Practical Applications of Advanced Endoscopic Imaging Techniques

Julia J. Liu, MD, MSc

CIHR New Investigator
Center of Excellence for Gastrointestinal Immunity and Infection Research (CEGIIR)
University of Alberta

Objectives

• To understand the principles & performance of advanced endoscopic imaging modalities
• To familiarize with the impact on clinical practice of new imaging methods
• To know the limitations of new endoscopic imaging techniques
• To determine which modalities may be useful
Goals of New Imaging Methods

- Increase resolution to microscopy
- Scan GI tract in real-time
- Sensitive: detect early changes
- Discriminate: dysplasia/cancer from inflammation
- Localize: dysplastic area → biopsy
- Interpretable: good inter-observer variability
- Acceptable cost and time

New Imaging Methods

- High definition and magnification endoscopy
- Chromoendoscopy
- Narrow band imaging & light filters
- Autofluorescence imaging
- Confocal laser endomicroscopy
- Optical coherence tomography (OCT)
Methods under Development

- Endocytoscopy
- Reflectance spectroscopy
- Fluorescence and Raman spectroscopy
- Multimodal spectroscopy
- Multiphoton microscopy

High Definition Endoscopy
Lesion: Adenoma of the Cardia

Standard Definition

High Definition

High Definition = High Yield

Methods:
- Healthy patients undergoing screening colonoscopy randomized to high definition colonoscopy +/- narrow band imaging (NBI)

Results:
- In 434 patients > 50 yrs, prevalence of adenoma is 58%
- NBI not superior to high definition in detecting adenomas

Rex et al. Gastroenterology 2007;133:42
Magnification Endoscopy

- Enlarge image from 1.5X to 150X
- Increased pixel density
  - Conventional endoscopy 100,000 to 200,000
  - Magnification endoscopes up to 850,000
  - Discriminates objects 10 to 71 microns
- Used alone or with filters (NBI) or stains
- Included as part of many studies
- Endoscope tip kept very close to lesion

Chromoendoscopy

- Topical application of stains or dyes to improve tissue
  - Characterization
  - Differentiation
  - Localization
- Improves detection and diagnosis when properly utilized and interpreted
Chromoendoscopy Applications

- Barrett’s esophagus
- Squamous esophageal cancer
- Gastric metaplasia and cancer
- Colon polyps
- Ulcerative colitis
Classification of Stains

- **Vital/absorptive**
  - Lugol’s solution
  - Methylene blue
- **Contrast**
  - Indigo carmine
- **Contrast enhancement**
  - Acetic acid

Accessories for Staining

- Spray Catheters
- EMR caps
Lugol’s Iodine Solution

- Lugol’s solution 5% iodine + potassium iodide
- **Technique:** Dilute to 2% (8 mL Lugol’s and 12 mL water) and apply with spray catheter
- **Mechanism:** Absorptive dye binds to normal squamous epithelium (glycogen containing)
- **Indication:** To diagnose and delineate esophageal squamous neoplasms
- ** Interpretation:** Dysplastic cells do not uptake the dark brown stain.

Squamous Cell Esophageal Cancer with Lugol’s

Katada et al. Gastrointest Endosc 2005;61:219
Lugol’s Solution Limitations

- Irritant that damages normal epithelium
- Rare abdominal pain, nausea, heartburn and bronchospasm
- Allergic reactions (to iodine)
- Thiosulfate solution 5% spray may reduce adverse events
- Examination interval of minimum 3-4 weeks

Methylene Blue

- **Methylene blue technique**
  - **For esophagus**, 0.5% instill for 1-2 minutes, then excess dye removed and washed with water
  - **For colon**, 0.1% instill for 1 minute in segments, then excess dye removed and washed with water
- **Mechanism**: Intestinal epithelium actively absorbs stain
- **Indication**: To diagnose and delineate Barrett’s and to detect dysplasia in ulcerative colitis
- **Interpretation**: Dysplastic cells do not uptake the blue stain
Methylene Blue Stain of Barrett’s with Intramucosal Carcinoma

Canto et al. Gastrointest Endosc 2000;51:560

Kudo Classification for Pit-Pattern

Kudo et al. Gastrointest Endosc 1996;44:8
Indigo Carmine

- Indigo carmine is a blue contrast dye
- **Technique:** Dilute to 0.2% (5 mL 0.8% Indigo carmine and 15 mL water) and apply with spray catheter or a syringe in accessory channel
- **Mechanism:** Enhances surface topography as dye pools in mucosal crevices
- **Indication:** To diagnose and delineate non-polypoid gastric and colonic neoplasms
- **Interpretation:** Mucosal pit pattern identification
- **Rare Adverse events:** Hypertension, bradycardia

