Abstract

Cancer in the gastrointestinal tract develops in multiple steps through metaplasia, low-grade dysplasia to high-grade dysplasia, which currently remains the best marker of cancer risk. These changes are often invisible and detected with random biopsy. Optical imaging in vivo is a potential solution to obtain early detection and facilitate immediate treatment. In particular several methods are being developed for identification at endoscopic examination using narrow band imaging, fluorescence and spectroscopic assessment. Our group has concentrated on vibrational spectroscopies and have shown that Raman and infrared spectrosopies have the potential to identify markers associated with malignant change. Developments in instrumentation have enabled their application to tissue to allow the objective identification of molecular markers associated with neoplastic progression. Raman spectroscopy is compatible with endoscope technology enabling the targeting of biopsies in vivo with improved levels of sampling and measurement of the extent of disease. In addition these methods can be used in the diagnosis of many other cancers including breast, colon, prostate and parathyroid. Cancer spreads initially through the lymphatic system to local and regional lymph nodes. The examination of lymph nodes with optical techniques may allow the early detection of metastatic involvement and act as intraoperative assessment of the sentinel lymph node to guide surgery.

Introduction

Detection of cancer currently depends on the patients’ symptomatic presentation, with physicians accurately identifying any visible abnormality, with biopsy removal to confirm the diagnosis. For more than a hundred years clinicians have relied on the histological appearance of tissues in order to establish the diagnosis of most malignant and inflammatory conditions. Although a trusted technique; histological assessment is subjective, time consuming and expensive; with delay between diagnosis and treatment. Much normal tissue is removed as a result of the precautionary principle to exclude disease and reassure the patient. This risks complications, and is dangerous in vulnerable areas such as the eye and brain. Agreement between pathologists on the presence of early disease is very difficult to achieve. The delays to the patient pathway are very distressing for our patients and the
cost very substantial for our health services. Real-time in vivo optical diagnosis at first examination offers the prospect of bringing forward the diagnosis and allowing early or indeed immediate treatment. It may be possible for the patient to receive both diagnosis and therapy together.

**Oesophageal Cancer**

Oesophageal cancer represents the seventh most common malignancy worldwide and has the sixth highest cancer mortality rate. A major area for advanced *in-vivo* optical imaging is in the early diagnosis of oesophageal cancer and identification of the degeneration in the pre-malignant condition of Barrett’s oesophagus. This is now well-recognised as representing a metaplastic change from the normal squamous epithelial lining of the oesophagus to a columnar epithelium, predisposing to an increased risk of oesophageal adenocarcinoma. It is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1cm) above the gastro-oesophageal junction and confirmed histopathologically from oesophageal biopsies.

There is an urgent clinical need for novel diagnostic tools since standard white light endoscopic examination and biopsy sampling with subsequent histological diagnosis can be extremely subjective. Kerkhof et al., demonstrated a poor level of interobserver agreement between expert histopathologists (K=0.58) in the grading of Low-Grade (LGD) and High-Grade (HGD) oesophageal dysplasia [1]. However, this distinction has vital consequences for patient management as LGD can be monitored by serial surveillance endoscopy whereas HGD necessitates early endoscopic therapy or even surgery, and carries a significant risk of malignant progression.

Although histological assessment remains the ‘gold standard’ at present, there is a clear need for an objective diagnostic test which relies on biochemical or molecular analysis of target tissues rather than an individual’s assessment of cellular appearance. As well as being difficult to classify histologically, early neoplasia/dysplasia and Intramucosal Carcinoma (IMC) can be extremely difficult or even impossible to recognise at endoscopy even for skilled endoscopists. Progression to dysplasia or IMC in Barrett’s oesophagus is rare and the lack of familiarity of most endoscopists with the typical appearances of early neoplasia is a significant limiting factor in its detection [2-4]. Guidelines therefore advise that multiple biopsies are taken whenever Barrett’s oesophagus is identified at endoscopy. Most endoscopists take four quadrant biopsies every 2cm of Barrett’s oesophagus, or fewer. Surveillance biopsy protocols sample less than 5% of the mucosa and may miss up to 57% of early neoplastic lesions [5]. In addition, patients with HGD are known to have a 30-40% chance of occult adenocarcinoma which may be missed by sampling error in up to 50% of patients when using a standard biopsy regimen.

