Novel Optical Research at UPMC

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Background

- Patients with UC and CD of the colon are at an increased risk for the development of colorectal dysplasia and cancer

- Although IBD is relatively rare, it is 1 of the 3 high-risk conditions predisposing to CRC

- In patients with long standing disease (>30 yrs), the risk of developing CRC is approximately 1 in 5

Kornbluth A, et al. Am J Gastroenterology. 2010;105:500-523.
Eaden JA, et al. Gut 2001; 48:526-535.

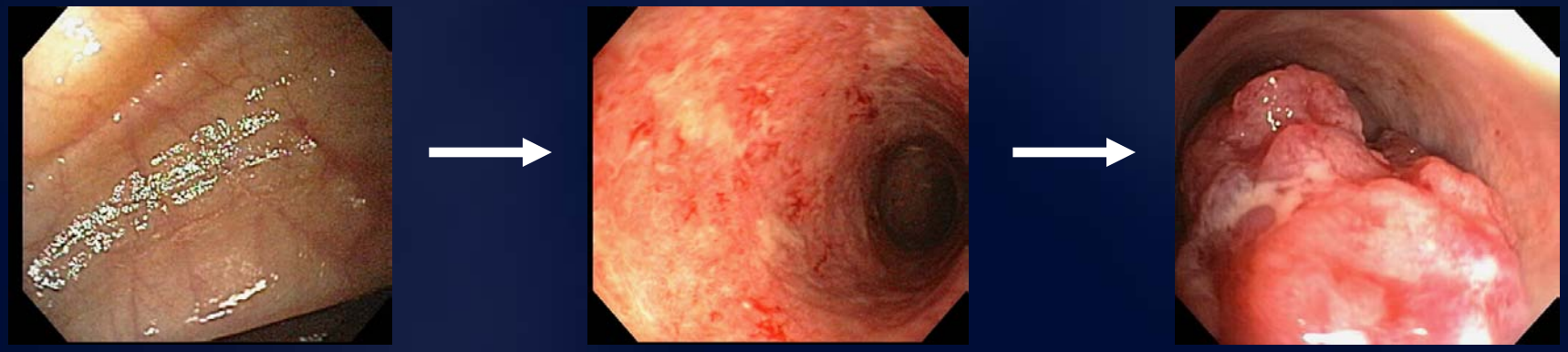
PSC-related research projects

- Stratify the small number of UC patients at high risk for colonic dysplasia and colorectal cancer in whom intensive surveillance is warranted from the majority of UC patients in whom frequent surveillance colonoscopies are not required

- Improve the diagnostic accuracy of cholangiocarcinoma on bile duct biopsies

Natural History of Dysplasia

- CRC can develop in patients without dysplasia
- Dysplasia is present in 75% to 90% of patients with CRC
- In most cases:
  - CRC develops in an inflammation → low grade dysplasia → high grade dysplasia → carcinoma



Current Surveillance Guidelines

- All patients should undergo a screening colonoscopy 8 years after onset of symptoms

- Four quadrant biopsies every 10 cm
  - at least 33 biopsies (in pancolitis)
  - more extensive sampling in the left colon esp rectum
  - focus on masses, nodules, polyps, strictures

- Chromoendoscopy by experts for targeted biopsies
  - No need for the numerous random biopsies

Current surveillance guidelines

- Concomitant PSC
  - Start surveillance at time of diagnosis and then yearly
- Optimal surveillance interval has not been defined
  - Extensive colitis or Lt sided colitis should → Q1-2 years
  - After 2 negative exams → Q1-3 years
- Ideally, plan surveillance colonoscopy when disease is in remission

