

Capsule Endoscopy of the Small Bowel and Esophagus: Current Technology, Indications, and Clinical Relevance

Charles D. Ulrich, II, M.D., FACP, FACG

Associate Professor of Internal Medicine
Director of University Hospital Gastroenterology and Pancreatology

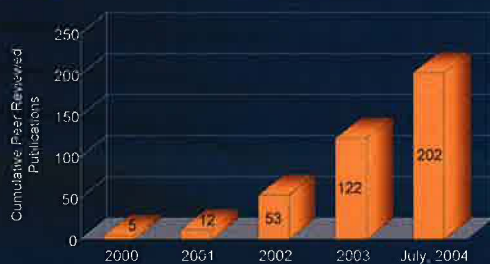
PillCam™ Endoscopy of the Small Bowel

- First line diagnostic exam for visualization of small bowel mucosa
- One internal analysis study reviewed 32 independent studies which indicate CE diagnostic yield of 71% vs. 41% diagnostic yield for all other modalities combined
- Has become the gold standard for diagnosis of disease of small intestine
- Now cleared in the US for pediatric population from 10-18 years old

Internal data at Given Imaging Ltd, Reviewed by the FDA; Rex *et al*, *Am J Gastroenterol* 2003;98:1295-1298

Clinical Acceptance

- In use in over 1,800 sites worldwide
- More than 100,000 ingestions worldwide



Data on file www.givenimaging.com

PillCam SB: Diagnostic Yield vs Push-Enteroscopy

N	PillCam SB	Push Enteroscopy	Ref
32	66 % (p<0.001)*	28 %*	1
57	75 % (p=0.04)	56 %	2
29	59 % (p<0.05)	28 %	3
21	55 %	30 %	4
89	56 % (p<0.05)**	24 %**	5

* lesions = definite source of symptoms. ** method only was diagnostic

1. Ell et al. Endoscopy 2002;34:665-669
2. Delvaux et al. Gastrointest Endosc 2002;55:AB38
3. Dornadis et al. Gastrointest Endosc 2002;55:AB146
4. Lewis and Swain. Gastrointest Endosc 2002;56:349-353
5. Pennazio et al. Endoscopy 2002;34(suppl 1):A91

PillCam SB Diagnostic Yield versus Radiology

N	PillCam™ SB	Radiology	Ref
20	70 %	32 - 37 %	1
20	85 %	15 %	2
14	22 lesions	8 lesions	3

1. Ellakim et al. European J Gastroenterol Hepatol 2002;15:1
2. Costamagna et al. Gastroenterology 2002;123:896-1005
3. Vodenholzer et al. Gastrointest Endosc 2002;55:AB129

PillCam SB Capsule Components



1. Optical dome
2. Lens holder
3. Lens
4. LEDs (light emitting diodes)
5. CMOS (Complementary Metal Oxide Semiconductor) image
6. Battery
7. ASIC (Application Specific Integrated Circuit) transmitter
8. Antenna

Dimensions: Height: 11mm
Width: 26mm
Weight: 3.7gr

PillCam SB Exam Set



1. The PillCam™ Capsule
2. SensorArray™ SB
3. Given® DataRecorder™

PillCam SB Patient Experience

- Liquid diet from lunch the day before
- Oral preparation solution optional
- 12 hour fast the night before
- Capsule ingested in the morning with simethicone
- Prokinetics may be used in those with delayed gastric emptying
- Liquid diet after 2 hours
- Light meal 4 hours after ingestion
- Disconnect after 8 hours and return recorder

RAPID® 3 Software Platform Small Bowel Imaging



PillCam SB Normal Small Bowel



Video Capsule Endoscopy to Prospectively Assess Small Bowel Injury with Celecoxib, Naproxen plus Omeprazole, and Placebo

Goldstein JL, Eisen GM, Lewis B, et al. Clin Gastroenterol Hepatol 2005;3:133-141

