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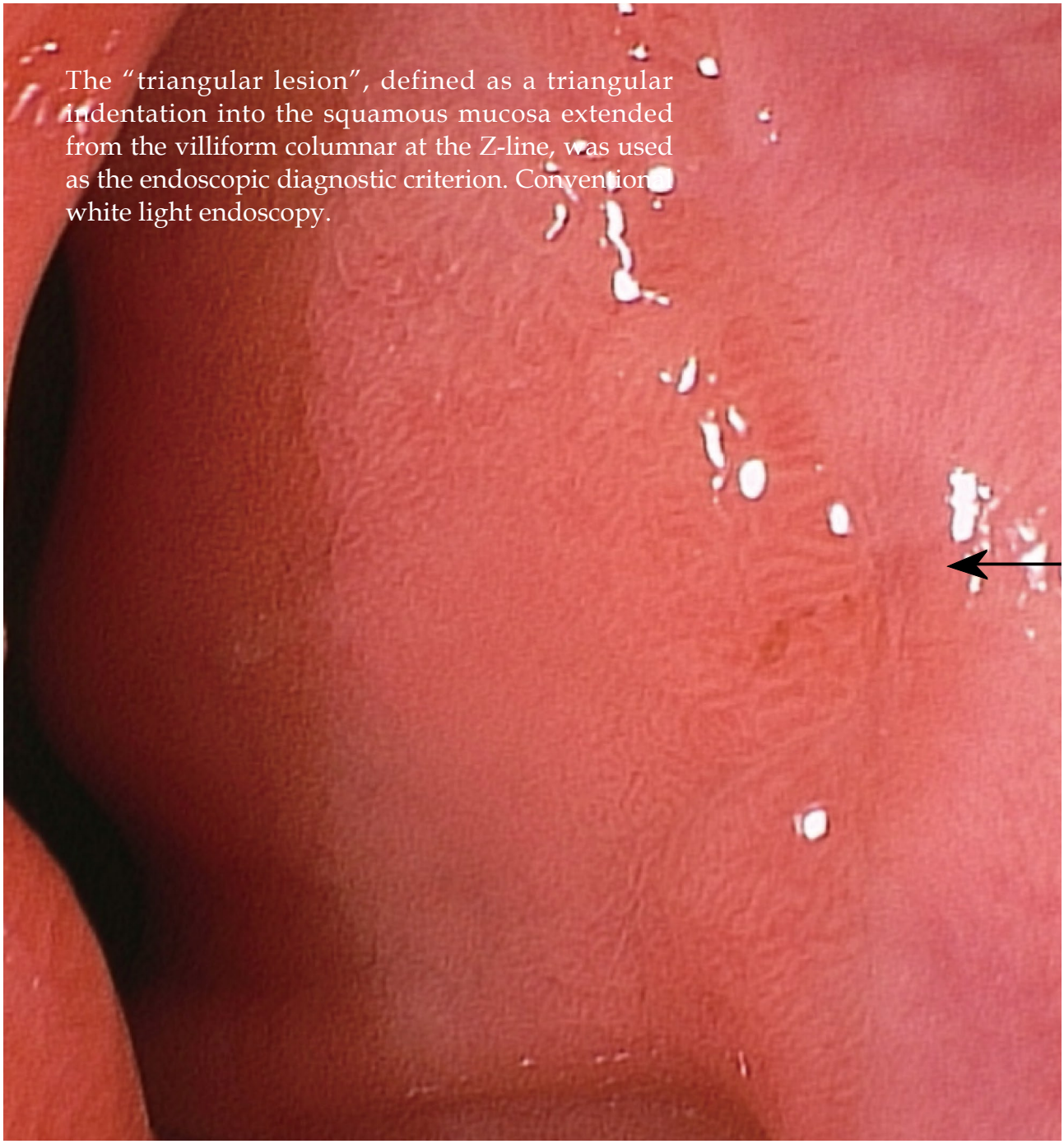

The "triangular lesion", defined as a triangular indentation into the squamous mucosa extended from the villiform columnar at the Z-line, was used as the endoscopic diagnostic criterion. Conventional white light endoscopy.

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EDITORIAL

Endoscopic ultrasonography and idiopathic acute pancreatitis

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Abstract

Idiopathic acute pancreatitis is a diagnostic challenge for gastroenterologists. The possibility of finding a cause for pancreatitis usually relies on how far the diagnostic study is taken. Endoscopic explorations such as endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography can help to determine the cause of pancreatitis. Furthermore, microscopic bile examination and magnetic resonance cholangiopancreatography can also be helpful in the work up of these patients. In this article an approximation to the diagnostic approach to patients with idiopathic acute pancreatitis is made, taking into account the reported evidence with which to choose between the different available explorations.

Key words: Endosonography; Cholangiopancreatography; Endoscopic retrograde; Cholangiopancreatography; Magnetic resonance; Microscopic bile examination; Idiopathic pancreatitis; Acute; Diagnosis

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INTRODUCTION

Acute pancreatitis might be defined as an inflammatory process of the pancreas clinically characterized by upper abdominal pain and elevated levels of pancreatic enzymes in the blood. In up to 10% of patients with a single episode of acute pancreatitis and in 30% of patients with acute recurrent pancreatitis, the aetiology is not found after the initial examination. Initial work up should include a detailed clinical history with records of recent infectious diseases, abdominal traumas or surgery; personal records of systemic diseases and ethanol or medicine intake; serum calcium, triglycerides levels, liver enzymes and autoantibodies (ANA, IgG4, rheuma factor); and at least one transabdominal ultrasonography although two are advisable. These patients are diagnosed with idiopathic acute pancreatitis (IAP)[1,2].

This situation represents a diagnostic challenge since in many cases the possibility of finding a cause for the pancreatitis depends directly on how deep the etiological search is made. Thus, when more accurate explorations are performed, gallbladder microlithiasis, sphincter of Oddi dysfunction, pancreas divisum or chronic pancreatitis is usually found. Less commonly, pancreatic tumours or cysts, anatomic anomalies such as a long pancreatobiliary junction (> 15 mm), annular pancreas, choledococele, a duodenal duplication cyst and a periampullary diverticulum can also be found as the cause of the acute pancreatitis bout. In the absence of mechanical and anatomic causes of acute pancreatitis in patients under 40 years of age, gene mutations such as mutations of the cationic trypsinogen gene, in the serine protease inhibitor Kazal type Ⅰ or in cystic fibrosis gene must be considered as a possible cause of the IAP.

Autoimmune pancreatitis, a pancreatic disorder characterized by imaging criteria (enlargement of the pan creatic gland, diffuse narrowing of Wirsung duct with an irregular wall), laboratory criteria (elevation in IgG4 serum levels and positive autoantibodies) and histopa thologic criteria (marked lymphoplasmacytic infiltration and dense fibrosis)[3] has been more frequently diagnosed recently. Using a cut off value of 135 mg/dL, the sensitivity and specificity of the serum IgG4 for distinguishing autoimmune pancreatitis from pancreatic cancer are 95% and 97% respectively[4]. Recent studies indicate that two different types of AIP exist: Type I which is predominantly found in Western Europe and the United States (IgG4 negative) and Type II which is more frequently found in Asia[5,6].

It is of great importance to identify the cause of pancreatitis because if it is not corrected recurrence is common; up to 70% depending on the cause[7]. Moreover, the mortality rate for acute pancreatitis is between 4% and 9% but can be higher for IAP[8].

In order to find the cause of the IAP, several explorations such as Endoscopic Retrograde Cholangio-Pancreatography (ERCP), Magnetic Resonance Cholangio-Pancreatography (MRCP), Microscopic Bile Examination (MBE) or Endoscopic Ultrasonography (EUS) can be performed. By performing one of these explorations or a combination, an etiological diagnosis can be made in up to 90% of cases of IAP.

However, some considerations must be made regarding the etiological diagnosis of patients with IAP.

WHAT THE FIRST LINE DIAGNOSTIC EXPLORATION IN PATIENTS WITH IAP SHOULD BE: ERCP *vs* MBE *vs* EUS *vs* MRCP

ERCP has been the first choice of diagnostic procedures in these patients for over three decades with a diagnostic yield of up to 80% but with a rate of potentially severe complications of 10%-15%[9,10]. An important advantage of ERCP is that it is possible to perform therapeutic manoeuvres necessary in up to 75% of these patients. Taking into account its morbidity rate, some authors recommend an ERCP only after the second episode of IAP or after the first in severe IAP[7,11]. Other authors support the indication of ERCP systematically after the first episode of IAP[12].

In patients with gallbladders, the most frequent cause of the IAP is microlithiasis which is present in up to 80% of these patients[2,13]. The exploration considered as the gold-standard to diagnose microlithiasis is currently the MBE[14] with a sensitivity of 65%-90% and a specificity of 88%-100%[15]. However, this exploration has some drawbacks which should be noted. In 29%-50% of patients with known gallbladder lithiasis, the MBE is falsely negative[16]. Moreover, it is a time consuming exploration which might take up to one hour. It is also not feasible in up to 20% of patients due to it being impossible to place the nasoduodenal probe in the second duodenal portion, aspiration of inadequate material or the patient's intolerance. This rate of exploration failure has also been reported by other groups[17].

Dahan *et al*[18] compared the diagnostic accuracy of EUS with MBE in detecting microlithiasis in patients with IAP or abdominal pain mimicking a biliary colic with transabdominal ultrasonography within normal limits. Results were significantly better with EUS compared to MBE.

However, to my knowledge, these results have not been confirmed by other groups. In a prospective blinded comparative study, we found similar accuracies for EUS and MBE (100% *vs* 95%, $P > 0.05$) in diagnosing the presence of microlithiasis but EUS diagnosed the presence of other pancreatic diseases which could be responsible for the acute pancreatitis bout in 25% of patients[19]. Therefore, MBE should not be currently considered as a first line procedure in the examination of patients with IAP.

Recently EUS has proved to have a diagnostic accuracy between 60% and 80%[20-27] in patients with IAP similar to ERCP but with a lower complication rate comparable to gastroscopy[28]. This gives an idea of the clinical impact of EUS on the management of these patients. Theoretically, with EUS we might be able to diagnose the majority of possible causes of IAP stated previously. Besides the high diagnostic accuracy for detecting gallbladder lithiasis and microlithiasis[29], EUS is considered one of the most accurate techniques in diagnosing chronic pancreatitis[30]. The presence of at least 5 endosonographic criteria of chronic pancreatitis offers a sensitivity of 60% and a specificity of 83% to diagnose chronic pancreatitis with a high positive predictive value, an excellent correlation with ERCP for moderate and severe chronic pancreatitis ($\kappa = 0.82$) and a good interobserver correlation ($\kappa = 0.45$)[31,32]. On the other hand, the presence of less than 3 endosonographic criteria has a high negative predictive value for chronic pancreatitis (85%)[31].

EUS has also proved its value to diagnose biliary and pancreatic tumours with a diagnostic accuracy higher than CT especially in those tumours smaller than 2.5 cm in diameter[33,34] with a negative predictive value close to 100%[35]. Furthermore, in these cases EUS allows a correct staging with a resectability accuracy of 67%[36] and the ability to obtain a cytological diagnosis with a sensitivity of around 89%, a specificity of 99% and a diagnostic accuracy of 96%[37].

EUS can also diagnose the presence of pancreatic cysts which might be responsible for the acute pancreatitis bout, especially those cysts communicated with the pancreatic duct such as Intraductal Papillary Mucinous Neoplasm (IPMN)[38]. This entity can cause recurrent pancreatitis, probably by means of intermittent pancreatic duct obstruction related to mucus plugs. EUS is fairly reliable in differentiating IPMN from chronic

pancreatitis[39]. Mucinous and serous cystic neoplasms rarely communicate with the pancreatic duct and therefore rarely cause pancreatitis. Thus, EUS can help to distinguish between serous and mucinous cystic neoplasms by the morphological aspects, although no endosonographic features have proved to be consistently reliable for distinguishing benign from malignant lesions[40]. Furthermore, EUS offers the possibility of performing FNA and analysing the cyst fluid with determination of tumor antigens, fluid viscosity, mucin staining, amylase concentration, analysis of genetic mutations associated with tumours and cytology. These determinations may improve diagnostic accuracy[41]. However, EUS findings by themselves are not accurate enough to definitively diagnose the nature of the pancreatic cystic lesion and cyst fluid cytological or laboratory analysis may not provide a reliable and definitive diagnosis which is sometimes impossible until surgical excision is done[42].

Besides the diagnostic accuracy, the possibility of performing sphincterotomy on EUS[43] has recently been described. This therapeutic role of EUS should be confirmed in the next few years.

MRCP is a non invasive exploration which has also proved its value in diagnosing entities responsible for an acute pancreatitis bout such as chronic pancreatitis, sphincter of Oddi dysfunction, anatomic anomalies and choledocolithiasis[44,45]. Studies testing the role of MRCP in the setting of IAP are scarce but it can be useful, especially when MRCP is combined with secretin test showing a positive predictive value for the diagnosis of sphincter of Oddi dysfunction of 100%, but with a disappointing negative predictive value of 64%[44]. However, to my knowledge, MRCP and EUS have never been prospectively compared in this setting.

The main support for performing EUS in patients with IAP is its high diagnostic accuracy especially in diagnosing the presence of microlithiasis[34] which is the most frequent finding. In these cases, performing a cholecystectomy reduces the recurrence of pancreatitis from 66%-75% in untreated patients to 10% in patients who undergo cholecystectomy[2,13,17]. EUS is a relatively invasive technique with a minimum but present risk of complications and it might be more uncomfortable for the patient. On the other hand, MRCP has not yet proved its value in patients with IAP although it can diagnose the majority of causes for pancreatitis except for microlithiasis.

Taking this background into account, in my opinion but not shared by other authors[46], it is out of discussion that the first diagnostic exploration for patients with IAP and gallbladder in situ is EUS. Debate must be open in patients already cholecystectomized, in whom chronic pancreatitis, sphincter of Oddi dysfunction and pancreas divisum are the most frequent etiological findings and MRCP has demonstrated good accuracy to diagnose these entities[45]. However, EUS has proved to be superior in detecting choledocholithiasis smaller than 5 mm[47,48]. Therefore, when choledocholithiasis is strongly suspected, a negative MRCP should be followed by EUS. So the decision to perform EUS or MRCP as the first choice diagnostic procedure in cholecystectomized pa tients must be made by taking into account other factors. These factors include local expertise and personal records of patients such as claustrophobia, gastric surgery etc. ERCP should remain as a therapeutic exploration when necessary[46].

Unfortunately, to my knowledge, there are still no prospective reports comparing the diagnostic accuracy of EUS with MRCP on patients with IAP. We are currently performing a prospective double blinded study comparing the diagnostic yield of EUS and MRCP in order to clarify their role in the diagnostic work up of patients with IAP.

DO WE HAVE TO STUDY EVERY PATIENT WITH IAP OR ONLY THOSE WITH A RECURRENT DISEASE?

There is some controversy in the literature about this subject. Some authors have questioned the efficacy of EUS in cases of relapsing pancreatitis[49]. This topic has been evaluated in previously published papers comparing the diagnostic yield of EUS in IAP patients with a single episode or a recurrent disease, proving that the diagnostic yield of EUS does not significantly change between both groups[23-25]. So, it seems that the diagnostic yield of EUS is similar both in patients with a single episode of pancreatitis and in patients with recurrent disease and is therefore useful in both situations. This opinion is shared by other authors[50,51].

WHAT IS THE BEST MOMENT TO PERFORM EUS?