Limitations to Current Surveillance Guidelines

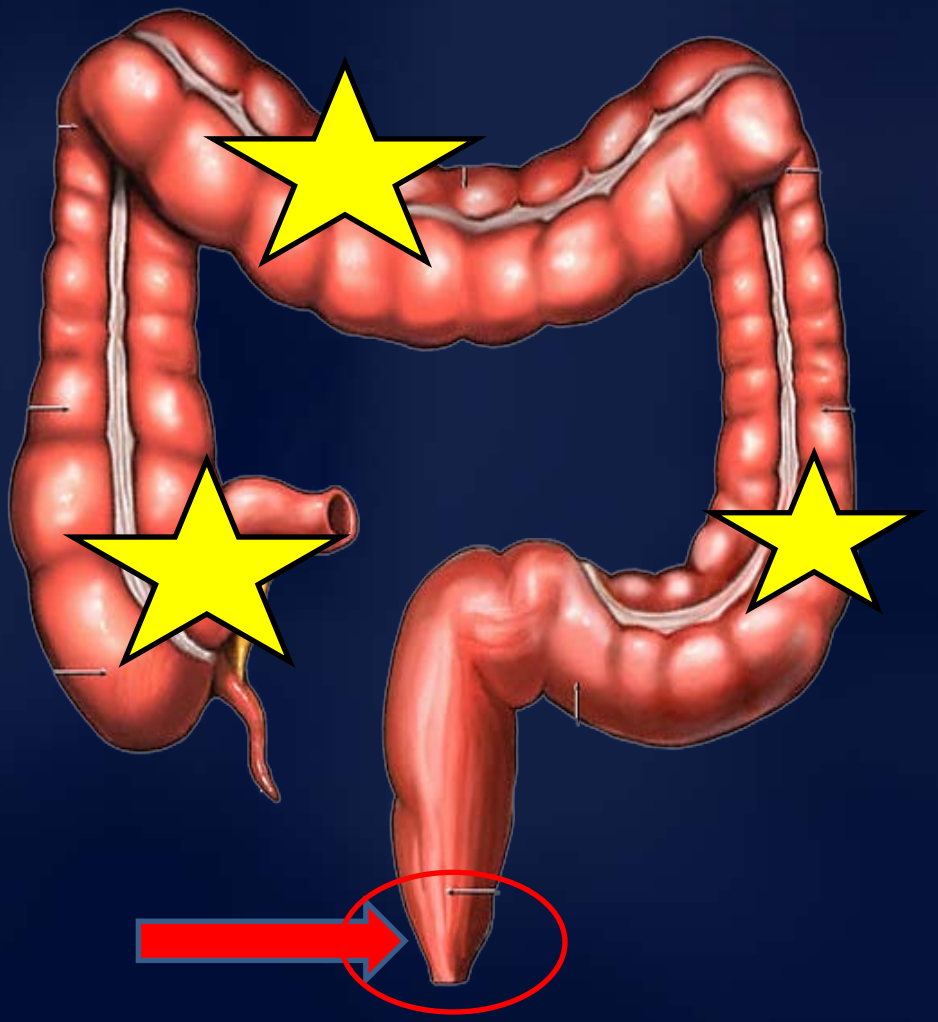
- Colonoscopy: invasive and expensive test with risk
- Only detects neoplastic processes that are morphologically obvious
- Yield of random biopsies is variable, the majority of which are negative for dysplasia

Our Goal

- Early detection of dysplasia to prevent progression to neoplasia or CRC
  - Surveillance
  - Cost effectiveness
  - Patient acceptance for better compliance

Field Effect

- The genetic or environmental milieu that results in a neoplastic lesion may be detected by remote sampling
- A similar technology has been applied in colon cancer screening (not IBD patients)

