Intraoperative evaluation of margins

8th Aarhus Workshop in Breast Surgery, Aarhus University Hospital, Skejby, Denmark, 22.-23.05.2019

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Frankfurt am Main, Germany

Disclosures

	Applicability	Company
(1) Advisory role		Amgen, AstraZeneca, Biom'Up, Celgene, Daiichi Sankyo, Eisai, Genomic Health, Lilly, MSD, Norgine, Neodynamics, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, Tesaro
(2) Lecture/speaker engagement fees		Amgen, AstraZeneca, Aurikamed, Celgene, Clovis, ConnectMedia, Eisai, Genomic Health, Hexal, Lilly, MCI, Medtronic, MSD, Novartis, OncoLive, Omniamed, Pfizer, pfm Medical, Roche, RTI Surgical
(3) Manuscript fees		Amgen, Celgene, Roche
(4) Other remuneration	Trial Funding	Genomic Health

Current guidelines

Guideline	DCIS	IBC
NICE, 2014	≥2 mm	Negative margin
NZGG, 2009	≥2 mm	Negative margin
ESMO, 2015	≥2 mm	Negative margin
NCCN 2019	≥2 mm	Negative margin
AGO, 2019	≥2 mm	Negative margin
German S3, 2018	≥2 mm	Negative margin

Re-excision rate after BCS (IBC + DCIS)

- To receive negative margins it is common to perform a re-excision in both IBC and DCIS

Study	Re-excision rate*	N
Morrow et al (2008)	22%	2030
Smitt et al (2003)	49%	535
Waljee et al (2008)	46%	714
McCahill et al (2012)	23%	2206
Jeehan et al (2012)	29,5%	2803
Jeehan et al (2012)	18%**	45793

**rate for DCIS and IBC*
***only IBC without DCIS*

Morrow, Expert Rev. Anticancer Ther. 8(8), 1193-1196 (2008)
Smitt, Int J Rad Onc Biol Phys. 57(4), 979-985 (2003)
Waljee, Ann Surg Onc. 15(5), 1297-1303 (2008)
McCahill, JAMA (2012)
Jeehan, BMJ (2012)

How to reduce the re-resection rate?

Optimal pre- and intraoperative preparation/planning

preparation/planning

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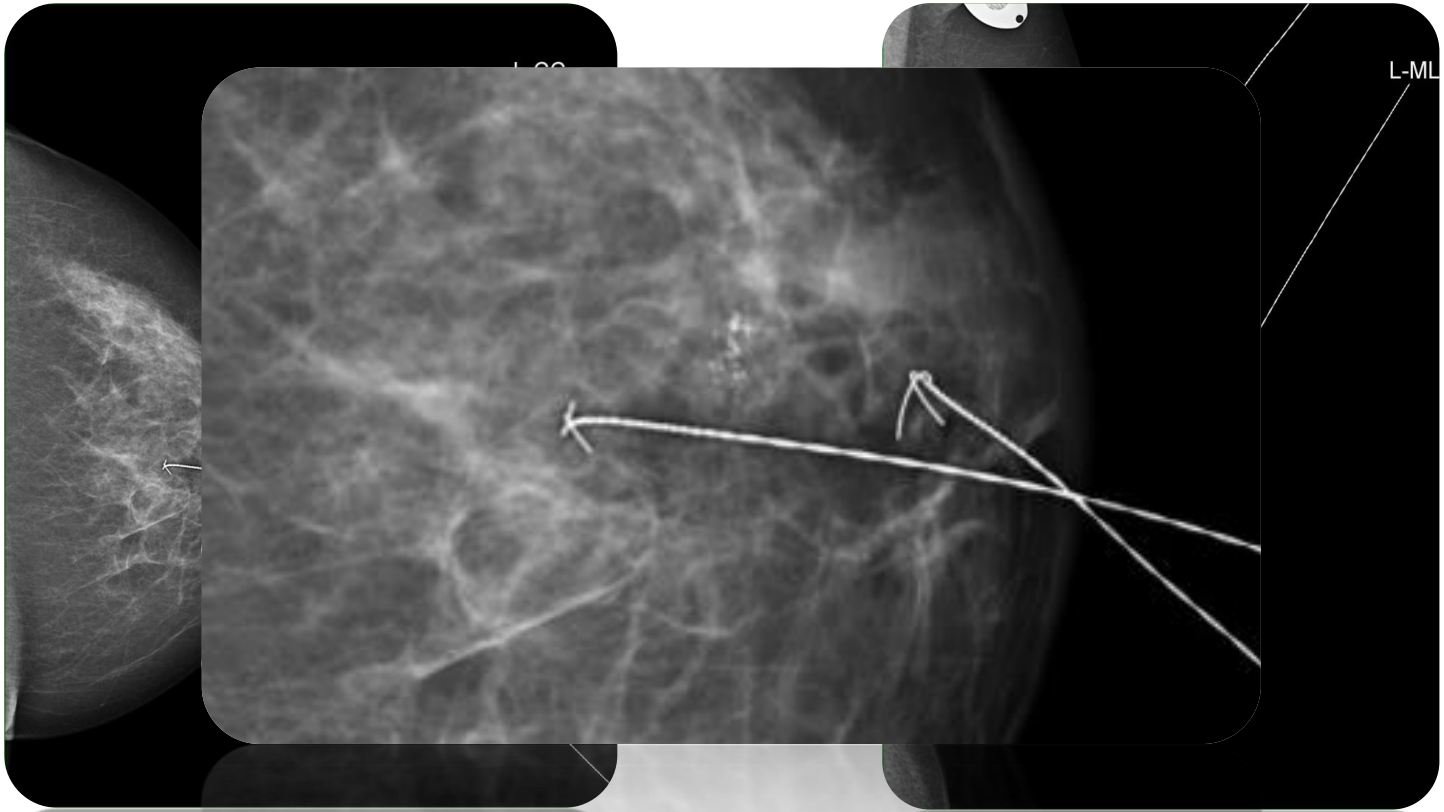
DCIS – preoperative planning



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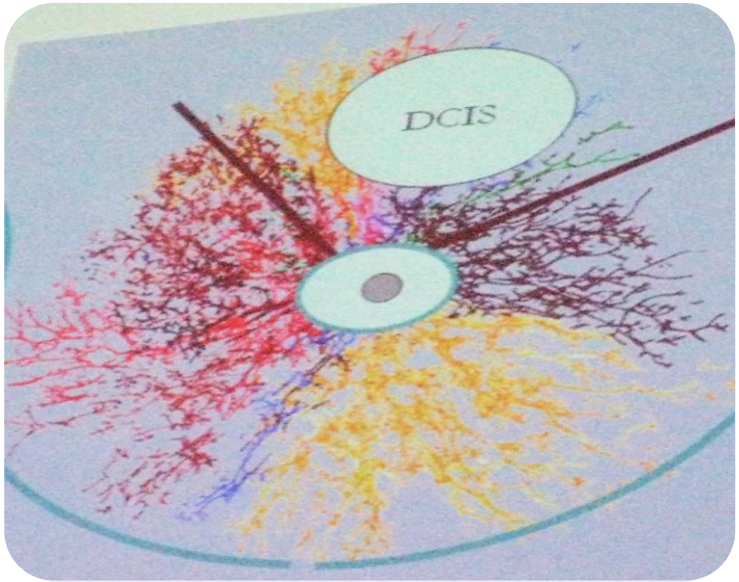
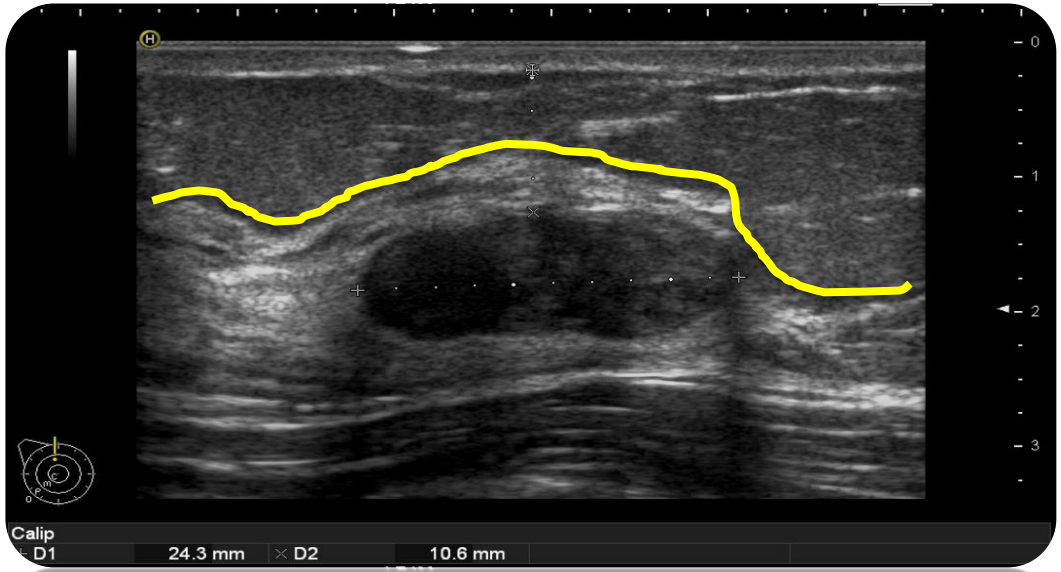
Sectorial excision



- Standardized surgery:
  - Excision of the specimen from the superficial fascia down to the M. pectoralis major



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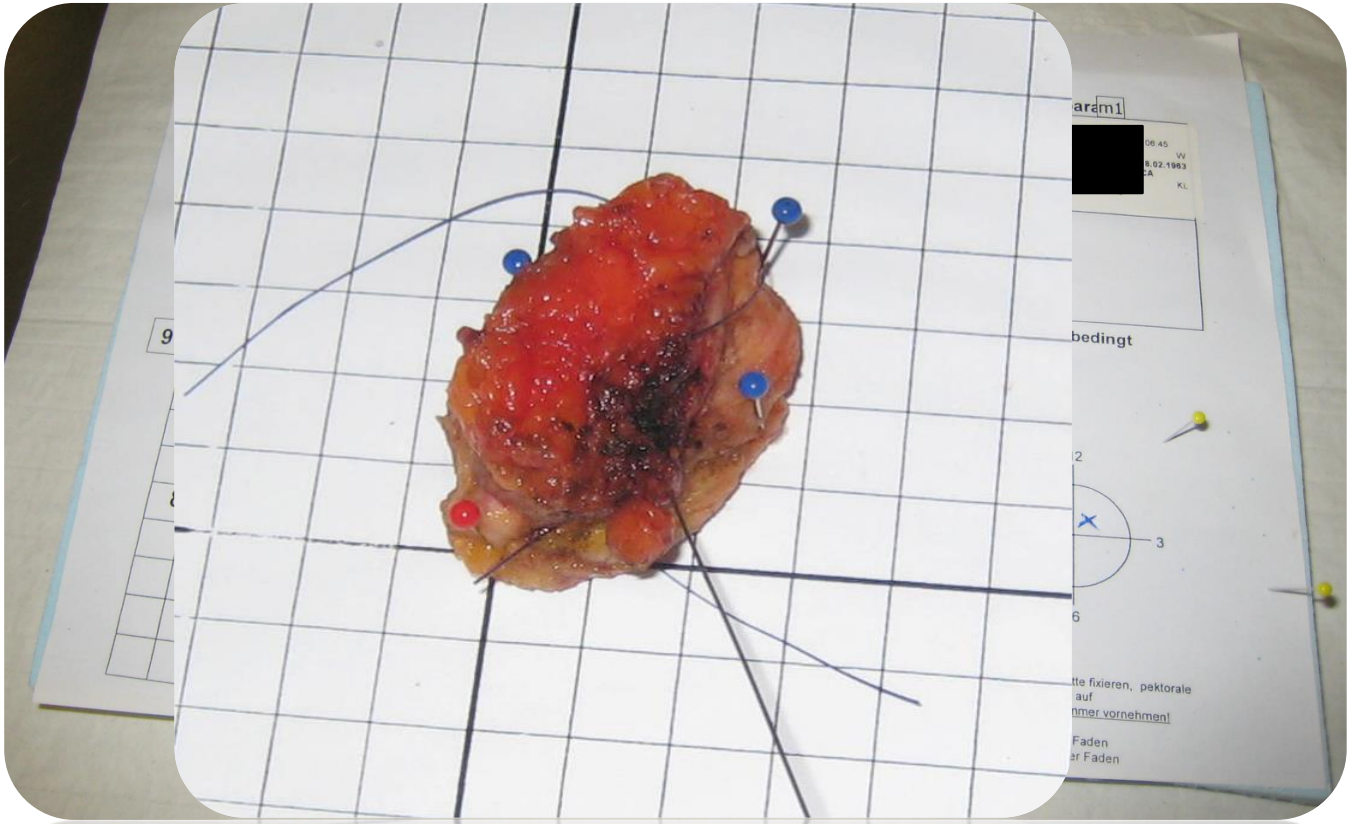
Specboard fixation



