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Fluorescence-guided surgery of cancer: applications, tools and perspectives

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Thousands of patients die each year from residual cancer that remains following cytoreductive surgery. Use of tumor-targeted fluorescent dyes (TTFDs) to illuminate undetected malignant tissue and thereby facilitate its surgical resection shows promise for reducing morbidity and mortality associated with unresected malignant disease. TTFDs can also improve i) detection of recurrent malignant lesions, ii) differentiation of normal from malignant lymph nodes, iii) accurate staging of cancer patients, iv) detection of tumors during robotic/endoscopic surgery (where tumor palpation is no longer possible), and v) preservation of healthy tissue during resection of cancer tissue. Although TTFDs that passively accumulate in a tumor mass provide some tumor contrast, the most encouraging TTFDs in human clinical trials are either enzyme-activated or ligand-targeted to tumor-specific receptors.

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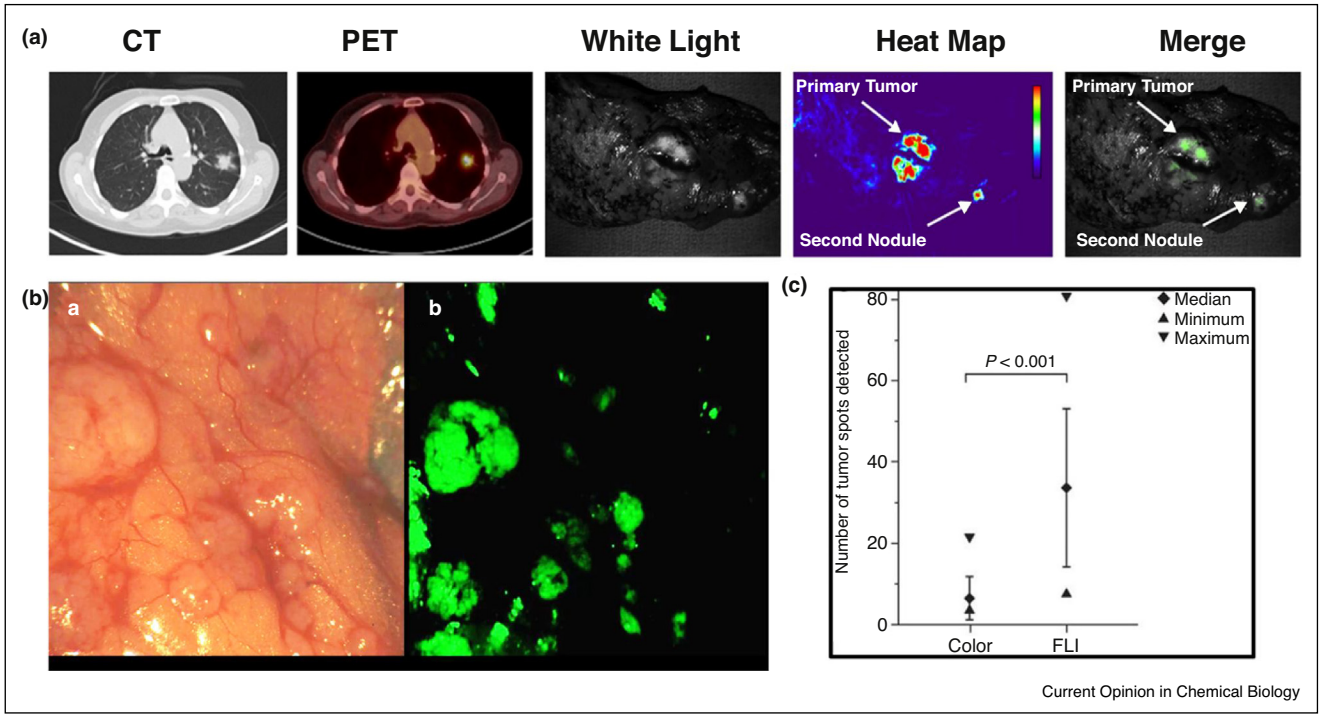
Introduction

The National Cancer Institute estimates that 1.7 million new cases of cancer will be diagnosed in the USA in 2017 and 600 000 patients will die from the disease (URL: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html). While many of these patients will eventually receive an adjuvant therapy, surgery is usually the preferable therapy because minimization of cancerous tissues renders immunotherapies and chemotherapies more effective [1–3,4••,5–9]. Motivated by this consideration, ~61% of early stage (stage I or II) breast cancer patients underwent breast-conserving surgery in 2017, and an additional 36% chose total mastectomy as their initial treatment (URL: https://www.cancer.org/research/cancer-facts-statistics/survivor-facts-figures.html). In the cases of early stage colon, lung and urinary cancer patients, the fraction of patients who were treated with surgery as their first line of therapy was 98%, 69% and 93%, respectively. Complete resection of all malignant tissue remains the standard approach to cure non-hematogenous localized cancers, however, the primary challenge remains localization of all malignant lesions. Thus, in order to reduce this major impediment to quantitative cancer removal, the ability to see more cancer would enable more complete removal of cancer cells. Although the use of fluorescence-guided surgery (FGS) for this purpose is still in its infancy, sufficient preclinical and clinical data exist to anticipate FGS will facilitate localization, identification and resection of malignant lesions. The review will examine recent innovations in the development of tumor-targeted fluorescent dyes (TTFD) for FGS and then explore future perspectives for expanded use of FGS in treating cancer.