Several studies have compared the results of endoscopic biopsy assessment to surgical pathology following oesophagectomy for the detection of adenocarcinoma in dysplastic Barrett’s segments. Falk et al., demonstrated that over a third of cancers (38%) were missed when quadrantic biopsies every 2cm were taken from patients with HGD. Jumbo biopsy forceps made little difference to detection rates (67% versus 62%) [6]. Cameron and Carpenter found 2/19 (10.5%) unsuspected adenocarcinomas following quadrantic 2cm biopsies in patients who subsequently underwent oesophagectomy [7]. Similarly, Reid et al., showed that this biopsy regimen would have missed 13/26 (50%) of cancers in their cohort. They also demonstrated that targeted biopsies of endoscopically visible suspicious lesions were only able to establish the correct diagnosis in 15 out of 45 (33%) patients who were subsequently proven to have cancer [8]. There is a clear clinical need for advanced imaging tools that could improve endoscopic detection of HGD and IMC and enable targeted treatment.

*In-vivo* optical techniques: *Wide-Field detection techniques*
**High Resolution Endoscopy (HRE):** Modern high resolution endoscopes which generate up to one million pixel images (compared to the 300,000 pixel images of traditional scopes) have been shown to have a higher sensitivity than standard white light endoscopy for the detection of early neoplasia provided they are used by expert endoscopists [9]. So not to negate their effect these endoscopes should be used in conjunction with a high definition television to further enhance the projected image quality and prevent loss of resolution when larger images are required. Even in the hands of experts, Kara et al., showed that targeted biopsy using HRE was only capable of detecting 79% of dysplasia, and differentiation from LGD for the purposes of targeted treatment was difficult [10]. HRE should replace standard WLE where possible. Although to significantly improve endoscopic diagnosis of dysplasia, HRE may be best utilised in conjunction with additional endoscopic optical technology.

**Chromoendoscopy:** Chromoendoscopy involves exogenous administration of stains to the oesophageal mucosa in order to improve tissue characterization during endoscopy. Absorptive stains (such as methylene blue) cross epithelial membranes selectively, whereas contrast stains (such as indigo carmine) permeate into mucosal crevices highlighting surface topography and mucosal irregularities [11]. Studies utilising chromoendoscopy in Barrett’s oesophagus have had mixed results and have highlighted problems such as difficulties in uniformly coating the oesophageal mucosa with the stain and excessive times necessary for stain spraying. The technique has not been shown to consistently out-perform HRE in the detection of early neoplastic lesions. Chromoendoscopy is relatively widely available and does not require any particular equipment except for a spray catheter which is easy to use and cheap to purchase. However, chromoendoscopy is often both labour-intensive and operator-dependent and is therefore unlikely to become widely utilised.

**Narrow Band Imaging (NBI):** Narrow band imaging illuminates the mucosa with blue and green light in order to enhance the resolution of the mucosal surface by relying on the principle that longer wavelengths of light penetrate deeper into tissue than shorter wavelengths. Narrow band blue light displays the superficial capillary networks, while green light displays the sub epithelial vessels, and a combination of the two images produces an extremely high definition image of the mucosal surface allowing visualisation of subtle mucosal irregularities and alterations in vascular patterns consistent with dysplasia and IMC. NBI is a widely available technique which avoids the need for staining or intravenous contrast agents. It has shown promise in detection of dysplastic lesions when in the hands of experienced users. A review of NBI with magnification demonstrated high accuracy for the diagnosis of HGD in Barrett’s oesophagus based on recognition of irregular mucosal pit patterns and/or irregular micro vascularisation [12]. However, NBI is time-consuming and results have been mixed due to high levels of inter-observer variability. Overall, data on the accuracy of NBI in Barrett’s oesophagus are inconclusive and results of multicentre randomised controlled trials are awaited.

**Autofluorescence Imaging (AFI):** AFI detects fluorescence radiation following excitation of tissue using light of short wavelengths. Variation in the type and concentration of fluorophores enables differentiation between normal, metaplastic and neoplastic tissue. Several studies have suggested that AFI is sensitive for detection of HGD in Barrett’s oesophagus although the technique appears limited by low specificity. Curvers et al., demonstrated an increased detection rate of HGD/IMC using AFI compared to WLE alone (53% Vs 90%) but this came at the expense of a high false positive rate of 81% [13]. Further trials are necessary to demonstrate improvements in specificity through combination with other imaging techniques such as confocal microscopy.

