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- Omics group has organised 500 conferences, workshops and national symposium across the major cities including SanFrancisco,Omaha,Orlado,Rayleigh,SantaClara,Chicago,Philadelphia,Unitedkingdom,Baltimore,SanAntanio,Dubai,Hyderabad,Bangaluru and Mumbai.

2th International Conference and Exhibition on Lasers, Optics & Photonics

Application of multiphoton microscopy in diagnosis and therapy of early cancer

Jianxin Chen

Key Laboratory of OptoElectronic Science and Technology for Medicine of Ministry of Education
Fujian Normal University, China

September, 2014

Multiphoton Microscopy (MPM)

M Goppert-Mayer

Theoretically Maria Goppert-Mayer proposed the concept of two-photon excited fluorescence in 1931.

Göppert-Mayer M., Űber Elementarakte mit zwei Quantensprüngen (On elementary processes with two quantum steps), Ann. Phys. 401 (1931) 273-294

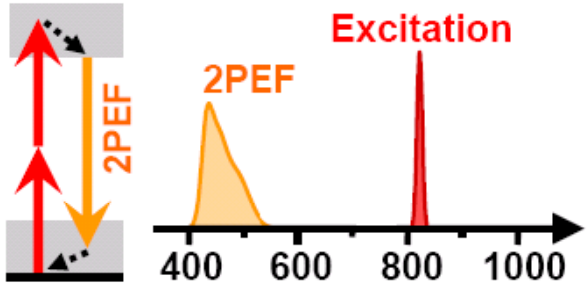
W. W. Webb

Experimentally Watt W. Webb presented the first multiphoton images as late as 1990.

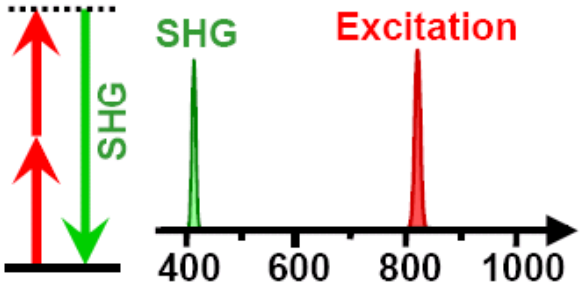
Winfried Denk, James H. Strickler and Watt W. Webb
(Two-Photon Laser Scanning Fluorescence Microscopy)
Science, 248 (1990) 73-76

Multiphoton Microscopy (MPM)

- **Multi-photon Excited Fluorescence**
  - Two-photon
  - Three-photon



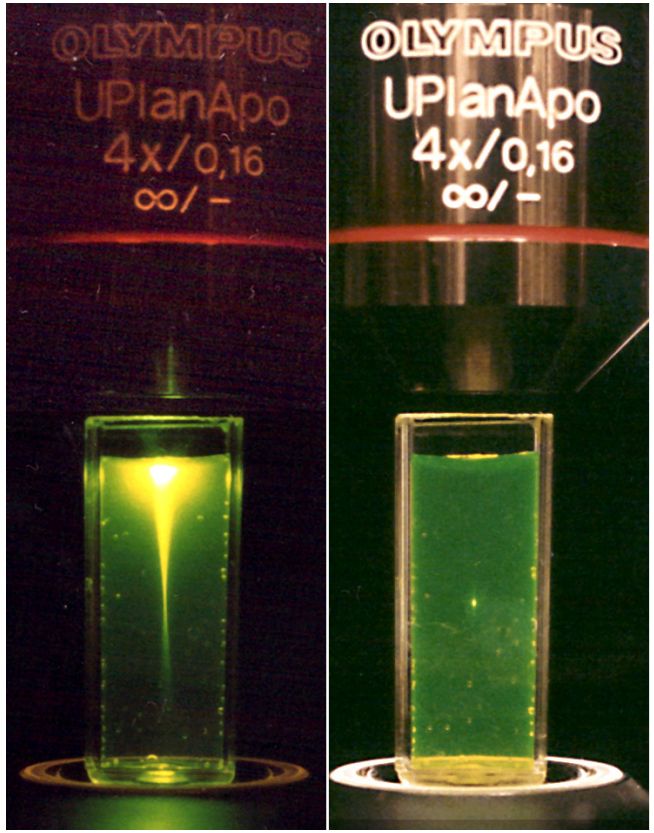
- **Multi-harmonic generation**
  - Second-harmonic generation
  - Third-harmonic generation



Advantages of Multiphoton Microscopy

- ✓ Intrinsic optical sectioning ability
- ✓ Deeper penetration depths in scattering tissue,
- ✓ Reduced overall specimen photodamage and photobleaching

Single photon excitation (488 nm) | **Two photon excitation (900 nm)**



(From Web's Group)

Applications of Multiphoton Microscopy

It has a wide variety of biological and clinical applications

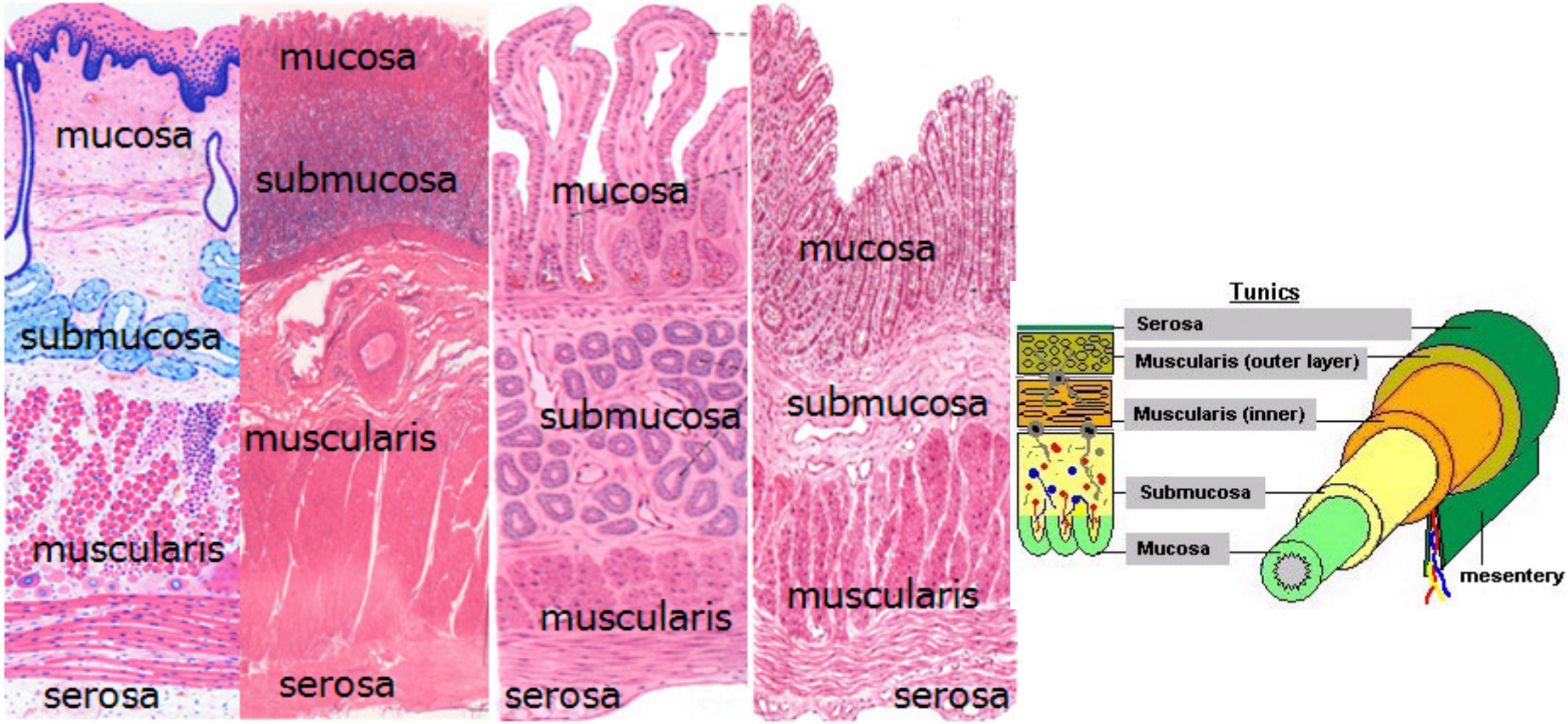
- **Gene expression**
- **Protein interactions**
- **Calcium concentrations**
- **Neural activity**
- **Disease diagnosis and treatment**
- **Optical biopsy**

Applications of Multiphoton Microscopy

- Cancer is a leading cause of death around the world
- WHO estimates that without intervention 84 million people will die of cancer between 2005 and 2015.
- Early detection of cancer greatly increases the chances for successful treatment.

http://www.iarc.fr/en/publications/books/wcr/wcr-cover.php

Applications of Multiphoton Microscopy



Esophagus **Stomach** **Small intestine** **Large intestine**

http://www.vivo.colostate.edu/hbooks/pathphys/digestion/basics/gi_microanatomy.html

Instrument in our lab

Ti:sapphire laser and LSM 510 META Microscope

Applications of Multiphoton Microscopy

- To differentiate between normal and dysplastic tissues
- To differentiate between normal and cancerous tissues
- To monitor cancer progression
- To perform photoablation of preinvasive cancer cells

