Fiberoptic diffuse reflection spectroscopy for intraoperative evaluation of resection margins during breast cancer surgery.





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Breast cancer

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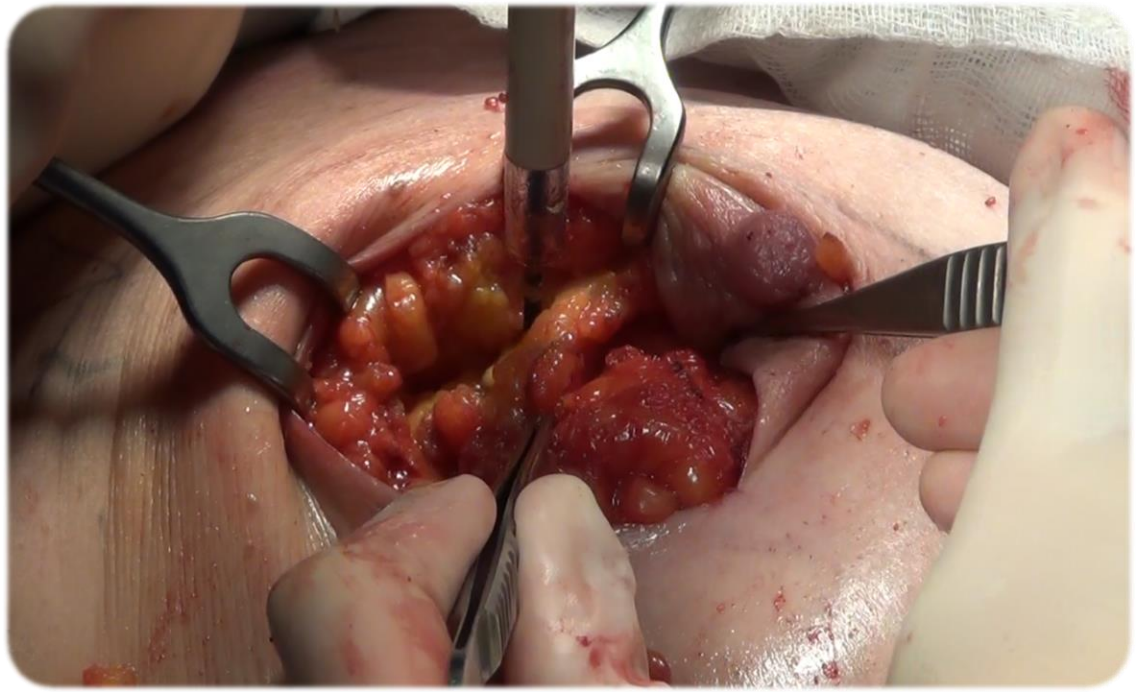
- No metastasis:
  - Excellent survival (>95% @ 5 years)
  - Treated with surgery
    - Previously: mastectomy
    - Currently: breast conserving surgery

- Metastasis:
  - Different ballgame

- 500.000 breast conserving surgeries annually (Europe + US)
- **180.000 incomplete resections (37%)**
- Additional radiotherapy
- Or additional surgery
- Nightmare for the patient
- Dilemma for the surgeon:
  High resection rate vs low cosmetic result
- 3 b€ in additional direct costs (Europe+US).
- ++? b€ in additional indirect costs
  (psychological trauma, plastic surgery etc.)

Dilemma



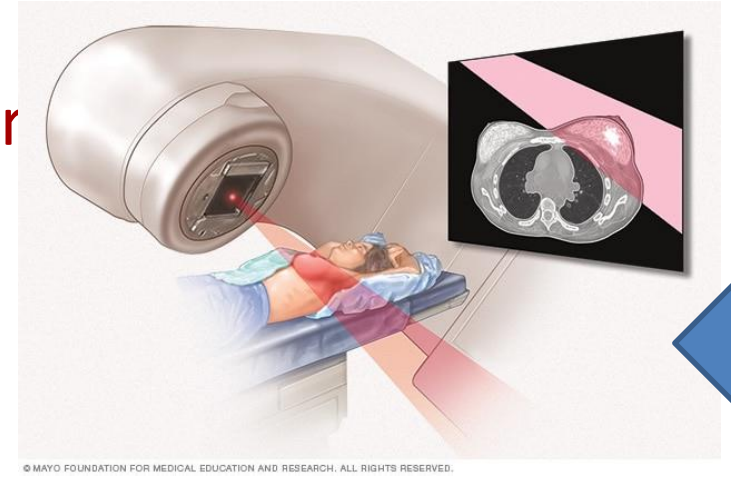
Too small

Too extensive

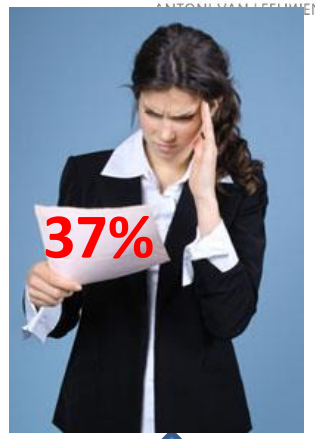
Positive resection margins

Unfavourable for cosmesis

Breast conserving surger



Partly radiotherapy



Partly additional surgery

3-10 days

Many retreatments could be prevented if the proper information would be available during surgery:

Real-Time Margin Assessment

Paint

Slice

Formalin fixation and staining

Investigation

Positive margin

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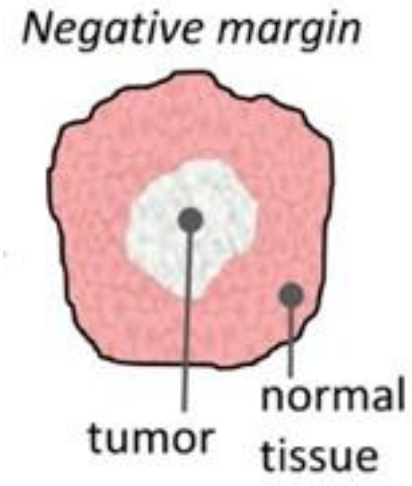
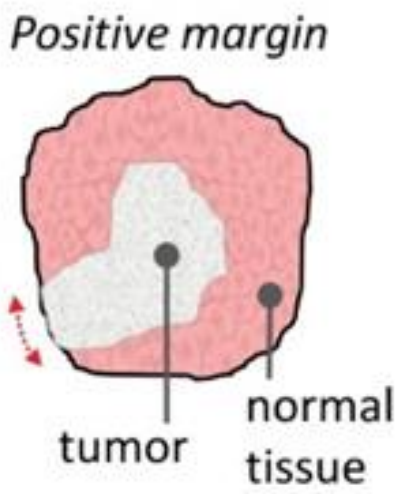
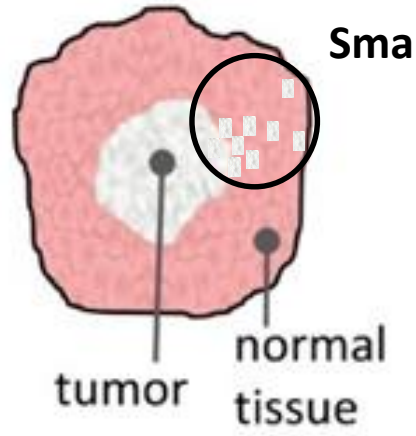
Theory is simple





Reality more complicated



Surgical Guidelines

- 2 mm tumor free zone
- Regular updates
- Are different in different countries.

Ductal Carcinoma in Situ (DCIS) probably responsible for large proportion of positive margins

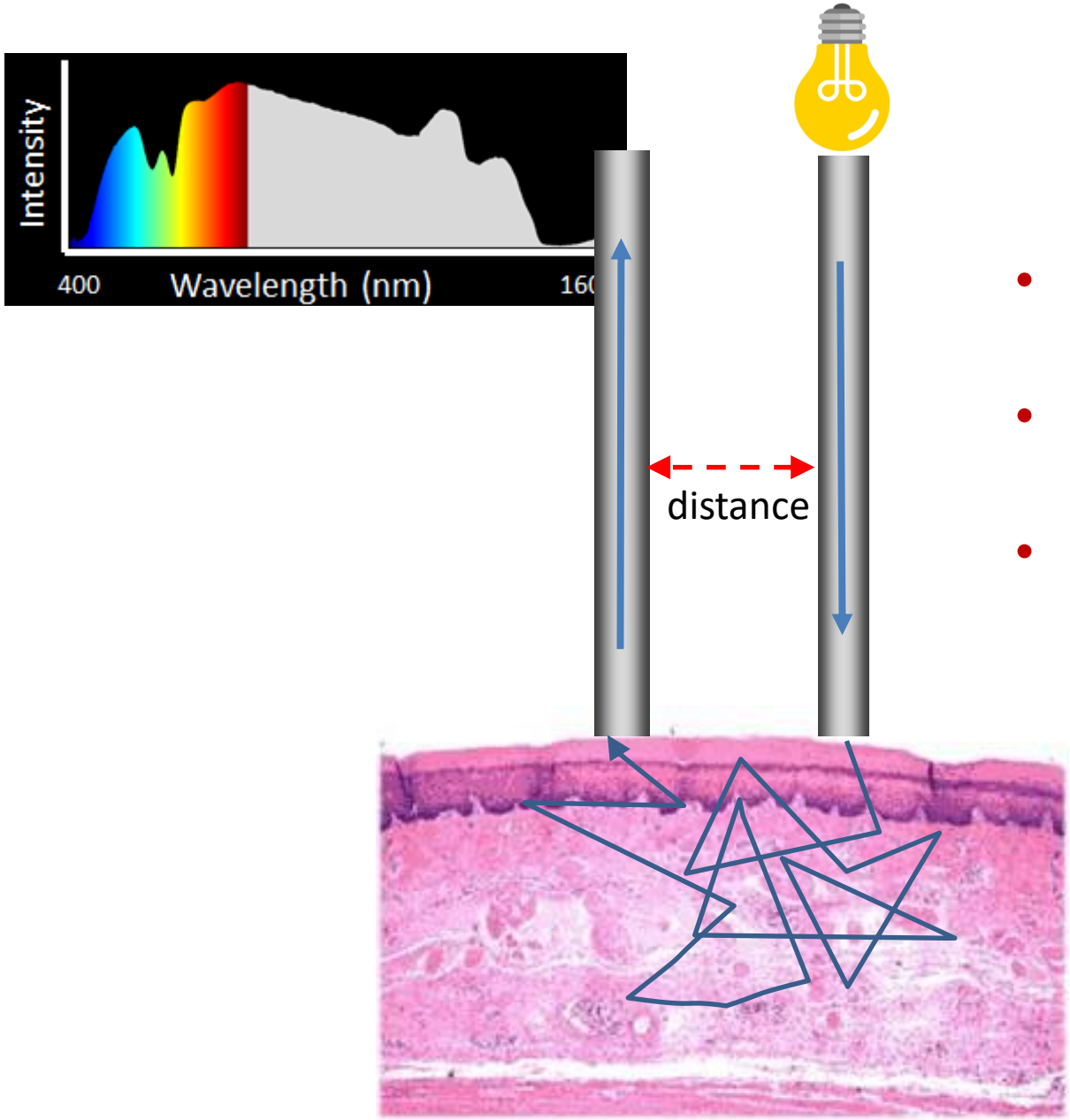
Solution: Boundary conditions

A method for realtime margin assessment in breast cancer surgery should be able to:

1. Distinguish cancer at the resection plane from normal.
2. Detect small pockets (size 2 mm) of cancer below the resection plane at depths of max 2 mm.
3. Sufficiently Real Time, i.e. within minutes so surgeon can take action before the end of the operation.