Indigo Carmine and Colon Polyps

A: Hyperplastic
B: Adenomatous
Acetic Acid

- Acetic acid absorptive and mucolytic
- Not a coloring agent
- **Technique**: Spray 1.5% to 3% acetic acid then wash
- **Mechanism**: Alters tertiary protein structure which increases opacity of columnar epithelium
- **Indication**: To diagnose intestinal metaplasia
- **Interpretation**: Increased contrast of columnar epithelium

Magnification: Acetic Acid

Hyperplastic

Kiesslich et al. Eur J Gastroenterol 2005
Magnification: Acetic Acid

Adenoma

Kiesslich et al. Eur J Gastroenterol 2005

Effects of Chromoendoscopy

Prevalence of flat adenomas: without Chromoendoscopy 1-5%
with Chromoendoscopy 20-35%
Chromoendoscopy in UC

Increase of diagnostic yield (chromo versus white light):

- 3-fold  Kiesslich et al. Gastroenterology 2003
- 4-fold  Hurlstone et al. Gastroenterology 2004
- 4.5-fold Rutter et al. Gut 2004
- 3-fold  Hurlstone et al. Endoscopy 2005
- 4-fold  Kiesslich et al. Gastroenterology 2007

Total number of patients = 1442

Consensus Conference: Colorectal Cancer Screening and Surveillance in Inflammatory Bowel Disease

Steven H. Izakowitz, MD, and Daniel H. Present, MD, for the Crohn's and Colitis Foundation of America Colon Cancer in IBD Study Group

- “Chromoendoscopy can greatly enhance the detection of dysplastic lesions in colitic colons”
- The Committee endorses the incorporation of chromoendoscopy into surveillance colonoscopy for appropriately trained endoscopists

Inflamm Bowel Dis 2005;11:314
Chromoendoscopy in Ulcerative Colitis

Kiesslich et al. Gastroenterology 2003

Dysplasia in Ulcerative Colitis

Photo courtesy of Dr. Jerome Waye
Summary: Chromoendoscopy

- Several techniques have proven value, but methods not standardized
- Combine with magnification/high definition
- Overall safe, but rare adverse events
- Learning curve to properly perform
- Longer procedure times
- Cost effectiveness not proven

Electronic Chromoendoscopy

- Chromoendoscopy without dye
  - Narrow Banding Imaging (NBI) Olympus
  - Fuji Intelligent Color Enhancement (FICE) Fujinon
  - I-Scan Pentax
Narrow Band Imaging (NBI)

- High intensity blue light with narrow band filters
- Emphasizes mucosal details like chromoendoscopy
- Images capillary pattern
- Combined with high magnification
NBI: advantage

- NBI highlights superficial vascular patterns akin to chromo-endoscopy
  - Cleaner and simpler
  - Contrast image does not dissipate
  - Instant on/off
  - Entire mucosal view
- Very high resolution images with Hi-Def
- 1.5 x magnification

NBI - The Basics

- White light penetrates shallow and deeper mucosal layers and has a certain degree of scatter
- Hemoglobin absorbed at 415 nm & 540 nm wavelengths
- NBI filters light to these 2 specific bands to enhance superficial vessels where hemoglobin absorbs the light
- Superficial structures are highlighted because blue light has a shorter wavelength and shallower penetration (red light has deeper penetration)
- Digital processing to “color” the image obtained from each wavelength:
  - 415 nm: BROWN
  - 540 nm: CYAN
Configuration of 2-band NBI

NBI - Increased Vascular Pattern

Increased visibility of vascular pattern is one of the most notable NBI features
Increased Vascular Pattern and Mucosal Detail

Glandular mucosa with regular vascular and pit pattern by NBI

Applications of NBI

Analysis of distinct types of epithelium in which distinctive vascular patterns are present
- Barrett’s esophagus and dysplasia
- Dysplasia in ulcerative colitis
- Inflammation
- Atrophy
- Superficial neoplastic lesions
Barrett’s and NBI

- 51 pts with Barrett’s: 8 LGD and 7 HGD

BE

Ridge/villous

Circular

Regular vascular

HGD

Distorted

Irregular corkscrew

Sharma et al. Gastrointest Endosc 2006;64:167

Results

- Sensitivity, specificity and PPV of ridge/villous pattern for IM without HGD = 94%, 87% and 95%
- Sensitivity, specificity and PPV of irregular or distorted pattern for HGD = 100%, 99% and 95%
- NBI unable to identify LGD reliably

Sharma et al. Gastrointest Endosc 2006;64:167
NBI Patterns in Barrett's and HGD

Barrett's without dysplasia
- Regular villous/gyrus patterns
- Flat w/ long vessels

