Virtual chromoendoscopy for the real-time assessment of colorectal polyps in vivo: a systematic review and economic evaluation

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Declared competing interests of authors: Joanne Lord reports membership of the National Institute for Health Research Health Technology Assessment Commissioning Board from 2011 to 2016. Sophie Whyte reports personal fees from Southampton Health Technology Assessments Centre during the conduct of the study.

Published December 2017
DOI: 10.3310/hta21790

Scientific summary

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Health Technology Assessment 2017; Vol. 21: No. 79
DOI: 10.3310/hta21790

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Background

Colorectal polyps are small growths on the lining of the colon or rectum. They are common, particularly in people aged > 60 years, and they do not usually cause symptoms. Histopathology can distinguish between polyps that are adenomas and those that are hyperplastic. It is important to identify adenomas because these polyps may eventually become cancerous if undiagnosed and untreated, whereas hyperplastic polyps usually do not carry a risk of developing into cancer.

Current clinical practice is to detect colorectal polyps during a colonoscopy when the colon and rectum are examined using conventional white-light endoscopy (WLE). Dyes may also be used (chromoendoscopy) to enhance visualisation of tissues being inspected. Usually, each detected polyp is removed (by polypectomy) and sent for histopathological examination to determine whether it is an adenoma or hyperplastic. The surveillance interval is set based on the number and size of adenomas found.

An addition to conventional WLE is virtual chromoendoscopy (VCE), an electronic imaging technique that enables the endoscopist to differentiate between adenomatous and hyperplastic colorectal polyps in real time during colonoscopy (optical assessment). There are three commercial systems of relevance to this diagnostic assessment report: narrow-band imaging (NBI), flexible spectral imaging colour enhancement (FICE) and i-scan. It has been suggested that VCE can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive (≤ 5 mm) colorectal polyps to replace histopathological diagnosis. It is typically proposed that, when the endoscopist has high confidence in the diminutive polyp characterisation, adenomas should be removed and discarded (i.e. not sent to histopathology), whereas hyperplastic polyps would be left in situ (because the risk for colorectal cancer is very low). If the endoscopist cannot confidently characterise a polyp, it should be resected and sent for histopathological examination. The potential benefits of VCE include fewer polyp resections and a possible reduction in associated complications (e.g. bleeding and bowel perforation), patients receiving results faster (so less anxiety associated with waiting for results) and a reduction in health-care resource use (e.g. fewer histopathological examinations). However, a potential downside of VCE is that it is not as accurate as histopathology, and so some adenomas may be missed and then left in situ, potentially developing into cancer. For VCE to be incorporated into clinical practice for the real-time assessment of polyps, evidence is needed that it provides an appropriate and efficient standard of care compared with existing practice.

Objectives

To determine, through a systematic review and economic evaluation, the clinical effectiveness and cost-effectiveness of the VCE technologies NBI, FICE and i-scan for the characterisation and management of diminutive (≤ 5 mm in size) colorectal polyps.

Methods

Systematic review of clinical effectiveness

We undertook a systematic review of studies assessing diagnostic accuracy and other health outcomes when NBI, FICE and i-scan are used to characterise the histopathology of diminutive colorectal polyps in real time. A comprehensive search strategy was designed to capture relevant clinical effectiveness and cost-effectiveness studies. We searched the following databases from inception to June 2016: MEDLINE, PREMEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, the Cochrane Database

