Assessment of intra-operative surgical margins in skin cancer using high-definition optical coherence tomography imaging

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MOHS bakery: Tübinger torte, muffins & bread
MOHS: late but no too late
1. Skintell: HD-OCT the first high resolution working in real-time.

2. The path into in-vivo diagnostics: morphology & cellular elements

3. MOHS: workflow & situation
   - MOHS situation:
   - Challenge for in- & ex-vivo imaging
   - First results: Germany, USA, Australia

4. Conclusion and how to continue...
Optical Coherence Tomography

Uses Light: NIR (Near Infra Red) 1300 µm

Time Domain

Uses optical components

Creates an image

Low Coherent No Laser Interferometry Light=Ultrafast

3D images
Vertical = “scan”
Horizontal = “en-face”

“Ultrasound Imaging with Light”
Comparing Imaging: resolution vs depth

Comparison to other non-invasive technologies

- High-Frequency Ultrasound
- Multi-Beam Optical Coherence Tomography
- High-Definition Optical Coherence Tomography
- Reflectance Confocal Microscopy
- Dermoscopy

Penetration Depth:
- 2 cm
- 2 mm
- 570 μm
- 200 μm
- Surface

Lateral Resolution:
- High: 1 μm, 3 μm, 7.5 μm
- Low: 50 μm

Surface Penetration Depth and Lateral Resolution Comparison
SKINTELL: High-Definition Optical Coherence Tomography

• HD-OCT and RCM are imaging techniques allowing real time and non-invasive quality monitoring of tissue
A signal is only produced if:

“time of flight” from mirror to detector = “time of flight” from a structure to detector

Interferometer: Depth selection/Signal generation

Low coherent source

Skin with structures

Light power

Detector

“A-scan”

Depth

Moving mirror to select depth
Suppression of scattered light

A sharp image is only produced by light rays that go directly (on a nearly straight line) from the object to the detector (eye).

Scattered light rays from other objects which do not reach the detector (eye) on a straight way lead to an un-sharp image (shower curtain effect).
Suppression of scattered light: interferometry in OCT

OCT can blank out scattered light using only the “coherent” part of light → sharp image

“the interferometric technique can be understood as a time of flight measurement”
Dynamic focus tracking guarantees high resolution in all depths;
→ resolution of 3 µm in all dimensions;
“Voxel” size: 3µm x 3 µm x 3 µm
The “classical” OCT mode: lateral x depth
2d images are generated in real time (“like a cut with a razor blade”). The image size is 1,8 mm by 1 mm (640x200) with a resolution of 3 µm. The tool can be slowly be moved over the skin while imaging.

Special mode in real time: lateral x lateral
2d images are generated in real time. The imaging depth can be chosen freely down to 1 mm (“like peeling off the upper layers”). The image size (FOV) is 1.8 mm by 1.5 mm (640x512) with a resolution of 3 µm. The tool can be slowly be moved over the skin while imaging.

Special mode fast 3d capture: lateral x lateral x depth
A full 3d volume is captured. Arbitrary cuts and perspectives can be chosen by software after capturing. The tool has to be static for 1 sec to capture the cube (640x512x200).
Image on the workstation

A-scan

“en-face”

en face

Image comment
3D view

4D view X: 204, Y: 55, Z: 245

4D view X: 262, Y: 51, Z: 245

4D view X: 264, Y: 55, Z: 245

Slice

wetransfer-40e75dHMT2 03A0001.avi
Scattering at small particles is the main mechanism of image generation but also of image fade out.
What you will see in the skin with OCT

- The incoming light is absorbed (limits the depth) and reflected (creates the image).
- Reflection occurs by change of the refractive index (mean index=1.4) at the borders of structures: high reflection = white
  - Fibers are highly reflective
  - Keratin and melanin: highly reflective and refractive
  - Nucleus, organelles = moderate reflective
  - Water and intra- and interstitial fluid = low reflective (black)
  - Artifacts: transition air-skin or air-water = “blinding” reflection. Use coupling gel !!

