. Medical Center, Netherlands) then presented an LED based set up used to compare the NIR sensitivity of 3 different cameras, with potential for surgical imaging guidance. This was followed up by a presentation on tissue mimicking tissue phantoms for protoporphyrin IX fluorescence detection in the brain, by Yijing Xie (Univ. College London, UK), and then a Raman-encoding approach to imaging of topically applied nanoparticles for intraoperative guidance, by Yu Wang (Univ. of Washington, US).

A second session on imaging systems continued with an invited presentation by John Fengler (Novadaq Technologies Inc, Canada) who lead the market in fluorescence cameras for FDA cleared surgical procedure guidance in tissue perfusion. He presented the state of clinical imaging systems today with a focus on some of the newest features being developed for human guidance, such as imaging intensity which is independent of the distance to the tissue, with the goal of making it easier for the surgeon to fully exploit the fluorescence images that are captured. This was followed by a presentation from Nan Cui (Washington Univ. St Louis) on use of Microsoft HoloLens imaging as a tool for fluorescence image display and interaction between the surgeon and the patient. Next Ali Behrooz presented work from PerkinElmer Inc., on their Solaris open imaging system for multichannel fluorescence imaging in surgery. This system demonstrates high sensitivity while being capable of imaging with the room lights on. This work was followed up by two microscopy talks, the first being from Adam Glaser (Univ. of Washington) on a new approach for 3D digital pathology imaging using dual axis light sheet acquisition of images. The 3D volumes captured in minutes allow for true 3D pathology of intact tissue specimens, which could lead to a radical change in how small samples could be imaged in pathology analysis. Jeffrey Watson (Univ. Arizona) presented the final talk of the day, on intraoperative visualization of plasmon resonant liposomes in an augmented surgical microscope, so that the surgeon could see the signal directly in real time, with high brightness, and directly on the tissue.

2.3 Contrast Agents

The contrast agent section kicked off Sunday morning with an invited presentation by James Basilion (Case Western Reserve Univ.) on Theranostic Imaging. Their work has taken photodynamic agents from the phthalocyanines and utilized both standard and targeted approaches to enhance detection and therapy of specific molecular targets. This second invited talk was from Matthew Bogoyo (Stanford Univ.) who presented an overview of their labs work on protease targeted covalent bonding agents which are activated by the presence of the enzyme and are then locked into intracellular locations by the bonding to the protease. Hisataka Kobayashi (US National Cancer Institute) presented his work on sprayable activatable enzymes for mapping of the smallest lesions on mucosal surfaces. Connor Barth (Oregon Health & Science Univ.) presented their work on topical application of nerve staining fluorescent probes, to

guide nerve sparing surgeries. Finally, Ana Luiza Ribeiro de Souza (Dartmouth) presented her work on evaluation of cold-dose administration of therapeutic antibodies as a way to increase the specific contrast available in EGFR positive tumors targeted with a fluorescent tracer affibody.

3.0 CLINICAL TRIALS & GUIDANCE

3.1 Clinical Translation & Applications

The clinical translation and application section was kicked off with an invited presentation by Vasilis Ntziachristos (Helholtz Zentrum Munchen GmbH, Germany) who presented on the need for fluorescence standardization between imaging systems, and presented data on a proposed test phantom which is used to measure fluorescence in a tissue simulating environment, with assessment of the flatness of the field, scatter and absorber sensitivity, concentration sensitivity. This was followed by a comprehensive overview of the FDA device process by Paula Jacobs (US National Cancer Institute), with thoughts about where fluorescence guided surgery devices will gain clearance first and how devices and agents may or may not be coupled in the approvals process. Corinne Laplace-Builhe (Institut Gustave Roussy, France) presented their clinical experience with a range of fluorescence imaging instruments in surgical use, including the in vivo confocal system by Mauna Kea Technologies. Finally Zhenzhen Dai (U. Michigan) presented their clinical trial data on use of fluorescent peptide in the detection of colorectal neoplasia, summarizing work which has gone on for several years towards this human imaging effort.

A second session on clinical translated was kicked off by Joseph Liao (Stanford U.) who reviewed the use of fluorescence imaging in bladder studies, showing temporal videos and angiographic imaging of the bladder from the inside with fluorescent cystoscope systems. Eric Henderson (Dartmouth) gave an invited review on the needs in orthopaedic surgery of sarcoma tumors and demonstrated the use of the Solaris system to identify tissue phantom margins from mock sarcoma tumors, embedded within tissue simulating media, as way to approach the needs in sarcoma surgery. Alexander Vahrmeijer (Leiden Univ, Netherlands) presented an invited overview on their work in several surgical clinical trials using targeted fluorescent agents to guide surgery, with the goal of detected tumor margins. Keith Paulsen gave an invited talk reviewing the experience with multi-probe fluorescence imaging to guide neurosurgery, using aminolevulinic acid induced protoporphyrin IX as well as iv injected fluorescein. The similarities and synergies of using the two probes at the same time were discussed using case clinical examples.

3.2 Regulatory

A single regulatory talk was given by invited speaker Abbas Bandukwala (US Food and Drug Administration) who presented a complete overview of the regulations, procedures, and experiences in translation of fluorescence guided surgery methods into clearances and approvals. The state of the field was discussed and pathways forward to gain approval were indicated.

3.3 Discussion Panel

The meeting ended with a discussion panel, moderated by Brian Pogue PhD, Dartmouth College (USA), including six panelists: (1) **Ian McDowall**, Intuitive Surgical Inc.; (2) **Vasilis Ntziachristos**, Helmholtz Zentrum Munchen GmbH; (3) **Paula Jacobs**, National Cancer Institute; (4) **John Fengler**, Novadaq Technologies Inc.; (5) **Ute Resch-Genger**, Bundesanstalt für Materialforschung und -prüfung; (6) **Abbas Bandukwala**, US Food & Drug Administration. Discussion started around the theme of standardization of technology for Fluorescence Guided Surgery, and the needs, potential and influencing factors. The needs such as test objects, phantoms, measurements needed, system corrections, quality audit goals, guidance and regulatory issues were all discussed.

4.0 OPTICAL AND IONIZING RADIATION INTERACTIONS FOR IMAGING AND THERAPY

This part of the conference was a special symposium jointly sponsored with the Optical Methods for Tumor Treatment and Detection conference, with several invited speakers and a few contributed talks.

5.0 SUMMARY AND DISCUSSION

The presentation of 20 invited and 20 contributed talks and 6 posters was an outstanding show of success for the conference, growing by about 10 talks and posters from the previous year. Attendance throughout the two days was likely between 100-200 people at almost all times, with the room largely filled in the clinical sessions. The discussion panel was shortened to 1 hour this year to match the more limited scope of focusing on device standardization. Still the discussion panel was viewed as one of the more positive additions to the conference, and was followed by a focus group from the American Association of Physicists in Medicine sub-committee on fluorescence guided intervention, discussing strategies for clinical system performance validation with appropriate tools such as tissue phantoms. A discussion panel focusing on this aspect of the conference will be presented in the 2018 version of the conference.

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