**Biomarkers labels:** Visually tagged probe molecules have been engineered which selectively bind to neoplastic cells [14,15]. Lu et al., identified a cell surface peptide specific to adenocarcinoma which they labelled using a fluorescein-tagged antibody delivered topically. The oesophagus was then washed to remove any unbound antibody and a fluorescence endoscope was used to visualise neoplastic disease. Similarly, Fitzgerald et al.,
demonstrated that alterations in cell-surface glycans during progression to adenocarcinoma could be identified through changes in their lectin binding properties [16]. Selective binding of a candidate lectin (wheat germ agglutinin) sprayed into an ex vivo oesophagus enabled visualization of high-grade dysplastic lesions, which were not detectable by conventional endoscopy. These highly promising molecular techniques require further work in order to identify novel molecular targets to improve sensitivity and specificity before clinical implementation can be considered.

Point measurement techniques

Optical Coherence Tomography (OCT): OCT is analogous to ultrasound but can produce higher quality images as it relies on backscattering of near-infrared light (as opposed to radio waves) to generate cross-sectional images of epithelial and sub-epithelial tissues. It is performed using probes passed through the instrument channel of endoscopes. It does not require the use of exogenous contrast and unlike with ultrasonography, tissue contact is not required.

Several studies have assessed the role of OCT in the detection of dysplasia. In a study of 55 patients with Barrett’s oesophagus, OCT was shown to delineate between HGD and adenocarcinoma with a sensitivity of 83% and a specificity of 75% [17]. Another study of 33 patients demonstrated a diagnostic accuracy of 78% for the identification of dysplastic Barrett’s oesophagus, however considerable user discrepancy (56% to 98%) was demonstrated [18]. Further clinical evaluation is required to assess the diagnostic performance of OCT in the oesophagus. In the future the technique may have a greater role in the staging of early oesophageal tumours rather than in the detection of dysplasia.

Confocal Microscopy (CM): CM magnifies the mucosa 1000-fold enabling real-time visualisation of cellular structures. CM has shown considerable potential in Barrett’s oesophagus with reported accuracy of up to 97.4% for the detection of dysplasia [19]. However, due to considerable inter-user variation these results have not been universally achieved [20]. The technique has also been criticised for being both time-consuming and expensive as well as requiring considerable training to interpret and relying on the use of exogenous contrast to demonstrate the irregular neovascularisation that is characteristic of neoplastic tissue. Further trials are required before this technique can be recommended for widespread use.

Elastic Scattering Spectroscopy (ESS): ESS uses a fibre-optic probe passed through the instrument port of an endoscope to generate morphological information about the nature of the Barrett’s segment. White light is elastically scattered from the mucosa and submucosa with varying signal depending on the size and shape of the cell nuclei and the degree of cellular crowding. Spectral signal can be acquired in short acquisition times which approach ‘real-time’ imaging. Dysplastic and malignant tissues have been shown to have a characteristic ESS signature however, due to signal interference from deeper structures the accuracy of ESS appears limited to around 85% [21]. Lovat et al., measured spectra from 181 tissue sites from 81 patients which were correlated with consensus histopathology. ESS identified HGD with a sensitivity of 92% and a specificity of 60% and was able to differentiate these sites from inflammation with a sensitivity and specificity of 79% [22]. This current level of accuracy is probably not sufficient to support clinical uptake of ESS unless it can be improved through refinement of the technology or the use of a concomitant imaging modality.

Raman Spectroscopy (RS): We have been developing a novel, custom-built Raman probe for potential application as an in vivo diagnostic tool in the oesophagus. Raman spectroscopy is a well-established analytical technique which is capable of probing the biochemical changes associated with neoplastic progression in oesophageal tissue. RS relies on measurement of subtle inelastic scattering signals following monochromatic laser excitation. Clinical utilisation of RS within hollow organs requires accurate collection and transmission of signal through fibre-optic cables. We evaluated the ability of a custom
built fibre-optic Raman probe, in conjunction with multivariate classification models, to
differentiate between benign and neoplastic oesophageal cancer and precancer. The need
for spectral stability and reproducibility are addressed, as are difficulties associated with
multi-system reliability. In addition, the biochemical bases of spectral classification were
evaluated [23]. The biochemical basis of the spectral changes was explored using Raman
maps of the excised tissue [23-25].