The best moment to perform the EUS exploration in patients with IAP is another confusing and difficult question to answer and there are as many possibilities as published reports. Norton *et al*[20] perform EUS when patients resume food intake; Liu *et al*[22] perform EUS when the acute pancreatitis bout has resolved normally during admission; Tandon *et al*[23] when symptoms of acute pancreatitis have subsided, normally 2 or 3 wk after the acute phase; and Yusoff *et al*[25] perform the exploration at least 4 wk after the acute episode in order to assure that acute pancreatic parenchymal changes have resolved when EUS is performed.

In our endoscopy unit we agree with the latter author and perform EUS at least four weeks after hospital discharge in order to assure a complete resolution of the acute parenchymal alterations which would lead to misdiagnosis. Another reason to do so is to differentiate gallbladder microlithiasis related to acute pancreatitis fasting which would be a consequence of the disease from previously present microlithiasis which would be the cause of the disease. To perform EUS at least four weeks after

hospital discharge has two major disadvantages: firstly, an existing prepapillar choledocholithiasis might not be diagnosed with the potential of a re-bout. Secondly, since there is a potential risk of losing the patient for follow up after clinical improvement, a small pancreatic tumor might be missed.

In conclusion, EUS offers a high diagnostic yield in patients with IAP and should be considered the first diagnostic procedure to perform in these patients, even in those with a single episode. MRCP can also be valuable in this setting, but its role should be defined in prospective comparative studies, especially in cholecystectomized patients.

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TOPIC HIGHLIGHT

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Is the 'driving test' a robust quality indicator of colonoscopy performance?

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Abstract

Colorectal cancer is a major cause of death in the western world and is currently the second commonest cause of death from malignant disease in the UK. Recently a "driving test" for colonoscopists wishing to take part in the National Health Service Bowel Cancer Screening Program has been introduced, with the aim of improving quality in colonoscopy. We describe the accreditation process and have reviewed the published evidence for its use. We compared this method of assessment to what occurs in other developed countries. To the authors' knowledge no other countries have similar methods of assessment of practicing colonoscopists, and instead use critical evaluation of key quality criteria. The UK appears to have one of the most rigorous accreditation processes, although this still has flaws. The published evidence suggests that the written part of the accreditation is not a good discriminating test and it needs to be improved or abandoned. Further work is needed on the best methods of assessing polypectomy skills. Rigorous systems need to be in place for the colonoscopist who fails the assessment.

INTRODUCTION

Colorectal cancer is a major cause of death in the western world and is currently the second commonest cause of death from malignant disease in the UK. High quality video colonoscopy is a central tenet in the investigation of symptomatic patients with bowel disorders, and is part of the UK National Health Service Bowel Cancer Screening Programme (NHS BCSP).

Colonoscopy is not a perfect test. Several studies have highlighted important limitations in its accuracy. Ineffective bowel preparation, inability to consistently intubate the caecum and rapid withdrawal times are all important contributors to missed lesions at colonoscopy[1-3]. Moreover, a systematic review of tandem colonoscopy has shown a miss rate of 22%[4] for polyps < 10 mm. Recent large computed tomography colonography studies have confirmed a significant miss rate[5-7]. In these studies, segmental unblinding was used to ascertain the miss rate for optical colonoscopy. It was revealed that 2%-12% of polyps > 10 mm were missed.

Assuming that the colonoscopies in a trial setting would all have been performed by experienced colonoscopists, the miss rate in clinical practice, where experience varies, might actually be higher. Perhaps the most important driver for change in the UK was a large prospective study of colonoscopy demonstrating poor practice. Prior to commencement of the NHS BCSP in June 2006 this study showed an adjusted caecal intubation rate of only 56.9%[8], well below the recommended target of 90%.

Undoubtedly there are inherent limitations to colonoscopy and sensitivity will never reach 100%. It is also unclear what proportion of missed lesions is due to correctable aspects of colonoscopy technique and performance. With these factors in mind, as well as the risks inherent in the procedure, it was decided that bowel cancer screening with colonoscopy would only begin in centres with high achievement on the Global Rating Scale, and by colonoscopists who had had a formalised assessment of their skills. The Joint Advisory Group on Gastrointestinal Endoscopy (JAG), a national body tasked with a role in the quality assurance of endoscopy training and services across the UK, has subsequently instigated a rigorous accreditation process for colonoscopists whose practices include colonoscopy as part of the NHS BSCP.

We sought to examine the accreditation process, the evidence for its use, and the wider implications for endoscopists and endoscopic practice.

ACCREDITATION PROCESS

The NHS BCSP has set out in detail the criteria required for accreditation in screening colonoscopy in their document 'Accreditation of screening colonoscopists: BCSP Implementation Guide No.3 (Version 8: 12th February 2009)'[9]. The process is summarised in Figure 1 and outlined below.

In order to be assessed for accreditation in screening colonoscopy, individuals must first fulfil the following criteria: (1) Be attached to a screening centre approved for the BCSP. (2) Minimum lifetime colonoscopy experience > 1000 procedures. (3) > 150 procedures in year preceding assessment. (4) Unadjusted completion rate on an intention to treat basis of > 90% over preceding year. (5) Documentation of preceding year audit data including number, median sedation levels (under 70 years/over 70 years), completion rate, details of failures, polyp detection rate (expected to be > 20%) and complications. and (6) Audit should have been verified by Endoscopy Unit Sister and consultant colleague/clinical director/medical director.

If the above criteria are met, on submission of an application to the NHS BCSP, individuals will be invited to attend one of several accredited assessment centres, where they will be assessed.

The first part of the assessment process is a written test comprising a one-hour multiple-choice questionnaire (MCQ) consisting of 30 questions. This is based on a list of topics for study and suggested sources for reading

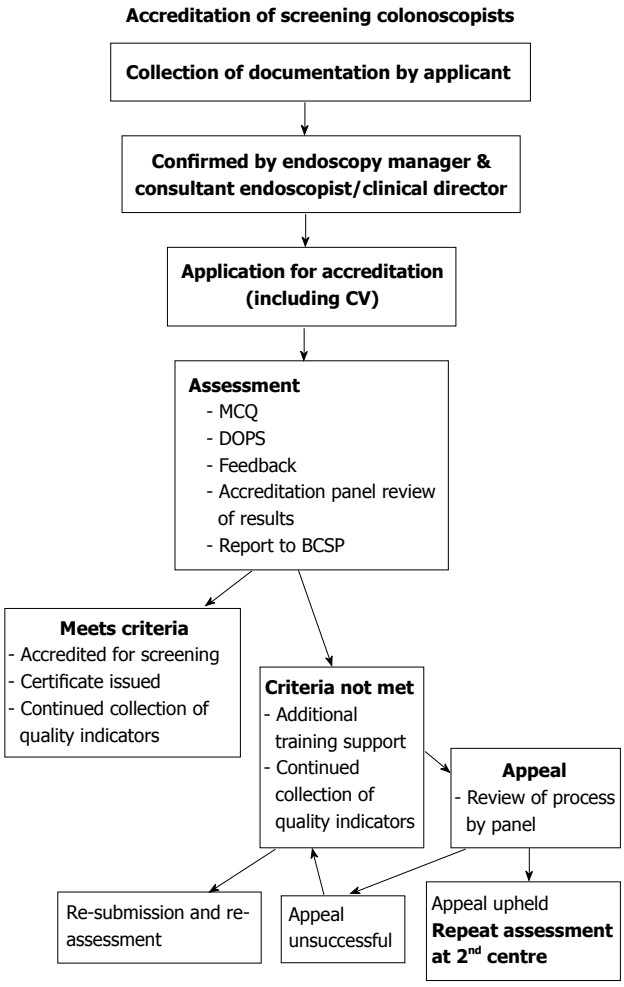

Figure 1 Pathway for accreditation of screening colonoscopists.

given in the pre-assessment documentation. The MCQ paper is positively marked, and candidates are encouraged to answer all questions. The main part of the accreditation process consists of direct observation of practical colonoscopy on two consecutive cases, where skills are scored against standardised criteria by two assessors. This is know as a directly observed procedural skill (DOPS) assessment, and is used widely in the UK to assess practical skills of trainee doctors. This DOPS assessment of endoscopy is also normal practice for trainee registrars in gastroenterology who are required to complete many such procedures during their time in training, before being deemed competent to practice independently. However, those undergoing the accreditation process for bowel cancer screening will generally have already been deemed competent to practise independently.

Candidates are assessed on consent, pre-procedure preparation, sedation practice, and colonoscopic technique, including therapeutic ability and the discussion of results and management with the patient. Assessors allocate a grade score for each criterion assessed and use these grades to inform their final decision as to whether or not a candidate has met the criteria required for accreditation. Interestingly, the assessors are advised that some aspects of a domain may be irrelevant to cases in

an assessment, but should still be marked. For example, a patient may have no polyps and therefore require no therapy. Assessors are advised that a grade 3 or 4 (pass grades) can still be awarded in these domains. In this way, a colonoscopist undergoing assessment could be deemed 'highly skilled' at polypectomy without ever having been observed removing a polyp. We know that approximately 30% of patients undergoing screening will have adenomas requiring removal for histopathological analysis[10,11]. As it is impossible to select patients with polyps for the accreditation colonoscopy, this represents a significant weakness in the process.

Following the assessment, candidates are given written and verbal feedback on their performance. Written feedback covers areas of good practice as well as areas for further training or development. Results and feedback take place in private and do not last longer than 10 min.

There are two possible outcomes of the assessment process: (1) The candidate meets the criteria for formal accreditation. and (2) The candidate does not yet meet the criteria/needs further development.

After initial accreditation, candidates must submit to further accreditation procedures on an annual basis, after which accreditation is renewed, provided that candidates can meet the following criteria: (1) An intention to undertake > 150 screening colonoscopies per annum. (2) Agree to the submission of quality monitoring data on an annual basis, while continuing to meet the application criteria. and (3) Maintenance of an acceptable level of complications over a prolonged period, specifically, below the national average as defined in recent published series[8].

IS THIS ACCREDITATION PROCESS A VALID AND RELIABLE METHOD OF ASSESSING COLONOSCOPISTS?

Prior to the institution of this formalised assessment for screening colonoscopists, there was considerable anxiety amongst the endoscopic community. Concerns were raised about the assessment process itself, and the appropriateness of such a test. There were also concerns about validity and reliability.

Barton attempted to allay some of these concerns with two studies published in abstract form in 2008[12,13]. The first study examined the performance and outcomes of candidates in the assessment and their perceptions of the process[12]. 76 assessments undertaken by 67 candidates were reviewed. These initial colonoscopists were experienced practitioners with a mean number of colonoscopies of 2490 (range 500-7500) and a mean polyp detection rate of 29% (range 18%-53%). It is interesting that the procedural experience of some of these candidates fell outside the current guidelines laid out in the NHS BCSP accreditation document (minimum lifetime number procedures > 1000, polyp detection rate > 20%). The mean score in the MCQ paper was 80% (range 59%-98%). No pass mark was given, although it appears that no candidates failed their accreditation as a result of their MCQ paper score. From this we can infer that the pass mark was > 59%.

8 assessments had to be repeated - 3 for breach of protocol with the DOPS assessment and 5 as a true re-sit assessment. Of 73 secure assessments, 54 (74%) candidates met the criteria required for accreditation, giving an overall failure rate of 26%. The perceptions of the process by candidates highlighted particular flaws with the MCQ paper, notably a degree of ambiguity in some questions, poor clarity of some images, and concerns about the content and relevance of some questions. The comments regarding the DOPS assessment were of particular interest. Some commented that the process was hugely stressful, and that a degree of luck was involved in the allocation of cases. Others commented that some of the difficulties lay with assessment taking place in an unfamiliar unit. Despite these comments, candidates felt welcomed, and that the assessment was fair. Only 5 appeals against the results were referred back to the Accreditation Panel,with one upheld as a breach of protocol.

The validity and reliability of the MCQ and DOPS assessment have also been assessed[13]. In this study self reported, verified performance and demographic data, as well as assessment data from both the MCQ and DOPS over two cases assessed by two assessors, were collected prospectively from 76 candidates as well as 17 assessors. Semi-structured questionnaires were completed by both the candidates and the assessors. In 2284 paired judgements of 76 candidates, during 151 cases, there was 96% congruence across the pass/fail divide, 98% for major domains. The expert global opinion agreed with the grading system in 74/76 (97%) of cases. Gradings correlated weakly with self-reported caecal intubation rates and MCQ scores (r = 0.24 and 0.27, P < 0.01). Overall, 27/30 candidates felt the DOPS assessment was fair/very fair, while 27/32 felt the MCQ was fair/very fair. Of the assessors, 12/16 felt the DOPS was valid/very valid, while 17/17 felt the overall process was fair/very fair.

These data suggest that the DOPS assessment is reliable and valid. The MCQ test appears to be a poor discriminator, as there have been no failures. In addition, no data for evaluating the validity of the test for important outcomes such as polyp detection rate, miss rates, patient comfort and complications exist.

WHAT HAPPENS TO THE COLONOSCOPIST WHO FAILS THE TEST?

Significant questions remain as to what happens the candidate who fails the test and how this should impinge on their daily practice.

However, the accreditation process sets out clear guidelines to cope with this eventuality. In the first instance, if a candidate feels the process was flawed, they have a right to appeal, although candidates cannot dispute the

Table 1 The differing eligibility criteria in the two categories of accreditation available in the UK

Criteria	JAG accreditation	NHS BCSP accreditation
Lifetime number	> 200	> 1000
Lifetime Perforations	< 0.5%	Not documented
Number last 12 mo	> 100	> 150
Sedation		
Under 70 years	Midaz < 5 mg/ Pethidine < 50 mg	Midaz < 5 mg/Pethidine < 50 mg
70 years +	Midaz < 2.5 mg/ Pethidine < 25 mg	Midaz < 2.5 mg/Pethidine < 25 mg
Caecal intubation	> 90%	> 90%
Polyp detection & Removal	> 10%	> 20%
Data certified	Endoscopic supervisor	Endoscopy sister & consultant colleague/clinical director/ medical director

JAG: Joint Advisory Group on Gastrointestinal Endoscopy; NHS BCSP: National Health Service Bowel Cancer Screening Programme.

judgement of the assessors or the Accreditation Panel. If the appeal against the process is successful, then the candidate would have to undergo a repeat assessment at a second centre (Figure 1).

If a candidate does not meet the criteria for accreditation at their first sitting, they are eligible for one more attempt within a 12 mo period with two different assessors. If they do not meet the criteria at the second attempt, then they cannot re-apply until 12 mo have passed from the date of their first assessment.

If there are serious concerns about the competency of an individual colonoscopist, procedures are in place which allow assessors and the Accreditation Panel to take appropriate action, including informing the medical director of the trust where the candidate is employed, if necessary.

One can infer from the guidelines that it is entirely conceivable for candidates to fail the accreditation process repeatedly and continue their routine NHS service colonoscopy practice outwith the NHS BCSP. However, if a failed candidate continued his/her NHS practice, but was unfortunate enough to encounter a complication, followed by a legal challenge, would his/her practice be defensible?

WILL THIS TEST LEAD TO A TWO-TIER ENDOSCOPY SERVICE?

With the NHS BCSP accreditation process in place, there are currently 2 forms of colonoscopy accreditation for practicing endoscopists in England - the aforementioned BSCP accreditation and that of the standard JAG. Whilst these two forms of accreditation are similar, there are subtle differences between them, with the BCSP accreditation having slightly more stringent criteria (Table 1).