Barrett's with high grade dysplasia
- Irregular disrupted patterns
- Irregular or abnormal vessels

Detection of Dysplasia in Barrett’s

- 63 Barrett’s pts- blinded evaluation of learning (52 sites) and validation sets (123 areas) of histology from magnified NBI images
- 37 pts with prior diagnosis of HGD
- Features of BE
  - 80% had regular villous/gyrus patterns & regular vascular patterns
  - 20% had flat mucosa with regular normal appearing long branching vessels
- Features of dysplasia in NBI
  - Irregular/disrupted mucosal patterns
  - Irregular vascular patterns
  - Abnormal blood vessels
  - 85% had > 1 feature
  - Magnification plus NBI required

Magnification/NBI: sensitivity of 94% and NPV of 98% for HGD

Kara M et al. Gastrointest Endosc 2006;64:155
NBI of Colon

- Surveillance in IBD—potential role in detecting dysplasia and flat neoplastic lesions in inflamed mucosa
- Differentiate neoplastic from non-neoplastic colon polyps
- Define boundaries of neoplastic lesions seen on conventional imaging
- Improved visibility of flat lesions—need excellent prep

Flat Colon Polyp

White light  NBI
NBI vs. Chromo vs. Conventional Colonoscopy for Colon Polyps

- 78 patients with 110 colon polyps
  - 65 adenomas (32 tubular, 13 tub/vill & 20 villous)
  - 40 hyperplastic
  - 5 adenocarcinoma
- Conventional colonoscopy, then NBI followed by indigo carmine (0.2%)
- Histologic confirmation of all polyps

Su MY et al. Am J Gastroenterol 2006;101:2711

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### Diagnosis of Neoplastic vs. Non-Neoplastic Polyps

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
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<tbody>
<tr>
<td>Conventional Colonoscopy</td>
<td>83</td>
<td>80</td>
<td>82</td>
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<tr>
<td>NBI</td>
<td>96</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>Chromo-endoscopy</td>
<td>96</td>
<td>88</td>
<td>93</td>
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<tr>
<td>P value</td>
<td>0.014</td>
<td>0.363</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Su MY et al. Am J Gastroenterol 2006;101:2711
Fujinon Intelligent Color Enhancement (FICE)

- Spectral estimation technology
- 10 preset spectral frequency combinations
- Ability to customize a combination of any 3 spectral frequencies (red, green & blue)
- Enhance surface and vascular details
- No prospective studies to date

FICE of Barrett’s Esophagus
FICE of Esophageal Cancer

Pentax I-Scan Filter

- Surface enhancement technology
- Computer processing to enhance tissue contrast
- Limited studies to date
I-Scan Filter

Summary: NBI and Filters

- Available in many centers
- Benefits: detection of Barrett’s, small flat lesions in upper and lower GI tract
- Not shown to be superior than magnification + white light
- Further research to define role is needed
AutoFluorescence Imaging (AFI)

- Autofluorescence (AF) occurs when a small proportion of excitation light causes a light-tissue interaction resulting in a change in its wavelength
- Chromophores: absorb photons without emission of fluorescence (hemoglobin)
- Fluorophores: biochemical substances that emit fluorescent light (long wavelength) when exposed to short-wavelength light (ultraviolet or blue light)
  - collagen, NADH, aromatic amino acids, porphyrins
- Dysplastic tissue is biochemically different as tissues differ in concentration and distribution of chromophores and fluorophores

AutoFluorescence Endoscopy
AFI and Endoscopy

• Light-Induced Fluorescence Spectroscopy
  – Small probe through scope channel
    • Central delivery fiber connected to light source (laser)
    • Multiple surrounding fluorescent detector fibers
  – Limitation in that samples very small area

• Autofluorescence Endoscopy
  – Real time wide angle view switches between white light and AF endoscopy
    • Life-II system by Xillix Technologies Corp.
    • AFI by Olympus Corp. and Storz Ltd

Barrett’s and AFI

EGD vs. AFI in 60 patients with Barrett’s
21 pts with endoscopically detectable HGD/Ca
—6 detectable only with AFI

Kara et al. GIE 2005;61:679
Barrett’s Dysplasia Detection by AFI followed by NBI

- 20 pts with Barrett’s & known/suspected HGD
- 47 suspicious lesions detected with AFI (28 HGD, 19 false positive)
  - 28 true positives: 25 were definitely suspicious and 3 were not suspicious on NBI
  - 19 false positives: 14 were not suspicious on NBI
- Combination of AFI followed by NBI increased accuracy for detection of HGD in Barrett’s