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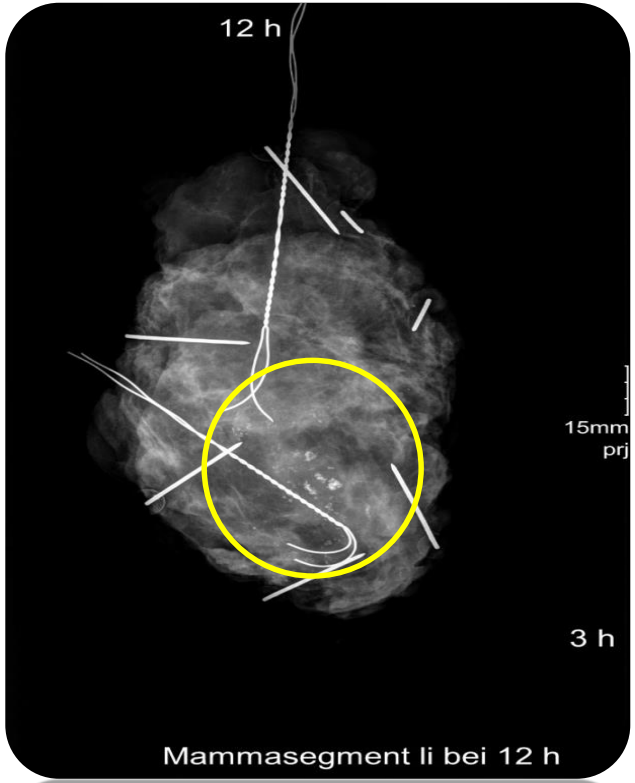
Intraoperative radiography



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Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 184 (2002) 89–93
Scientific paper

The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer

Roger A. Graham, M.D.[a,e]*, Marc J. Homer, M.D.[b], Judith Katz, M.D.[b], Janice Rothschild, M.D.[a], Homa Safaii, M.D.[c], Stacey Supran, M.A.[d]

[a]*Department of Surgery, New England Medical Center, Boston, MA 02111, USA*
[b]*Department of Radiology, New England Medical Center, Boston, MA 02111, USA*
[c]*Department of Pathology, New England Medical Center, Boston, MA 02111, USA*
[d]*Biostatistics Reseach Center, Department of Medicine, New England Medical Center, Boston, MA 02111, USA*
[e]*750 Washington St., Box 1043, Boston, MA 02111, USA*

Manuscript received December 10, 2001; revised manuscript April 29, 2002

Measurement of the breast specimens by the surgeon and the pathologist

	Surgeon's measurements	Pathologist's measurements	Mean difference	Percent decrease
Mean volume of breast specimen (cm^3)	46.13	29.18	16.95 P <0.001 95% CI = 9.48–24.42	30% P <0.001 23%–37%
Mean height of breast specimen (cm)	2.57	1.36	1.20 P <0.001 95% CI = 1.03–1.37	46% P <0.001 42%–50%

CI = confidence interval.

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Graham RA et al., Am J Surg 2002 © M. Thill

Is this enough?

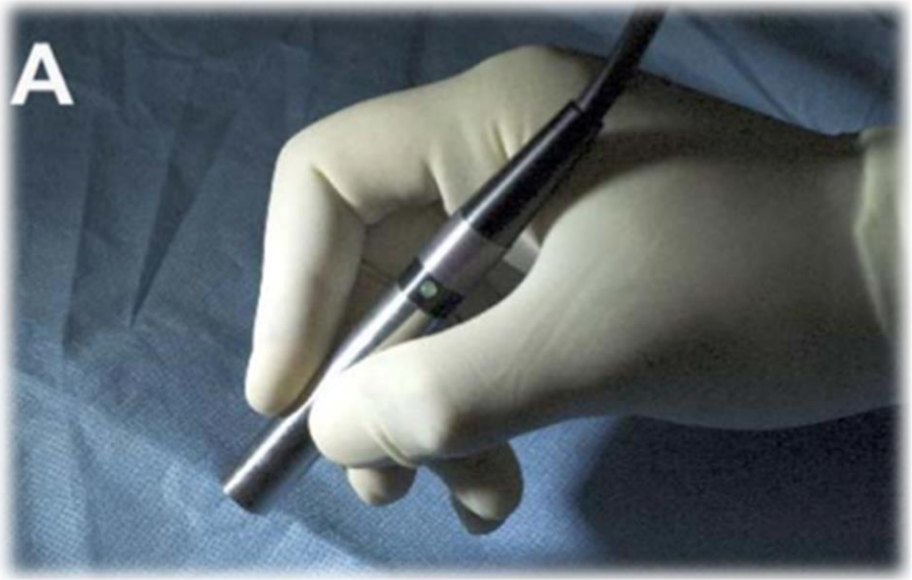
Techniques for intraoperative margin assessment

- Due to the high rate of re-excision, different tools have been used to attempt to lower the rate of positive margins
  - Frozen section
  - Touch prep cytology
  - Intraoperative ultrasound
  - High frequency ultrasound
  - Near-infrared fluorescence optical imaging
  - X-ray diffraction technology
  - Spectroscopy
  - Micro-CT
  - Diffusion-weighted MRI
  - Optical coherence tomography

Aydogan F et al., Breast Care 2012
Eichler C et al. , Anticancer Res 2012
Esbona K, Ann Surg Oncol 2012
Veronesi U et al., Oncologist 2010
Thill M, Expert Rev Med Dev 2013
Thill M et al., J Surg Oncol 2014
Thill M et al., SABCS 2018

A Handheld Spectroscopic Device for In Vivo and Intraoperative Tumor Detection: Contrast Enhancement, Detection Sensitivity, and Tissue Penetration

Aaron M. Mohs[1], **Michael C. Mancini**[1], **Sunil Singhal**[2], **James M. Provenzale**[3,4], **Brian Leyland-Jones**[5], **May D. Wang**[6], and **Shuming Nie**[*,1]



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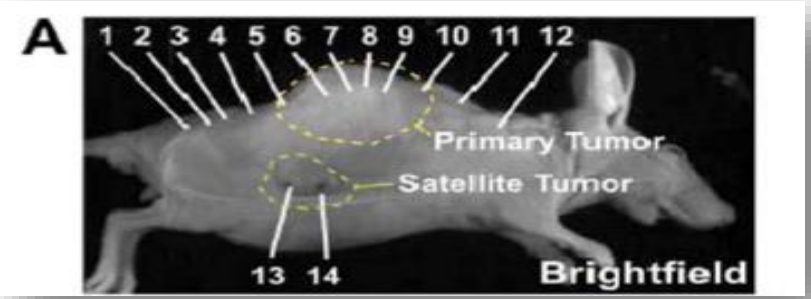
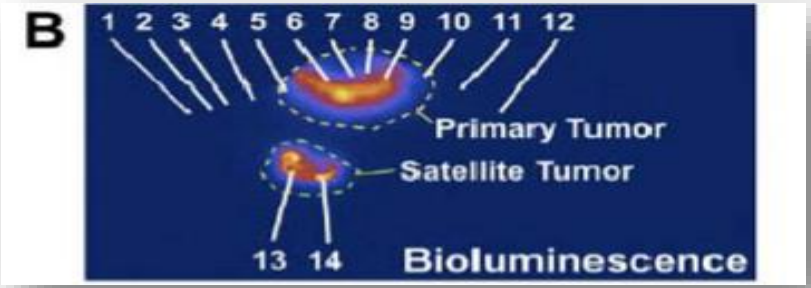
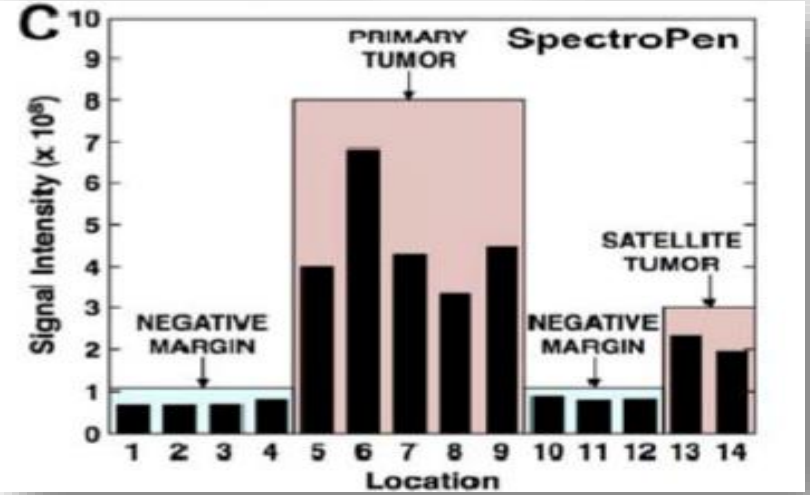
Mohs AM et al., Ann Chem 2012

Hand-held pen - SpectroPen







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Mohs AM et al., Ann Chem 2012 © M. Thill

Tissue scanner – schematic diagram

Combines both diffuse reflectance spectroscopy (DRS) and intrinsic fluorescence spectroscopy (IFS)

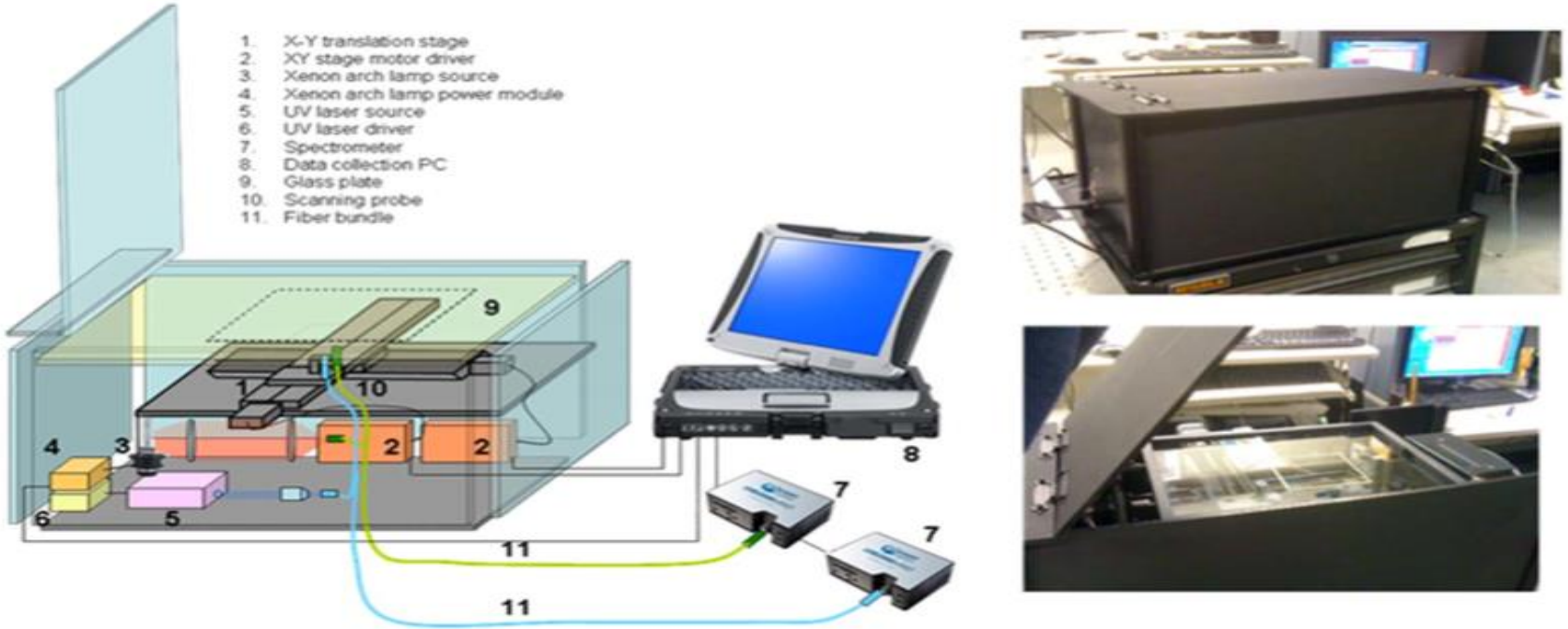

Figure 1. Tissue Scanner. Schematic diagram of the tissue scanner and photographs of the unit from different views.
doi:10.1371/journal.pone.0030887.g001