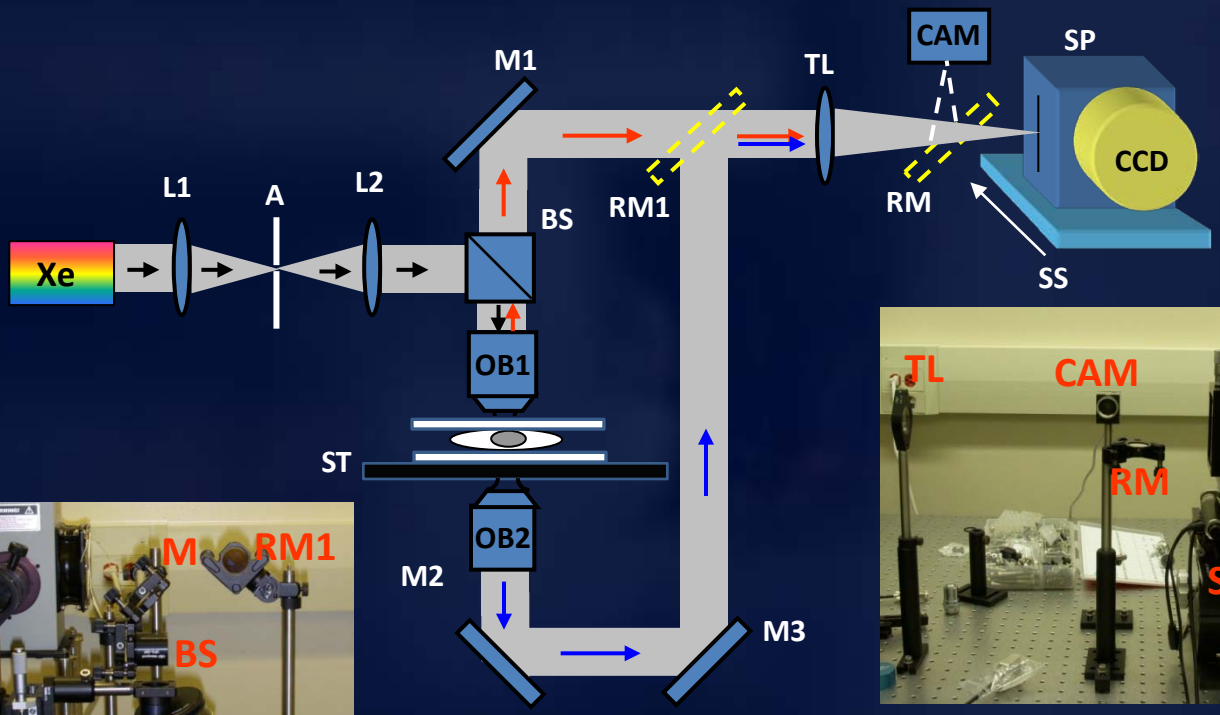


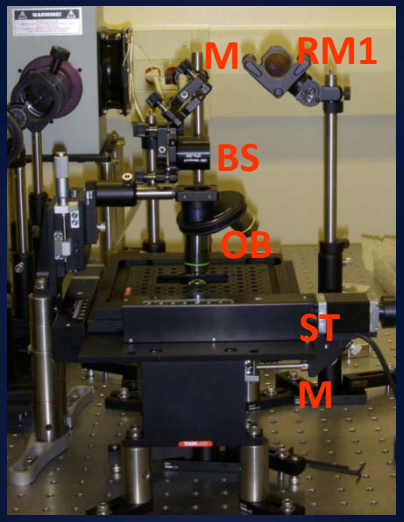
Spatial-domain Low-coherence Quantitative Phase Microscopy (SL-QPM)

Yang Liu, PhD

Kevin Staton, BS; Shikhar Uttam, PhD;
Rajan Bista, PhD

Spatial-domain Low-coherence Quantitative Phase Microscopy (SL-QPM)

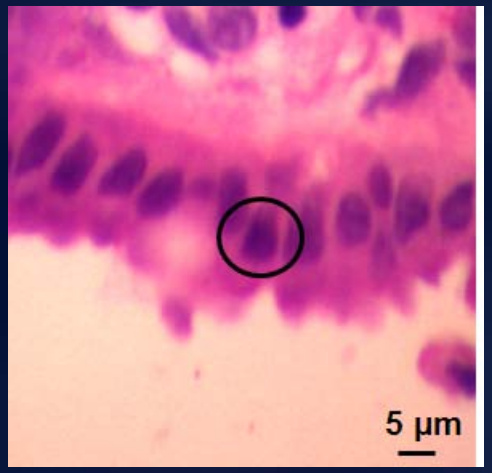


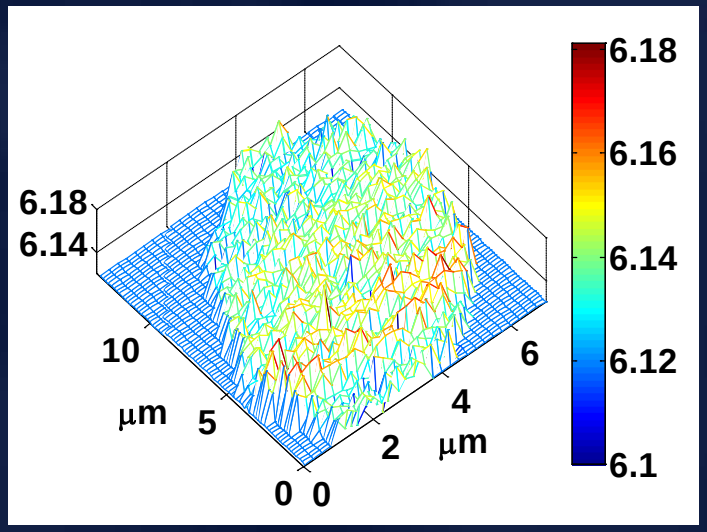


Wang P et al, Optics Letters, 35, 2840 (2010); Wang P et al, J Biomed Opt, 15, 066028 (2010) .

