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REVIEW ARTICLE

Fluorescence Imaging for Cancer Screening and Surveillance

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Abstract

The advent of fluorescence imaging (FI) for cancer cell detection in the field of oncology is promising for both cancer screening and surgical resection. Particularly, FI in cancer screening and surveillance is actively being evaluated in many new clinical trials with over 30 listed on Clinical Trials.gov. While surgical resection forms the foundation of many oncologic treatments, early detection is the cornerstone for improving outcomes and reducing cancer-related morbidity and mortality. The applications of FI are twofold as it can be applied to high-risk patients in addition to those undergoing active surveillance. This technology has the promise of highlighting lesions not readily detected by conventional imaging or physical examination, allowing disease detection at an earlier stage of development. Additionally, there is a persistent need for innovative, cost-effective imaging modalities to ameliorate healthcare disparities and the global burden of cancer worldwide. In this review, we outline the current utility of FI for screening and detection in a range of cancer types.

Key words: Cancer screening, Early detection of cancer, Neoplasms, Diagnostic imaging, Optical imaging, Molecular imaging

Introduction

For many cancers, early detection is key to improving survival and reducing the morbidity associated with radical resections due to late presentation. This is particularly true for cancers of the cervix, breast, and many other organs. In fact, cervical cancer is now largely preventable due to the availability of two approved vaccines, a myriad of effective screening techniques, and prompt intervention of pre-cancerous lesions [1]. Similarly, favorable outcomes related to early intervention for patients with breast cancer have long been established. Despite these advances, cervical and breast cancers are responsible for killing more women in developing nations than any other cancer [1]. Additionally, there is an ever-widening gap between developing and industrialized nations, which has led to a geographical "cancer divide" in cancer morbidity and mortality among poor and rich countries [1]. In 2008, for example, the ratio of cervical cancer deaths to cervical cancer incidence in the USA was 0.27, while it was 0.67 in sub-Saharan Africa [1].

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In the field of oncology, many tools have been developed for early cancer detection. Despite advances in modern imaging, cancer screening and surveillance remain imperfect. That is, many of these modalities lack sufficient specificity and/or resolution, which precludes their use for accurate cancer detection [2]. In fact, many are simply unable to detect small amounts of malignant cells, which is indispensable for early detection of new or recurrent tumors [2].

Fluorescence imaging (FI) for cancer cell targeting utilizes a variety of optical imaging technologies in order to improve detection of early neoplasia based on molecular signatures specific to cancer (Table 1) [3]. Since 2013, there has been a rapid increase in the number of clinical trials utilizing FI. In fact, cancer screening and surveillance represent the largest sub-group of all currently listed clinical trials on clinicaltrials.gov, with more than 50 % falling into this category (Table 2). This sub-group focuses on detection of malignant or pre-cancerous lesions using FI for screening or surveillance purposes. Screening is generally intended for patients considered to be high risk based on a combination of lifestyle factors, genetics, or personal history of disease, while surveillance is reserved for patients with a diagnosis of dysplasia or in whom malignancy is suspected based on clinical presentation. FI may aid in identifying malignant lesions with improved specificity and sensitivity compared to currently available techniques. Furthermore, FI may provide a less invasive, more cost-effective way to detect cancerous or pre-cancerous lesions. Specifically, the ability to detect lesions earlier than conventional methods will not only result in improved treatment outcomes but reduced treatment costs as it will prevent the need for multimodality care required for those diagnosed at advanced presentation. This is of particular interest in low- and middle-income countries where healthcare access, transportation, specialist availability, and primary and secondary prevention are often lacking. The primary struggle with screening methodologies lies in their fundamental requirement for possessing both high sensitivity and specificity in order to provide correct diagnosis while also preventing unnecessary follow-up procedures. Furthermore, screening devices should be inexpensive, low risk, and used only for cancers where evidence suggests early diagnosis favorably affects overall survival [4].

As the field of FI continues to grow, it is unclear which patient population will benefit the most from the use of FI. Here, we outline the usage of FI for cancer detection in a number of cancer types (Fig. 1) with attention to prior studies and outcomes.

Cervical Cancer

Cervical cancer is caused by certain strains of the human papillomavirus (HPV), the most common sexually transmitted infection globally. In the USA alone, HPV infections occur in 80 to 90 % of women by age 45 [5, 6]. Annually, more than 500,000 women are diagnosed with cervical cancer and there are greater than 275,000 deaths worldwide, 88 % of which occur in low- and middle-income countries [7, 8]. This is due to inadequate prevention and screening techniques as a result of cost barriers, insufficient healthcare access, poor health literacy, an overall lack of awareness, and inadequately trained health care personnel [9]. Furthermore, the progression from HPV infection to cervical cancer has a latency period of 5 to 30 years, thus affording several screening and diagnostic opportunities prior to malignant transformation [10]. In fact, cervical cancer screening decreases the incidence of invasive cervical cancer, reduces the rate of late-stage disease, and improves survival [11]. With the combination of primary prevention and slow disease progression, cervical cancer has the potential to be a highly preventable disease with proper vaccination and/or reliable, cost-effective screening.