Diffuse Reflection Spectroscopy

Diffuse Reflection Spectroscopy



- Wavelength range
  400-1600 nm
- Sampling depth varies
  with fiber distance
- Acquisition time
  ~0.1 sec/spectrum

General approach to classification

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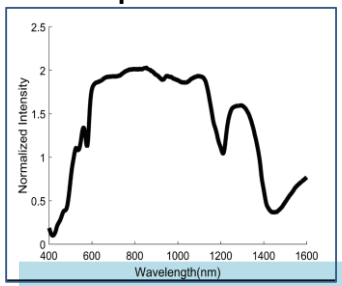
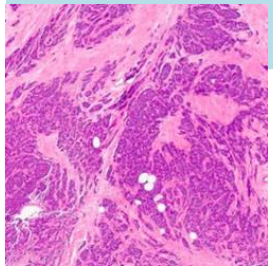
Spectra



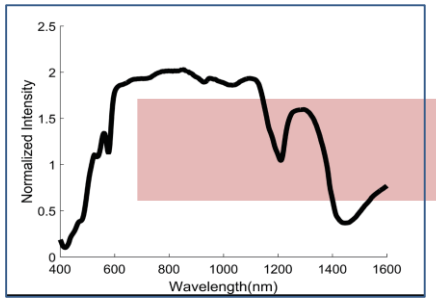
Feature reduction

Database

Training



Gold Standard



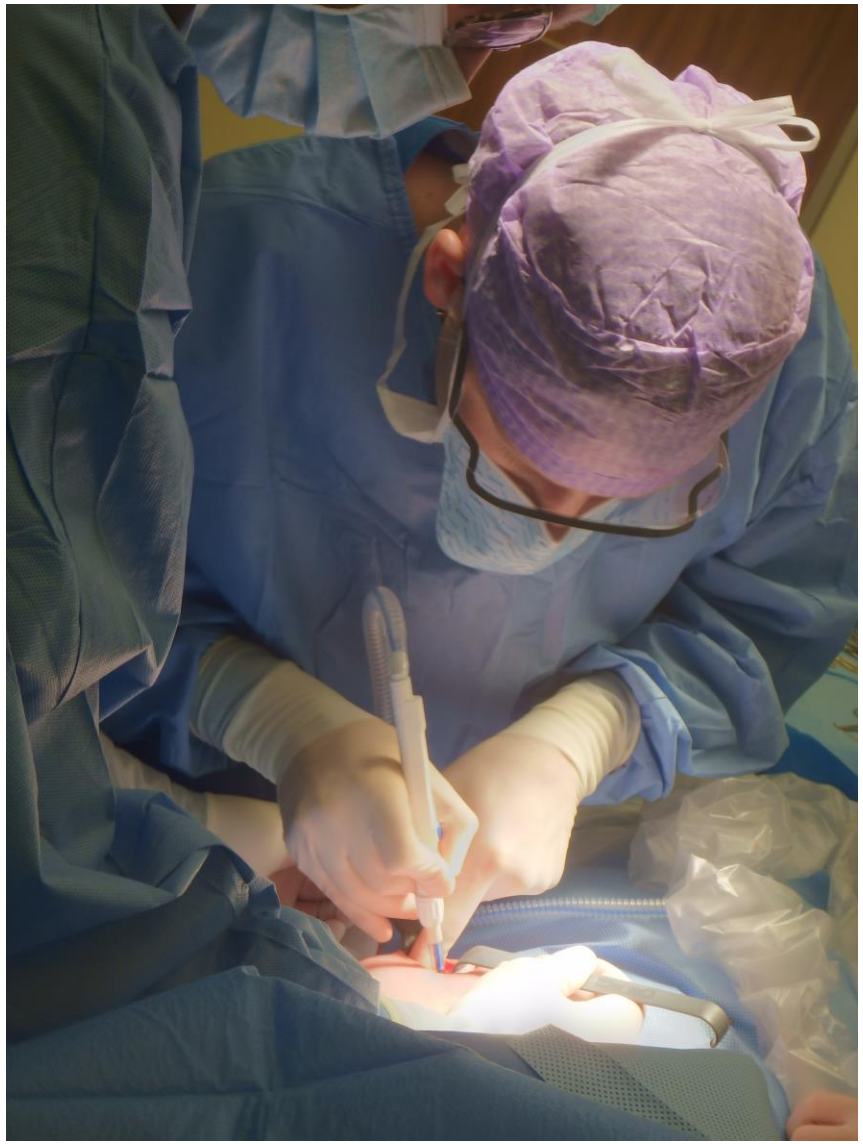
Feature reduction

Algorithm

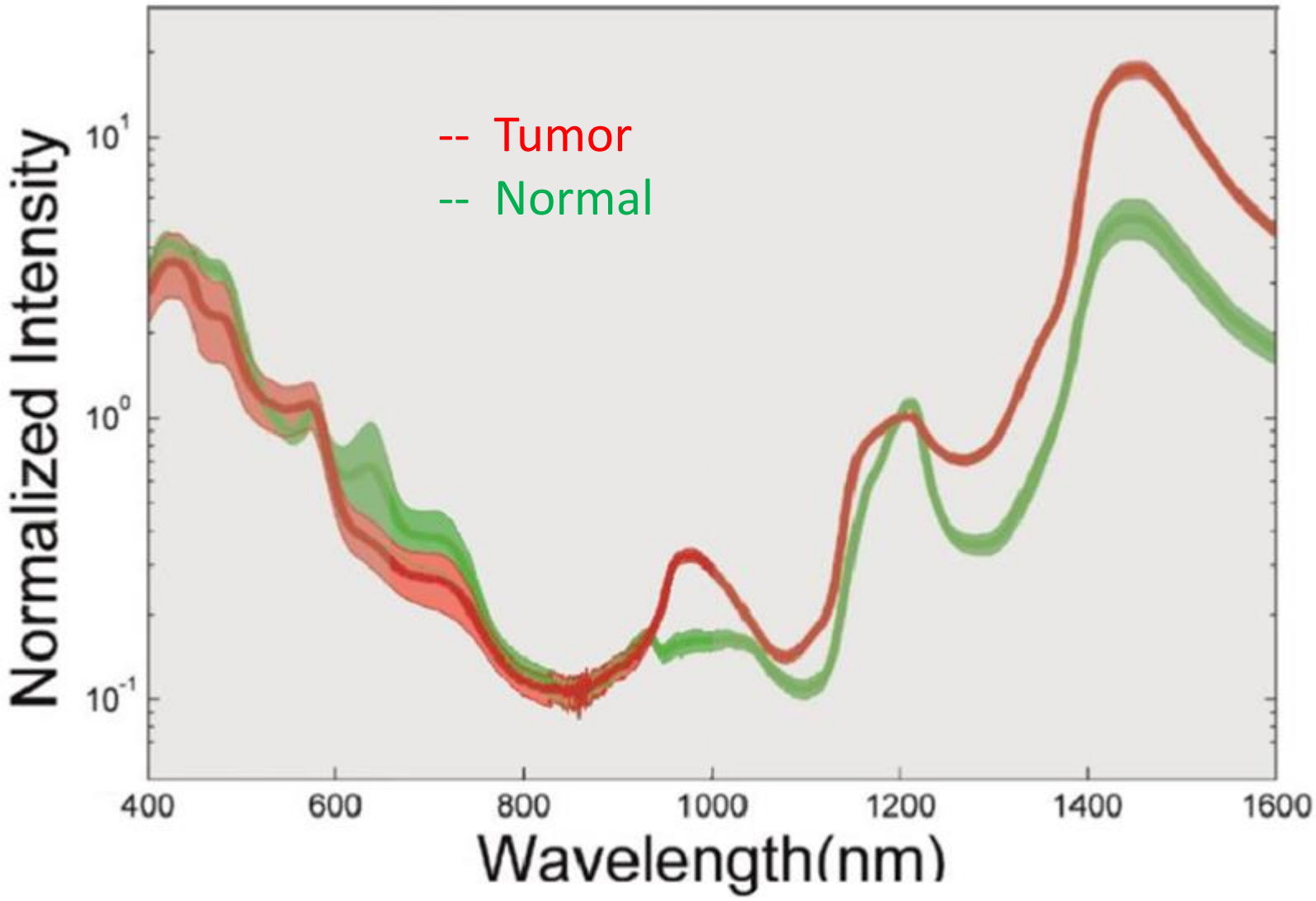
Diagnosis

Early days: ***ex vivo*** spectroscopy: lets play around

- Point measurement
  - Fresh resection sample
  - Cut it in half to expose tumor
  - Measure ***ex vivo***
  - Take spectrum
  - Take biopsy