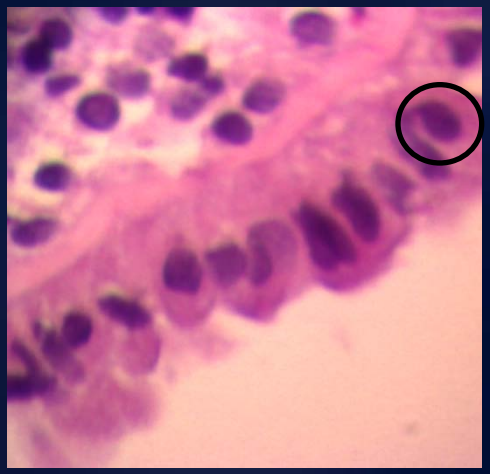
Optical Path Length (OPL) Map

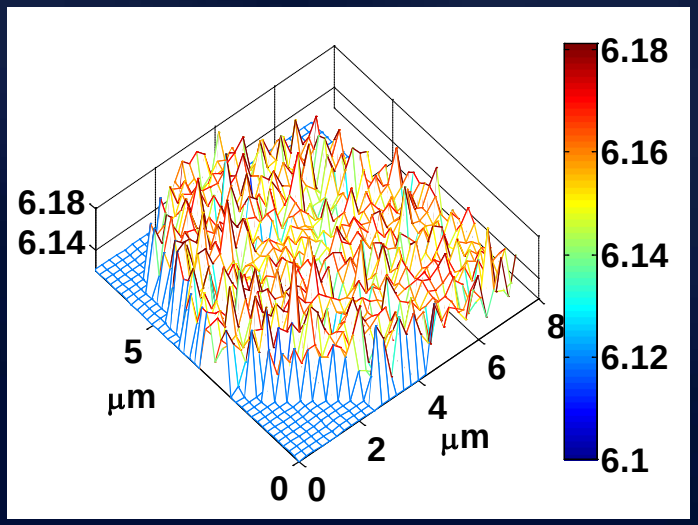
Low-risk





High-risk





Rectal Tissue Spectral Markers Predict the Presence of Dysplasia in Ulcerative Colitis

Jana Al Hashash, MD

Aim

- To determine if rectal biopsies from normal-appearing mucosa, analyzed by spectral biomarkers predict dysplasia or cancer in UC patients undergoing surveillance

Methods

- Prospective study of UC patients undergoing surveillance colonoscopy
- Two additional rectal biopsies were taken for spectral marker analysis
- Fresh tissue biopsies in PBS buffer delivered to lab for optical analysis within 4 hours of being obtained
- This interim report from **65** UC patients

Results – Nano-morphology Markers

LOW-risk patients	50
HIGH-risk patients	15
-- Colon cancer	0
-- High grade dysplasia	1
-- Low grade dysplasia	4
-- Indefinite for dysplasia	2
-- Sporadic tubular adenoma	8

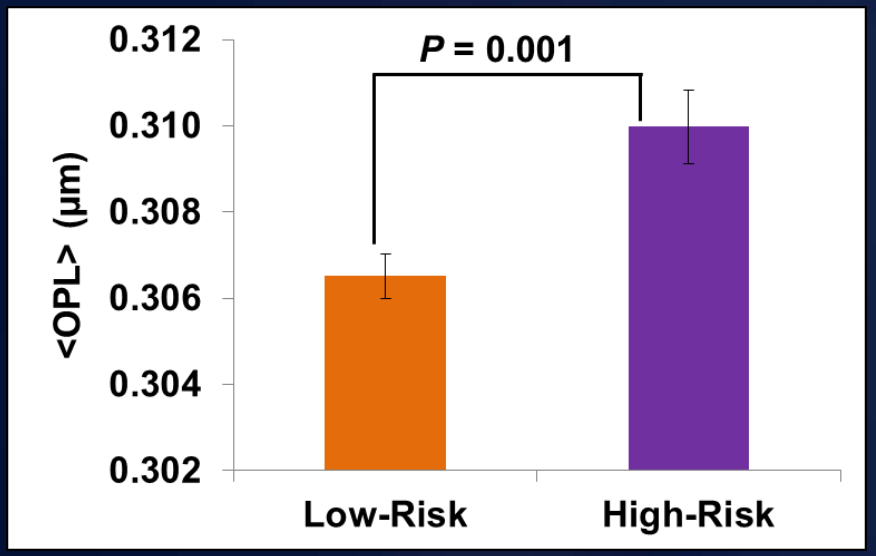
Nano-morphology Markers

- Average Optical Path Length (<OPL>)
  - Associated with nanoscale changes in nuclear density

