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Title

Making optical biopsy a clinical reality in colonoscopy: Deep learning and DISCARD-lite.

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Main Manuscript

Background

Abandoning conventional pathology even for low risk lesions would be a paradigm shift for gastroenterological practice; however, the advent of virtual chromoendoscopy (VCE) systems, such as narrow band imaging (NBI, Olympus), an easily learned and widely available method to perform “optical biopsy” has made this a possibility. Potential cost savings of VCE based optical biopsy strategies are estimated to exceed one billion dollars per year in the US alone. In 2010 the American Society of GI Endoscopy (ASGE) started to consider how optical biopsy might work clinically by drawing up practice standards which technology would have to meet to be acceptable to replace pathology for diminutive colorectal polyps¹. The threshold was set such that at least 90 % of the time the technology would allocate the same surveillance interval to patients that they would receive based upon pathology results, additionally with a negative predictive value of 90% for adenomas, so that hyperplastic polyps could potentially be left in situ. If this could be achieved, diminutive adenomas could be resected and discarded without pathological examination. Subsequent studies have suggested that these standards can be met by experts in academic centres using VCE, and in some but not all community based settings. The differences between successful and unsuccessful studies are not fully understood but maybe due to differences in training packages^{2,3}. The large DISCARD 2 study which delivered results falling far short of required standards was based upon a short and simple training package. In 2014 the ESGE and in ASGE both supported the use of some of the available commercial technologies (Box 1 - online) for VCE for diminutive colorectal polyps with restrictions^{4,5}; however, alongside the unsuccessful studies there remained reluctance to change clinical practice.

NICE

In May 2017, the National Institute for Clinical and Healthcare Excellence (NICE) in the United Kingdom issued a guidance document on the use of virtual chromoendoscopy for colonic polyps⁶. This non-departmental public body which defines healthcare standards endorsed the clinical and cost effectiveness of VCE to replace histopathology for diminutive colorectal polyps under specific conditions, specifically giving recommendations around training and accreditation of endoscopists. This guidance did not, however, address how the gap to clinical application should be addressed. The British Society of Gastroenterology, and The Joint Advisory Group for GI endoscopy (JAG) have been charged with spanning this gap by agreeing how training, accreditation and quality assurance might be delivered, with the support of the NICE adoption team. The best training methodology needs to be established to enable long lasting high quality diagnostic performance, with additional ongoing quality assurance of accuracy of VCE. In addition, current colonoscopy quality assurance processes

rely on histopathology to confirm adequate adenoma detection rates. Changing to virtual adenoma detection rates would require an additional culture shift. Other issues, including the retention of high definition images of polyps to replace pathology slides as the permanent record of a lesion have yet to be resolved. In addition, patient views are crucial to this process and clinicians will need to consider how consent is obtained and whether an opt should be available (Table 1 - online). The rate of colorectal cancer in diminutive polyps is exceptionally low but not zero. This is a potential area of concerns however NICE modelling suggests equivalent cancer survival whether histology or VCE is used. It is important to stress that a “detect and resect” policy may not send all polyps for histology but would usually entail removal of polyps negating the risk of leaving cancer in situ. Nevertheless, legitimate concerns regarding the safety of VCE may mean that cost savings for the wider healthcare community are not realised if practice does not change. On the other hand, the pressure to achieve cost saving may be so great that endoscopists may feel pushed into offering VCE against their will, and the GI community will need to guard against savings at any cost.

CAD and Deep learning

Although data from experts is broadly consistent, achieving a level of diagnostic accuracy similar to pathology, a number of large community based studies have reported results not acceptable for VCE to replace pathology³. Whilst this may be a training issue, it maybe that non-enthusiasts find it harder to reach and maintain the performance of experts. Computer aided diagnosis through artificial intelligence and machine learning based approaches to image analysis approaches may provide a solution, with real time clinical decision support tools to help clinicians with VCE ⁷. More recently artificial intelligence based deep learning, which uses neural network based approaches to computer vision, have been applied to VCE. These differ fundamentally from other approaches to computer polyp image analysis as they do not require human derived classifiers or segmentation of the polyp from the image, with promising results⁸. Critical to the introduction of such technologies is a consideration as to where they would lie within the diagnostic decision-making tree (Figure 1). Would they provide a check for the endoscopist, a simultaneous opinion, a first read, or even replace clinical decision making? The levels of test performance required for each of these scenarios would vary, especially for autonomous machine decisions where the diagnostic performance would need to be exceptional.

DISCARD-lite

An alternative approach to the perceived complexity of VCE at endoscopy would be to simplify the approach related to the relative risks in different parts of the colon. In essence, most polyps detected proximal to the recto-sigmoid are potentially pre-malignant being either adenomas or sessile serrated polyps. Both appear to elevate future colorectal cancer

risk, by relatively similar amounts⁹. It might be logical therefore to abandon VCE for the proximal colon altogether. VCE could thus be reserved for the recto-sigmoid to differentiate adenomas from hyperplastic polyps. The latter are not thought to be premalignant, do not predict future colorectal cancer risk. This combination of resect and discard for adenomas in the recto-sigmoid, leaving hyperplastic polyps in situ, combined with removing and discarding all proximal polyps has been termed “DISCARD-lite”¹⁰. It is potentially simpler, requires less skill, and may be easier for regulators to accept as perceived risk is lower if only hyperplastic polyps are left in situ. It would, however, require a change in surveillance guidelines to combine diminutive sessile serrated polyps and adenomas as risk equivalent. Recent data modelling this on previous optical biopsy datasets suggest that such “non-optical” strategies might be feasible with performance close to PIVI requirements and a further reduction in the need for pathological evaluations of between 58% and 79%¹¹.