The NHS BCSP criteria place greater emphasis on experience, with large volumes of endoscopy practice required, which precludes newly qualified trainees from becoming screening colonoscopists. Of the key quality criteria caecal intubation rate is the same (> 90%) in both processes whilst polyp detection and removal is higher in the NHS BCSP accreditation (> 20% *vs* > 10%). Despite the NHS BCSP accreditation process having been developed to minimise the risk of complications, the current eligibility criteria do not require candidates to include their lifetime perforation rate.

Unlike the NHS BCSP accreditation, there is no formal written assessment for JAG accreditation in colonoscopy. However, new Specialty Trainee registrars have to complete a knowledge- based written assessment [Specialty Certificate Examination (SCE)] in order to qualify for their Certificate of Completion of Training prior to obtaining a substantive post. Whilst this is not directed at colonoscopy per se we suspect that many of the topics covered in the 30 question MCQ for NHS BCSP will also be covered in the SCE. As outlined above, the evidence published has shown that the MCQ is a poor discriminator and no candidates have failed accreditation on this part.

The formative DOPS assessments in the two groups are virtually identical, the only difference being that NHS BCSP candidates must achieve < 4 grade 2 s across the minor domains (with JAG accreditation candidates being allowed < 6).

In England, the current accreditation will undoubtedly lead to a to a 'two-tier' colonoscopy service. Over time, 3 distinct groups of colonoscopists will be in practice - those who have JAG accreditation but who do not, because of need or eligibility, have NHS BCSP accreditation; those who have NHS BCSP accreditation; and lastly those who have attempted NHS BCSP accreditation and failed. Clearly the latter gives the greatest cause for concern, as some of these practitioners may have failed on grounds that would also have caused them to fail to achieve JAG accreditation. As discussed previously, missed cancers are sometimes unavoidable, but the question is whether it is morally, ethically or legally justifiable for individuals who have failed a formalised accreditation process, to continue to be permitted to practice on symptomatic patients?

WHAT DO OTHER COUNTRIES DO?

Within the UK there is considerable disparity in accreditation practice for screening colonoscopists. England, Scotland, Northern Ireland and Wales all have different criteria for accreditation that vary in the methods of assessment, number of procedures carried out, and key quality criteria. In England the accreditation process is as previously described.

Scotland

In Scotland the Bowel Cancer Screening Programme has not followed the route of accreditation of screening colonoscopists. There are however, some criteria set for screening colonoscopists: (1) There should be a caecal intubation rate of at least 90% (the endoscopist

should be able to clearly demonstrate that they had reached the caecum, an indication that they were able to examine the entire colon); (2) A minimum of 150 colonoscopies a year should be being performed; and (3) A JAG- accredited colonoscopy course should have been attended.

Wales

In Wales the process is different again. They have developed a 3-phase assessment process that JAG has approved for operation.

Phase 1 - Pre-assessment: Attendance at a preparatory course covering therapeutic techniques, mock DOPS assessments, and review of performance data.

Phase 2 - Progress review visit: A member of the assessment faculty visits the potential screening colonoscopists in order to check their progress in achieving their training goals.

Phase 3 - Assessment visit: The formal summative assessment process involves at least two members drawn from the Welsh Assessment Team and in many cases an external assessor from England is also included. The assessors aim to perform all necessary assessments on the day of the assessment visit to the potential screener's Trust. The candidates must complete an MCQ (JAG approved) as in the English programme.

Northern Ireland

Perhaps the Northern Ireland proposals (Northern Ireland Cancer Network Draft Document) most closely mirror English accreditation process. Figure 2 below summarizes the route by means of which potential screening colonoscopists must progress prior to approval in Northern Ireland.

United States

In the USA, training in gastrointestinal endoscopy is outlined in the Gastroenterology Core Curriculum[14]. This curriculum suggests a minimum number of colonoscopy procedures of 140 including a minimum of 30 snare polypectomy and haemostasis before competency can be assessed. The curriculum also suggests objective performance criteria for the evaluation of colonoscopy, namely intubation of the splenic flexure, intubation of the terminal ileum (desirable skill) and retroflexion. Similar to that of the UK, the core curriculum in the US also has a formalised diagnostic colonoscopy procedural competency form. This competency form highlights the key quality criteria (caecal intubation, ileal intubation, retroflexion in the rectum and polypectomy ability), although, unlike JAG, it does not set minimum standards for competence.

Hospitals or institutions where endoscopy takes place grant accreditation in the US. The American Society of Gastrointestinal Endoscopy[15] has issued guidelines for this process. Determination of competence based on these guidelines is as follows: (1) The applicant should have completed a residency program that incorporates structured experience in gastrointestinal endoscopy. Competence should be documented by the instructor(s); (2) The applicant should be able to demonstrate proficiency in endoscopic procedure(s) and clinical judgement equivalent to that obtained in a residency program; and (3) The applicant's endoscopic director should confirm in writing the training, experience (including the number of cases for each procedure for which privileges are requested) and actual observed level of competency. Such experience includes indications, complications and their management, and alternative approaches. The training director's opinion and recommendation should be considered prima facie evidence for the trainee's acceptance as an individual qualified in gastrointestinal endoscopy.

Canada

In Canada responsibility for accreditation for colonoscopy is the responsibility of the endoscopists local institution or facility. However, The Canadian Association of Gastroenterology has suggested specific recommendations as a guide for institutions[16]. These Canadian guidelines list key quality criteria similar to those issued by other national societies: (1) Technical competence can be assessed after 150 procedures, however, completion of a specified number of colonoscopies does not imply competence; (2) Competence should be based on the completion of > 100 unassisted procedures; (3) Caecal intubation should have taken place in at least 85%-90% of all cases and in > 95% of screening cases in healthy adults; (4) Mean completion time of approximately 30 min with an emphasis on methodical, careful withdrawal; (5) Withdrawal times generally in excess of 7 min; (6) Photodocumentation of caecal intubation is encouraged for quality assurance purposes; (7) When colonoscopy is performed for cancer screening, adenomata should be detected in > 25% of men and > 15% of women > 50 years of age; (8) As a threshold for competency, > 30 supervised unassisted snare polypectomies should have been completed; (9) Perforation rate of 0.2% for all patients and < 0.1% for patients undergoing screening; and (10) Post-polypectomy bleeding rate of < 1%.

As part of an Endoscopy Quality Initiative the Canadian Gastroenterology Association are currently implementing the UK Global Rating Scale in an effort to improve and maintain high standards of endoscopy service.

Australia

In Australia, training is assessed by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy. This is a national body comprising representatives from the Gastroenterological Society of Australia, the Royal Australasian College of Physicians (RACP), and the Royal Australasian College of Surgeons (RACS).

Training is assessed by the Conjoint Committee, usually in the context of the Specialist Advanced Training

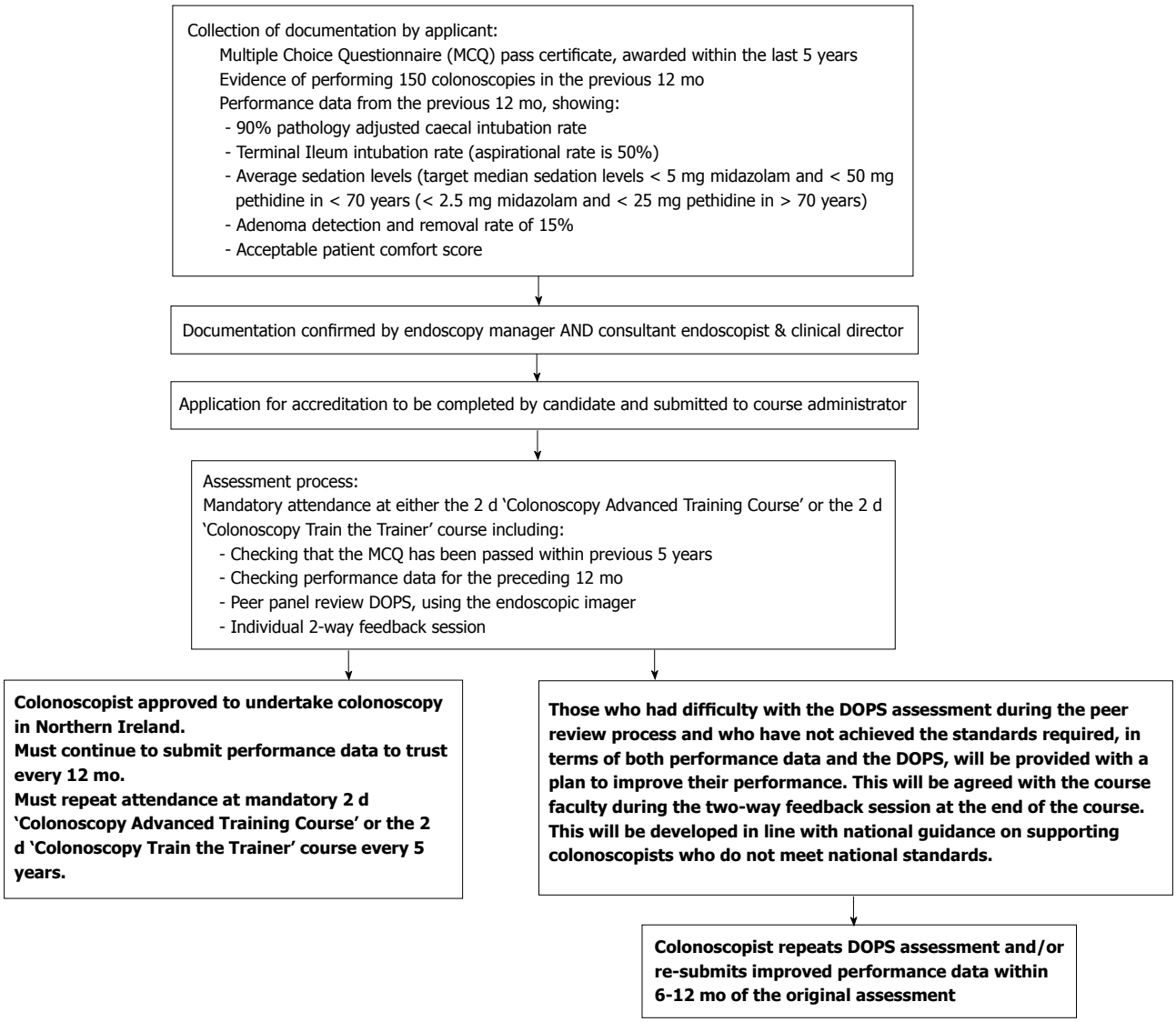

Figure 2 Summary of approval process in Northern Ireland (Northern Ireland Cancer Network Draft Document).

Program of either the RACP or RACS. Full recognition is therefore dependent on appropriate training, experience and supervision pursuant to those Training Programs. Assessment for certification of training in colonoscopy primarily involves assessment of the caecal intubation rate in intact colons at the completion of training. The reference criteria are as follows[17]. Candidates must: (1) Perform a minimum of 100 unassisted, supervised, complete colonoscopies to the caecum, and preferably to the ileum in patients with intact colons (i.e. with no prior colonic resection); (2) Perform successful snare polypectomies on a minimum of 30 patients; and (3) Achieve at least a 90% caecal intubation rate by the completion of training.

We are unaware of further assessment or accreditation of colonoscopic performance in Australia at this time.

New Zealand

New Zealand has a similar accreditation process, although they allow a caecal intubation rate of only 85%[18]. At present neither Australia nor New Zealand have population screening programs in place for screening for colorectal cancer.

The authors are unaware of any formalised accreditation process similar to that in England that occurs under the auspices of JAG and NHS BCSP in other countries. Although the accreditation process in other countries does not incorporate a 'driving test' or DOPS, we are not aware of any evidence that the quality of colonoscopy performed in these countries is substandard.

IS THE INTRODUCTION OF SUCH A TEST LIKELY TO LEAD TO SIMILAR ACCREDITATION PROCESSES BEING USED IN OTHER AREAS OF MEDICAL OR SURGICAL PRACTICE?

In general, higher medical training in the UK has be-

come more structured and formalised with the introduction of Modernising Medical Careers. Trainees now have to submit written evidence of competencies, including practical procedural competencies, using Directly Observed Procedural Skills (DOPS) forms. Many specialties (cardiology, respiratory, gastroenterology) have guidelines for the minimum number of executions of any one procedure before an individual trainee can undergo a competency assessment. Competency assessments are written and recorded in the trainee's logbook and therefore represent a quality assurance initiative. Higher surgical training in the UK follows similar procedures. Trainee surgeons have to undergo workplace-based assessments and record details of all procedures carried out, including the degree of independence involved, complications, etc. This logbook, along with the workplace- based assessments, form the basis for the annual review of competence of each trainee, and assess the trainee's suitability to progress to the next stage of, or complete, the training program.

In the UK the JAG offers the quality framework and standards by which endoscopic practice is measured. JAG offers accreditation in the following endoscopic procedures: (1) Diagnostic upper GI endoscopy; (2) Therapeutic upper GI endoscopy; (3) Flexible sigmoidoscopy; (4) Colonoscopy; and (5) Endoscopic retrograde pancreatography.

JAG suggests that practicing endoscopists might use the frameworks provided to demonstrate competence and for their own endoscopic professional development. This will not only benefit patients by improving practice, but will also protect endoscopists in the event that a known complication of endoscopy occurs.

Although there is no legal requirement to complete JAG accreditation in endoscopic procedures at present, this may change as Department of Health and GMC initiatives for revalidation and recertification begin. Recertification is a new idea that was set out in the Government's 2007 White Paper - 'Trust, Assurance and Safety - the Regulation of Health Professionals'[19]. The recertification component of this White Paper is aimed at doctors who are on the GMC's specialist register or GP register. In future, these doctors will need to demonstrate, through recertification, that they continue to meet the particular standard(s) that apply to their specialty or area of practice. It is entirely conceivable that, for practicing gastrointestinal endoscopists, this could mean JAG accreditation/re-accreditation. We can only speculate as to what the future holds across other medical or surgical disciplines. For example, will competent, practicing surgeons have to have their surgical skills assessed by their peers as in the UK colonoscopy 'driving test' in order to be able to continue their practice?

WHAT ARE THE ALTERNATIVES?

The main alternative to a formalised external accreditation process would be for colonoscopists to submit an annual record of procedures carried out, with key quality measures (caecal intubation rate, ileal intubation rate, withdrawal time, polyp detection and removal rates) and complication rates noted. These data could be scrutinised by a fellow gastroenterologist working in the same trust, co-signed and presented to a national body for accreditation. The addition of a 'driving test' may not add to the validity of this process.

CONCLUSION

Large randomised controlled trials have shown that screening for colorectal cancer using faecal occult blood testing and subsequent colonoscopy for those with positive tests reduces mortality[20-22]. Where the screening program differs from other screening programs in the UK (e.g. breast cancer, cervical cancer), is the invasive nature of the diagnostic test (colonoscopy), and the moderate risk of serious and potentially fatal complications in an asymptomatic population. For these reasons it seems right and proper that those carrying out screening colonoscopy are skilled practitioners with the highest completion rates and the lowest complication rates. How best to ensure this remains a contentious issue.

At present the UK appears to have one of the most rigorous accreditation processes, although even this still has some major flaws. The evidence published to date suggests that the written part of the accreditation is not a good discriminating test, and it needs to be improved or abandoned. The fact that candidates are able to pass their accreditation without having completed a colonoscopy or removed a polyp during the assessment is also not ideal, although how one would rectify this is not clear. One possibility would be to increase the number of procedures required for accreditation. This would provide the dual benefits of a longer observation time, and also increase the chance of the need for polypectomy. The drawbacks would be the time and expense of the longer assessment. Given that peer assessment is only required once, this may be an option worth pursuing.

