Advances in Ocular Imaging

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**Ocular Imaging**

- Continues to revolutionize our field
- Improvements in imaging
  - Allow early diagnosis
  - Allow us to treat earlier/appropriately
  - Allow us to monitor patients over time
- Improvements in Imaging
  - Seem to occur daily

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**What it's like to buy a new machine**

"I need something between cutting-edge and new-fangled."
Which is the best imaging test to buy?

I won’t argue about which tool is the best
Before I buy a system, is it useful?

- What information can be gained?
- How does it impact patient care?
- Reality – in times of cost containment – we have to prove why its worth the cost and time

Purpose of this lecture

- Discuss three relatively new imaging modalities and impact on clinical practice
  - Wide field Imaging
  - OCT Angiography
  - Intraoperative OCT
- Discuss the future of software development and its impact
What does wide field offer?

Since 1970: Contact Systems
Heidelberg Non-Contact Widefield

Courtesy Prithvi Mruthyunjaya, MD
**Heidelberg Non-Contact Widefield**

Courtesy Heidelberg Engineering

**Optos**

Courtesy Optos Plc
Optos

Optos Artifacts
Widefield Imaging Clinical Utility

- Documentation
- Diagnosis
- Treatment
- Analysis
Diabetes

Identification of Neovascularization

- NVD
Identification of Neovascularization

- NVE
Peripheral Ischemia

Peripheral Ischemia
Diabetic Eye Exam

Diabetic Eye Exam
Diabetic Eye Exam
Sickle cell
What about Uveitis?

- Inflammatory disease may be an ideal disease
- Consequences of inflammation are often beyond the posterior pole
- Decisions on therapy sometimes are made on incomplete information
- Especially true for retinal vasculitis, pars planitis

16 year old girl presents with decreased vision right eye greater than left eye for 12 months

- Diagnosed with uveitis
- Treated with low dose methotrexate
- CME is gone, OCT is normal
- Why can’t she see
- Few cells in the back of the eye
Wide field angiography

- Identification of leakage – sign of activity
**Case Presentation**

- 29 year old female
- SLE
- Presents with complaints of recurrent vision changes OS
- Loses vision then comes back
- 20/20 OU
Case Presentation

- FA quiet
- But symptomatic – increase immunosuppression
Case Presentation

- Over next few months – a few episodes of vision loss OS
- Quiet exams
- Neg FA
- Then…
Case Discussion

- Next step?
Case Presentation

- Next step
- Yell at the fellow
Retinal Detachment and Schisis
What’s the evidence?

  - Disease activity in widefield + exam 63% vs. standard imaging + exam 51%
  - Disease management changed widefield 48% vs. standard 16%
- Campbell JP, Leder HA, Sepah YJ et al J Ophthalmic Inflamm Infect
  - Disease activity in retinal vasculitis with wide field 68% vs. 45% standard angiogram

Cleveland Clinic Experience

- IRB approved retrospective review
- Patients evaluated using Optos 200Tx between May 2012 and December 2013
- Wide field images were compared to simulated 50 degree image (high magnification)
- Designed and implement a custom Imaging analysis software to quantitate leakage
Peripheral findings on Wide Field Angiography

- 254 patients x 2 eyes = 508 eyes
- Non-perfusion: 14% of eyes
- Leakage: 47.4% of eyes
- Peripheral Lesions: 7.7% of eyes
- Neovascularization: 3.7% of eyes
- Peripheral exudates: 1.5% of eyes

Fluorescein Leakage

- 1053 eye images reviewed
- 600 eyes identified with fluorescein leakage
- Central leakage only: 138 eyes
- Central and Peripheral Leakage: 63 eyes
- Diffuse leakage: 221 eyes
- Peripheral leakage: 188 eyes
**Impact of Widefield Angiography**

- Without it – miss 27% of eyes with peripheral leakage only
- **Severity:**
  - Central and peripheral leakage now seen
  - Diffuse leakage more accurately identified
- If limit analysis to just findings in periphery only:
  - Impacted decision on therapy: 27% of patients
  - Used to rule out inflammation: 19% of patients

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**Fluorescein Leakage and Inflammatory Activity**

- 600 eye images with leakage
- 567 eye images with leakage were deemed clinically active
- 13 eyes were found clinically active of 408 eyes without leakage
**Sensitivity and Specificity**