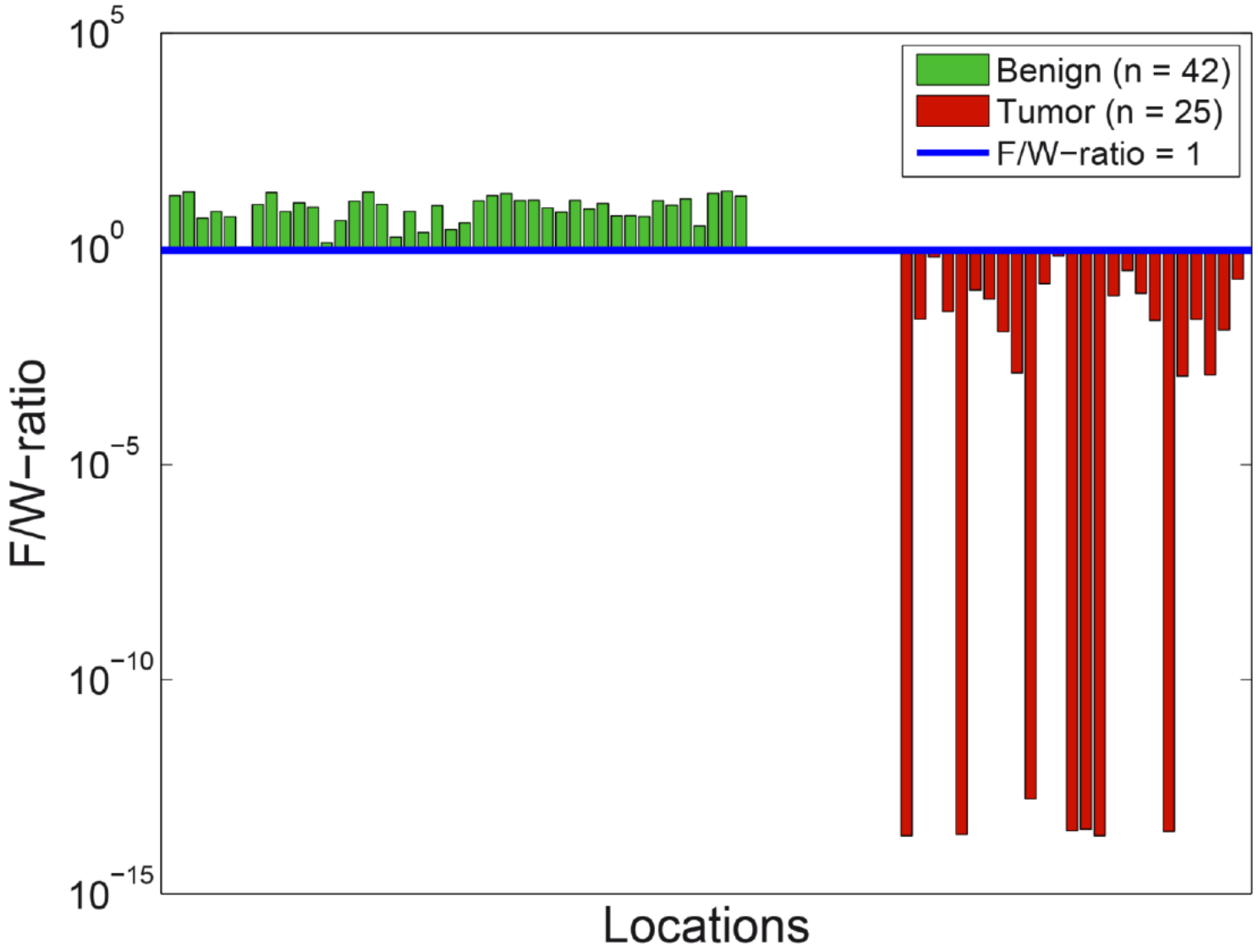
Measured spectra



Average and standard deviation of all measurements

(N=67)

Conclusions Experiment 1



- Feature reduction:
  Fit diffusion model.
- Algorithm:
  Fat/Water ratio<1
- Accuracy = 1

- Beginners luck?
- Too good to be true?

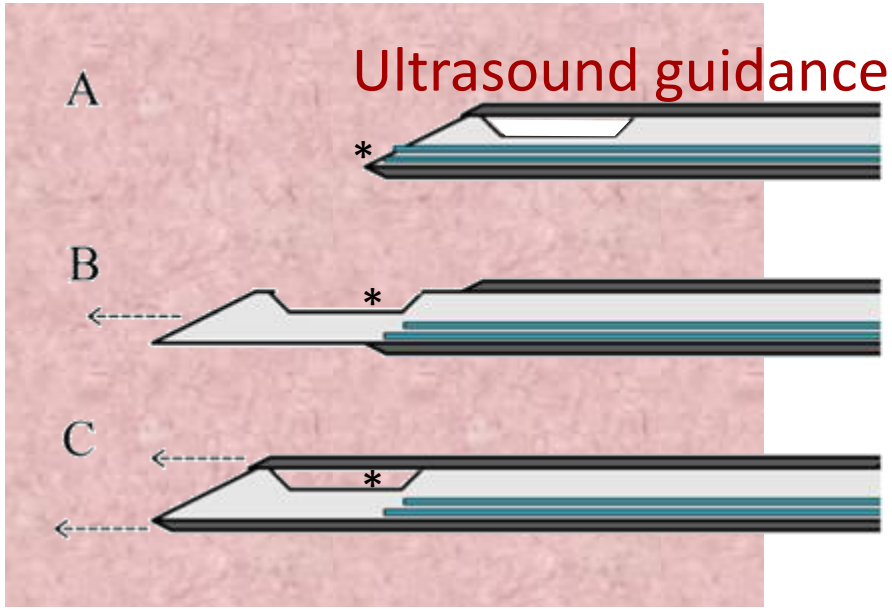
De Boer et al. Breast Cancer Res. Treat. 2015.

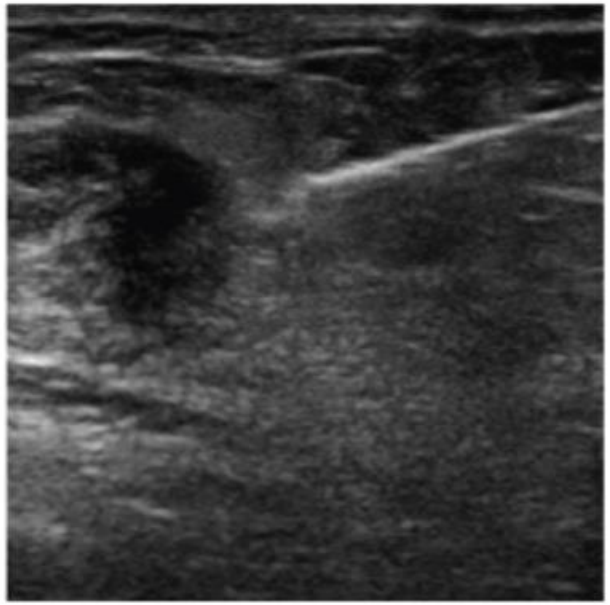
In vivo spectroscopy

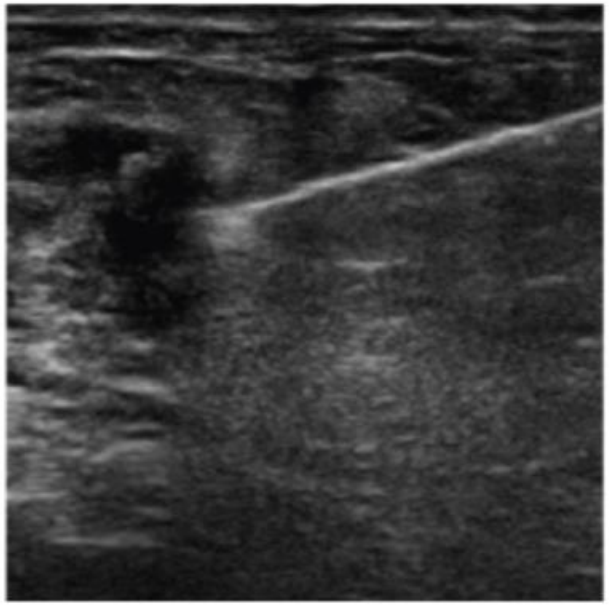
- Through specially designed biopsy needle
  - Take spectrum
  - Take biopsy
  - Ex vivo as well as in vivo

+ Guarantees perfect correlation between location of measurement and optically sampled volume.
+ Enables determination of the presence of spectral differences.
+ Enables evaluation of differences ex vivo-in vivo.
- May not realistically reflect the surgical margin.