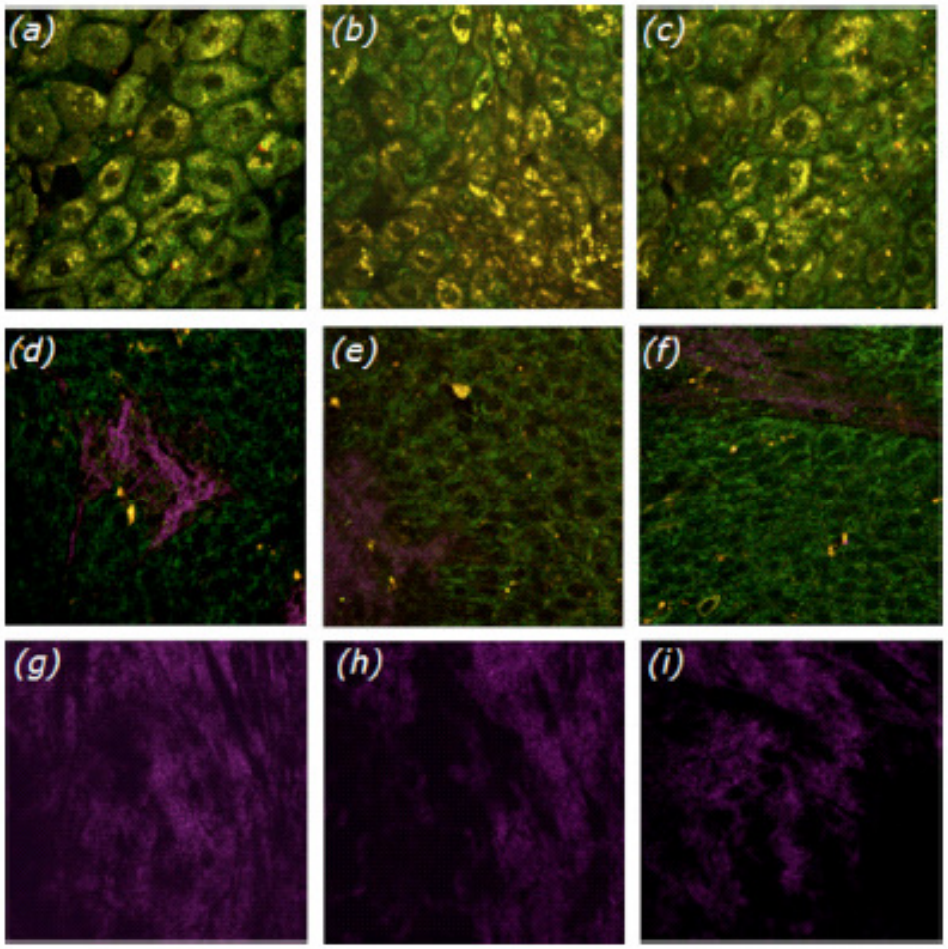
We examined if MPM has the potential to differentiate between normal and dysplastic epithelial tissues

Differentiating between normal and dysplastic cervical tissues

Epithelium

Basement Membrane

Stroma



Normal tissue **Inflammatory tissue** **Displastic tissue**

Applied Physics Letters 97, 173701, 2010

Differentiating between normal and dysplastic cervical tissues

TABLE I. Depth-cumulated epithelial redox ratio from normal, inflammatory, and dysplastic epithelial tissues. Superscript numbers of value: serial numbers of patient.

	Sample No.					
Tissue type	1	2	3	4	5	Average
Normal case	$^{(1)}63.8 \pm 4.9$	$^{(2)}62.4 \pm 3.2$	$^{(3)}58.9 \pm 2.6$	$^{(4)}61.7 \pm 3.7$		61.7 ± 4.3
Inflammation	$^{(1)}48.7 \pm 3.6$	$^{(2)}54.2 \pm 2.0$	$^{(3)}50.4 \pm 2.9$			51.1 ± 3.8
Dysplasia	$^{(1)}64.7 \pm 6.5$ (CINI)	$^{(5)}71.0 \pm 5.7$ (CINII)	$^{(6)}68.5 \pm 3.9$ (CINII)	$^{(7)}77.4 \pm 7.4$ (CIN III)	$^{(4)}79.9 \pm 6.2$ (CIN III)	72.3 ± 6.1

TABLE II. Depth-cumulated stromal collagen quantity from normal, inflammatory, and dysplastic epithelial tissues. Superscript numbers of value: serial numbers of patient.

	Sample No.					
Tissue type	1	2	3	4	5	Average
Normal case	$^{(1)}27.1 \pm 1.7$	$^{(2)}25.8 \pm 1.1$	$^{(3)}26.6 \pm 2.2$	$^{(4)}24.9 \pm 1.4$		26.1 ± 1.9
Inflammation	$^{(1)}19.5 \pm 3.0$	$^{(2)}21.7 \pm 3.4$	$^{(3)}20.1 \pm 2.4$			20.4 ± 3.2
Dysplasia	$^{(1)}23.5 \pm 1.8$ (CINI)	$^{(5)}22.6 \pm 2.9$ (CINII)	$^{(6)}21.0 \pm 2.1$ (CINII)	$^{(7)}16.8 \pm 3.4$ (CIN III)	$^{(4)}15.1 \pm 2.7$ (CIN III)	19.8 ± 2.7

Applied Physics Letters 97, 173701, 2010

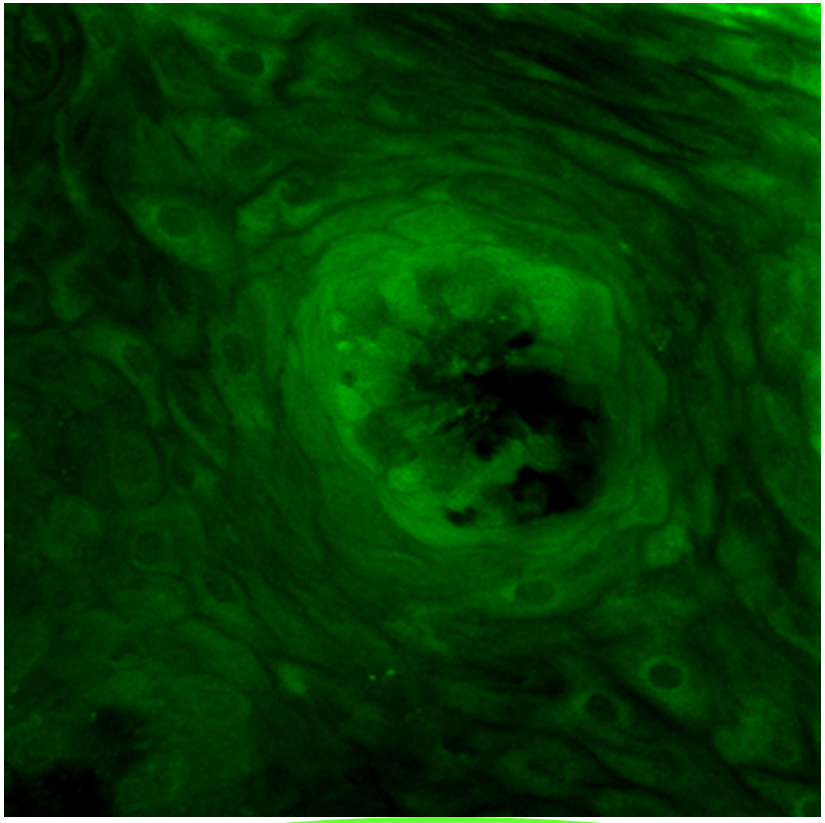
Differentiating between normal and Barrett esophageal tissue

