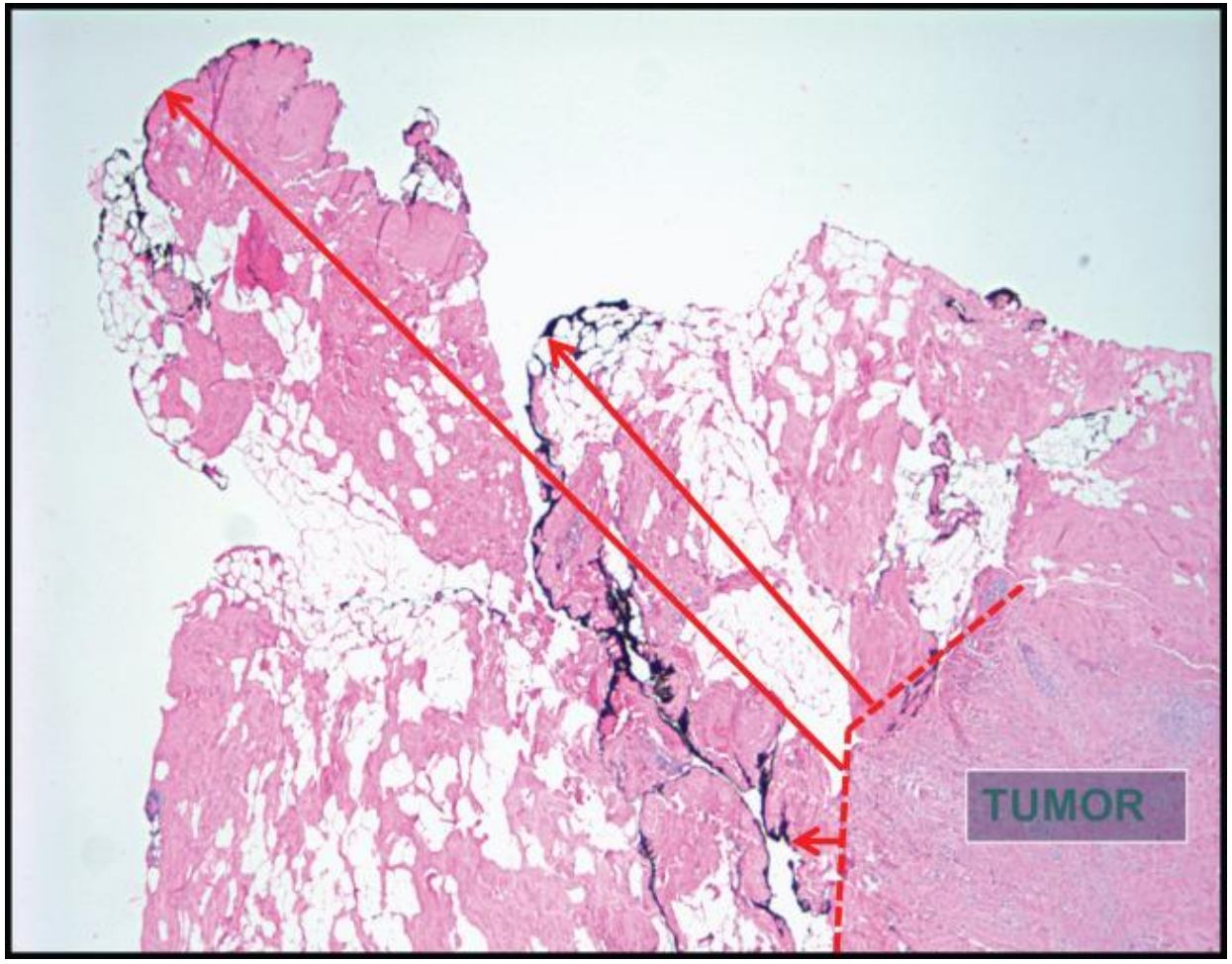
VÅRMÖTE I PATOLOGI
NPM 2025
19–21 MAY
NORDIC PATHOLOGY MEETING

Surgical margins and margin assessment - correlation to recurrence of breast cancer



Anikó Kovács

Dept. of Clinical Pathology

Sahlgrenska University Hospital
Gothenburg, Sweden

Breast surgery in the past

The guillotine-like instrument
by Gerard Tabor in 1721

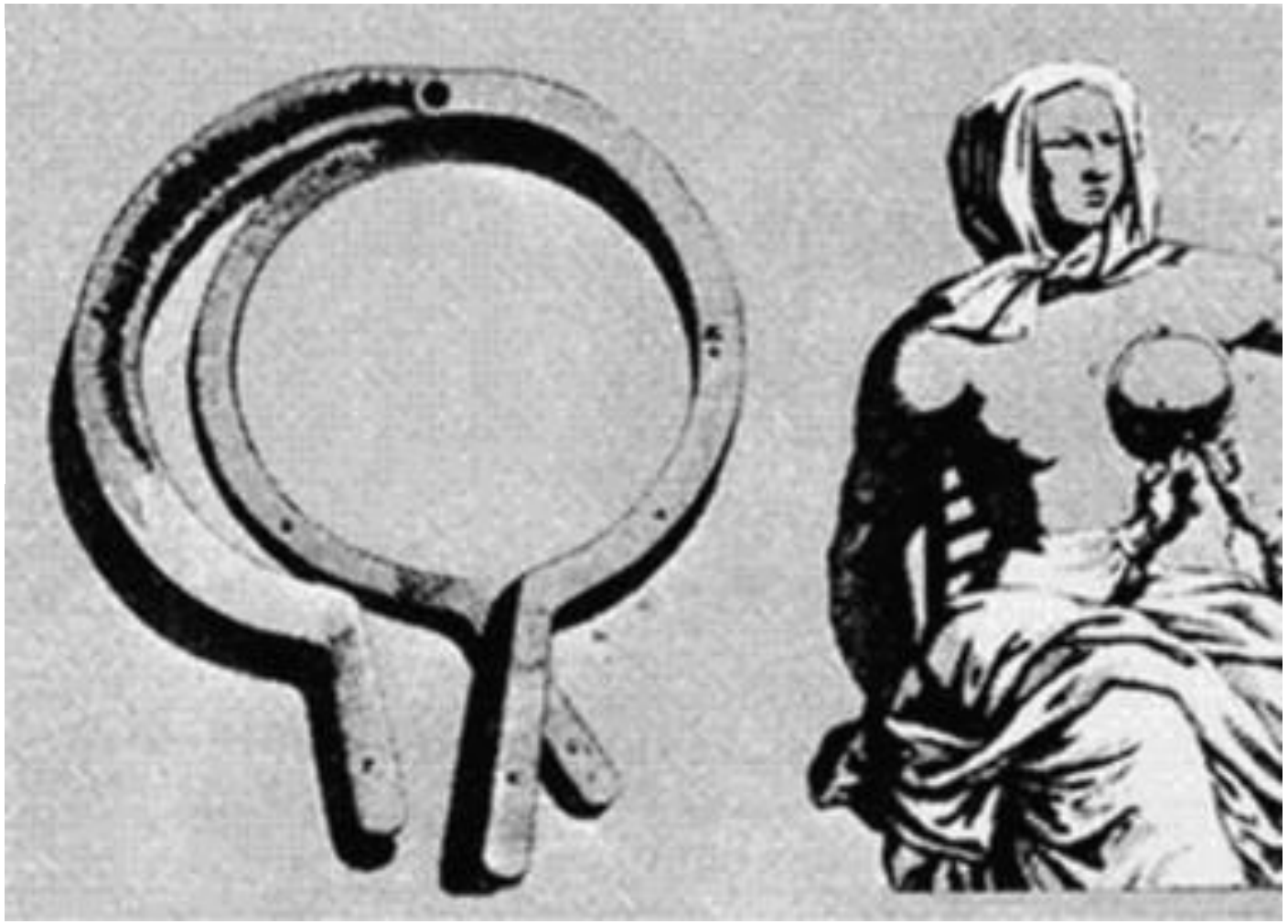
Acta Biomed 2024; Vol. 95, N. 2: e2024083 DOI: 10.23750/abm.v95i2.15765

MEDICAL HUMANITIES

From the treatment of breast cancer to the treatment of the woman with cancer: History of breast surgery and its prejudices

Francesca Depaoli[1], *Rosagemma Ciliberti*[2]

[1]Breast Surgery Clinic, San Martino Policlinic Hospital, Genoa, Italy; [2]Department of Health Sciences, Section of History of Medicine and Bioethics, University of Genoa, Genoa, Italy



VÅRMÖTE I PATOLOGI
NPM 2025
19–21 MAY
NORDIC PATHOLOGY MEETING

Medicine and art
at the Mori Art Museum in Tokyo, Japan

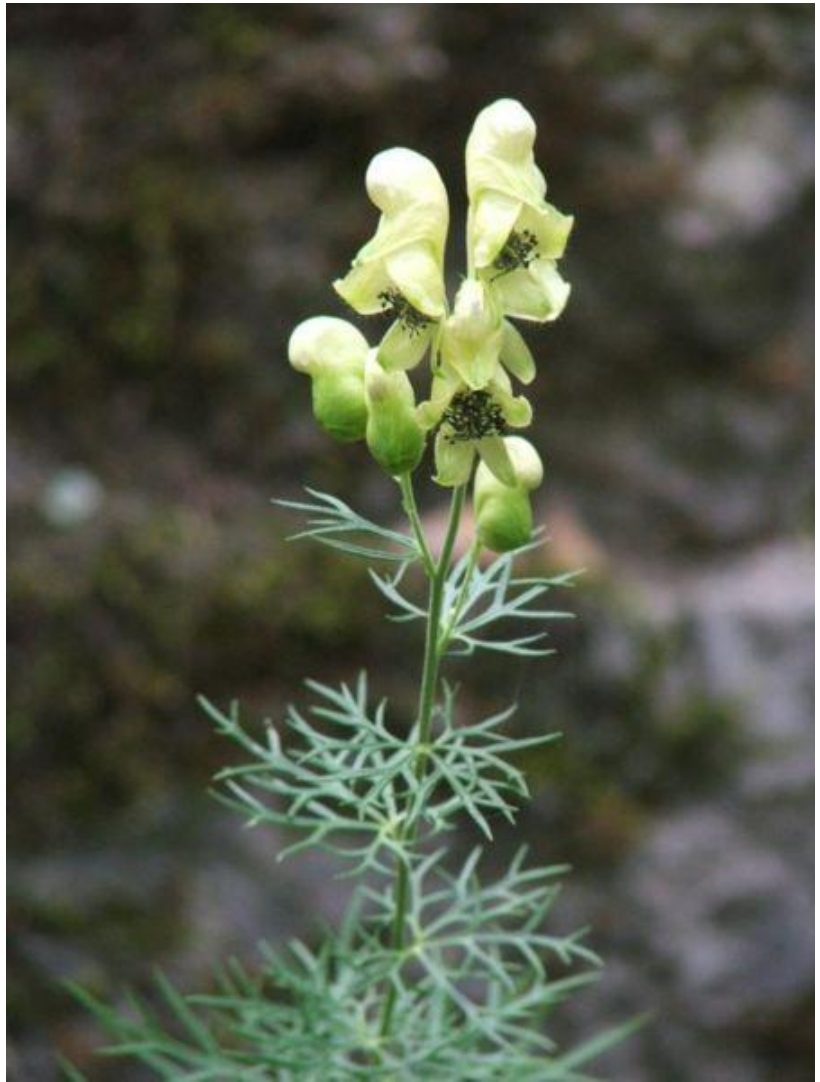
Kamata Keishu (1794-1854)
Surgery for Breast Cancer 1851

In 1851, Kamata Keishu compiled
a ten-volume medical treatise
"*Geka kihai*".

Excision of a **cancerous growth**
from a **woman's breast**
in **1804** using general anesthetic.

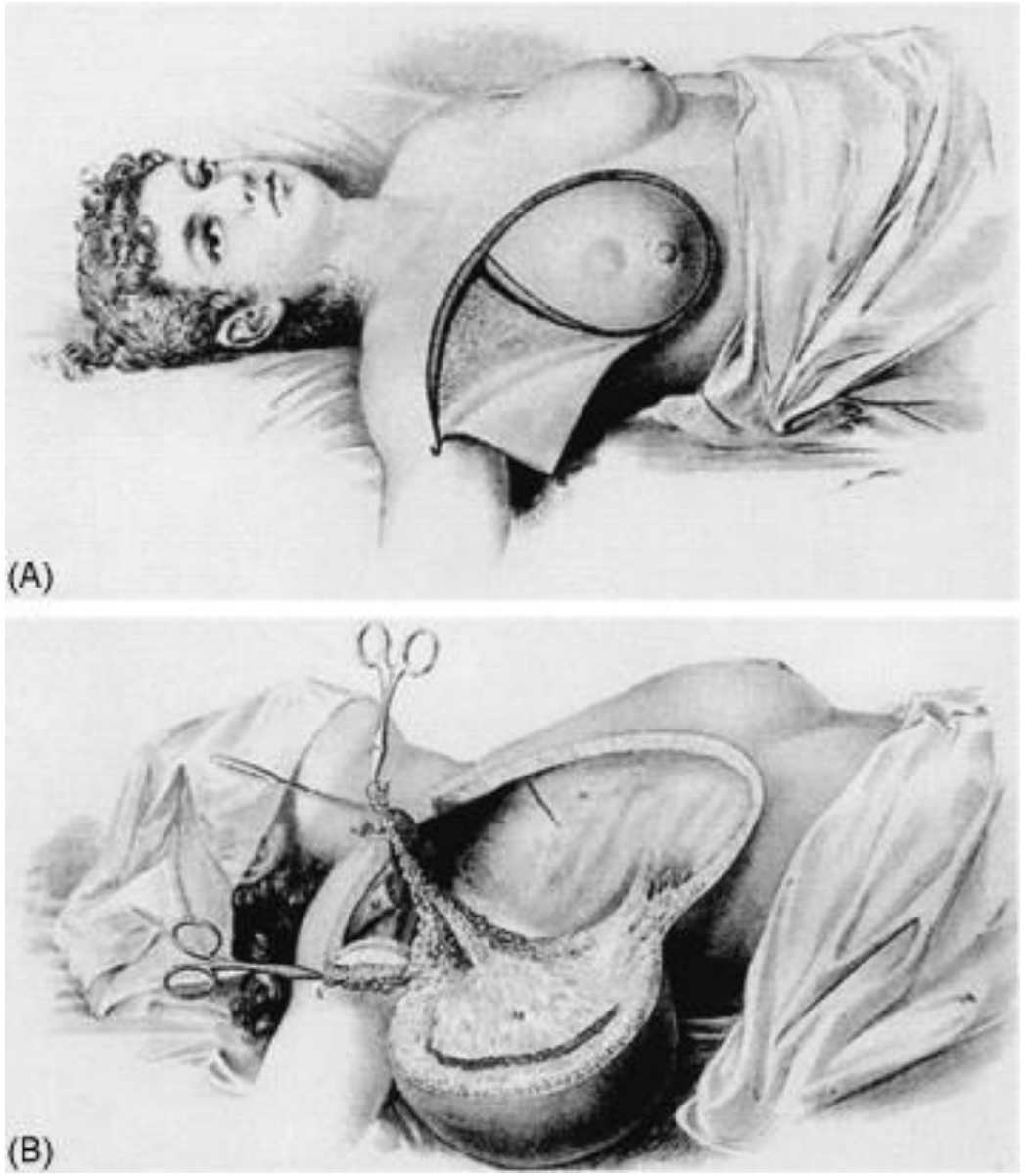
Breast surgery 1804 Japan

Tsusensan - a mixture of herbs :
thorn-apple /Datura = spikklubba/ and wolf´s bane /Aconitum = stormhatt/
led to unconsciousness for 6-24 hours



In 1846 John Collins Warren gave permission to William T.G. Morton to provide ether anesthesia while Warren performed a minor surgical procedure.
News of this first public demonstration of surgical anesthesia quickly circulated around the world.