Biopsy needle



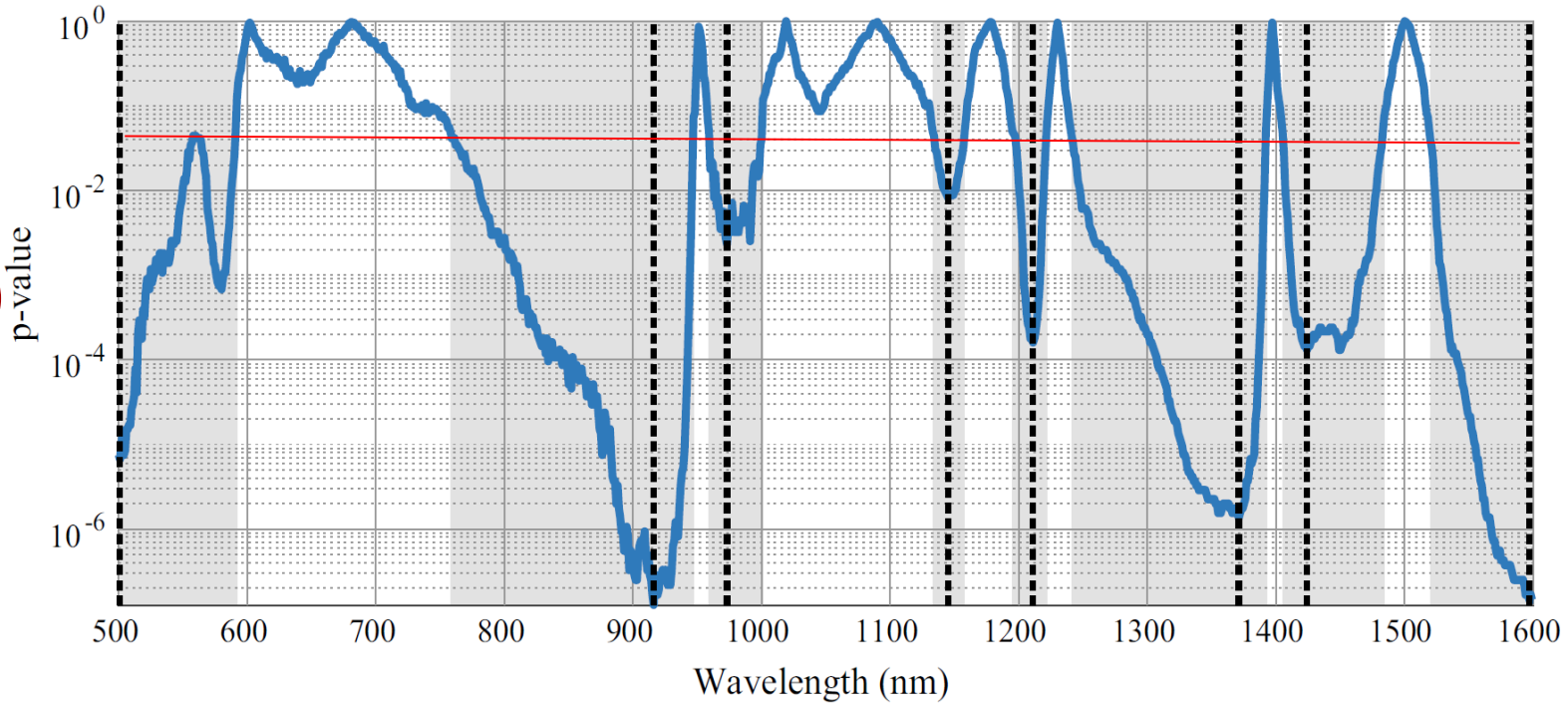




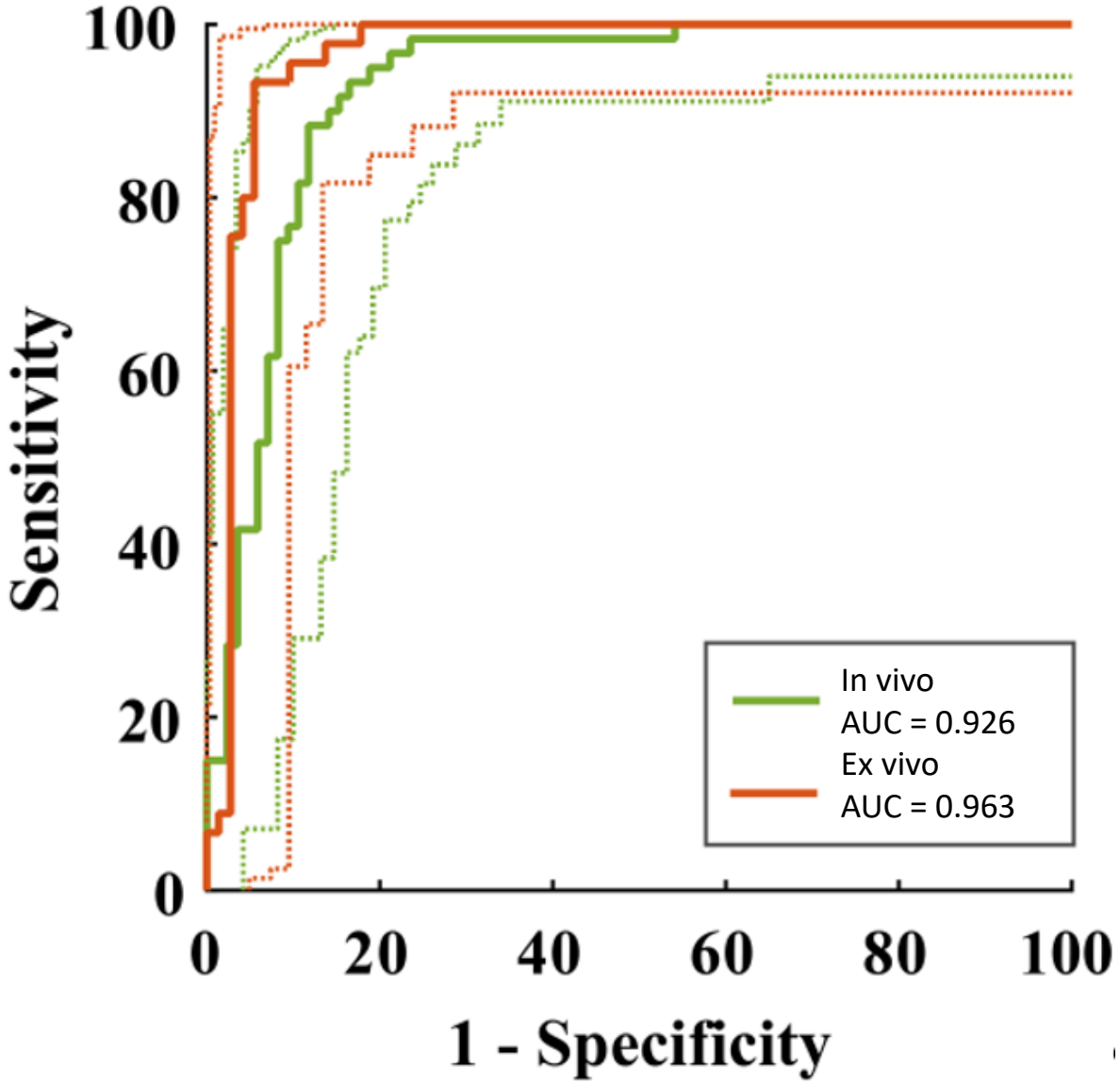
Data analysis: different approaches

- Feature Reduction: Fit diffusion theory and extract chromophore concentrations.
  - Simple classifier based on Diffusion theory Fit and Fat/water ratio: **Accuracy = 0.85**

- Support Vector machine
  - Based on 8 selected wavelengths (Wilcoxon's rank-sum test)
  - **Accuracy = 0.93**



Results biopsy needle



Excellent results

No significant differences in diagnostic performance between ***in vivo*** and ***ex vivo***.

Main spectral differences between ***in vivo*** and ***ex vivo*** in the visible Hb-HbO2 region.

Conclusions

Fit diffusion theory + linear classifier

Accuracy = 0.85

8 selected wavelengths + Support Vector Machine

Accuracy = 0.93

De Boer et al. Biomed Opt Express 2016

Main conclusion:

Excellent result.

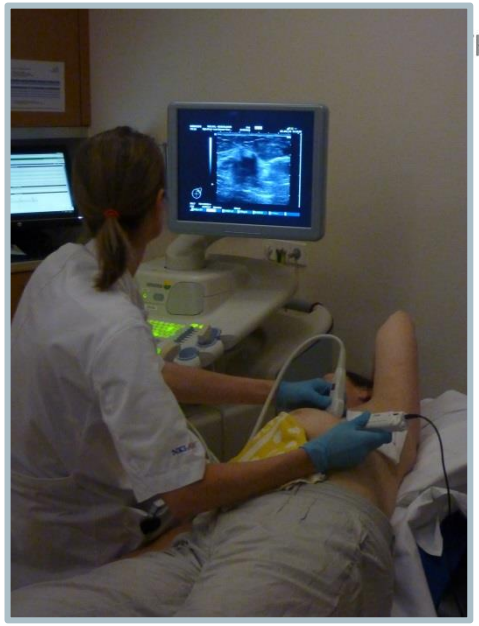
(Not as good as previously, but more realistic dataset)

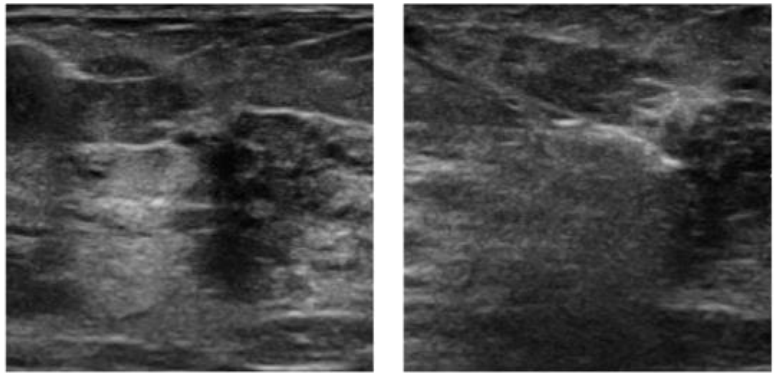
Secondary conclusion:

We can perform evaluation of resection margins either ***in vivo*** during surgery on patients, or ***ex vivo*** immediately after surgery on excised material.

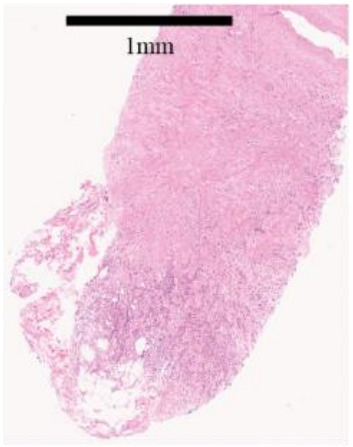
Step aside: Biopsy guidance?

- Use previously trained algorithm for real-time feedback during biopsy procedure
- Convince clinicians that we can make it work in real time during surgery

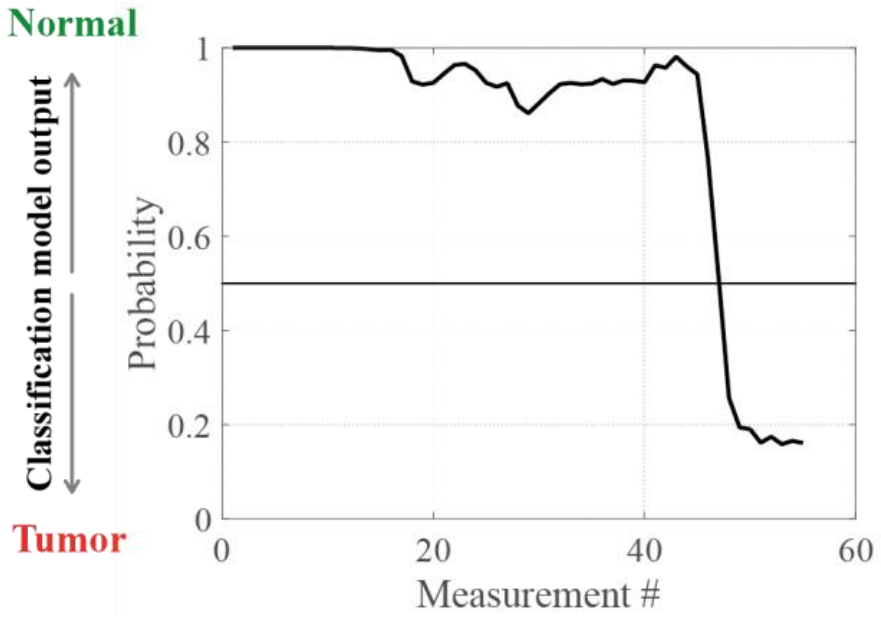




Normal Tumor



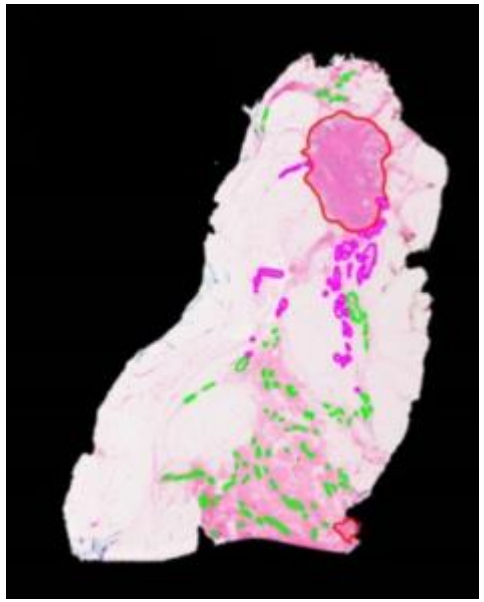
Invasive ductal carcinoma



De Boer et al. 2018 J Transl Med

How to get a maximum amount of data from sample

- Measurement on sliced lumpectomy
  - Take multiple spectra at well controlled locations
  - Make RGB image
  - Register digitized pathology slide to RGB image
  - Determine exact pathological classification of each measurement location



\+ Good correlation with pathology.

\+ Is measurement on a surface.

\+ Large number of measurement locations per patient.

\+ All possible pathology labels will be obtained.

\- Geometry different from in surgical margin.