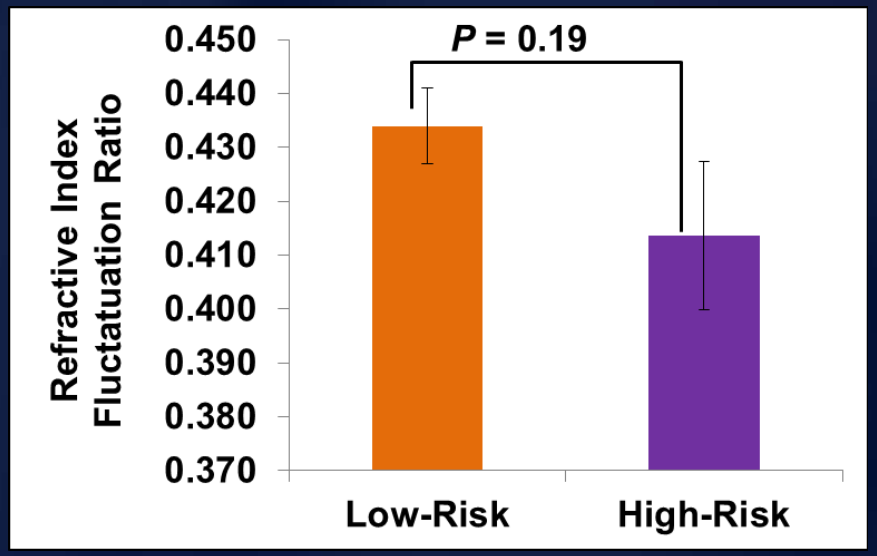
- Standard Deviation of Optical Path Length (σ_{OPL})
- Refractive Index Fluctuation Ratio
  - Associated with the structural heterogeneity within the cell nucleus

Bista RK et al, Breast Cancer Res Treat 2012; 135(1): 115-124; Bista RK et al, J Biomed Opt, 2012; 17(6): 066014; Uttam S et al , J Biomed Opt, 2011; 16(11): 116013; Bista RK et tal, Inflamm Bowel Dis, 2011; 17(12): 2427-2435. Bista RK et al, J Biomed Opt (Letters), 2011; 16(7): 070503.

Nano-morphology Markers

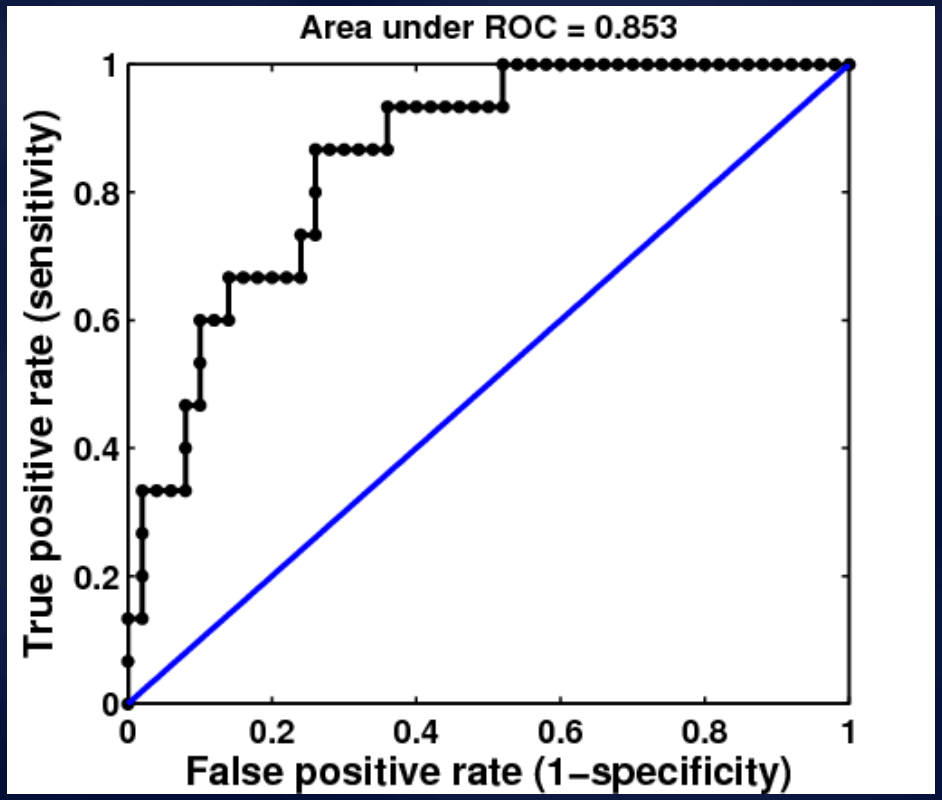


N = 50 N = 15



Specificity & Sensitivity of Nano-morphology Markers

- From the ROC curve, we found that we can distinguish **HIGH** from **LOW** risk UC patients with a **85.3%** accuracy
  - 93.3% sensitivity, 63% specificity



Conclusions

- The spectral markers of normal-appearing rectal tissue shows a promise to detect the presence of dysplasia/cancer anywhere in the colon of patients with chronic UC

- We are currently looking at additional spectral markers to improve the specificity of this technique

Future Directions

- Long term, if successful, spectral markers could:
  - Allow for proctoscopy and risk stratification improving overall resource utilization
  - Potentially develop portable probe for in-vivo exams
  - Other applications: post-op recurrence of Crohn's disease, dysplasia/neoplasia in UC patients using formalin fixed histology slides

