EBioMedicine 56 (2020) 102808

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

The "light" guide for surgery

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ARTICLE INFO

Article History:
Received 5 May 2020
Accepted 7 May 2020
Available online xxx

Recent development in medical imaging and diagnosis enables physicians to make more precise surgical treatment decisions. Surgical innovations such as endoscopy, laparoscopy, and robotic surgeries, enhance minimally invasive approaches to achieve successful resection. However, surgeries still depend mainly on the naked eye. Since surgeons are not able to detect the border between tumours and normal tissue with the naked eye, surgical resection with negative margins should be performed; however, the positive rate of the margins has not improved over the years [1]. The emerging field of fluorescence image-guided surgery (FIGS), allows the detection of subclinical disease areas, which cannot be performed with the naked eye. Compared to conventional imaging methods, fluorescence imaging techniques require less expenses and space. Visualization with FIGS provides more precision in cytoreduction, artery and nerve detection, and prevents unnecessary injuries and postoperative complications.

The two studies by Kleinmanns et al. recently published in *EBioMedicine*, describe CD24-targeted near-infrared (NIR) fluorescence imaging in patient-derived xenograft (PDX) models of high-grade serous ovarian carcinoma (HGSOC), and confirm an improvement of cytoreduction of ovarian cancer in PDX orthotopic surgical model with CD24-targeted NIR FIGS [2,3]. These studies utilised patient-derived tumour materials to make translational systems in order to evaluate CD24-targeted fluorescence imaging. CD24 is a cell surface protein widely overexpressed in a variety of cancers, making it a promising target for theranostic applications [4]. These studies revealed that CD24 is expressed in 90% of epithelial ovarian carcinoma tissues, suggesting that CD24 is primarily expressed in ovarian cancers across all histologic types. With CD24-targeted fluorescence imaging in the HGSOC preclinical model, this CD24-targeted fluorescence imaging approach has the advantage of metastatic detection, especially in the early stages, and subsequent disease progression. With these advantages, CD24-targeted FIGS helped detect a greater number of metastases than control (white light) in preclinical models, and improved cytoreduction, thus demonstrating the potential to improve the degree of cytoreduction and survival in patients with advanced ovarian cancer.

There are many fluorescence imaging spectra, visible spectra (400−700 nm), and NIR spectra (700−900 nm). US-FDA currently approves indocyanine green (ICG), methylene blue (MB), 5-Aminolevulinic acid (5-ALA), fluorescein sodium, folate-FITC, IRDye800CW conjugates, and IRDye700DX conjugates. amongst them, the NIR spectrum (700−900 nm) has better tissue penetration, which allows deeper tissue imaging. On the contrary, wavelengths under 700 nm are absorbed more in tissues, such as haemoglobin and myoglobin, and wavelengths over 900 nm are of limited use, due to water and lipid absorption [5]. Thus, FIGS using NIR range fluorophores, has excellent potential compared to the visible spectrum range. Fluorescence imaging using the NIR range, gives surgeons superior cancer-site navigation, safer resection, higher sensitivity to preoperative imaging, and visual inspection with the naked eye. The two studies by Kleinmanns and colleagues in *EBioMedicine*, also utilised NIR range fluorophores, Alexa Fluor 680 for HGSOC tumour fluorescence imaging, and AF750 for FIGS of cytoreductive surgery with real-time feedback [2,3]. Along with the translational view, CD24-targeted NIR-fluorescence imaging has the potential to be used in clinical environment.

Generalised FIGS probes are composed of monoclonal antibodies (mAb) conjugated to a fluorophore. Promising preclinical examples of targeted fluorescence imaging include epidermal growth factor receptor (EGFR), carcinoembryonic antigen (CEA), human epidermal growth factor receptor type 2 (EGFR2, HER2), prostate-specific membrane antigen (PSMA), and vascular endothelial growth factor (VEGF) [6]. With the two studies by Kleinmanns and colleagues in *EBioMedicine*, CD24 antibody was also added as a promising target for FIGS [2,3] However, few of these mAb-conjugated fluorophores have progressed to the clinical trials phase. Current examples include Cetuximab-IR800CW, used in head and neck cancers, and bevacizumab-IR800CW in familial adenomatous polyposis coli [7,8].

Along with the development of both mAb and NIR-fluorophores, fluorescence imaging systems have also been implemented into successful clinical FIGS. Most FIGS have been performed with the Novadaq SPY system. Recently, simultaneous images of white light images

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2020.102782, http://dx.doi.org/10.1016/j.ebiom.2020.102783.
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https://doi.org/10.1016/j.ebiom.2020.102808

and fluorescence imaging have been enabled with cameras such as the Quest spectrum and VS3 Iridium [9]. The two studies by Kleinmanns and colleagues in *EBioMedicine*, also demonstrated the combined imaging of white light and fluorescence imaging to achieve the preclinical results. Thus, the ideal FIGS device system should display white light imaging, fluorescence imaging, and overlay imaging [10]. Moreover, recent technology enables projection mapping of the surgical site.

In conclusion, FIGS techniques have to be developed and introduced into all areas of surgery; thus, additional studies that optimize the translation of promising targets and fluorophores are welcome.

Declaration of Competing Interest

The author has no conflicts of interest to disclose.

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