Incoming infrared light

reflected infrared light

Skin surface

Scanning depth
Origin of the OCT image: model

Image

organelle
nucleus
cell
refraction

refractive index

nucleus of cell

nucleus

Image

x
Correlation with histology: model
From HD-OCT to histology
OCT OF FOREARM
OCT AND AGEING

Younger skin:
- Upper part of papil ~age
- Elastase increases with age

Older skin:
Skin with Nev Doveret.
IMAGING ACTINIC KERATOSIS BY HIGH-DEFINITION OPTICAL COHERENCE TOMOGRAPHY

- HD-OCT facilitates the in vivo diagnosis of actinic keratoses
- Allows the grading of different actinic keratosis lesions
- Able to identify subclinical AK
- Therefore useful to survey photodamaged skin in setting of field cancerisation
What we need is consistent imaging: before – during - after

Actinic Keratosis
Graded AK KIN III
Bowenoid histologic variant

Before therapy

After 3 weeks of therapy

After 3 months

Photo-damaged “normal looking” skin
• Dx: margins? No biopsy
• # of cuttings: 1 - ? Time & cost
• Success/relapse
• 13 million skin-biopsies/yr
• 3.6 million new skin cancers/yr
• ¼ treated with MOHS by >900 recognized MOHS surgeons
• 1000 MOHS surgeries/yr/surgeon
• “cheaper” alternative to local treatment.
• Is a real business.. Difficult to change
Finding the margins: concordance?

Fig 3. Pretreatment (A) fluorescence under Wood lamp after 13-hour preincubation with methyl aminolevulinate (MAL) (Metvixia, Galderma Laboratories, LP, Fort Worth, TX) (35 mm²) and post-Mohs micrographic surgery defect size (B) (42 mm²) with MAL fluorescence underestimation of microscopic margins by 16%.
Role of “3D in-vivo” imaging

- OCT or RCM: are powerful in NMSC Dx
- Determining margins in vivo: difficult positioning and localization and limited FOV (even in mosaic image)
- Imaging of specimen: both sides possible (control of depth of tumor), FOV is limited,
- SKINTELL: FOV is 1.5x1.8 mm, depth 650 µm, approx 1.5 sec for 3D image.
- HD-OCT Criteria for SCC & BCC
• Moving the probe to the right, shifts the field of view up in the GUI
• Moving the probe up, shifts the field of view to the right in the GUI
MOHS in Munich 2012: 20 BCC cases

Ex vivo high-definition optical coherence tomography of basal cell carcinoma compared to frozen-section histology in micrographic surgery: a pilot study

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• 4 views (every 90°) per fresh ex-vivo specimen. Incomplete!
• In 2012 no clear BCC algorithm in place. Will be published soon.
• Sens = 74%, spec = 64%, PPV = 61% << than in-vivo results
1. ED architectural disruption, thickening….
2. DEJ disappears: SCC?
3. DEJ line broken = invasive?
4. DEJ “pushed down” superficial BCC?
5. Spheric volumes: nodular BCC?

Grey > Black > White
BCC Diagnosis with Skintell
Preliminary results from country N°1

- Pre-study test:
- Sample preparation:
  - Fresh sample (full thickness): best (but excision artefacts)
  - Frozen sections: rapid degrading of cells (swelling)
  - Frozen and stained:
    - Optimal thickness: 3.5 µm (normal routine): difficult and little information (resolution is 3 µm), 30 µm gives already information.
    - “en-face” images @ different depths: coherent information.
    - Localization and positioning possible with color markers.
    - Need to be confirmed with series.
MOHS excision fresh (1st cutting), epidermal side, depths
Thickness & staining of excision samples

- 30µm without gel
- 30µm with gel
- 30µm middle
- En-face
- En-face
Sample thickness: 30 vs 3 µm
Real-time through specimen
Margin determination pre & intra-operative

In-vivo

Ex-vivo

1.5mm
En face HD-OCT Images of dermal matrix
Matrix remodeling upon incubation in the presence of fibroblasts

Without cells  With cells (9 days)  With cells (19 days)