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

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Molecular-Guided Surgery II: Introduction to the conference

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ABSTRACT

The Molecular Guided Surgery II conference grew in attendance and scope from the previous year, when it originated. While several speakers and research groups presented as in the past year, the inclusion of surgeons involved in MGS was specifically increased by more invited and contributed speakers from this group. The interaction of basic scientists, translational scientists, companies and practicing surgeons is exactly the intersection of driving factors that the conference has strived for, and definitely achieved this year. The presentations started with Advanced Molecular Imaging Methods, and then transitioned into Molecular Contrast Agents, and then to Imaging Systems. The conference then continued with Pre-clinical applications and the Clinical Translation of this, and led to ongoing Clinical Applications. The program finalized with a discussion panel on the topic of future potential and current limitations in the field, having input from surgeons, translational academics, industry and with input from a working group from the American Association of Physicists in Medicine (AAPM).

1.0 INTRODUCTION

Surgical techniques evolve slowly out of necessity for safety and confirmation of improved outcomes with each change. Yet interesting tools continue to evolve which allow the surgeon to explore new features of contrast, function, and confirm or diagnose procedure potential or outcome. These methods are developed in response to surgical needs, or are pulled into existence by the clinical needs, whereas some are pushed into surgeon's hands based upon interesting technological capability, seeking to find a niche value. This conference stream brings together both influences, which are the essential 'push' and 'pull' components of technology advancement. Additionally, the company finance and regulatory approvals process are equally essential components of what will be feasible for successful implementation. Many new procedures are iteratively adopted, some even without consensus trials, while others are widely scrutinized and carried through multicenter studies.

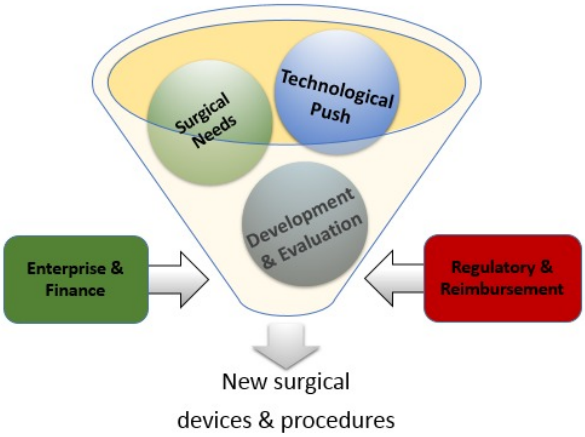

Figure 1. Illustration of the ingredients to the conference, mixing surgical needs, technology push, development and evaluation, and the discussion panel focusing towards enterprise and finance issues and regulatory approval issues and which procedures it can be reimbursed for.

2.0 METHODS: MOLECULES & TOOLS

2.1 Advanced Molecular Imaging Methods

The conference has traditionally started with a technology focus, because of the standing of SPIE BIOS as the largest engineering venue in the world for biomedical optics. As such, new technologies is the primary focus for most attendees who come each year. Advanced methods in this conference tend to focus on relatively new approaches to surface or sub-surface imaging tools which would provide information to a surgeon. The advancement of spatial frequency domain imaging (SFDI) (a.k.a. structured illumination or modulated imaging), has taken a primary role in much of the conference, due to the ease of potential implementation for quantitative surface imaging. Advanced molecular imaging methods is very much related to both agents and imaging systems (the next sections) but was separated by the novelty of the methodology. This is placed at the start of the conference in order to maximize enthusiasm for the latest and greatest technology. Stephen Kanick (Dartmouth) was invited to present on sub-diffuse structured light illumination for macroscopic field imaging of sub-microscopic structural elements. Jessica Ramella-Roman (University of Central Florida) was invited to present on collagen structure imaging in vivo with polarized light. Bruce Tromberg (University of California at Irvine, Beckman Laser Institute) was invited to present on diffuse optical imaging for patient treatment and monitoring. James Tunnell (University of Texas at Austin) was invited to present on attenuation correction methods for molecular fluorescence imaging. Finally Kenneth Tichauer (Illinois Institute of Technology) was invited to present on paired-agent imaging in molecular guided surgery. Each of these presented unique methods, developed by leaders in the field, which advance the technology available for imaging in surgery. From the contributed presentations, a high focus was placed on instrumentation and methods, for endogenous contrast or exogenous contrast (e.g. fluorescence) imaging, in open or minimally invasive surgery. All of this activity clearly indicates an important activity in developing novel and advanced imaging methods towards more sensitive and accurate imaging of the surgical field, the future of image-guided surgery that has not yet reached the patient.