- Baseline VCEs in asymptomatic controls not taking NSAIDs found small bowel lesions in 13.8% (57/413)
- Small bowel mucosal breaks of varying severity were found in:
 - 55% of patients taking naproxen/omeprazole
 - 16% of those taking celecoxib
 - 7% of those taking placebo
- NSAID ingestion must be considered when interpreting the findings of VCE studies involving the small bowel

PillCam SB and GI Bleeding

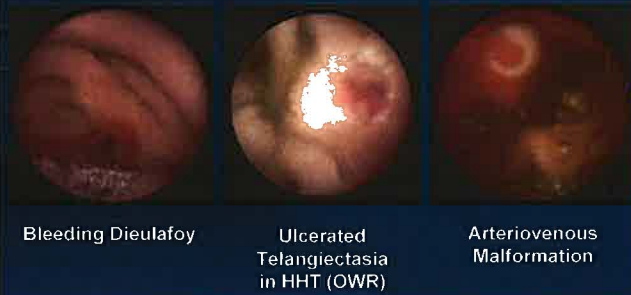
- Capsule endoscopy provides a less invasive means to image the length of the small intestine in patients with overt or occult GI bleeding and negative endoscopic evaluation
- Fireman and Friedman have reported the results of 31 studies examining 293 patients with chronic occult blood loss
 - definitive findings in 213/293 (72%)
 - detected lesions missed by other procedures in 22/293 (8%)
 - 77.1% small bowel, 44% vascular, 24.6% inflammatory
- Modalities available to confirm the diagnosis and treat lesions include push enteroscopy, double-balloon endoscopy, intraoperative endoscopy, surgical resection, and angiography

Fireman et al. Digestion 2004;75:201-208; Tang et al. Gastrointest Endosc Clin N Am 2004;14:87-100

PillCam SB – Sources of GI Bleeding



PillCam SB – Sources of GI Bleeding



PillCam SB – Sources of GI Bleeding



PillCam SB GI Bleeding Video



Outcome of Patients with Obscure GI Bleeding after Capsule Endoscopy: Report of 100 Suspected Cases

Pennazio M, Santucci R, Rondonotti E, *et al*, *Gastroenterology* 2004;126:643-653

- 100 consecutive patients underwent CE
 - 26 with ongoing overt bleeding (Group A)
 - 31 with previous overt bleeding (Group B)
 - 43 with guaiac-positive stools + IDA (Group C)
- All with recent upper and lower endoscopy
- Yield of positive findings was 92.3% Group A, 12.9% Group B, and 44.2% Group C ($p < 0.0001$, A vs. B, A vs. C, $p = 0.003$ B vs. C)
- Angiodysplasia (29%) and Crohn's (6%) were the most common diagnoses, 2 tumors were identified (1 via capsule retention)

Outcome of Patients with Obscure GI Bleeding after Capsule Endoscopy: Report of 100 Suspected Cases

Pennazio M, Santucci R, Rondonotti E, *et al*, *Gastroenterology* 2004;126:643-653

- When patients with previous obscure-overt bleeding were stratified according to the time to last bleeding episode, the yield of CE decreased in parallel with the length of the time interval
- CE found a source of bleeding in 18 of 36 patients with a negative push enteroscopy
- Push enteroscopy identified lesions in 3 of 21 patients with a negative CE
- The CE diagnosis was verified in 56 patients, 36 of these had a positive diagnosis, 20 had a negative diagnosis

Outcome of Patients with Obscure GI Bleeding after Capsule Endoscopy: Report of 100 Suspected Cases

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- The CE diagnosis was verified in 56 patients, 36 of these had a positive diagnosis, 20 had a negative diagnosis

Sensitivity	88.9 %
Specificity	95.0 %
Positive predictive value	97.0 %
Negative predictive value	82.6 %

- The overall accuracy of CE was 91.1% (51 of 56)

Outcome of Patients with Obscure GI Bleeding after Capsule Endoscopy: Report of 100 Suspected Cases

