Endoscopically targeted detection of angiogenesis and its inhibition

Alexander Meining
Angiogenesis occurs early and is a necessary condition for sustained tumor growth

Ferrara, Oncologist 2004
Magnifying endoscopy

- Area formation
- Microvascular proliferation

(courtesy of Dr. H. Inoue)
Methods available for improved visualization

• Modification of emitted light spectrum
  – Narrow Band Imaging (NBI)
  – Autofluorescence Imaging (AFI)
• Post procedural color change/ computerized virtual chromoendoscopy (CVC)
• Dynamic imaging => fluorophore IV
  – Fluoresceine enhanced AFI (FAFI)
• Visualization/ Determination of vessel density => confocal laserendomicroscopy (CLE)
• Biology of „whole“ tumor angiogenesis
  – Fluorescence Tomography
  – PET Scan
Conventional White Light

- White light is composed of an equal mixture of RGB wavelength.

Narrow Band Imaging - NBI

- Narrow band light is composed of two specific bands that are strongly absorbed by hemoglobin.
- The light absorption characteristic of hemoglobin as a function of wavelength.

Short wavelengths have shallow penetration characteristics whereas long wavelengths penetrate deeper into the mucosa.

415 nm light
- Short wavelengths penetrate only the superficial layers of the mucosa.
- Absorbed by capillary vessels in the surface layer of mucosa.

540 nm light
- Longer wavelengths penetrate deeper compared to 415 nm light.
- Absorbed by blood vessels such as veins which are located deeper than capillary vessels in the surface layer of the mucosa.
NBI for better tumor detection?!
Narrow-Band-Imaging (and CVC)

• Microvessels become better visible
• Images are better perceived
• Comparison with white light imaging: no benefit!
• Objective assessment difficult

Wolfsen et al., Gastroenterology 2008
Curvers et al. Gastroenterology 2008
Wouters et al., Gastroenterology 2008
Kaltenbach et al., Gut 2008
Adler et al., Gut 2008
NBI-images are better perceived but detection rate of lesions is similar to standard imaging

Fluorescein-enhanced imaging for detection of angiogenesis?

1. Standard
2. Autofluorescence
3. NBI
4. AFE (+ Fluorescein)

Lim LG 2010
Before injection  
Successive image captures after fluorescein injection
Combination of different imaging methods for better detection and monitoring of angiogenesis?
Step 1: know where to look (red flag)
Step 2: look closer
Step 3: apply color
Sufficient information about smaller streets?

Sufficient information about microvessels?
Step 4: maximize zoom
Confocal laserscanning endomicroscopy
Non-neoplastic BE

Micro vessel density (150 biopsies/sequences): 22% (BE neoplasia) vs 12% (no neoplasia); p<0.01

*Becker et al. Endoscopy 2008*

Low grade IEN BE

High grade IEN BE
Endoscopically guided confocal laserscanning microscopy (CLSM)

Vessel length

Vessel area

CLSM

IHC

Becker, V./Kerle, I.
CLSM for monitoring of anti-angiogenic therapies

AOM

\[ \text{Sunitinib} \]

\[ \text{CLSM} \]

**vessel length**

Before: \[ p < 0.0001 \]

After: \[ p < 0.0001 \]

**vessel area**

Before: \[ p < 0.0001 \]

After: \[ p < 0.0001 \]

Becker, V./Schwitalla, S.
Step 5: analyze “landscape” beyond/around!

In vivo imaging underneath the surface?
Endoscopic ultrasound
Conclusion

- Angiogenesis is the hallmark of neoplasia
- Endoscopic imaging aims to better detect angiogenesis
- Combination of various endoscopic methods appears most appealing

**Perspectives:**
- Dynamic imaging using fluorophores
- Imaging of deeper layers
- Further integration of various/other imaging modalities