Normal squamous epithelium

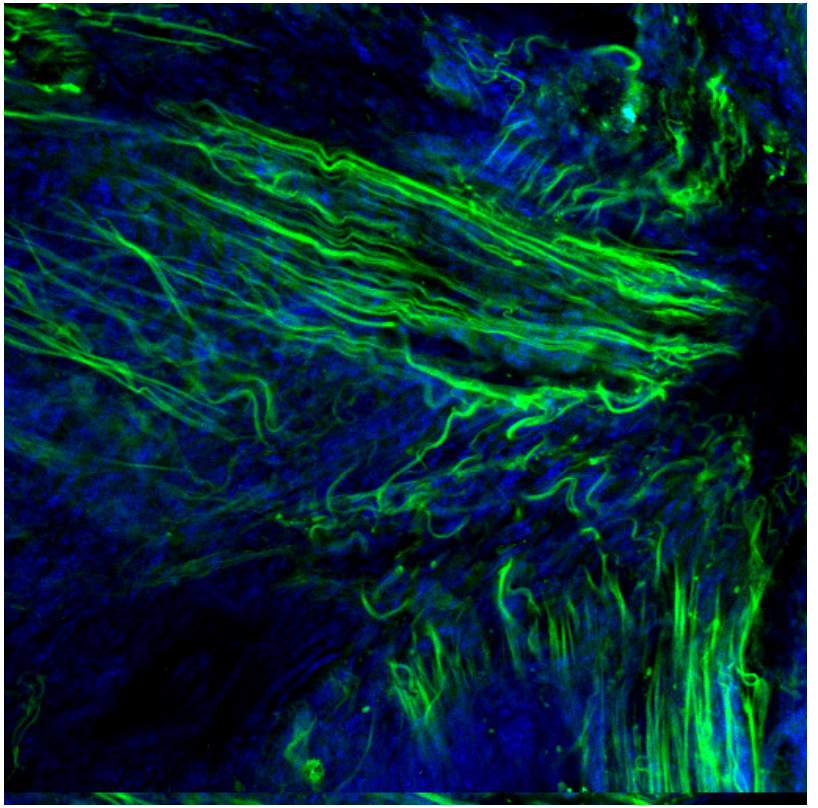
Barrett's esophagus

Arch Pathol Lab Med 138, 204 , 2014

Differentiating between normal and Barrett esophageal tissue



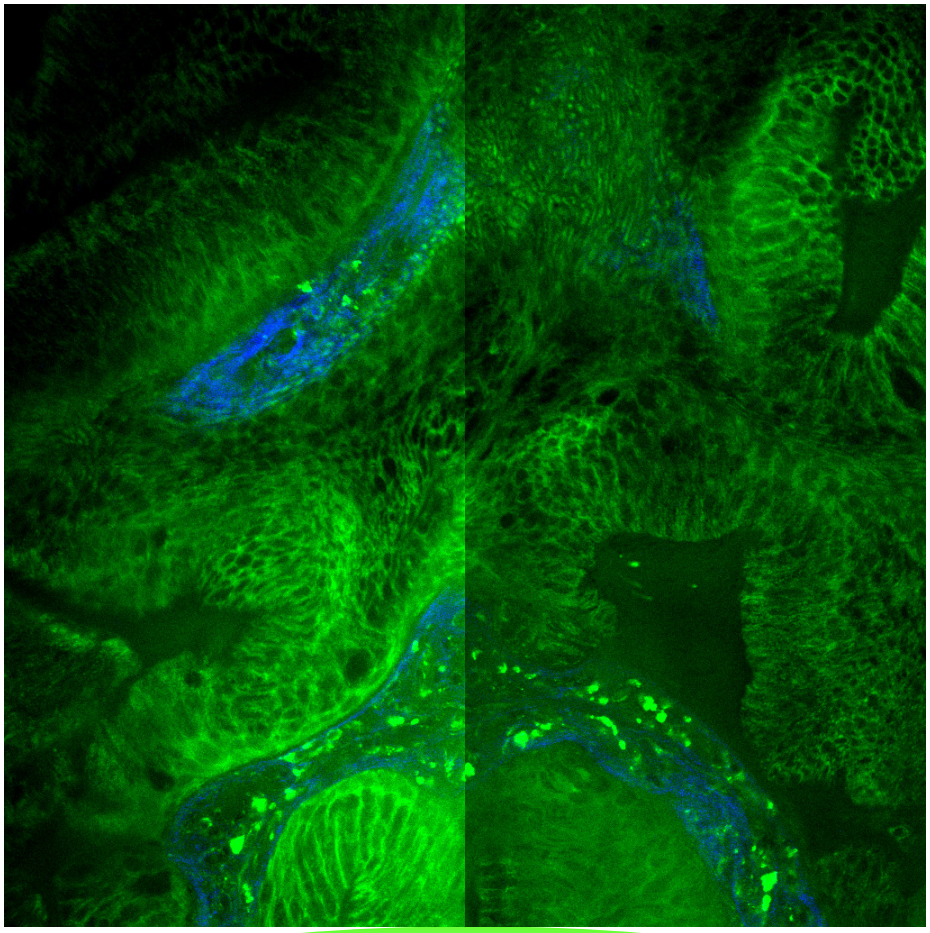
Normal squamous epithelium

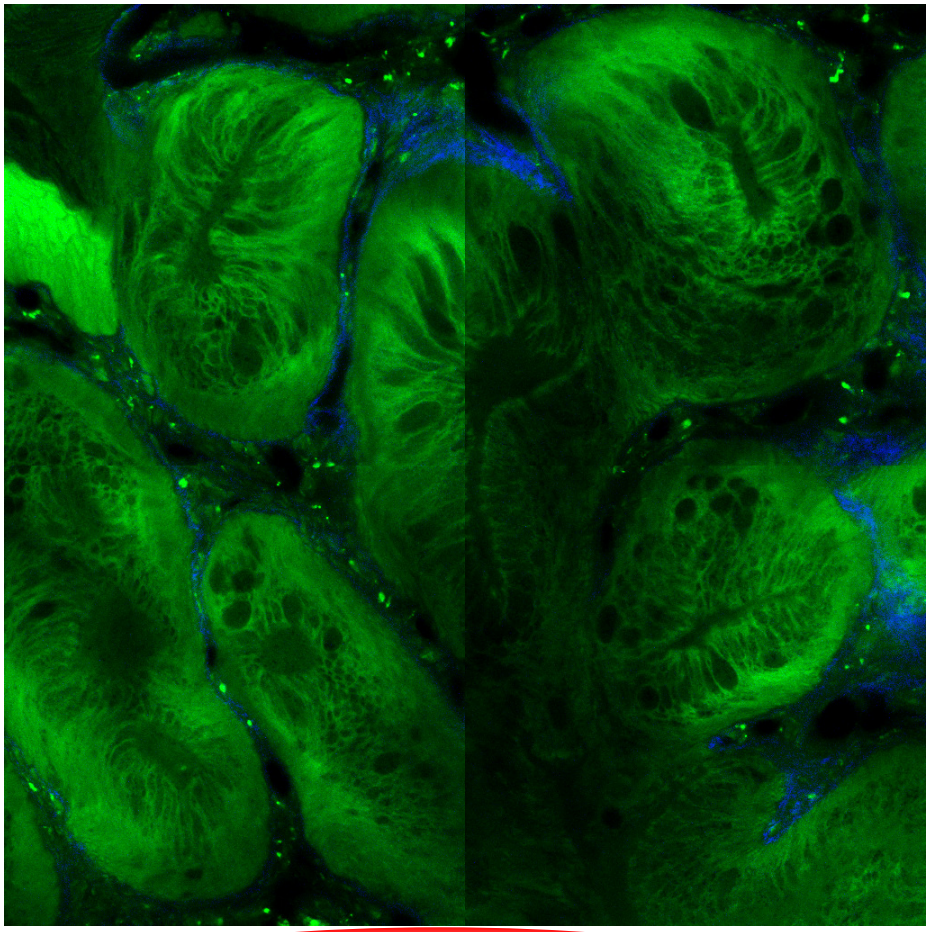


Connective tissues in lamina propria layer

Arch Pathol Lab Med 138, 204 , 2014

Differentiating between normal and Barrett esophageal tissue





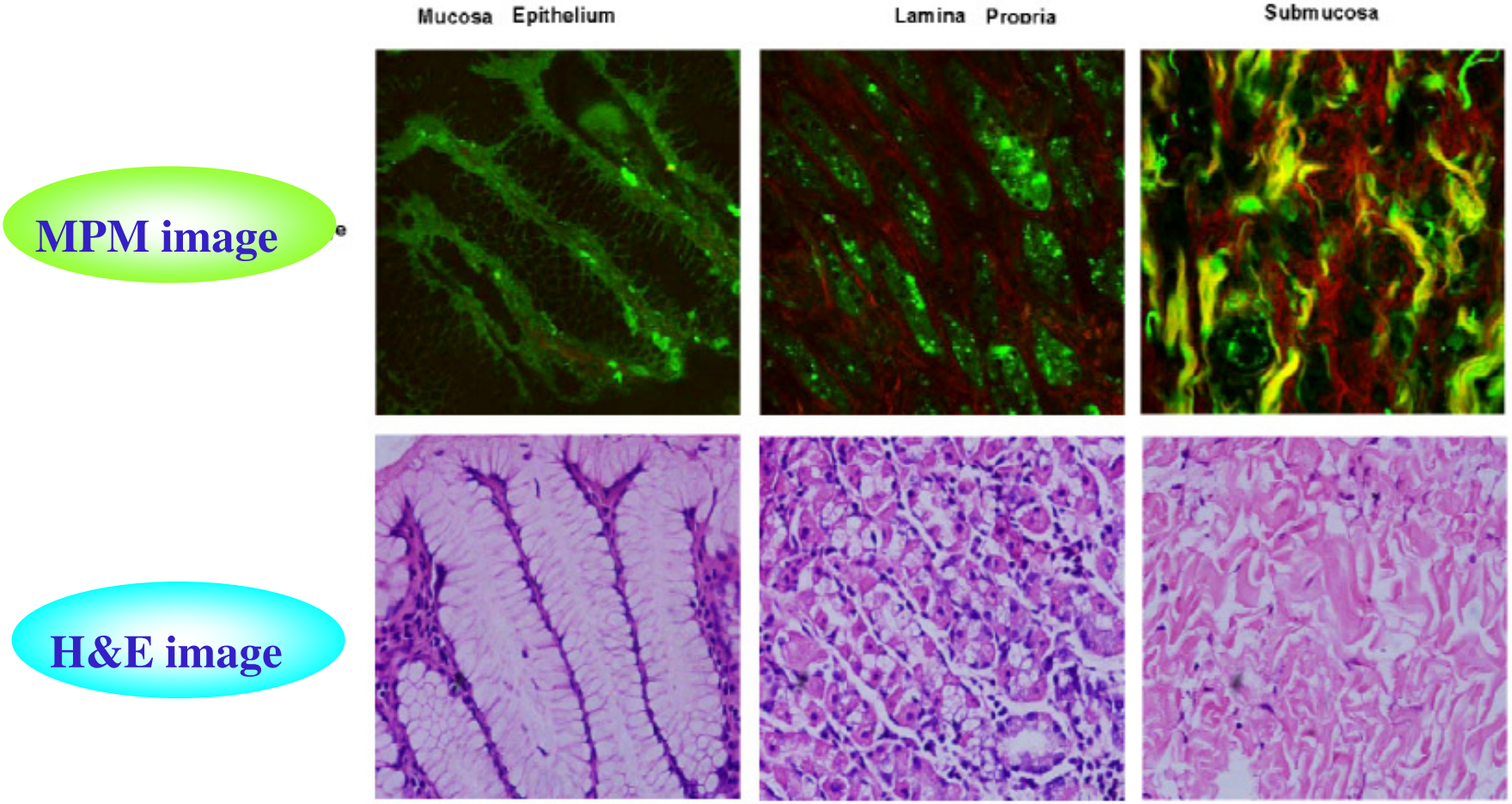
Barrett epithelium at the upper part of mucosa

