Intraoperative evaluation of margins

Marc Thill, MD, PhD
Director
Department of Gynecology and Gynecologic Oncology
Certified Breast Cancer Center
Certified Gynecologic Cancer Center, Certified Gynecologic Dysplastic Unit
Certified Sarcoma Center, Certified Endometriosis Center
AGAPLESION MARKUS KRANKENHAUS
Frankfurt am Main, Germany

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

<table>
<thead>
<tr>
<th>Item</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Advisory role</td>
<td>Amgen, AstraZeneca, Biom’Up, Celgene, Daiichi Sankyo, Eisai, Genomic Health, Lilly, MSD, Norgine, Neodynamics, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, Tesaro</td>
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<tr>
<td>(2) Lecture/speaker engagement fees</td>
<td>Amgen, AstraZeneca, Aurikamed, Celgene, Clovis, ConnectMedia, Eisai, Genomic Health, Hexal, Lilly, MCI, Medtronic, MSD, Novartis, OncoLive, Omniamed, Pfizer, pfm Medical, Roche, RTI Surgical</td>
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<tr>
<td>(3) Manuscript fees</td>
<td>Amgen, Celgene, Roche</td>
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<tr>
<td>(4) Other remuneration</td>
<td>Trial Funding</td>
</tr>
<tr>
<td></td>
<td>Genomic Health</td>
</tr>
</tbody>
</table>
# Current guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>DCIS</th>
<th>IBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE, 2014</td>
<td>≥2 mm</td>
<td>Negative margin</td>
</tr>
<tr>
<td>NZGG, 2009</td>
<td>≥2 mm</td>
<td>Negative margin</td>
</tr>
<tr>
<td>ESMO, 2015</td>
<td>≥2 mm</td>
<td>Negative margin</td>
</tr>
<tr>
<td>NCCN 2019</td>
<td>≥2 mm</td>
<td>Negative margin</td>
</tr>
<tr>
<td>AGO, 2019</td>
<td>≥2 mm</td>
<td>Negative margin</td>
</tr>
<tr>
<td>German S3, 2018</td>
<td>≥2 mm</td>
<td>Negative margin</td>
</tr>
</tbody>
</table>
To receive negative margins it is common to perform a re-excision in both IBC and DCIS

<table>
<thead>
<tr>
<th>Study</th>
<th>Re-excision rate*</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrow et al (2008)</td>
<td>22%</td>
<td>2030</td>
</tr>
<tr>
<td>Smitt et al (2003)</td>
<td>49%</td>
<td>535</td>
</tr>
<tr>
<td>Waljee et al (2008)</td>
<td>46%</td>
<td>714</td>
</tr>
<tr>
<td>McCahill et al (2012)</td>
<td>23%</td>
<td>2206</td>
</tr>
<tr>
<td>Jeehan et al (2012)</td>
<td>29.5%</td>
<td>2803</td>
</tr>
<tr>
<td>Jeehan et al (2012)</td>
<td>18%**</td>
<td>45793</td>
</tr>
</tbody>
</table>

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

McCahill, JAMA (2012)
How to reduce the re-resection rate?
Optimal pre- and intraoperative preparation/planning
DCIS – preoperative planning
Sectorial excision

- Standardized surgery:
  - Excision of the specimen from the superficial fascia down to the M. pectoralis major
Specboard fixation
Intraoperative radiography
The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer

Roger A. Graham, M.D., Marc J. Homer, M.D., Judith Katz, M.D., Janice Rothschild, M.D., Homa Safaii, M.D., Stacey Supran, M.A.