Breast surgery in the past



Halsted's
radical mastectomy
in 1894

Breast surgery nowadays

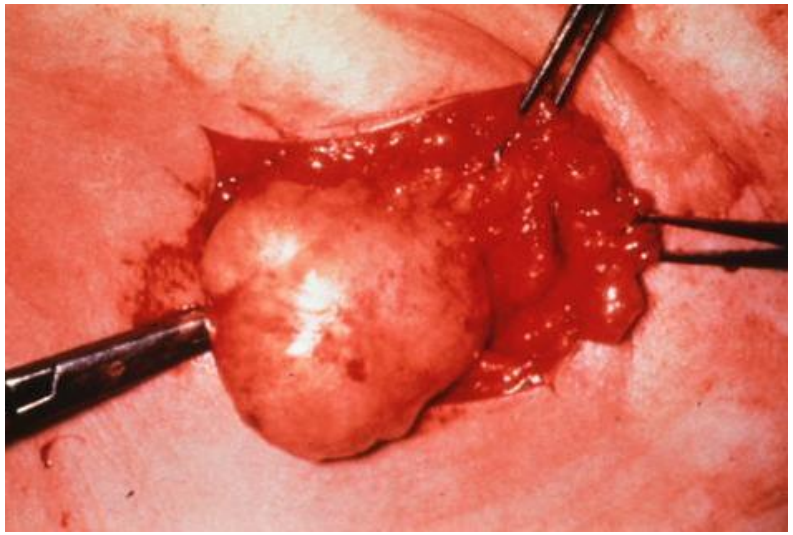
Types of breast surgery

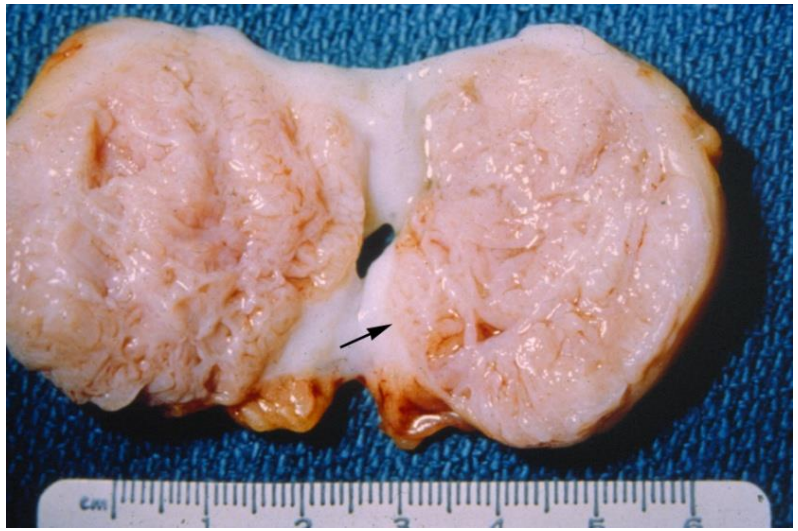
1. **Excision biopsy** (benign tumors)

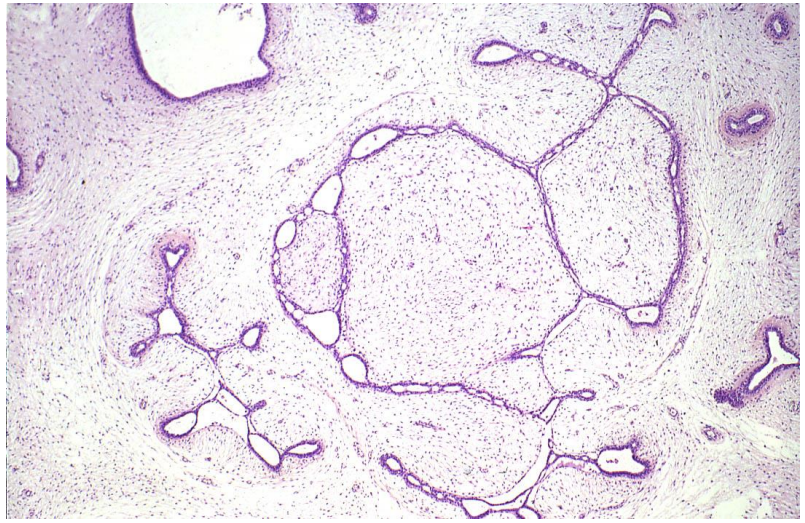
2. **Partial mastectomy/ sector resection / lumpectomy**
   (small breast cancers)

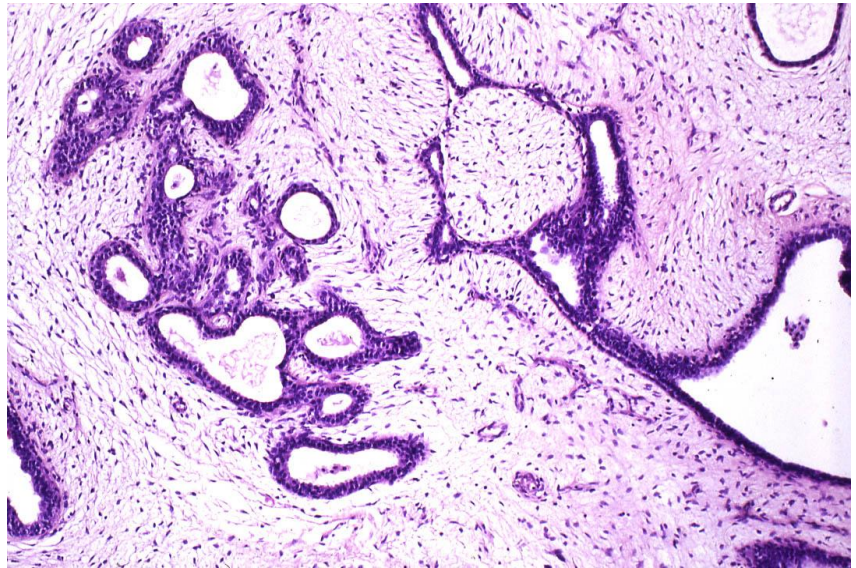
3. **Total mastectomy / ablatio**
   (large cancers or bi-/multifocal cancers)

1. Excision biopsy (benign tumors)
Fibroadenom





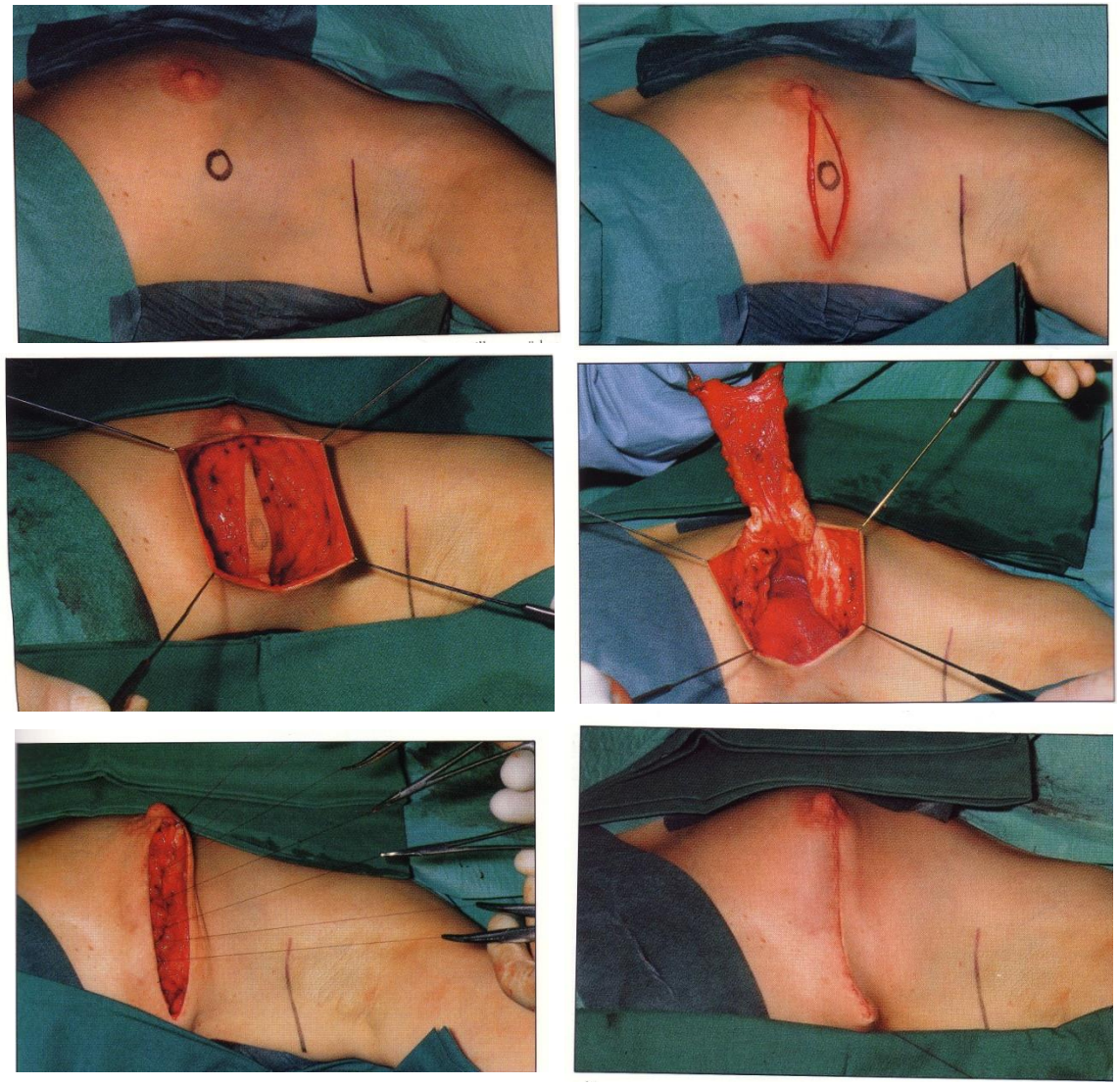


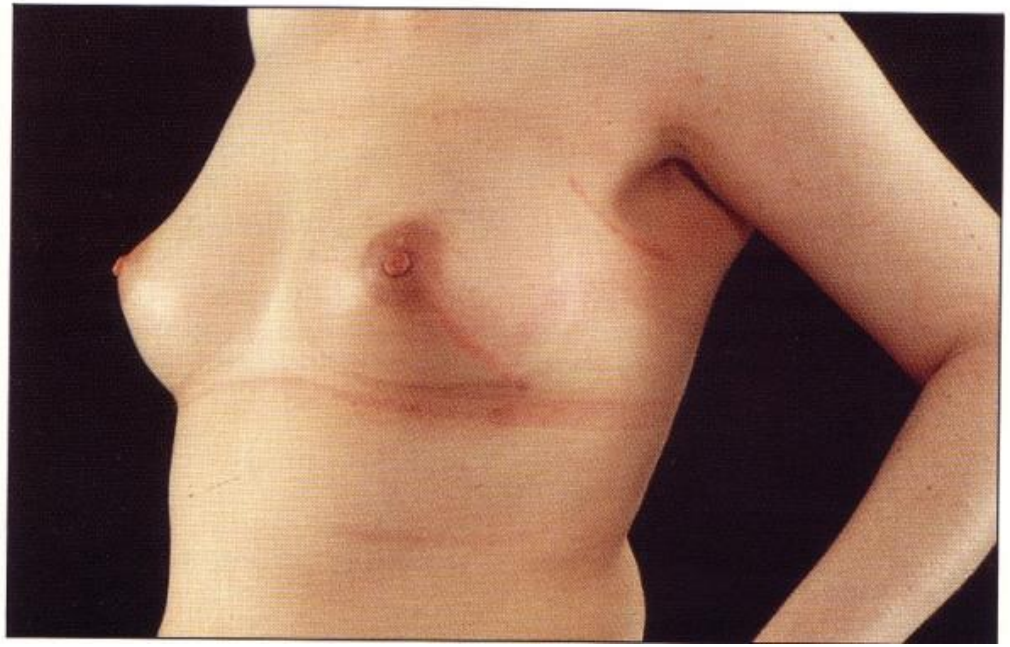


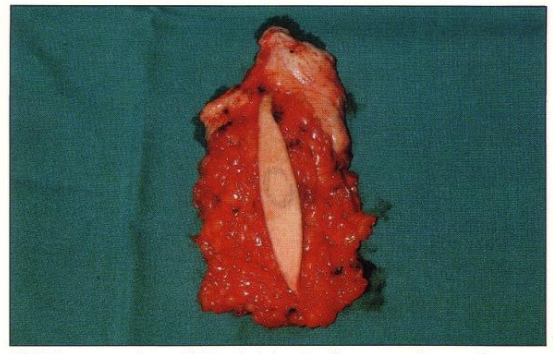
2. Partial mastectomy/ sector resection / lumpectomy

(small breast cancers)