<table>
<thead>
<tr>
<th>FA Leakage</th>
<th>Active Yes</th>
<th>Active No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>567</td>
<td>33</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>395</td>
</tr>
</tbody>
</table>

Sensitivity: 97%
Specificity: 92%
Positive Predictive Value: 94.5%
Negative Predictive Value: 96.9%

**Comparison of Widefield to Clinical Activity**

<table>
<thead>
<tr>
<th></th>
<th>Leakage on Widefield</th>
<th>No Leakage on Widefield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AC Cell</td>
<td>.22*</td>
<td>.12</td>
</tr>
<tr>
<td>Mean Vitreous Haze</td>
<td>.54*</td>
<td>.15</td>
</tr>
</tbody>
</table>

* P < .005
**Impact of resolution of leakage?**

**Vision Change in eyes with Baseline Leakage in Retisert Clinical Trials**

<table>
<thead>
<tr>
<th>Level</th>
<th>No Leakage at 24 Months</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>-0.12 (-0.18,-0.07)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Retisert Implant Eyes</td>
<td></td>
<td>-0.17 (-0.23,-0.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fellow Eyes</td>
<td></td>
<td>-0.05 (-0.15,0.05)</td>
<td>0.36</td>
</tr>
<tr>
<td>Standard of Care eyes</td>
<td></td>
<td>-0.19 (-0.39,0.00)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

Srivastava et al ARVO 2012
How much leakage should we treat?

After Ozurdex, 20/40 (2 months later 20/20)
**What about this eye? 20/20**

**IBD patient – 20/20 OU**
IBD patient 20/20 OU – Treat?

6 months later
6 months later

6 months later – still 20/20 Treat?
**Widefield Angiography**

- Can identify consequences of inflammation not seen previously
- May impact treatment decisions
- Which one should I buy?
- Both systems are great and have their own advantages and disadvantages
- Both now perform wide field ICG

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**But, Imaging can only enhance**

- Can’t replace a great clinical exam
- Can’t replace an accurate and careful history
- Imaging findings enhance a clinician’s ability
- Imaging ultimately limited by software and interpretation
- Improvements in imaging can help answer subtle, but complex questions
**OCT Angiography**

- Uses motion of red blood cells against static background to identify retinal vessels
- Requires high speed OCT, motion correction, lots of math and enface imaging
- No leakage, but structural components now visible into choroid

www.youtube.com/watch?v=U6Ubp7ILaM
En Face Visualization of layers based on retinal anatomy
Potential Advantages

- Advantages
  - No injection
  - High magnification of macular flow characteristics
  - With Enface technology – can analyze flow anatomy in a specific layer

- Disadvantage
  - No information about leakage
  - Limited quantitative tools (for now)
  - Subject to imaging artifacts
OCTA in Retinal Diseases

- AMD
- DME
- PDR
- RVO
- CME

OCTA in Uveitis Patient with CME
OCTA – CNVM Formation in Uveitis

Patients

- 65 people with uveitis were enrolled
- 103 imaging sessions
- 86% of patients had posterior uveitis or panuveitis
- 66.7% were female
Patients with CNV

- 8 patients with PIC
- 6 patients with MCP
- 1 patient with AZOOR
- 1 patient with VKH
- 15/16 had been previously treated with bevacizumab for choroidal neovascularization
Findings in patients with inflammatory CNV

- In the 16 patients suspected of having CNV, OCTA identified CNV in 15 patients.
- A network of hyperreflective vessels seen at the level of the choriocapillaris, sometimes extending into the outer retina.
**OCTA vs. FA**

- Corresponding FA was available for 8 patients.
  - In 4 of 8 patients FA suggested presence of CNV
  - In 4 of the 8 patients it was difficult to distinguish leakage from staining of inflammatory lesions.
  - CNV was identified on OCTA in all 8 patients

**FA vs. OCTA**
SD-OCT Findings in PIC/MCP Patients

- Three different types of outer retinal lesions were seen on standard SD-OCT in the patients with PIC/MCP/VKH

OCTA revealed mature vascular formations consistent with a CNV.

The vessels of the CNV tended to be less distinct.

