Capsule Endoscopy Versus Magnetic Resonance Enterography for the Detection of Small Bowel Polyps in Peutz-Jeghers Syndrome

Urquhart P, Grimpen F, Lim GJ, Pizzey C, Stella DL, Tesar PA, Macrae FA, Appleyard MA, Brown GJ

Introduction

Peutz-Jeghers Syndrome (PJS) is a rare familial polyposis syndrome characterized by hamartomatous polyps of the gastrointestinal tract and muco-cutaneous pigmentation[1,2]. In addition to higher rates of malignancy[3], patients with PJS commonly suffer from the polyp-related complications of intussusception and small bowel obstruction, as well as bleeding and anaemia[4]. These complications commonly occur in the first and second decade of life, and frequently necessitate emergent surgical intervention[5]. While regular surveillance and polyp removal is recommended to reduce the incidence of secondary complications, prospective evidence supporting the optimal technique of polyp detection is lacking[6].

For many years barium follow-through (BaFT) was considered the preferred modality for small bowel surveillance[7,8]. Its ongoing use however, particularly in children and adolescents, has been encumbered by the inherent radiation exposure. Its use in PJS patients has largely been surplanted by the emergence of capsule endoscopy (CE). The lack of ionizing radiation, accuracy and ability of CE to directly visualize the small bowel, has made it an attractive tool for use in small bowel surveillance programs. A prospective study directly comparing BaFT and CE reported CE to have both a superior polyp detection rate and greater levels of patient comfort and overall preference[9]. Recent European expert consensus guidelines (Mallorca Group)propose CE performed every 3 years as the preferred method of small bowel surveillance in patients with PJS[6].

More recently, Magnetic Resonance Enterography (MRE) has been proposed as an alternate non-invasive imaging modality for small bowel surveillance in PJS[10]. A study evaluating both MRE and CE in intestinal polyposis syndromes found comparable rates of detection for large (>15mm) polyps[11]. A subsequent study comparing MRE to CE in PJS patients alone demonstrated its equivalence for polyps >10mm as well as a trend towards more accurate detection of larger polyps[12].

The increasing detection of small bowel polyps during surveillance has resulted in a need for a safe and effective technique to facilitate polypectomy. While balloon enteroscopy (BE) is unsuitable as a surveillance technique due to its inability to reliably visualize the entire small bowel, it has developed into the technique of choice for small bowel polypectomy. Surgical-assisted enteroscopy also has a role in polyp removal but given its high level of invasiveness is now generally reserved for cases where direct enteroscopy has been unsuccessful.

This prospective study aimed to assess the diagnostic utility of CE compared to MRE for the detection of small bowel polyps in patients with PJS, with BE correlation where clinically justified. We also evaluated the comfort and convenience of each investigation as judged by the patient, as well as their overall preference of screening modality.

Patients and methods

The primary endpoint of the study was a comparison of the total number of 'clinically significant' polyps, defined as greater than or equal to 1cm in size, detected by CE and/or MRE. The secondary endpoints included a comparison of the number of patients in whom at least one significant polyp was detected; a comparison of the findings on CE and MRE with respect to subsequent BE; a comparison of the patients' ratings of comfort and convenience for each modality; and an assessment of their overall preferred surveillance technique. This study was reviewed and approved by the Ethics Departments at both The Royal Melbourne Hospital and the Royal Brisbane and Womens Hospital.

Patients with PJS that were attending a familial cancer clinic at either of the two participating hospitals and due for endoscopic surveillance were identified and invited to participate in the trial. Exclusion criteria included overt symptoms of bowel obstruction, the need for inpatient care, pregnancy, and the presence of a cardiac pacemaker or other contraindications to MRE.

Participants first underwent a standardized MRE[13] on a 1.5 Tesla scanner (Signa 5x, GE Healthcare, Milwaukee, USA). This was performed prior to the CE to avoid safety concerns arising from the possibility of a retained capsule. The MRE studies were evaluated independently by an experienced radiologist (DS or PT) blinded to the findings of CE.