of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment database and the NHS Economic Evaluation Database. We also identified publications through conference proceedings, websites, bibliographies of included studies and relevant systematic reviews, and our Expert Advisory Group. Studies were eligible for the review if they were randomised controlled trials (RCTs), prospective longitudinal cohort or cross-sectional studies that evaluated NBI, i-scan or FICE [using high-definition (HD) endoscopy systems, without magnification] for the real-time diagnosis of diminutive colorectal polyps in people undergoing colonoscopy for screening or surveillance or to investigate symptoms suggestive of colorectal cancer. The reference standard was histopathology with at least one of the following outcomes reported: diagnostic accuracy; number of polyps designated to be left in place, resected, discarded or sent to histopathology; recommended surveillance intervals; examination time; number of medical consultations; health-related quality of life (HRQoL) (including anxiety); adverse effects of polypectomy; incidence of colorectal cancer; and mortality. We assessed the risks of bias of the included studies using the quality assessment of diagnostic accuracy studies (QUADAS) instrument and narratively synthesised included studies. We conducted bivariate meta-analyses, where possible, to provide pooled estimates of diagnostic sensitivity and specificity for each technology. An Expert Advisory Group of four independent experts was invited to comment on the protocol and draft report.

Systematic review of economic studies

A systematic review of cost-effectiveness studies was conducted to identify relevant evidence to inform the economic evaluation. The review used the same set of references identified in our systematic review of diagnostic accuracy with an additional filter using the keyword 'cost'. Studies were included if they were a full economic evaluation that included long-term outcomes such as the incidence of colorectal cancer, or life-years or quality-adjusted life-years (QALYs) gained.

Economic evaluation

We developed an independent cost–utility decision-analytic model to estimate the cost-effectiveness of VCE to optically characterise diminutive polyps compared with histopathology. The model used a decision tree for patients undergoing endoscopy, combined with estimates of long-term outcomes (e.g. incidence of colorectal cancer and subsequent morbidity and mortality), derived from The University of Sheffield School of Health and Related Research's bowel cancer screening (SBCS) model. The decision tree follows a cohort of patients who receive endoscopy and who have at least one diminutive polyp identified (and no non-diminutive polyps). For the histopathology strategy, all diminutive polyps identified are resected and sent to histopathology. In the base-case analysis for VCE, polyps characterised with low confidence are resected and sent to histopathology, polyps characterised with high confidence as hyperplastic are left in situ whereas those characterised as an adenoma are resected and discarded (i.e. not sent to histopathology). The model uses the diagnostic accuracy estimates for VCE from our systematic review of diagnostic accuracy. In the long-term SBCS model, patients progress through the development of adenomas, colorectal cancer and subsequent death. Costs are included in the model for colonoscopy, histopathology, adverse events from colonoscopy (polypectomy) and the costs of treating colorectal cancer. Health outcomes are quantified in terms of incremental QALYs, including mortality and impacts on HRQoL associated with adverse effects of polypectomy and colorectal cancer. Costs and benefits are discounted at 3.5% per annum. The perspective of the analysis is that of the NHS and Personal Social Services. The model uses a lifetime horizon and reports results as costs per QALY gained.

Results

Clinical effectiveness

From 2070 titles and abstracts screened, 125 full texts were retrieved for detailed examination. The 32 references that met the inclusion criteria described 30 separate studies. Most studies evaluated NBI ($n = 22$), with an additional two studies also evaluating one of the other interventions of relevance (NBI and i-scan, NBI and FICE). Four further studies evaluated i-scan and two further studies evaluated FICE.

We assessed the studies as being generally at a low risk of bias across the domains measured by the QUADAS.