Seven hundred and ninety-eight 1 second Raman probe spectra were acquired from
673 oesophageal tissue samples from 62 patients. 5 second and 0.1 second spectra were
also recorded for comparison. Principal component fed linear discriminant analysis was
used to calculate probe accuracy by reference to a consensus histopathological ‘gold
standard’ diagnosis. All results were statistically cross validated, based on characteristic
spectral signatures. High-grade dysplasia and adenocarcinoma could be discriminated
from Barrett’s oesophagus, low-grade dysplasia and normal squamous oesophagus with a
sensitivity of 86% and a specificity of 88%. The ability to detect early superficial mucosal
disease, including discrimination between low-grade and high-grade dysplasia, was also
demonstrated despite short, clinically applicable (1 second) spectral acquisition times.
Background subtraction and green glass correction algorithms were not shown to increase
diagnostic performance. However, enhanced diagnostic accuracy was demonstrated when
using 5 s acquisition times [26].

A single probe was shown to measure consistent spectra over an 18 month period. In
addition, a potential algorithm for multi-system spectral classification was defined and
consistent measurements were recorded by two independent operators using two identically
built probes. The potential for bimodal diagnosis using a combination of RS and narrow
band imaging was also demonstrated. No single incident of thermal tissue injury was
reported [26,27].

The ability for rapid, accurate, objective diagnosis of a range of oesophageal pathologies
using a novel endoscopic Raman probe has been demonstrated. RS has the potential to aid
targeting of high-grade dysplasia and intramucosal cancer during endoscopic resection in
order to maximise complete resection rates. A potential barrier to clinical application of RS
will be the transferability and repeatability of spectral measurements acquired with different
Raman systems. This will require further evaluation following the construction of multiple
probes.

![Figure 1: The mean 1 second tissue spectra for 3 oesophageal pathologies. Spectra have been offset for clarity and spec-
tral peaks have been tentatively assigned [26]. The spectra are obtained following air background subtraction (left) and
green glass correction (right). The prominent peaks have been labeled. This demonstrates clear spectral differences can
be detected in real-time using probe based measurement.](image-url)
Recently a clinical study has demonstrated real-time Raman spectroscopy can differentiate neoplastic progression and target dysplasia in Barrett’s oesophagus [28]. Currently, none of these advanced endoscopic imaging techniques have yet been widely adopted into clinical practice. This reflects a variety of limitations including insufficient sensitivity or specificity, inter-observer variability, cost and technical difficulties. There is a continuing need for a novel imaging technique that could enable objective assessment of Barrett’s segments in order to minimise missed disease and aid targeted Endoscopic Resection (ER). The advent and now widespread use of ER has meant that accurate targeting of focal HGD/IMC has become essential. However, a study by Vieth et al., showed that a complete (R0) resection was achieved in just 26.8 % (87/326) of patients at the first attempt due to inadequate endoscopic assessment of lesion margins [29]. This improved to 74.8% (244/326) following repeat endoscopy. The study concluded that failure to achieve R0 resections at the initial endoscopy would introduce an unnecessary time delay and may increase complication rates and the development of improved endoscopic imaging techniques was strongly advocated. The potential ability to objectively target neoplastic lesions makes endoscopic imaging an intriguing and exciting possibility and has led to the exploration of this technology.

<table>
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<tr>
<th>Imaging modality</th>
<th>Concept</th>
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<tr>
<td>Autofluorescence imaging (AFI)</td>
<td>Short-wavelength light causes excitation of endogenous biological tissues with subsequent release of longer wavelength fluorescent light.</td>
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<tr>
<td>Narrow-band imaging (NBI)</td>
<td>Narrow-bandwidth green and blue light (with exclusion of red light) only superficially penetrates mucosa, improving visualisation of mucosal microvasculature and surface morphology</td>
</tr>
<tr>
<td>Confocal microscopy (CM)</td>
<td>Real-time magnification of the mucosa up to 1000-fold enables visualisation of cellular structures.</td>
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<tr>
<td>Elastic scattering spectroscopy (ESS)</td>
<td>Elastic scattering of white light generates real-time morphological information about the size and shape of the cell nuclei and the degree of cellular crowding in the mucosa and submucosa.</td>
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<tr>
<td>Trimodal imaging</td>
<td>Incorporates HRE, AFI and NBI in a single endoscope with ability to switch between modalities during procedure.</td>
</tr>
<tr>
<td>Molecular imaging</td>
<td>Fluorescently-tagged molecular probes bind selectively to metaplastic or dysplastic cells.</td>
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<tr>
<td>Raman Spectroscopy</td>
<td>Prospect of direct molecular analysis in real time</td>
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Table 1: Advanced endoscopic imaging modalities being investigated for use in Barrett’s oesophagus surveillance programmes and for the facilitation of targeted endoscopic resection. In our viewpoint based measurements and spectroscopy offer clear advantages as a optical diagnostic based measurement and can be combined with a wide field overall assessment of the whole segment.