The other major flaw in the process as it stands is the separation between JAG accreditation and NHS BCSP accreditation. It would seem more logical to have a single accreditation process through which all colonoscopists should pass. This would include senior registrars coming to the end of their training as well as existing consultants, who would benefit from the accreditation process both for the screening program and for the GMC recertification process when it comes online in the future. Marrying the two accreditation processes does not seem an unreasonable proposition, as the actual DOPS assessments are nearly identical. As outlined above, the main differences are in the entry criteria, specifically the lifetime number of procedures and the polyp detection/removal rate. We know that colonoscopic skills improve over time, but we also know

that experience does not necessarily equate to expertise. Perhaps the total number of colonoscopies required to undergo either accreditation should be in the region of 400-500, in order to allow adequate exposure to the relevant procedures for developing the technical skills required, but also to ensure that newly appointed skilled colonoscopists would be in a position to undergo NHS BCSP accreditation if required. This would also help NHS trusts with future workforce planning issues. Polyp detection and removal rate is a more rigorous quality measure. Perhaps standard JAG accreditation should reflect this, and introduce the higher figure of 20% in order to match the BCSP accreditation.

In addition, there should be a more rigorous system in place for the individual who fails the assessment. An accreditation process needs to be rigorous - if no one fails the test, this would suggest that the test is too easy. Candidates who fail should have the opportunity to retake the test at the earliest possible opportunity, and there should be systems in place to allow rapid and high quality retraining if necessary.

Furthermore, the process itself should be continuously measured and evaluated in order to ensure it is equitable and fair. Such audit procedures will also help to identify any deficiencies in the training of gastroenterology registrars or even regional variations in practice.

In conclusion, the 'driving test' has become an accepted process for establishing that a trainee has achieved the required competency to practice independently as a colonoscopist. However, it is not clear if, for a previously trained colonoscopist, the 'driving test' in addition to performance data, is necessary for the selection of screening colonoscopists or as a tool for revalidation.

To go back to the analogy of a driving test, once a driver passes, does he/she need to be retested after many years of driving? Is there evidence that doing such a thing will reduce accidents? Or is the presence of an unblemished driving record proof enough that he/she is a safe driver?

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GUIDELINES FOR CLINICAL PRACTICE

Role of digital chromoendoscopy in detecting minimal change esophageal reflux disease

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Abstract

Endoscopy is a widely used diagnostic tool to detect reflux esophagitis. Although its specificity was reported to be excellent at 90%-95%, its sensitivity was only 50%. Therefore, it is quite difficult to detect these lesions under the standard white light endoscopy especially in patients with minimal change esophageal reflux disease (MERD). In recent years, endoscopic technologies have evolved tremendously; these include high resolution and magnification digital chromoendoscopy. These technologies are useful practically for detecting various subtle lesions along the gastrointestinal tract starting from esophagus to colon. Currently, these technologies can be classified in 2 systems; pre-processed system (NBI, Olympus) and post processed system (FICE and i-SCAN, Fujinon and Pentax respectively). Over a few years, there have been many emerging publications on the benefit of these systems on MERD detection. The overall sensitivities to diagnose MERD were reported as much better than controls. However, large, multi-center and randomized controlled studies comparing these new imaging modalities with the conventional white light chromoendoscopy are warranted to validate its accuracy. Standard, simple and precise endoscopic reading criteria for the identification of MERD are also required.

Key words: Digital; Chromoendoscopy; Minimal change; Erosive reflux esophagitis; Diagnosis; Pre-processed; Post processed

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a major acid related health problem which is increasing in prevalence all over the world[1]. During the last two decades, when GERD was defined by symptoms of at least weekly heartburn and/or acid regurgitation, its prevalence was approximately 20% in Western countries whereas its prevalence was less than 5% in Eastern countries[2]. However, its trend in Asia has recently increased to almost 10%[3].

Endoscopy is a widely used diagnostic tool for reflux esophagitis detection. Although its specificity was reported to be excellent at 90%-95%[4], its sensitivity was only 50%[5]. More than half of patients with GERD symptoms have been diagnosed as non-erosive reflux disease (NERD) and this is more common in Asian (59%-87%) than in Western patients (54%)[6-8].

Indeed, by careful analysis, the majority of NERD patients did not have completely normal endoscopic finding but were found to have subtle distal esophageal mucosal changes from acid refluxate such as reddish or whitish colors, edema of mucosal folds, blurring with friability of mucosal junction, increased vascularity and microerosion[9-10]. Unfortunately, it is quite difficult to detect these lesions under the standard white light endoscopy, particularly by inexperienced endoscopists (kappa value for interobserver agreement by inexperienced endoscopist for minimal change was reported to be low and ranged between 0.19 and 0.36)[10]. Over a few years, endoscopic technologies have evolved tremendously including high resolution and magnification digital chromoendoscopy. These technologies are practically useful for detecting various subtle lesions along the gastrointestinal (GI) tract starting from esophagus to colon. Other than the detection of subtle change reflux esophagitis, these have proven to be beneficial for Barrett's epithelium detection[11], targeted biopsy of the suspicious area in gastric intestinal metaplasia[12] and detecting early gastric and colon cancers[13-14]. This review will address the concept and provide a practical use of these novelties for the detection of subtle changes in GERD. In particular, all minimal change reflux disease will be called "minimal change esophageal reflux disease (MERD)".

USE OF CHROMOENDOSCOPY IN DIAGNOSING GERD AND MERD

The idea of using dye for tissue staining in gastrointestinal endoscopy is mainly to enhance the contrast of different GI mucosa. Currently, there are 2 groups of dye that are categorized by the effect on tissue staining. First is the vital stained dye that is absorbed into mucosal cells and the color of the absorbed mucosa will change depending on the type of dyes and absorptive cells. Examples of these vital stains are Lugol's solution, methylene blue and Congo red Lugol's solution is the most widely used dye for diagnosing reflux esophagitis. This agent is rapidly absorbed by normal squamous epithelial cells containing glycogen and it subsequently yields a dark-brown color. The unstained area is delineated as abnormal mucosa since the inflamed mucosa contains no glycogen. Another use of Lugol's solution is to detect neoplastic squamous mucosa including high grade dysplasia and early squamous cell carcinoma of the esophagus. Another agent, methylene blue, is not absorbed into metaplastic or dysplastic epithelial cells and helps the delineation of the area of esophageal metaplasia from normal mucosa. It is mostly used for Barrett's epithelium detection. With its pH dependent character, Congo red is another dye that is occasionally used for detection of abnormal lesions in the stomach. It turns dark when the pH of the mucosa drops to acidic level and this in turn is helpful to identify the undark area of atrophic gastritis which is prone to develop gastric cancer.

The other dye is non-vital dye which can not be absorbed into the cells but can emphasize the contrast enhancement between different structures by filling in the grooves and folds of the gastrointestinal mucosa. The prototypes for this dye are indigocarmine and crystal violet that are practically used for the detection of flat and depressed lesions of the GI tract. In addition, this dye can be helpful for highlighting the mucosal irregularities in Barrett's esophagus.

Chromoendoscopy was introduced to facilitate mucosal characterization and localization of abnormal area of the esophageal mucosa in the 1970's[15]. In 1989, Misumi *et al*[16] demonstrated the benefit of Lugol chromoendoscopy as a potential useful diagnostic tool in suspected GERD. Twenty one patients whose reflux esophagitis was diagnosed by conventional endoscopy were examined under Lugol's stain and biopsies were taken from the stained and unstained mucosa for pathological comparison. The positive findings from Lugol' s unstained images were more concordant with positive histological findings. In addition, the extension and degree of reflux changes were also better defined with Lugol's (89.9% *vs* 69.7%, $P < 0.001$).

In 2005, Yoshikawa *et al*[17] reported the usefulness of endoscopy with Lugol's iodine solution for the diagnosis of NERD. Sixty-one patients with typical reflux symptoms and 42 controls underwent a standard white light upper endoscopy. Twenty-two of 61 (36%) reflux patients and 4 of 42 controls had visible esophageal injuries by standard endoscopy. Thirty-nine patients with endoscopy-negative but positive reflux symptoms (NERD) and 38 endoscopy negative asymptomatic controls later underwent Lugol chromoendoscopy. Unstained streaks in the distal esophagus were observed in 19 of 39 (49%) patients with NERD whereas only one out of 38 controls (2.6%) was positive. The biopsy specimens were obtained from the Lugol unstained areas and the adjacent stained mucosa for histopathological comparison which served as the gold standard. When compared to the stained mucosa, the unstained areas significantly contained more typical pathologic changes related to reflux esophagitis, namely thicker basal cell layers (30.9 ± 7.6% *vs* 12.3 ± 4.5% of total epithelial thickness, $P < 0.001$), longer papillae (57.9 ± 12.6% *vs* 38.1 ± 12.6% of total epithelial thickness, $P < 0.01$), and higher numbers of intraepithelial lymphocytes (9.6 ± 5.7 *vs* 6.0 ± 4.0 per 3 high-power fields, $P < 0.01$). Although this method was helpful in diagnosing microerosions in NERD patients and claimed to be safe and easy, it was time consuming and needed additional spraying equipment. In addition, the adverse reactions of Lugol's solutions which include esophageal mucosal irritation causing retrosternal chest pain or discomfort[18], acute necrotizing esophagitis[19] and allergic reactions (laryngospasm, bronchospasm and cardiac arrest)[20] need to be considered.

USE OF HIGH-RESOLUTION AND MAGNIFICATION ENDOSCOPY IN DIAGNOSING MERD

The recent advances in optical engineering that include charge couple device (CCD) and zoom lens, provide high resolution and magnifying (up to 150-fold) images. This technology can enhance the visualization of mucosal details. Kiesslich *et al*[21] compared the endoscopic results by magnifying endoscopy (EG3470ZK, Pentax, Hamburg, Germany and 160Z, Olympus, Hamburg, Germany) in NERD patients with the results in asymptomatic controls. The positive endoscopic criteria included increased vascular markings at proximal and distal to Z-line, punctate erythema at proximal to Z-line, squamous islands at distal to Z-line and villous-appearing mucosa adjacent to distal Z-line. They reported that the punctate erythema was the only criterion found more often in NERD patients than controls (44% *vs* 10%, $P = 0.009$). When all criteria were combined, the sensitivity and specificity of magnifying endoscopy were 64% and 85% respectively. The positive predictive value (PPV) was 80%, the negative predictive value (NPV) was 70% and the accuracy was 74% for the diagnosis of MERD.

COMBINATION OF CHROMOENDOSCOPY AND HIGH-RESOLUTION MAGNIFYING ENDOSCOPY

The diagnostic criteria for MERD using the combination of Lugol chromoendoscopy with high-resolution magnifying system was proposed by Tam *et al*[22]. Ten patients with reflux symptoms were examined by conventional upper endoscopy followed by high resolution magnifying endoscopy (Fujinon 850K CCD, Omiya, Japan). Lugol's dye was sprayed during the procedure. The examinations were performed before and after a 4 wk course of oral omeprazole. In patients with unremarkable examination by conventional endoscopy, they found that certain subtle changes at the distal esophagus including pin-point capillaries, loss of longitudinal vessels and branching blood vessels were very useful to increase the yield for MERD diagnoses. Another study was performed by Edebo *et al*[23]. Eleven NERD patients diagnosed by questionnaire or conventional endoscopy and 10 controls were examined by high resolution magnifying chromoendoscopy (optical magnification of x35 and digital magnification of x2, EG485-ZH, Fujinon Co., Omiya Japan) and 24 h pH monitoring was also used as another mode for reflux diagnosis. Six of 8 control subjects had negative results on pH test whereas 8 of 11 symptomatic patients had positive results on the pH test. The patients were reexamined with magnifying endoscopy after 4 wk of PPI treatment. Still images were assessed by experienced endoscopists. Seven endoscopic criteria for diagnosis of MERD were proposed as follows: triangular indentations of villiform columnar mucosa into the squamous mucosa, apical mucosal breaks at the vertex of a triangular indentation, obscured pallisade blood vessels above the squamocolumnar junction (SCJ), pin-point blood vessels above the SCJ, branching blood vessels below the SCJ, serrated SCJ and villiform mucosa below the SCJ. When only symptomatic criteria were used as a gold standard for reflux diagnosis, triangular lesions, apical mucosal breaks and the presence of pin-point blood vessels above the SCJ were found more frequently in MERD patients than controls (86% *vs* 63%, 57% *vs* 38% and 55% *vs* 38% respectively). Moreover, the prevalence of triangular lesions, apical mucosal breaks and the presence of pin-point blood vessels above the SCJ decreased in MERD patients after PPI treatment (43%, 10% and 22%, respectively). When the pH monitoring test was used as the gold standard for reflux diagnosis, these 3 findings presented significantly more frequently in patients than in controls (92% *vs* 45%, 60% *vs* 20% and 67% *vs* 25% respectively, $P < 0.05$). Likewise, in the symptomatic criteria cases, the frequencies of these positive criteria were significantly decreased after PPI treatment to 45%, 10% and 21% respectively in the reflux group. Unfortunately, the interobserver agreement was quite low for each criterion (kappa value, 0.18-0.28). Therefore, these criteria are still too premature to be used as standard criteria to diagnose MERD. Easier MERD diagnostic criteria are necessary for practicing endoscopists for a short learning curve and better interobserver agreement value.

Concept of digital chromoendoscopy

Generally, white light can be visibly shaded into 7 colors. Different colors carry different wavelengths. The depth of light penetration into gastrointestinal mucosa depends conversely on the wavelength. For instance, violet has the shortest wavelength at 400 nm. Therefore, violet is not able to penetrate the mucosa as deep as red which has a longer wavelength at 700 nm. Blue, green and yellow are colors that have wavelengths in between violet and red. Thus, the depths of penetration of these colors are ranged from 0.15 mm to 0.30 mm[24].

Hemoglobin is the main substance that is responsible for visible light absorption with the peak absorption in the blue part (415 nm). Mucosal structures containing hemoglobin such as blood vessels can absorb 415 nm light and produce a dark brown color that is different to the brighter surrounding mucosa that reflects the blue light. Hypervascularized tissues including malignant or inflammatory masses absorb this blue light and can be identified in a dark brown area.