Currently, visual inspection with application of acetic acid (VIA) or Lugol's iodine (VILI) is used as a "see and treat" method of screening in low-resource settings, whereby acetic acid or Lugol's iodine is applied to the cervix and ensuing epithelial whitening indicates cancerous or pre-cancerous lesions [12, 13]. However, this method is associated with a relatively low specificity (49 %) [14] and leads to a high number of false positives, thus burdening

Table 1. Summary of currently available fluorescent imaging technologies

Technique	Depth penetration	Applications	Limitations
High-resolution microendoscopy (HRME)	50 μm	•Handheld fluorescence imaging	•Usage limited to superficial mucosa
Optical coherence tomography (OCT)	Up to 3 mm	•Handheld fluorescence imaging •Intraoperative fluorescence imaging	•Issues with stability and sterility •Difficulties with reproducibility •Suboptimal resolution •Results highly operator dependent
Autofluorescence	Up to 5 mm	•Handheld fluorescence imaging •Intraoperative fluorescence imaging	•High background •Low specificity
NIR imaging	Up to 10 mm	•Handheld fluorescence imaging •Intraoperative fluorescence imaging •Endoscopic fluorescence imaging •Fluorescent lymphoscintography	•Improved depth penetration •Reduced background autofluroescence •Tumor-specific
Photoacoustic imaging	3–20 mm	•Intraoperative fluorescence imaging •Fluorescent lymphoscintography	•Improved depth penetration

Table 2. Summary of clinical trials utilizing fluorescence imaging for detection of various types of cancer or pre-cancerous lesions, the types of fluorescent agents used, and available outcome measures. Data was gathered from Clinicaltrials.gov in May 2016 using the search term "fluorescence," which resulted in 465 results. Of those results, only 36 pertained to screening, which is demonstrated in the table

Organ system	Number of clinical trials	Fluorescent agents	Outcomes
Gynecologic (cervical)	9	Autofluorescence	•Good NPV •Reduced FP rate •Improved accuracy with CIN 2 or greater
Urologic (bladder)	12	5-ALA, hexaminolevulinate ®	•Improved detection of residual tumors •Improved detection of recurrent tumors •Improved detection of CIS and dysplasia
Head and neck (oral)	4	Autofluorescence	•High specificity and sensitivity with autofluorescence •High accuracy in diagnosing severe dysplasia/CIS and/or invasive carcinoma
Gastrointestinal (esophageal, gastric, colorectal)	8	Autofluorescence, GI-heptapeptide, FITC, colon HCC heptapeptide	•Improved detection of flat lesions •Improved detection of dysplasia •No significant difference in overall accuracy among novice and expert endoscopists
Skin	3	Autofluorescence, fluorescein	•Detection of malignancy