CNV formation in only some eyes

OCTA vs OCT

- Multiple PEDs and CNVMs seen on OCTA
  - In regions with concern for activity the OCTA showed less distinct vessels while there was stability of vessels in the regions that did not appear clinically active.
Change in CNV Over Time

- Initially intraretinal fluid on OCT but no obvious CNV seen clinically or on FA. OCTA shows evidence of early CNV formation.
- OCTA images at subsequent 4 week to 7 week visits after treatment with bevacizumab
- Note the progressive change of the CNV, with small, finer vessel apparent in the earlier images with larger, more distinct vessels in the later images as she is treated with bevacizumab.

OCTA Change Over Time

- 35 year old with MCP
- s/p triamcinolone
- s/p bevacizumab
CNV in PIC

- Rate of CNV in PIC is up to 77%
- Channa et al previously published a case series describing the OCT findings in patients with PIC thought to have isolated inflammatory lesions without underlying CNV.
  - Lesions had elevation of the retinal pigment epithelium and loss of photoreceptors
  - Our study may suggest that those patients did in fact have underlying CNV that could not be appreciated on FA.


Retinal Vasculitis
Retinal Vasculitis Patients

- 19 total patients
  - 9 patients with Susac Syndrome
  - 4 with Behcets’ Syndrome
  - 3 with idiopathic retinal vasculitis
  - 1 with retinal vasculitis associated with PMR
  - 1 with retinal vasculitis associated with anti-synthetase syndrome
  - 1 with intermediate uveitis

Vasculitis with Obvious RAO on OCT

- 44 year old female with Susac syndrome who has had a BRAO in the left eye
- FA shows temporal microvascular remodelling but normal perfusion
- OCT shows thinning in region of RAO
Superficial/Deep Capillary Plexus

Retinal Vasculitis

- 50 year old female with Susac Syndrome

FA appears normal
**Vasculitis without thinning on follow up OCT**

- 48 year old male with Behcets’

**Vasculitis without obvious RAO on final OCT**

- At follow up VA 20/30 and FA with normal appearing perfusion
**Vasculitis without change to perfusion**

- 32 yo with retinal vasculitis from anti-synthetase syndrome

**Limitations**

- Small number of patients enrolled
- No control
- Not masked
- Many do not have corresponding FA, none have ICG
- Our analysis of OCTA at this point
  - Qualitative
  - Rudimentary
  - ? Artifact
**Artifact 1: PROJECTION ARTIFACT**

Light that passes through moving blood encounters tissue below blood vessels. If it hits bumps in the RPE, the RPE will seem to have the pattern of overlying retinal vessels.
Artifact 2: MOTION ARTIFACT

AXIAL MOTION: pulsation of retina and choroid due to cardiac cycle

TRANSVERSE MOTION: from saccades

Artifact 3: THRESHOLDING

OCTa only processes structures with a strong flow signal ➔ the choroid has a low signal if the RPE and CC are intact

In areas of atrophy of RPE or CC, choridal vessels will seem to have flow
How about the OR?

Intraoperative OCT (iOCT): Premise

- High resolution anatomic information is a natural complement to the operating room theater.
- Visualization of the acute impact of surgical maneuvers on the ultrastructure of the eye.
- Provides immediate feedback and guidance to the surgeon.
- Allows assessment of surgical goal completion.
- In essence – with greater visualization, more information, can we become even better surgeons?
Why Perform iOCT?

- Would you like histology-level visualization of tissue during surgery?
- Would you like immediate feedback to know if surgical goals are accomplished?
  - Have I removed the membrane?
  - Is the retina attached?
  - Is the traction relieved?

iOCT: How to use it currently?

- Handheld SDOCT Probes
  - Portable
  - Allows for versatile imaging in multiple situations
  - Limited scan repeatability
  - Lack of eye tracking
  - User dependent
  - Bioptigen, Optovue
**iOCT: How to use it currently?**

- Microscope mounted portable system

**iOCT: Microscope Integrated OCT Systems**

- Current Systems:
  - Cole Eye Institute/Cleveland Clinic
  - Duke University
  - Carl Zeiss Meditec
    - External Cirrus System
    - Rescan 700
  - Haag-Streit iOCT and Moller-Wedel System (outside US)
  - Bioptigen/Leica
**iOCT: Microscope Integrated OCT Systems**

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Ehlers JP, Kaiser PK, Srivastava SK, BJO 2014
Before I buy a system, is it useful?