The ability of NBI to correctly identify diminutive polyps as adenomas (i.e. the sensitivity of the test) in the whole colon ranged from 55% to 97% (17 studies) for all assessments, regardless of endoscopist confidence (studies did not state how high confidence was defined or measured). For high-confidence characterisations, sensitivity ranged from 59% to 98% (13 studies) for the whole colon, and from 83% to 96% (five studies) for high-confidence characterisations in the rectosigmoid colon. The ability of NBI to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) was typically lower, ranging from 62% to 95% (16 studies) for all assessments in the whole colon, from 44% to 92% (11 studies) for high-confidence characterisations in the whole colon, and from 88% to 99% (five studies) for high-confidence characterisations in the rectosigmoid colon. A bivariate meta-analysis using available data (16 of the 24 NBI studies) produced a summary value for sensitivity of 0.88 [95% confidence interval (CI) 0.83 to 0.92] (i.e. 88%) and for specificity of 0.81 (95% CI 0.75 to 0.85) for all characterisations in the whole colon. Bivariate meta-analysis of high-confidence NBI characterisations in the whole colon produced summary values for sensitivity of 0.91 (95% CI 0.85 to 0.95) and for specificity of 0.82 (95% CI 0.76 to 0.87) (11 studies), and for high-confidence characterisations in the rectosigmoid colon summary values for sensitivity of 0.87 (95% CI 0.80 to 0.92) and for specificity of 0.95 (95% CI 0.87 to 0.98) (four studies). We found that endoscopists with prior experience of using NBI to characterise diminutive colorectal polyps achieved higher sensitivity and specificity than endoscopists with no prior experience of using NBI.

The five included studies evaluating i-scan varied in how they reported results. One reported results for all polyp assessments in the whole colon and four reported assessments made in particular parts of the colon. Sensitivity was above 90% in four studies (range 93–95%) and was 82% in a study that used a per patient (rather than per polyp) analysis. Specificity ranged from 83% to 96%. Sensitivity and specificity for high-confidence assessments ranged from 94% to 98% and from 90% to 96%, respectively. A bivariate meta-analysis of two studies reporting on high-confidence characterisations of polyps in the whole colon produced a summary sensitivity of 0.96 (95% CI 0.92 to 0.98) and specificity of 0.91 (95% CI 0.84 to 0.95).

The three included studies evaluating FICE assessed polyps in any part of the colon and did not provide analyses by confidence level. Sensitivity and specificity ranged from 74% to 88% and 82% to 88%, respectively. A bivariate meta-analysis produced a summary value for sensitivity of 0.81 (95% CI 0.73 to 0.88) and for specificity of 0.85 (95% CI 0.79 to 0.90) (three studies).

The negative predictive value (NPV; i.e. the probability that patients who are diagnosed by VCE as having a hyperplastic polyp truly do not have an adenoma) was more variable across the NBI studies than the FICE or i-scan studies. On this outcome, the most favourable results were consistently achieved by i-scan, but this may have been as a result of the higher proportion of i-scan studies involving endoscopists with prior experience of i-scan.

The percentage agreement between surveillance intervals allocated following NBI (13 studies) and those allocated following histopathology ranged from 84% to 99%. The agreement following i-scan (two studies) ranged from 93% to 97% and for FICE (two studies) from 97% to 100%. When considering only studies in which surveillance intervals were assigned in accordance with the two Preservation and Incorporation of Valuable endoscopic Innovation programme (PIVI) criteria (guidance on the requirements that new technologies should meet before a 'resect and discard' strategy can be applied in practice), eight of the nine NBI studies reporting this outcome achieved a level of agreement that was $\geq 90\%$, thus meeting the first PIVI criterion. Both the i-scan studies reporting this outcome achieved an agreement $\geq 90\%$. All NBI (five) and i-scan (one) studies that assessed NPV for high-confidence assessments of diminutive polyps in the rectosigmoid colon met the second PIVI criterion of achieving a NPV of $\geq 90\%$. There was no evidence for FICE in relation to the PIVI criteria.

None of the identified studies measured HRQoL, anxiety, number of outpatient appointments or telephone consultations, incidence of colorectal cancer or mortality. Four studies assessed adverse effects, stating that there were none. Data on the number of polyps that would be left in place, resected, discarded or sent to histopathology, and the time to perform the colonoscopy, were too limited for the review to draw conclusions about these outcomes.

Cost-effectiveness

We included two studies of VCE compared with histopathology in our systematic review of economic evaluations. Both compared a resect and discard strategy with current practice of submitting all polyps to histopathology. The evaluations were published in the USA and found that there were cost savings for the resect and discard group ranging between US$25 and US$174 per person.