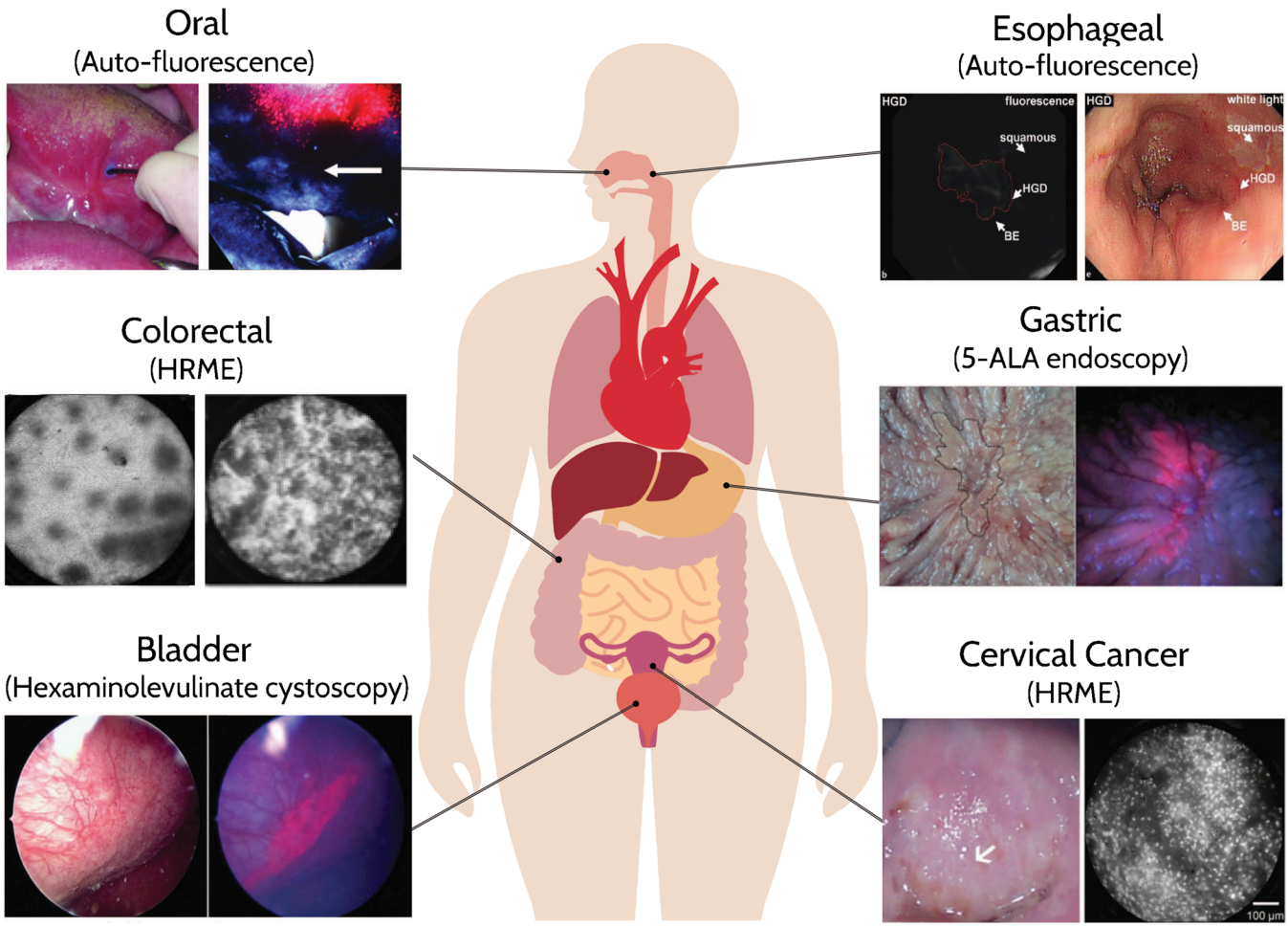

Fig. 1. Real-time images highlighting visual differences between standard white light (WL) and FI for different organ systems. From *left*: oral cavity showing severe dysplasia of left mid-tongue on WL (*L*) and AFI (*R*) (image from Pierce et al. [22]); high-grade esophageal dysplasia demonstrated on FI (*L*) and WL (*R*) (image from Joshi et al. [3]); gastric papillary adenocarcinoma on WL (*L*) and 5-ALA induced FI (*R*) (image from Namikkawa et al. [71]); colposcopic images of CIN3 on WL (*L*) and with FI using HRME (*R*) (image from Quinn et al. [88]); recurrent non-muscle invasive bladder cancer shown with WL (*L*) and FI with hexaminolevulinate cystoscopy (*R*) (image from Daneshmand et al. [89]); HRME demonstrating difference in normal colonic mucosa (*L*) and adenocarcinoma (*R*) (image from Okabayashi et al. [63]). This figure was created using Adobe Illustrator licensed by Creative Commons with fluorescent images obtained from previously published studies as cited.

these low-cost programs with over-treatment expenses [13]. As such, FI has the potential to provide a significant advantage over current "see and treat" methods by providing an effective, low-cost method of detecting aberrant lesions with true malignant potential.

Currently, there are a number of clinical trials underway to evaluate handheld microendoscopes or digital colposcopes. One study used high-resolution microendoscopy (HRME) to detect pre-cancerous cervical lesions, which utilizes a small fiberoptic probe to image and evaluate tissue in real time for changes in epithelial morphology without need for biopsy [13, 15]. Using the exogenous contrast agent proflavine for enhanced nuclear visualization, HRME demonstrated 100 % sensitivity (12 out of 12 with at least cervical intraepithelial neoplasia [CIN] II or greater) and 67 % specificity (38/57) in identifying pathologically confirmed non-neoplastic tissue [13]. In contrast, VIA/colposcopy revealed a false positive rate of 83 % (57/69 pathologically non-neoplastic sites demonstrated abnormalities with VIA/colposcopy) [13]. A second study (#NCT02335372) by this group showed similar results when separating 59 biopsy sites into <CINII and >CINII using HRME in a low-resource setting of Sao Paolo, Brazil [12]. They demonstrated 92 % sensitivity (34/37) and 77 % specificity (17/22) and further found a significant association between HRME positivity and increasing cervical dysplasia, particularly with CINII or higher ($p < 0.001$) [12]. Moreover, this method reduced the false positive rate resulting from chronic inflammation in the prior study by using additional criteria to classify HRME images (23 vs 35 % previously) [12, 13]. While FI is unlikely to replace conventional screening methods exercised by industrialized countries, these results are promising in low-resource settings and suggest that HRME may favorably complement colposcopy and other "see and treat" methods.

Current data suggest that the use of FI for screening of cervical cancer has the potential to reduce false positives and improve accuracy in detecting grade II CIN or higher, particularly when used in conjunction with other "see and treat" methods. One disadvantage may be the requirement for two screening methods; however, the ensuing enhanced specificity translates to improved overall survival secondary to early detection and quality of life (QOL) by reducing the need for highly morbid surgical procedures. Additionally, the possibility of forgoing invasive biopsy procedures further translates to improved QOL.