Barrett epithelium at the deeper part of mucosa

Arch Pathol Lab Med 138, 204 , 2014

We examined if MPM has the potential to differentiate between normal and cancerous epithelial tissues

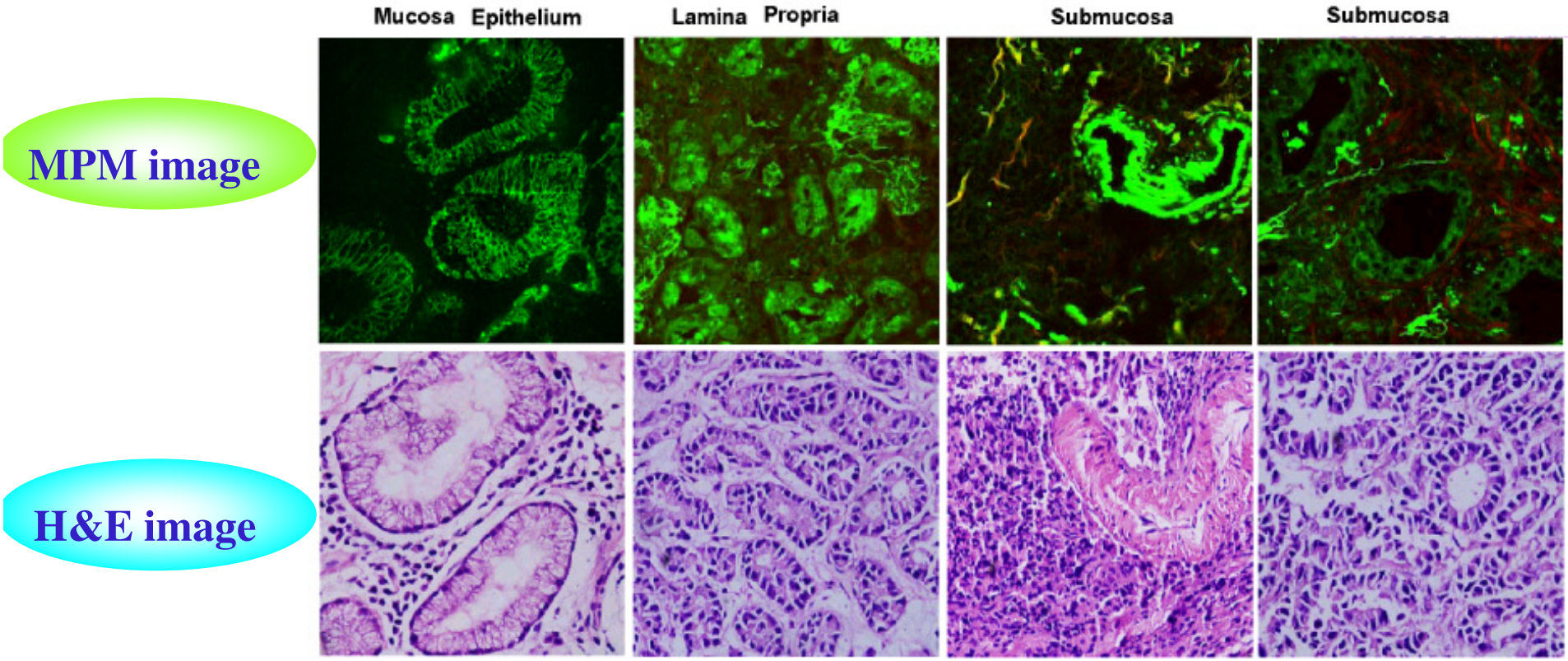
Differentiating between normal and cancerous stomach tissue



Comparison of MPM images and H&E images from normal mucosa and submucosa

Gastrointestinal Endoscopy, 73, 802-807, 2011

Differentiating between normal and cancerous stomach tissue



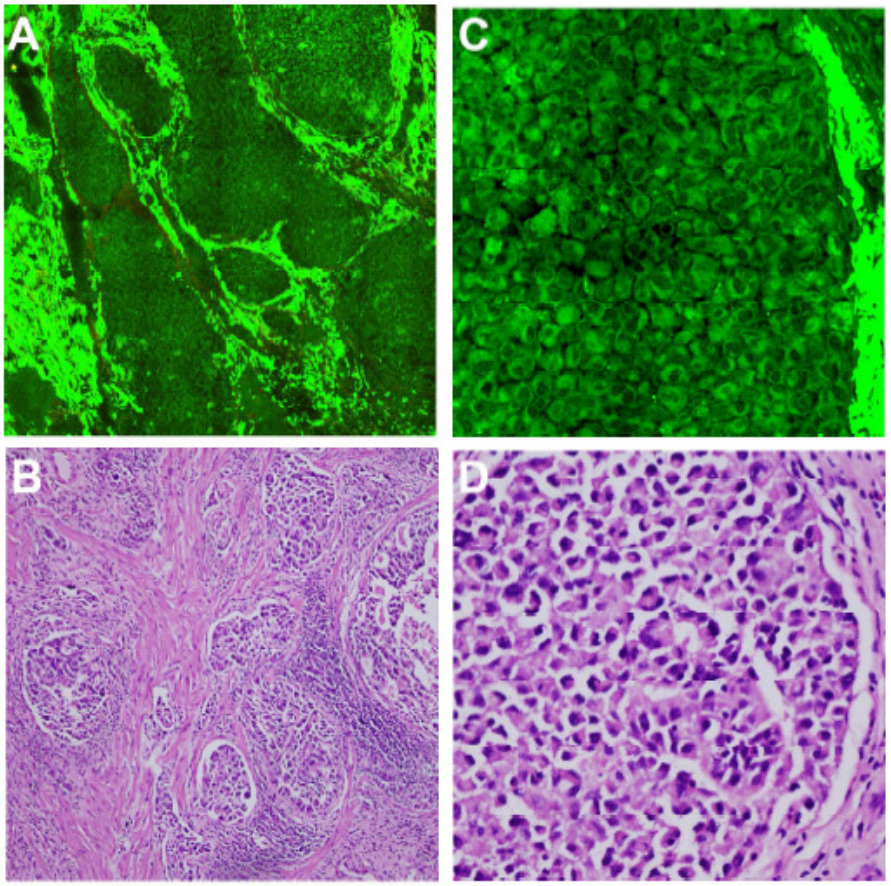
Comparison of MPM images and H&E images from cancerous mucosa and submucosa

Gastrointestinal Endoscopy, 73, 802-807, 2011

Differentiating between normal and cancerous stomach tissue

MPM image

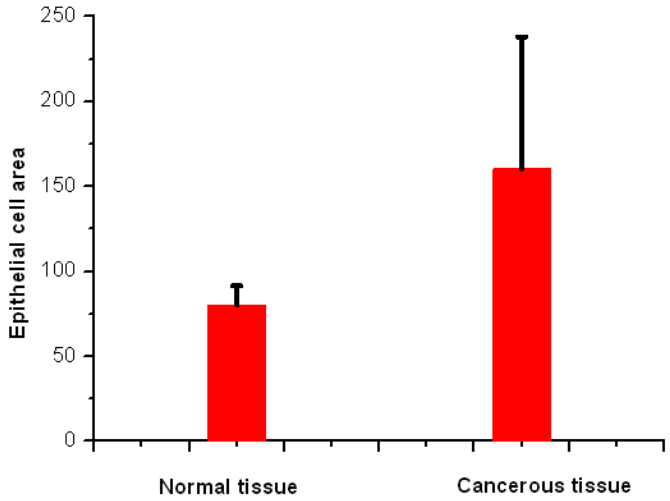
H&E image



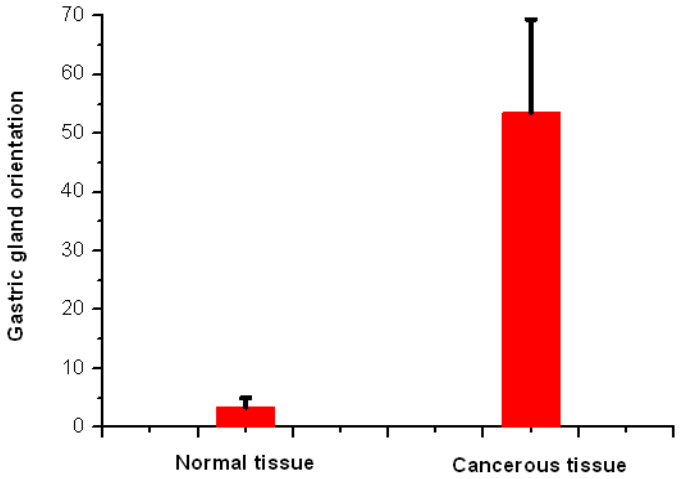
MPM image of the nest of cancer and the surrounding fibrous stroma.