Breast conserving surgery

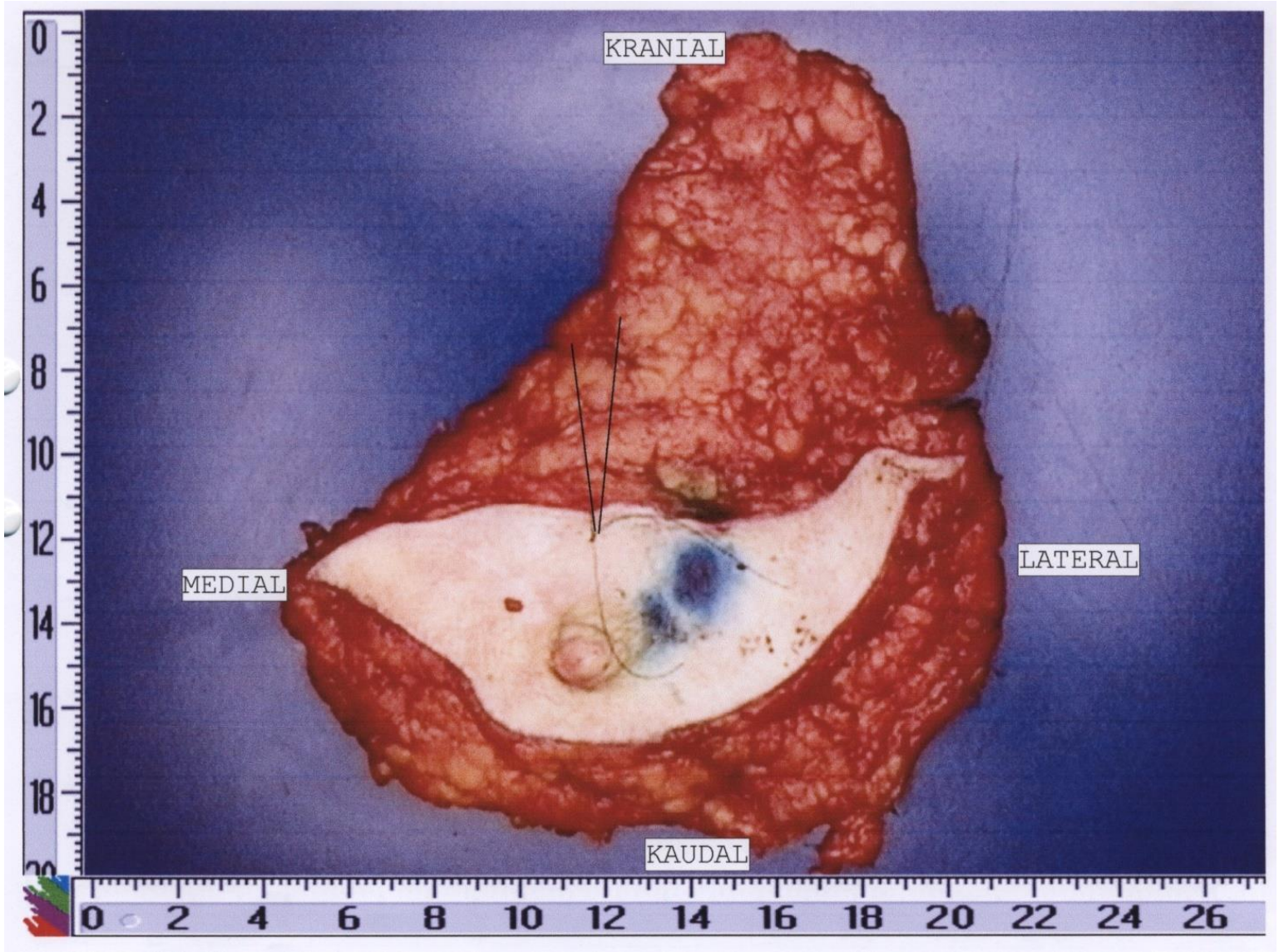




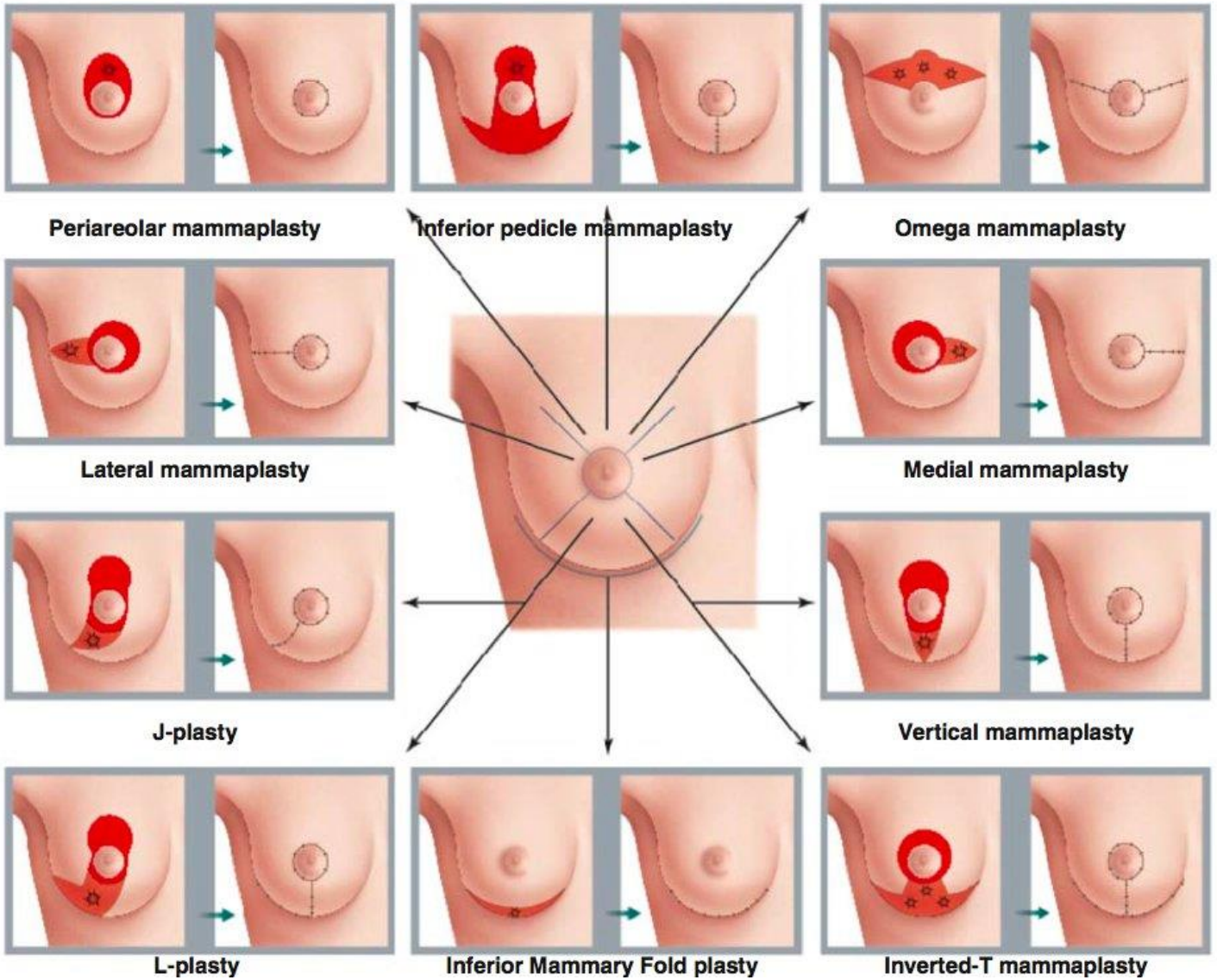


3. Total mastectomy /ablatio

(large cancers or bi-/multifocal cancers)

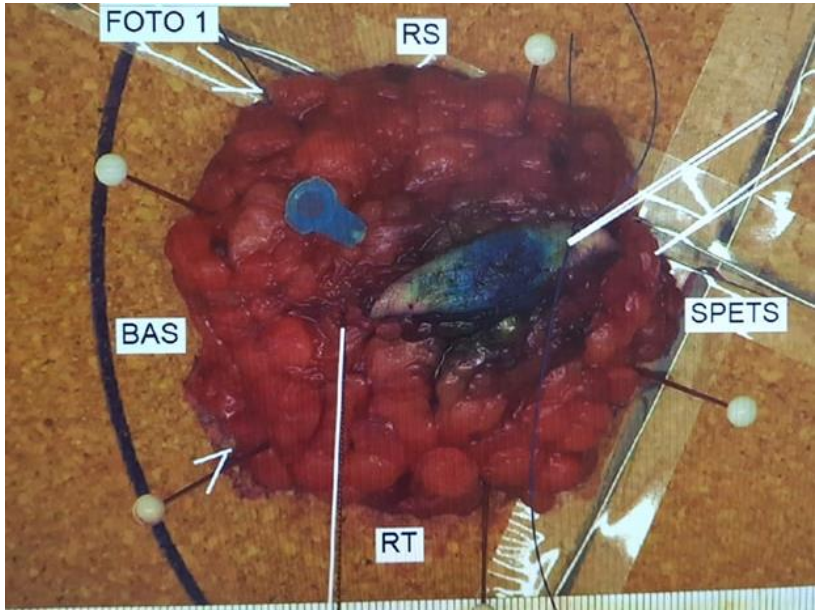


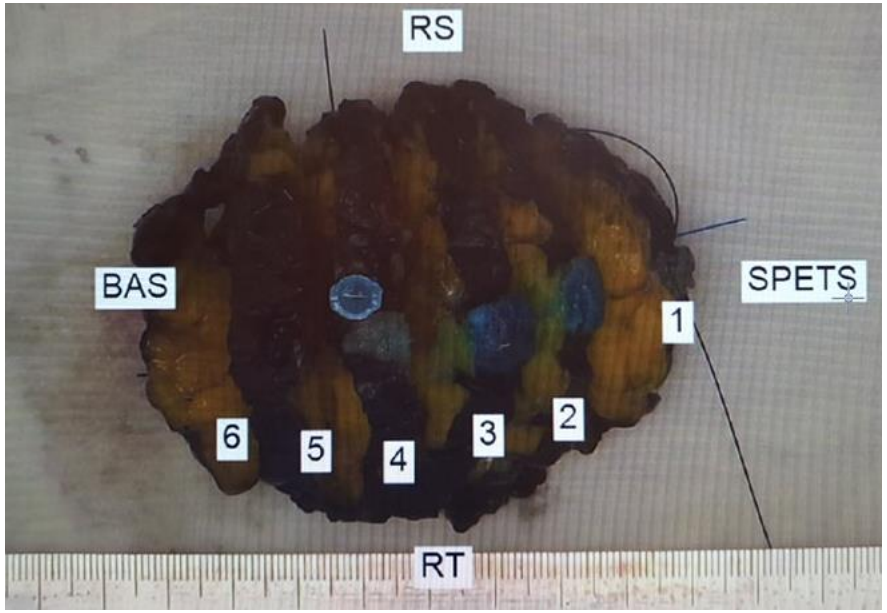
Oncoplastic surgery

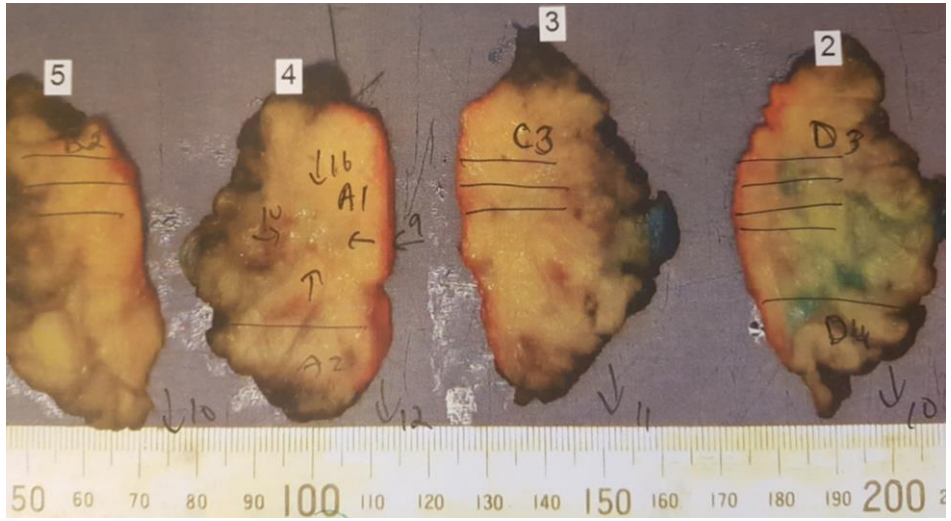


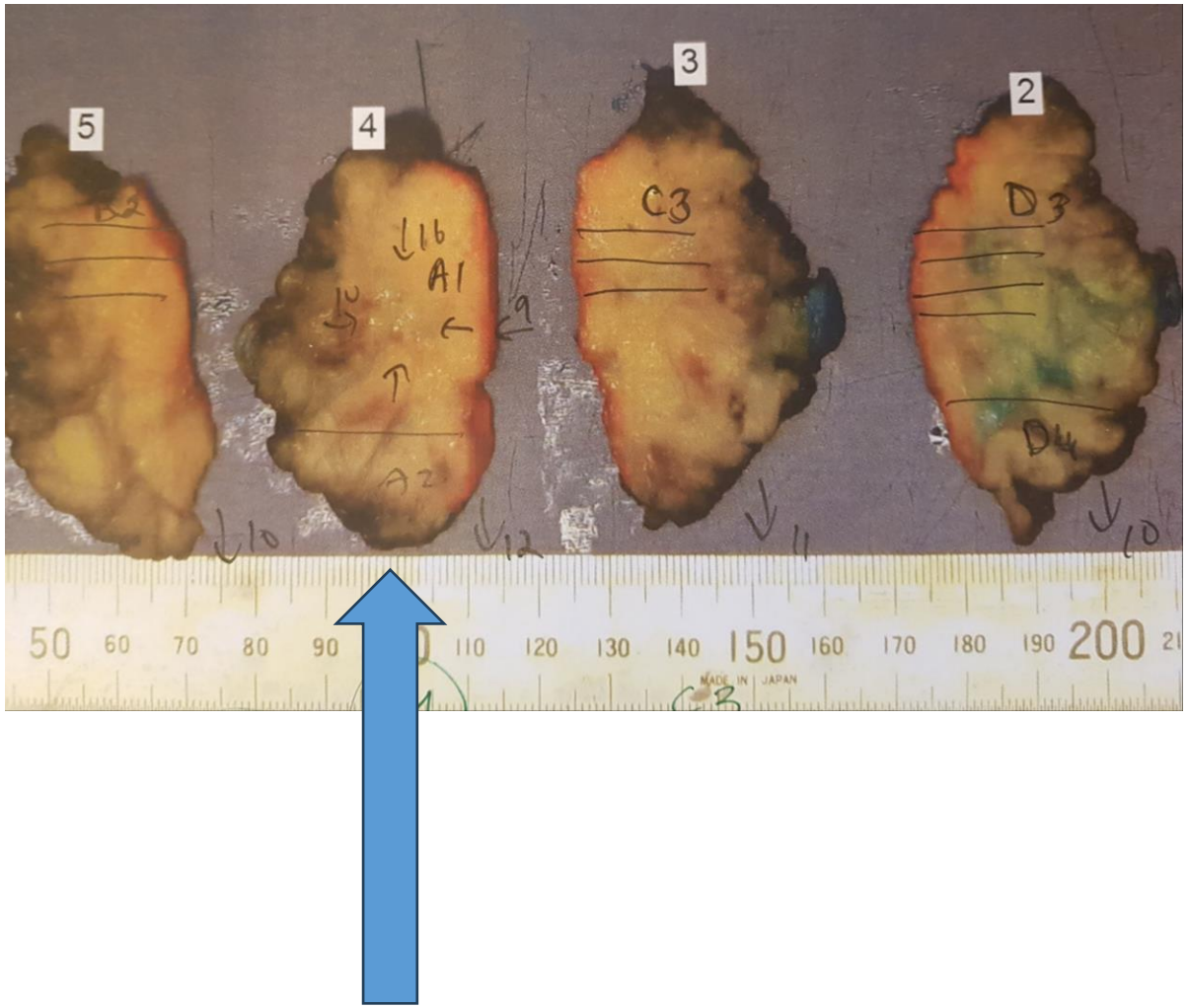
Histopathological report for the surgeon : Is the tumor ”in toto” excised ? ” Radikalt avlägsnat ? ”