Currently, digital chromoendoscopy can be categorized into 2 systems; the system that filters only the blue wave length to spot on the object can be called the pre processed whereas the post processed system is the system that reprocesses only certain wave lengths from

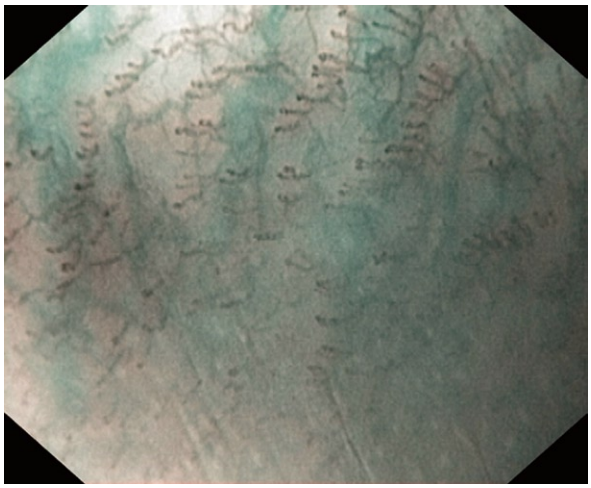

Figure 1 Images from magnifying non-sequential NBI show increased number and dilated and tortuous of intrapapillary capillary loops.

the objective picture after white light illumination. The representative of the pre processed is a narrow band imaging (NBI) that has been introduced by Olympus Company. Currently, Olympus provides 2 systems for the market; non-sequential system (Excera Ⅱ 180 series) and sequential system (Lucera Ⅱ 280 series). Excera system uses a color charge coupling device (CCD) and uses an additional filter that selects only blue band (415 nm). This system is widely available outside Japan. Another system, Lucera system, contains 2 filters; one is an RGB filter for black and white CCD and the other is an NBI filter. This system is mainly available in Japan, South Korea, the UK and some tertiary academic research centers. By contrast, the post processed system relies on the computer system that enhances the image contrast by reprocessing the captured images. By selecting only the preferred spectrum of wavelength, the computer can generate a new picture that can highlight the area of inflammation and cancer. There are 2 models currently available; Intelligent Color Enhancement [Fujinon (FICE)] and I-scan (Pentax). FICE generates a very large number of wavelength permutations with increments of 5 nm. There are 10 stations that the factory assigned for an instant use. These stations are adjustable according to users' preference. The advantage of the post processed system is that all preferred wavelengths are adjustable. Since there has been no standard guideline that advocates the use of these different colors another question to be answered is what wavelength is more preferred for the detection of different gastrointestinal tract lesions and locations.

i-SCAN is a new computerized dynamic digital image processor which provides high resolution enhanced images. There are currently 4 modes available; standard (HD+) mode, contrast enhancement (CE) mode, surface enhancement (SE) mode and tone enhancement (TE) mode. Each mode provides different images features and can be used alone or combined with the others. CE mode highlights the mucosal surface and pit pattern and SE mode enhances the mucosal surface, pit pattern, vascularity and tissue topography. Both CE and SE mode provide pictures in natural color tone whereas TE mode provides images like those obtained from chromoendoscopy. Other than the use for diagnosis of MERD, preliminary data also reported its utility for detection of early gastric cancer lesions[25].

Utility of NBI for detection of MERD

NBI is an innovative technique that uses the optical narrow band filters of blue light for object illumination. As mentioned above, the depth of penetration depends conversely on the wavelength; hence the blue light which is the short wavelength (450 nm) can attain only the superficial layers. This in turn can provide the images of the superficial structure of the mucosa including the capillaries and details of the mucosal patterns. In conjunction with the magnification system, it enables highlighting the patterns of "intrapapillary capillary loops (IPCLs)" which contains abnormal figures indicating the inflammatory process and neoplasia[26-27] (Figure 1). This is considered a great advantage over the simple chromoendoscopy that can not clearly detail the vascular patterns because they are concealed by the stain agents.

The utility of NBI magnification system as the diagnostic tool of GERD has been increasingly explored[28-30]. The landmark study on NERD was recently conducted in 50 symptomatic GERD patients and 30 controls by Sharma *et al*[29]. The still images of 4 quadrants of the distal 5 cm of esophagus were captured by both conventional endoscopy and sequential NBI with magnification (Olympus GIF Q240 Z, 115x, Olympus Evis Lucera system). Patients with mucosal breaks identified by standard upper endoscopy were classified as erosive esophagitis based on the Los Angeles classification. Patients with no visible mucosal break on standard upper endoscopy were classified as NERD. Positive endoscopic criteria to diagnose reflux esophagitis were proposed as follows: microerosions, increased vascularity at SCJ, ridge or villous pattern below SCJ, columnar islands in the distal esophagus and increased/tortuous/dilated IPCLs. They showed that the increased number of IPCLs was a predictor of the presence of erosive esophagitis (OR 17.8; 95% CI: 4.7-67.8). The increased number (OR 4.7; 95% CI: 1.1-21.2) and dilated IPCLs (OR 6.2; 95% CI: 1.5-25.3) were shown to be the best parameters for the diagnosis of MERD. The average numbers of 117 IPCLs per field yielded 90% sensitivity and 70% specificity to determine minor change of reflux disease (MERD) and the average count of 123 IPCLs per field provided a sensitivity of 86% and a specificity of 76% for the diagnosis of significant erosive esophagitis (GERD). Additionally, good interobserver and moderate intraobserver agreements among the investigators

were noted with kappa value ranged from 0.48-0.88 and 0.39-0.52 respectively. Although this technique is very promising, there are significant limitations for practical use. Firstly, it was impractical to use some of these endoscopic criteria since they are too ideal. For instance, dilated and/or tortuous IPCLs are very subjective whereas the objective criteria, particularly the number of IPCLs, are quite difficult to accurately count. In addition, the non- magnified standard scope cannot be used because the zoom mode is mandatory to allow optimal inspection of IPCLs and the scope tip needs to be focused closer to the mucosa than the white light system. Therefore, a transparent plastic cap attachment is a requisite to maintain the precise distance between scope tip and the mucosa. As a result, it requires tremendous familiarity and a long learning curve to adjust the scope use. Secondly, the examination time required during the procedure was not mentioned. This method is anticipated to be time-consuming and quite complicated because only a small area can be magnified and examined in each scope touch. Therefore, adequate duration of examination is required for a complete study of the whole esophageal circumference and for a complete manual count of the IPCLs amount in each field. Thirdly, the original article used only two investigators for the assessment of the images and the differences in the values of intraobserver agreement rates were not clearly explained. Therefore, the validation of interobserver agreements and simpler criteria are mandatory before applying this method for the routine clinical practice. Lastly, the sequential NBI system that was used in this study is available only in some countries and research centers. We need to clarify that the results can be reproducible with the commercial non-sequential system.

Very recently, the role of NBI in the diagnosis of MERD has been re-evaluated by Fock *et al*[30]. They compared the conventional endoscopy and non-sequential NBI (Olympus CLV-160B, Olympus Evis Exera Ⅱ system) under normal and digital magnification of 1.5 x in symptomatic GERD patients and asymptomatic controls. Erosive esophagitis was diagnosed by using the Los Angeles Classification whereas NERD was defined by the presence of reflux symptoms without mucosal breaks on standard white light endoscopy and the response to PPI treatment. Mucosal morphology at SCJ from conventional endoscopy and NBI were compared among 41 erosive reflux disease (ERD), 36 NERD and 30 control patients. The endoscopic criteria comprised of the presence of micro-erosions (mucosal breaks only visible on NBI but not on standard white light endoscopy), increased vascularity at the SCJ (vascular spots or punctuate erythema above the SCJ), increased erythema just below the SCJ and the presence of columnar epithelium island above the SCJ. When comparing this with the study using magnifying scope with the Olympus sequential system, the punctuate erythema by Olympus non-sequential system corresponded with the IPCLs described by Sharma *et al*[29]. The results showed that the presence of micro-erosions and the increase in vascularity at SCJ were significantly more common in NERD patients compared to controls (52.8% *vs* 23.3% and 91.7% *vs* 36.7% respectively). The investigators also reported a significant difference in mucosal pit patterns at the distal esophagus between NERD patients and control. The round pit pattern which represents the gastric epithelial mucosa was found less frequently in NERD patients than in the control group (5.6% *vs* 70%, $P < 0.001$). Interestingly, the prevalence of the increase in vascularity and round pit pattern was similar in patients with ERD and NERD. Therefore, the increase in vascularity with the absence of round pit pattern was helpful to differentiate NERD from controls with a sensitivity of 86.1% and specificity of 83.3% respectively. In addition, interobserver agreement determined among 3 endoscopists who performed the endoscopic procedures appeared to be very good for the presence of micro-erosions (kappa value, 0.89; SE, 0.08), increased vascularity at SCJ (kappa value, 0.95; SE, 0.08) and good for round pit pattern (kappa value, 0.80). The most beneficial part of this study is the practical use that may be duplicated by others[28-29]. The criteria used in this study were much simpler since there was no need for magnification system. However, the limitation was the nature of preliminary study, the reproducibility of the results conducted from multi-centers and good interobserver agreement were required before applying this technique into daily practice.

Usefulness of FICE for detecting MERD

FICE is another evolution in digital chromoendoscopy which has emerged for the evaluation of MERD[31]. This technique combines a high-resolution endoscopy with adjustable wavelength to improve visualization of subtle lesions of GERD. We recently conducted a study in 21 patients with typical symptoms of heartburn and/or acid regurgitation compared with 9 controls. The endoscopy was performed under the conventional white light endoscopy and the FICE system that included 2 stations; station 0 and 4 which representing the RGB wavelength of 540, 415 and 415 nm and of 560, 500 and 475 nm respectively. Patients with esophageal erosions diagnosed by the standard white light endoscopy were excluded from the study. Gold standard for the diagnosis was based on typical symptoms of reflux. The "triangular lesion", defined as a triangular indentation into the squamous mucosa extended from the villiform columnar at the Z-line, was used as the endoscopic diagnostic criterion (Figure 2). The preliminary data showed that FICE provided higher sensitivity, NPV and accuracy than the standard white light endoscopy. Sensitivity, specificity, NPV, PPV and accuracy of each station are shown in Table 1[31]. This technique appears to provide similar results comparable to the NBI system[31]. However, the values of interobserver agreement are still

Table 1 Comparison of the outcomes from various types of standard and digital chromoendoscopy for minimal change reflux disease diagnosis

	Endoscopy with magnification[21]	NBI with magnification[29]	NBI without magnification[30]	FICE without magnification[31]
Sensitivity	64	55	86.6	77.8
Specificity	85	87	83.3	83.3
NPV	70	NA	83.3	55.6
PPV	80	NA	86.1	93.3
Accuracy	74	NA	NA	79.2
Criteria for the diagnosis	Punctuate erythema	Increased IPCLs	Increased vascularity with absence of round pit patterns	Triangular lesions
Interobserver[1] agreement	NA	Fair	Good	Poor
Intraobserver[1] agreement	NA	Fair	NA	NA

NA: Not available; [1]Gold standards for GERD diagnosis were different in each study.

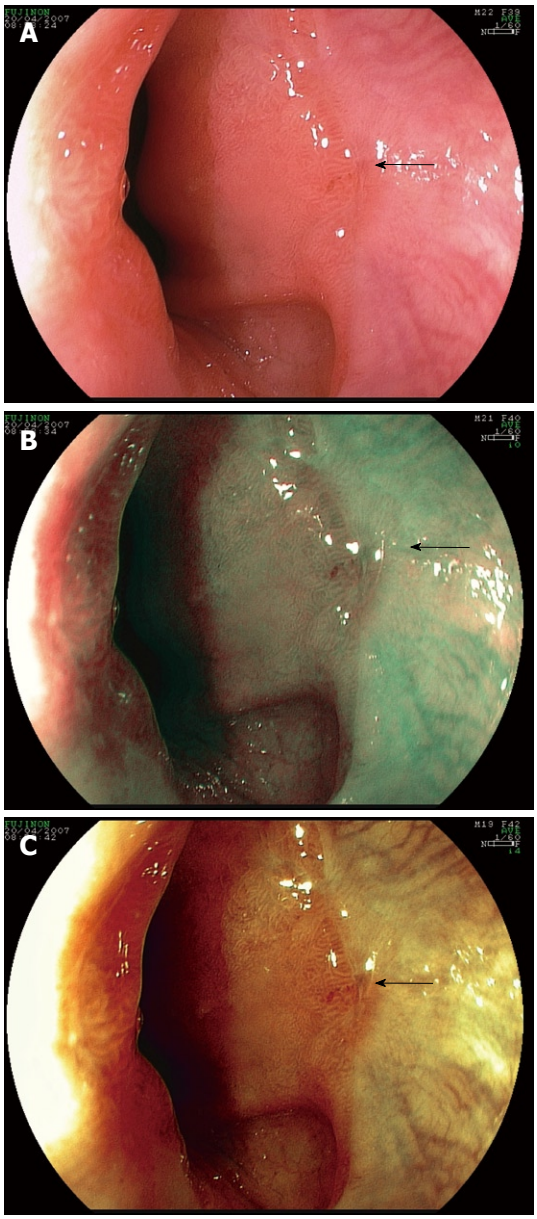

Figure 2 Triangular lesion (arrow). A: Conventional white light endoscopy; B: FICE station 0 (RGB wavelength of 540, 415 and 415 nm); C: FICE station 4 (RGB wavelength of 560, 500 and 475 nm).

suboptimal and need to be improved. It is speculated that the optimal wavelength has not been standardized yet and more learning curves may be also required. Moreover, further validation of the results in a larger population is also necessary.

In addition, the magnification system can be added as a combination to FICE. This may help to enhance the details of vascular pattern of esophageal mucosal of MERD. The increased numbers of tortuous and dilated IPCLs can be visualized by magnifying FICE similar to magnifying NBI (Figure 3). However, the same limitations of using magnifying FICE in practice are similar to magnifying NBI that was mentioned earlier.

At the moment, FICE system may be useful for targeted biopsy in reflux patients with negative study on conventional endoscopy.

Feasibility of i-SCAN for the detection of MERD

High-definition endoscopy with i-SCAN, a post-processing digital filter which enhances the detailed mucosal surface and vasculatures, has been recently evaluated for detection of mucosal breaks in reflux disease[32]. The distal esophagus of 50 patients with reflux symptoms were inspected by a high-definition (HD) endoscopy, with i-SCAN and Lugol's staining method in stepwise manner. The examination with i-SCAN was initially performed under surface enhancement (SE) mode and clearly identified the mucosal changes. Subsequently it was performed under pattern mode (P-mode) and vascular mode (V-mode) which were able to characterize the details of the lesions. Mucosal breaks were detected in 9 of 50 patients with HD endoscopy. The detection rate was slightly increased to 12 of 50 patients with i-SCAN and significantly increased to 25 of 50 patients with Lugol chromoendoscopy (Figure 4). The degree of esophagitis was upgraded in 5 and 14 patients by using i-SCAN and chromoendoscopy respectively whereas one patient with esophagitis LA grade B diagnosed by i-SCAN was downgraded to LA grade A by Lugol chromoendoscopy. In addition, when compared to

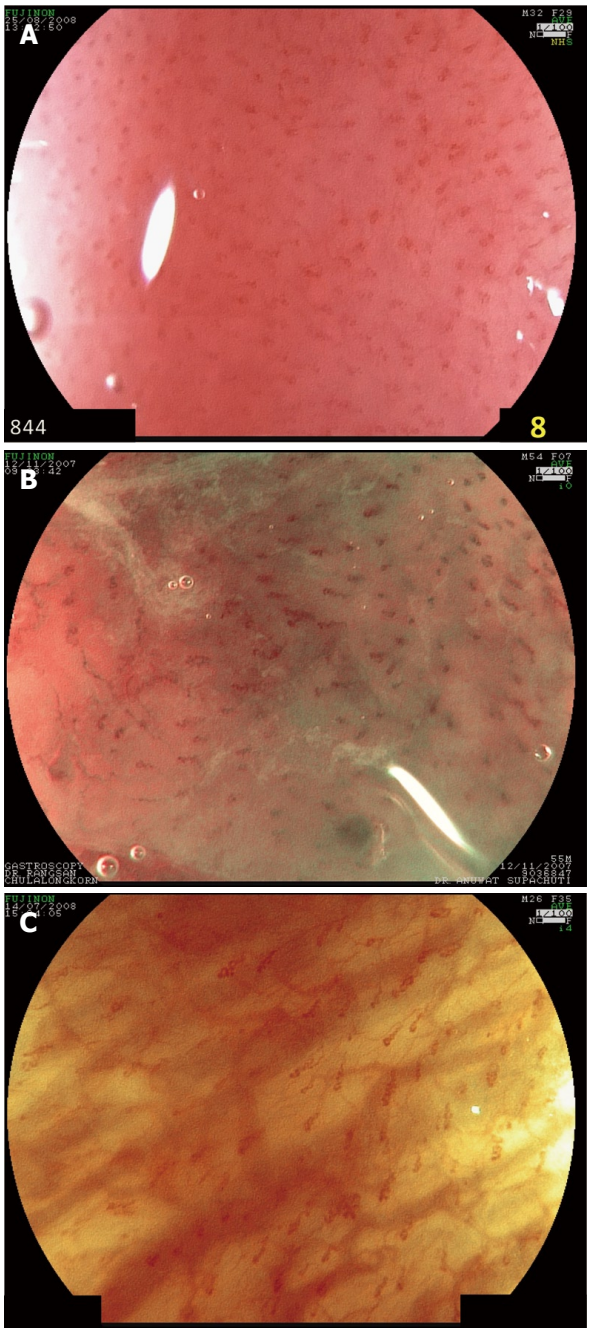

Figure 3 Images from magnifying FICE of × 100 show increased number and dilated and tortuous of intrapapillary capillary loops (IPCL). A: Conventional white light endoscopy; B: FICE station 0 (RGB wavelength of 540, 415 and 415 nm); C: FICE station 4 (RGB wavelength of 560, 500 and 475 nm).

