Commentary

Near-infrared (NIR) fluorescence imaging with a novel fluorophore: ZW800-1

Kim S de Valk[1,2,*], Marion M Deken[2], Maxime JM van der Valk[2] and Alexander L Vahrmeijer[2]

Kim S de Valk[1,2,*], Marion M Deken[2], Maxime JM van der Valk[2] and Alexander L Vahrmeijer[2]

[1]Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands
[2]Centre for Human Drug Research, Leiden, the Netherlands

Correspondence

Kim S de Valk

Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands

E-mail: K.S.de_Valk@lumc.nl

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Intraoperative near-infrared (NIR) fluorescence imaging is a novel technique that combines the use of a fluorescent agent with a dedicated near-infrared camera system, to allow real-time visualization of lymph nodes, tumor tissue and/or vital anatomic structures for surgical guidance (Vahrmeijer et al. 2013). NIR light ranges in the wavelength of 700-900 nanometers, is invisible to the naked eye and can only be detected with dedicated NIR imaging systems, which are currently available from various commercial companies. Fluorescent agents are mainly administered intravenously at a given time prior or during surgery, in order to enable real-time imaging during the procedure. The time of injection is dependent on the biodistribution of the specific agent. After injection the fluorescent agent is cleared by either the liver or kidneys and accumulates in the target (i.e. lymph node, tumor or vital structure) by either physiological processes (enhanced permeability and retention effect), specific targeting or through their clearance route.

A known challenge in the field of fluorescence guided surgery is the development of ideal NIR (tumor-targeted) fluorophores. Currently, the only clinically available NIR fluorophores are methylene blue (MB) and indocyanine green (ICG), both non-specific dyes. MB emits light at a wavelength of approximately 700 nm and is simultaneously cleared by the liver and kidneys. Previous clinical studies have shown that MB, due to its partial renal clearance, allows intra-operative ureter imaging after an intravenous injection (Verbeek et al. 2013). However, the fluorophore is suboptimal due to its fluorescent properties, resulting in higher auto-fluorescence and reduced penetration capacity (Verbeek et al. 2013). ICG is well-known and is the most used fluorophore in clinical studies, particularly due to its remarkable safety profile and more favorable fluorescent properties (Benya, Quintana & Brundage 1989). ICG emits light at a wavelength of approximately 820 nanometers, which is advantageous compared to 700 nanometers as a higher wavelength causes less auto fluorescence. It is applied in clinical practice for several surgical indications including demarcation of liver metastasis, bile duct imaging, sentinel lymph node mapping, and perfusion assessment (Boogerd et al. 2017; Schaafsma et al. 2011). Even though its widely implemented, ICG has several disadvantages due to its exclusive hepatic clearance, as the high uptake in the liver and excretion into bile compromises imaging of the gastrointestinal tract (Schaafsma et al. 2011). Both MB and ICG are non-targeted fluorophores and cannot easily be conjugated to other molecules, which is conversely an essential part for the development of novel tumor-targeted fluorescent agents and advancement in image-guided surgery. IRDye800CW for example, is a well-known fluorophore which has previously been conjugated to antibodies such as cetuximab and bevacizumab and evaluated in different clinical studies (Gao et al. 2018; Harlaar et al. 2016; Lamberts et al. 2017; Rosenthal et al. 2017). However, IRDye800CW has the same drawbacks as it shows similar uptake in the liver and gastrointestinal tract, hindering the applicability for intra-abdominal surgery (Choi et al. 2013). The future of NIR fluorescence imaging seems promising, yet the next steps should embrace the further improvement and development of conjugatable fluorophores to advance in the development of tumor-targeted fluorescent agents and overcome the current limitations of image-guided surgery.

Recently, the novel 'zwiterrionic' ZW800-1 has been introduced which is a NIR fluorophore with improved optical and biodistribution properties. ZW800-1 emits light at a wavelength of approximately 788 nm and has a unique renal-exclusive clearance. This fluorophore produces a high fluorescent signal with low non-specific binding and uptake in normal tissue (Choi et al. 2013; 2011). ZW800-1 was extensively investigated in small and large animal validation studies which showed that ZW800-1 was particularly suitable for NIR fluorescence imaging of the ureters (Choi et al. 2011; Hyun et al. 2012). Iatrogenic ureteral injury is a rare but feared complication of lower abdominal surgery, with incidence varying from 0.5% up to 10% (Andersen, Andersen & Iversen 2015; Delacroix & Winters 2010; Engel, Rink & Fisch 2015; Minas et al. 2014). Most of the iatrogenic ureteral injuries occur in patients during oncologic surgeries, as these patients have risk factors such as previous surgeries or radiotherapy in the pelvic area. Urethral injury can often be restored during surgery; however most injuries remain undetected and come to light a few days later, resulting in long term complications. Since avoiding iatrogenic urethral damage is of clinical importance, NIR fluorescence imaging with ZW800-1 may be a solution for adequate and safe ureter visualization during surgery as it can facilitate in identifying and/or confirming the location of the ureters.

Though ureteral imaging is a major step forward in the clinic, the true promise of this novel fluorophore

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lies in the conjugation to targeting moieties. ZW800-1 can easily be conjugated to other molecules, which can potentially solve the longstanding problem of optimal fluorophore development, creating endless possibilities for developing novel targeted ligands. These targets can either be tumor-specific molecules, known to be upregulated on malignant cells or tumor-associated tissue, or mechanisms involved in tumor survival such as neoangiogenic vessel formation or stroma. Discriminating between malignant and benign tissue during surgery remains challenging since oncologic patients frequently receive neo-adjuvant chemo-radiotherapy, which can diminish tumor visibility during surgery. Different strategies, such as the use of tumor-targeting agents, are being explored in clinical trials to overcome this. However, the most optimal tumor-targeted fluorescent agent still needs to be found.

Enhancing tumors or vital structures using NIR (tumor-targeted) fluorescent agents is an innovative technique that is currently under extensive development. Visual inspection and palpation have always been the principle methods in surgery to differentiate between different types of tissue or uncover vital structures. However, due to the technical advancements such as the introduction of minimal invasive procedures including the use of robotics, the palpation aspect in surgery has disappeared in most cases and surgeons are limited to visual inspection. With the use of NIR fluorescence imaging, tumor tissue and vital structures can be enhanced to assist surgeons and conceivably improve surgical (i.e. improved radical resections and less iatrogenic damage of vital structures) and hopefully patient outcomes.

A translational study with ZW800-1 is currently being performed to adapt this promising fluorophore into the clinic, ultimately implement it in standard-of-care and broaden its applicability with the development of novel tumor-targeted fluorescent agents.

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