CE (EndoCapsule, Olympus Corporation, Tokyo, Japan) was subsequently performed within 3 months in all patients. This examination was facilitated by a trained clinical research nurse experienced in CE and performed according to study protocol. Patients were requested to fast for at least 6 hours. No bowel preparation or premedication was given. Following capsule ingestion patients were allowed to drink and eat after 2 and 4 hours respectively. The CE studies were evaluated by an experienced gastroenterologist (GB or MA) blinded to the findings of the MRE.

For the purposes of this study, intestinal polyps of greater than or equal to 1cm in size were considered to be clinically significant. Polyps less than 1cm in size were disregarded. The attribution of 'significance' to intestinal polyps in PJS is contentious due to the difficulties in accurately estimating polyp size, particularly on CE. A diameter of 1cm was consistent with previous studies in PJS and was chosen so as not to miss significant polyps capable of causing clinical complications.

The finding of a significant polyp on either imaging modality prompted a balloon enteroscopy for verification and attempted polyp removal. This procedure was carried out under anaesthetic-administered sedation and performed with either a single balloon enteroscope (Olympus Corporation, Tokyo, Japan) or double balloon

enteroscope (Fujifilm Corporation, Tokyo, Japan) depending upon availability. The choice of approach was left to clinician discretion although the '2/3 vs 1/3' rule was generally employed with the antegrade approach favoured for polyps localized to the upper 2/3 of the small bowel. A tattoo was placed at the point of maximal insertion as a reference point for assessing complete visualization of the small bowel in patients who underwent both antegrade and retrograde procedures. As recommended in current guidelines a gastroscopy and colonoscopy were also performed as part of patients' routine surveillance. Sample size calculations were based on limited available data with most comparable studies in PJS enrolling fewer than 20 patients.

Following both investigations, participants were asked to rate their experience in terms of the comfort and convenience of each modality, as measured by a 100mm visual analogue scale (VAS). The Wilcoxon signed-rank test was used to compare the average measurements. Patients were also asked to rate their overall preferred modality of surveillance.

Figure 1: PJS polyps detected by MRE

Figure 2: PJS polyps detected by CE

Results

Twenty-two patients were recruited across two tertiary centres during 2008 and 2009. One patient subsequently withdrew consent for the study and a further patient was unwilling to submit to the MRE. A total of 20 patients (male 7, female 13; mean age 34.9 years) underwent both CE and MRE and were included in the primary analysis. The CE was ingested orally in 19 patients (95%) and required deployment into the duodenum in 1 patient (5%). The CE reached the caecum during recording in 17 patients (85%). While 15 patients were identified as have a significant polyp on either CE or MRE, 3 patients refused to undergo BE. Therefore twelve patients had a total of 19 balloon enteroscopies performed: 14 antegrade and 5 retrograde. Two patients underwent 3

procedures each, while 3 patients underwent 2 procedures each. Complete enteroscopy (visualization of the previously placed tattoo) was not achieved in any of the 4 patients who underwent BE from both directions.

Number of Significant Small Bowel Polyps per Patient

The total number of significant polyps detected by CE was 47 compared with 14 by MRE (Table1). The Wilcoxon signed-rank test revealed a significant difference between the two methods (p=0.02, median number of polyps per patient found by CE compared with MRE, 1.5 polyps versus 0 polyps respectively).

Table 1: Number of polyps detected by CE, MRE and BE (n=20)

Number of Patients with at least One Significant Small Bowel Polyp

The number of patients with at least one significant polyp identified by CE was 11 (55%) compared with 7 (35%) identified by MRE. The difference in proportions was not significant (P=0.25).

Agreement between CE and MRE

The percentage agreement between CE and MRE as to the presence or absence of at least one significant polyp was only 40% (8/20) (95% CI=19%, 64%).

Verification of Findings with BE

Of an eligible 15 patients, twelve underwent a total of 19 procedures, of which 8 (67%) patients were found to have at least one significant polyp. A total of 26 significant polyps were identified and removed. When the total number of polyps detected by each modality was compared in these twelve patients, BE identified an additional 14 polyps compared to MRE (P=0.19), but 11 fewer polyps compared with CE (P=0.16).

Table 2: Number of polyps detected per modality in patients undergoing all three tests (n=12 patients)

An analysis of the agreement between BE and the two modalities on a 'per patient' basis was also performed. This demonstrated agreement as to the presence or absence of a significant polyp in 9/12 patients (75%) for BE and MRE, compared to 6 out of 12 patients (50%) when BE and CE were correlated. The positive predictive value (PPV) of finding a polyp at BE based on a positive result at CE and MRE were 60% (6/10) and 100% (5/5) respectively.

