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Review

Real-time near-infrared fluorescence guided surgery in gynecologic oncology: A review of the current state of the art

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HIGHLIGHTS

- Near-infrared fluorescence imaging is a promising technique, which allows real-time intraoperative visualization of tumor tissue, lymph nodes and vital structures.
- Increasing experience is gained with near-infrared fluorescence imaging in gynecologic oncology.
- This technology will be of increasing importance in the field of cancer surgery in the following years.

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ABSTRACT

Near-infrared (NIR) fluorescence imaging has emerged as a promising complimentary technique for intraoperative visualization of tumor tissue, lymph nodes and vital structures. In this review, the current applications and future opportunities of NIR fluorescence imaging in gynecologic oncology are summarized. Several studies indicate that intraoperative sentinel lymph node identification in vulvar cancer using NIR fluorescence imaging outperforms blue dye staining and provides real-time intraoperative imaging of sentinel lymph nodes. NIR fluorescence imaging can penetrate through several millimeters of tissue, revealing structures just below the tissue surface. Hereby, iatrogenic damage to vital structures, such as the ureter or nerves may be avoided by identification using NIR fluorescence imaging. Tumor-targeted probes are currently being developed and have the potential to improve surgical outcomes of cytoreductive and staging procedures, in particular in ovarian cancer. Research in the near future will be necessary to determine whether this technology has additional value in order to facilitate the surgical procedure, reduce morbidity and improve disease-free and overall survival.

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Introduction

Advanced imaging technologies, such as multidetector computed tomography (MDCT) and three-dimensional magnetic resonance imaging (3D-MRI), have introduced a new era in preoperative planning and treatment of gynecologic malignancies. However, as these imaging modalities are mainly used in the preoperative setting, translation of these images to the surgical theater is often challenging and does not always correspond to the intraoperative findings.

Over the past years, near-infrared (NIR) fluorescence imaging has emerged as a promising complimentary technique for intraoperative visualization of tumor tissue, sentinel lymph nodes (SLN) and vital structures. This technology provides real-time images, which allows accurate guidance during surgery. In gynecologic oncology, NIR fluorescence imaging has been used for intraoperative identification of SLN in vulvar, cervical and endometrial cancer, detection of ovarian tumors and abdominal or peritoneal metastases and imaging of vital structures such as the ureter [1]. NIR light has a wavelength range of 700 to 900 nm and is invisible to the naked eye. Therefore, it does not alter the surgical field when used. NIR fluorescence can penetrate several millimeters into blood or soft tissue, allowing identification of structures even when they are not yet directly exposed to the surface. This property is the consequence of less absorption of light within the NIR spectrum by water and most biomolecules, such as hemoglobin and lipid. Several NIR fluorescent probes are currently being evaluated in a preclinical setting [2]. Moreover, NIR fluorescence imaging systems for image-guided surgery are developing rapidly. It is expected that this technology will be of increasing importance in the field of cancer surgery in the following years.

This review aims to summarize current opportunities using NIR fluorescence imaging in gynecologic cancer surgery with special attention to SLN mapping, tumor imaging and imaging of vital structures.

NIR fluorescence imaging systems and currently available fluorophores

NIR fluorescence imaging uses NIR light, which is safe when used at the relatively low intensity needed for this technique. Requirements are a NIR fluorescent probe (fluorophore) combined with an imaging system which is able to excite this fluorophore and to detect the emitted fluorescence. By displaying the detected fluorescence on a screen, it becomes visible to the human eye. Some systems are able to merge white light images with NIR fluorescence images, which enhance anatomical orientation [3].

Due to the increasing opportunities in the surgical field, more fluorescence imaging systems are becoming available for both open and laparoscopic surgery. During open surgery, most published clinical studies used the Photodynamic Eye (PDE, Hamamatsu Photonics Co., Hamatsu, Japan), Mini-FLARE (Beth Israel Deaconess Hospital, Boston, MA, USA), SPY (Novadaq Technologies Inc., Toronto, Canada) or Fluobeam (Fluoptics, Grenoble, France). During laparoscopic surgery, often used systems are the Karl Storz high definition fluorescence laparoscope (Karl Storz GmbH & Co. KG, Tuttlingen, Germany), Pinpoint endoscopic fluorescence imaging (Novadaq Technologies Inc., Toronto, Canada) or the FireFly endoscope for the Da Vinci Si surgical robot (Intuitive Surgical, Inc., Sunnyvale, CA, USA). Prices of NIR fluorescence imaging systems are starting from $40,000. Currently available systems are described in Table 1 and reviewed by Gioux et al. [4].

To date, indocyanine green (ICG) and methylene blue (MB) are the only fluorophores approved for clinical use by the Food and Drug Administration and the European Medicines Agency. ICG costs approximately $4 per mg, is cleared exclusively by the liver and emits light with a wavelength of approximately 820 nm [5]. MB costs approximately $1 per mg, is cleared simultaneously by liver and kidneys and emits light with a less optimal wavelength of approximately 700 nm, which has less tissue penetration capacity and more tissue autofluorescence [6]. Both ICG and MB are non-targeted dyes and their chemical structures do not allow conjugation to tumor specific ligands. Therefore, they are mainly suitable for indications such as SLN mapping, e.g. in vulvar and cervical cancer, since they do not bind to tumors, but only follow the lymphatic drainage pattern. Furthermore, they can be used for ureter or bile duct visualization.

NIR fluorescence imaging has a steep learning curve, especially since most gynecologists are already trained in operating while using a monitor in laparoscopic surgery. If surgeons are able to identify structures more easily with help of NIR fluorescence imaging, operating and anesthesia time may be reduced, which simultaneously may reduce costs and associated risks. On the other hand, setting up the NIR fluorescence imaging system can be time consuming. Randomized trials with endpoints such as surgical duration and costs are lacking. Therefore, there is not yet an indisputable claim that NIR fluorescence imaging will be cost effective.

Sentinel lymph node mapping

Sentinel lymph node detection in vulvar cancer

Vulvar cancer accounts for approximately 5% of gynecologic malignancies [7]. In case of early stage squamous cell cancer of the vulva less than 4 cm in diameter and unifocal tumor, SLN biopsy for identification of lymph node metastases to the groins has been proven safe [8]. Morbidities, such as lymphocele, recurrent erysipelas and lymphedema of the leg, decrease significantly if only SLN biopsy has been done, compared to full lymphadenectomy of the groins [8,9]. Combining radiotracer ^{99m}Technetium-nanocolloid and blue dye is currently regarded as standard-of-care for SLN detection and gives the highest identification rates (94.4%; 95% confidence interval 92.4–95.9) [10]. However, both modalities have several disadvantages. For example, although blue dye can be used for intraoperative imaging of the SLN, it cannot be seen through the skin or soft tissue and has a lower sensitivity (68.7%; 95% CI 63.1–74.0) compared to radioisotopes (94.0%; 95% CI 90.5–96.4) [11]. Furthermore, radioisotopes can only be detected using a gamma counter, but real-time intraoperative visual guidance to exactly locate the SLN is lacking. When intraoperatively searching for the SLN, the radioactive signal can be disturbed by a high background signal originating from the injection spot around the vulvar tumor (shine effect) [12]. In recent years, NIR fluorescence imaging has been introduced in SLN mapping in vulvar cancer, because this technique has the potential for accurate, real-time, intraoperative SLN mapping [1] (Fig. 1).