Oral Cancer

The current standard of care for detection of oral lesions is visual inspection and palpation. Due to lack of sensitivity in this approach, cancerous or pre-cancerous lesions may be mistakenly identified as benign lesions, such as lichen planus or others [16]. In fact, less than one third of cases are diagnosed at local-stage disease [17] with many patients presenting with advanced tumors, for which treatment is more expensive, complicated, and less effective [18]. Current 5-year survival rate for oral SCCs is 63 % in the USA [17] with evidence suggesting this rate is reduced to 30 % in developing nations [19]. This survival variation further supports the need for a simple, cost-effective device that accurately detects oral neoplasia. Additionally, a lack of specificity in current screening methods may lead to a high number of false positives. Specialized training in the detection of pre-malignant and invasive oral cavity tumors is sparse, despite the fact that nearly 70 % of lesions are initially identified by a general dental practitioner, dental hygienist, or primary care physician. While good clinical practice includes biopsy of suspicious-appearing lesions, it is possible that more accurate screening could reduce the incidence of these invasive, costly, and uncomfortable procedures. This is especially important when the possibility of obtaining a false negative exists and clinical suspicion for malignancy is low. Additionally, biopsy results are not immediate, which further contributes to patient anxiety and stress. Nevertheless, early treatment for oral cancers represents the most effective method for achieving optimal results with respect to cure, quality of life (QOL), and overall patient outcomes [18, 20]. Unfortunately, given the low incidence of oral and oropharyngeal carcinoma, widespread screening options are not currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines [21]. Thus, new tools are required for early-stage screening and surveillance of high-risk patients at risk for recurrence [22].

There are several ongoing studies that use non-invasive FI to exploit the intrinsic autofluorescent properties of certain tissues to detect oral neoplasia (Fig. 2). The handheld VELscope® (LEDDental, Inc., White Rock, BC, Canada) was FDA-approved in 2006 for qualitative autofluorescence visualization in the oral cavity [23]. Since the original study demonstrated 98 % sensitivity and 100 % specificity for differentiation of normal mucosa from severe dysplasia/CIS or invasive carcinoma using direct fluorescence visualization, there have been several additional publications with at least four ongoing clinical trials (clinicaltrials.gov #NCT00764569, NCT01167790, NCT00502580, NCT00542373) exploring the diagnostic utility of optical FI for improved oral neoplasia detection [23]. However, there is currently no evidence to support the superiority of currently available handheld optical FI devices compared to an experienced clinical exam [24]. In fact, the use of a handheld autofluorescence device is not currently reimbursed by the Centers for Medicare and Medicaid Services (CMS) due to lack of clearly proven patient benefits, thus greatly limiting its clinical use. Despite the lack of available data, many dentists routinely use handheld FI devices as screening tools to identify mucosal lesions in the office [25].

Recently, there has been significant clinical interest in multimodal optical imaging systems (MMIS) to further improve detection of malignant and pre-malignant lesions. In a trial by Pierce et al., MMIS (combination of HRME and autofluorescence) was used to measure 100 anatomical sites from 30 patients [22]. Using this combination, MMIS was able

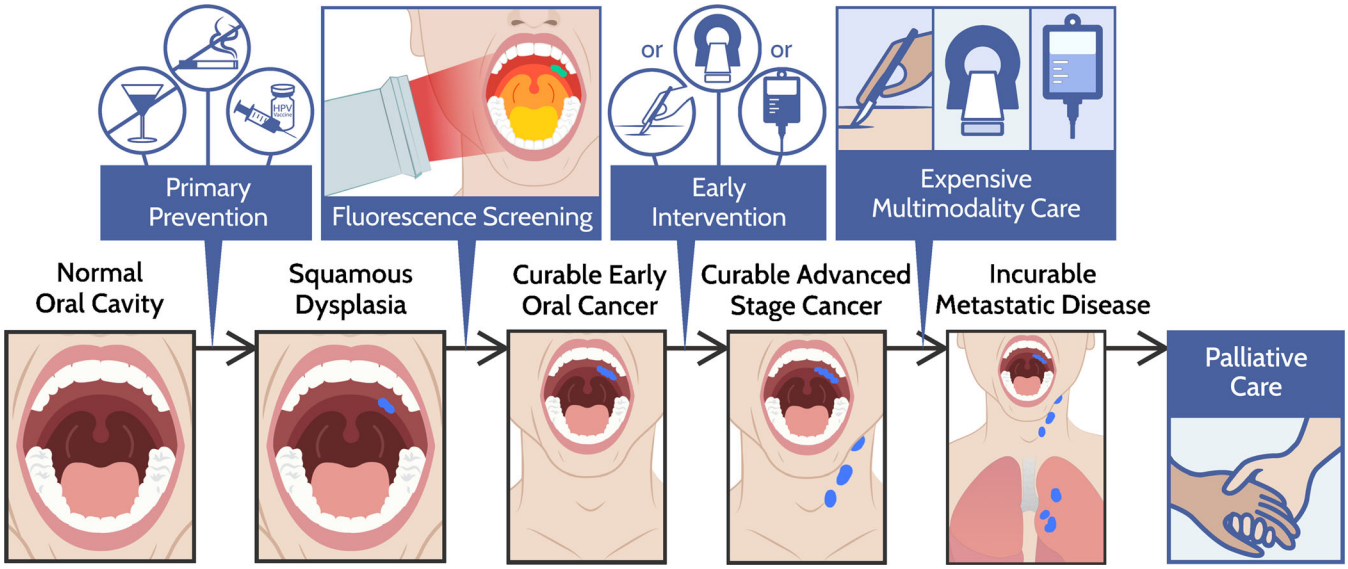

Fig. 2. Illustrative continuum of prevention and screening with fluorescence imaging that can reduce morbidity and mortality from oral cancer. This figure was created using Adobe Illustrator licensed by Creative Commons.

to correctly classify 98 % of histopathologically confirmed normal tissue and 95 % of those pathologically classified as moderately dysplastic, severely dysplastic, or cancerous [22]. Mild dysplasia was only correctly classified as abnormal in 35 % (6/17 tissue sites), but tumor stratification with p63—an immunohistochemical marker increasingly expressed with degree of CIN dysplasia—improved optical imaging to a sensitivity and specificity of 93 and 96 %, respectively [22, 26]. Although results are promising, there is continual need for additional clinical trials and optimization of these imaging modalities to generate the highest quality diagnostic and screening results, while also maintaining costs and sensitivities comparative to those of a traditional clinical exam.