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Assessment of nuclear refractive index to improve the diagnostic accuracy of cholangiocarcinoma on bile duct biopsies

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Background

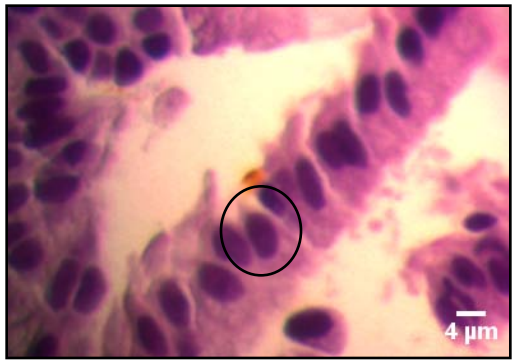
- A histologic diagnosis of malignancy is often limited
  - scant amount of available tissue
  - rarity of frankly malignant cancer cells
  - identification of neoplastic cells in the setting of inflammation.
- Sensitivities range from 30-80% for ERCP with biopsy
  - Sensitivity increases with intraductal endoscopy

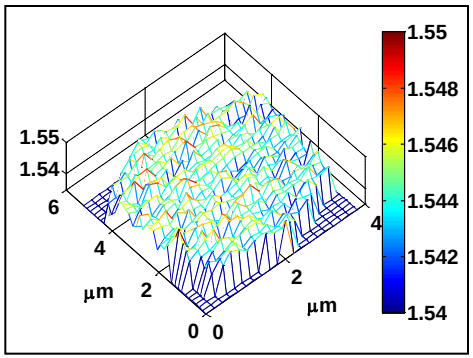
Methods

- Bile duct biopsies were obtained by ERCP or SpyGlass® intraductal endoscopy
- 14 patients with benign strictures
  - Benign course on extended follow-up
- 20 patients with adenocarcinoma
  - Histologically uninvolved cells from 16 cancer patients
  - Histologically malignant cells from 13 cancer patients
- Unmodified H&E stained histology slides
- Nuclear refractive index analysis was performed on ~40-60 epithelial cells for each case