Procedure

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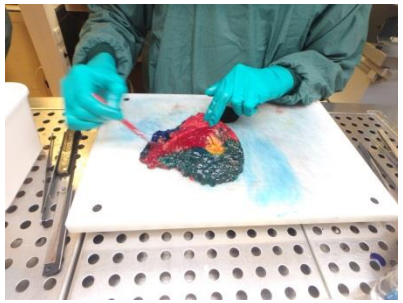
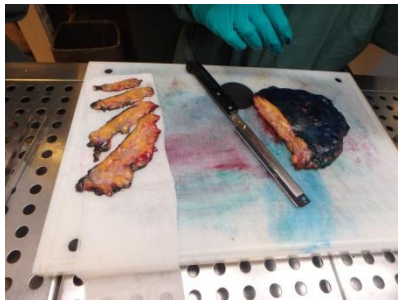
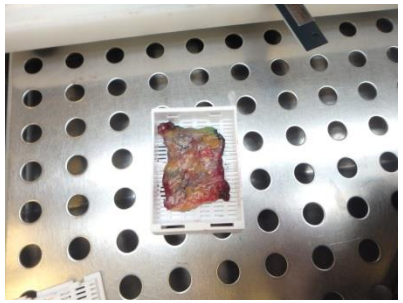
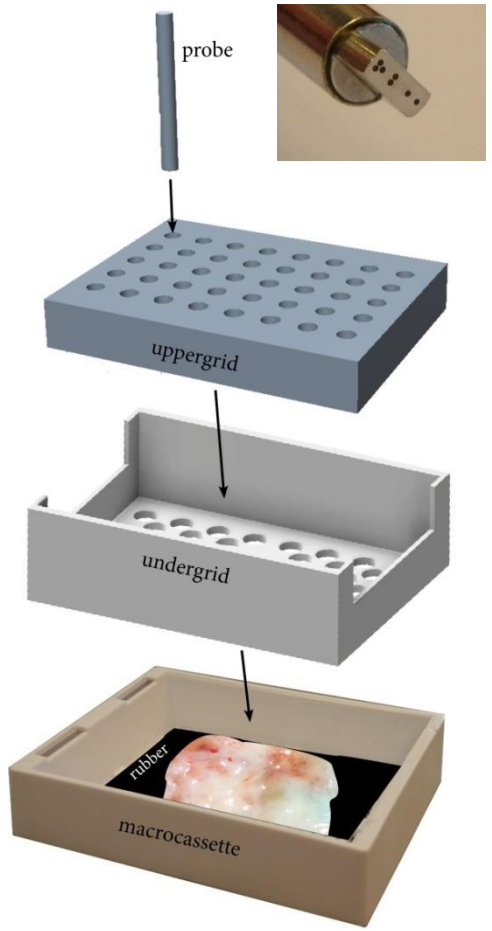
Pathology Department



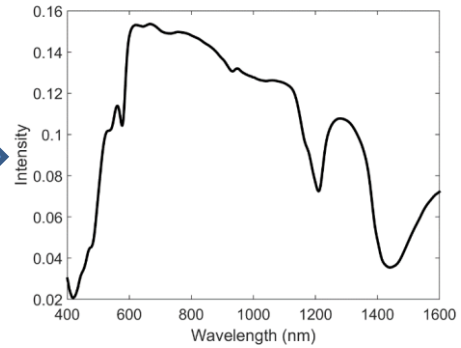




- Measure spectra in predefined locations



Spectra…



… which have to be correlated to histopathology

Registration of H&E slide to RGB image with measurement locations

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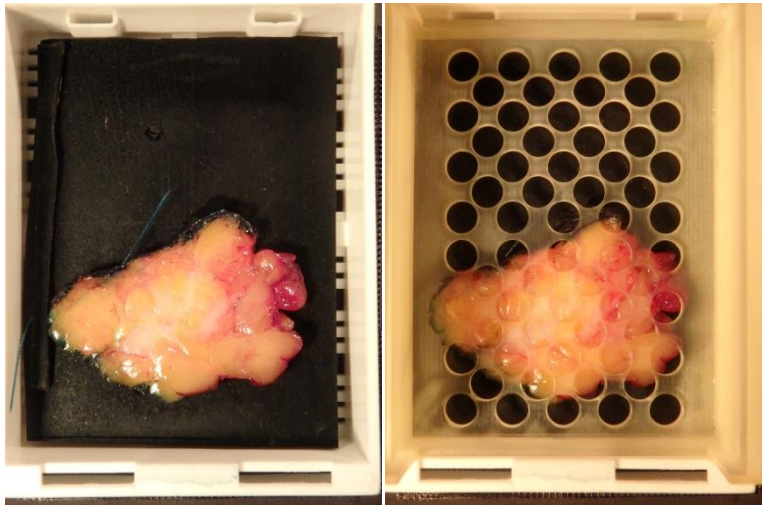
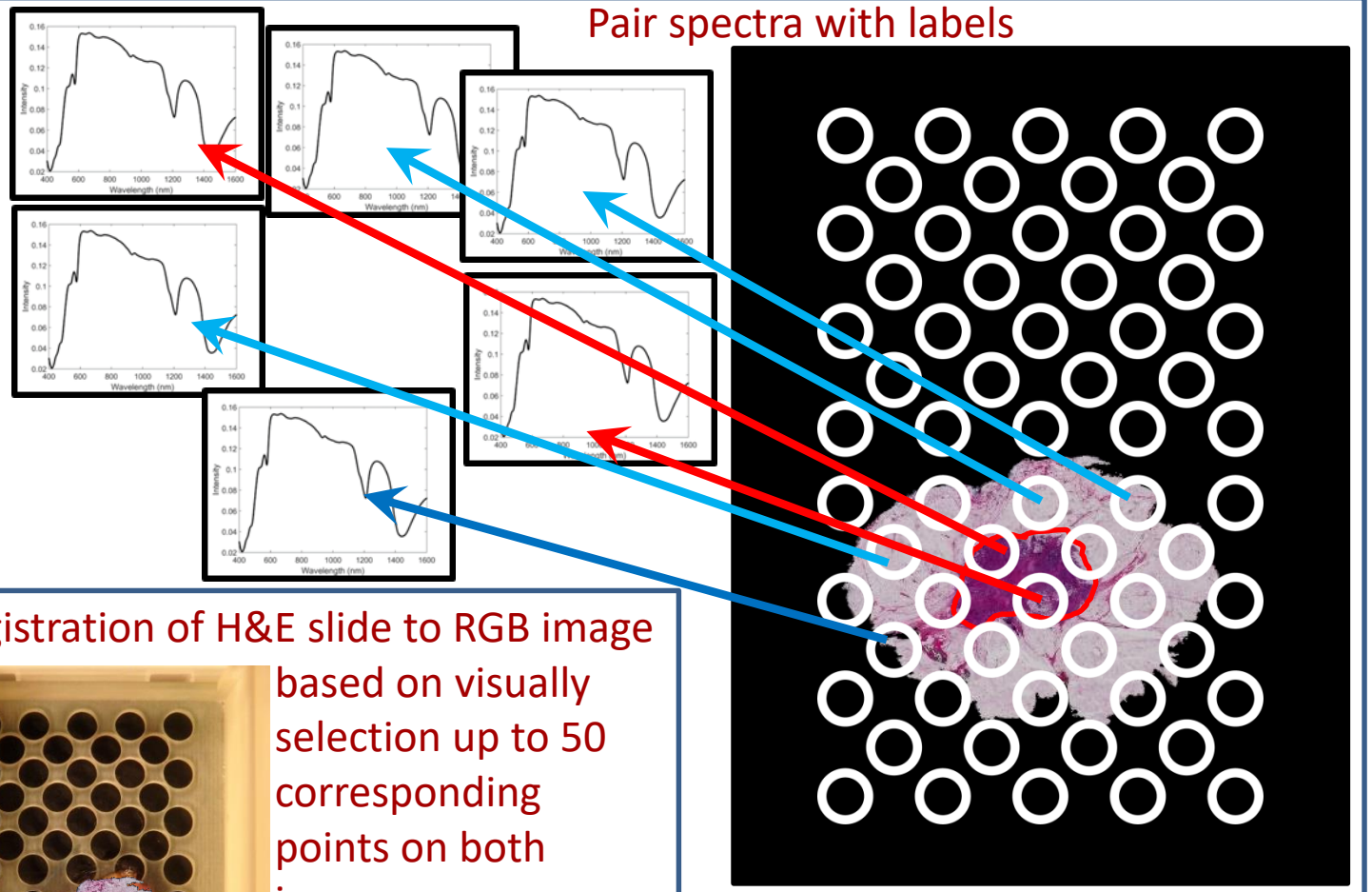
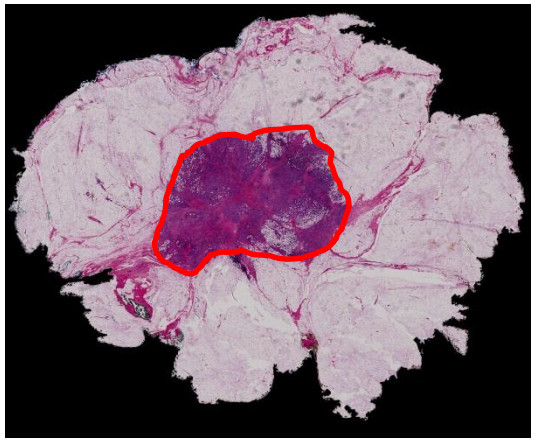
RGB photographs



Pair spectra with labels



Annotated H&E slide



Registration of H&E slide to RGB image

based on visually selection up to 50 corresponding points on both images.

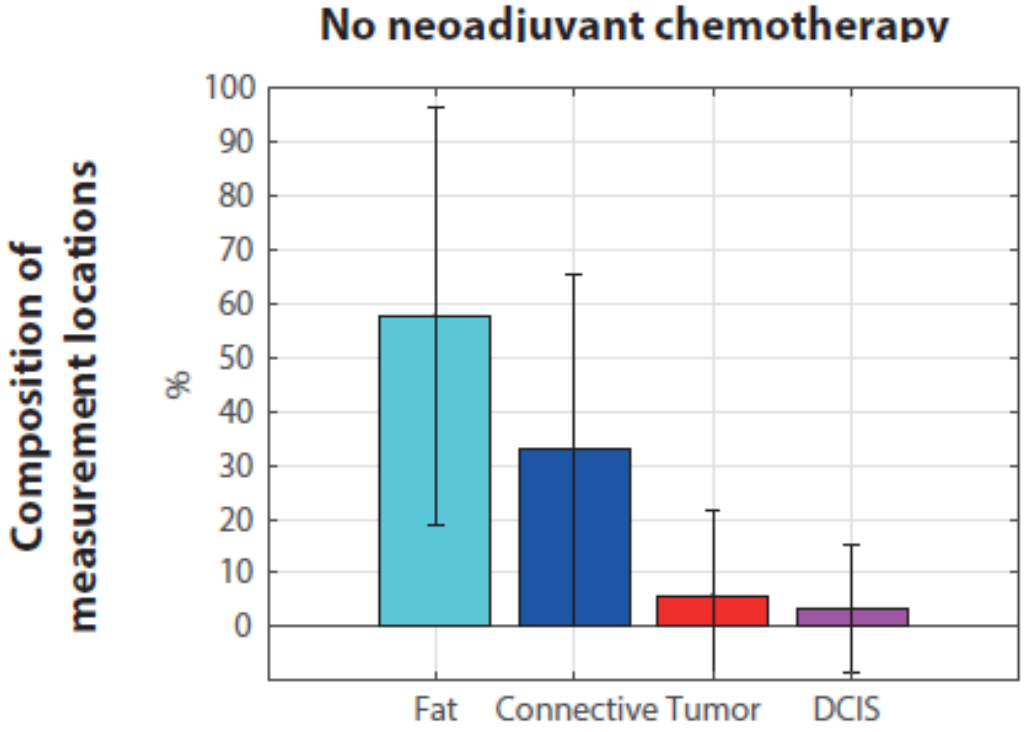
Conclusions

Improved approach seems to work. Correlation with pathology accurate. Large number of data points per sample.