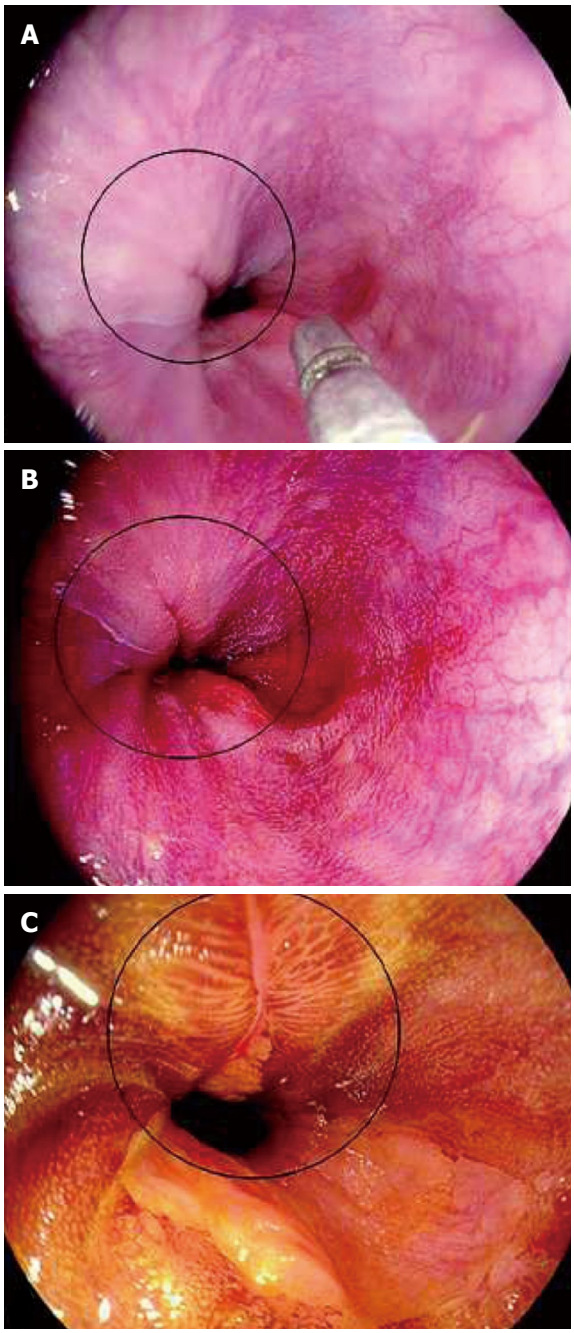

Figure 4 Images from i-SCAN. A: HD+: A mucosal break is not clearly visible; B: i-SCAN can better depict the mucosal break; C: Lugol's stain reveals a larger extent of the mucosal break which can help upgrade the degree of esophagitis according to Los Angeles classification. (with permission from Georg Thieme Verlag KG).

standard HD endoscopy, both enhancing methods demonstrated more significant numbers of small circumscribed lesions (58 lesions diagnosed by i-SCAN, 85 lesions diagnosed by chromoendoscopy *vs* only 21 lesions diagnosed by HD endoscopy). Compared to the previous studies, the criteria used for MERD diagnosis in this study were different from those used in NBI and FICE studies that were mentioned earlier. We can assume that i-SCAN can improve detection rates of minute mucosal breaks in smaller numbers of patients than HD chromoendoscopy. However, more studies using the combination of i-SCAN and magnification system is required to demonstrate the practical benefit.

CONCLUSION

Digital chromoendoscopy is an important tool with a high potential for GERD diagnosis particularly for MERD since it provides the endoscopist with a simple, safe and rapid method for a better detection of the

subtle esophageal lesions. In our speculation, over the next few years it may become a standard tool for GERD and MERD diagnosis. However, large, multi-center and randomized controlled studies comparing these new imaging modalities with the conventional white light chromoendoscopy are warranted to validate its accuracy. Standard, simple and precise endoscopic reading criteria for the identification of minor mucosal changes in reflux disease are required. Lastly, intra- and interobserver agreements have to be improved before utilizing these innovations in clinical practice.

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REVIEW

Advances in endoscopic retrograde cholangiopancreatography cannulation

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Abstract

Endoscopic retrograde cholangiopancreatography is an important tool in the diagnosis and treatment of pancreatobiliary diseases. A critical step in this procedure is deep cannulation of the bile duct as failure of cannulation generally results in an aborted procedure and failed intervention. Expert endoscopists usually achieve a high rate of successful cannulation while those less experienced typically have a much lower rate and a greater incidence of complications. Prolonged attempts at cannulation can result in significant morbidity to patients, anxiety for endoscopists, unnecessary radiation exposure and inefficient patient care. Here we review the most common endoscopic techniques used to achieve selective biliary cannulation. Pharmacologic aids to cannulation are also discussed briefly in this review.

Key words: Endoscopic retrograde cholangiopancreatography; Cannulation techniques; Fatty meal; EUS guided cholangiography; Double-balloon endoscopy

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an important tool in the diagnosis and treatment of pancreatobiliary diseases. It has been used in clinical practice for more than three decades[1]. A critical step in this procedure is cannulation of the common bile duct (CBD) and/or the pancreatic duct as failure of cannulation generally results in an aborted procedure and failed intervention. Cannulation and wire access is required for diagnostic and therapeutic interventions such as sphincterotomy, stone extraction and stent placement. Expert endoscopists usually achieve a high rate of successful cannulation while those less experienced typically have a much lower rate and a greater incidence of complications. With typical anatomy, the pancreatic duct enters the ampulla in a straight fashion, predisposing to pancreatic duct cannulation[2]. The pancreatic duct is more frequently cannulated first by trainees. A periampullary diverticulum, surgically altered anatomy, edema or strictures in the small bowel and blood or excessive fluid in the lumen all increase the procedural difficulty. Prolonged cannulation can result in significant morbidity to patients, anxiety for endoscopists, unnecessary radiation exposure and inefficient patient care[3].

Table 1 ERCP cannulation techniques in patients with normal anatomy

Technical methods
Standard techniques
Catheters
Papillotomes
Guide wires in conjunction with catheters and papillotomes
Placement of pancreatic stent or guide wire to facilitate cannulation
Precut techniques
Precut papillotomy (needle knife papillotomy)
Transpapillary pancreatic sphincterotomy (precut pancreatic sphincterotomy)
Suprapapillary puncture of the common bile duct (needle knife fistuolotomy)
Endoscopic ultrasound-guided cholangiography
Pharmacologic methods
Minor papilla
Intravenous injection of Secretin
Topical Methylene blue
Intraduodenal acid infusion
Major papilla
Intravenous injection of CCK
Topical nitroglycerin
Fatty meal before ERCP

ERCP: Endoscopic retrograde cholangiopancreatography; CCK: Cholecystokinin.

Various methods have been described to facilitate cannulation during ERCP for patients with normal anatomy. These can be divided into technical or pharmacological (Table 1). The cannulation techniques for patients with surgically altered anatomy are reviewed here briefly.

TECHNICAL METHODS TO FACILITATE CANNULATION

Commonly used techniques

The current most commonly used technique of cannulation is the wire-guided cannulation (Figure 1). In this technique, a dual lumen catheter is preloaded with a hydrophilic tipped guide wire and the catheter tip is inserted into the papilla in the direction of the bile duct. The guide wire is then manipulated while attempting to advance it into the bile duct. Fluoroscopy is used to verify its location once it has advanced several centimeters[4]. If the pancreatic duct has been cannulated, the wire is withdrawn. The sphincterotome is repositioned and the wire is advanced again under fluoroscopic guidance. If the guide wire cannulation fails, contrast can be injected to define the anatomy[4]. Another approach to selective biliary cannulation is to use a catheter with contrast injection without a guide wire. A cannula or papillotome is inserted into the papilla and contrast is injected into the bile duct to outline the biliary anatomy. If the common bile duct is injected, the sphincterotome is advanced deeper into the common bile duct. Alternatively, the catheter can be advanced into the bile ducts and fluoroscopy used to assess its direction.

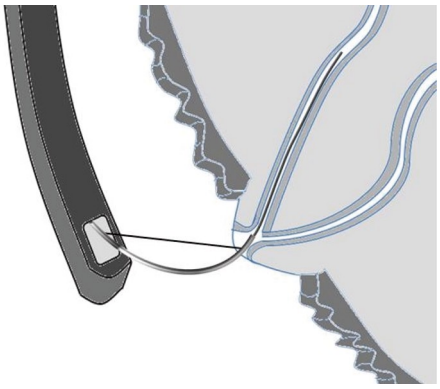

Figure 1 Papillotome and guide wire cannulation.

Contrast can then be injected to confirm that the CBD is cannulated. Cannulation using the cannula with contrast injection has a reported success rate of 60%-70%[5-6] while using a papillotome for contrast injection increases cannulation success rate up to 97%[5-7]. Repeated contrast injections into the pancreatic duct should be avoided because of increased risk of acute pancreatitis[8,9]. The guide wire technique for bile duct cannulation may lower the likelihood of post-ERCP pancreatitis (PEP) compared to the contrast injection methods by avoiding unintentional pancreatic duct injection and reducing the need for precut sphincterotomy[4,10,11]. However, a conflicting study found no difference in the incidence of PEP and suggested that successful cannulation with fewer attempts at the papilla is a more important factor than whether guide wire or contrast is routinely used first to achieve biliary cannulation[12]. It was also reported that using a hydrophilic guide wire achieves a higher rate of selective CBD cannulation compared to a standard ERCP catheter but the complication rates including PEP were similar in both groups[13]. A meta-analysis of the above randomized controlled trials[4,10-13] showed that the wire-guided technique increases the primary cannulation rate and reduces the risk of PEP compared with the standard contrast-injection method[14]. However this meta-analysis excluded the studies by Bailey *et al*[12] and Katsinelos *et al*[13] in calculating PEP outcomes because of their crossover design. This finding was confirmed by another meta-analysis study[15]. A third meta-analysis included the study by Bailey and used PEP outcomes before crossover[16]. This meta-analysis showed only a non-significant reduction in the rate of PEP with the use of wire guided cannulation. In summary, we recommend the use of the wire guided cannulation technique because of its proven superior cannulation rate and potential decrease in PEP rate.

The size of the ERCP cannulas varies but it is typically 5F to 7F with a tapered tip that accepts a 0.035-inch guide wire[17]. Some endoscopists may use ultra tapered (5F-4F-3F) tip catheters for cannulation of the biliary and pancreatic ducts which require smaller caliber guide wires (down to 0.018 inch). A smaller 3F cannula can be passed through the channel of a standard cannula or papillotome

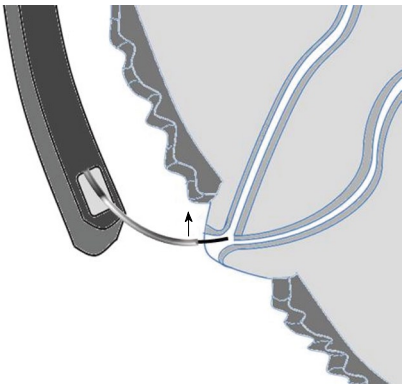

Figure 2 Needle knife precut papillotomy.

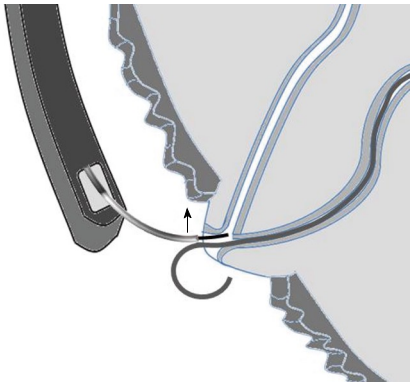

Figure 3 Precut papillotomy using needle knife over pancreatic stent.

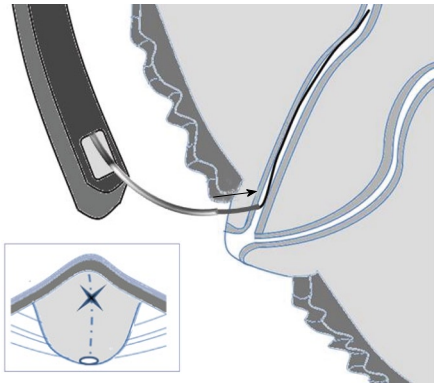

Figure 4 Suprapapillary puncture of the common bile duct (fistulotomy) followed by insertion of guide wire. Inset shows location of the puncture[31] (see text).

to convert to a smaller diameter[17]. In a randomized trial of 107 patients undergoing CBD cannulation, the 4F and 5F sphincterotomes were not significantly different in terms of success rates, number of attempts, time to cannulation or complications[18].

Precut techniques

Precut papillotomy using a needle knife[19] or a "precut" papillotome[20] is a method used to facilitate cannulation when the aforementioned standard methods fail (Figure 2). An electrocautery needle knife can be used to create an incision through the anterior wall of the major papilla. This technique is referred to as needle knife sphincterotomy, needle knife papillotomy or needle knife fistulotomy depending on the extent and location of the incision on the papilla[9,21-23]. The correct technique is important for success and for prevention of complications. Repeated longitudinal strokes with the needle knife should be shallow enough to prevent perforation and dynamic so that the needle does not adhere to the tissue[9]. The incision should be directed along the longitudinal course of the intraduodenal portion of the papilla. The length of the incision on the mucosal surface is usually 5-8 mm[9]. The needle knife assisted technique was shown to markedly improve the success rate of selective biliary cannulation without increasing the rate of complications[9,24]. However, the technique carries a risk of bleeding, perforation of the duodenal wall and acute pancreatitis if the procedure is performed by less experienced hands[25]. Placing a pancreatic stent prior to precut sphincterotomy may aid in defining the anatomy and protecting the pancreatic sphincter from injury (see below, Figure 3). It has been debated whether the complications related to precut papillotomy are due to the precut itself or to the prior prolonged attempts at cannulation. A recent meta-analysis of six randomized controlled trials (total 966 subjects) compared early precut implementation with persistent attempts by the standard cannulation approach[26]. Overall cannulation rates were 90% in both groups. PEP developed in 2.5% of patients randomized to the early precut groups and in 5.3% of patients from the persistent cannulation attempts groups. The overall complication rates including pancreatitis, bleeding, cholangitis and perforation rates were 5.0% in the early precut groups and 6.3% in the persistent cannulation attempts groups. The authors concluded that in experienced hands the early implementation of precut and persistent cannulation attempts have similar overall cannulation rates and early precut implementation reduces PEP risk but not the overall complication rate[26]. In another analysis, the number of attempts at cannulating the papilla was independently associated with PEP and the risk increased with increasing number of attempts[27,28]. Needle knife sphincterotomy was not an independent predictor of PEP[28]. It should be emphasized that precut sphincterotomy, which is generally followed by conventional sphincterotomy, should be performed only by experienced endoscopists as complication rates are high when performed by inexperienced endoscopists performing one sphincterotomy per week or less[29].