The use of FI for the detection of oral cancer lesions carries the advantage of allowing a simple, cost-effective device with increased specificity when compared to current screening methods. Furthermore, the minimally invasive nature of this technology additionally contributes to an improved patient QOL through reducing patient anxiety and stress while simultaneously permitting improved patient outcomes through early cancer detection. One current limitation of this technology is the issue of CMS reimbursement, which has limited its use in the clinic. In order to overcome this barrier, additional clinical studies are required to better demonstrate the advantages of this technology.

Bladder Cancer

Despite a relatively low mortality rate, bladder cancer requires lifelong surveillance due to a high risk of recurrence. In fact, the 5-year risk of recurrence is 70 % for non-muscle invasive bladder cancers (NMIBC) [27, 28]. Thus, it is not surprising that bladder cancer is the most expensive cancer to treat due to this prolonged need for surveillance and repeat treatment, which costs an average of $200,000 per patient [29]. Currently, white light cystoscopy (WLC) is the diagnostic gold standard for evaluating patients with positive voided urinary cytology, which itself has a high sensitivity for high-grade urothelial carcinoma [30]. In patients with positive urinary cytology in whom WLC is negative, however, there remains a clinical quandary. That is, while urinary cytology may be indicative of CIS, dysplasia, small tumors, or other flat lesions lacking epithelial thickening, they are highly difficult to visualize on WLC, which often precludes accurate diagnosis [31].

Bladder cancer detection and surveillance have been studied widely with the use of protoporphyrin-based contrast agents such as 5-ALA and hexyl aminolevulinate (HAL), a derivative of 5-ALA that is currently approved for use worldwide due to its superior pharmacological profile as compared to 5-ALA [32, 33]. In a review of 41 studies by Rink et al., cystoscopy with photodynamic diagnosis (PDD) using 5-ALA or HAL was found to be superior to WLC in the detection of both papillary NMIBC and CIS [30]. Indeed, PDD-guided cystoscopy had overall sensitivities ranging from 76 to 97 % vs 46–80 % for WLC [34]. For the detection of papillary Ta/T1 tumors specifically, PDD-cystoscopy also proved favorable to WLC, identifying 8.6 to 29 % (Ta) and 7 to 25 % (T1) more tumors than standard WLC [30]. Similarly, detection of CIS with PDD-cystoscopy ranges from 49 to 100 % vs 5 to 68 % with WLC [30]. This translates to an improved CIS detection rate of approximately 25 to 30 % with PDD vs WLC [30]. Furthermore, PDD-cystoscopy demonstrated enhanced detection of dysplastic lesions when compared to WLC (80.6–100 % vs 48–69.7 %) [35–38]. Rink et al. further reported a variable false positive rate ranging from 1 to 26 %; however, this rate has decreased with time [30].

Newer studies have emerged using cancer-specific molecular imaging agents to further improve bladder cancer diagnosis. In one ex vivo study of excised human bladders, blue-light cystoscopy with anti-CD47 demonstrated a sensitivity and specificity of 82.9 and 90.5 %, respectively [39]. The results are promising for bladder cancer detection and additionally present certain advantages over protoporphyrin-based PDD. For example, both 5-ALA and HAL are not recommended in patients who have recently undergone tumor resection or treatment with intravesical Bacillus Calmette-Guérin immunotherapy due to a high false positive rate [39]. Furthermore, HAL is indicated for one-time use only due to associated hypersensitivity risk [39]. While these results are promising, *in vivo* clinical studies are needed for accurately assessing the effectiveness of cancer-specific molecular imaging agents in bladder cancer detection.

In addition to the demonstrated benefits in bladder cancer detection, there have been a number of studies demonstrating cost savings from the use of PDD; however, savings are primarily due to reduction in additional transurethral resection of the bladder (TURB) rather than due to earlier NMIBC detection [30]. As long-term cost-benefit ratios continue to be determined, it is clear that papillary NMIBC detection is improved with PDD-cystoscopy as compared to standard WLC, particularly in patients with multifocal disease [30].

FI for screening bladder cancer has the potential to improve both tumor sensitivity and specificity. The current limitation of this technology is that studies have failed to demonstrate improved survival outcomes and reduced tumor recurrence rates resulting from improved tumor detection and a more complete TURB. However, the relatively low mortality rate of early-stage bladder cancer may require long-term studies to better demonstrate such outcomes. Nevertheless, the ability to improve tumor detection and reduce subsequent surgical procedures represents important advantages of FI in this population by contributing to cost-effective medicine and a reduction in patient anxiety.