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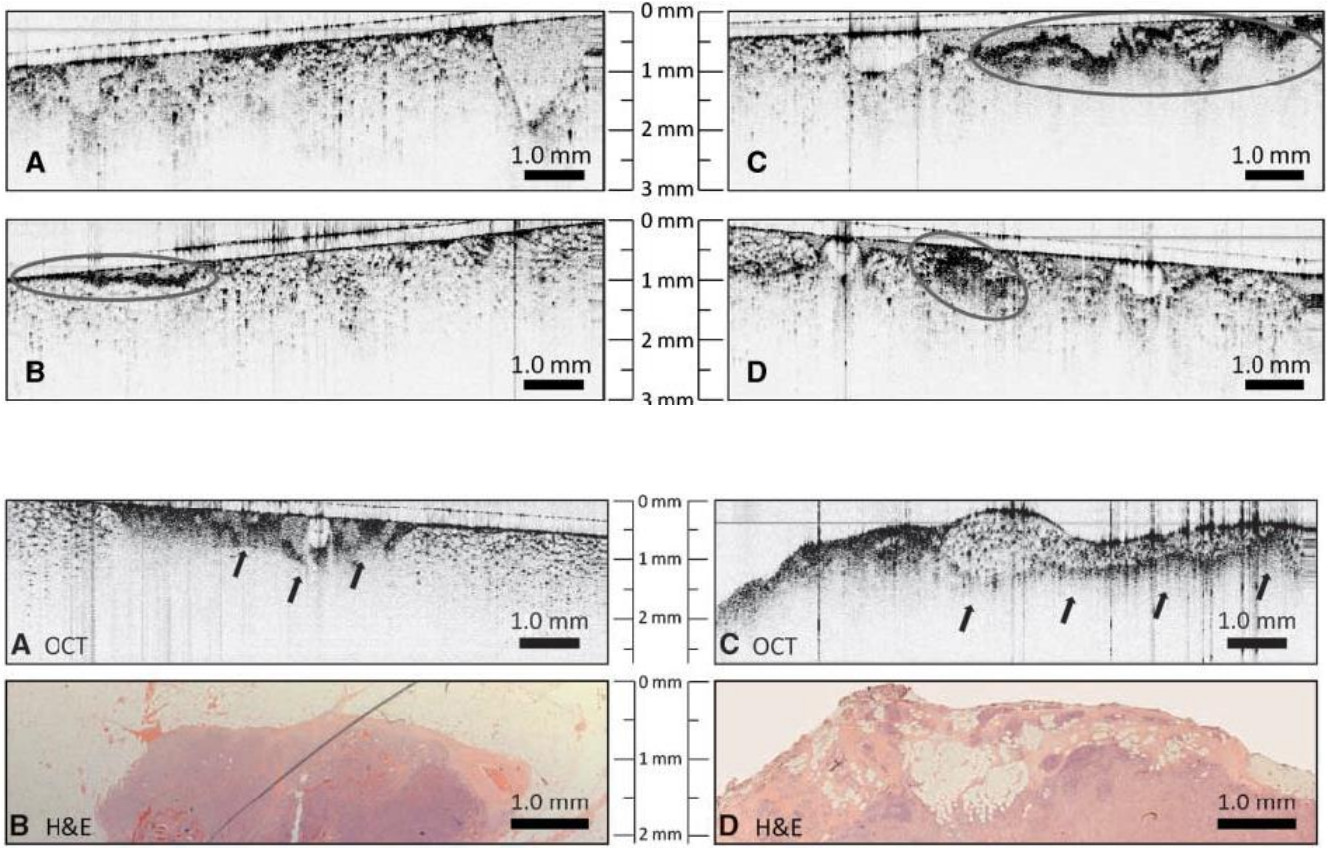
Lue N, 2012, PLoS ONE 7(1): e30887. doi:10.1371/journal.pone.0030887

ClearEdge (Bio-impedance spectroscopy)

TOUCH's tissue imaging technology is based on clinically acceptable standards of bio-impedance spectroscopy. *TOUCH* provides real time images that depict the status of excised breast tissue margins. The device images an area of 13x13 mm with a spatial resolution of a fraction of a millimeter and penetration depth of several millimeters.

Optical coherence tomography



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Nguyen FT et al. Cancer Res 2009 © M. Thill

Optical coherence tomography

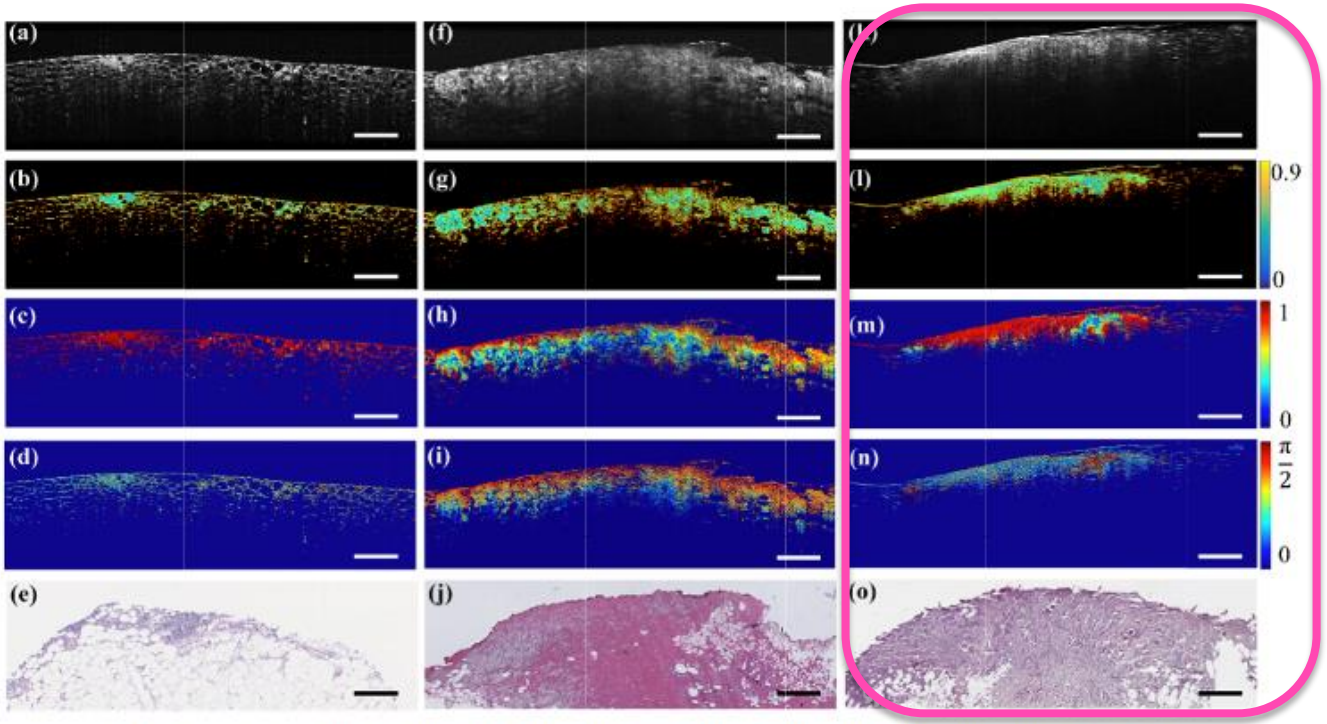

Fig. 2. Representative structural OCT images (a, f, k), coefficient of variation (CV) (b, g, l), degree of polarization uniformity (DOPU) (c, h, m), retardation (d, i, n) and H&E-stained histology (e, j, o) of fibro-adipose tissue (a-e), stroma (f-j), and invasive ductal carcinoma (k-o), respectively. Scale bar: 500 µm. Note, CV (b, g, l) is shown on a base 10 logarithmic scale.

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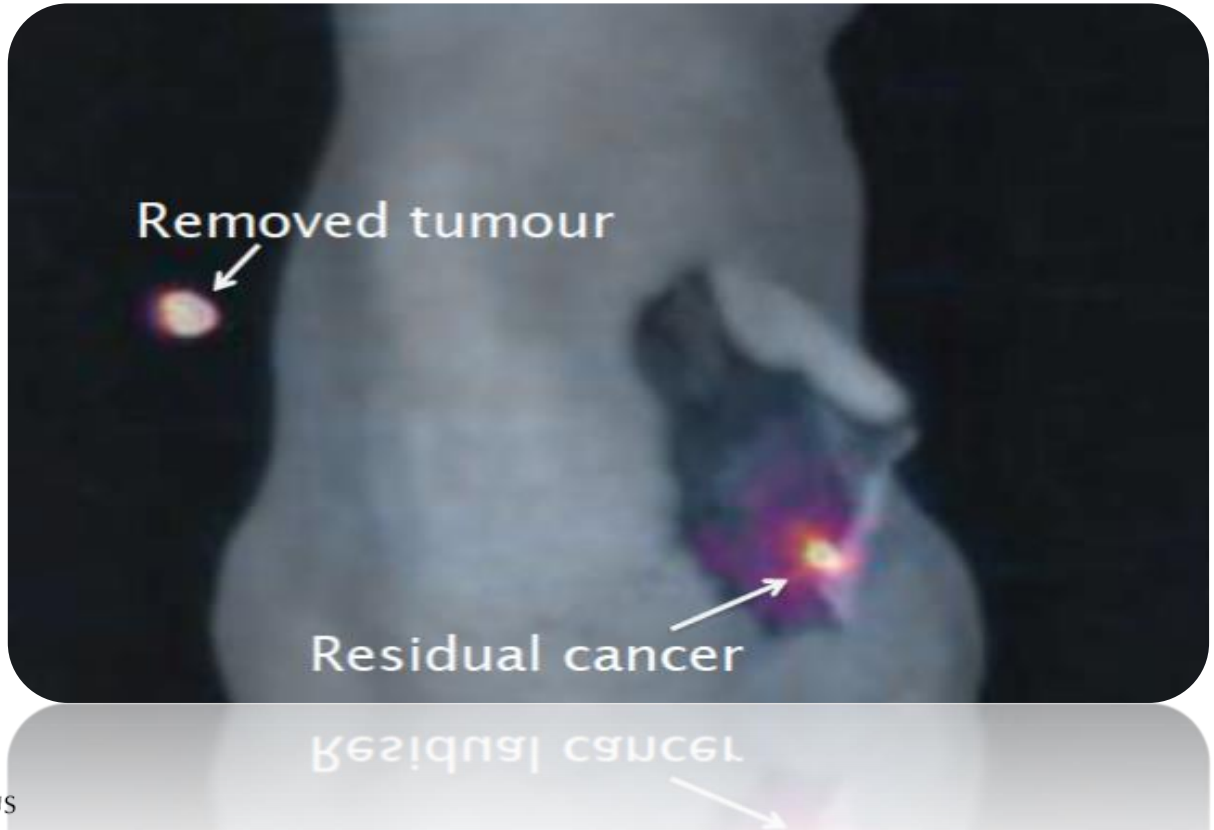
Wang J et al. Biomedical Optics 2018 © M. Thill