Aim of breast surgery: excision of the tumor in toto

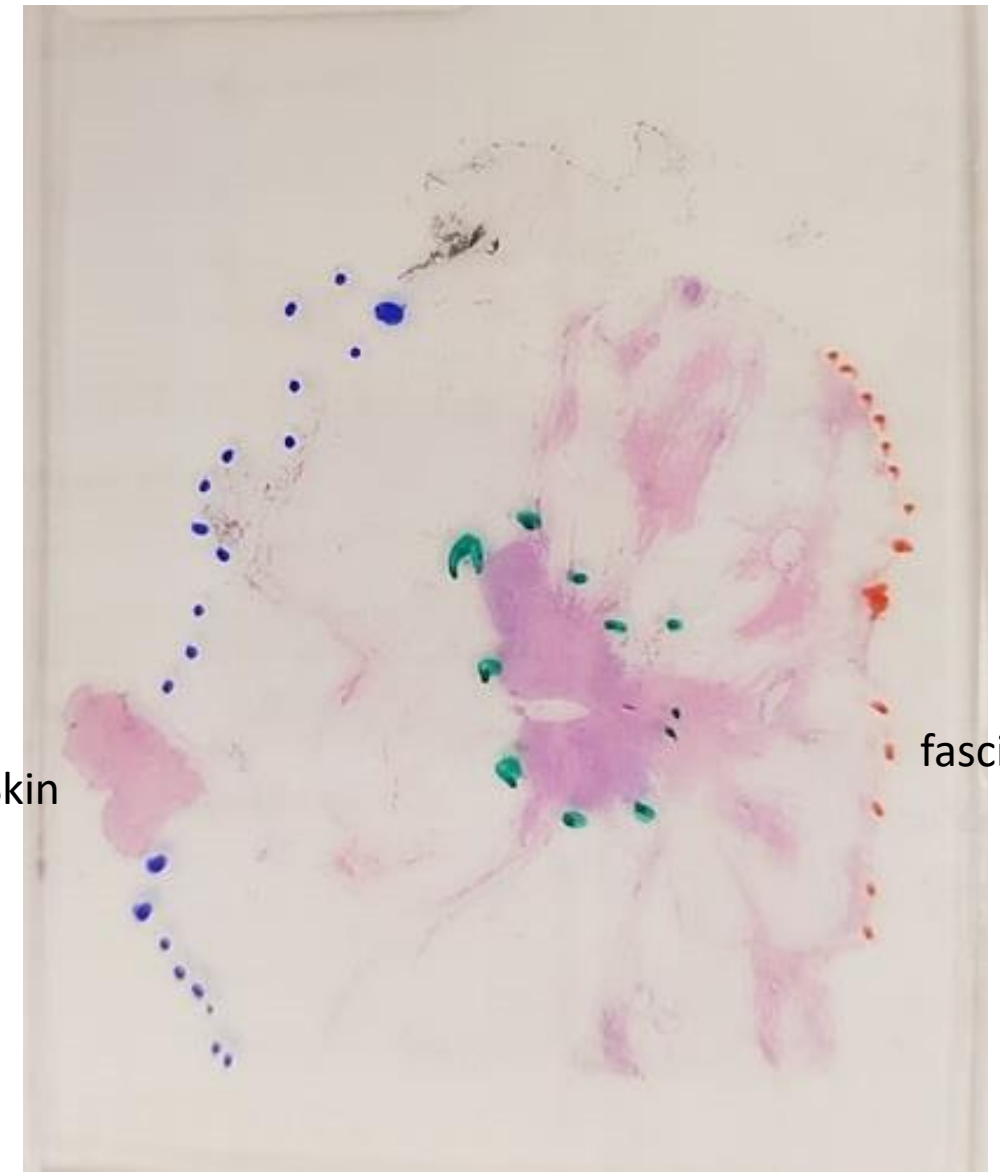








Slice 4, Block A1

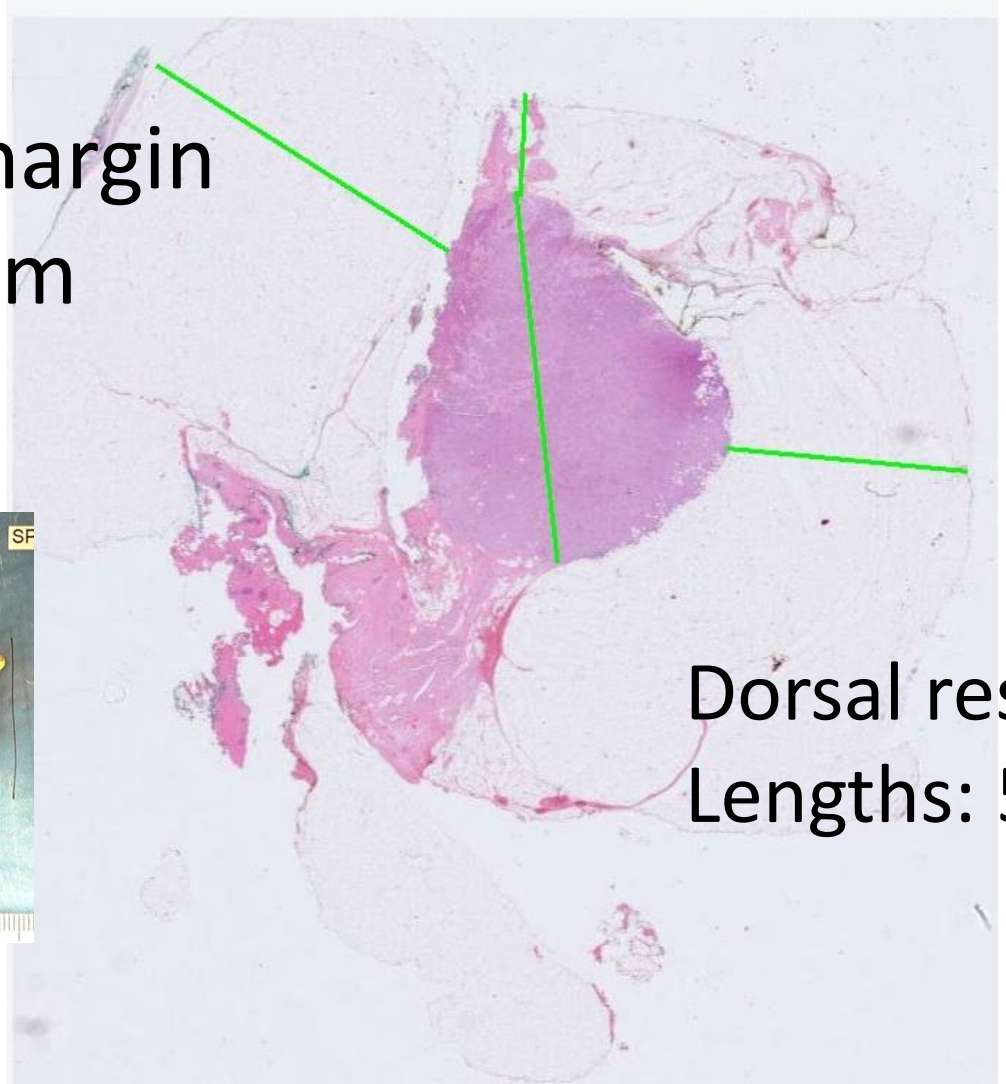


Skin

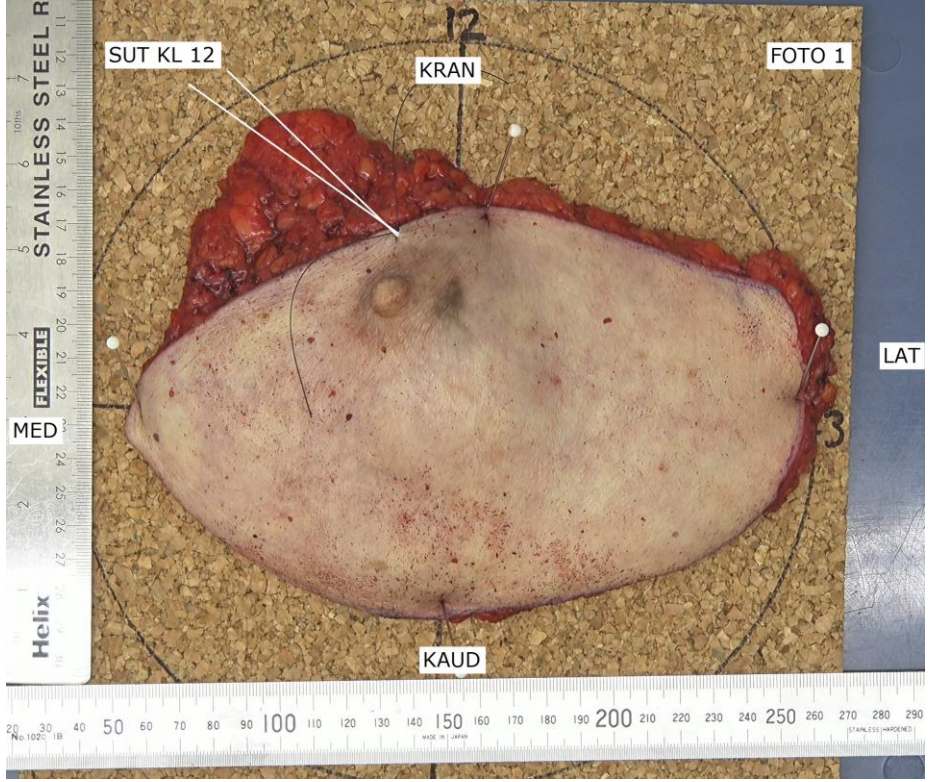
fascia

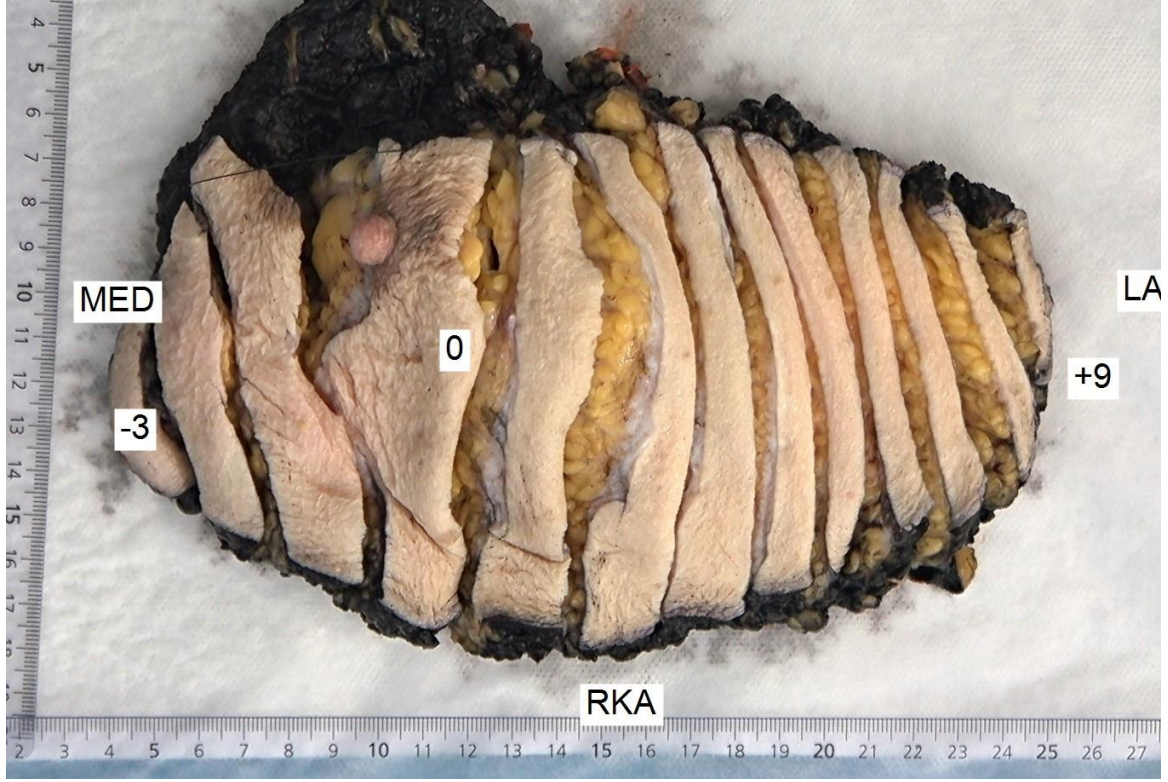
Digital pathology:
Measurement of distance and tumor size

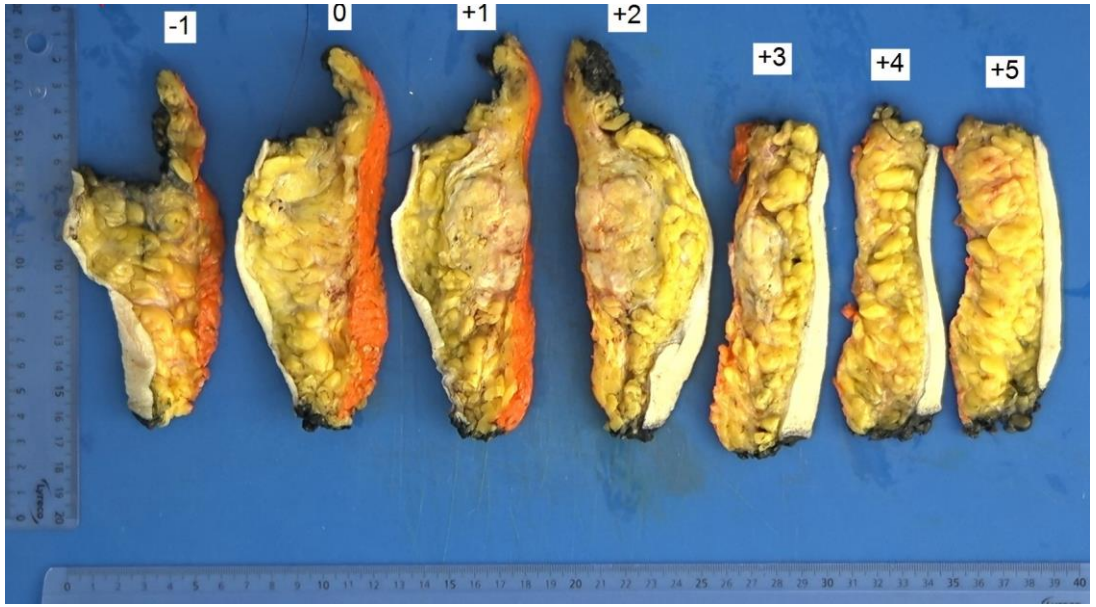
Ventral resection margin
Lengths: 7171,07 µm