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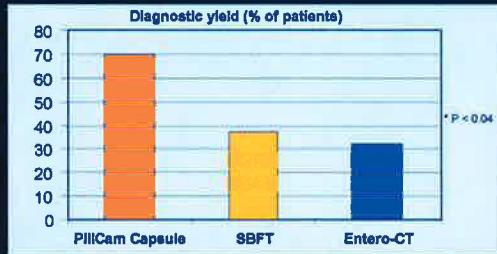
- Complete resolution of bleeding occurred significantly more often with ongoing obscure-overt bleeding and obscure occult bleeding than in patients with previous obscure-overt bleeding
- CE results lead to treatment resolving the bleeding in 86.9% of patients undergoing the procedure while actively bleeding
- In the 39 patients with obscure-occult bleeding, CE was positive in 16, suspicious in 9, and negative in 14 – complete resolution occurred in 69.2% (surgery 6, endoscopy 5, medical 18, none 10)

PillCam Endoscopy and Crohn's Disease

- 75% of patients with Crohn's disease have small bowel involvement, 33% have disease isolated to the small bowel
- Recent capsule data reveals that there is more extensive small bowel involvement in Crohn's disease than previously recognized
- A number of clinical studies have demonstrated that capsule endoscopy is more sensitive for small bowel ulcers than the best enteroclysis available
- Exhibits the potential to influence management in those with otherwise undetectable disease and known disease refractory to medical therapy

Rex et al. *Am J Gastroenterol* 2003;98:1295-1298

PillCam SB in the Detection of Crohn's Disease Comparison to SBFT/Entero CT in Suspected Cases



Eliakim *et al*, Eur J Gastroenterol Hepatol 2003;15:1-5

PillCam SB – Images of Crohn's Disease



PillCam SB Crohn's Video



Initial Experience with Wireless Capsule Endoscopy in Diagnosis and Management of Crohn's Disease (CD)

Mow WS, Lo SK, Targan SR, *et al*. *Gastroenterology* 2004;2:31-40

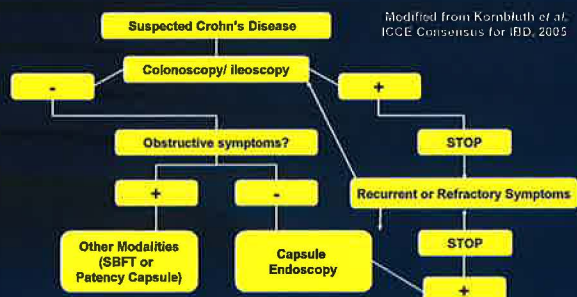
- Fifty patients with symptoms consistent with persistent, recurrent, or possible IBD underwent WCE.
- Indications included assessment of:
 - small bowel involvement in patients with isolated colitis (n = 22)
 - extent of small bowel disease in patients with CD (n = 20)
 - suspected IBD (n = 8)
- WCE findings were diagnostic in 20 (multiple ulcers), suspicious in 10 (≤ 3 ulcers)
- Seventeen of 20 with diagnostic and 7 of 10 with suspicious WCE findings clinically improved following alteration in medical therapy
- Identification of small bowel ulcers via WCE in 5 patients with isolated colitis resulted in a change in diagnosis to CD

Diagnosing Crohn's Disease: An Economic Analysis Comparing Wireless Capsule Endoscopy (WCE) with Traditional Diagnostic Procedures

Goldfarb NI, Pizzi LT, Fuhr JP, *et al*. *Dis Management* 2004;7:292

- A simple decision tree model compared 2 arms – colonoscopy and SBFT or WCE
- The published diagnostic yield was 53.87% for colon/SBFT, 69.59% for WCE
- Perforation rate with colonoscopy and capsule retention rate for WCE in Crohn's were both taken into account
- Patients were assumed to be previously undiagnosed, without strictures, and have disease detectable in the SB
- WCE was less costly than colon/SBFT as long as the diagnostic yield of WCE was 64.10% or better