Esophageal Carcinoma The annual incidence of esophageal cancer is nearly 500,000 worldwide and despite current technology and screening efforts, incidence rates are on the rise [40]. In fact, incidence has increased >460 % in men over 65 within the past 30 years [41]. While esophageal adenocarcinoma (EAC) and SCC arise from distinct epithelial subtypes, they both share several important similarities, including a common etiology rooted in chronic inflammation [42]. Furthermore, the most important prognostic factor in both subtypes is the stage at which cancer is detected [42]. However, both are often diagnosed late in the course of disease due to delayed symptomatic onset resulting from eventual invasion of the muscularis propria [42].

EAC is the fastest growing cancer globally [43] with a 5-year overall survival of <15 %; approximately 85 % of these cases will end in death [40]. Barrett's esophagus (BE), due to chronic gastroesophageal reflux disease (GERD), increases the risk of developing EAC by a factor of almost 30 [44]. The sequential progression of BE to low-grade, then high-grade dysplasia, and eventually EAC, represents a unique opportunity to intervene with screening techniques that specifically exploit these pathophysiologic interval gaps. Early detection of EAC is critical as it facilitates curative treatment options and reduced morbidity. Current imaging modalities include esophagogastroduodenoscopy (EGD); however, this is frequently associated with sampling error due to undetectable flat lesions or a patchy distribution within the esophagus [45]. The use of FI has improved the ability to detect pre-cancerous lesions not visible with traditional white light endoscopy. One clinical trial (#NCT01630798) recently demonstrated good *in vivo* specificity (94 %) and a 96 % positive predictive value (PPV) for early-stage EAC identification with the use of multimodal endoscopy after application of a fluorescently labeled peptide [3]. Multimodal molecular endoscopy with FI was able to detect 28 flat lesions that were poorly demarcated with standard white light endoscopy [3]. Currently, there is a pilot study (#NCT02129933) evaluating the use of bevacizumab-IRDye800CW for early, tumor-specific detection of EAC or high-grade dysplasia.

For detection of esophageal squamous cell neoplasia, a study by Protano et al. (#NCT01384708) evaluated the use of HRME as an adjunct to current screening and surveillance methods in high-risk populations. HRME was used in addition to Lugol's chromoendoscopy (LCE), which is the current, poorly specific (<65 %) [46] standard for screening and surveillance among high-risk populations, such as those in northern China, Central Asia, and Iran [47–50]. The results of this study demonstrated a significantly increased specificity (79 vs 29 %, $p < 0.001$) and overall accuracy (83 vs 47 %, $p < 0.001$) with combination use of LCE and HRME vs LCE alone [51]. Furthermore, researchers were able to determine that concomitant use of HRME with LCE in this study could have spared 57 patients (50 %) from unnecessary biopsy due to a false positive result on initial LCE [51]. Importantly, there was no significant difference in overall accuracy among novice and expert endoscopists (90 vs 88 %), which is paramount in providing accurate, high-quality care in resource-limited populations [51]. Overall, these results suggest that FI, when used in conjunction with LCE, is an accurate, low-cost screening tool for high-risk populations.

The use of FI for screening of esophageal carcinoma has the advantages of being cancer-specific, improving detection of dysplastic lesions, and reducing the need for invasive biopsies. Furthermore, the ability to detect flat lesions represents a major advancement over current methods, which use white light EGD. In resource-limited areas lacking an abundance of specialists, the ability of FI to

reduce the learning curve for novice endoscopists represents a significant advantage in the detection of dysplastic lesions. Together, this results in improved cancer detection, which translates to improved QOL, overall survival, and reduced need for highly morbid procedures.

Colorectal Carcinoma

The benefits of early colorectal carcinoma (CRC) detection with routine white light colonoscopy are widely established, with evidence suggesting a 76 % reduction in CRC incidence and significant decreases in CRC-related mortality [52, 53]. Although the death rate from CRC has traditionally decreased in previous years, nearly 1.5 million new cases of colorectal carcinoma (CRC) were diagnosed worldwide and resulted in approximately 694,000 deaths in 2012 [8]. Due to trending increases in the obesity epidemic, these numbers are projected to double over the next two decades [54]. While routine colonoscopy has been the mainstay for early CRC detection, traditional colonoscopy is based primarily on structural abnormalities, which can miss up to 25 % of pre-malignant lesions [55–57]. Additionally, less than half of resected polyps represent neoplastic adenomas demonstrating true malignant potential, which leads to increased rates of adverse events during colonoscopy and high costs from unnecessary histopathological analysis of excised polyps [58, 59]. In fact, these extra costs from histopathological analysis are estimated to cost upwards of 30 million dollars annually [60, 61]. To better accommodate this deficit and concurrent rise in CRC incidence, there must be greater emphasis on early detection with attention to tumor-specific screening modalities [62]. In one CRC clinical study (#NCT01384240), HRME showed overall diagnostic accuracy of 96 % (p = 0.003) with 97 % sensitivity (p = 0.01) and 96 % specificity (p = 0.02) in detecting neoplastic colorectal polyps [63]. While this showed promising results, newer pre-clinical studies have emerged using tumor-specific molecular markers for detection of pre-malignant or malignant lesions. One such study in murine models demonstrated good target-to-background ratios for both polyps and flat lesions (4.0 ± 1.7 and 2.7 ± 0.7, respectively) with the use of topical peptide-specific EGFR targeting contrast agent [64]. Because EGFR is overexpressed in up to 97 % of colonic adenocarcinomas [65, 66], this study further exploited this fact by demonstrating a 19.4-fold higher mean fluorescence intensity in human dysplastic tissue when compared to normal tissue [64]. Additionally, the EGFR specific peptide had 90 % sensitivity and 93 % specificity for binding human colonic dysplasia [64].