- What information can be gained?
- How does it impact patient care?
- Reality – in times of cost containment – we have to prove why it’s worth the cost and time

Could this be useful?
Could this be useful?

Clinical Feasibility and Utility:
PINIONEER Study
**iOCT: Purpose**

- **PIONEER Study**
  - To assess the feasibility and utility of intraoperative and perioperative OCT in the management of surgical ophthalmic diseases
  - Anterior segment surgery
  - Vitreoretinal surgery


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**iOCT: PIONEER**

- **PIONEER Study**
  - Cole Eye Institute Ophthalmic Imaging Center
  - IRB-approved prospective single-center multi-surgeon study for use of iOCT across ophthalmic surgery.
  - Includes:
    - 6 VR surgeons, 5 anterior segment surgeons
    - iOCT research coordinators
  - Standardized imaging protocol
iOCT: PIONEER

- PIONEER Study
  - Microscope-mounted handheld SD-OCT probe (Bioptigen SDOIS)
  - Surgeon feedback questionnaire administered for select cases to better identify areas of utility

iOCT: 24-Month PIONEER Overall Results

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>275</td>
<td>256</td>
</tr>
<tr>
<td><strong>Most Common</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative Diagnosis</td>
<td>Fuchs</td>
<td>82 (30%)</td>
</tr>
<tr>
<td></td>
<td>Cataract</td>
<td>66 (24%)</td>
</tr>
<tr>
<td></td>
<td>Bullous</td>
<td>32 (12%)</td>
</tr>
<tr>
<td></td>
<td>Keratopathy</td>
<td>23 (8%)</td>
</tr>
<tr>
<td></td>
<td>Failed DSAEK</td>
<td>16 (6%)</td>
</tr>
<tr>
<td></td>
<td>Keratoconus</td>
<td>56 (20%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ERM</td>
<td>90 (35%)</td>
</tr>
<tr>
<td></td>
<td>Macular hole</td>
<td>58 (23%)</td>
</tr>
<tr>
<td></td>
<td>Retinal detachment</td>
<td>44 (17%)</td>
</tr>
<tr>
<td></td>
<td>PDR</td>
<td>32 (13%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>32 (12%)</td>
</tr>
<tr>
<td><strong>Most Common</strong></td>
<td></td>
<td></td>
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<tr>
<td>Procedures</td>
<td>DSAEK</td>
<td>135</td>
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<tr>
<td></td>
<td>CE/IOL</td>
<td>29</td>
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<tr>
<td></td>
<td>Femto CE/IOL</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>DALK</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPV/SB</td>
<td>253</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
**PIONEER 24 Month Results: Time**

- Average duration surgery paused per scan session:
  - Posterior Segment: 3.4 minutes
  - Anterior Segment: 1.9 minutes
- Total time surgery paused:
  - Posterior segment: 6 minutes
  - Anterior Segment: 3.2 minutes

**iOCT: 24-Month PIONEER Overall Results**

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan Sessions</td>
<td>2 (1-4)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Total Scans</td>
<td>4 (1-14)</td>
<td>10 (1-24)</td>
</tr>
<tr>
<td>Total Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery Paused</td>
<td>3.2 (0.4-17.8)</td>
<td>6.6 (1.0-26.7)</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgery paused per</td>
<td>1.9 minutes</td>
<td>3.4 minutes</td>
</tr>
<tr>
<td>scan session</td>
<td></td>
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</tbody>
</table>
**iOCT: PIONEER Adverse Events and Safety**

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<tr>
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<th>Anterior</th>
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<tr>
<td><strong>Serious Adverse Events</strong></td>
<td></td>
<td></td>
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<tr>
<td>Endophthalmitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other Adverse Events:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial defect</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Elevated IOP</td>
<td>6</td>
<td>39</td>
</tr>
<tr>
<td>Hypotony</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Fibrin</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Hyphema</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

**Impact on Decision Making**

- Membrane Peeling (146 cases)
  - 43% of cases iOCT impacted the surgeon’s understanding of the anatomy and decision making.