Cerenkov Luminescence Imaging
- Optical imaging of PET Tracers -



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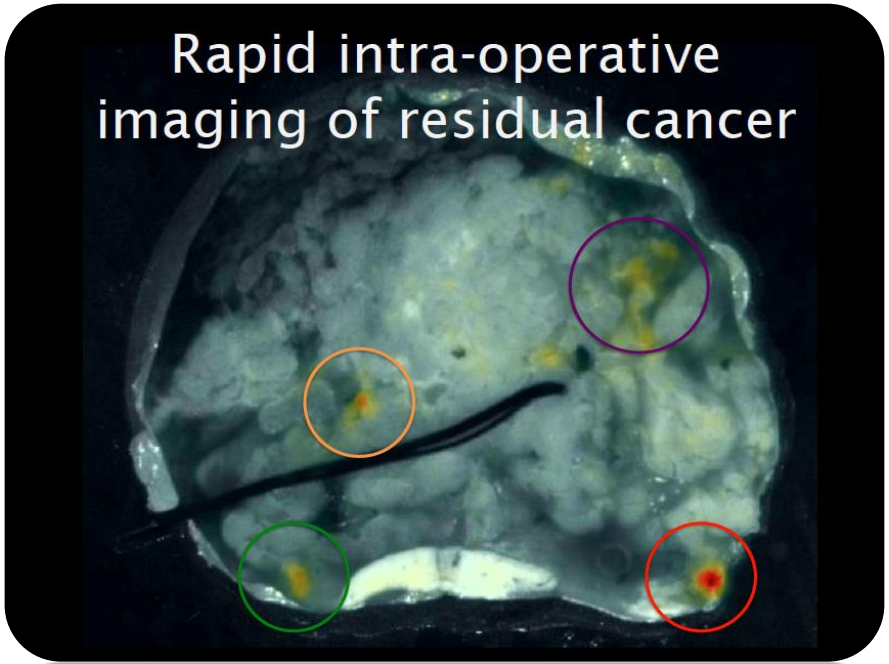
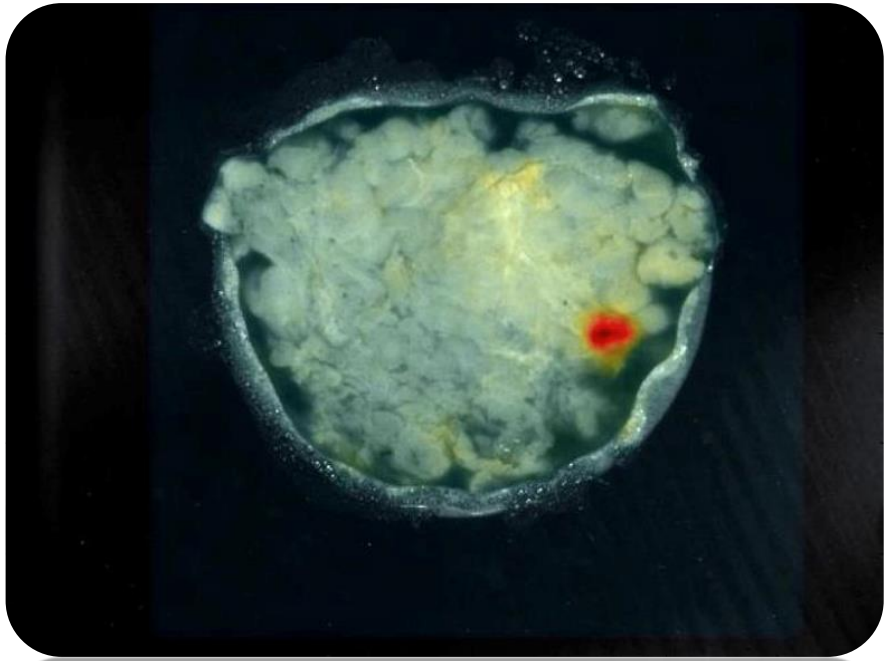
LightPath

LIGHTPOINT —MEDICAL—

BREAST NET Rhein-Main





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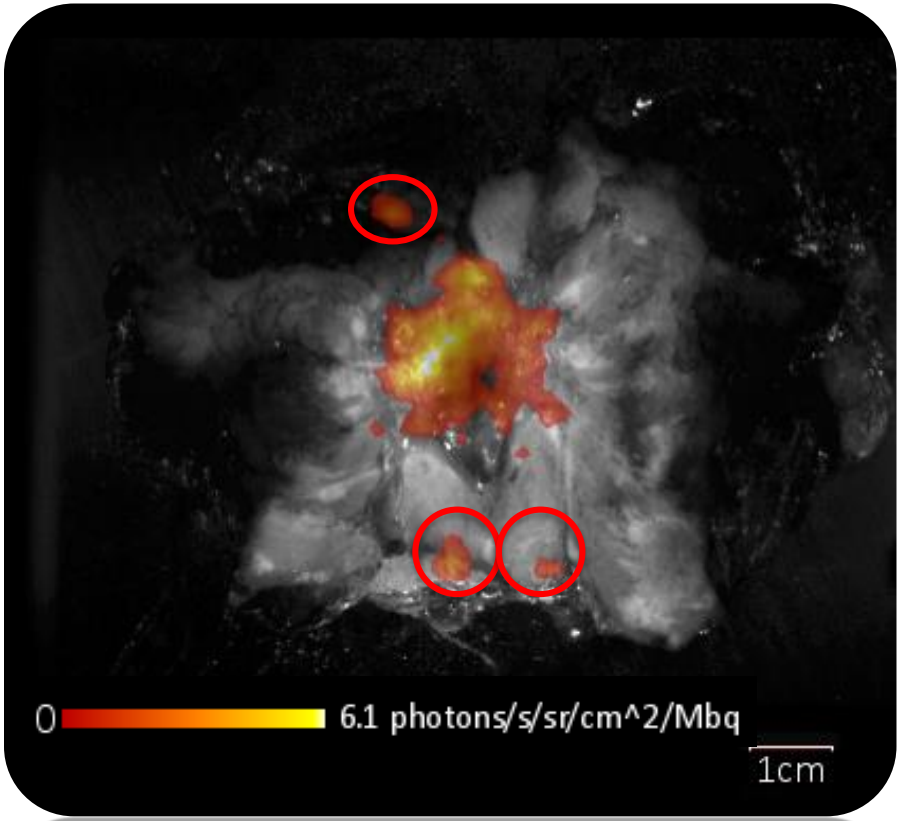
FDG CLI of BCS lumpectomy specimen



Normalised radiance (SD): 6.05 (1.07) TBR: 1.88

- 24mm, grade 2, ER+/HER2- invasive lobular carcinoma admixed with lobular carcinoma in situ
- Tumour resection margins were clear (≥ 5mm)

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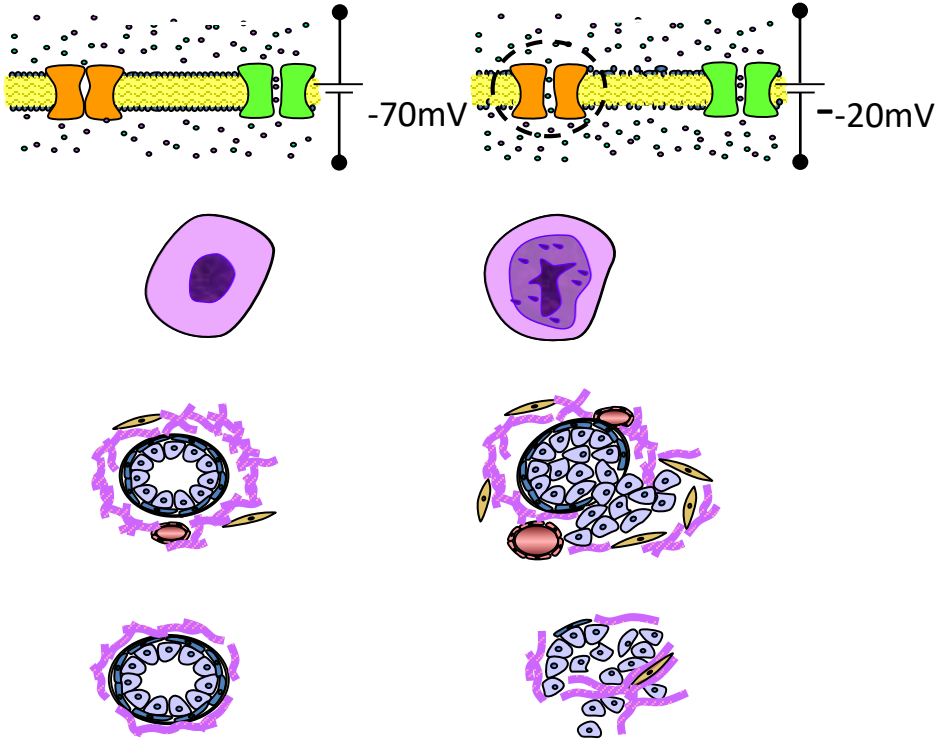
Radiofrequency spectroscopy

Bioelectric differences between normal and cancer tissue



Membrane de-polarization

Alterations in nuclear morphology

Increased vascularity

Cell to cell connectivity

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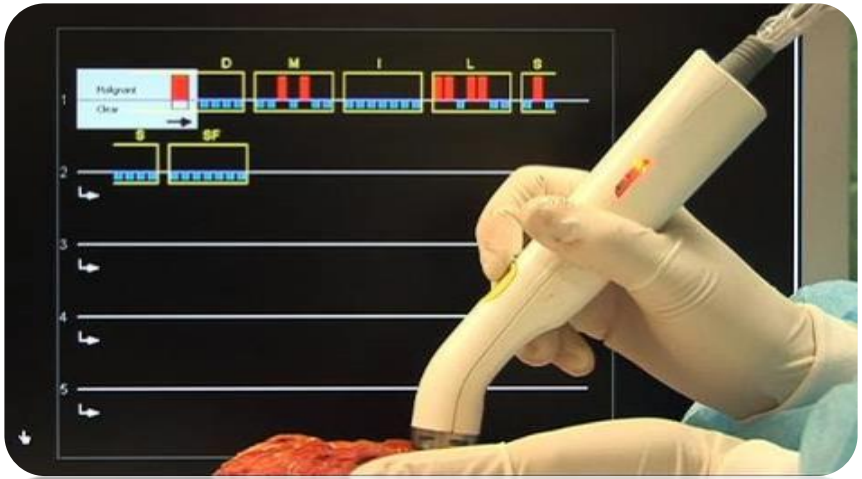
MarginProbe®



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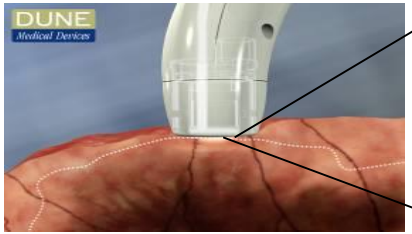
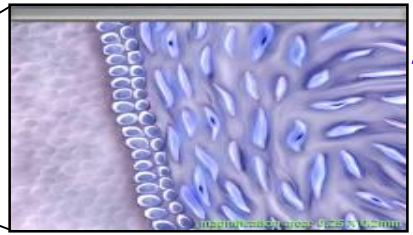
MarginProbe® - measuring of the dielectric properties real-time