In CRC, FI has the advantages of improving detection of dysplastic polyps and reducing the need for invasive biopsies and their associated adverse risks. This results in improved cancer detection and a reduction in invasive biopsy procedures, which translates to improved QOL, reduced need for highly morbid procedures, and cost-effective medicine. Current limitations are the relative lack of clinical trials utilizing cancer-specific targets. Therefore, further clinical studies are warranted to evaluate the effectiveness of cancer-specific fluorescent agents in the detection of CRC.

Gastric Cancer

In 2012, gastric cancer had an incidence of nearly one million and was the fifth most common cancer globally [8]. While the incidence of gastric cancer has dropped significantly since 1975, it is the most prevalent cancer in Japan and East Asia and is the third commonest cause of cancer-related death in both men and women [8]. Currently, 5-year survival for early-stage gastric cancer is over 90 % when treated surgically [67–69]. However, prognosis is poor when diagnosed at late presentation; in fact, early detection is paramount in achieving better outcomes [70]. White light endoscopy (WLE) is the currently accepted imaging modality for diagnosing gastric cancer; however, several limitations exist [70]. For example, the extent of malignant infiltration can be difficult to appreciate due to indiscernible tumor margins and/or the absence of typical morphological features [71]. Furthermore, early pre-malignant lesions such as intestinal metaplasia and mucosal atrophy, two established risk factors for the development of gastric cancer [72], are difficult to detect due to their subtle, often flat appearance on WLE [70].

Recently, one study reported the efficacy of PDD with 5-ALA in 26 lesions and found a sensitivity and specificity of 82.4 and 100 % for intestinal-type gastric cancer, respectively [73]. Although overall specificity was reported at 100 %, overall sensitivity was only 57.7 % [73]. While few studies have reported on the use of FI with PDD using 5-ALA in gastric cancer, it is a promising technique offering good visualization and strong specificity, particularly for intestinal-type gastric cancer [73]. FI using a combination of autofluorescence imaging (AFI) and narrow band imaging (NBI) for detection of early gastric cancer has additionally been studied in a high-risk Singaporean population (NCT01132534) [70]. The use of AFI-NBI detected significantly more patients with intestinal metaplasia than WLE alone (68 vs 34 %, p = 0.011) [70]. While sensitivity and diagnostic accuracy for both modalities were limited in diagnosing intestinal metaplasia and mucosal atrophy, the improved recognition of intestinal metaplasia with FI suggests it may have a role in identifying populations with well-known histological risk factors for developing gastric cancer [70]. As such, FI may serve as an early “red flag” for identifying patients who may benefit from more intense surveillance [70].

FI for screening of gastric cancer possesses the advantage of improving the detection of intestinal-type gastric cancer.

In high-risk populations, the ability to detect early metaplasia translates to better survival and QOL outcomes. Limitations to this technology include suboptimal sensitivity in current studies and the relative inability to adequately detect the diffuse variant of gastric carcinoma. Nevertheless, several studies predict PDD to have a significant role in supplementing current imaging modalities for gastric cancer detection by allowing improved visualization of tumor margins and extent of invasion [74]. This would be particularly useful as an adjunct to endoscopic submucosal dissection, which is a commonly used, less-invasive treatment of early-stage gastric cancer in Japan [75, 76]. Additionally, fluorescence navigation with 5-ALA has the potential to define surgical margins in real time during gastrectomy, as well as assist in pathological diagnosis at the benchtop [74]. Lastly, it may aid in the diagnosis of preoperative peritoneal metastasis during staging laparoscopy, which may help guide subsequent therapy by avoiding unnecessary laparotomy [74].

Skin Cancer

Non-melanoma skin cancer (NMSC) is the most common cancer in the world and, in the USA alone, has an incidence of nearly 3.5 million [77]. While infrequently fatal, NMSC can be progressive and locally destructive with the potential to spread to surrounding tissues. Melanoma, however, represents some 70,000 new cases annually in the USA and is the leading cause of death in patients with skin cancer [78]. Five-year survival for distant melanoma is a mere 15 % [78, 79]. While clinical examination is useful in detecting these frequently pigmented lesions, there is little diagnostic correlation with gold standard histopathological evaluation. For example, the diagnostic accuracy of general practitioners is somewhere between 24 and 44 %, while that of dermatologic specialists is only 77 % when compared to the gold standard [80, 81]. Optical imaging with fluorescence spectroscopy, which uses a dual light source to measure any differences in fluorescence in underlying tissue, has proven to be promising for detecting both malignant melanoma (MM) and NMSC. In fact, several optically based devices for the detection of MM are currently available with good diagnostic accuracy [82–84]. These include MoleMax (Derma Medical Systems, Vienna, Austria), MelaFind (MELA Sciences, Inc., Irvington, NY), MoleMate (Biocompatibles, Surrey, UK), and SolarScan (Polartechnics Ltd., Sydney, Australia) [85]. To optimize the clinical utility of these non-invasive devices, however, they must be developed for the detection of both MM and NMSC. Furthermore, they must be both highly specific and sensitive to avoid over treatment with invasive biopsies and under-diagnosis of potentially aggressive lesions, respectively.