Surgical Endoscopy, 25, 1425-1430, 2011

Differentiating between normal and cancerous stomach tissue



Epithelium cell boundary



Gastric gland orientation

Chen et al

Diagnostic features for gastric cancer

TABLE 1. Comparison of the collagen area in the mucosa and submucosa of normal and cancerous gastric tissues

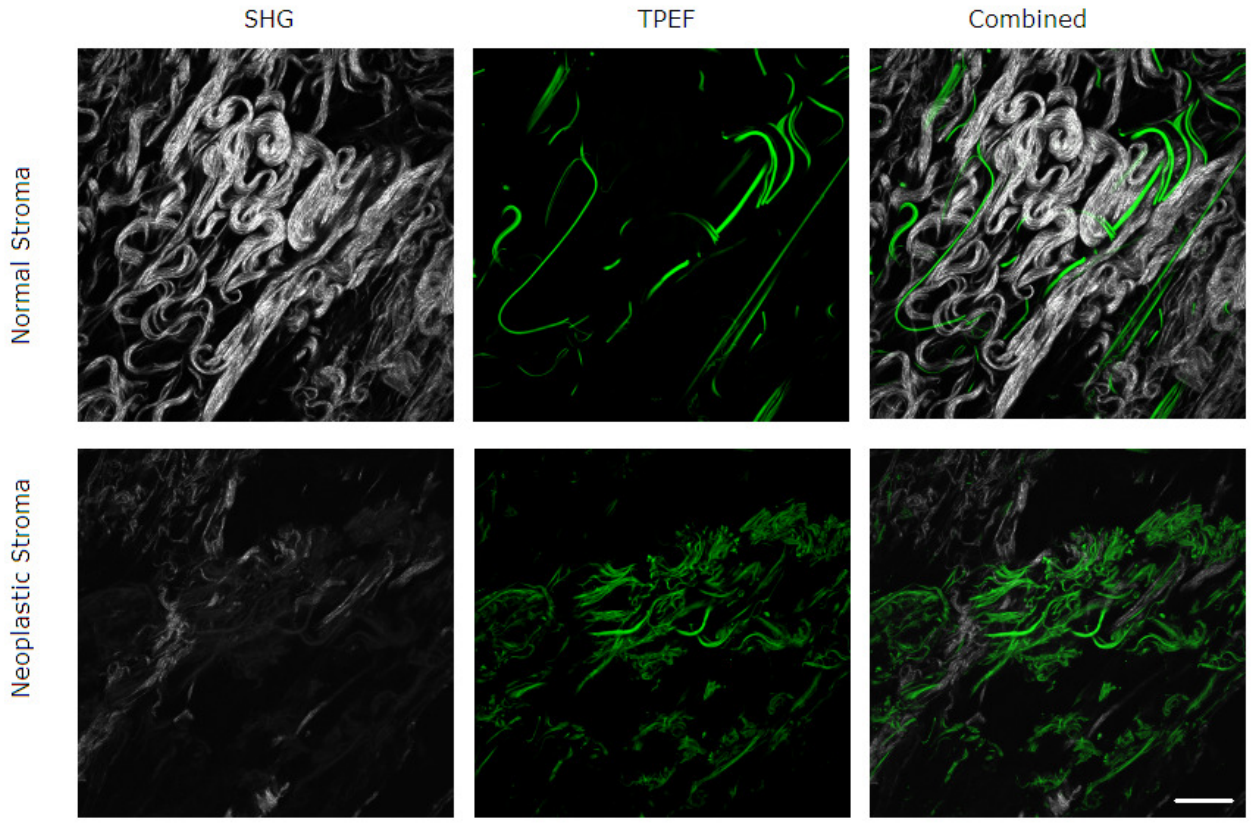
Tissue layer	Mucosa epithelium	Lamina propria	Submucosa
Normal tissue	0.042 ± 0.007	0.317 ± 0.021	0.629 ± 0.008
Cancerous tissue	0	0.075 ± 0.014	0.061 ± 0.002 (row 3)
			0.226 ± 0.019 (row 4)

The collagen area

Differentiating between normal and cancerous esophagus tissue

Normal stroma

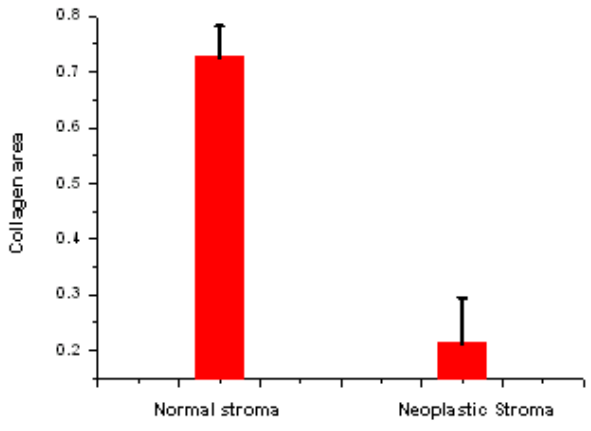
Neoplastic stroma



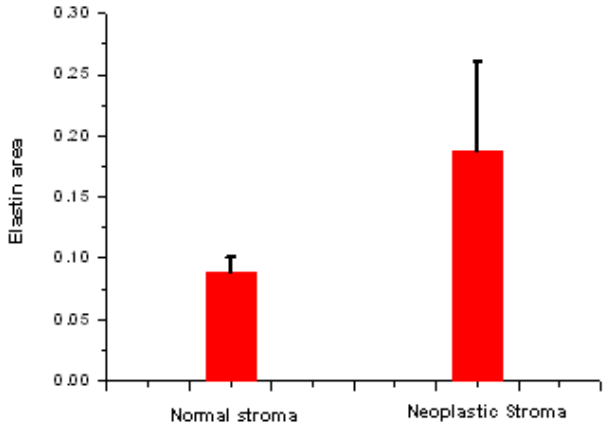
Representative multiphoton images of the human esophageal stroma

Journal of Biomedical Optics Letters 14, 020503, 2009

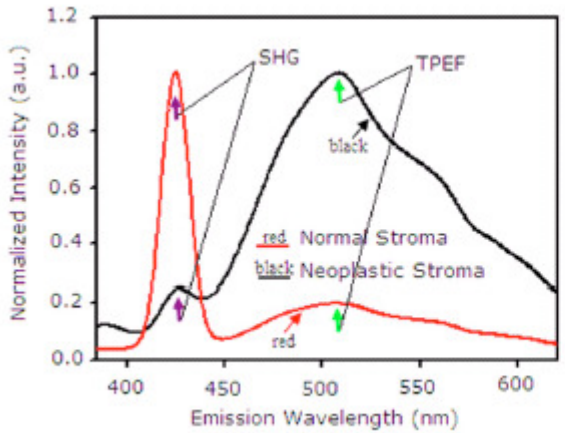
Differentiating between normal and cancerous esophagus tissue



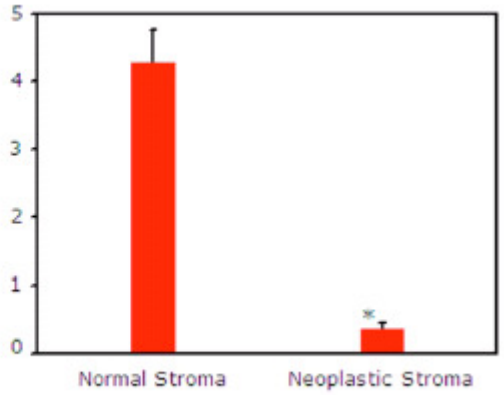
Collagen area



Elastin area



Emission spectra



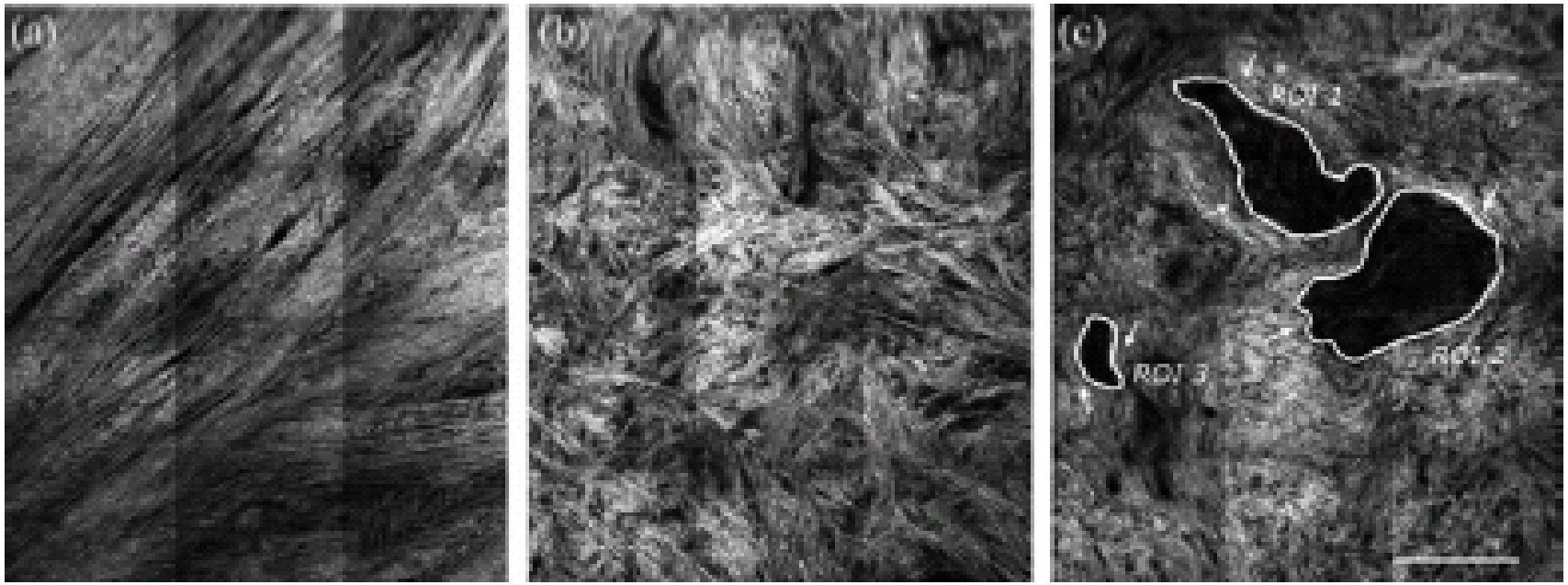
Ratio of SHG/TPEF

Indicating MPM has the ablitiy to differentiate normal and cancerous esophageal stroma