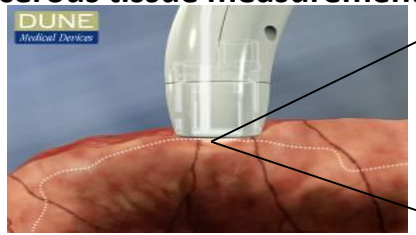
Normal tissue measurement



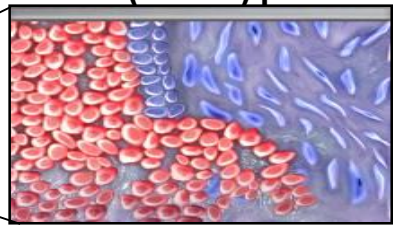
Clean point



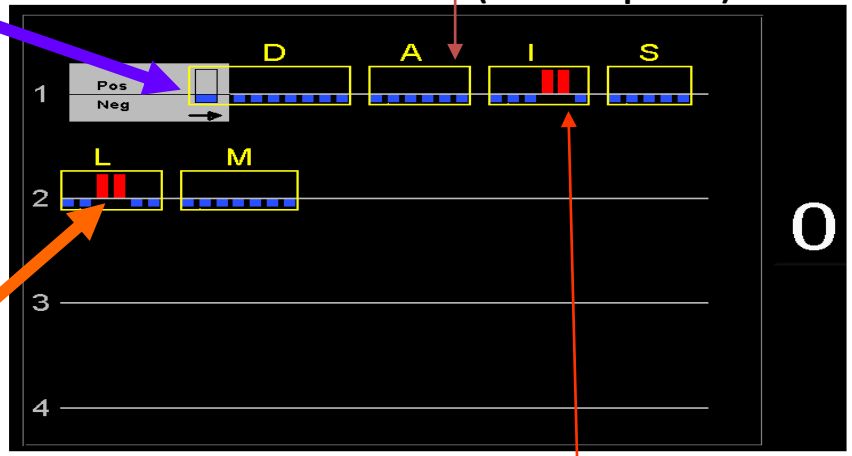
Cancerous tissue measurement



Positive (cancer) point



Clean Margin
(all clean points)



Positive Margin
(at least one positive point)

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The Breast 20 (2011) 579–580

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Short report

Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy

Marc Thill*, Kathrin Röder, Klaus Diedrich, Christine Dittmer

Department of Obstetrics and Gynaecology, University Hospital of Schleswig-Holstein, Campus Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany

The Breast 23 (2014) 94–96

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

MarginProbe® – Final results of the German post-market study in breast conserving surgery of ductal carcinoma in situ

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[b] *Breast Cancer Center, Hospital Essen Mitte, Germany*
[c] *Department of Obstetrics and Gynaecology, University Hospital of Schleswig-Holstein, Campus Luebeck, Germany*
[d] *Mammazentrum Hamburg, Germany*
[e] *Department of Gynecology and Obstetrics, St. Gertrauden Hospital, Berlin, Germany*

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REVIEW

Intraoperative Assessment of Margins in Breast Conservative Surgery—Still in Use?

MARC THILL, MD, PhD,[1]* KRISTIN BAUMANN, MD,[2] AND JANA BARINOFF, MD[1]

[1]*Department of Gynecology and Obstetrics, Breast Center, AGAPLESION Markus Hospital, Frankfurt am Main, Germany*
[2]*Department of Obstetrics and Gynecology, Breast Center, University Hospital Schleswig-Holstein, Lübeck, Germany*

A positive margin in breast conserving surgery is associated with an increased risk of local recurrence. Failure to achieve clear margins results in re-excision procedures. Methods for intraoperative assessment of margins have been developed, such as frozen section analysis, touch preparation cytology, near-infrared fluorescence optical imaging, x-ray diffraction technology, high-frequency ultrasound, micro-CT, and radiofrequency spectroscopy. In this article, options that might become the method of choice in the future are discussed.
J. Surg. Oncol. © 2014 Wiley Periodicals, Inc.

KEY WORDS: intraoperative margin assessment; breast conserving surgery; optical imaging; breast cancer; ductal

Device Profile

EXPERT REVIEWS

MarginProbe®: intraoperative margin assessment during breast conserving surgery by using radiofrequency spectroscopy

Expert Rev. Med. Devices 10(3), 301–315 (2013)

Marc Thill

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In breast conserving surgery, the tumor should be removed with a clean margin, a rim of healthy tissue surrounding. Failure to achieve clean margins in the initial surgery results in a re-excision procedure. Re-excision rates are reported as being 11–46% for invasive carcinoma and ductal carcinoma *in situ* (DCIS). Re-excisions can have negative consequences such as increased postoperative infections, negative impact on cosmesis, patient anxiety and increased medical costs. Therefore, the surgical margin of invasive and intraductal (DCIS) breast tissue is a subject of intense discussion. Different options for intraoperative assessment are available, but all in all, they are unsatisfying. Frozen section margin examination is possible but is time consuming and restricted to the assessment of invasive carcinoma. In the case of DCIS, there is

Study overview (3 clinical trials)

Study	n	Countries (sites)	Study design	Note	Definition of positive margin
Pre-market					
MAST	293	Israel	Device performance as adjunct to SOC[#] vs. SOC, all BCS patients	Pilot randomized trial, looking at re-excision rate, tissue volume, and cosmesis (@ 6mo)	1mm
Pivotal	596	US, Israel	Device performance as adjunct to SOC vs. SOC, non-palpable lesions	Device use on main specimen only. Complete Surgical Resection (CSR) is the primary endpoint.	1mm
Post-market					
German	42	Germany	Single arm, pure DCIS patients	Device use on main specimen, optional on additional resected tissue	5mm

[#] *SOC = Standard of Care*

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Allweis TM, et al., Am J Surg 2008
Schnabel F et al., SABCS 2011
Thill M, Exp Rev Med Dev 2013
Thill M et al., Breast 2013

Clinical trials - Results

Study	Reduction of re-excision rate	p-value
MAST	56%	p=0.039
PIVOTAL	50%	p<0.001
German Multicenter	56%	p=0.018

Thill M et al., Breast 2013
Schnabel F et al, SABCS 2011
Allweis et al, Am J Surg 2008

MarginProbe - Conclusion

- MarginProbe® is a device that provides a fast and effective technique for intraoperative margin assessment that is already used in daily routine.
- It lowers the re-excision rate for both DCIS and invasive cancer significantly, by >50%, without any influence on patient's cosmesis.
- It may allow the surgeon to perform oncoplastic or reconstructive breast surgery and IORT more safely in the future.
- However, it has a relevant false negative rate of 24%, as measurements results are better in less dense and fatty breast tissue. Sensitivity of 75,2%

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Thill M et al., Breast 2013
Schnabel F et al., Ann Surg Oncol 2016

Diffusion weighted MRI

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The ClearSight™ Surgical Specimen MRI

ClearSight™ **MRI System**

\+

ClearPack™ **Single Use Tissue Container**

Left: Current system in clinical trials, CE marked

Right: Next generation, commercial version

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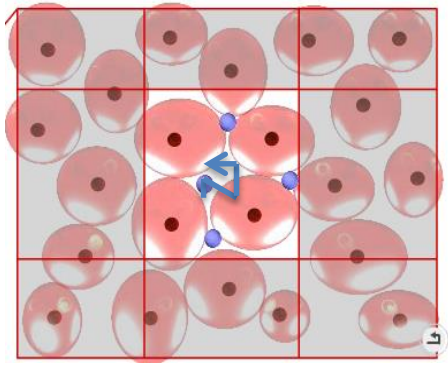
Principle Diffusion-Weighted MRI

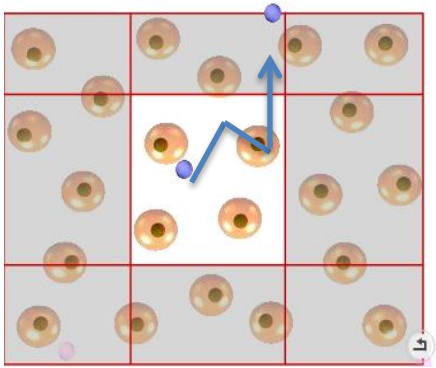
Malignant Tissue



Restricted diffusion
(slower diffusion)

Lower ADC
(Apparent Diffusion Coefficient)

Higher T_2^*

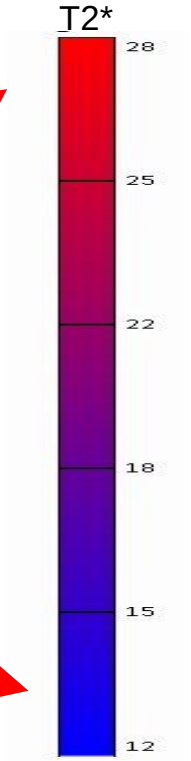


Benign Tissue

Free diffusion
(faster diffusion)

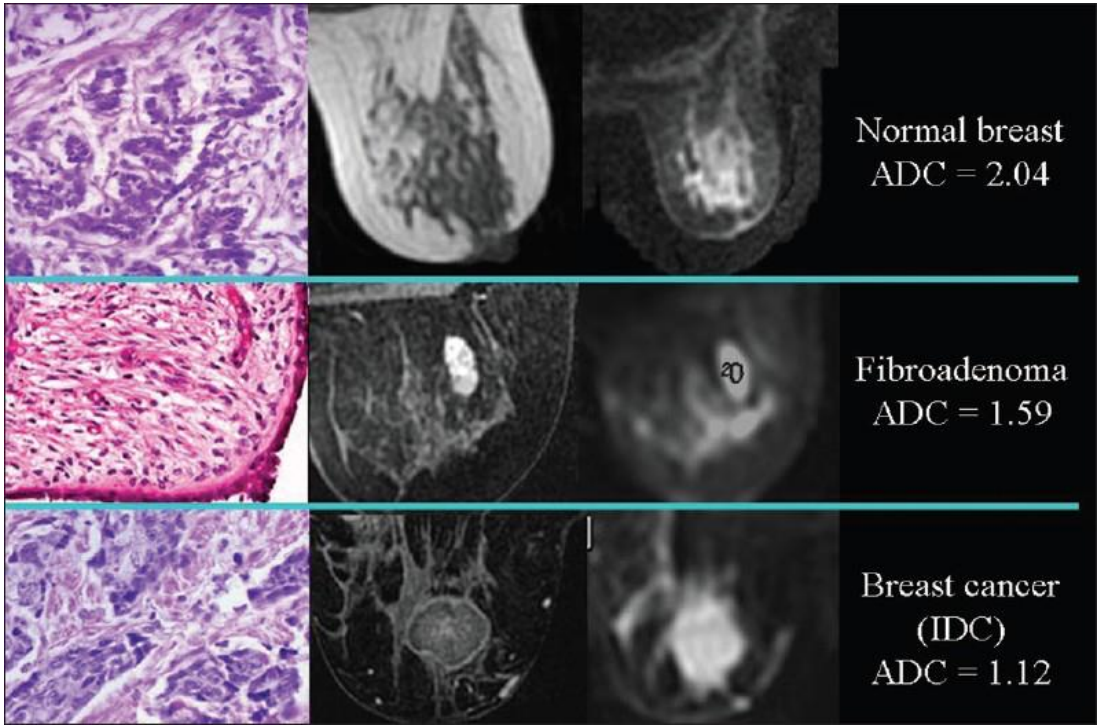
Higher ADC

Lower T_2^*



* Guo et. al., Differentiation of Clinically Benign and Malignant Breast Lesions Using Diffusion-Weighted Imaging, J. MRI, 172-178, 2002.
* Tsushima et al., MR Differential Diagnosis of Breast Tumors Using Apparent Diffusion Coefficient on 1.5-T, J. MRI, 249-255, 2009.