Suprapapillary puncture of the CBD (also referred to as needle knife fistulotomy) was described for diagnostic ERCP as early as 1978[30] and recently reported in more detail for therapeutic procedures[31] (Figure 4). This technique uses a specially designed polyethylene catheter (Artifon Catheter) with an 18-gauge needle and a flexible metallic sheath at the distal end which allows puncture of the bile duct and insertion of a guide wire. Suprapapillary puncture of the bile duct is performed by

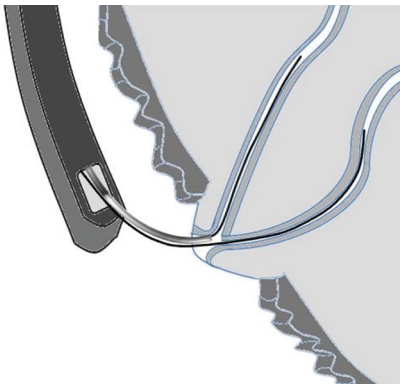

Figure 5 Pancreatic guide wire to aid cannulation.

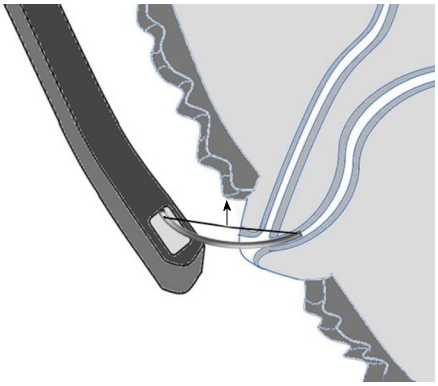

Figure 6 Transpapillary pancreatic sphincterotomy.

using the Artifon Catheter in the direction of the CBD at a point corresponding to the proximal third of the line between the transversal fold and the papillary ostium. This is followed by insertion of a guide wire and slow injection of contrast to obtain a cholangiogram. In the first pilot study, suprapapillary puncture was successful in 25 out of 28 patients. None of the patients developed post-ERCP pancreatitis. However, there was a higher complication rate, including 2 perforations, 2 minor bleeds and 1 submucosal injection[31]. A subsequent study reported the efficacy and safety of needle knife fistulotomy in a retrospective analysis of 352 patients after unsuccessful standard guide wire cannulation[32]. The successful cannulation rate in these patients was 90%. The complication rate was significantly higher for the patients who underwent fistulotomy than for those who did not (4.8% *vs* 2.1%) which was mainly related to higher rate of mild bleeding in the fistulotomy group. There was no significant difference in pancreatitis or perforation rates. This technique appears promising and there is growing evidence for it but more studies are needed before it can be recommended for difficult cannulations.

Pancreatic techniques

Use of pancreatic techniques is a new and useful method to improve biliary cannulation. Pancreatic guide wire placement (P-GW) has been shown to be effective in increasing the rate of selective biliary cannulation[33-36]. It involves inserting a guide wire into the pancreatic duct from a cannula after pancreatic duct cholangiography (Figure 5). This stabilizes the ampulla of Vater and straightens the terminal common bile duct. After withdrawal of the cannula, the guide wire is left in the pancreatic duct and is monitored by fluoroscopy[35]. The cannula is then reinserted next to the guide wire and cannulation of the bile duct is attempted[37]. This method can be followed by placement of a small caliber (3F or 4F) pancreatic stent for prophylaxis of post-ERCP pancreatitis. In one study of 113 patients, selective bile duct cannulation with P-GW was achieved in 73% of patients who were difficult to cannulate. Post-ERCP pancreatitis occurred in 12% of patients. The rate of pancreatitis was lower in patients who underwent prophylactic pancreatic stenting (4.7%) compared to those who did not (22%)[36]. In a later study of 107 patients undergoing ERCP, selective biliary cannulation was difficult in 53 patients (unsuccessful after 10 min) and these patients were randomly assigned to either preinsertion of a guide wire into the pancreatic duct or persistent attempts with a conventional catheter[35]. In the pancreatic duct guide wire group (n = 27), the success rate was significantly higher than in the conventional group (93% *vs* 58%). Pancreatic duct stenting was not used in this study but there were no cases of post ERCP pancreatitis in either group. The pancreatic duct guide wire group had more hyperamylasemia compared to the conventional group but no patients had abdominal pain[35]. A more recent randomized controlled trial compared the pancreatic duct guide wire technique and standard cannulation technique in 188 patients with difficult CBD cannulation[38]. No significant differences were observed in success rates, cannulation times or number of attempts. A higher rate of post-ERCP pancreatitis was seen in the pancreatic duct guide wire group although this was not statistically significant[38]. We recommend the use of the pancreatic guide wire technique in difficult cannulation cases as it is the most efficient and safe method in our experience.

Transpapillary pancreatic sphincterotomy, also called transpancreatic sphincterotomy or pancreatic precut sphincterotomy (PPS), is also used to achieve selective biliary cannulation (Figure 6). This is performed by deep cannulation of the main pancreatic duct and orienting the sphincterotome in the direction of the bile duct at 11 o'clock and performing the pancreatic sphincterotomy with the aim of exposing the bile duct orifice or the bile duct itself[39]. In a prospective study evaluating the use of PPS in patients who failed standard cannulation (n = 116), immediate biliary access was achieved after PPS in 99 cases (85%). Pancreatic stents (7F) were placed in 29 patients (25%) at the discretion of the endoscopist if pancreatic drainage was considered inadequate. Complications occurred in 14 patients (12%): 3 (2.6%) postsphincterotomy bleeding, 9 (8%) pancreatitis (8 mild, 1 moderate) and 2 (1.7%) retroperitoneal perforations managed conservatively[39]. A retrospective analysis comparing PPS with needle knife sphincterotomy showed

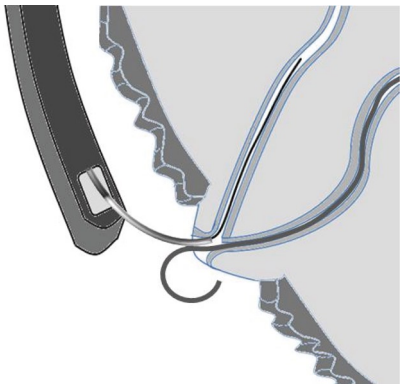

Figure 7 Pancreatic stent and guide wire cannulation.

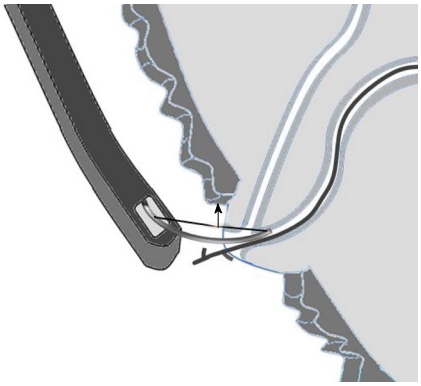

Figure 8 Transpancreatic sphincterotomy over pancreatic stent.

no significant difference in the success rates between the two techniques (90.0% *vs* 90.8% respectively)[40]. The overall complication rate and acute pancreatitis were also similar in both groups.

Another technique involves placing a pancreatic stent to facilitate biliary cannulation as this stent can deflect a guide wire or a catheter into the bile duct (Figure 7). If this fails, the pancreatic stent can serve as a guide and aid in performing a precut sphincterotomy as described above to gain access to the biliary duct. This sphincterotomy can be performed by either a needle-knife to make an incision from the pancreatic duct stent toward the biliary orifice (Figure 3) or a standard sphincterotome is inserted into the pancreatic duct above the pancreatic stent and a transpancreatic sphincterotomy is performed toward the biliary orifice (Figure 8)[40]. In a retrospective study of ERCPs with difficult cannulation, successful biliary access was achieved in 38 out of 39 patients (97.4%) where pancreatic duct stenting was used to aid cannulation: thirty-five patients had successful biliary cannulation at the initial attempt (89.7%) with an additional three patients having successful cannulation on the second attempt at a later time. In order to achieve cannulation, 23 patients (59%) required a precut sphincterotomy over the pancreatic duct stent. In 16 patients (41%), no precut sphincterotomy was required to gain access to the bile duct[41]. Post ERCP pancreatitis occurred in two patients (5%). Pancreatic duct stent placement was also shown to facilitate difficult biliary cannulation caused by periampullary diverticula where ampullary anatomy is distorted and can be straightened by the pancreatic stent[42].

ENDOSCOPIC ULTRASONAGRAPHY GUIDED CHOLANGIOGRAPHY

In recent years, interventional endoscopic ultrasound-guided cholangiography (IEUC) has been reported as an alternative to surgery or percutaneous transhepatic cholangiography (PTC) if ERCP is unsuccessful[43-46]. The technique involves puncturing the bile ducts under real time ultrasound control from the intestinal lumen. This is followed by inserting a wire through the needle and placing a stent through the wall of the stomach/duodenum. Using another "rendezvous" technique, the guide wire is manipulated through the stricture and the papilla and then captured with a standard duodenoscope and a biliary drainage is performed through the papilla in a regular fashion[45]. A recent study describing a single centre experience with IEUC was published: 49 patients underwent IEUC after failed ERCP. 35 had biliary obstruction due to malignancy and 14 had a benign etiology. The overall success rate of IEUC was 84 % with an overall complication rate of 16 %[44]. IEUC has possible advantages over PTC in patient comfort, lower morbidity and offers a possible alternative to patients with obstructive jaundice in whom ERCP has failed. However these advantages have not yet been proven in randomized trials.

PHARMACOLOGIC METHODS TO FACILITATE CANNULATION

In addition to the technical methods to increase the rate of successful cannulation, pharmacologic interventions have been used to facilitate cannulation at ERCP. The strongest data is for secretin in minor papilla cannulation. Secretin is a gastrointestinal polypeptide that is secreted from mucosal cells in the proximal intestine in response to luminal acidification. Circulating secretin acts via specific G-protein-coupled receptors to stimulate the secretion of water and bicarbonate from pancreatic duct cells[47]. Identification of the minor papilla may be facilitated by increasing the production of pancreatic secretions. This is particularly important in pancreas divisum where identification of the minor papilla, cannulation and contrast injection can be used to confirm dominant dorsal pancreatic duct drainage. In a randomized controlled trial in 29 patients with previously failed minor papilla cannulation, secretin improved cannulation rate from 7.7% in the placebo group to 81% in the secretin group; crossover to secretin allowed cannulation in a total of 89% of patients[47].

Methylene blue has also been used to aid in identification of the minor papilla and facilitate cannulation.

Techniques include methylene blue spraying over the duodenal mucosa in the vicinity of the minor papilla or injection of contrast medium containing methylene blue into the ventral pancreatic duct though the major papilla in cases of incomplete pancreas divisum. This was shown to be helpful in identification of an inconspicuous minor papilla[48].

Intraduodenal acid infusion (IDAI) is a physiological method to induce secretin release in the human body[49]. We examined the effect of intraduodenal hydrochloric acid infusion on minor papilla cannulation in a small pilot study[50]. IDAI improved cannulation rate from 14% in the placebo group to 80% in the IDAI group[50]. IDAI can potentially be a cost-effective method of increasing minor papilla cannulation rate.

The Sphincter of Oddi is a muscular valve that connects the bile duct and pancreatic duct within the duodenum. Cholecystokinin (CCK), a hormone that stimulates gallbladder contraction and relaxation of the sphincter of Oddi, may increase cannulation rate. Sincalide (Kinevac), a synthetic carboxyl-terminal octapeptide CCK agonist, was helpful in facilitating cannulation in a prospective nonrandomized, single centre study[51]. In this study sincalide was used in 19 patients with unsuccessful initial cannulation using the standard catheter technique. Successful cannulation was obtained in 12 patients and cannulation rate increased from 80.7% (88/109 patients) to 91.7% (100/109 patients) without the need for needle knife papillotomy or guide wire to aid cannulation. However, another randomized controlled trial showed that intravenous administration of CCK during ERCP had no effect on cannulation[52]. Topical nitroglycerin was also shown to relax the sphincter of Oddi but there was no effect on rates of selective bile duct cannulation[53,54].

A LIQUID FATTY MEAL BEFORE ERCP

Fats are the most potent natural stimulator of bile secretion and the relaxation of the sphincter of Oddi. Therefore, we postulated that ingestion of a fatty meal would improve the cannulation rate during ERCP. A randomized double-blind study in 84 patients examined the effect of a liquid fatty meal on deep CBD cannulation during ERCP[55]. In the study group, each patient had a liquid fatty meal orally about 1 h before the procedure. In the control group, each patient had the same volume of a non-fat meal. There was no difference in the success rates of cannulation between the study and the control group (88% *vs* 85% respectively). However, compared with the non-fat meal group, the orifice of the CBD/pancreatic duct was much more easily identified in the fatty meal group. The cannulation and the fluoroscopy times were significantly shorter in the fatty meal group. Ingestion of a fatty meal may provide a simple and less expensive method of facilitating cannulation and decreasing fluoroscopy times. However further larger studies are needed.

CANNULATION IN PATIENTS WITH SURGICALLY ALTERED ANATOMY

Although the cannulation success rate is greater than 90% in patients with normal anatomy[17], ERCP in patients with surgically altered anatomy, especially with a Roux-en Y anastomosis, can be more challenging: firstly, the endoscopic approach to the blind end, the afferent loop and the choledochojejunostomy site is difficult using a conventional endoscope because of the relatively long distance from the gastrojejunal anastomosis site and the unusual anatomical features after surgery. Secondly, even if the scope reach the papilla of Vater or the site of choledochojejunostomy, selective cannulation of the pancreatic and/or biliary duct is still more difficult than usual. Therefore, patients with surgically altered anatomy have been considered unsuitable for ERCP in the past despite of reported successful ERCP using colonoscopes in such patients[56].

However, the balloon enteroscopy, a recently developed technology, can be useful for performing ERCP in patients with such surgically altered anatomy. In particular, double- or "short" double-balloon endoscopy has been reported several times in this population of patients[57-62] and single-balloon endoscopy has also been reported[63-65]. The successful rates in those reports are above 60% for patients with a Roux-en Y anastomosis and up to 100% for patients with Billroth-Ⅱ anastomosis[57-65].

CONCLUSION

Since ERCP was first introduced in 1968[1], the techniques used to achieve successful deep bile duct cannulation have expanded significantly. Endoscopists should be familiar with the different techniques and equipment used to maximize the rates of successful cannulation and decrease the rate of complications. The addition of steps to decrease the rate of post ERCP pancreatitis such as placing a pancreatic stent should be considered in high risk patients. IEUC is evolving as an alternative to PTC when ERCP fails and is increasingly performed in specialized tertiary care centers. Intravenous injection of secretin can facilitate minor papilla cannulation. Intraduodenal acid infusion is a promising method in increasing minor papilla cannulation. Using single-, double- or "short" double-balloon enteroscopy has achieved a high successful rate of cannulation in patients with surgically altered anatomy.

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CASE REPORT

Diagnosis and endoscopic treatment of esophago-bronchial fistula due to gastric heterotopy

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Abstract

Heterotopic gastric mucosa patches are congenital gastrointestinal abnormalities and have been reported to occur anywhere along the gastrointestinal tract from mouth to anus. Complications of heterotopic gastric mucosa include dysphagia, upper gastrointestinal bleeding, upper esophageal ring stricture, adenocarcinoma and fistula formation. In this case report we describe the diagnosis and treatment of the first case of esophago-bronchial fistula due to heterotopic gastric mucosa in mid esophagus. A 40-year old former professional soccer player was referred to our department for treatment of an esophago-bronchial fistula. Microscopic examination of the biopsies taken from the esophageal fistula revealed the presence of gastric heterotopic mucosa. We decided to do a non-surgical therapeutic endoscopic procedure. A sclerotherapy catheter was inserted through which 1 mL of ready to use synthetic surgical glue was applied in the fistula and it closed the fistula opening with excellent results.