Journal of Biomedical Optics Letters 14, 020503, 2009

We examined if MPM has the potential to monitor cancer progression

Monitoring cervical tumor progression



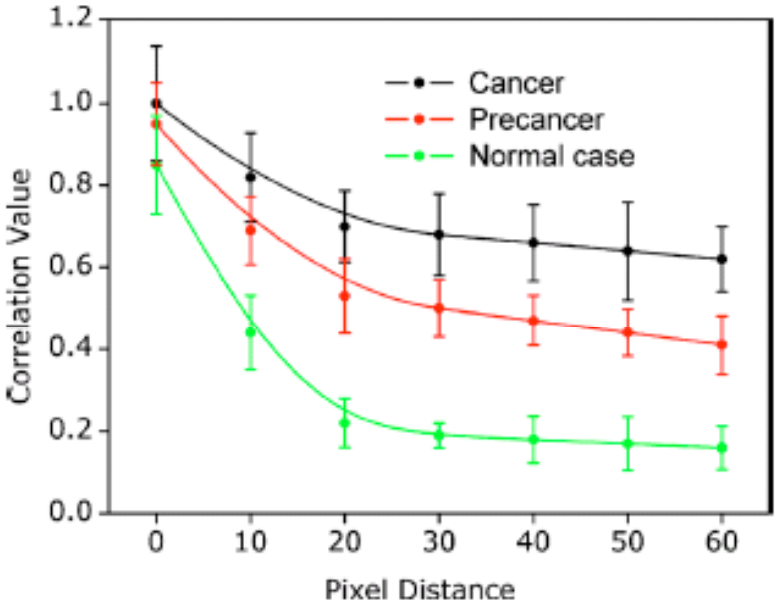
Normal tissue

Precancerous tissue

Cancerous tissue

Applied Physics Letters 96, 213704, 2010

Monitoring cervical tumor progression



Correlation value as a function of pixel distance.

TABLE I. Quantitative characterization parameters derived from SHG imaging.

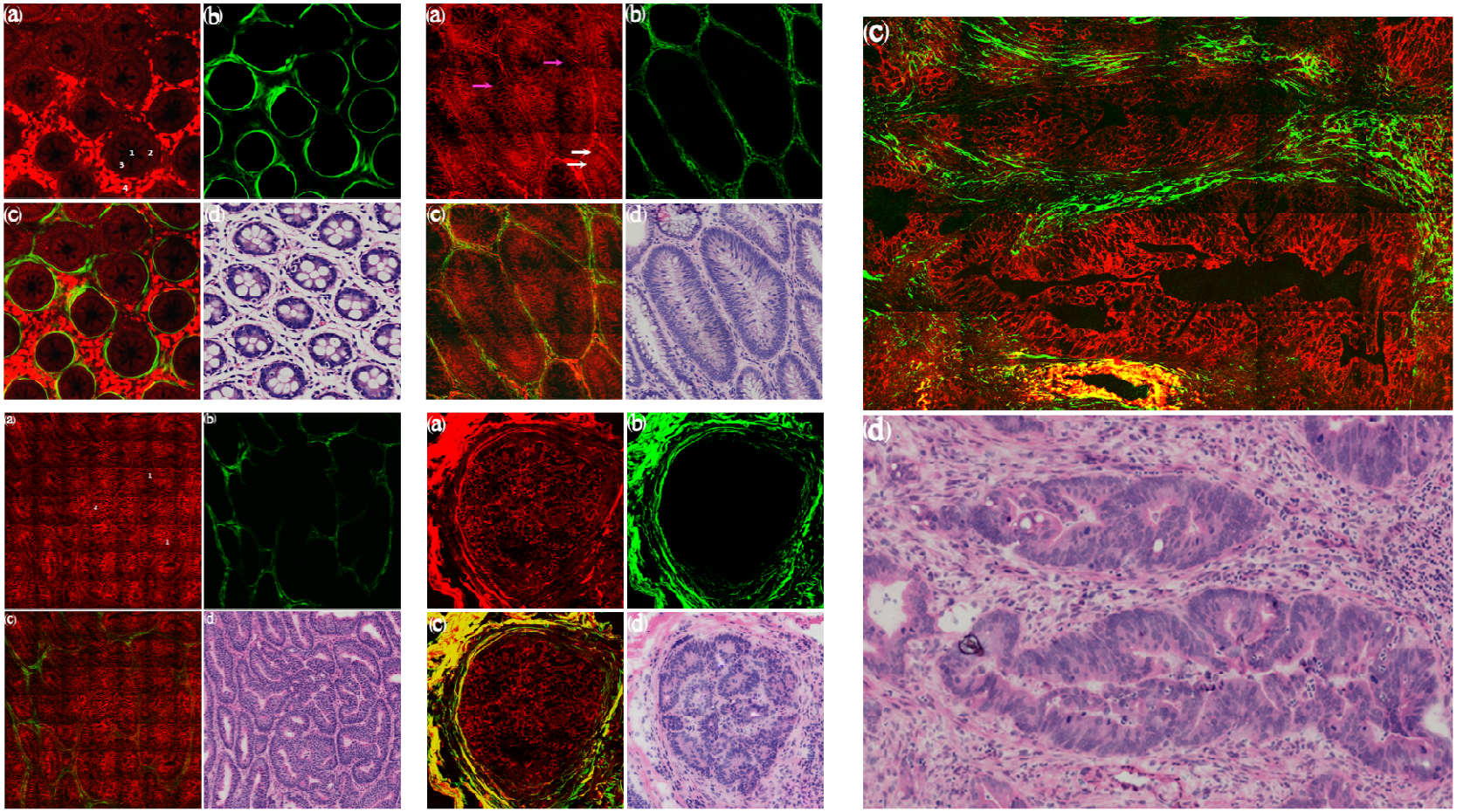
	Collagen presence	Collagen-fibril bundles orientation	Collagen fibril structure
Normal case	0.89 ± 0.05	0.21 ± 0.04	0.19 ± 0.03
Precancer	0.67 ± 0.11	0.53 ± 0.08	0.51 ± 0.07
Cancer	0.43 ± 0.12	0.86 ± 0.07	0.68 ± 0.10

Quantitative characterization parameters derived from SHG imaging

Quantitatively linking collagen alteration and epithelial tumor progression

Applied Physics Letters 96, 213704, 2010

Monitoring colorectal tumor progression



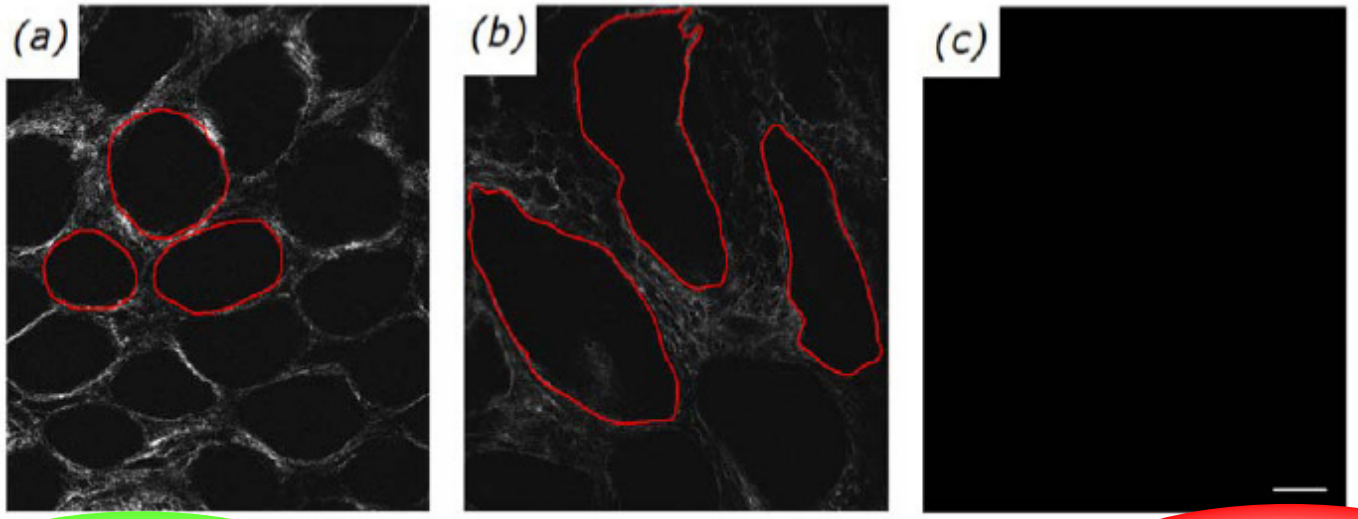
Laser Phys. Lett. 11 (2014) 065604

Monitoring colorectal tumor progression

Table 1. MPM identification of the colorectal adenoma–carcinoma sequence according to cellular and glandular structure, and invasive depth of a typical glands.