Diffusion-Weighted MRI in Oncology



The relationship of diffusion to the number of cells. ADC values are lower, because of the higher cellularity, in proliferative lesions than in normal breast tissue; in an invasive ductal carcinoma the diffusion is slower than in a fibroadenoma.

[Fornasa F. Diffusion-weighted Magnetic Resonance Imaging: What Makes Water Run Fast or Slow?. J Clin Imaging Sci 2011;1:27]

Good ADC differentiation of malignant vs benign tissues has been observed in:

- Breast
- Endometrium
- Lungs
- Lymph nodes
- Liver
- Thyroids
- Kidneys
- Prostate
- Brain
- …others

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What data do we have already?

ClearSight™ Point-to-Point Study (2016)

An intraoperative MRI system for margin assessment in breast conserving surgery: Initial results from a novel technique

Moshe Papa MD, FACS, FRCS(C)[1,2,*], Tanir Allweis MD[3], Tami Karni MD[2,4], Judith Sandbank MD[2,5], Myriam Konichezky MD[6], Judith Diment MD[7], Assaf Guterman MSc[8], Moshe Shapiro MSc[8], Zachi Peles MSc[8], Roi Maishar BSc[8], Assaf Gur MSc[8], Eyal Kolka MSc[8] andRachel Brem MD[9]

Version of Record online: 15 APR 2016

Background and Objectives
One of the major unmet needs in Breast Conserving Surgery (BCS) is a rapid and accurate margin assessment of the lumpectomy specimen. This study evaluates the ability of a novel MRI system (prototype of the ClearSight™ system; Clear-Cut Medical Ltd., Rehovot, Israel) to distinguish malignant and non-malignant tissues in freshly excised breast specimen by comparing MR measurements to histopathology results.

Methods
Seventy-seven samples were obtained from 22 patients undergoing BCS enrolled in the study. A T2* (T2 Star) value in milliseconds (ms) was calculated for each sample and correlated with histopathology results.

Results
Of the 77 samples, 35 samples were classified by histopathology as malignant and 42 as non-malignant. T2* values were significantly higher in malignant samples compared to non-malignant samples (15.3 ± 2.72 ms and 10.6 ± 1.47 ms, respectively [P < 0.00001]). Analysis for a determined cutoff of 11.7 ms revealed **91% sensitivity, 93% specificity, and 92% accuracy.** ROC curve analysis yielded AUC of 0.97.

Conclusions
This study demonstrates that the system is sensitive and specific in differentiating malignant and non-malignant tissues in freshly excised breast specimen. The system has the potential to be used for breast specimen margin assessment during BCS, with the goal of decreasing the need for re-operation. J. Surg. Oncol. 2016;114:22–26. © 2016 Wiley Periodicals, Inc.

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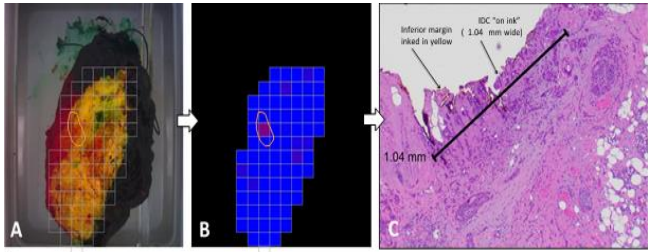
ClearSight™ Margin-to-Margin Study (2017)

- ***Design;*** Prospective, multicenter, single-arm, double blinded, open label, exploratory clinical study

- ***Methods;*** Patients undergoing BCS were enrolled to the study. The ClearSight system outcome was correlated to histopathological results, evaluating the ClearSight performance, while maintaining both surgeons and pathologists blinded.

- ***Results;*** Overall **220 female patients** were enrolled in 6 sites. According to SSO-ASTRO recommendations, initial results revealed 90 pathologically positives margins on the primary (main) lumpectomy. Of these cases the ClearSight™ system led to identification of **76 (84%) of the positive margins; 88% for IDC, 85% for DCIS and 82% for ILC.**



- ***Conclusions;*** The ClearSight™ MRI based system provides real-time, full surface assessment, thus overcoming possible under-evaluation. The System shows potential of being an effective, intraoperative MR margin assessment tool, which may assist surgeons and pathologists in reducing re-excision rates in BCS.

THE AMERICAN SOCIETY OF Breast Surgeons
ANNUAL 18TH MEETING
APRIL 26–30, 2017, LAS VEGAS, NV

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ClearSight™ M2M II Study (2018)

Study Design	Prospective, multi-center, single arm, open label, blinded, post marketing surveillance (PMS) clinical study
Principle Investigator	PD Dr. Marc Thill, Agaplesion Markus Hospital, Frankfurt, Germany
Study Objective	Further assess the ClearSight™ System ability to detect irregular tissue in margins of excised breast specimen in patients undergoing Breast Conserving Surgery
Study Population	Up to 110 patients undergoing BCS will be enrolled in up to 3 sites in Europe and Israel; • Agaplesion Markus Hospital, Frankfurt, Germany (completed) • Kaplan Medical Center, Rehovot, Israel (ongoing)
Primary Endpoint	To measure the ClearSight system's ability to assess presence of pathology findings within 1mm from excised breast specimen margins, compared to the gold standard histopathology examination
Secondary Endpoint	To assess the value of ClearSight maps for targeting of suspicious tissue during specimen grossing in pathology

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ClearSight™ M2M II Study (2018)

- 60 patients with DCIS and invasive breast cancer undergoing BCS participated in the M2M II study at the Agaplesion Markus Krankenhaus
- 348 aspects were scanned with diffusion-weighted MRI
- surgeons and pathologists were blinded
- accuracy was determined through comparison of final histopathology and ClearSight maps (applying T2* threshold).

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Agaplesion Markus KH Study Recruitment & Demographics

- 63 consented & screened
- 60 were found eligible
- 348 scanned margins

1 Formalin use prior scan, 1 prior CT, 1 pathologist's exclusion due to unidentified orientation by color

Characteristics	Mean ± std, n (%)
Age	61.2±10.5
BMI	
<18.5	8 (13)
18.5-25	27 (45)
25-30	22(37)
>30	3 (5)
Menopause status	
Pre-menopause	15 (25)
Post-menopause	45 (75)
Cancer Type	
IDC	42 (70)
DCIS	9 (15)
DCIS and IDC	4 (7)
ILC	5 (8)
Cancer grade	
Low	20 (33)
Moderate	38 (64)
High	2 (3)
Lesion volume (cm^3)	3.1±6.8

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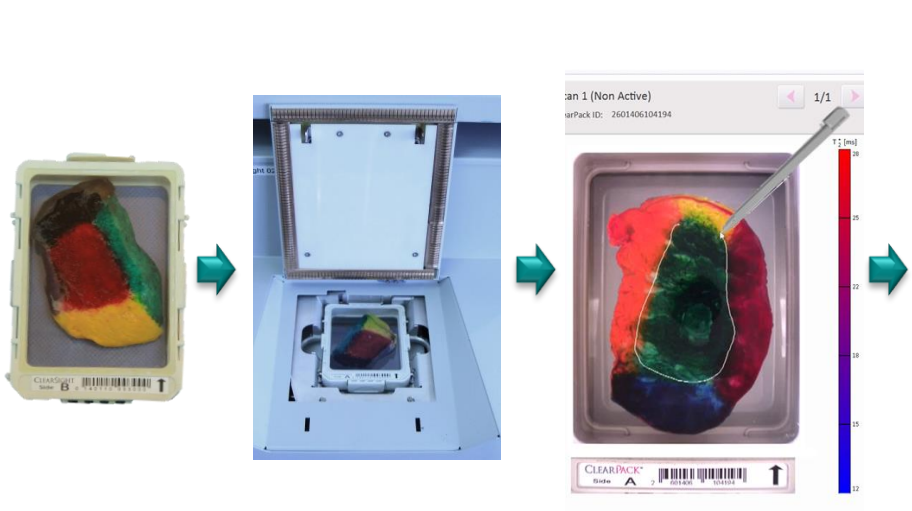
Workflow

ClearSight™ Operation



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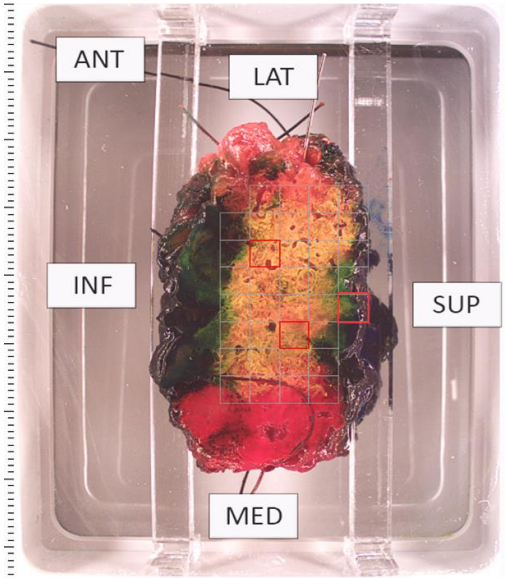
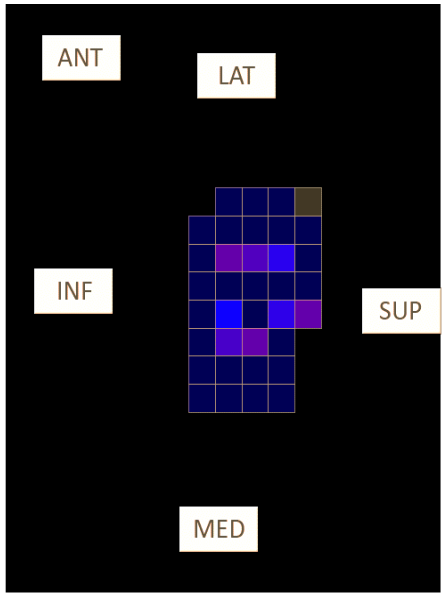
ClearSight™ System Output



Optical image for spatial orientation



DW-MRI surface map
4x4x1mm³ pixels (tunable)

High probability of malignancy

Low probability of malignancy

Fat

ClearCut

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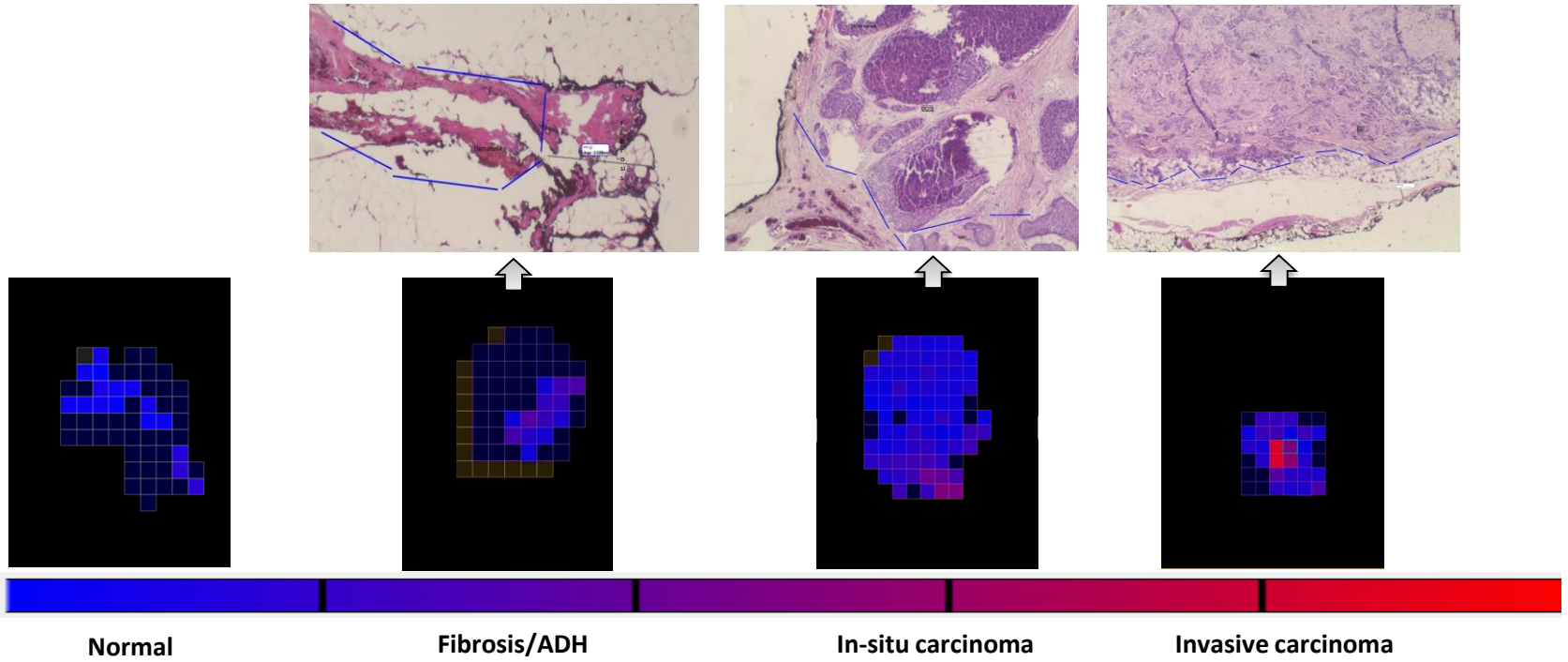
Typical ClearSight™ Image Contrast