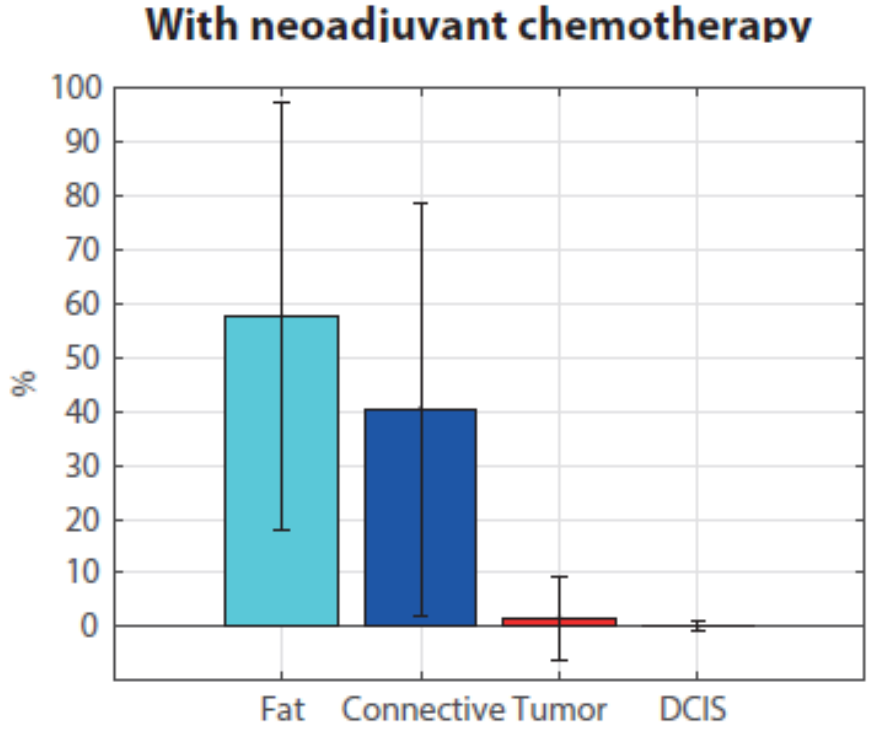
We can now generate large datasets based on ex vivo measurements on freshly excised samples.

2019 De Boer, J Biomed Opt

How about the effect of chemotherapy?



58 patients, 600 measurements



30 patients, 425 measurements

How about the effect of chemotherapy ?

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	Fat dataset		Connective dataset	
Fit parameter	Neo-adjuvant chemo	Menopausal status	Neo-adjuvant chemo	Menopausal status
F/W-ratio	0.51	0.43	0.19	0.77
Fraction Mie scat.	0.52	0.99	0.48	0.82
Collagen (µM)	0.07	0.73	0.61	0.24
α	0.49	0.19	0.12	0.94
b	0.88	0.63	1.00	0.66

	Fat & Connective dataset			Tumor cells & Connective dataset		
Fit parameter	Neo-adjuvant chemo	Menopausal status	% connective tissue	Neo-adjuvant chemo	Menopausal status	% connective tissue
F/W-ratio	0.21	0.41	0.00*	0.11	0.40	0.36
Fraction Mie scat.	0.13	0.22	0.054*	0.64	0.32	0.39
Collagen (µM)	0.26	0.48	0.00*	0.00*	0.01*	0.03*
α	0.56	0.10	0.00*	0.87	0.32	0.34
b	0.44	0.08	0.00*	0.91	0.28	0.99

2019 De Boer, J Biomed Opt. Under review

How about mixed classes?

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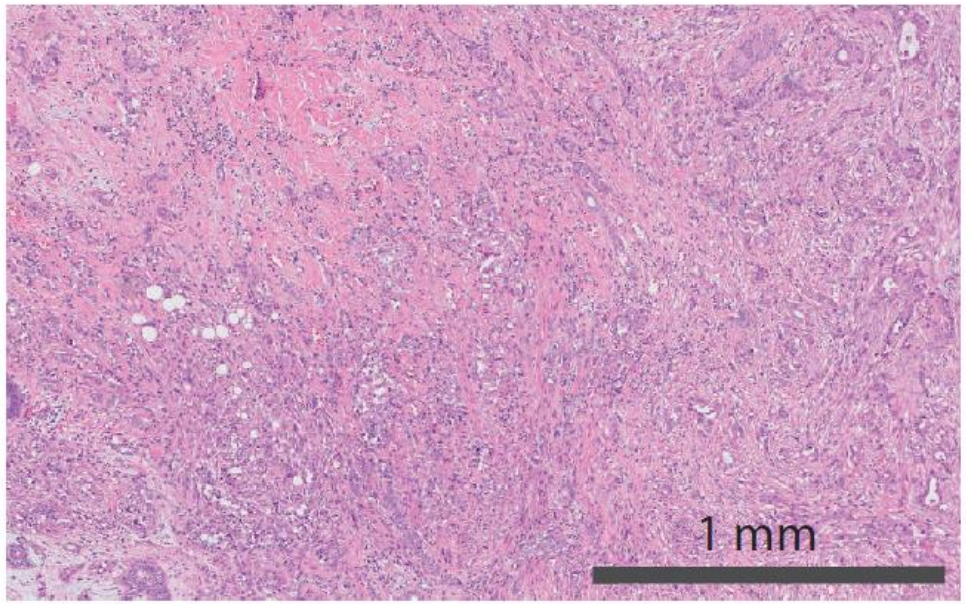
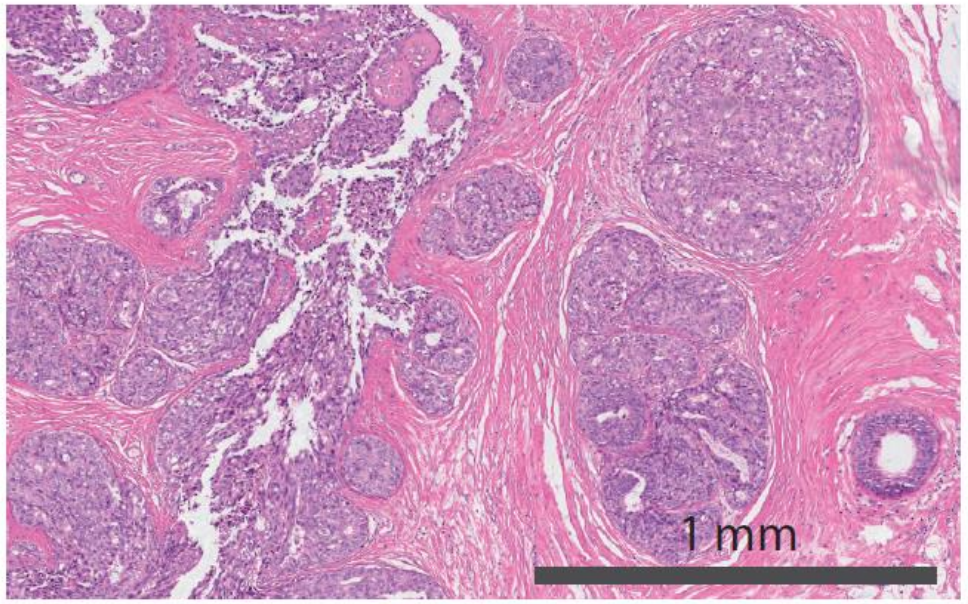
(a)



50% Invasive carcinoma cells, 50% connective tissue

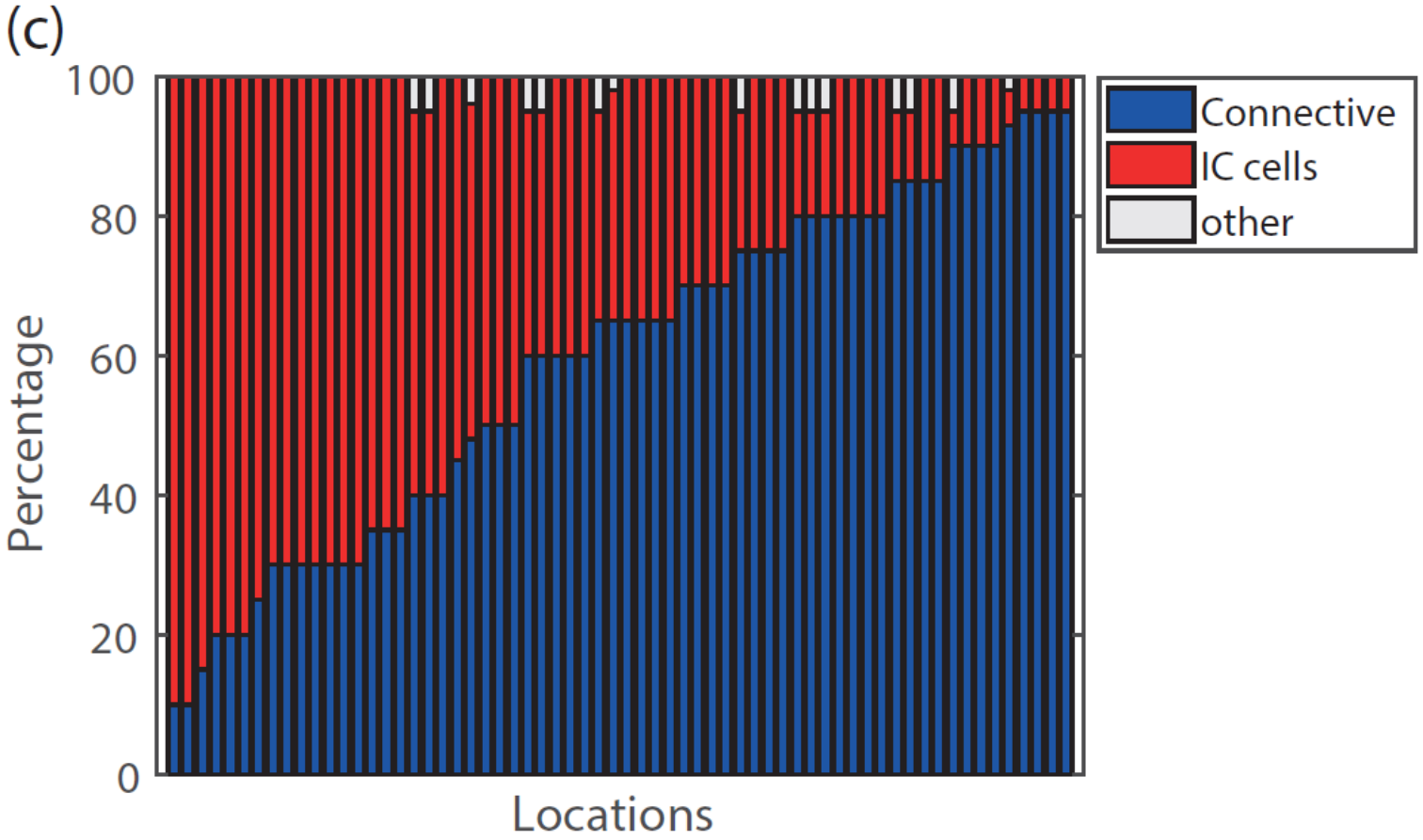
(b)