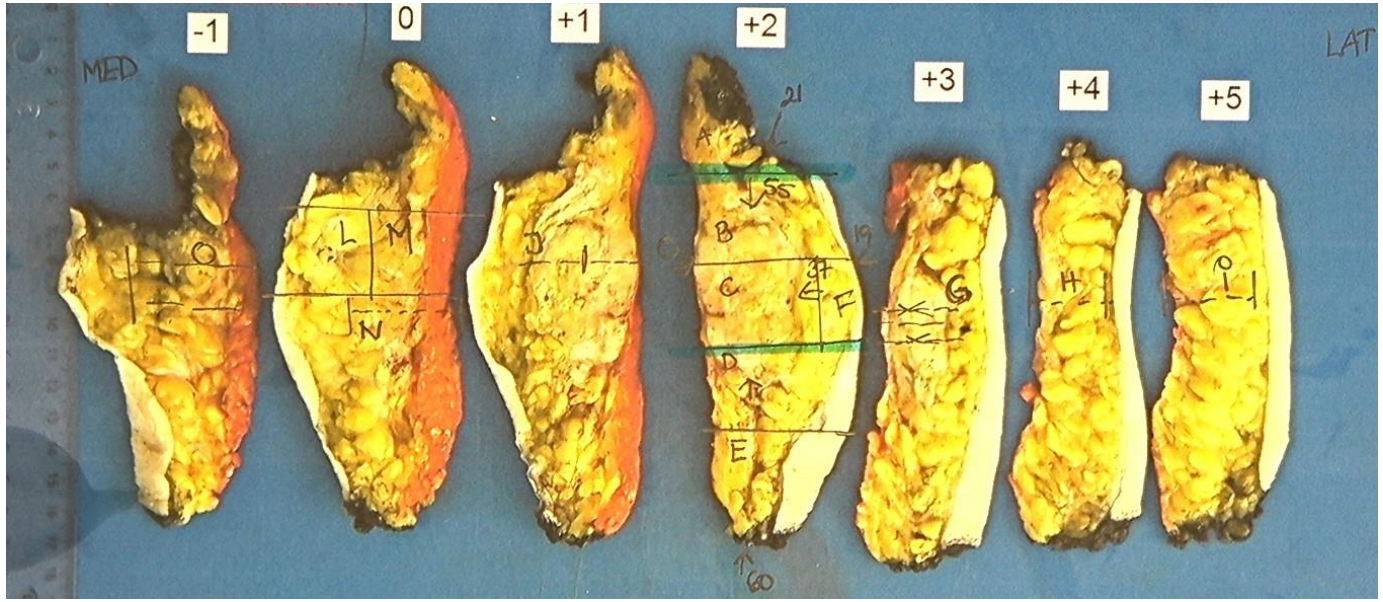


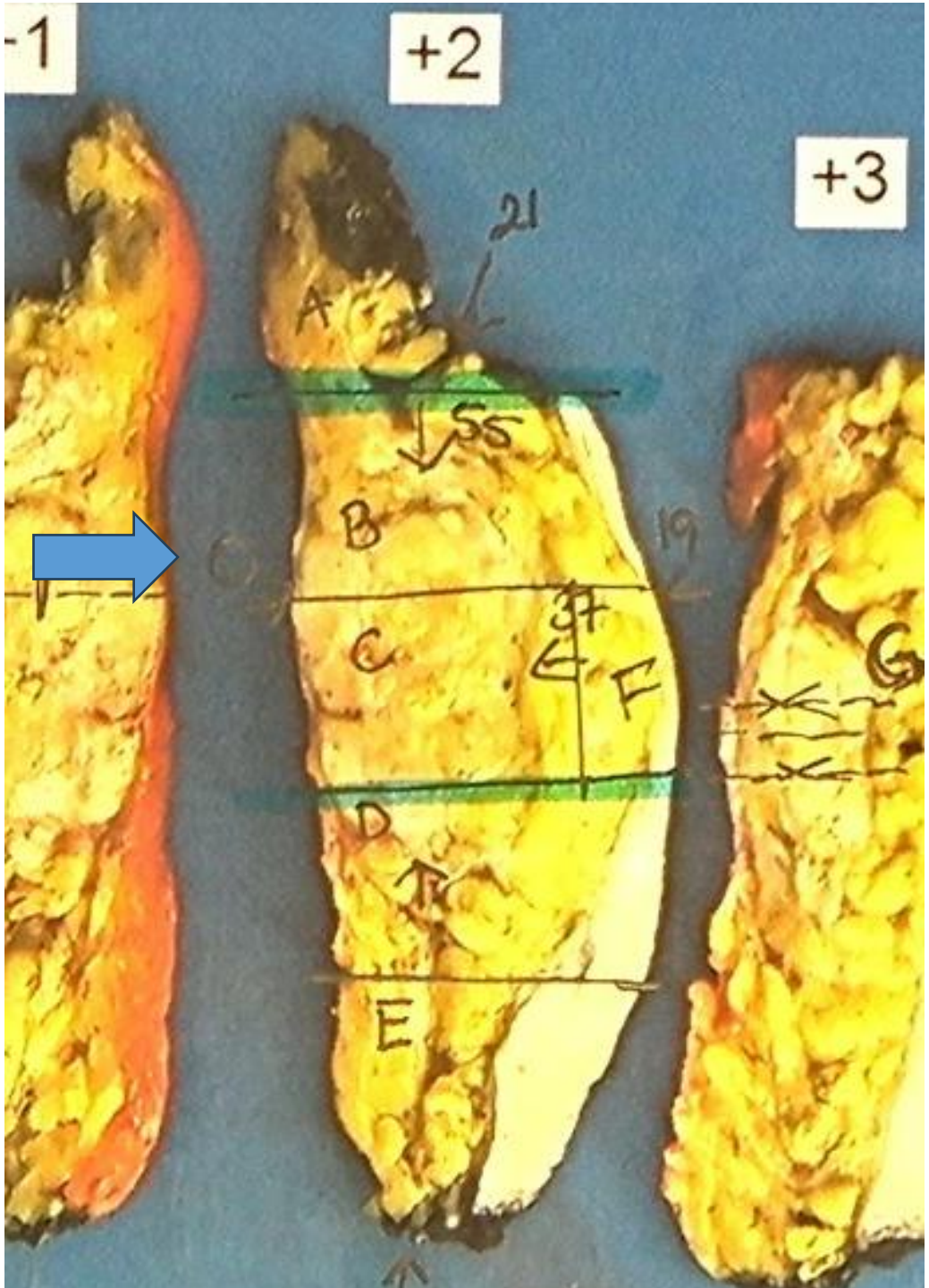
Dorsal resection margin
Lengths: 5022,48 µm