Proposed Diagnostic Algorithm for Suspected Crohn's Disease



PillCam Endoscopy and Celiac Disease

- Celiac disease can almost always be diagnosed through serologic testing (tissue transglutaminase - tTG IgA or IgG) and biopsy of the proximal small intestine
- Since the distribution of celiac sprue can be patchy, a small subset of patients will harbor the disease without duodenal involvement
- Capsule endoscopy provides a visual alternative to EGD without the possibility for histologic confirmation
- It may also be useful in patients with symptoms refractory to a gluten free diet or worrisome for complications complications such as stricture and malignancy

PillCam SB – Images of Celiac Disease



Untreated Sprue

Refractory Sprue

Jejunal Lymphoma

PillCam SB Celiac Sprue Video



Video Capsule Endoscopy (VCE) for the Diagnosis of Celiac Disease (CD): Preliminary Results from a Multicenter International Study

Franchis R, Riccioni ME, Cave D, *et al*, 4th ICCE Abstracts 2005, 163

- Consecutive untreated patients with a positive serology for CD were eligible, regardless of the presence of symptoms
- EGD and VCE were performed within 10 days of each other in all cases, at least 4 duodenal biopsies taken during EGD
- Duodenal biopsies were classified according to Marsh's criteria
- Capsule studies were evaluated for scalloping, fissures, or flat mucosa by Gastroenterologists unaware of EGD and biopsy findings
- Duodenal biopsy was considered the gold standard

Video Capsule Endoscopy (VCE) for the Diagnosis of Celiac Disease (CD): Preliminary Results from a Multicenter International Study

Franchis R, Riccioni ME, Cave D, *et al*, 4th ICCE Abstracts 2005, 163

- Twenty five patients were enrolled at the time of this report
normal duodenal histology - 7
partial villous atrophy (Marsh Grade II) - 1
total villous atrophy (Marsh Grade III) - 17
- VCE was 94.4% sensitive, 85.7% specific, with a PPV of 94.4% and NPV 85.7%
- The only "false positive" had positive anti-endomysial antibodies, dermatitis herpetiformis, and patchy mucosal lesions on VCE (likely a false negative of histology)

Evaluation of Capsule Endoscopy in Celiac Disease Patients with Ongoing Symptoms on a Gluten-Free Diet – First Results of a Prospective Blinded European Multicenter Trial

Krauss N, Cellier C, Collin P, *et al*, 4th ICCE Abstracts 2005, 165

- Prospective, blinded multicenter trial with a second blinded reviewer
- Main group consisted of 43 patients with histologically proven proximal villous atrophy and/or positive anti-tTG antibodies and complaints despite more than 1 year of a strictly gluten free diet
- Control groups included 16 with recently diagnosed CD (serology and histology) not yet on gluten-free diet or established CD at least 5 years off of a gluten-free diet

Evaluation of Capsule Endoscopy in Celiac Disease Patients with Ongoing Symptoms on a Gluten-Free Diet – First Results of a Prospective Blinded European Multicenter Trial

Kräuss N, Callier C, Collin P, et al. 4th ICCE Abstracts 2005, 165

- All controls showed changes typical of villous atrophy
- In 32 of 43 patients with persisting symptoms despite gluten-free diet, CE revealed either proximal (41) or diffuse (2) changes of villous atrophy in the small intestine
- One did not reach the duodenum, 1 yielded an insufficient view, and in 9 no atrophy was seen
- In 2 patients refractory to gluten-free diet benign-appearing luminal stenosis was seen, in 2 others gastrointestinal tumors were identified

PillCam Endoscopy and Small Bowel Tumors

- In one series of 562 patients undergoing CE for a variety of reasons, Cobrin and colleagues reported that 8.9% were found to have a small bowel tumor – 53% were malignant
- In another series of 416 patients undergoing CE, Bailey and colleagues diagnosed 6.49% with small bowel tumors – 66% were found to be malignant
- In yet another series of 257 patients, Keuchel and colleagues reported that 6.2% were found to have a small bowel tumor by CE – 50% were malignant

Cobrin et al. Gastroenterology 2004;126(suppl 2):AB1022
Bailey et al. J Gastroenterol Hepatol 2004;19(suppl 77)
Keuchel et al. Gastroenterology 2004;126(suppl 2):AB1095