Membrane Peeling

- Peel membrane (146 cases)
  - I think I am done: (91/146 cases) 62%
  - I think there is more to peel: (5/146 cases) 3%
  - I am not sure: (51/146 cases) 35%

Membrane Peel – iOCT Answer

- Peel membrane
  - I think I am done
    - 13% of cases additional membrane peeling required
  - I think there is more to peel
    - 40% of cases no additional peeling required
  - I am not sure
    - 94% of cases, iOCT gave definitive answer
Clinical Examples – “I am not sure”

- New discoveries in RD
  - 100% eyes had persistent submacular fluid under PFO

IOCT: Surgical Insights in RD
JPE4  Garbo for vitreous schisis
VMT for butler
Parsley for macula involving RD

Justis P. Ehlers, 10/16/2011
Can iOCT findings predict postop vision?

- Retinal detachment cases
  - Mean retinal thickness under perfluorone - 410 um
    - In eyes with good visual acuity - 389 um vs. 489 um in eyes with poor visual acuity (p < .02)
  - Outer retinal thickness (distance from outer plexiform layer to IS/OS (inner ellipsoid))
    - In eyes with good visual acuity - 94 um vs. 173 um in poor visual acuity eyes (p < .004)

Clinical Examples – Post-op Vision CF
Clinical Examples – Post-op Vision 20/40

iOCT, the move to true integration

- Advantages of Integrated iOCT systems
  - Provides visualization of instrument-tissue interaction for true "real-time" iOCT.
  - Parfocal with surgeon view
  - Rapid scan localization to area of interest
  - Seamless integration of OCT into the surgical procedure
  - Minimal to no increase in surgical time
  - “heads-up” display

Now that we have an integrated system—should I buy one

- Let's ask the same questions again
- Does it help?
- Change decisions?
DISCOVER Purpose

- DISCOVER Study
  - To evaluate the feasibility and utility of real-time intraoperative OCT (iOCT) with a microscope-integrated prototype with a heads-up display surgeon feedback system.
  - Anterior segment surgery
  - Vitreoretinal surgery

Rescan 700: 1 year results

- 227 eyes enrolled
- 121 woman, 106 men
- Average age: 62
- Successful imaging obtained in 99% (224/227)
- Anterior Segment Arm: 91 eyes
- Posterior Segment Arm: 136 eyes
**DISCOVER: Overall Integrated System Feedback**

- Provided valuable feedback: 71% (97/136)
  - Identified membrane edge
  - Lamellar vs full-thickness hole after peeling
  - Confirmation of peel completion
- Altered surgical procedure: 36% (49/136)
  - Aborted need for ICG staining
  - Less surgery/peeling
  - FTMH Identified
  - Placement of drainage retinotomy

**DISCOVER: Impact on Surgical Decision-Making**

- How does integrated iOCT change surgical approach membrane peeling?
  - iOCT revealed residual membrane requiring peeling in 22% of cases (9/41) where surgeon believed peeling was complete.
  - iOCT confirmed complete membrane peel in 14% of cases (4/26) where surgeon thought additional peeling was needed.
  - iOCT was discordant with surgeon observation in 19% of membrane peeling cases
DISCOVER: Overall Integrated System Feedback

- Preferred Heads-up Display: 79% (179/227)
- Preferred Real-time vs Static Feedback: 65% (148/227)
- Potentially Interfere with Case: 3% (7/227)
  - Reasons:
    - Rebooting microscope
    - Lack of foot pedal response

Clinical Examples from DISCOVER Study
Membrane Peel with Forceps

Dense Membranes
Membrane Identification

OCT-guided Fluid Evaluation
Complex anatomy evaluation

Complex Anatomy
Complex Anatomy - Viscodissection

DSAEK Case

Courtesy Prof. Oliver Findl – Vienna, Austria
Is that all?

- With current spectral domain platforms – great information
- To do real-time OCT guided surgery we need some additional enhancements.

Next Generation OCT-Friendly Instrumentation

- Prototypes
Real-Time Tracking and Accuracy

Real-Time Instrument Tracking

Collapsed Frames

5 mm

Software Analysis Algorithms

- Pathology-oriented segmentation algorithms:
  - Allow for pre- and post-analysis of changes associated with surgical manipulation
  - May provide input for surgical decision-making
  - Possible information regarding prognosis
OCT: Automated Ellipsoid Zone and Pathology Analysis

Instrument refinement
Subretinal injection

Future for VR surgery?
Accomplish Surgical Goals

Vitreo-retinal specific software
# Acknowledgments

- **Cole Eye Institute Ophthalmic Imaging Center**
  - Justis P. Ehlers, MD
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