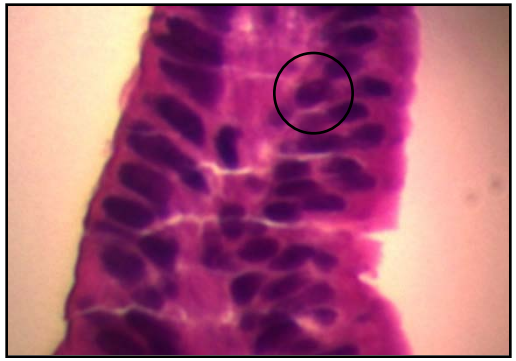
Nuclear refractive index map

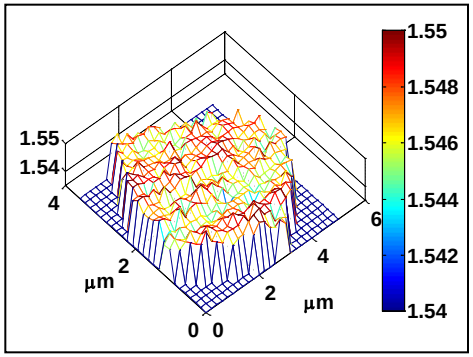
Benign



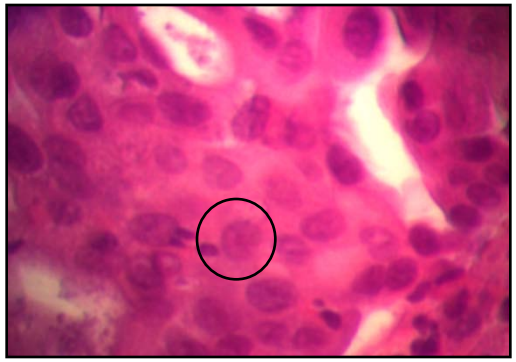


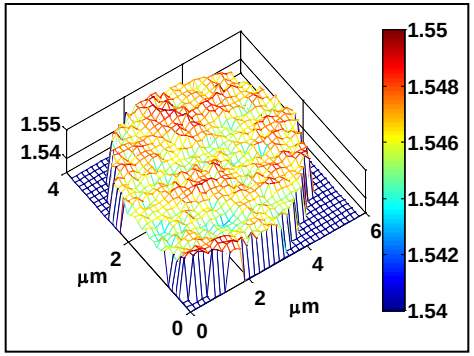
Uninvolved





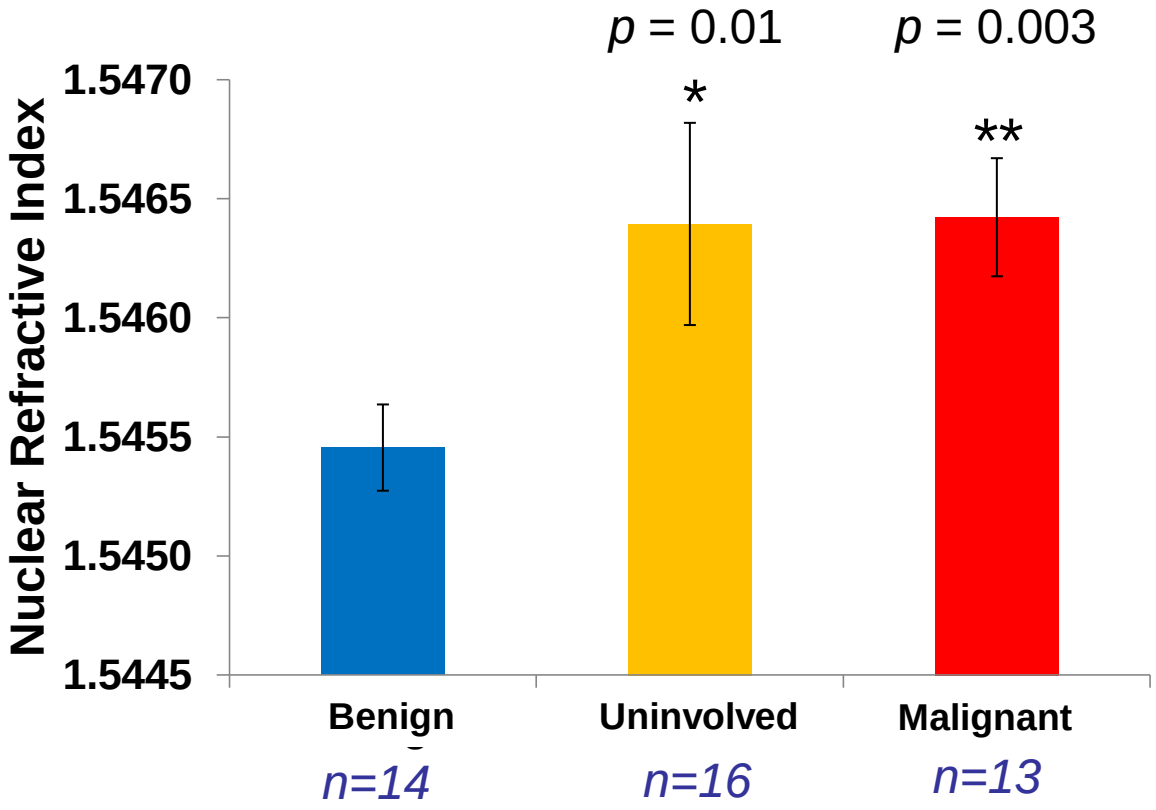
Malignant





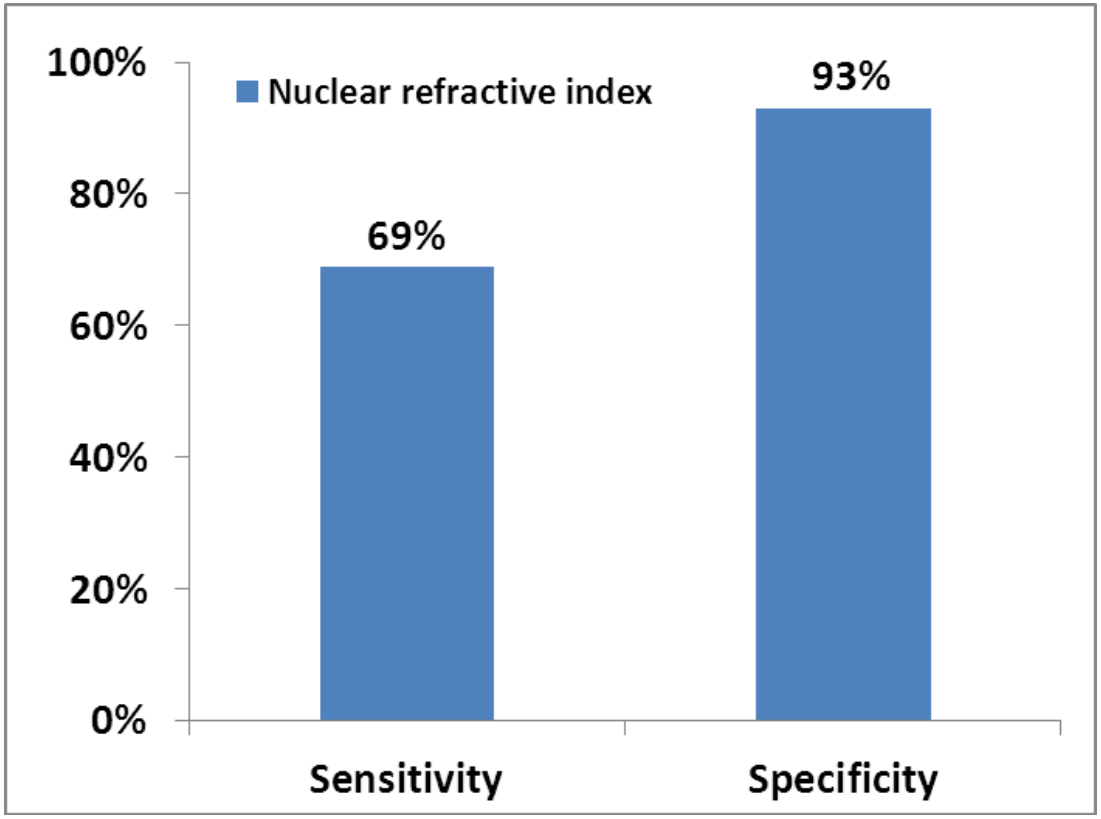
Results:

Malignant cells & uninvolved cells from cancer patients had significantly increased nuclear refractive indexes compared to benign cells from patients without cancer



Results

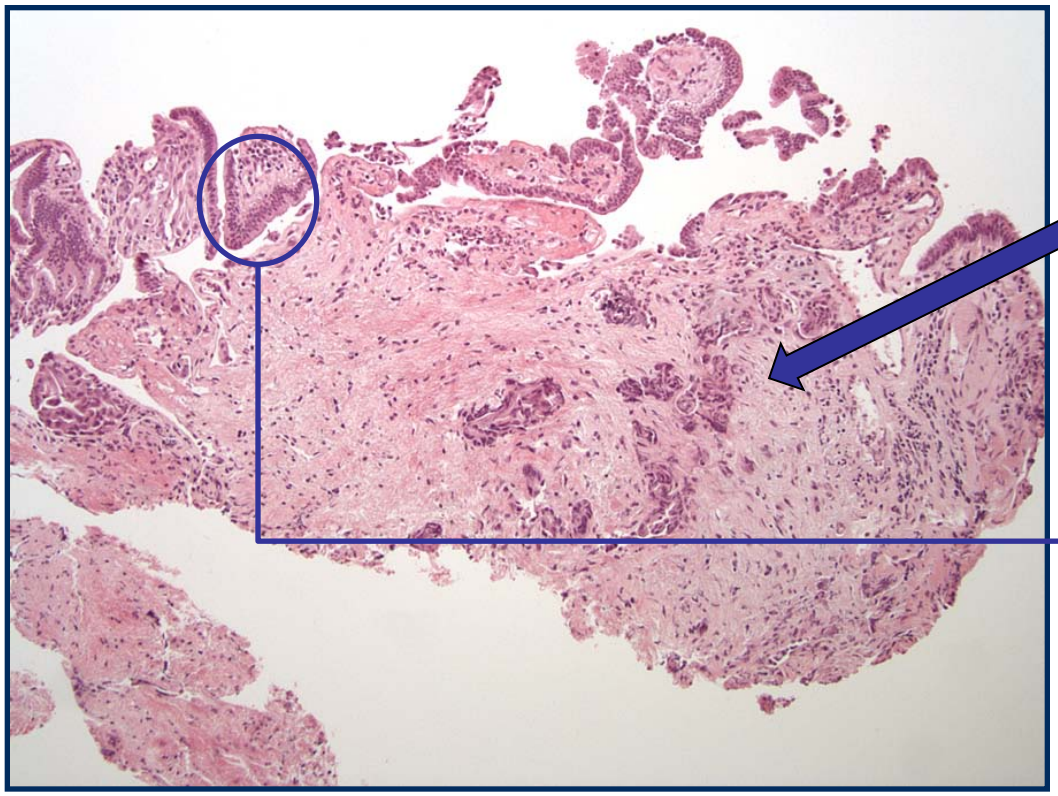
Performance to detect malignancy from histologically *uninvolved* cells



Conclusion

- Nuclear refractive index represents a novel type of biomarker for detecting malignancy in histologically uninvolved cells.
- This optical biomarker could assist in the diagnosis of malignancy.

Potential application



Histologic diagnosis
= **Atypical**

SL-QPM analysis of histologically uninvolved cells
= **Malignant**

- Future work is needed to validate the technology in a large patient population.

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