Lymph node and Tumour: Optical imaging

Cancer is a disease in which normal cell division has become uncontrolled and unregulated through mutations in the cell’s DNA. This leads to the formation of a growth or tumour made up of these abnormal tumours cells which can become malignant: gaining the ability to invade and spread to nearby tissues and organs.

Cancer cells from this growth may also break off from the primary tumour and invade the bloodstream or lymphatic vessels to be carried to places elsewhere in the body to multiply and form secondary tumours (metastases). In addition to lymph nodes, the most common places for metastases are the adrenals, lungs, liver, brain and bones. The progression of a primary tumour to formation of a secondary tumour or metastasis carries a worse prognosis, which in most cancer types, is linked with poor survival rates. The initial site of metastasis is usually the lymph nodes near the primary tumour (regional lymph nodes).

Therefore lymph node sampling and pathological examination is important in assessing whether a primary tumour has, or has the potential to spread to distant sites. We have demonstrated the ability of vibrational spectroscopy classification models to differentiate between cancerous and non-cancerous lymph nodes from patients. This was the first such study, to date, that has explored both Raman and infrared spectroscopy in parallel for lymph node diagnostics. No contrast agents are used and little tissue preparation is required, time,
cost and labour expenses are minimized, potentially providing faster diagnostic feedback to physicians and faster treatment initiation for patients [30,31].

**Figure 2:** Infrared spectroscopy demonstrating the average spectra measured from cancerous and non-cancerous lymph nodes [30]. This allows intraoperative realtime assessment of lymph node status. This is vital for targeted therapy and assessment prior to lymph node field dissection.

The ultimate goals of these spectroscopic studies is the potential of taking spectrometers into surgery for *in-vivo* measurements using fibre optic probes alone or in combination with existing surgical equipment for guided biopsy, tumour margin assessment and intraoperative diagnostic procedures [31].

**Breast cancer**

The detection of cancerous spread to locally lymph nodes in the armpit (axilla) during breast cancer surgery is vitally important. The last decade has seen the emergence of SLNB as the standard of care for the sampling of the axillary lymph nodes. The technique was developed on the principle that cancer cells that have invaded lymphatic vessels draining the breast will initially reach specific (sentinel) lymph nodes. The principle of the sentinel node and its role in predicting metastases from the primary tumour had been developed in penile cancer and malignant melanoma [30]. In many ways a deceptively simple idea it was proposed that all lymph drains via the guardian or sentinel node. Therefore sampling and then assessing this node will predict whether metastases to any of the nodes have occurred.

The status of the sentinel node has been demonstrated to reflect the overall status of the axilla in 97% of cases [32]. If the sentinel nodes are negative then the axilla is deemed clear of metastases and the rest of the nodes need not be dissected. This has been shown to reduce the morbidity and complications associated with traditional methods of node sampling. The technique of SLNB was first described in breast cancer in the early 1990s. A meta-analysis of 69 studies published in 2006 pooled data from more than 8000 patients and concluded that the technique was successful at identifying the sentinel node in 95% of cases and had a false negative rate of less than 7% [33]. These results, combined with the marked reduction in morbidity have meant that SLNB has now been adopted as the standard for the initial sampling of the axillary lymph nodes and is being used more and more widely throughout the UK. It is well accepted by patients due to its lower risks and the shorter associated hospital stay. The procedure involves the patient receiving either a sub dermal or intra dermal injection of Technetium99, a radioactive tracer, to the breast not more than 24 hours prior to surgery. Prior to the operation scintigraphy is performed to help localise the sentinel lymph nodes. At the time of surgery a further injection is made
in the peri-areolar region of 2.5% Patent V blue dye. The combination of these two markers has been shown to be the most effective method of correctly identifying the sentinel lymph node [34]. During the procedure the lymph node position is confirmed using a hand held gamma probe. A small incision is then made over the site and the node is identified visually before being excised.

**Raman optical imaging in-vivo**

Using a Raman spectroscopic probe we have demonstrated sensitivity of 96% and specificity of 99%. The other techniques are not so effective. Pathological assessment with frozen section (sensitivity 57-76%; Specificity 99%); Touch imprint cytology (sensitivity-33-81%; specificity-95-99%); molecular analysis (sensitivity-87-96%; specificity-92-97%). Thus immediate Raman spectroscopic allows immediate therapy to disease areas without resulting in the need for repeat surgery. Many patients can be reassured and the health service resources can be directed to those patients at high risk of cancer. Treatment is personalised with minimally invasive endoscopic resection for diagnosis, treatment or ablation of areas of degeneration. This prevents the development of symptomatic advanced cancer; the extreme hazards of radical surgical and oncological intervention [35,36].