*Department of Surgery, New England Medical Center, Boston, MA 02111, USA
Department of Radiology, New England Medical Center, Boston, MA 02111, USA
Department of Pathology, New England Medical Center, Boston, MA 02111, USA
Biostatistics Research Center, Department of Medicine, New England Medical Center, Boston, MA 02111, USA
750 Washington St., Box 1043, Boston, MA 02111, USA

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

<table>
<thead>
<tr>
<th>Measurement of the breast specimens by the surgeon and the pathologist</th>
<th>Surgeon’s measurements</th>
<th>Pathologist's measurements</th>
<th>Mean difference</th>
<th>Percent decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean volume of breast specimen (cm³)</td>
<td>46.13</td>
<td>29.18</td>
<td>16.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI = 9.48–24.42</td>
<td></td>
</tr>
<tr>
<td>Mean height of breast specimen (cm)</td>
<td>2.57</td>
<td>1.36</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI = 1.03–1.37</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.
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 et al., J Surg Oncol 2014
Thill M et al., SABCS 2018 © M. Thill
A Handheld Spectroscopic Device for In Vivo and Intraoperative Tumor Detection: Contrast Enhancement, Detection Sensitivity, and Tissue Penetration

Aaron M. Mohs¹, Michael C. Mancini¹, Sunil Singhal², James M. Provenzale³,⁴, Brian Leyland-Jones⁵, May D. Wang⁶, and Shuming Nie*¹
Hand-held pen - SpectroPen
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

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
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.
Cerenkov Luminescence Imaging
- Optical imaging of PET Tracers -

Removed tumour

Residual cancer
Rapid intra-operative imaging of residual cancer
FDG CLI of BCS lumpectomy specimen

- 24mm, grade 2, ER+/HER2- invasive lobular carcinoma admixed with lobular carcinoma in situ
- Tumour resection margins were clear (≥ 5mm)
Radiofrequency spectroscopy
Bioelectric differences between normal and cancer tissue

Membrane de-polarization

Alterations in nuclear morphology

Increased vascularity

Cell to cell connectivity
MarginProbe®
MarginProbe® - measuring of the dielectric properties real-time

- Normal tissue measurement
- Cancerous tissue measurement

- Clean point
- Positive (cancer) point

Clean Margin (all clean points)

Positive Margin (at least one positive point)

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 Gynecology, University Hospital of Schleswig-Holstein, Campus Luebeck, Ratzeburger Allee 160, 23538 Luebeck, 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.


Key Words: Intraoperative margin assessment; breast conserving surgery; optical imaging; breast cancer; ductal

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

Marc Thill a,b,*, Christine Dittmer b, Kristin Baumann c, Kay Friedriech d, Jens-Uwe Blohmer e

a Department of Gynecology and Obstetrics, Agaplesion Markus Hospital, Germany
b Breast Center, Hospital Essen Mitte, Germany
c Department of Obstetrics and Gynecology, University Hospital of Schleswig-Holstein, Campus Luebeck, Germany
d Maximazentrum Hamburg, Germany
e Department of Gynecology and Obstetrics, St. Gertrudian Hospital, Berlin, Germany

In breast conserving surgery, the tumor should be removed with a clear 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)

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

\(^\#\) SOC = Standard of Care

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Schnabel F et al., SABCS 2011
Thill M et al., Breast 2013 © M. Thill
Clinical trials - Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction of re-excision rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAST</td>
<td>56%</td>
<td>p=0.039</td>
</tr>
<tr>
<td>PIVOTAL</td>
<td>50%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>German Multicenter</td>
<td>56%</td>
<td>p=0.018</td>
</tr>
</tbody>
</table>
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%
Diffusion weighted MRI
The **ClearSight™ Surgical Specimen MRI**

Left: Current system in clinical trials, CE marked

Right: Next generation, commercial version
**Principle Diffusion-Weighted MRI**

Restricted diffusion (slower diffusion)
- Lower ADC (Apparent Diffusion Coefficient)
  - Higher T₂*

Free diffusion (faster diffusion)
- Higher ADC
  - Lower T₂*

---


* Tsushima et al., MR Differential Diagnosis of Breast Tumors Using Apparent Diffusion Coefficient on 1.5-T, J. MRI, 249-255, 2009.
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.