Patient Preference Questionnaire

The median VAS scores measuring comfort for CE were 94.5 (interquartile range (IQR) 90.5 - 97) and 84 for MRE (IQR 41.5 - 95). The median VAS scores for convenience were 92.5 for CE (IQR 78.5 – 98.5) and 83.5 for MRE (IQR 47 - 93). Of the 12 patients who rated the procedures, the majority preferred CE (10/12, 83%).

Discussion

CE is currently the modality of choice for small bowel surveillance in PJS having demonstrated superior rates of polyp detection as well as higher levels of patient comfort and convenience when compared directly to the traditional method of BaFT. The utility of MRE in the assessment of small bowel pathology has expanded greatly in the past decade with preliminary studies in patients with PJS suggesting this technique to be comparable to CE for the detection of significant polyps. The current study directly compared these two developing techniques in a prospective comparative trial, with findings compared to subsequent BE. The subjective measures of patient comfort, convenience and overall preference were also compared for MRE and CE.

CE was found to detect a greater median number of significant polyps compared with MRE. While incompletely verified by BE, this primary outcome is analogous to that used in most studies of PJS surveillance and therefore directly relevant when comparing to the outcomes of similar studies. The discrepancy in polyp detection rate in our study contrasts with findings by Gupta *et al*[12]who found no difference between the number of unverified polyps > 10 mm identified by CE and MRE. While they attempted to

validate their findings, only 5/9 patients assessed as having significant polyps then underwent either balloon or surgical enteroscopy. Likewise our findings are incongruent with those of Caspari *et al*[11]who assessed patients with both PJS and familial adenomatous polyposis (FAP) without confirmatory enteroscopy. They showed that while CE detected a greater number of smaller polyps, MRE was equivalent to CE for the detection of polyps >15mm.

While contrasting with previous studies on a 'per polyp' analysis, the current study yielded similar findings on a 'per patient' analysis, with no statistical significance shown between CE and MRI. This finding is consistent with that of Gupta *et al*[12] who found no difference between the two modalities on a 'per patient' analysis. In our study, agreement between CE and MRE as to whether a patient had at least one significant polyp was poor.

As the finding of a signficant polyp on screening in clinical practice usually results in a BE to facilitate polyp removal, the ability of each test to predict the presence of a significant polyp on subsequent BE was evaluated. In the current study BE detected over twice as many polyps when compared with MRE even given the limited reach and application of BE in the current study. This key finding highlights that at a minimum, MRE missed just over half of significant small bowel polyps in the study population as confirmed unequivocally by BE. Furthermore, this figure may in fact be an over-estimate of the sensitivity of MRE as additional polyps may have remained undetected by BE due to the inability of this technique to achieve complete visualization of the small bowel in any of the study participants. On the converse, the authors acknowledge that this lack of complete enteroscopy also makes it difficult to verify the high number of polyps reportedly detected by CE. However, despite missing significant polyps subsequently found at BE, MRE yielded a higher positive predictive value (PPV) compared with CE.

In the context of the use of MRE and CE as a screen for the detection of clinically significant polyps in this high cancer risk syndrome, PPV is less important than the NPV

or false negative rate of the screening test. Although we could not determine accurately the NPV or false negative rates precisely (as patients without a significant polyp on CE or MRE did not undergo a BE, and none of the patients undergoing BE achieved complete compete enteroscopy) we can say that there were 3 patients who had at least one BE-confirmed significant polyp detected by CE not seen on MRE; reciprocally there were 2 patients with at least one BE-confirmed significant polyp detected by MRE, not seen on CE. Complementing this difference on a per polyp basis, there were 19 BE-confirmed significant polyps detected by CE, and only 8 BE-confirmed significant polyps detected by MRE.