PillCam SB – Images of Small Bowel Tumors



Polyp

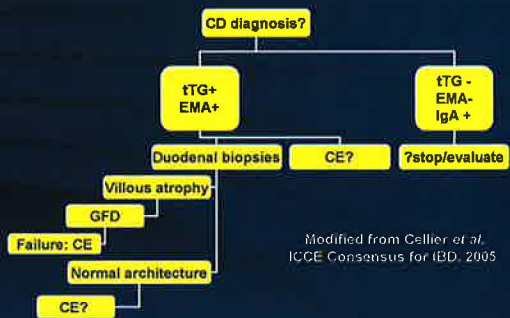
Carcinoid

Adenocarcinoma

PillCam SB Carcinoid Tumor Video



Proposed Diagnostic Algorithm for Suspected Celiac Disease



Proposed Diagnostic Algorithm for Complicated Celiac Disease



PillCam SB Conclusions

- PillCam SB is appropriate in patients with:
 - recent or ongoing overt or occult GI bleeding of unclear etiology
 - suspected Crohn's disease with negative ileocolonoscopy
 - established Crohn's disease refractory to medical therapy with negative ileocolonoscopy
 - suspected celiac disease with negative proximal duodenal biopsies
 - celiac disease refractory to gluten-free diet or with symptoms concerning for malignancy
 - suspected small bowel tumor(s) not within the reach of endoscopes requiring further preoperative evaluation
 - chronic diarrhea of unclear etiology after appropriate evaluation

PillCam SB Future Directions

- Gastric and colonic imaging studies are in development - limiting factors will include the inability to insufflate and cleanse these lumens
- The ability to direct these capsules and attain biopsies sounds intriguing but is impractical due to the time constraints involved
- The greatest current need is for a PillCam SB with dual video imaging capabilities - the rate limiting factor is battery technology

PillCam SB Reimbursement Developments in the US

- Assignment of a permanent CPT code by the AMA
- BC/BS Tech Assessment finds PillCam SB suitable for initial diagnosis of Crohn's disease
- Adopted by BC/BS carriers with 20 million covered lives in total



Includes suspected Crohn's disease and additional suspected small bowel pathologies

PillCam SB and ESO Contraindications

- In patients with known or suspected gastrointestinal obstruction, strictures, or fistulas based on the clinical picture or pre-procedure testing and profile
- In patients with cardiac pacemakers or other implanted electromedical devices
- In patients with swallowing disorders

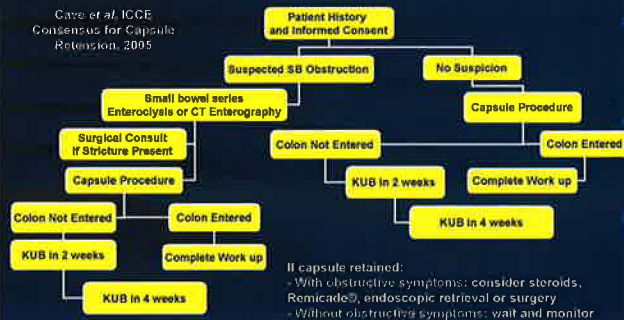
PillCam SB Capsule Retention

- Occurred in:
 - 0% of asymptomatic normal individuals
 - 1.4% of patients with obscure GI bleeding
 - 1.4% of those with suspected Crohn's disease
 - 5% in established Crohn's disease
 - 21% of patients with suspected small bowel obstruction
- Best means of reducing this risk is a good history
- SBFT of no predictive value (14/19 in literature had negative SBFT)
- Fortunately, due to their design, retained capsules rarely cause symptomatic obstruction or perforation

Cave et al. Endosc 2005;37:1-3

Proposed Algorithm for Management of Capsule Retention

Cave et al. ICCE
Consensus for Capsule
Retention, 2005



Given® Patency System

Given® Patency Capsule



26 mm long X 11 mm diameter
(same dimensions as
PillCam™ SB)