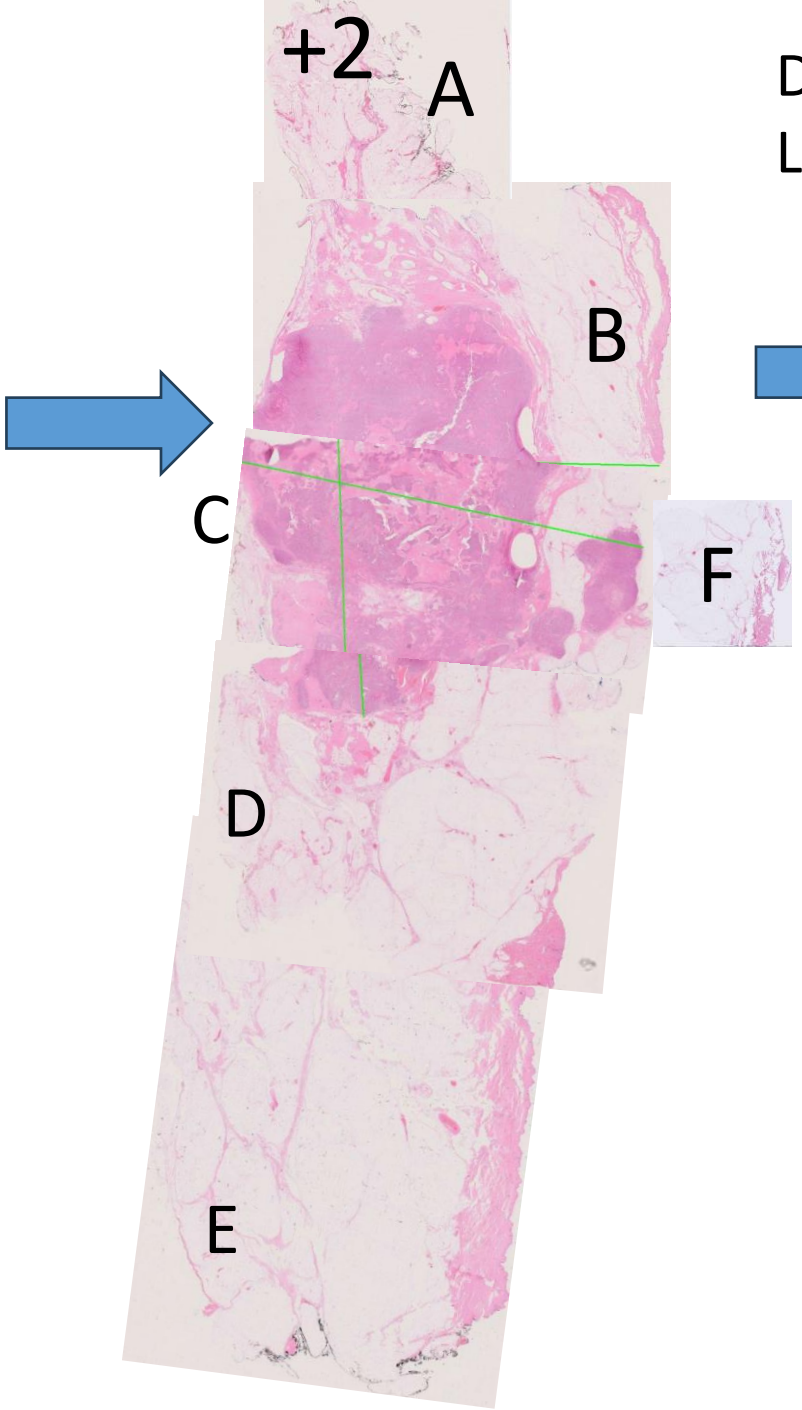

SUT KL 12
KRAN
FOTO 1
LAT
MED
KAUD


MED
0
-3
+9
LA
RKA

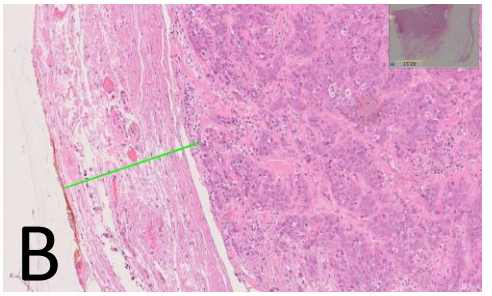

-1
0
+1
+2
+3
+4
+5


-1
0
+1
+2
+3
+4
+5
MED
LAT

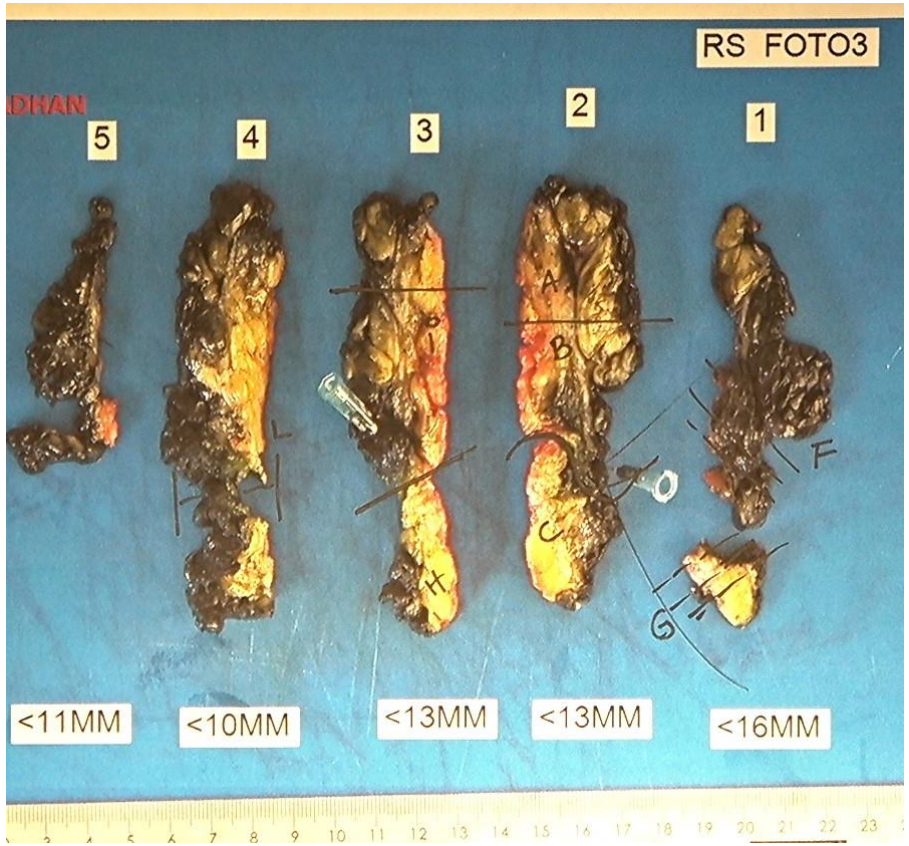


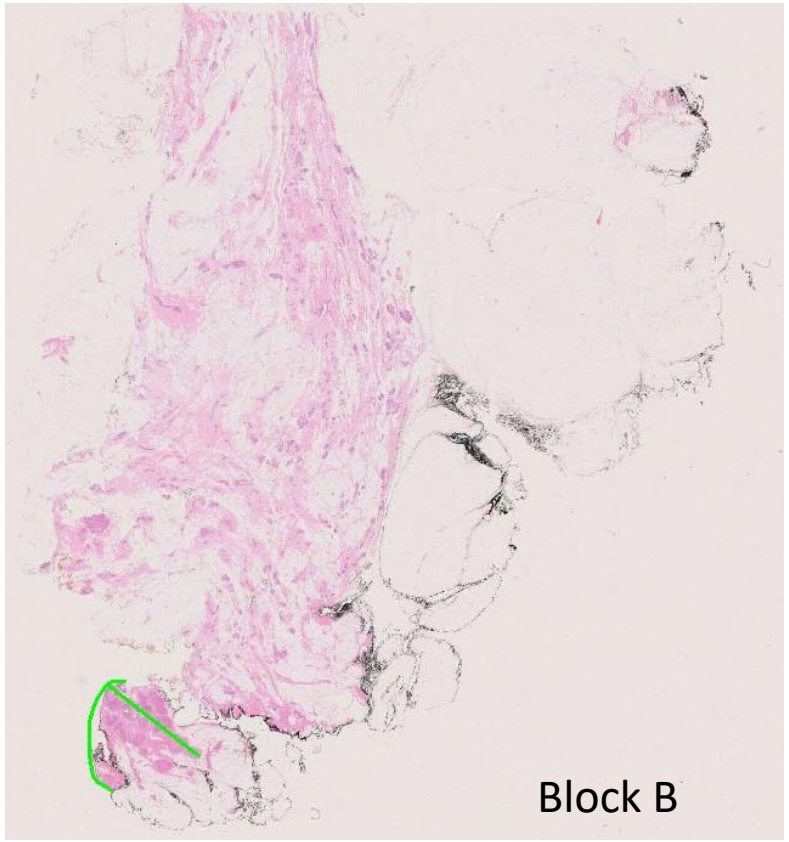


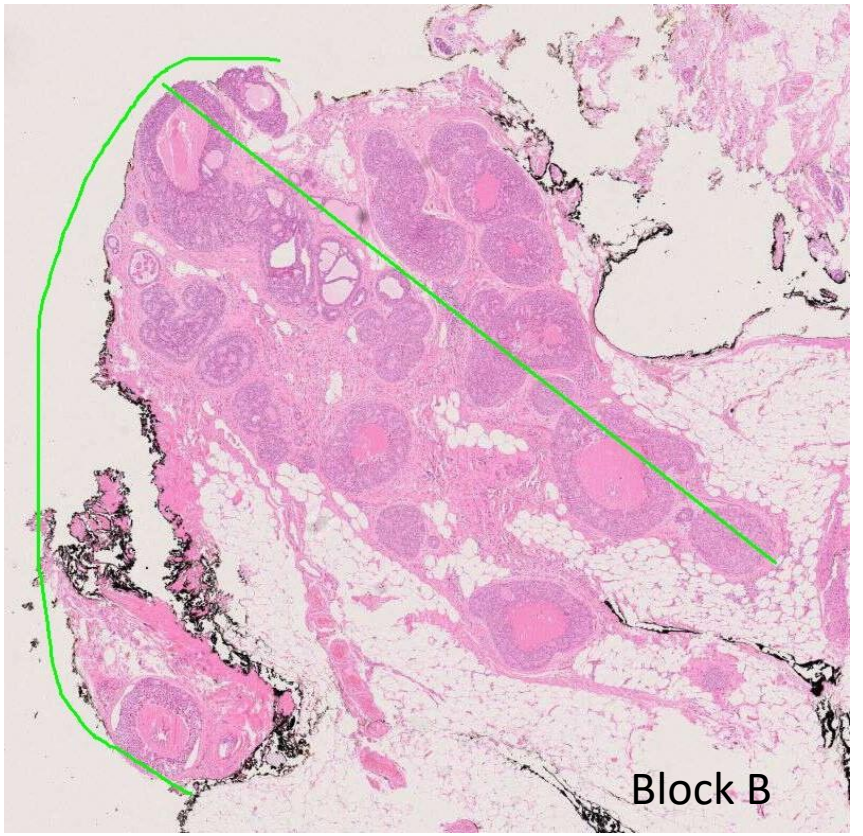
Dorsal resection margin
Lengths: 0,362 µm



Positive margin (tumor on ink) = reoperation





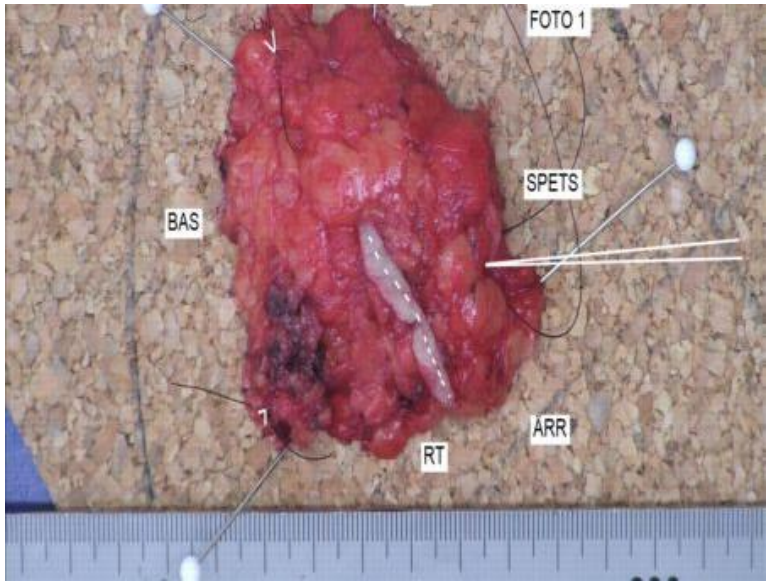


Not ”in toto” excised
” Icke radikalt avlägsnat ”
Reoperation: which part of the breast?

Positive margin = re-intervention is mandatory

Re-excision:

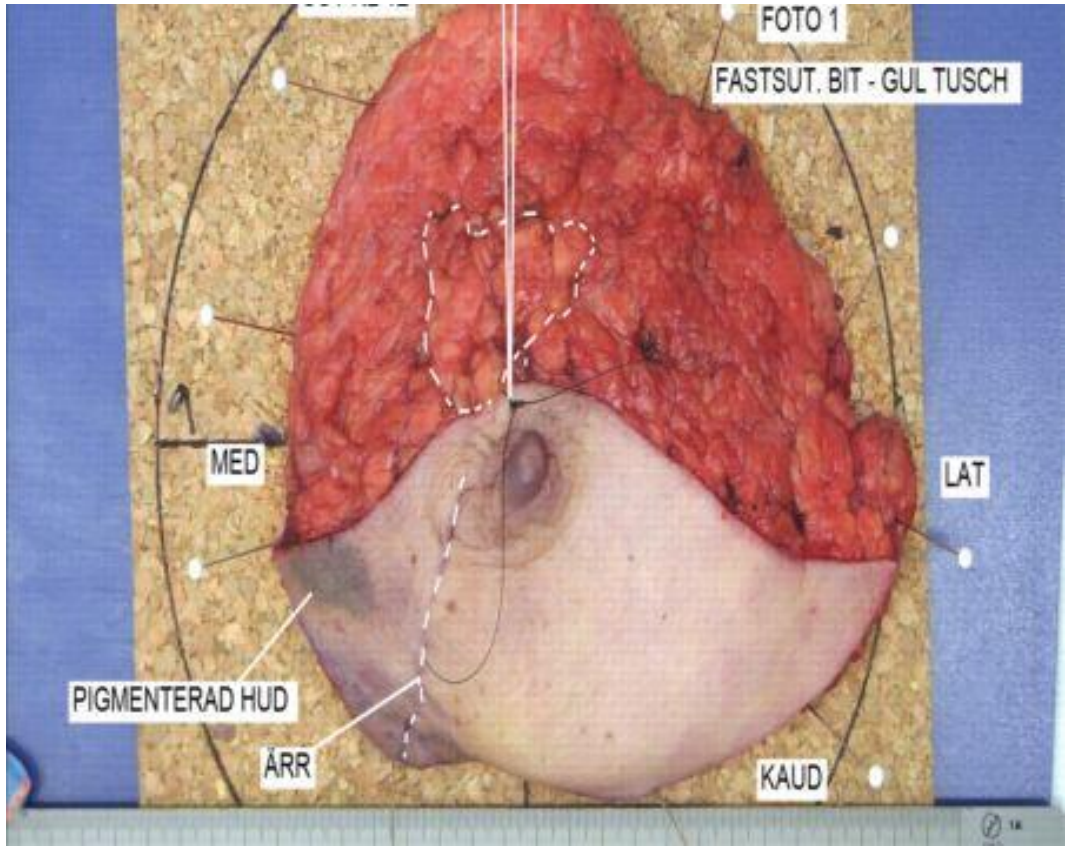
1. **extensive involvement of a single margin**
2. **multiple focally positive margins**



Sorrentino L et al. Involved margins after lumpectomy for breast cancer: Always to be re-excised? Surg Oncol 2019;30:141-146

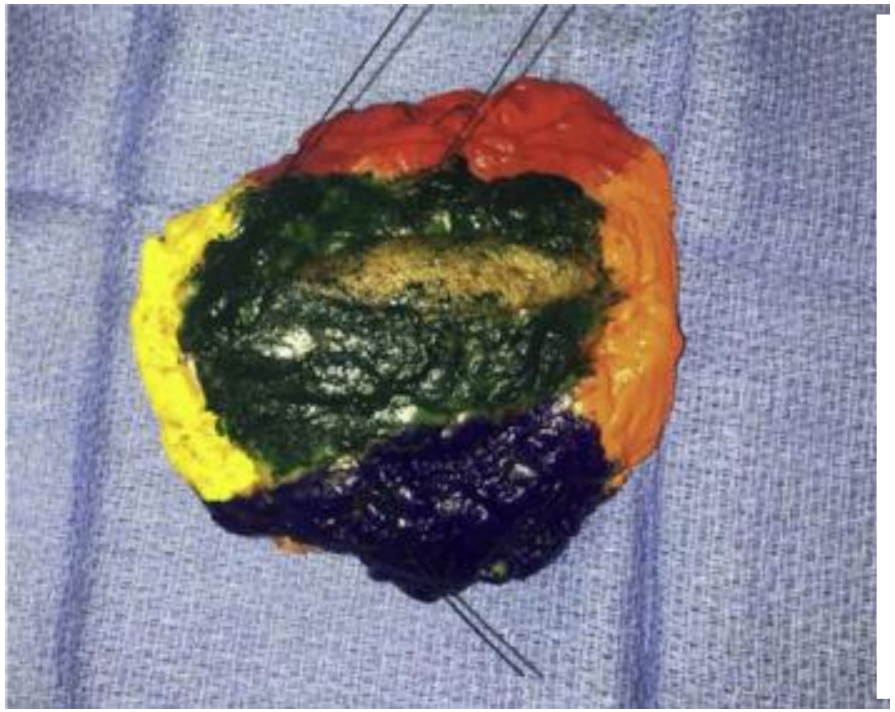
Total mastectomy:

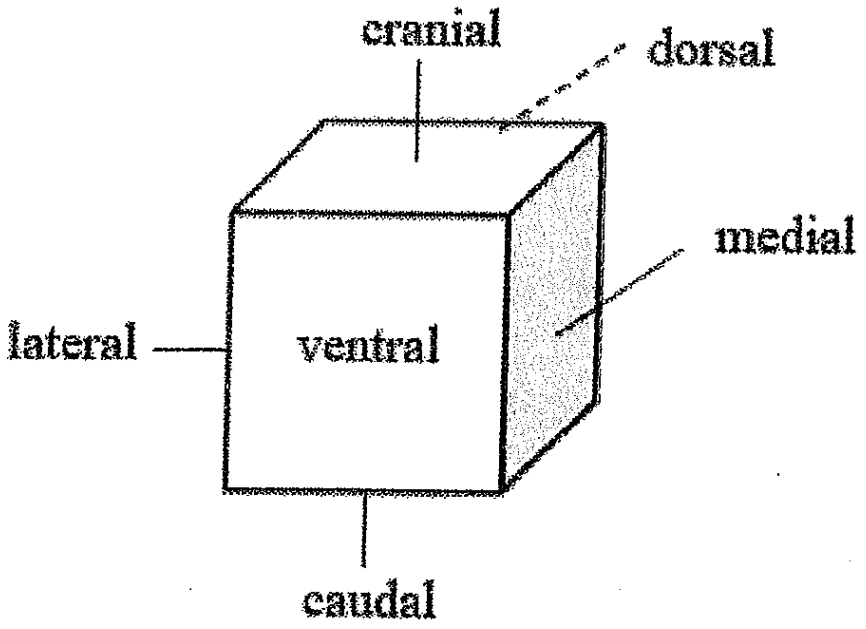
1. **multiple extensive margin**
2. **misdiagnosed multifocal disease**



Cost-effectiveness of surgeon performed intraoperative specimen ink in breast conservation surgery

Van Den Bruele et al. J Surg Res. 2018;231:441-447

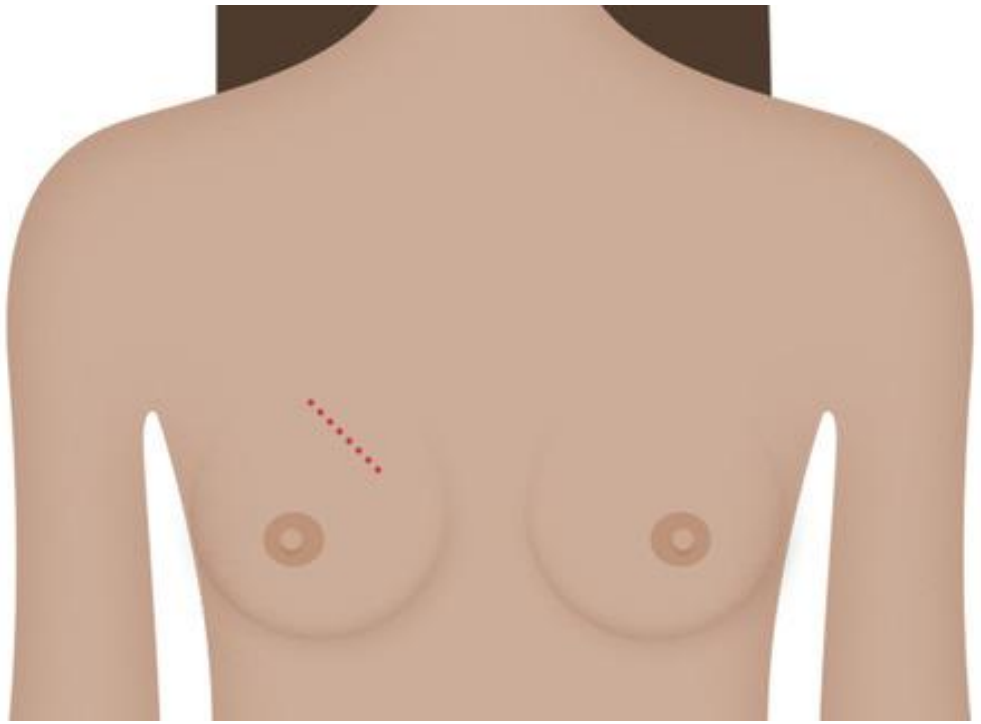




Breast–conserving surgery (partial mastectomy):
10-68% additional surgery due to positive or inadequate margin

- Increased rate re-excision causes:

- increased costs
- risk of complications
- stress to the patient
- poor cosmetic outcome
- delay of necessary adjuvant treatment