Tissue	Cell architecture based on TPEF image	Gland architecture based on TPEF image	Invasive depth based on TPEF and SHG images
Normal mucosa	• Nuclei with round shape, uniformly arranging along basement membrane • Plenty of cytoplasm • Plenty of mucin with distinctive flask-like shape in goblet cells	• Gland with round shape and regular distribution, being arranged at almost regular intervals • Gland opening with round shape	• A thin band with round shape surrounding individual glands, representing the position of basement membrane
Adenoma with low-grade dysplasia	• Nuclei with spindle-shaped architecture and minor loss of polarity,being obviously elongated,presenting a clumping pattern with slight pseudostratification, • Increased nuclear-cytoplasmic ratio • Decrease of mucin in goblet cells	• Gland with tubular shape,being relatively well-maintained,interglandular space being apparently reduced when compared to the normal case. • Gland opening with tubular shape	• Basement membrane with the tubular-shaped structure and larger size and lower population density in comparison with the normal case,still being relatively well preserved
Adenoma with high-grade dysplasia	• Nculei with roundish architecture but variable size and shape,marked pleomorphic structure,severe loss of polarity • Further increased nuclear-cytoplasmic ratio • Depletion and loss of goblet cells	• Gland with variable size and shape, presenting severely distorted architecture • Frequent intraglandular bridging and budding,presenting glandular fusion and back to back(cribriform pattern)	• Basement membrances with the obviously distorted structure in comparison with normal case, still being relatively well preserved
Adenocarcinoma invading submucosa	• Nuclei with roundish architecture but variable size and shape ,marked pleomorphic structure, severe loss of polarity • Increased nuclear-cytoplasmic ratio • Depletion and loss of goblet cells	• A simple tubular gland with the distorted gland opening with the cribriform pattern appears in the submucosa	• Collagen bundles surrounding the gland and the appearance of blood vessel,indicating invasion of submucosa.

Monitoring colorectal tumor progression



Normal tissue

precancerous tissue

Cancerous tissue

Table 1. Quantitative variables in different colonic cancer stages.

	Circle length of basement membrane (μm)	Population density of basement membranes (mm^{-2})
Normal case	342.7±27.2	103.2±10.6
Precancer	695.8±79.1	27.1±6.3
Cancer	1767.8±166.3	0.3±1.2

doi:10.1371/journal.pone.0038655.t001

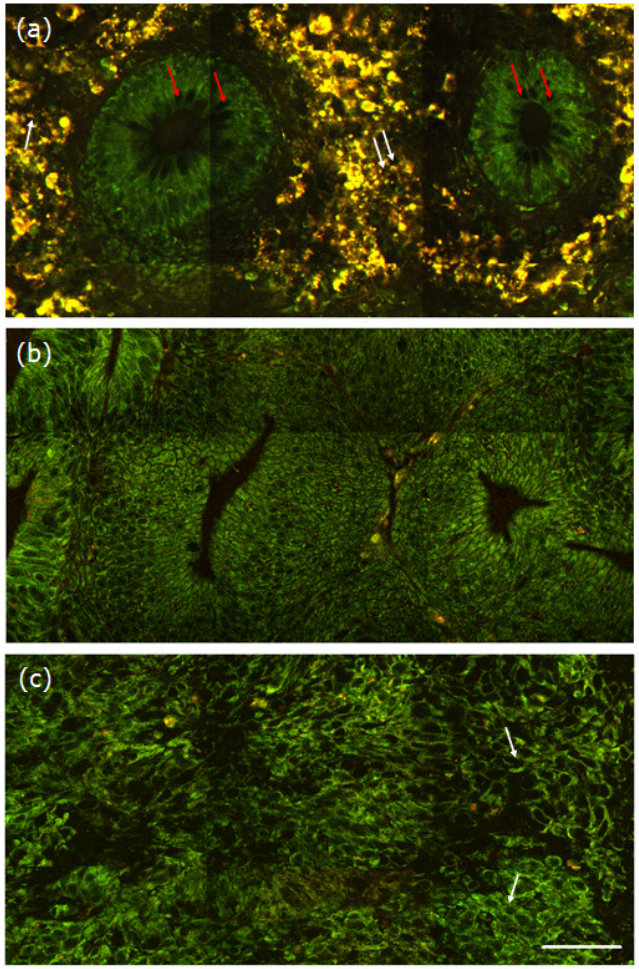
PLoS ONE 7(6): e38655, 2012

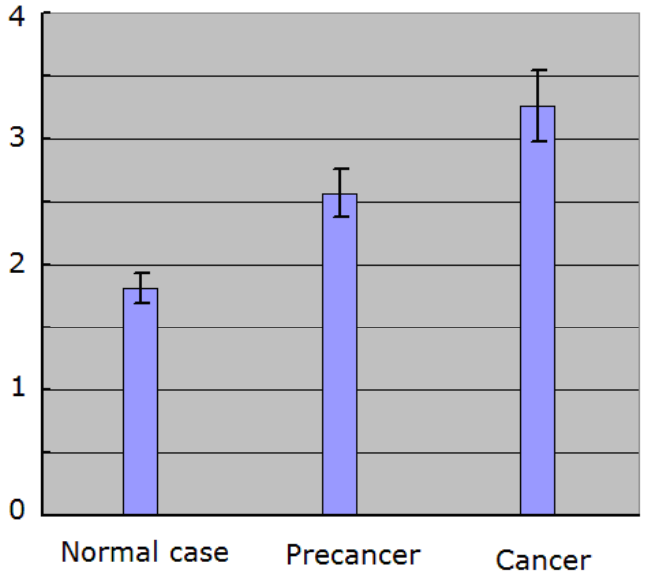
Monitoring colorectal tumor progression

Normal tissue

precancerous tissue

Cancerous tissue



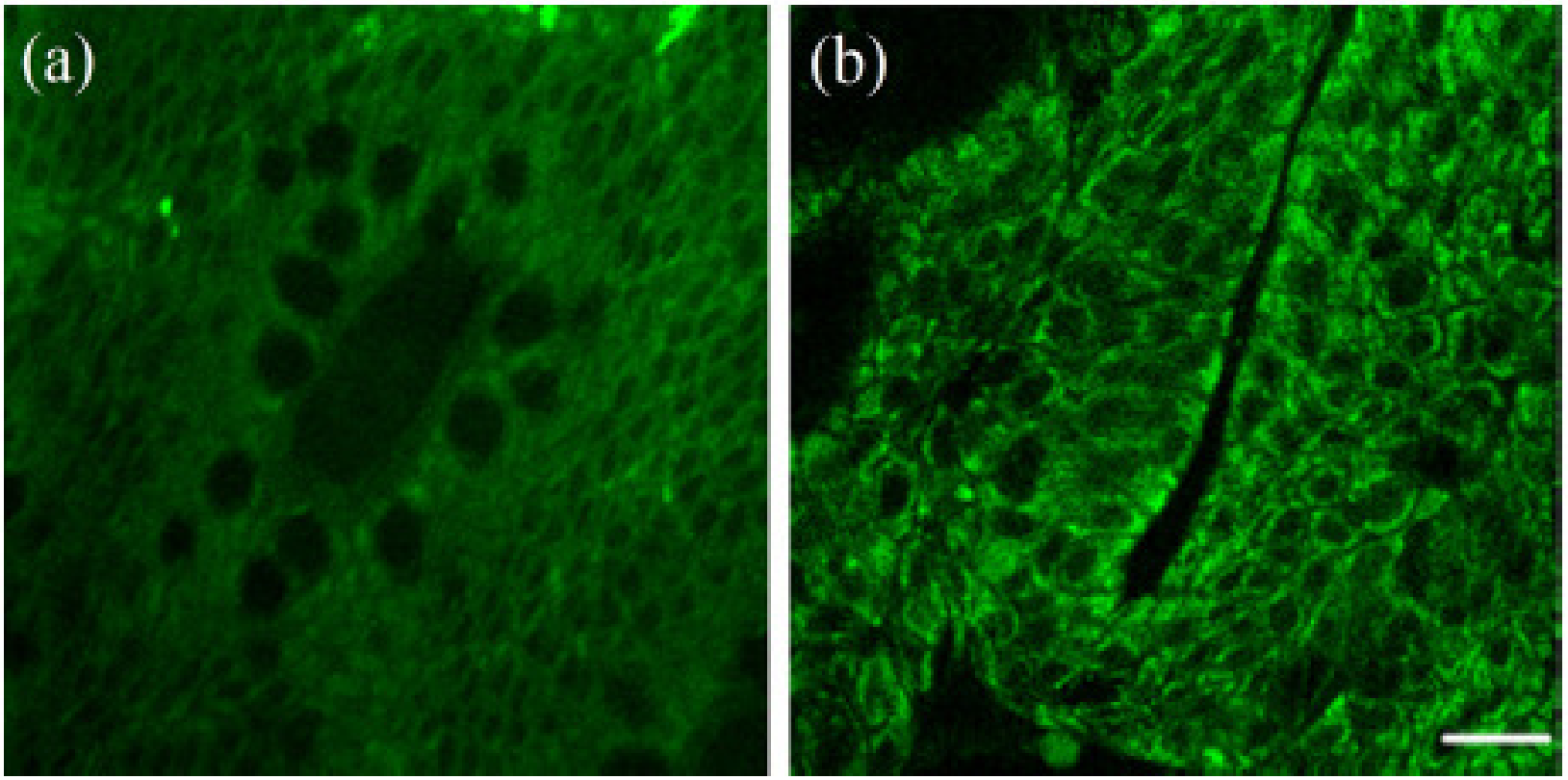


Redox Ratio

Biomedical Optics Express 2, 615-619, 2011

We examined if the combination of multiphoton imaging and absorption has the capability to perform photoablation of preinvasive cancer cells