The need for highly specific tumor-targeted fluorescent dyes

Initial diagnosis of a malignant mass is commonly obtained using methods that cannot reveal minor synchronous lesions, either because the spatial resolution of the method used is low (e.g. PET, MRI, CT, ultrasound imaging) or the method does not attempt to provide pathological information (e.g. liquid biopsies, lavage tests, etc.) [10]. Surgeries based on low resolution diagnostic tests are therefore often motivated by the need to remove the most prominent mass/nodule, with the hope that if additional lesions exist, they will be detected during surgery based on their abnormal morphology, coloration or tactile properties [11]. Unfortunately, many malignant lesions are not easily identified by such methods, and others may be buried, poorly accessible, or too small to be detected by visual inspection or palpation. In these cases, the availability of an optical signal from a tissue-translucent near-infrared TTFD has been shown to improve tumor detection [12–15]. Not only can such dyes enable identification of synchronous lesions that are too small to be discovered by unaugmented sensory perception, but TTFDs can also reveal the locations of buried lesions and other obscured nodules that would otherwise escape recognition (Figure 1) [16]. Based on the increasingly well-documented assumption that removal of more malignant tissue can improve overall survival [1–3,4••,5–9], the ability of FGS to facilitate resection of otherwise undetectable lesions can now be better appreciated [17,18•,19–22].

Figure 1



Detection of malignant lesions in lung and ovarian cancer patients using tumor-targeted fluorescent dyes. **(a)** Various images of patient with 2 cm lung adenocarcinoma viewed using CT and PET scans reveal only the most prominent malignant lesion. Intra-operative images of the same patient using a folate receptor-targeted TTFD (folate-fluorescein; EC17), however, demonstrate a synchronous nodule in the same pulmonary lobe. CT, Computed tomography; PET, positron emission tomography; white light, fluorescence image; heat map, map of fluorescence intensity; Merge, overlay of fluorescence on white light image. Adopted with permission from Ref. [22]. **(b)** White light **a** and fluorescence **b** image of tumor deposits in an ovarian cancer patient. **(c)** Quantitation of malignant lesions in ovarian cancer patients detected by visual inspection with normal (color) or fluorescence (FLI) light. Analysis reveals detection of ~5 times more cancerous lesions with the aid of a TTFD (EC17) than without it. Scoring was based on three different color images (median 7, range 4–22) and their corresponding fluorescence images (FLI) (median 34, range 8–81) $P < 0.001$ by five independent surgeons.
Adopted with permission from Ref. [17].

One of the major downstream benefits of identifying more synchronous lesions is the capability to more precisely stage a patient's cancer and thereby manage his/her disease. Thus, detection of a second metastatic nodule in a lung cancer patient will normally preclude surgery and dictate that the patient instead undergo chemotherapy [23]. However, in cases where a synchronous nodule can be detected using a TTFD and minimally invasive endoscopy, surgery-caused trauma and the associated lengthy recovery period can be avoided, thereby allowing the patient to immediately begin chemotherapy.

Highly specific TTFDs can also be exploited to eliminate positive tumor margins that exist when residual cancer tissue somehow escapes detection [24–27]. Thus, ~10–15% or more of breast cancers [28–30], ~37–76% of ovarian cancers [31,32] and ~10–33% of non-small cell lung cancers [33,34] recur at the site of surgery, suggesting that positive tumor margins existed after completion of many surgeries. With the aid of a TTFD that illuminates malignant tissue, any residual disease can be resected simply by excising fluorescent tissue until all fluorescence has been eliminated (Figure 1) [22,17]. This ability to 'shave off' tissue until the fluorescence has disappeared should also prove beneficial in surgeries where excision of excess healthy tissue is highly undesirable (e.g. brain cancer and breast cancer surgeries).

FGS will perhaps make its greatest contribution to surgeries in the future through its ability to compensate for deficiencies inherent in endoscopic and robotic methods [35••,36,37]. Thus, while such minimally invasive surgeries can reduce trauma associated with open surgical procedures, they will also deprive a surgeon of her/his ability to identify cancer tissue by finger palpation. Without the ability to distinguish cancer based on its enhanced rigidity/stiffness, the surgeon surrenders use of her/his two senses commonly employed for tumor detection [38]. However, if palpation