Summary

Optical diagnosis had reached something of a hiatus with conflicting results for different studies. Following the UK NICE guidance there is renewed momentum for implementation of VCE based optical biopsy in the UK over the next 3-5 years. This represents a first step down the VCE road that might lead elsewhere in the GI tract, particularly in the context of Barrett’s oesophagus where good quality data exist, but also other organ systems. It seems likely that VCE might replace pathology for a range of low risk lesions, representing a new relationship between endoscopist and pathologist. The role of computer algorithms, deep learning, and how surveillance strategies are developed will need to be defined.

Nevertheless, it is critical as we take these first steps that we carefully establish the accreditation, training, Key Performance Indicators and clinical pathways to ensure that VCE is taken forward safely. Small careful steps now with wide engagement will reap significant rewards in the future.

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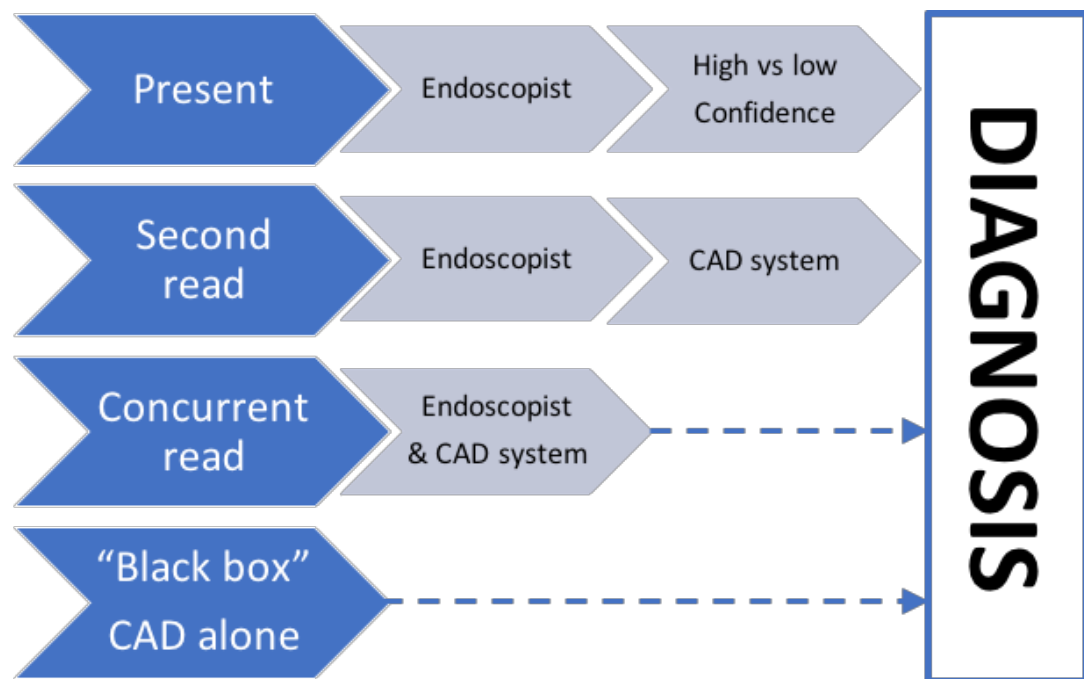
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Declaration of interests

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Figure 1. Integration of decision support tools to optical biopsy pathways at endoscopy



Box 1. Commercially available techniques to support optical biopsy

Enhancement technique	Mechanism	Manufacturer
Chromoendoscopy +/- magnification*	Dye-based	Non-proprietary
Narrow Band imaging (NBI)*‡§	Blue light	Olympus
NBI Bright (Excera III)*‡§	Blue light	Olympus
FICE*§	Digital enhancement	Fujinon
Blue light imaging (BLI)	Blue light	Fujinon
ISCAN*§	Digital enhancement	Pentax
ISCAN OE	Blue light	Pentax
Confocal endomicroscopy	Laser and IV fluorescein	Mauna Kea
WAVSTAT	Autofluorescence	SpectraScience

*Supported by ESGE⁵; ‡supported by ASGE⁶; § supported by NICE⁷

Table 1. Pros and cons of optical biopsy strategies at colonoscopy for diminutive polyps

Pros	Cons
Clinical and patient benefits <ul style="list-style-type: none"> • Immediate determination of surveillance interval • Streamlined patient pathway • Lower anxiety as not waiting for results 	Clinical and patient risks <ul style="list-style-type: none"> • No tissue for later review • Risk of leaving neoplasia in situ • Unknown patient acceptance
Procedural benefits <ul style="list-style-type: none"> • Increased focus on detailed mucosal observation • No loss of polyps or polyps destroyed by diathermy 	Procedural concerns <ul style="list-style-type: none"> • Changed standard for adenoma detection rate • Risk of ‘gaming’ to inflate adenoma detection rates • Limited data on sessile serrated polyps
Resource benefits <ul style="list-style-type: none"> • Reduced burden on pathology services • Reduced follow up appointments 	Resource issues <ul style="list-style-type: none"> • No current remuneration where this is histology dependent • Medicolegal position not yet clarified or tested

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