Comparative studies assessing the optimal method of screening in PJS are hindered by inherent limitations in study design. As PJS is a relatively uncommon condition, adequately powered studies are difficult to achieve. Despite the current study being conducted across two tertiary centres with large familial cancer clinics, our final analysis was limited to 20 participants, a figure reflected in many comparable studies. The comparative data with BE was further limited due to the refusal of three patients with a significant polyp identified on CE or MRE to undergo BE. The lack of a total enteroscopy for visualising the small bowel resulted in limited verification of findings seen on CE and MRE. Only four patients underwent BE from both directions, with none of the participants having complete visualization of their small bowel. While previous studies have utilized surgically-assisted enteroscopy for complete small bowel inspection and polyp clearance, this technique is invasive, particularly in patients having undergone previous surgery, and thus not widely utilized in our institutions.

The accuracy of CE in small bowel polyposis syndromes is limited by several factors, with previous studies suggesting that CE may be prone to overestimating the number and size of polyps. There is currently no standardized method of estimating polyp size on CE, with investigators reliant upon personal experience and comparison with luminal diameter. This potentially results in clinicians inaccurately classifying small polyps as ‘significant’ with a subsequent over-estimation of the number of significant polyps present. Due to the difficulties in accurately measuring polyp size we decided

upon a diameter of 1cm as representing 'significance'. We felt it more appropriate to have a lower cutoff and include smaller polyps, than to have a higher cutoff (15mm has been used in some studies) and risk misclassifying polyps as 'insignificant' that could have clinical implications. A measurement of 10mm has been used in similar studies in patients with PJS[9,12] which we consider appropriate given the evidence that complications can arise in polyps as small as 15mm. There are also difficulties associated with the counting of polyps on CE. While in the small bowel it is possible for the capsule to move in a retrograde fashion which may result in the same polyp being erroneously counted more than once if the capsule re-traverses a section of small bowel containing a polyp. These two factors imply a potential for CE to over estimate polyp findings which has serious implications if used to determine the need for further invasive procedures. On the converse, true polyps identified on CE (or MRE) may not have been identifed or removed by BE simply because they were out of reach of BE.

Studies to date suggest that the ability of MRE to detect significant polyps in PJS patients is comparable to CE. Overall, our study found CE to be significantly superior to MRE for the detection of significant (≥10mm) polyps. Comparison to the MRI scanner and sequences used in the like study performed by Gupta *et al*[12]showed that they had a superior MRI scanner available to them (two generations more advanced than that used in this study). Furthermore, they were able to perform 2mm thin slices whereas we were confined to performing 10mm slices, making detection of polyps as small as 10mm quite difficult due to partial voluming artifacts. Although difficult to establish with certainty, it is also possible that the oral contrast technique utilized in their study provided superior bowel distension, which is especially important for bowel polyp detection (particulalrly if the image examples provided in their publication is a reflection of bowel distension across all their patients). So our differing study results may simply reflect the difference between comparing state-of-the-art CE to MRE with a state-of-the-art MRI scanner (Gupta *et al*) versus to a now technologically obsolete MRI.

Enteroclysis (as compared to enterography) is an alternative technique that has been suggested as a means of enhancing mucosal detail and thus polyp detection. This

technique requires the instillation of a large volume of the contrast agent directly into the small bowel via a naso-jejunal tube. While more invasive and potentially less comfortable for patients, this technique may yield higher detection rates and thus further studies are needed. Advocates of MRE highlight its safety for use in patients with large polyps, or previous surgery where potential exists for adhesions or anastomotic strictures to cause capsule retention or even bowel obstruction . Furthermore the lack of radiation makes it ideal for use in children and adolescents.

The findings of greater comfort and convenience with CE, which proved to be overwhelmingly the preferred modality of patients, are consistent with those from previous studies. While the MRE protocol used in this study instilled rectal water, the recent introduction of newer enterography agents omitting this step, may improve patients' experience of MRE. In the current study only one patient required endoscopic capsule deployment.

There is currently limited data regarding the optimal imaging technique and timing interval for polyp surveillance in patients with PJS. While the PPV of MRE was superior to CE in this study, the poor sensitivity of MRE precludes us from recommending this modality as first line for small bowel surveillance. Its high specificity however make MRE a potentially useful adjunct for patients with equivocal findings on CE, or in symptomatic patients with a negative CE, including those in whom adhesions are a concern. In a condition such as PJS where the failure to detect polyps can have serious consequences, the need for a screening test with high sensitivity is paramount. This study therefore supports the current expert guideline advocating CE as the preferred modality of choice for small bowel surveillance in patients with PJS. However, with the advent of new MRI scanner technology (inluding 3T high field strength MRI scanners) that significantly surpasses that used in this and previous studies as well as improved enterography agents, further work in this area should be pursued. Given our data, there may be a role for CE and MRE as complementary studies in surveillance in PJS.