**Parathyroid Tumours**

The pathology and pathogenesis of hyperparathyroidism has always been obscure, although in the management of hyperparathyroidism histopathology is key and is considered the gold standard to differentiate parathyroid adenoma from hyperplasia. In a third of patients a definite pathological diagnosis based on single gland biopsies is difficult and a biopsy of a second gland is necessary to make the diagnosis. With the advent of minimally invasive parathyroid surgery increasingly single glands are biopsied. The pathologist is thus less likely to be able to give a definitive diagnosis because of this.

We have explored the potential of optical spectroscopy to replace the role of the pathologist by accurately differentiating adenomas from hyperplasia using their biochemical signatures. Optical spectroscopy can potentially diagnose in real time, compared to the intraoperative frozen section which takes 15-20 minutes. Optical spectroscopy would also be a useful adjunct to current histopathological methods to establish or support a diagnosis in more challenging cases. Spectra were measured from frozen sections of excised glands both by Raman and infrared spectroscopies. Both empirical and multivariate analyses were carried out. The empirical analysis for the two pathologies demonstrated spectral differences suggestive of a more active proliferative process in the adenomatous gland compared to the hyperplastic one. Notable differences were also present in nucleic acid peaks. Multivariate analysis culminated in a spectral predictive model that demonstrated a sensitivity and specificity for adenomas of 95 and 93% and hyperplasia 93 and 95% respectively. The model was cross-validated using a leave one spectrum out method and performed well. FTIR spectral analysis demonstrated similar results. The multivariate spectral model demonstrated a 93% sensitivity and specificity for both pathological groups. Cross-validation, using the leave one gland out method indicated that the model was as yet not robust enough to be tested with independent samples. Fresh tissue samples were also analysed using Raman spectrometry and a Raman probe. Although the sample numbers were small, empirical analysis did demonstrate similar spectral differences. Optical spectroscopy was therefore demonstrated to potentially be an excellent diagnostic tool and pathological adjunct [37-39].
Colorectal Cancer

Colorectal cancer incidence rate shows that there are around 75 new bowel cancer cases for every 100,000 males in the UK and around 56 for every 100,000 females. The natural history is well understood and a neoplastic precursor identified, the adenoma, or adenomatous polyp. Adenomas are dysplastic and therefore display a disordered, neoplastic epithelial growth pattern with failure of maturation and differentiation. However, only between 1 and 10% will become invasive bowel cancer. Early diagnosis and removal of adenomatous polyps reduces incidence of colorectal cancer. Regular bowel cancer screening has been shown to reduce the risk of dying from bowel cancer by 16% [39]. Excision of any adenomas through biopsy or polypectomy has become standard management and histological examination of the tissue remains the gold standard for diagnosis of dysplastic change and invasive adenocarcinoma. The recent focus of research efforts has been detection of hard to detect, flat right sided lesions and overall polyp yield. Similar techniques are available at endoscopy as described within the oesophagus however there is a lack of evidence in the sensitivity and generalizability of these methods and so their use is limited in clinical practise. As with the oesophagus, real-time optical diagnosis offers the opportunity of earlier diagnosis and potentially more efficient patient management. Using a confocal fibreoptic Raman probe designed to fit down the accessory channel of a colonoscope it is possible to characterise polyps in realtime. Three hundred and seventy five Raman spectra were measured from a total of 356 colon biopsies from 177 patients. These included normal, adenoma, cancer and inflammatory biopsies. Spectral classification accuracies comparing pathologies ranged from 72.1 to 95.9% [40]. Infrared spectroscopy has also demonstrated successful diagnostic potential in the colon and we are now using the technique to characterise early cancer change in colonic epithelium [41]. This method has the ability to provide, in a non-destructive and label-free manner, a biochemical fingerprint of cells and tissues.

Conclusion

Real-time optical diagnosis is now a robust validated methodology of tissue diagnosis. The challenge remains to translate into clinical practice. The barriers to this are a natural

Figure 3: The Raman spectra of parathyroid adenoma and parathyroid hyperplasia [38]. Assessment of the parathyroid during surgery will allow targeted minimally invasive therapy.
slow transition from well-established tissue removal and biopsy to a potentially disruptive technology that will alter patient and clinical pathways.

References