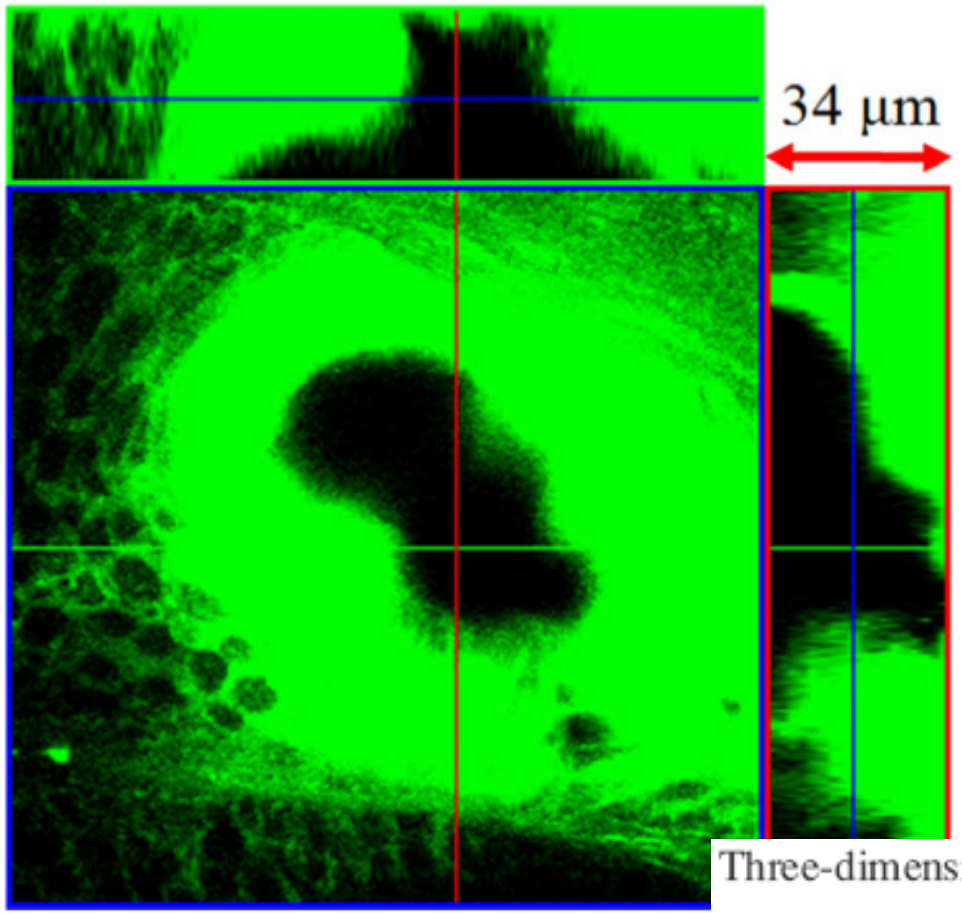
Photoablation of preinvasive cancer cells



Representative multiphoton images of the normal (a) and precancerous (b) epithelial tissues. Scale bar = 20 μm.

Applied Physics Letters, 100, 023703, 2012

Photoablation of preinvasive cancer cells



Three-dimensional reconstruction of precancerous epithelial tissues after laser processing.

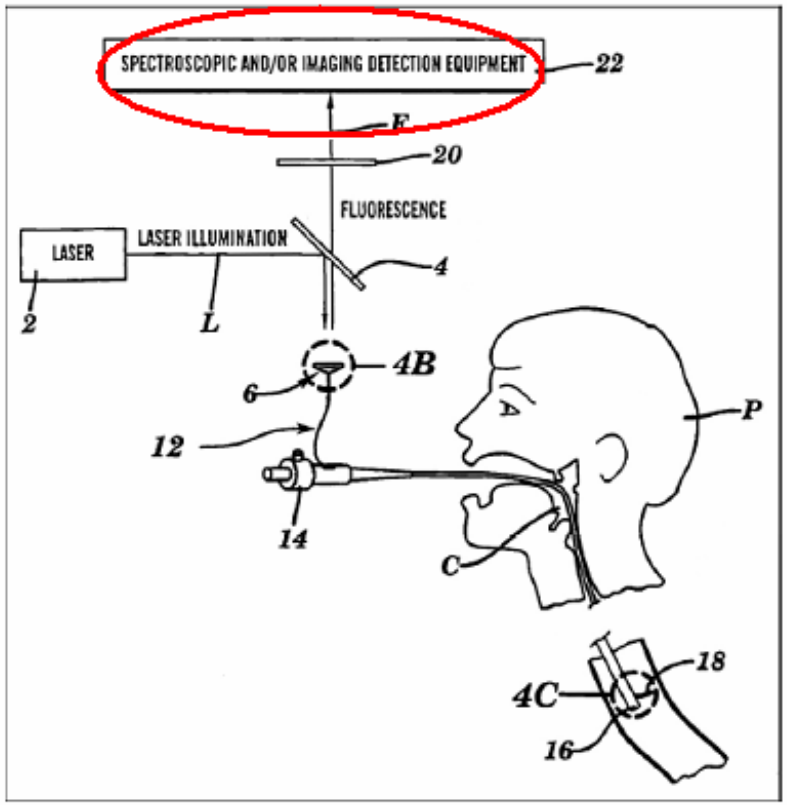
Applied Physics Letters, 100, 023703, 2012

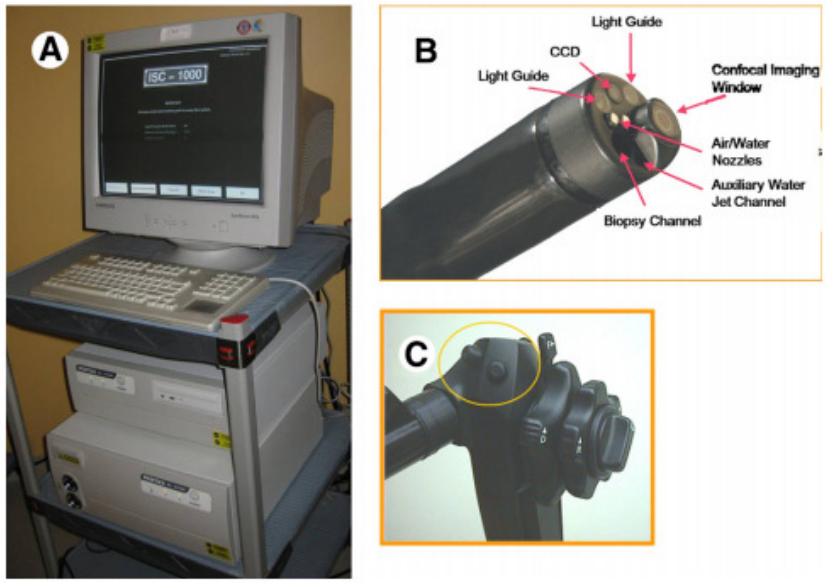
What is the future?

J. Biophoton. 1, No. 1, 13–23 (2008) / DOI 10.1002/jbio.200710022

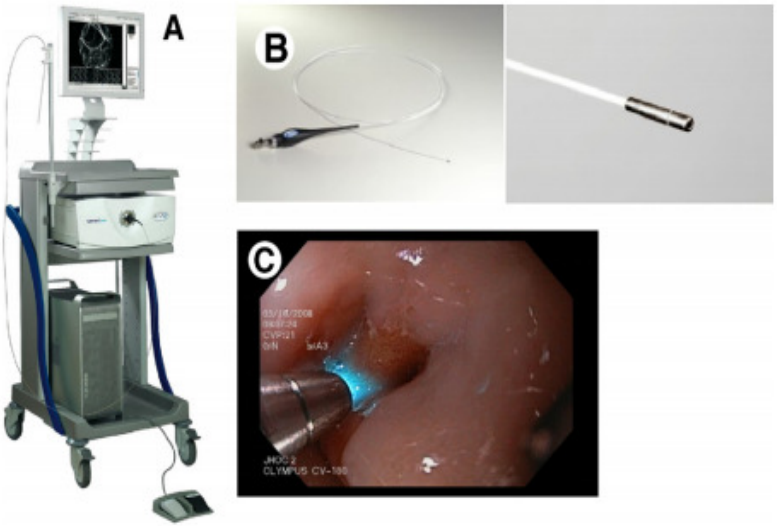
Journal of
BIOPHOTONICS

What is the future?





Confocal endoscope (eCLE)



Probe-based confocal endomicroscopy (pCIE)

Confocal Laser Endomicroscopy platforms and equipment

Techniques in Gastrointestinal Endoscopy (2010) 12, 90-99

Acknowledgements

National Natural Science Foundation of China

(60508017) (30970783) (81271620) (61275006) (81101209)

Program for Changjiang Scholars and Innovative Research Team in University (IRT1115)

Program for New Century Excellent Talents in University (NCET-07-0191)

Natural Science Funds for Distinguished Young Scholar in Fujian Province (2009J06031)

Acknowledgements

J X Chen S M Zhuo X Q Zhu L Q Zhen X S Jiang N R Liu

Yale School of Medicine

Yale UNIVERSITY

福建医科大学 FUJIAN MEDICAL UNIVERSITY

福建省肿瘤医院 福建省肿瘤研究所

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