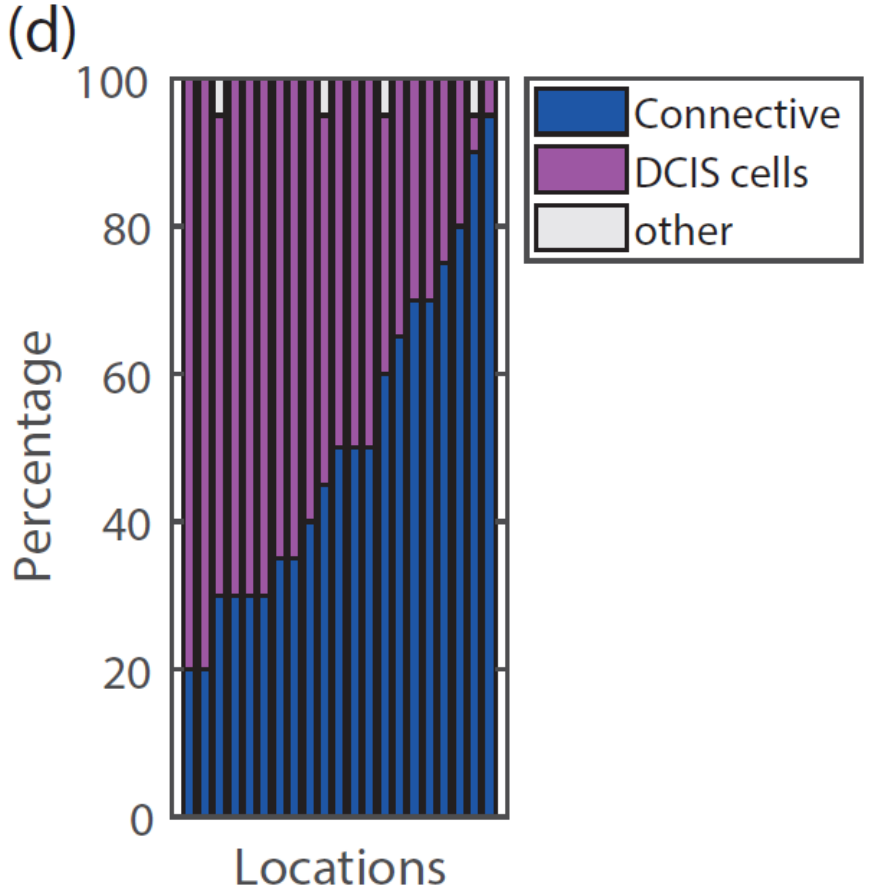
50% DCIS cells, 50% connective tissue

Mixing of different types of tissue within sampling volume complicates classification.

Mixed classes

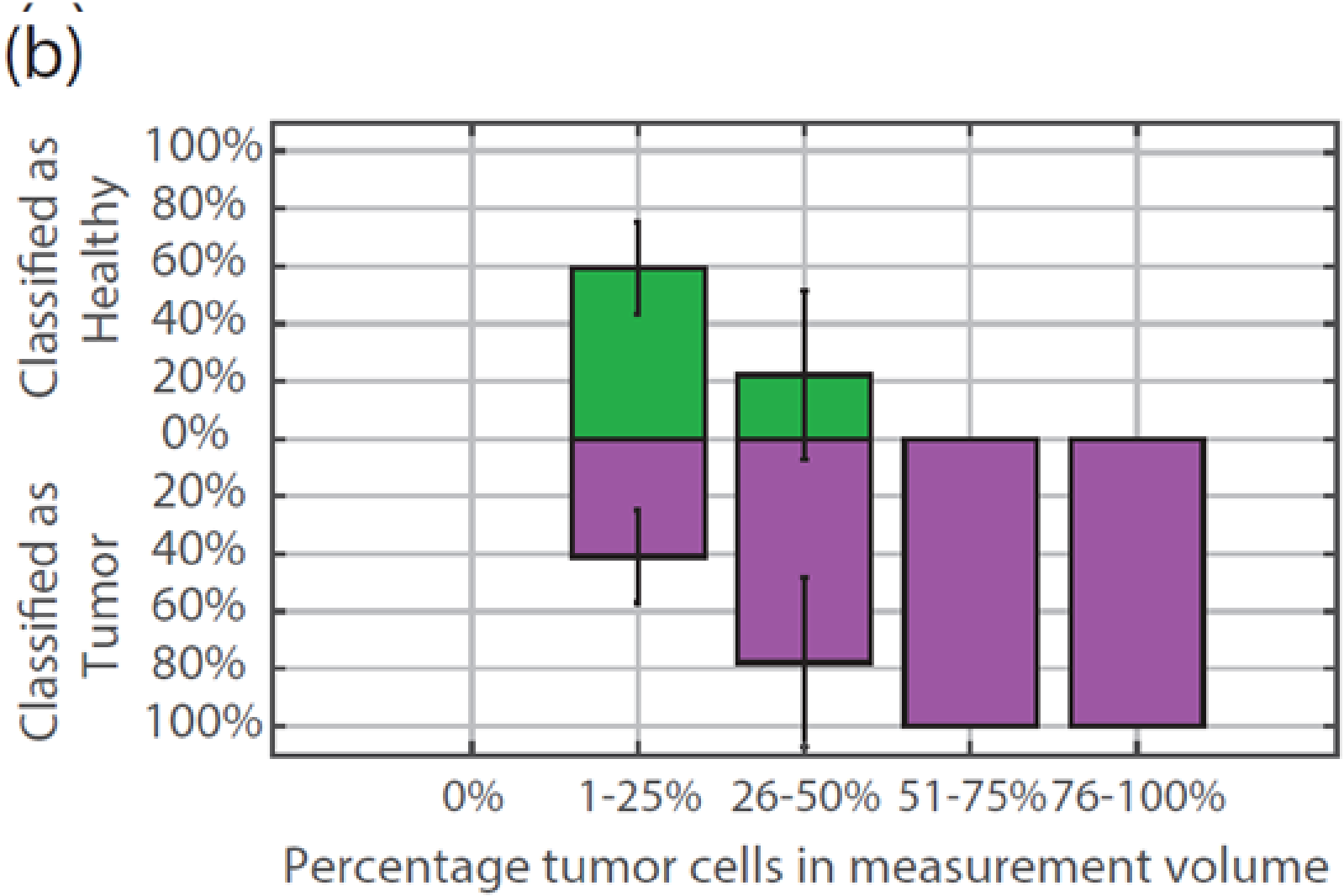


Percentage IC cells, distribution over all measured locations (32 patients, 69 locations)



Percentage DCIS cells, distribution over all measured locations (11 patients, 26 locations)

Mixed classes, Classification results



DCIS/Connective tissue

Conclusions

We can detect both IC and DCIS accurately, even with substantial amounts of connective tissue present.

However,

With smaller fractions of cancer cells more false negative results occur.

Connective tissue without cancer generates up to 20% false positives. **2020 De Boer, submitted**.

Use DRS to improve surgery, rather than try to replace the pathologist.

Can DRS improve surgery?

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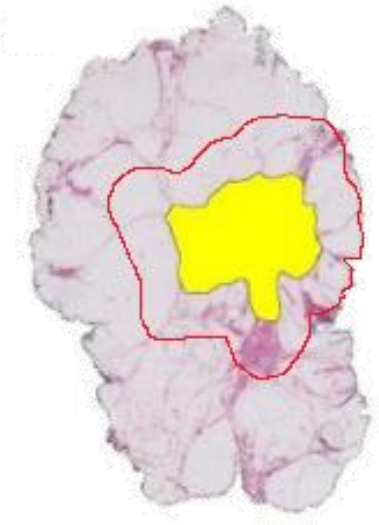
In current surgery significant amounts of tumor cells are missed by the surgeon in 20-40% of cases .

In current surgery the average CCR = 9.7 (32 patients, NKI)



Calculated Resection Ratio

$$CRR = \frac{Volume\ actually\ removed}{Volume\ of\ tumor + required\ margin}$$

Even with some **false negatives** of DRS the positive margin rate may actually go down!

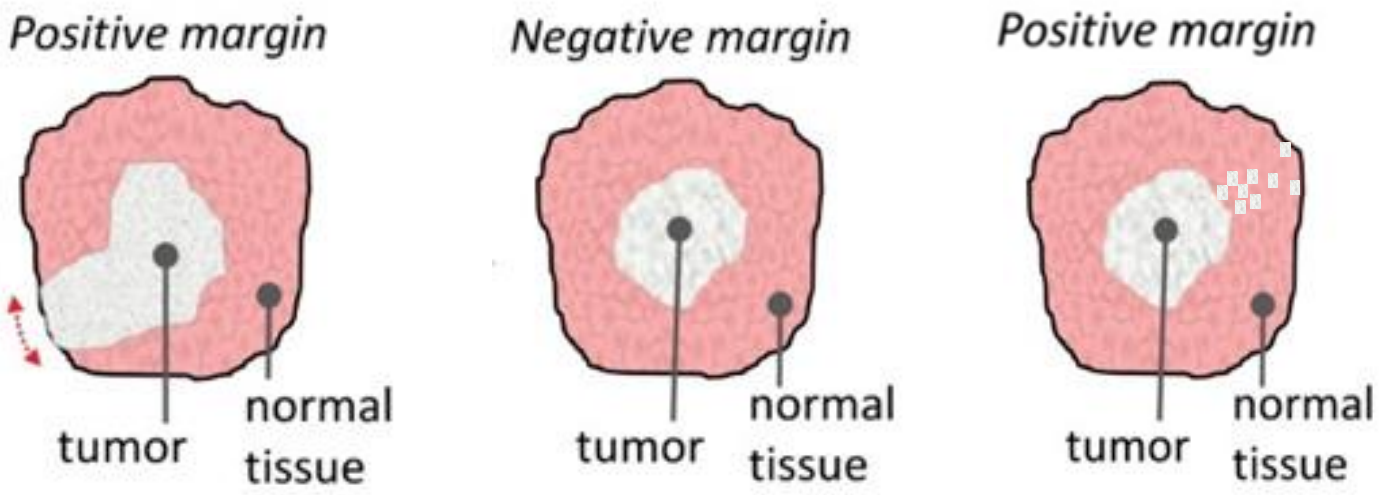
Even with some **false positives** of DRS the CRR may actually go down!

Towards ***in vivo*** measurements

Challenges

- Sampling depth and guidelines.
- Create a dataset on lumpectomy specimen.
- Train and implement algorithm.
- Develop system for scanning larger area’s
- Scan large area.