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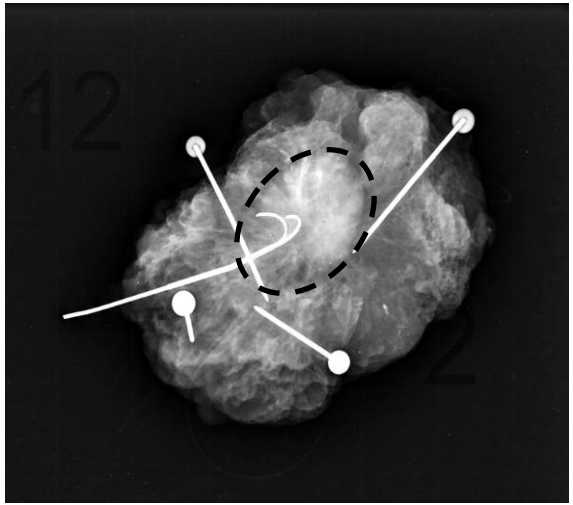
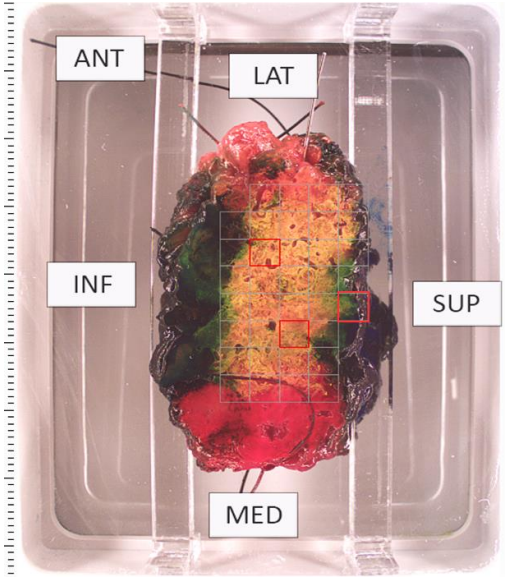
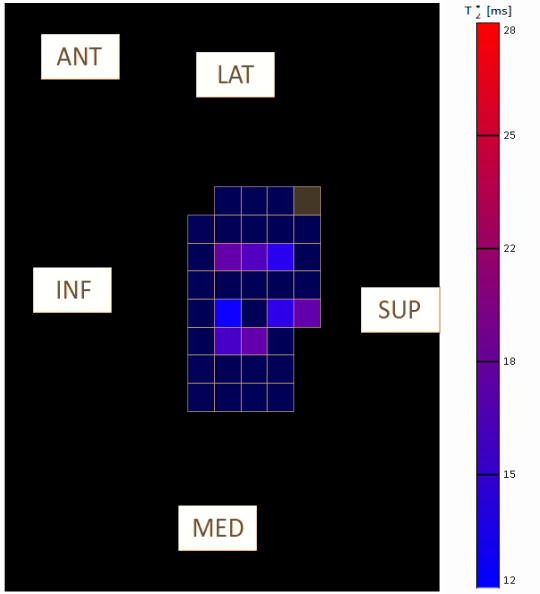
Technology Comparison: IDC On Ink



Specimen X-ray / Mammography



ClearSight™ Optical Image



ClearSight™ MR Surface Map

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Sensitivity - Specificity

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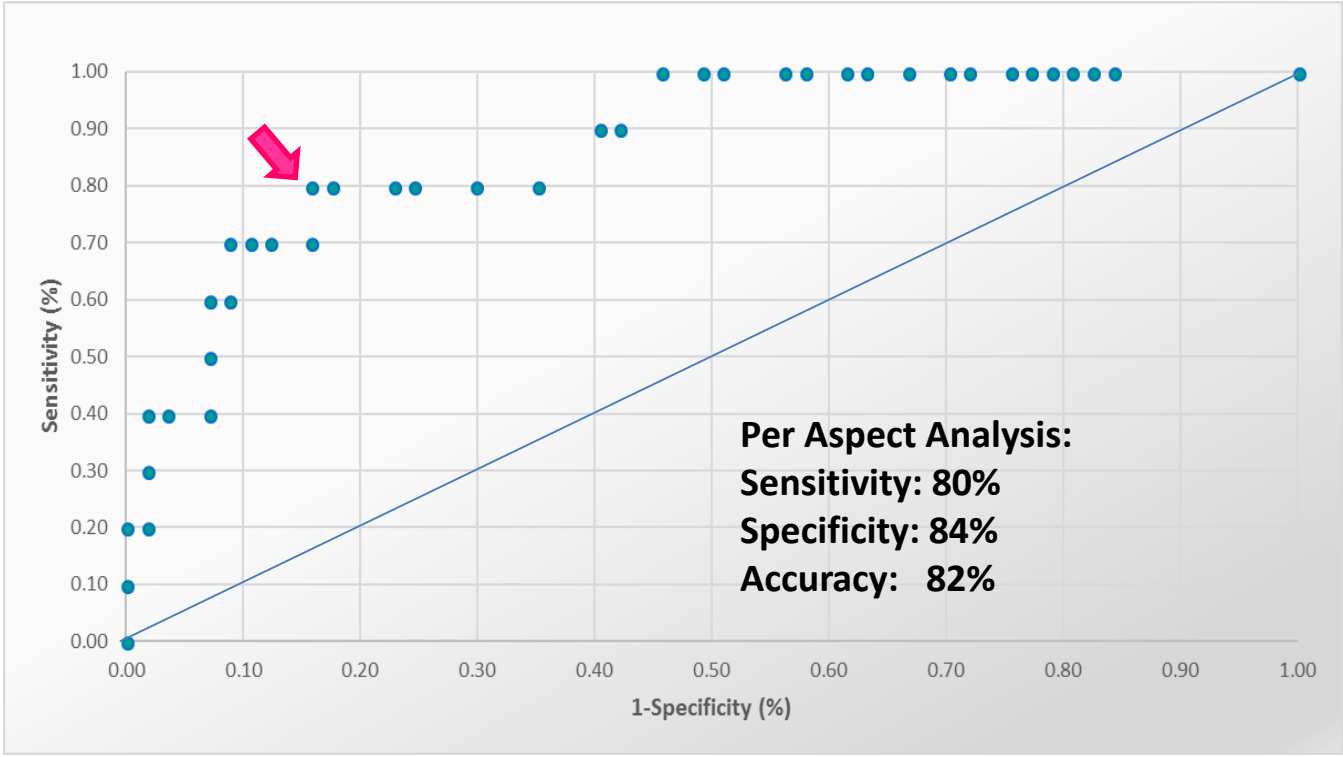
ROC (Receiver-Operating-Characteristics) Analysis For Invasive Cancers



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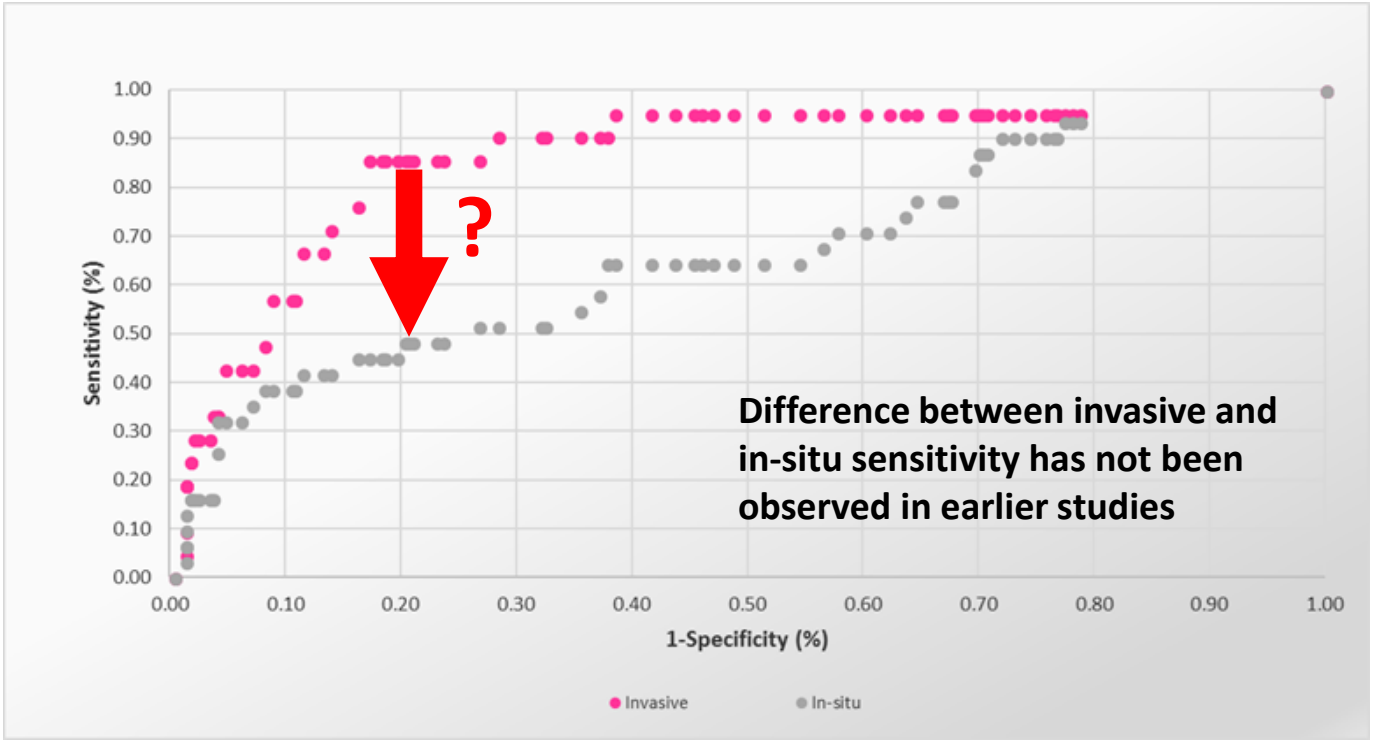
ROC Analysis: Invasive vs In-situ