2.2 Molecular Contrast Agents

Contrast agents are reported in several streams of SPIE BIOS, but this subsection of the Molecular Guided surgery conference has focused on those which are being translated or plan to be translated into human use, to guide surgical procedures. These range from small proteins, complex peptides, antibody fragments or full antibodies, all the way up to engineered nanoparticles made from lipids or proteins. The chemistry and basic research is not exactly the focus of this, but rather the features of each agent which gives value as an in vivo diagnostic tool. In this section, Bryan Spring (Harvard Medical School) was invited to present on optical probes for molecular-guided surgery with photodestruction of residual cancer, Anna Wu (University of California Los Angeles) was invited to present on engineered antibodies for optical fluorescence imaging in vivo and Amir Gandjbakhche (National Institutes of Health) was invited to present on fluorescence lifetime imaging of HER2 expressing tumors. Additional contributed presentations focused on pancreatic cancer guidance and on porphyrin lipid nanoparticles for photothermal therapy. Altogether, this session illustrated the high quality and diversity of contrast agent developments aimed at providing guidance during fluorescence-guided surgery.

2.3 Imaging Systems

Imaging technology is perhaps the most core part of the SPIE BIOS conference, and so system presentation is a key part of this stream. Several technologies for multispectral imaging were demonstrated along with fluorescence lifetime imaging. Real-time display of this information is a primary goal for clinical evaluation. Additionally, the development of calibration standards for fluorescence imaging and of clinically approved devices are key in ensuring proper translation and adoption of the technology. In this section, Eva Sevick-Muraca was invited to present on optical surgical navigation for nodal staging in humans. Contributed presentations focused on calibration standards for fluorescence imaging, wearable goggle devices, projection of information on the surgical field, and intraoperative microscopic imaging. In a similar manner to novel imaging methods, these novel devices clearly illustrate the effort in adapting novel technology efficiently in the clinical workflow by providing better, standardized, imaging, and in an ergonomic manner.

2.4 Pre-clinical Applications and Clinical Translation

Pre-clinical animal evaluation is a central part of validation of any new surgical imaging technique, and so this part of the conference provides the critical glue between technologies (methods and devices) and agents being developed and their clinical implementation. While technologies are widely developed, only a small fraction will advance into pre-clinical testing, and a much smaller fraction will advance into human clinical trial studies. The animal models used and the procedures imaged range from lymph node track imaging, to agent uptake and contrast evaluation in the relevant disease model. Several speakers presented early work on antibody and peptide based targeting, which was evaluated in murine xenograft tumors. In this section, Michael Bouvet (University of California San Diego) was invited to present on the topic of fluorophore-conjugated antibodies for imaging and resection of the GI tract in pre-clinical studies. Then Michele Diana was invited to present fluorescence-based enhanced reality tools for real-time estimation of bowel perfusion. Uptake, quantification of contrast and evaluation of the translation potential is the major topic. Contributed presentations focused on affibodies for glioma surgery, nerve-specific fluorophores for prostatectomy, breast positive surgical margin detection, head & neck cancer surgical resection, lymphatic mapping and fluorescence angiography. Altogether, the activity in translating devices and molecules through pre-clinical testing and towards human trials has never felt as important as it is today, and the findings clearly highlight a strong potential for fluorescence-guided surgery to impact patient-care in the near future.