Sampling depth and guidelines

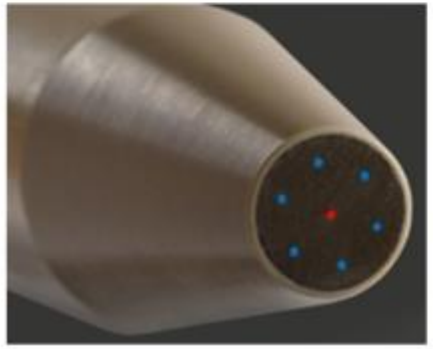


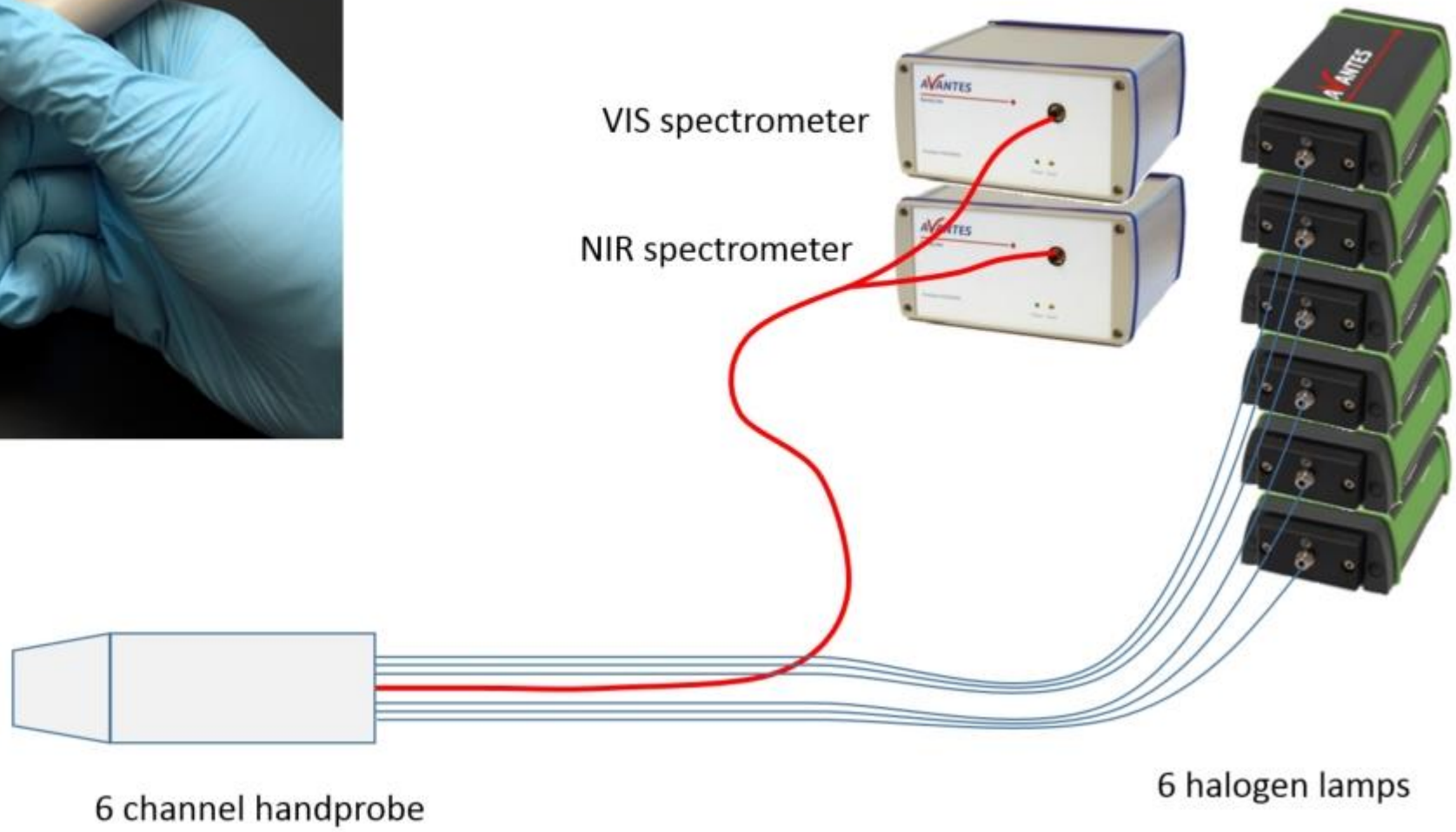
Important: Measure in the margin only; not the tumor in the centre.

Guidelines: 2 mm tumor free margin -> 2 mm sampling depth -> 2 mm fiber distance.

In vivo measurement system

Scan 1 cm^2 in a single shot of 2 seconds





In practice

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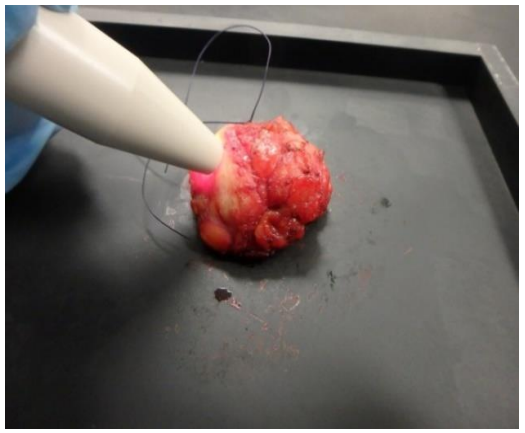

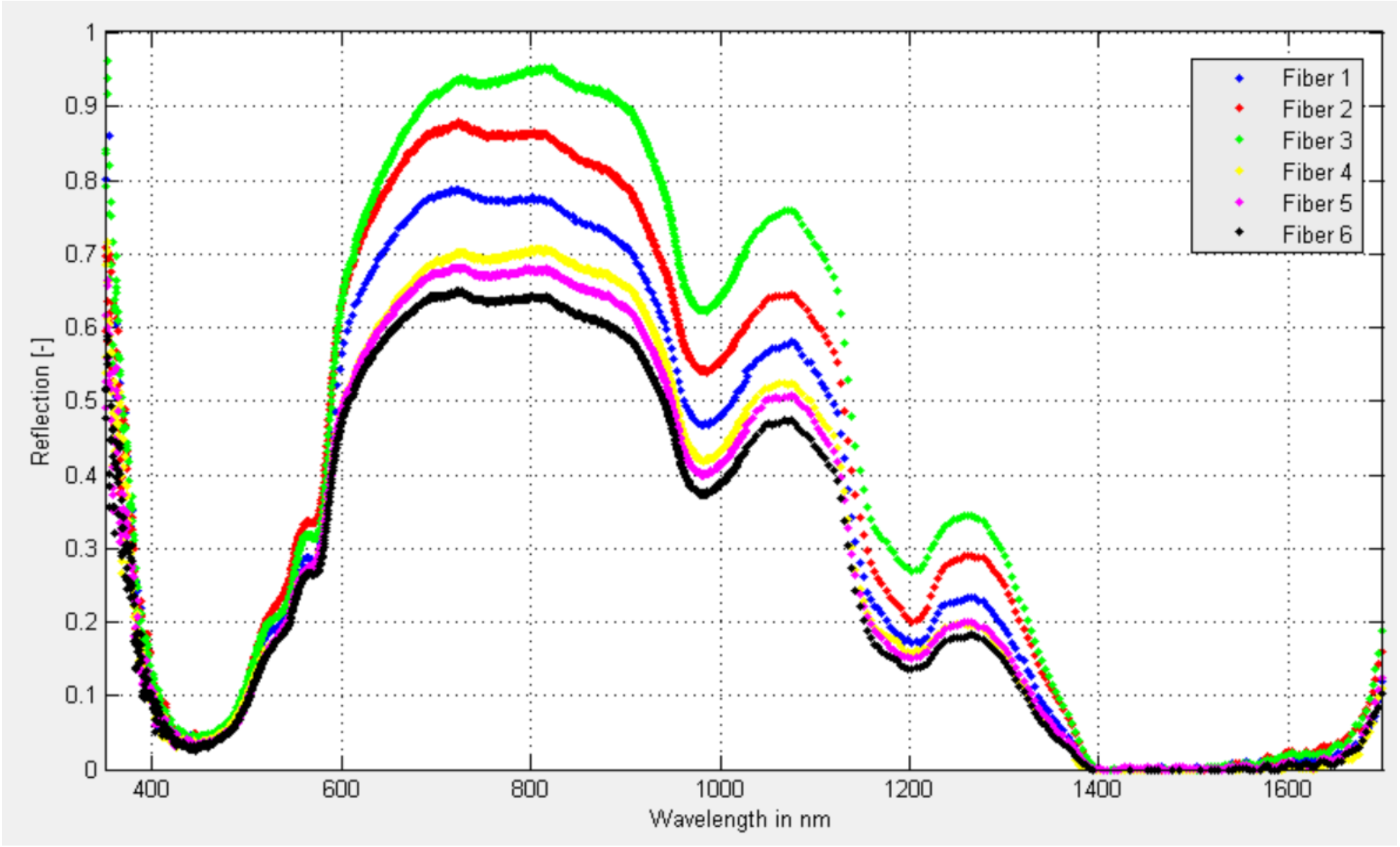

Create a large dataset

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Measurement on outside of intact lumpectomy.

—Locate suspect area visually/US.

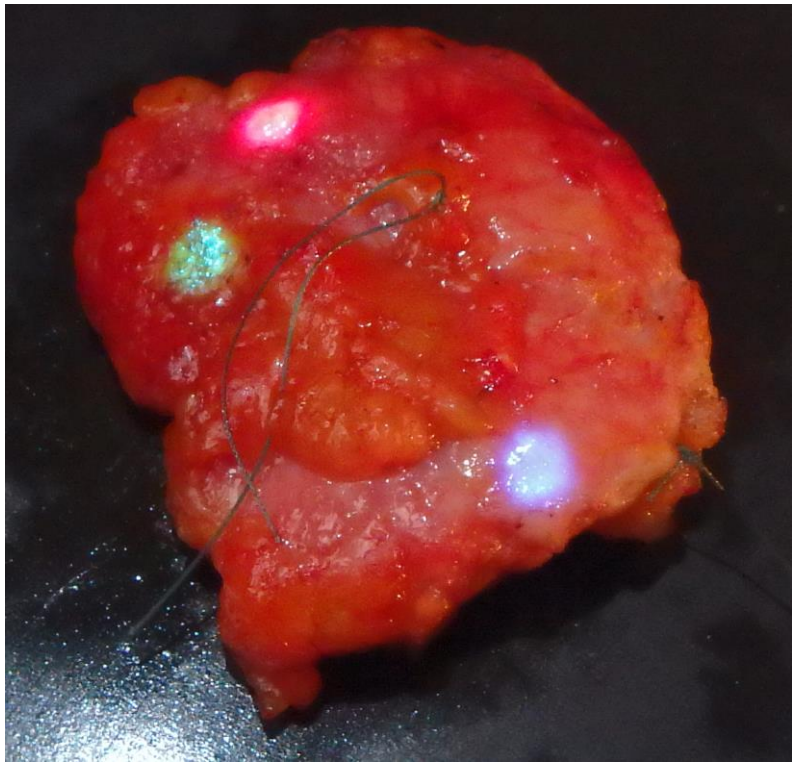
—Locate non-suspect area visually/US.

—Mark with aiming beam.

— Take measurement.

— Mark with ink.

— Do pathology of inked locations.



3-6 measurement sites per lump.

Ongoing: 20th patient on December 10th 2019

Where we are now

- Sampling depth and guidelines.
- Large area DRS system.
- Create a dataset on lumpectomy specimens.
- Train a diagnostic algorithm.
- Implement into system for scanning larger area’s
- In vivo study to test.

Conclusions

- DRS can accurately distinguish cancer from normal.
- DRS can distinguish IC from DCIS.
- DRS is not significantly influenced by preoperative chemotherapy.
- DRS can match sampling depth required by surgical guidelines.
- DRS hardware can measure 1 cm^2 in 2 seconds

- DRS is sensitive to different types of tissue in the sampling volume:
  - Small pockets are detected with less accuracy.
  - Some tissues generate false positives.

- DRS will be able to improve the outcome of Breast Conserving Surgery. To what extent is currently under investigation.

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