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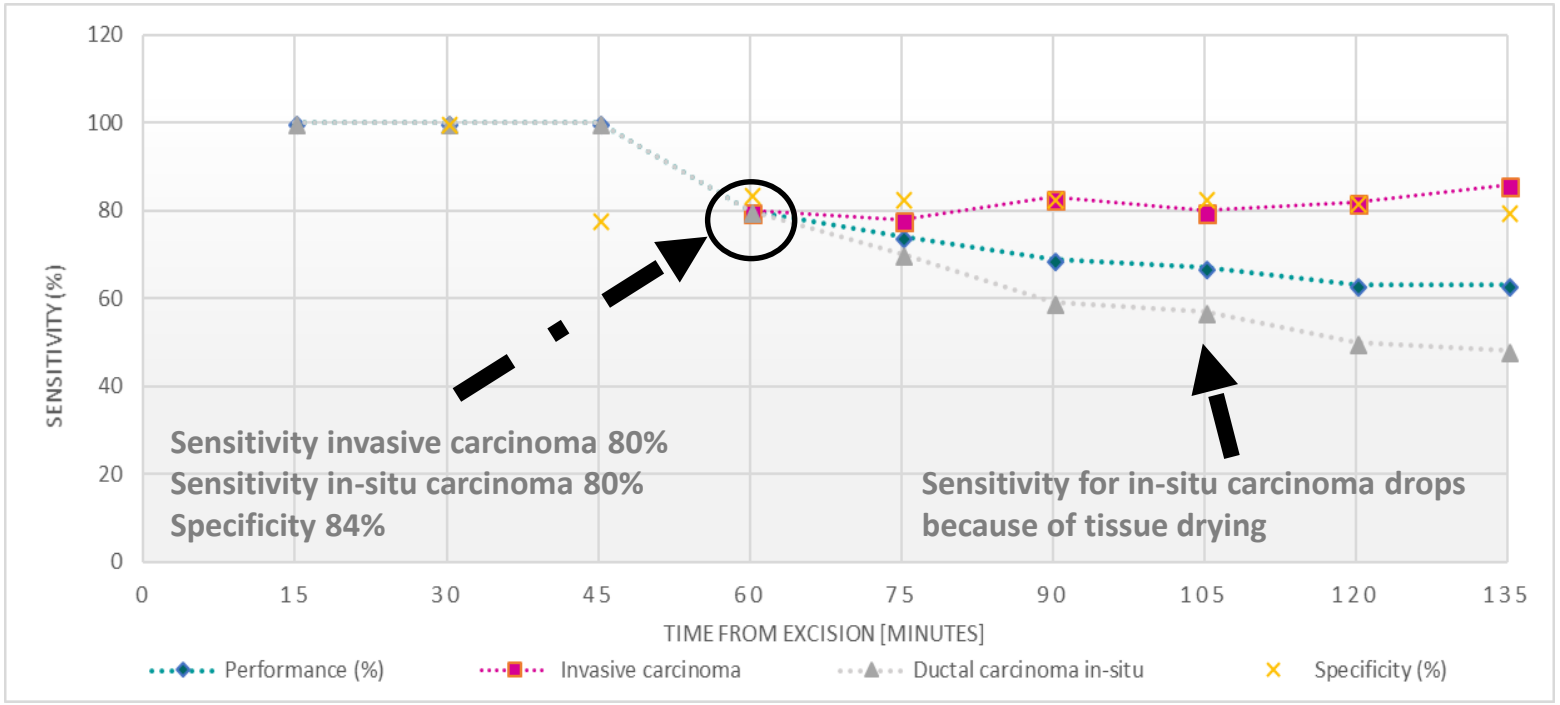
Tissue Drying Impacts DCIS Sensitivity



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Results

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Potential Re-Excision Rate Reduction

	AMK Re-Excisions	ClearSight™ Detection Rate
Overall rate	**38% (23/60)**	**61% (14/23)**
Invasive	22% (5/23)	80% (4/5)
In-situ	57% (13/23)	56% (7/13)
Invasive + In-situ	22% (5/23)	60% (3/5)

⇒ **For intra-operative use of ClearSight the potential reduction of re-excisions is 80%, in line with previous studies**

⇒ **Workflow delays inherent in local study setup reduced DCIS sensitivity to 56%, limiting the potential reduction to 61%**

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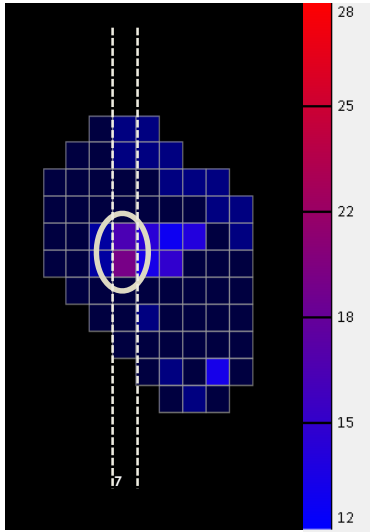
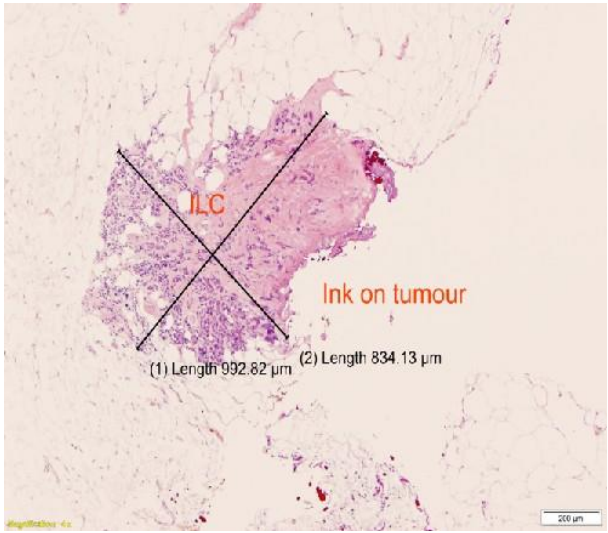
ClearSight™ Targeted Pathology

Guides pathologists during grossing to the suspicious spots of the tissue surface – improves accuracy and reduces the number of slices necessary for diagnosis

Intra-operative tissue photograph with pathology grossing slices overlay

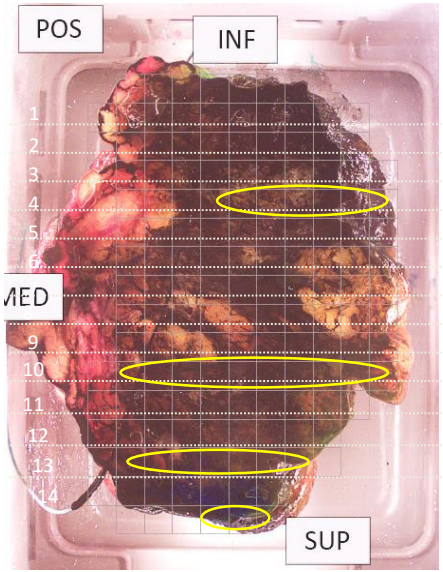


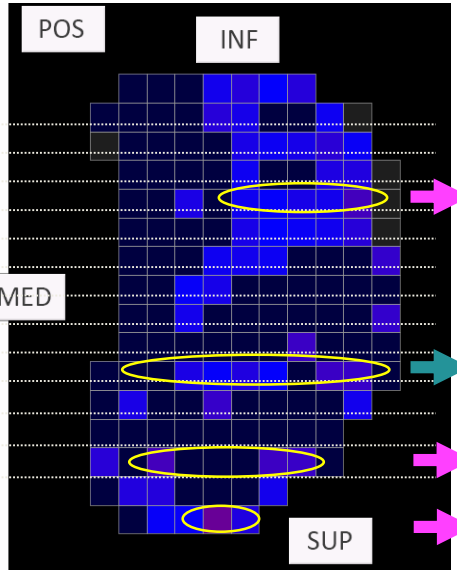
Intra-operative MR scan with positive finding and corresponding slice overlay



Small cancer focus (1x1mm²) in medial margin successfully located post-operatively by ClearSight™ MR guidance

ClearSight™ Targeted Pathology Case



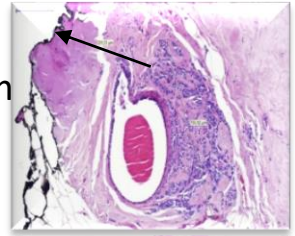


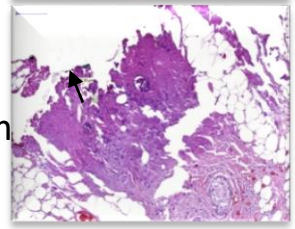
Target provided by ClearSight™ → ILC 0.18mm

Sampled under SOC → Clear margin

Targets provided by ClearSight™ → ILC 0.47mm

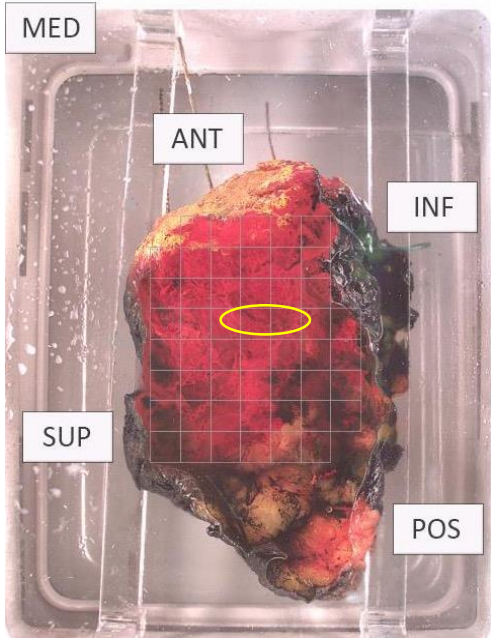
→ ILC on-ink

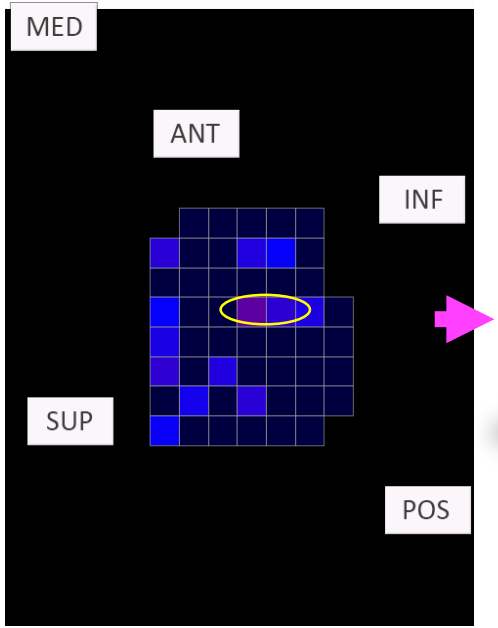




Pathologist sampled one location, diagnosed clean margin => False negative.
ClearSight™ provided three locations with Invasive Lobular Carcinoma in all three.

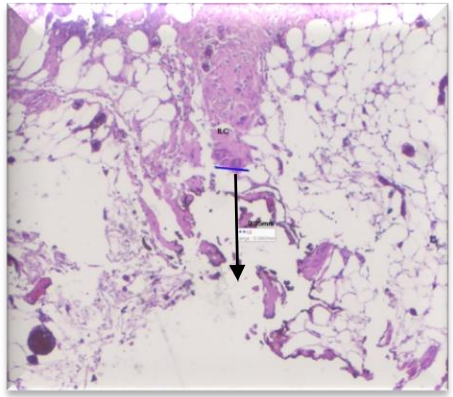
ClearSight™ Targeted Pathology Case





Target provided by ClearSight™

- ILC 0.35mm



Pathologist took no sample of medial margin => False negative.
ClearSight™ provided one location with Invasive Lobular Carcinoma.

Summary and Conclusions

- In both DCIS and IBC a sensitivity of 80% and a specificity of 84% have been observed
- Results are in line with previous studies
- For scans that have been performed longer than 1 hour after excision the sensitivity decreased rapidly in DCIS due to the dryness of the surface.
- If the surgeon would have known the results, 80% of the re-resection could have been avoided. Due to the dryness, the potential reduction of the whole cohort was decreased to 61%
- If the pathologist would have been unblinded to the scan results, it had led to corrected histology results in 3 cases
- ClearSight has the potential to reduce the re-resection rate by 80%

Thank you!

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