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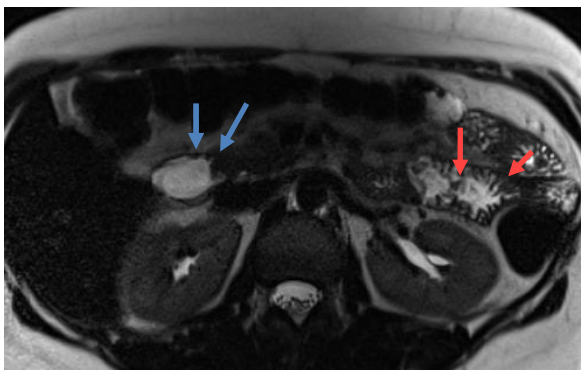

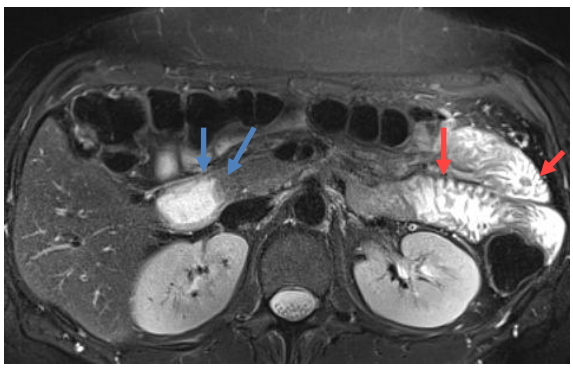

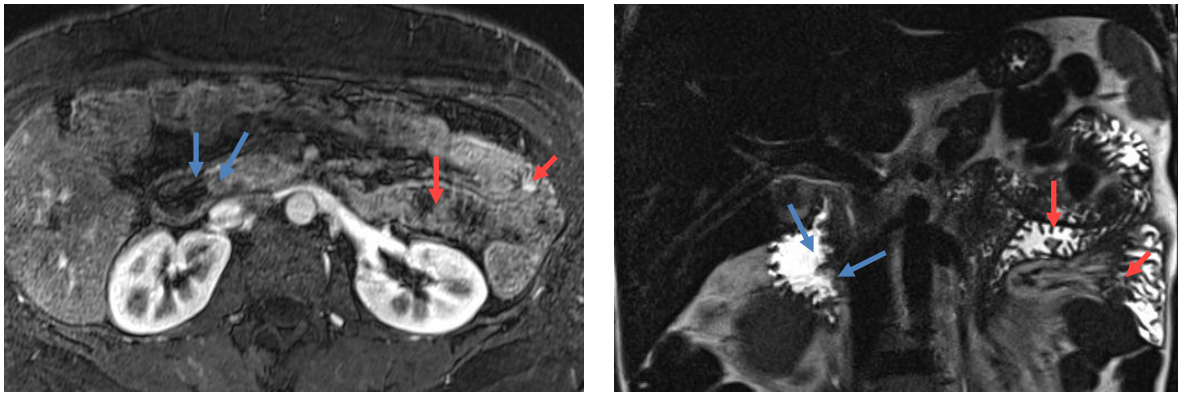

Figure 1: PJS polyps detected by MRE: Axial HASTE (A), fat-suppressed T2 (B), T1 fat-suppressed - post contrast (C), and coronal HASTE (D).