2.5 Clinical Applications

The critically important endpoint of this conference is to provide an exchange of ideas, which will help advance the clinical use of molecular guidance in surgery. As such, presentation and discussion of the clinical applications demonstrated by physicians and translational scientists is the culminating event of the meeting. Eben Rosenthal (Stanford University) was invited to present on optical contrast agents tested for surgical ablation and pathology evaluation of resected tissues. Heather Franklin (Blaze Biosciences) was invited to present on the status of their lead agent, BLZ-100 in clinical trials as a tumor reporter. Fernando Dip (Cleveland Clinic) was invited to give an overview on the clinical impact o fNIR fluorescence guided surgery, and Alex Vahrmeijher (Leiden University) gave an overview of image guided surgery using fluorescence, with a roadmap to clinical translation of novel compounds at their center. Finally, outstanding contributed presentations from groups in the University Medical Center in Groningen (Netherland) and Dartmouth College demonstrated the use of fluorescence for peritoneal carcinomatosis with a VGEF-targeted tracer, and intracranial tumor resection using quantitative PpIX detection. In summary, this session illustrates the large amount of activity in human trials for fluorescence-guided surgery, a necessary step for advancing the translation of this technology and demonstrating its efficacy for future human use.

2.6 Discussion Panel

The meeting ended with a discussion panel, composed of Panel Moderators: Sylvain Gioux PhD, University of Strasbourg (France) and Brian Pogue PhD, Dartmouth College (USA), along with six Panelists: (1) James Basilion PhD, Case Western Reserve Univ. (USA); (2) Michael Bouvet MD, Univ. of California San Diego (USA); (3) Philippe Rizo PhD, Fluoptics (France); (4) Eben Rosenthal MD, Stanford Univ. (USA); (5) Stefan Schorling PhD, SurgVision (The Netherlands); and (6) Alex Vahrmeijer MD PhD, Leiden U. Med. Ctr. (The Netherlands). Discussion was in response to a blue paper produced for the American Association of Physicists in Medicine, led by the moderators and some conference participants, on the topic of the emerging technology of Fluorescence Guided Surgery, and the needs, potential and influencing factors.

At the outset, a list of potential questions raised was divided into 4 categories:

1) **Clinical Needs:**
   What are the surgical needs in priority of need?
   Are current needs being met or not?
   Macroscopic system or microscopic imaging system?
   Label-free, topical or injected molecular probes signals?
2) **Engineering Issues:**
   Do existing or future systems meet the clinical needs?
   What is an ideal set of criteria for a system performance?
   Are systems over-designed or under?

Is precise localization needed or qualitative imaging?

3) **Financial & Regulatory Issues:**
Can injected molecular probes be cost effective for a company?
Which specialties do you see advancing into FDA INDs next?
Are there iterative pathways through FDA for this field?

4) **Professional Society Role:**
What educational role does the society have
Does an engineering society like SPIE or AAPM have a role in this?

In response to these general questions, significant discussion occurred, and was framed around addressing each of these topical conclusions in roughly the same order as the questions. A brief summary of what was said is included here:

1) **Clinical Needs:**
- Nerve identification – mitigate accidents & legal costs.
- Cancer - Specificity of detection & identification needed.
- Surgeon needs are not necessarily quantification but pattern detection.
- Seeing below the surface is a major unmet need.

2) **Engineering Issues:**
- Many engineering solutions exist, and convergence and optimization is hesitant to happen prior to identification of ideal indications.
- System performance needs are strong though and many companies exist to fill the technological needs right now, but we are likely in a 'technology matching mode'
- Quantification/calibration is needed between systems
- Need for calibration/verification phantoms

3) **Financial & Regulatory Issues:**
- Need initial indications with high potential for reimbursable costs.
- Production costs could likely be high, needing $100's of dollars per injection.
- Iterative pathways through FDA are needed, approving devices independent of the drug (analogous to gamma cameras or PET scanners).
- Comparative studies with x-ray imaging and visual detection are both used for 510(k) process approvals in new indications.

4) **Professional Society Role:**
- The society has educational role to show what is scientifically possible.
- The society has a professional role to put out statements around consensus.

3.0 SUMMARY AND DISCUSSION

The presentation of 15 invited and 20 contributed talks was an outstanding show of success for the conference. Attendance throughout the two days was likely between 100-200 people at almost all times, and the quality of speakers matched or bettered the inaugural conference event in 2015. The new venue at the Moscone center was a positive step, allowing sufficient room for all in attendance. 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 may be in the works for the 2017 version of the conference.

4.0 ACKNOWLEDGEMENTS

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