Key words: Gastric heterotopy; Esophago-bronchial fistula; Ectopic gastric mucosa; Heterotopic gastric mucosa; Esophagus; Esophageal fistula therapy

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INTRODUCTION

Ectopic gastric mucosa (EGM) can occur in the fore-, mid- and hindgut and, conceivably, at any of their derivatives[1]. The origin of EGM is either heterotopic (congenital) or metaplastic (acquired). The reported incidence of EGM in the endoscopic literature ranges from 0.29% to 10% but an incidence of up to 70% has been reported in autopsy studies[2]. Heterotopic gastric mucosa (HGM) patches are congenital gastrointestinal abnormalities and have been reported to occur anywhere along the gastrointestinal tract from mouth to anus[1-5].

HGM in the esophagus is thought to arise from

gastric precursor cells that remain after incomplete replacement of the original stratified columnar epithelium lining the embryonic esophagus by stratified squamous epithelium[6-8].

Diagnosis of HGM is often difficult and requires experience and a high degree of suspicion. At endoscopy, the HGM appears as a mainly flat or slightly raised, well circumscribed red-orange salmon-colored patch. This is mainly a solitary patch but can be multiple measuring from a few millimeters to several centimeters[9]. Complications of HGM patches include dysphagia, upper gastrointestinal bleeding[10], stricture[11] and fistula formation[12], upper esophageal ring[13] and adenocarcinoma[14-15]. Interestingly, HGM in the duodenum may also manifest as dyspepsia[16].

CASE REPORT

A 40-year old former professional soccer player was referred to our department for further investigation of a recently diagnosed esophago-bronchial fistula. Fistula diagnosis was made during investigation of relapsing episodes of acute dyspnea and upper abdominal discomfort during the previous six months.

The patient's family history was unremarkable except that his father was treated for tuberculosis twenty years previously. The patient was diagnosed with allergic rhinitis and mushroom allergy; he never smoked and rarely drank alcohol. For the last twenty years the patient had suffered from relapsing episodes of lower respiratory tract infections which were treated with antibiotics and one year ago he underwent coronary artery stenting.

The patient had previously been investigated for these acute dyspnea episodes and, as cardiologic and other routine evaluations were negative, he was started on bronchodilators and antibiotics without subsequent improvement. As his symptoms persisted, the patient developed stress-related sleeping disturbances and panic disorder and was followed up by a psychiatrist. After some weeks the patient consulted a gastroenterologist. As he could not tolerate endoscopy he underwent baium follow through which revealed an esophagobronchial fistula tract (Figure 1) and he was referred for further investigation and treatment.

On admission clinical examination was negative. The patient was on antidepressants, beta-blockers, clopidogrel, aspirin and simvastatin. Laboratory tests revealed nothing. Serum angiotensin converting enzyme was within normal limits. Mantoux was 18 mm at 48 h. Differential diagnosis included congenital fistula, active or latent tuberculosis, granulomatous diseases, neoplasia and possible blind trauma. Trauma probability was immediately excluded as the patient had never had any kind of endoscopy or history of complicated esophageal foreign body ingestion. Congenital fistula was improbable as the patient had been free of symptoms until twenty years of age. Thorax high resolution computed tomography showed infiltrations in the right lobe in contact with the mediastinum but not of lymph nodes and Tc-99m pertechnetate scintigraphy proved of no help.

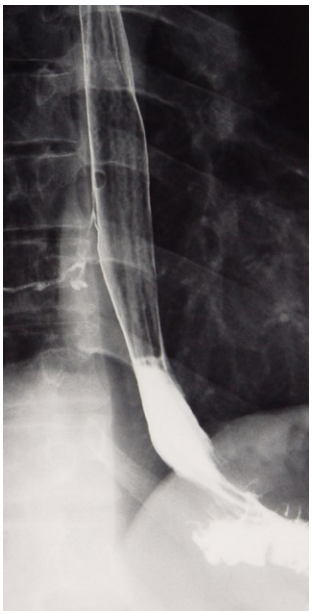

Figure 1 Barium follow through of the esophagus revealing the esophago-bronchial fistula.

Upper gastrointestinal endoscopy was performed with deep sedation. In the mid esophagus at 28 cm from the mouth incisors the proximal opening of the fistula tract was revealed and biopsies were taken (Figures 2A and B). A small gastro-esophageal hernia extended from 40-42 cm from mouth incisors with concomitant mild esophagitis but not Barrett's esophagus. In the stomach there was mild gastritis with some erosions and biopsies were taken. The first and second part of the duodenum was normal. Bronchoscopy including cytology, PCR and cultures for mycobacterium tuberculosis and other pathogens were negative.

Microscopic examination of the biopsies taken from the esophageal fistula revealed the presence in the lamina propria of mucus secreting cardiac-type glands and of fundic-type glands containing both parietal and chief cells. Furthermore, the mucosa was covered by tall, columnar foveolar epithelium, which at the edges merged with the adjacent esophageal stratified squamous epithelium. Goblet cells were not identified. There was no evidence of dysplasia. Microorganisms with the morphological characteristics of Helicobacter pylori were not observed with Giemsa special stain (Figures 3A and B).

In the biopsies from the antral gastric area, microscopic findings consistent with chronic active gastritis were noted. Helicobacter pylori micro-organisms were observed with Giemsa special stain.

We decided on a non-surgical therapeutic endoscopic procedure. During upper gastrointestinal endoscopy performed by one of us (E.V.T), a sclerotherapy catheter was inserted through which 1 mL of ready to use synthetic surgical glue (Glubran 2, GEM Srl, Viareggio Italy) closed the fistula opening with excellent results (Figures 4A and B). The patient is completely asymptomatic at 6 mo follow up.

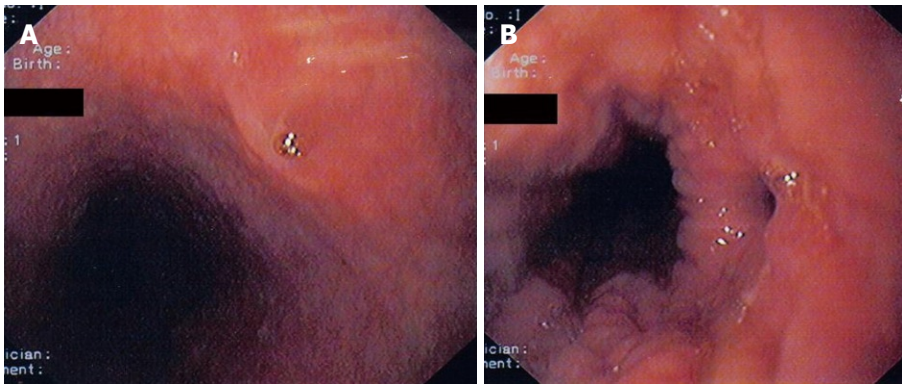

Figure 2 Endoscopic view of the proximal opening (open and closed) of the esophago-bronchial fistula caused by heterotopic gastric mucosa. A: Closed; B: Open.

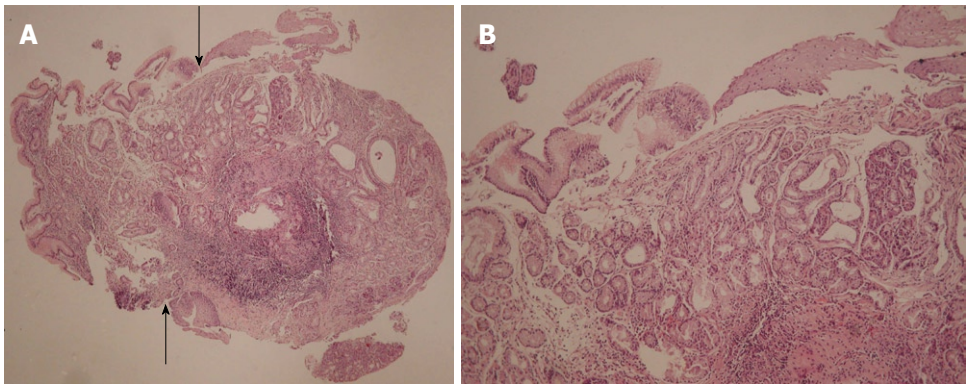

Figure 3 Heterotopic gastric mucosa in middle esophagus. A: Arrows denote the transition between the columnar foveolar epithelium and the esophageal stratified squamous epithelium (H&E, × 40); B: Columnar epithelium merges with stratified squamous epithelium. At the lamina propria cardiac and fundic-type glands are evident (H&E, × 200).

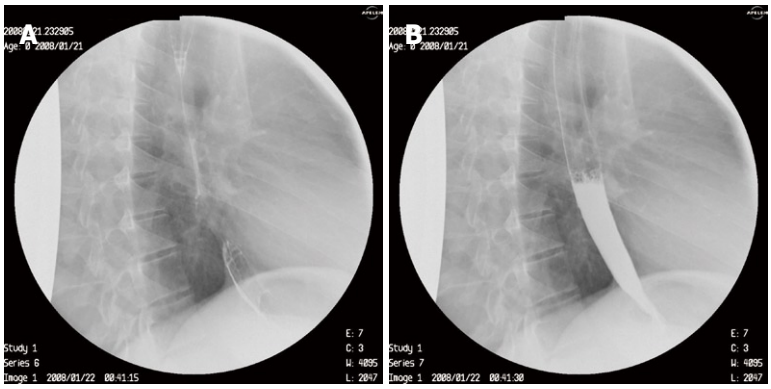

Figure 4 Gastrografin follow through 1 mo after endoscopic therapy of esophago-bronchial fistula with glue.

DISCUSSION

To the best of our knowledge this is the first case of esophago-broncheal fistula due to HGM in the esophagus and the second case ever reported on esophageal fistula related to HGM. The other case reported on a 50-year-old male patient with a fine fistula between the esophagus and the trachea located near the upper thoracic aperture. In that case[12] the only item worthy of note was diagnosis of lung tuberculosis followed by a fistula diagnosis four years later.

It is noteworthy that the fistula and HGM diagnosis in our patient was possible after a very prolonged period of atypical lower respiratory tract symptoms. In fact, HGM patches have been associated with a broad spectrum of symptoms such as ulceration, bleeding, perforation and malignant transformations[2]. If asymptomatic the clinical importance of esophageal HGM patches is debatable[5].

The asymptomatic nature of these HGM patches, simple oversight and sometimes technical difficulty can mean that endoscopists are unfamiliar with these lesions. The characteristic 'salmon-colored' appearance of the HGM patch, not evident in the fistula opening of our case, can confirm diagnosis using Congo red dye application (1% in distilled water) to the suspected area; according to the authors[9] after 5 min small punctuate areas within the patch turn from red to black, confirming a fall in pH and that this patch is acid-producing. Although pertechnetate scintigraphy (Tc-99m) has been suggested[17] in order to confirm HGM diagnosis and to localise other possible patches, it proved of no help in our case.

Our patient had a small gastro-esophageal hernia and no evidence of concomitant Barrett's esophagus. Traditionally, esophageal HGM is considered a distinct entity from Barrett's esophagus. The presence of speci-

alized columnar epithelium characterized by acid mucin-containing goblet cells has been accepted as diagnostic of Barrett's esophagus. The American College of Gastroenterology and its Practice Parameters Committee provided a definition of Barrett's esophagus as a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed by biopsy to have intestinal metaplasia[18]. A healing process of the lower esophagus in response to injury from gastric reflux is believed to be its primary etiology[7-12].

The presence of an esophageal HGM patch has been associated with gastroesophageal reflux disease[8]. Of interest, immunohistological studies suggested a similarity between Barrett epithelium and HGM patch[18-19]. These studies have shown that Barrett epithelium and HGM have the same mucin core protein expression and cytokeratin pattern (cytokeratins 7 and 20)[19], thus suggesting a pathogenetic link between these two diseases. However, in the study of Borhan-Manesh *et al*[5], the incidence of esophagitis and Barrett's epithelium in a population of 64 veterans with endoscopically found HGM patches did not significantly differ from that observed in 570 patients without these patches. On the other hand, it is possible that occasional cases of Barrett's mucosa at the distal end of the esophagus are nothing but the failure of the squamous epithelium to carpet the area resulting in Barrett's epithelium. However, the 10 cm distance of HGM from the gastro-esophageal junction and the absence of concomitant Barrett's lesions exclude this probability in our patient. Furthermore, histological changes of the squamous epithelium distally adjacent to the HGM area in our patient did not show changes consistent with reflux esophagitis.

Despite the fact that the HGM patch in this patient was Helicobacter pylori negative, we cannot exclude the probability that Helicobacter pylori causing chronic gastritis in our patient may also have previously colonized the HGM patch contributing to ulcerogenesis and subsequent fistula formation[20-22].

In our patient, as HGM was obviously related to recurrent respiratory symptoms, fistula closure was the only definite therapy. We decided to treat our patient using a technique similar to that applied in the previous fistula case. In that case[12], a two-step endoscopic therapy was made to close off the esophagotracheal fistula with the aid of the same type of glue we also used. The adhesive was selectively applied into the fistula track *via* a 1.5m long irrigation catheter passing down the biopsy channel of the endoscope. Four days later, a further 2 mL of fibrin adhesive was selectively instilled into the fistula opening.

Treatment of symptomatic HGM is necessary in order to relieve symptoms and to further prevent the development of other complications. Efficient treatment can be successfully offered with the use of proton pump inhibitors. If appropriate and when medical therapy fails to promote regression of symptoms, transcevical or endoscopic biopsy and/or excision are warranted[1]. Endoscopic laser ablation is an acceptable treatment modality because of the rarity of malignant transformation. However, if a small focus of malignancy is suspected, complete local excision with narrow margins is the treatment of choice in order to exclude further progression[23]. Mucosectomy of the patch aided with chromoendoscopy with 0.5% methylene blue has been also suggested[4] and long-term follow up of these patients seems of great importance.

The criteria for gluing are defined on an individual basis and parallel the experience of every physician in such a method. In general, small in size and length, well-defined, non-inflamed fistula with no concomitant regional abscess can be treated with glue.

In conclusion, we presented herein an exceptional case of symptomatic esophageal gastric heterotopia with esophago-bronchial fistula formation. We have discussed pathophysiological and diagnostic issues and have described the endoscopic therapy which should be the treatment of first choice in such cases.

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Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

February 11-13
Fort Lauderdale, FL, United States
21th Annual International Colorectal Disease Symposium

February 26-28
Carolina, United States
First Symposium of GI Oncology at The Caribbean

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-17
Landover, Maryland, United States
12th World Congress of Endoscopic Surgery

April 14-18
Vienna, Austria
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April 28-May 01
Dubrovnik, Croatia
3rd Central European Congress of surgery and the 5th Croatian Congress of Surgery

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New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 15-19
Minneapolis, MN, United States
American Society of Colon and Rectal Surgeons Annual Meeting

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

June 20-23
Mannheim, Germany
16th World Congress for Bronchoesophagology-WCBE

August 28-31
Boston, Massachusetts, United States
10th OESO World Congress on Diseases of the Oesophagus 2010

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 11-12
La Jolla, CA, United States
New Advances in Inflammatory Bowel Disease

September 16-18
Prague, Czech Republic
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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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