Given® Patency Scanner



A dissolvable capsule containing a detectable Radio Frequency Identification (RFID) tag and is propelled through the GI tract by natural peristalsis

Given® Patency Capsule



Parylene coating

Exposed window

Timer plug

Lactose body w/ barium



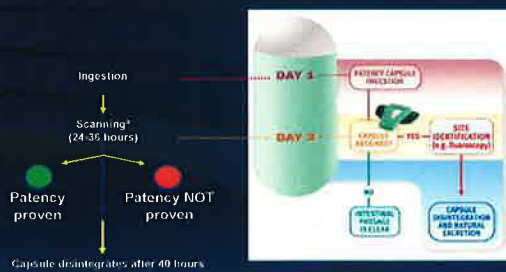
RFID tag



12mm

Given® Patency Procedure

- Capsule disintegrates after 40 hours
- Capsule excreted intact in >80% of patients in less than 40 hours

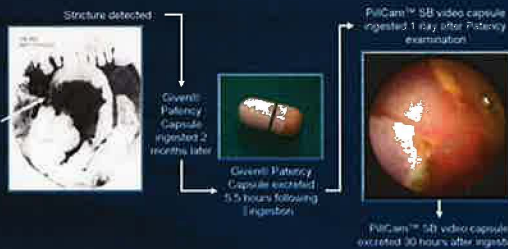


Possible Indications for a Given® Patency Study

- To assess suspicion or clinical significance of strictures from
 - chronic NSAID use
 - Crohn's disease
 - radiation enteritis
 - tumor
- To identify strictures not seen radiographically
- Management of post-operative obstructive symptoms
 - assessment of anastomosis
 - adhesion-related disease

Cave et al, Endosc 2005;37:1-3

Given® Patency Capsule Indicates Patency, PillCam SB Passes Naturally



PillCam SB video capsules excreted naturally following intact excretion of Given® Patency Capsule (17/17 w/SBFT based strictures, all sites)

Cave et al, Endosc 2005;37:1-3

Given® Patency Capsule System Conclusions

- Patency capsule appears to be a practical test to assess suspicion of strictures
- May provide direct indication of functional patency, even in cases where radiology indicates physiological stricture – clinical significance unclear
- After Given® Patency Capsule is excreted intact, ingestion of PillCam SB video capsule may follow

Patency Capsule System Conclusions

- Patency capsule may be of use in patients with:
 - suspicion of small bowel stricture despite other negative imaging studies
 - question of functional stricture patency
 - a known stricture where a PillCam SB study has been deemed necessary prior to medical or surgical intervention

The clinical relevance of this system in any of these settings has yet to be demonstrated

Electromagnetic Interference with Implantable Cardiac Pacemakers by Video Capsule

Dubner S, Dubner Y, Gallino S, *et al*, *Gastrointest Endosc* 2005;61:250

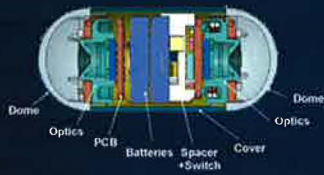
- Electromagnetic fields may interfere with normal pacemaker function
- It was unknown whether the PillCam would interact with implanted pacemakers
- 100 consecutive patients with a pacemaker (70 dual chamber and 30 ventricular inhibited) were exposed to an external device that exactly reproduced PillCam characteristics

Electromagnetic Interference with Implantable Cardiac Pacemakers by Video Capsule

Dubner S, Dubner Y, Gallino S, *et al*, *Gastrointest Endosc* 2005;61:250

- In 4 of 100 patients pacemaker interference (noise-mode function forcing a synchronous mode) was registered during the test – 3 dual and 1 single chamber – reproducible
- None of the pacemakers tested were affected by oversensing
- The authors concluded that electromagnetic interferences with pacemakers from the PillCam SB can occur, but is of no clinical significance
- There have been no reported adverse events in patients with implanted pacemakers or AICDs undergoing PillCam SB or ESO video endoscopy