Good ADC differentiation of malignant vs benign tissues has been observed in:
- Breast
- Endometrium
- Lungs
- Lymph nodes
- Liver
- Thyroids
- Kidneys
- Prostate
- Brain
- …others
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 MD3, Tami Karni MD2,4, Judith Sandbank MD2,5, Myriam Konichezky MD6, Judith Diment MD7, Assaf Guterman MSc8, Moshe Shapiro MSc8, Zachi Peles MSc8, Roi Maishar BSc8, Assaf Gur MSc8, Eyal Kolka MSc8 and Rachel Brem MD9

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.
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.
# ClearSight™ M2M II Study (2018)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Prospective, multi-center, single arm, open label, blinded, post marketing surveillance (PMS) clinical study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle Investigator</td>
<td>PD Dr. Marc Thill, Agaplesion Markus Hospital, Frankfurt, Germany</td>
</tr>
<tr>
<td>Study Objective</td>
<td>Further assess the ClearSight™ System ability to detect irregular tissue in margins of excised breast specimen in patients undergoing Breast Conserving Surgery</td>
</tr>
<tr>
<td>Study Population</td>
<td>Up to 110 patients undergoing BCS will be enrolled in up to 3 sites in Europe and Israel;</td>
</tr>
<tr>
<td>• Agaplesion Markus Hospital, Frankfurt, Germany (completed)</td>
<td></td>
</tr>
<tr>
<td>• Kaplan Medical Center, Rehovot, Israel (ongoing)</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>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</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td>To assess the value of ClearSight maps for targeting of suspicious tissue during specimen grossing in pathology</td>
</tr>
</tbody>
</table>

*Thill M et al., SABCS 2018 © M. Thill*
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).
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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± std, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.2±10.5</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>8 (13)</td>
</tr>
<tr>
<td>18.5-25</td>
<td>27 (45)</td>
</tr>
<tr>
<td>25-30</td>
<td>22 (37)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Menopause status</td>
<td></td>
</tr>
<tr>
<td>Pre-menopause</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Post-menopause</td>
<td>45 (75)</td>
</tr>
<tr>
<td>Cancer Type</td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>42 (70)</td>
</tr>
<tr>
<td>DCIS</td>
<td>9 (15)</td>
</tr>
<tr>
<td>DCIS and IDC</td>
<td>4 (7)</td>
</tr>
<tr>
<td>ILC</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Cancer grade</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Moderate</td>
<td>38 (64)</td>
</tr>
<tr>
<td>High</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Lesion volume (cm³)</td>
<td>3.1±6.8</td>
</tr>
</tbody>
</table>

Thill M et al., SABCS 2018  © M. Thill
Workflow
ClearSight™ Operation
ClearSight™ System Output

Optical image for spatial orientation

DW-MRI surface map
4x4x1mm³ pixels (tunable)

High probability of malignancy

Low probability of malignancy

Fat
Typical ClearSight™ Image Contrast

- Normal
- Fibrosis/ADH
- In-situ carcinoma
- Invasive carcinoma
Technology Comparison: IDC On Ink

Specimen X-ray / Mammography

ClearSight™ Optical Image

ClearSight™ MR Surface Map

Thill M et al., SABCS 2018 © M. Thill
Sensitivity - Specificity
ROC (Receiver-Operating-Characteristics) Analysis For Invasive Cancers

Per Aspect Analysis:
- Sensitivity: 80%
- Specificity: 84%
- Accuracy: 82%
ROC Analysis: Invasive vs In-situ

Difference between invasive and in-situ sensitivity has not been observed in earlier studies
Tissue Drying Impacts DCIS Sensitivity

Sensitivity invasive carcinoma 80%
Sensitivity in-situ carcinoma 80%
Specificity 84%

Sensitivity for in-situ carcinoma drops because of tissue drying
Results
## Potential Re-Excision Rate Reduction

<table>
<thead>
<tr>
<th></th>
<th>AMK Re-Excisions</th>
<th>ClearSight™ Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall rate</td>
<td>38% (23/60)</td>
<td>61% (14/23)</td>
</tr>
<tr>
<td>Invasive</td>
<td>22% (5/23)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>In-situ</td>
<td>57% (13/23)</td>
<td>56% (7/13)</td>
</tr>
<tr>
<td>Invasive + In-situ</td>
<td>22% (5/23)</td>
<td>60% (3/5)</td>
</tr>
</tbody>
</table>

⇒ 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%

Thill M et al., SABCS 2018 © M. Thill
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 (1x1 mm²) in medial margin successfully located post-operatively by ClearSight™ MR guidance

© M. Thill
ClearSight™ Targeted Pathology Case

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