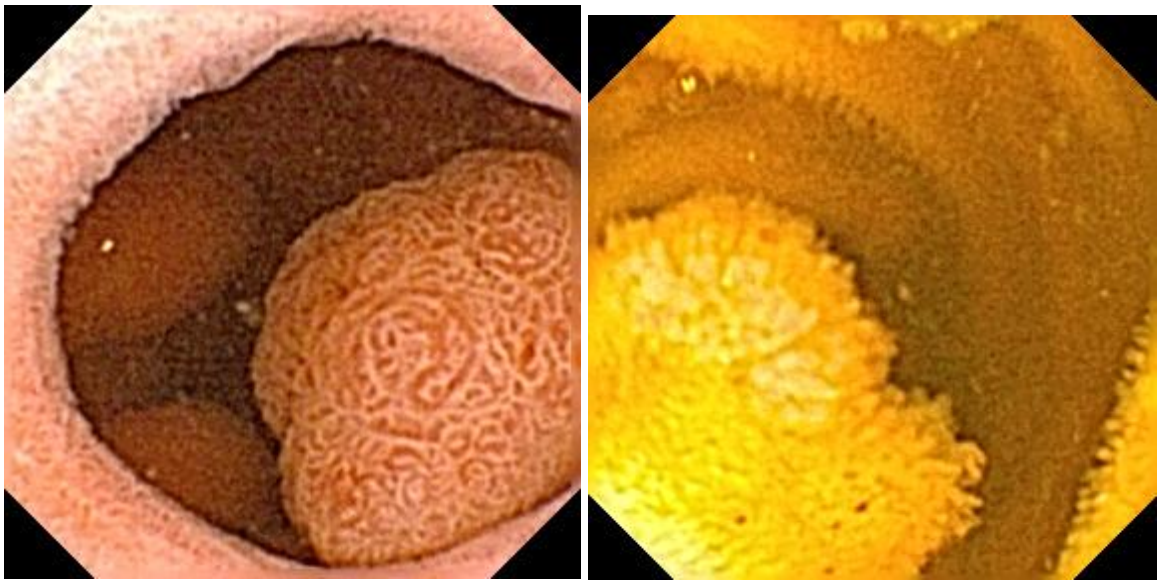

Figure 2: PJS polyps detected by CE

	CE	MRE	BE
Patient No.	Number of significant polyps	Number of significant polyps	Number of significant polyps
1	0	1	4
2	4	6	2
3	0	1	
4	10	2	6
5	0	1	
6	10	0	
7	2	0	0

8	7	2	9
9	0	0	
10	0	1	1
11	1	0	0
12	4	0	2
13	0	0	
14	0	0	
15	2	0	1
16	2	0	0
17	3	0	0
18	0	0	
19	0	0	
20	2	0	1
Total	47	14	26

Table 1: Number of polyps detected by CE, MRE and BE (n=20)

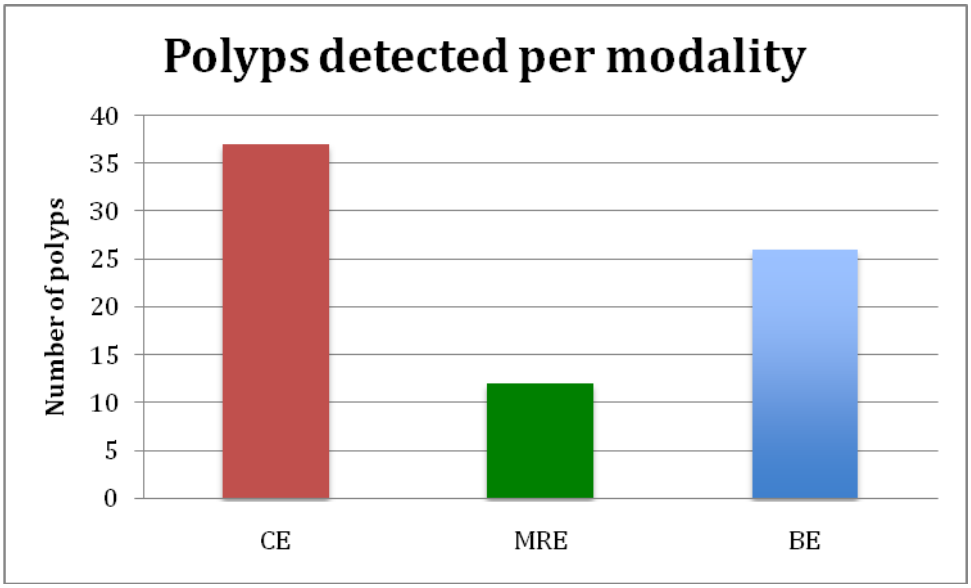

Table 2: Number of polyps detected per modality in patients undergoing all three tests (n=12 patients)

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