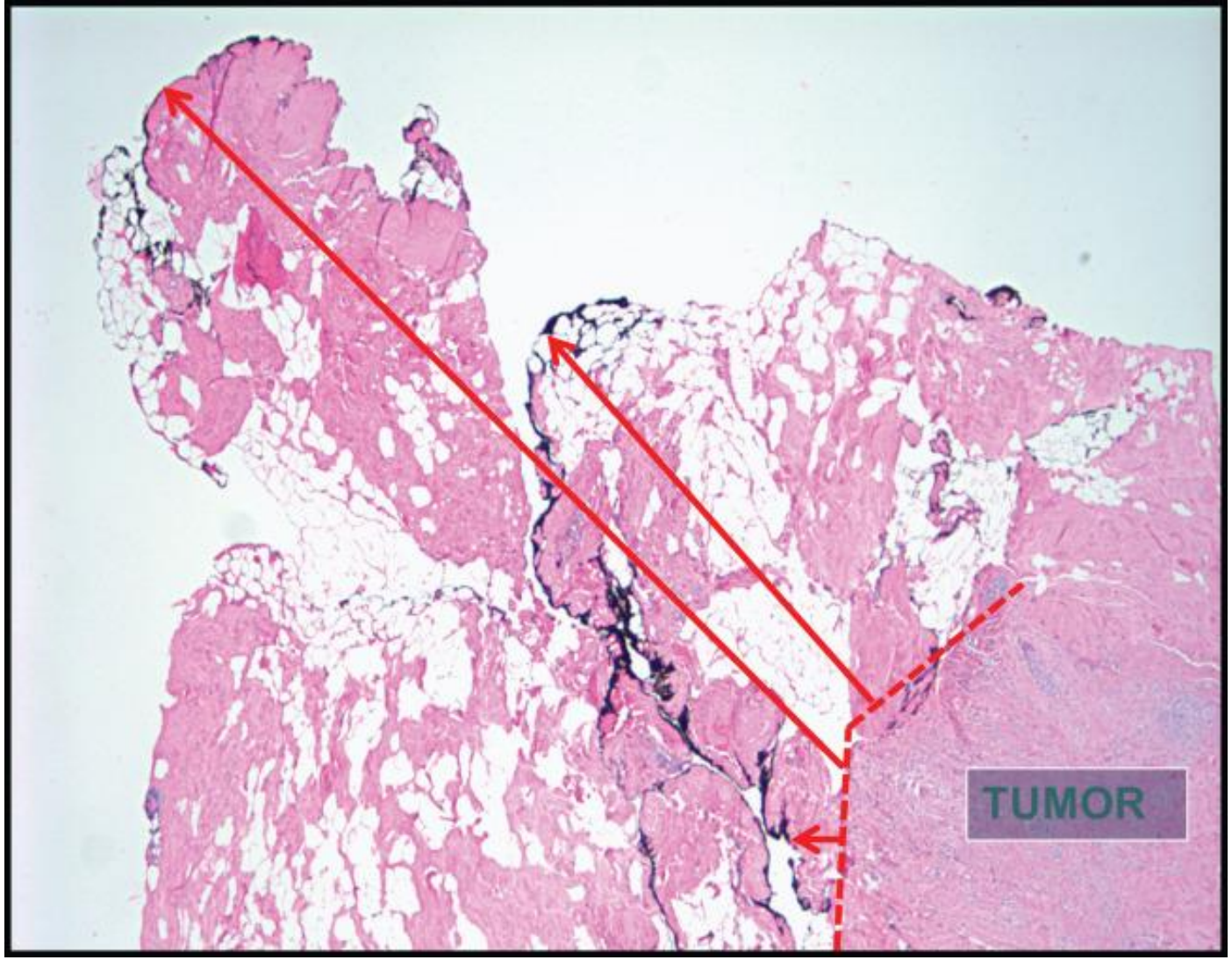


2017 Vienna, Austria
15th St.Gallen International Breast Cancer Conference

Surgical margin for breast cancer based on 33 studies incl 28.000 patients:

- 2 mm for ductal carcinoma in situ
- No tumor on ink for invasive breast cancer

Increasing the size of a negative margin is not significantly associated with an improvement in local control.



Ink used to define the margin surface can be seen at various distances from the tumor edge because of the irregular nature of the specimen surface and ink tracking through the breast fat.
This makes reproducible measurements of the margin width challenging.

Consensus statement about negative margin: **no ink on tumor**

- After consensus guideline : rapid reduction of additional surgery !

  Re-excision rate fell from 21% to 15%;

- the rate of additional surgery after initial lumpectomy, including both re-excision and conversion to mastectomy, decreased by 16%.
- Adoption of the margin guideline would save more than $18 million annually

(not include the time and costs saved by patients and families for missed work)

Breast speciment processing and reporting with an emphasis on margin evaluation

A College of American Pathologists survey of 866 laboratories

Guidi AJ et al. Arch Pathol Lab Med 2018;142:496-506

CAP
COLLEGE of AMERICAN PATHOLOGISTS

- 94% (716 of 764 respondents) define positive margin as ”tumor on ink” for invasive carcinoma
- 91% (699 of 769 respondents) follow the CAP guidelines for DCIS
- **Methods of margin evaluation**:
- 77% exclusively examine perpendicular margins
- 23% examine en face margins in at least a subset of specimen
- Cavity shave margin:
- 88% ink these specimen
- 12% do not!

Cancer

Margins in breast cancer: How much is enough?

Melissa Pilewskie, Monica Morrow

Cancer 2018;124:1335-1341.

”Margin measurement is an inexact science.”

The negative margin width reported by the pathologist is dependent on :

- the **number of sections** examined,
- the **technique** of margin assessment (perpendicular, shaved, or cavity margins),
- what is defined as the margin when **ink tracks through** the irregular fatty surface overlying the tumor.

It has been estimated that **3000 sections** would be required

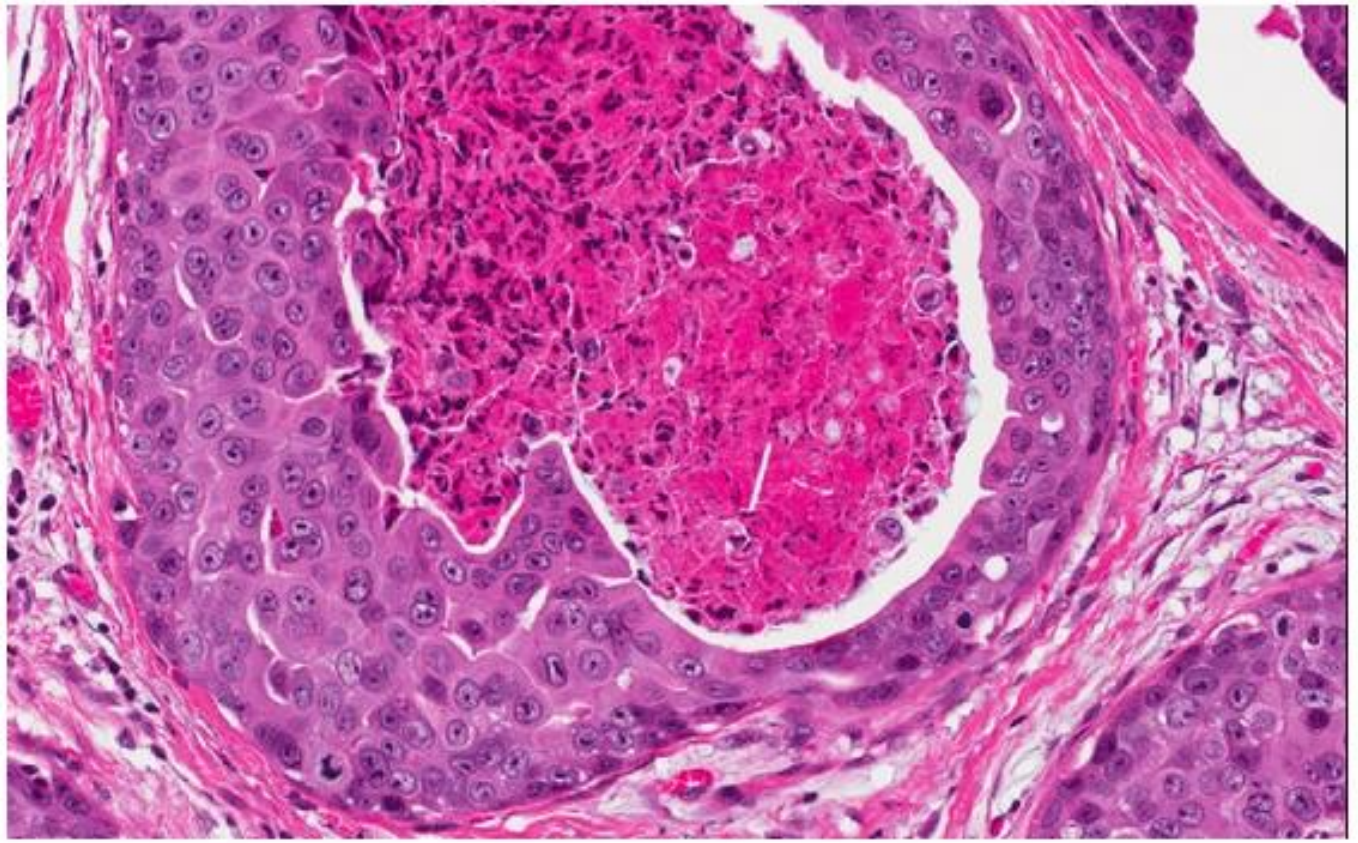
to completely examine the margin surfaces of a spherical lumpectomy specimen

Ductal carcinoma in situ – 2 mm

- in 2015, an SSO-ASTRO-ASCO multidisciplinary consensus panel:

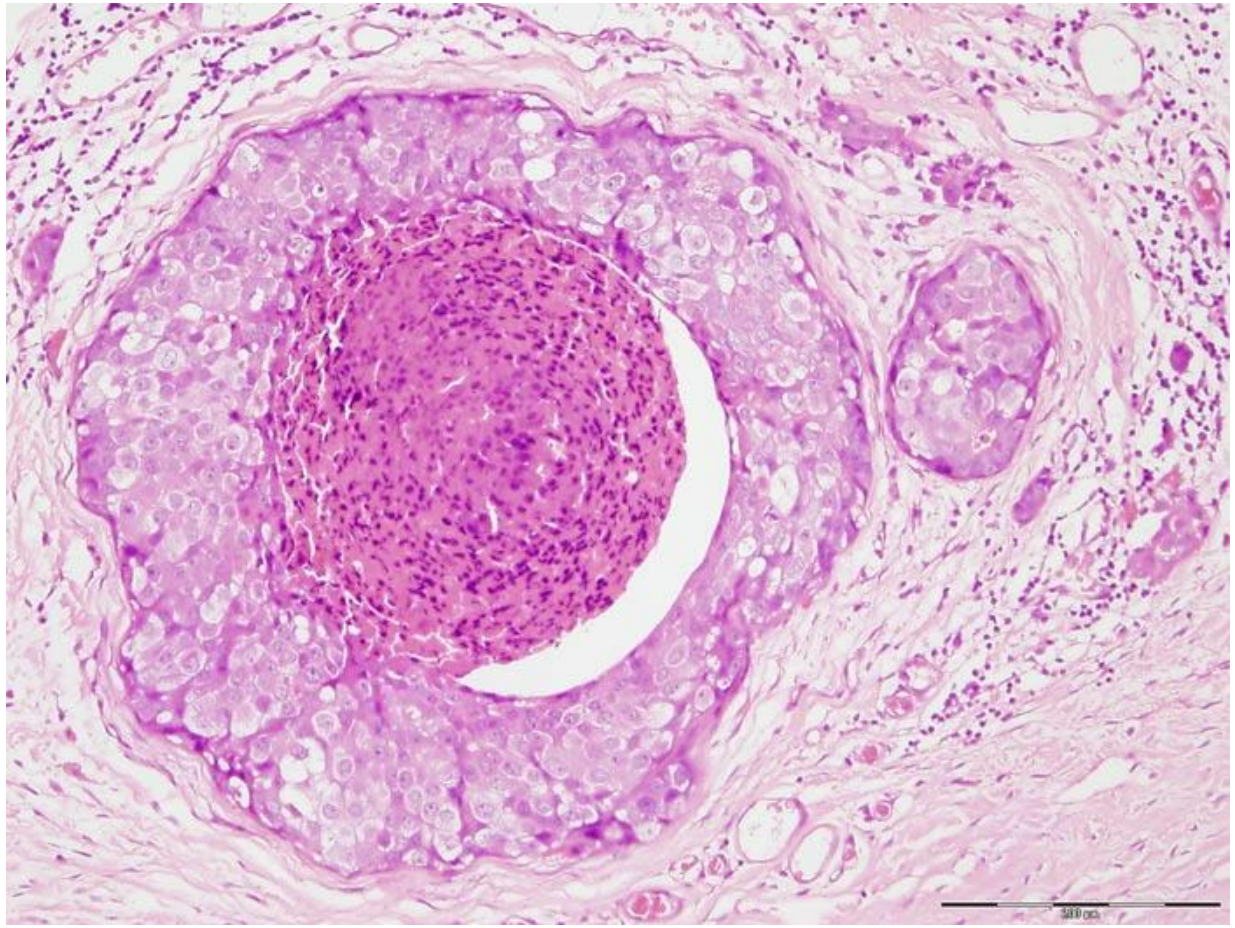
a 2 mm margin minimizes the risk of local recurrence in comparison with smaller negative margins.