Kara et al. Gastrointest Endosc 2006;64:176

AFI – NBI in High Grade Dysplasia
False Positive AFI, Normal NBI

AFI in 2012

- Promising approach to improve Barrett’s esophagus surveillance
- AFI draws attention to high yield areas for targeted biopsies
- Still need to do 4 quadrant biopsies
- Other applications need to be evaluated
Confocal Microscopy

Confocal Endomicroscope
**Fiber Optic Confocal System**

- **Detector**
- **Scan mechanism**
- **Laser**
- **Ex** = 488nm
- **Em** = 505-585nm or LP505
- **Objective lens**
- **Optical fibre**
- **Tissue**
- **Imaging plane**

**Endomicroscopy**

- **Field of view:** 500x500µm
- **Lateral resolution:** <1µm
Optical Sectioning in Live Human Mucosa

Dysplasia
Dysplasia in Ulcerative Colitis

Hyperplastic Polyp With Stellate-Shaped Crypt Openings
Hyperplastic Polyp

Tubular Adenoma
Tubulovillous Adenoma with Focal Adenocarcinoma
Correlation Between eCLE Imaging and Histology

<table>
<thead>
<tr>
<th>Confocal Diagnosis</th>
<th>Sites</th>
<th>Normal</th>
<th>Hyperplasia</th>
<th>Inflam</th>
<th>Intraepithelial Neoplasia</th>
<th>Cancer</th>
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<tr>
<td>Normal tissue</td>
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<td>255</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Regeneration</td>
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<td>5</td>
<td>78</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>39</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>35</td>
<td>3</td>
</tr>
</tbody>
</table>

Kiesslich R et al. Gastroenterology 2004
Accuracy of eCLE for Colorectal Neoplasia

- Neoplastic changes (intraepithelial neoplasia) could be predicted with confocal endoscope with:
  - Sensitivity of 97.4%
  - Specificity of 99.4%
  - Accuracy of 99.2%

Kiesslich R et al. Gastroenterology 2004

Confocal Endomicroscopy as a Novel Method to Diagnose Colitis associated Neoplasias

- 161 patients with long-term UC in clinical remission (8 pts excluded)
- Randomised in a 1:1 ratio
  A: Conventional endoscopy with random biopsy
  B: Panchromoendoscopy and Endomicroscopy with targeted biopsy

- Results
  A: 73 patients; 4 Neoplastic lesions
  B: 80 patients; 19 Neoplastic lesions

Sensitivity: 94.7%; Specificity: 98.3%; Accuracy: 97.8%

Kiesslich et al. Gastroenterology 2007;132:874
pCLE Histopathology Results

- 119 polyps from 75 patients
  - Hyperplastic 38
  - Neoplastic 81
    - Tubular 62
    - Tubulovillous 13
    - Villous 2
    - Cancer 4
- Polyp size (median) 10 mm [2-60]

Results: pCLE Accuracy

- Compared to gold standard histology:
  - Sensitivity 91% (83-96%)
  - Specificity 76% (60-89%)
  - PPV 89% (80-95%)
  - NPV 81% (64-92%)
Confocal imaging of Small intestine

- Intestinal epithelial cells (IECs) normal physiologic renewal, entire mucosal surface turned over in 3-4 days
- epithelial gaps: residual spaces left in the epithelium after extrusion of IECs, can be visualized using confocal endomicroscopy
Epithelial Cell Shedding

Epithelial Gaps in Small Bowel

Normal epithelial gaps

Abnormal gaps
Confocal in irritable bowel syndrome

Kao D et al, ACG 2012

• Promising technique for better detection of dysplasia in Barrett’s esophagus and IBD surveillance
• New findings in irritable bowel syndrome patients
• Limitations
  – Endoscopist have to become pathologists
  – Time consuming
• Need more prospective blinded studies
NvisionVLE™ Imaging System

Imaging Equipment

Single-Use Optical Probe

Normal Squamous Mucosa

SQUAMOUS EPITHELIUM
LAMINA PROPRIA
MUSCULARIS MUCOSA
SUBMUCOSA
MUSCULARIS PROPRIA
Clinical Impact of New Imaging Methods

- To reduce the need for biopsies: hyperplastic polyps, celiac disease
- To allow for smarter/fewer targeted biopsies in Barrett’s and ulcerative colitis surveillance
- To make small or flat lesions easier to detect
- To facilitate polypectomy & EMR due to sharper demarcation of lesion borders

Fundamentals to new imaging techniques

- Practicality?
  - cost, time, learning curve, inter-observer agreement
- Effectiveness?
- Advantage over available modalities?
- Benefit to patients, i.e. improve outcomes?
The Future