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Seeing the Invisible during Surgery

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For centuries, the major "imaging system" used by surgeons has been the eyes and brain. However, visible light (400 to 650 nm) penetrates only a few hundred micrometres into living tissue. Near-infrared (NIR) light within the wavelength range of 700 to 900 nm is capable of penetrating millimetres to centimetres into tissue and thus promises improved visualisation of buried objects, such as tumours, blood vessels, and nerves, which would otherwise be invisible to the human eye. NIR light also provides quantitation of physiological parameters, such as tissue oxygenation, which are otherwise difficult to measure (reviewed in [1]).

NIR light is invisible to the human eye. Approximately two decades of work in the fields of engineering, physics, and chemistry was required to lay the foundation for its practical use during human surgery. What has emerged are two ways to exploit NIR light to provide information during surgery: endogenous contrast methods and exogenous contrast methods. The former uses the natural optical properties of normal and diseased tissues to provide contrast,[2] while the latter requires the administration of a chemical (a.k.a. contrast agent) to provide contrast.[3]

Endogenous methods do not require administration of contrast agents; therefore, no costly regulatory approval is necessary, and these methods can provide valuable information, such as oxygenation measurements, over the entire surface of a tissue. Thus, for the first time, surgeons will be able to visualize the oxygenation status of tissues on which they are operating. Endogenous methods can also potentially detect the presence of certain tumours, although they suffer from relatively low sensitivity and specificity, and some techniques require postprocessing that can add time to surgery.

Exogenous methods typically employ administration of a chemical called a *fluorophore*, which simply absorbs one NIR wavelength and converts it to a different NIR wavelength. The property of fluorescence creates high contrast (i.e., high sensitivity), and because fluorophores can be targeted to specific tumours and tissues, also creates high specificity. The major drawback to exogenous methods is that each contrast agent needs separate regulatory approval, costly in terms of time and money, and an administration time long enough before the surgical procedure so that adequate biodistribution, targeting, and clearance can occur. Exogenous contrast agents can be administrated intravenously,

CONFLICT OF INTEREST STATEMENT:

A.L. Vahrmeijer, M.D., Ph.D.: None.

J.V. Frangioni, M.D., Ph.D.: All FLARE™ technology is owned by Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School. As inventor, Dr. Frangioni may someday receive royalties if products are commercialized. Dr. Frangioni is the founder and unpaid director of The FLARE Foundation, a non-profit organization focused on promoting the dissemination of medical imaging technology for research and clinical use.

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intraparenchymally, intraluminally, or applied directly to a surface depending on the clinical application.

Enabling the use of NIR light for surgical guidance is a host of recently described imaging systems from academic and industrial sources (reviewed in [4]). As described above, these imaging systems are designed for either endogenous or exogenous imaging applications, and can be further sub-divided into those for open surgery or minimally invasive surgery. Based on their initial performance, and the quality of the groups and companies working in this field, it is safe to say that NIR imaging systems will improve rapidly over the next decade, and the availability of high-quality systems will no longer be the barrier to clinical investigation.

Looking into the future, we predict that endogenous and exogenous imaging systems will reach the clinic almost simultaneously, but for vastly different clinical applications. Endogenous imaging systems will likely focus on the measurement of tissue oxygenation and will provide the surgeon with an "image" of the functional status of tissue.[5] This information might prove critical during neurosurgery, heart surgery, burn surgery, transplant surgery, and bowel surgery, where unrecognised, poor perfusion can lead to post-operative morbidity. Real-time information during surgery provides the surgeon with the opportunity to intervene and correct defects.

Exogenous imaging systems will likely focus on either oncologic applications, such as sentinel lymph node (SLN) mapping[6,7] or tumour resection,[8] or a variety of other surgeries, such as cardiac surgery[9] and plastic and reconstructive surgery,[10] where assessment of perfusion using NIR fluorescence angiography adds value. The reason exogenous imaging systems will even have a chance to gain a foothold is that two drugs already approved for other indications, indocyanine green (ICG) and methylene blue (MB) are, coincidentally, NIR fluorophores. Thus, off-label investigation is already occurring with these agents, and future regulatory approval is at least feasible. MB absorbs and emits close to 700 nm and ICG absorbs and emits close to 800 nm, so even two-wavelength applications can be envisioned.

To date, the largest volume of reported clinical data for exogenous imaging systems is in the area of SLN mapping using ICG as the contrast agent. NIR fluorescence imaging using ICG has been shown to visualise the lymphatic channels transcutaneously, and has the potential to improve localisation of the SLN so that only a small incision is necessary. Over the next decade, newer, improved, NIR fluorophores should become available clinically for SLN mapping, tumour resection, and nerve avoidance. MB and ICG have limited targeting capabilities and should only be viewed as "enablers" of exogenous imaging systems until optimised NIR fluorophores clear regulatory hurdles.

It is important to understand that NIR light does not provide x-ray vision. Although much better than visible light, NIR light is still scattered by living tissue, resulting in significant blurring and fading of objects buried deeper than a few millimetres. Although there is intense effort being applied to newer techniques that will permit visualisation of objects several centimetres below the surface, at the present time NIR-guided surgery is a surface technique, with excellent results for millimetre depths and relatively poor results for centimetre depths.

Many stakeholders are taking interest in NIR-guided surgery. For the surgeon, it promises improved outcomes and shorter surgeries. For the patient, it promises more personalised care. For the healthcare system, it promises lower costs through faster turnarounds and lower rates of post-operative complications. In addition, it promises to deliver all of this with relatively low-cost technology, small footprints in the operating room, and no ionising radiation. The next decade should provide a definitive answer as to whether this technology can deliver on one or more of these promises.

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List of Abbreviations

ICG	indocyanine green
MB	methylene blue
NIR	near-infrared
SLN	sentinel lymph node

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