We have identified three clinical trials (#NCT02193581, #NCT00476905, #NCT02704039) currently using optical FI techniques to diagnose cutaneous malignancies. In one recently completed trial (#NCT00476905), researchers studied the diagnostic accuracy of multimodal spectral diagnosis on 137 lesions for *in vivo* detection of both melanoma and NMSC [78]. The following three fiberoptic-based FI modalities were combined: diffuse optical spectroscopy (DOS), laser-induced fluorescence spectroscopy (LIFS), and Raman spectroscopy (RS) [78]. With this tri-modal optical imaging system, this study demonstrated a sensitivity/specificity of 100/100 % for accurate classification of malignant melanoma vs benign pigmented lesions (12 vs 17 lesions), a sensitivity/specificity of 95/71 % for accurately detecting SCC and/or BCC vs pre-malignant actinic keratosis (AK) (57 vs 14 lesions), and a sensitivity/specificity of 90/85 % for identifying AK, SCC, and/or BCC vs normal, benign skin (71 vs 71 lesions) [78].

The use of FI for screening of skin cancer has not been widely studied. Nonetheless, such high diagnostic performance is promising for future use in clinical practice, but larger clinical trials are necessary to fully evaluate the effectiveness of this non-invasive diagnostic tool. One limitation to consider with regard to FI for detection of melanoma is the issue of pigment-associated autofluorescence, which may prohibit accurate screening of pigmented lesions.

Optimal Clinical Trial Endpoints and Limitations for Diagnostic Screening and Surveillance

Specific clinical endpoints will depend on cancer subtype but ideally include those with overall survival benefits as well as those with clearly defined morbidity benefits as a result of early detection and/or intervention. For example, cancers commonly diagnosed at late presentation when treatment becomes more expensive, less effective, and increasingly radical. Phase 1 clinical trial endpoints will evaluate the safety profile of FI agents and their ability to detect pre-malignant and/or malignant lesions. Later phase studies will compare the efficacy of FI in detection of these lesions when compared to standard white light imaging or the currently accepted detection mechanism. Thus, the need for trial randomization into two separate study arms is unnecessary and of limited use since the FI technique will be held to gold standard histopathologic evaluation with the use of interpatient controls (Table 1).

A major factor to consider in this specialized field of FI is that contrast agents should possess a very limited toxicity profile, which may exclude exogenous agents. That is, they should possess minimal side effects as determined by a previously established safety profile. Furthermore, both imaging probes and devices should be less invasive and with favorable cost-benefit profiles when compared to current screening techniques. Ultimately, the use of fluorescence should provide significant improvements in sensitivity and specificity while minimizing user variability between novice and experienced physicians in order to

maximize the use of such technology in resource-limited areas.

One major concern in the field of FI is the issue of depth penetration, which is typically limited to 5–10 mm [86]. In fact, above a depth of 5 mm, there is often significant light scattering that results in a diffuse image [86]. This is particularly important to consider as it practically precludes the use of this technology for both whole body imaging and deep-seated tumors for which surface access is not possible. However, the high resolution of underlying tissue in areas allowing surface access makes superficial tumors or those with surface access particularly well suited for FI. As such, the utility of FI for cancer detection is currently limited and best reserved for tissues with minimal overlying tissue or mucosal surfaces with contact access.

Additionally, there remains another important issue that may potentially hinder the widespread use of FI for cancer screening: tissue autofluorescence. While autofluorescence permits visualization of underlying pathological processes, it is a phenomenon also present in many living, non-cancerous cells causing non-specific background fluorescence. This is often reduced with NIR irradiation; however, it presents particular concern in pigmented lesions such as melanoma, which contain melanin and emit fluorescence within the NIR range [87]. This pigment-associated autofluorescence may conceal the true fluorescent signal and interfere with the accuracy of FI. As such, FI of pigmented lesions should be cautiously evaluated in efforts to reduce the unwanted effects of pigment-associated background autofluorescence that may interfere with the diagnostic accuracy of FI techniques.

Conclusion

Despite advances in diagnostic techniques and adjuvant therapies, the global burden of cancer-related disease remains exceedingly high with over 14 million new cases diagnosed in 2012 [8]. Cancer treatment, diagnosis, and follow-up pose immense costs to both patient and healthcare industry. The use of FI as both a diagnostic tool and surgical guide enhancement has the potential to ameliorate the increasing cost of healthcare while simultaneously improving survival and QOL outcomes [34]. As new epidemiologic patterns evolve in response to improved life expectancies and changing lifestyle habits of the developing world, there is evidence that the incidence of cancer is growing [1]. While imperfections in cancer screening and surveillance are multifactorial, there is a pressing need for both improved cancer detection and innovative, cost-effective imaging modalities. Thus, the shift to develop low-cost, tumor-specific fluorescent screening devices and contrast agents represent a major advantage in minimizing healthcare disparities among industrialized and developing nations while making a formidable impact on the global burden of several cancer types.

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Compliance with Ethical Standards

Conflict of Interests

The authors declare that they have no conflict of interest.

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