In addition, a study by Olympus, the manufacturer of NBI systems, describes a budget impact analysis of NBI for the NHS in England. The decision tree model has a time horizon of 7 years and in each year there is a cohort of patients who undergo endoscopy. The study estimated that NBI offers cost savings of £141M over 7 years.

The results of our independent economic model suggest that VCE is cost saving compared with histopathology, with a mean saving of between £73 and £87 per person over their lifetime for the different VCE technologies. QALYs are similar between histopathology and VCE technologies, with a very small increase in QALYs for NBI and i-scan compared with histopathology of between 0.0005 and 0.0007 QALYs per person, whereas FICE is associated with 0.0001 QALYs fewer per person than histopathology. VCE technologies have a cost saving of about £50 per polyp resection avoided compared with histopathology. The model estimates that the correct surveillance interval would be given to 95% of patients with NBI, 94% of patients with FICE and 97% of patients with i-scan. The results are most sensitive to the pathology cost, the probability of perforation with polypectomy and the proportion of patients who die from perforation. Probabilistic sensitivity analyses (PSAs) were conducted for pairwise and incremental comparisons for histopathology with VCE technologies. The probabilistic incremental cost-effectiveness ratios (ICERs) were similar to the base-case deterministic ICERs. At a willingness-to-pay threshold of £20,000 and £30,000, i-scan was most cost-effective in 95% and 33% of simulations, respectively.

Discussion

Evidence was limited for FICE and i-scan, and was generally limited for high-confidence characterisations in the rectosigmoid colon. The heterogeneity among the NBI studies in setting, country, endoscopists' experience and training makes it difficult to determine the diagnostic accuracy of NBI. Uncertainties include the generalisability of the evidence base to the UK, how the settings of studies may have impacted on the results (e.g. academic centres compared with community hospitals), and a lack of data on longer-term health outcomes among patients undergoing VCE for assessment of diminutive polyps. Studies providing evidence on the diagnostic accuracy of characterising polyps did not relate this to the prediction of surveillance intervals of patients in order to predict disease progression in patients. The economic analysis includes only diminutive polyps and does not differentiate between the type of polyp, such as depressed polyps or sessile serrated polyps. Limitations in the data available for the prevalence of adenomas across risk classification, the distribution of polyps and the proportion of patients in the higher-risk categories with small and large adenomas necessitated assumptions in the economics model. There are also limitations in the data on recurrence rates post polypectomy. The full uncertainty around the model results has not been explored in the PSA as the long-term outcome parameters have not been varied.

Conclusions

Implications for service provision

Virtual chromoendoscopy technologies, using HD systems without magnification, have the potential for use in practice for the real-time assessment of diminutive colorectal polyps, if endoscopists have adequate experience and training. NBI and i-scan, when used with high confidence, generally meet the PIVI requirements to be used to perform a resect and discard strategy, but it is unclear how the findings generalise to UK practice. VCE was estimated to be cost saving compared with histopathology. It was associated with a small gain in QALYs for NBI and i-scan, and a small decrease in QALYs for FICE. The least costly and most effective of the technologies in terms of diagnostic accuracy was i-scan, which might be explained by the sparseness of data on diagnostic accuracy for i-scan, and the fact that most of the studies involved experienced endoscopists working in specialist centres.

Suggested research priorities

Future research priorities include head-to-head RCTs of all three VCE technologies; more research on the diagnostic accuracy of FICE and i-scan (when used without magnification); further studies evaluating the impact of endoscopist experience and training on outcomes; studies measuring adverse effects, HRQoL and anxiety; and longitudinal data on colorectal cancer incidence, HRQoL and mortality.

Study registration

This study is registered as PROSPERO CRD42016037767.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 15/17/05. The protocol was agreed in February 2016. The assessment report began editorial review in September 2016 and was accepted for publication in March 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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