PillCam™ ESO Capsule Components



Dimensions:
Height: 11 mm
Width: 26 mm
Weight: 3.7 gr

PillCam ESO Examination Set



1. PillCam™ ESO Capsule
2. SensorArray™ ESO
3. Given® DataRecorder™ 2

PillCam ESO Test Protocol

- Fast at least 2 hours
- Drink 100 mL of water
- Ingest the capsule in supine position
- Incline body gradually up to sitting position: 5-minute procedure
- Take a sip of water
- Wait 15 more minutes in waiting room



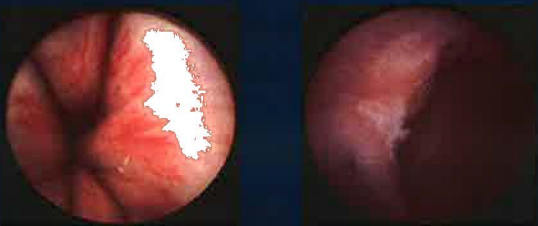
RAPID® 3 Software Platform Esophageal Imaging



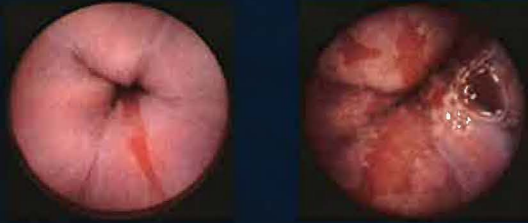
PillCam ESO Normal Z-line



PillCam ESO Esophageal Inflammation



PillCam ESO Suspected Barrett's



A Prospective Study of the Diagnostic Accuracy of PillCam ESO Video Capsule versus Conventional Upper Endoscopy in Patients with Chronic GERD

Eliakim R, Sharma VK, Yassin K, *et al*, J Clin Gastroenterol 2005 (In Press)

- Barrett's esophagus carries a risk of 0.5% per patient-year of esophageal adenocarcinoma
- ACG Guideline Recommendations
"Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy"
- 106 patients (93 GERD; 13 Barrett's) underwent ECE followed by EGD with biopsy when appropriate (gold standard)
- ECE was evaluated by a reader blinded to EGD findings

A Prospective Study of the Diagnostic Accuracy of PillCam ESO Video Capsule versus Conventional Upper Endoscopy in Patients with Chronic GERD

Eliakim R, Sharma VK, Yassin K, *et al*, J Clin Gastroenterol 2005 (In Press)

- 66 of 106 patients had positive esophageal findings
- With regard to Barrett's esophagus, ECE exhibited 97% sensitivity, 99% specificity, 97% PPV, 99% NPV
- With regard to esophagitis, ECE demonstrated 89% sensitivity, 99% specificity, 97% PPV, 94% NPV
- ECE was preferred over EGD by all patients
- There were no adverse events from ECE

PillCam ESO Esophageal Varices



Evaluation of Esophageal Varices by PillCam™ ESO as Compared to Upper Endoscopy

Eisen G, de Franchis R, Eliakim R. 4th ICCE Abstracts 2005, 199

- EGD has traditionally been used to screen for varices in patients with suspected or established portal hypertension
- The same modality has been used in the surveillance of patients who have undergone variceal obliteration
- 27 patients being screened for varices or enrolled in surveillance programs underwent both EGD and ECE
 - 22/27 had esophageal varices on EGD
 - all 22 cases were also identified by blinded ECE
 - 100% PPV and NPV
 - grading of varices was performed on 18/22 cases, complete agreement in 11/17, agreement within 1 grade in 17/18

PillCam ESO Summary

- Should be considered as an alternative to EGD in patients with:
 - GERD of at least 5 years duration
 - suspected or established portal hypertension in an attempt to identify and grade esophageal varices
- Capable of detecting other esophageal, gastric, and duodenal pathology
- Contraindications similar to those for PillCam SB
- Currently being approved by insurance companies and reimbursed on a case by case basis
- Cost effectiveness yet to be established