- more widely clear margins do not further reduce the risk of local recurrence



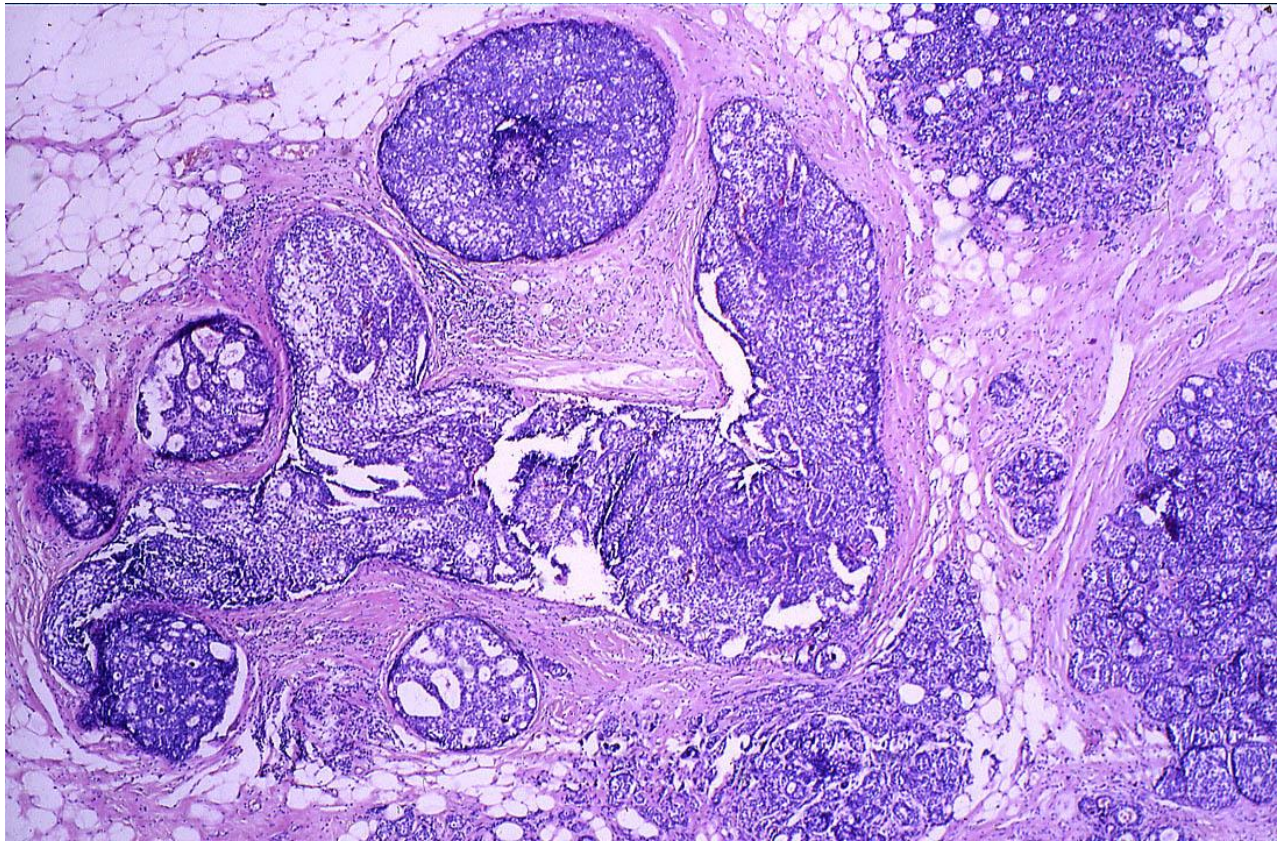
- SSO: Society of Surgical Oncology
- ASTRO: American Society for Radiation Oncology
- ASCO: American Society of Clinical Oncology

Ductal carcinoma in situ with microinvasion



- 2 mm margin required
  same as for DCIS

Invasive ductal carcinoma with extensive DCIS component



- No tumor on ink
  both for the invasive
  and the in situ component

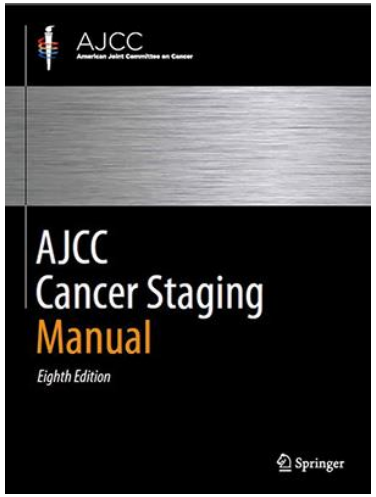
Pleomorphic lobular carcinoma in situ (PLCIS)

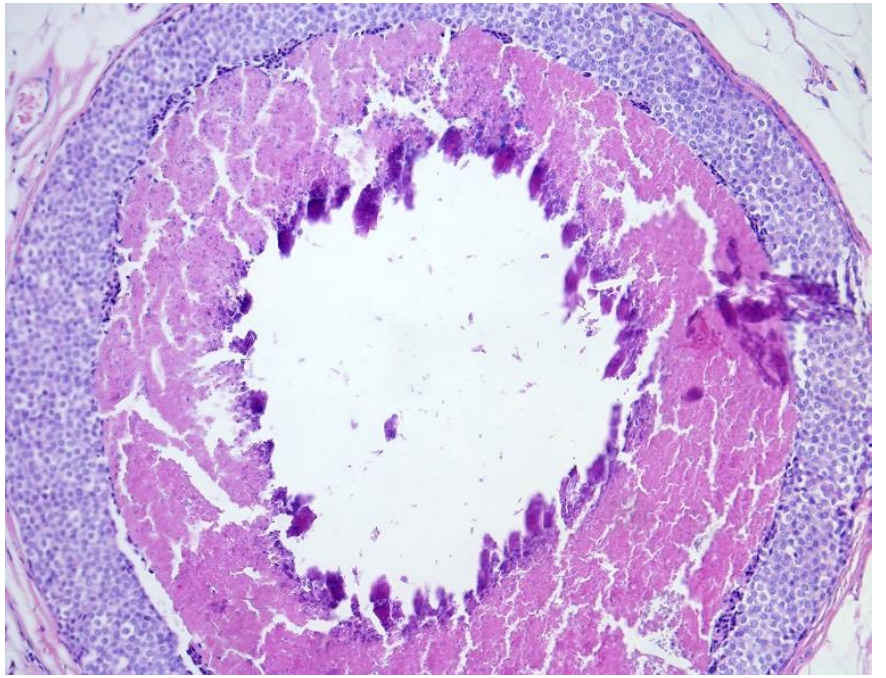
Treat like DCIS ?!?

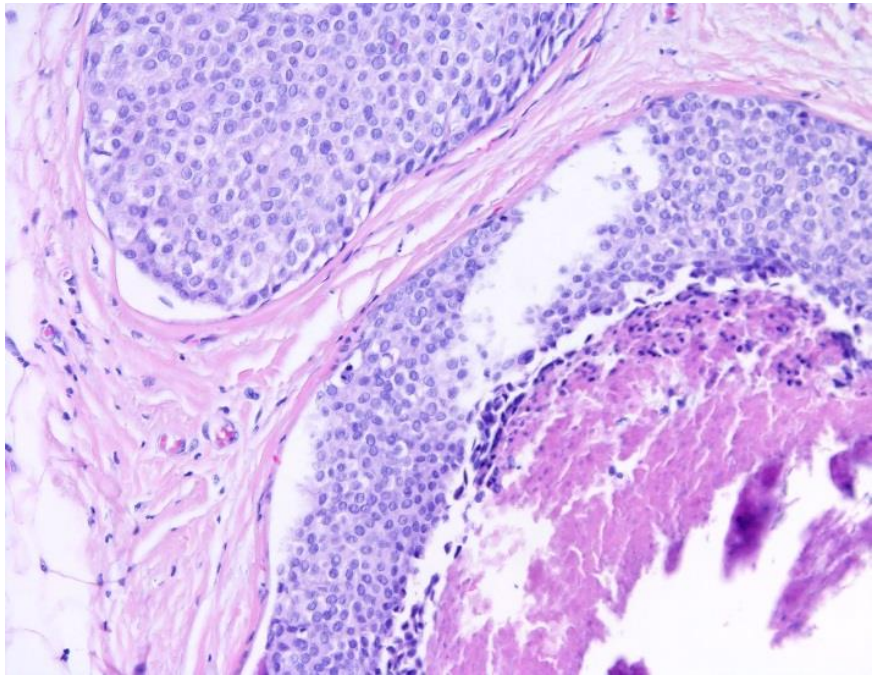
- Nuclear pleomorphism; Comedo necrosis; ”Bad ” biomarkers
- More like DCIS than LCIS
- Displays histomorphologic features and biomarker expression profile similar to PLCIS with invasion
- Evidence is insufficient at present, primarily due to low prevalence of this form of high grade LCIS, to establish definitive recommendation for treatment

AJCC 8th edition

AJCC
American Joint Committee on Cancer

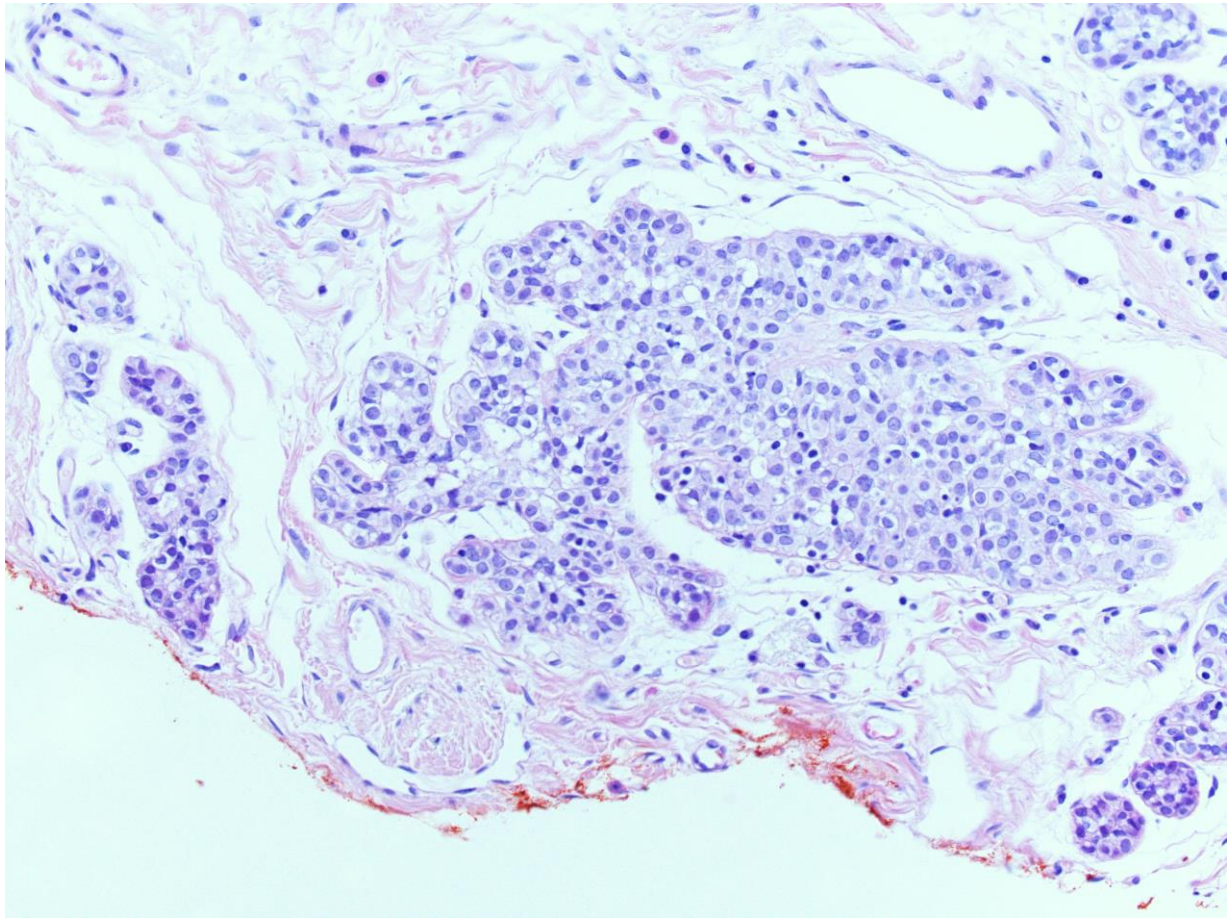


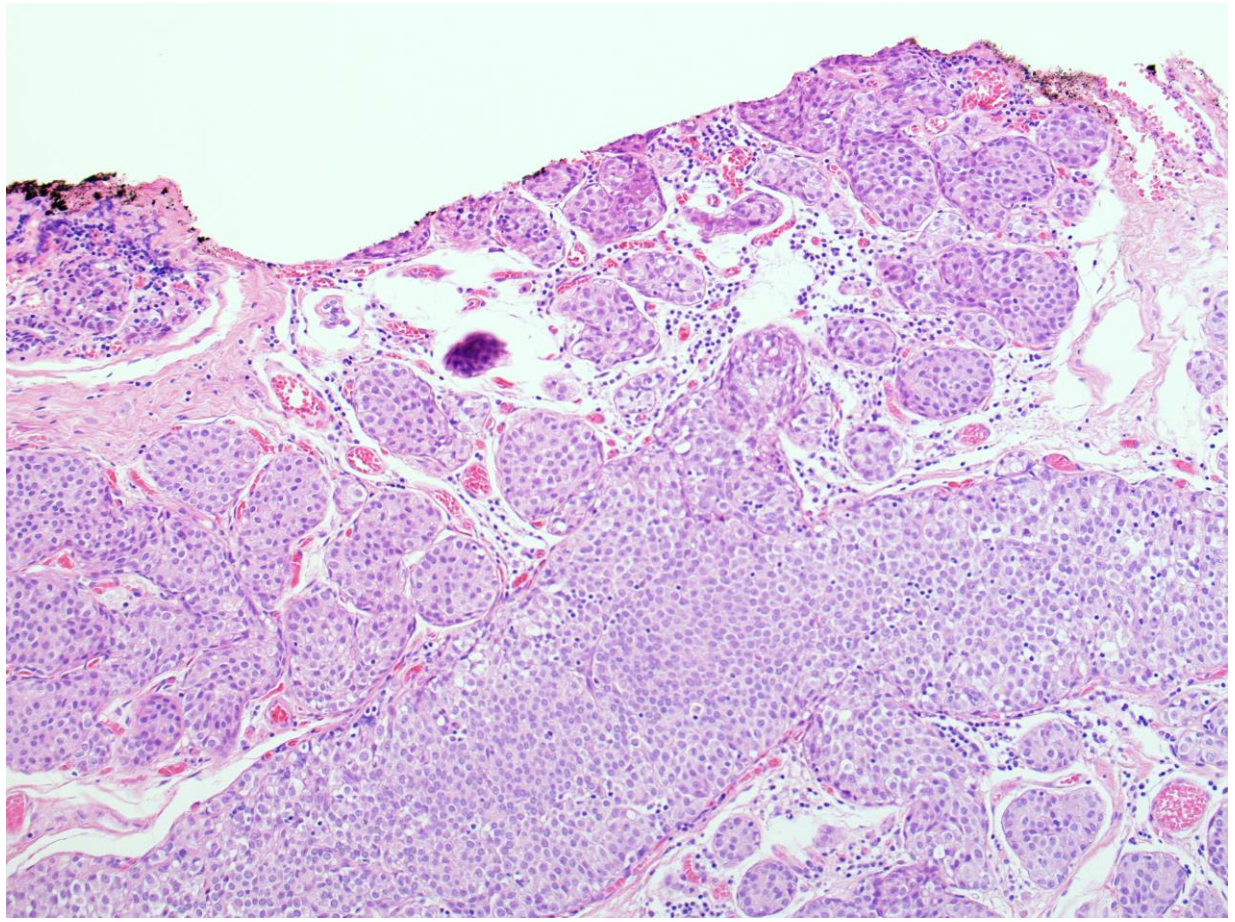




Sneige N. et al. Clinical, histopathologic, and biologic features of pleomorphic lobular CIS of the breast: a report of 24 cases Mod Pathol 2002;15(10):1044-1050

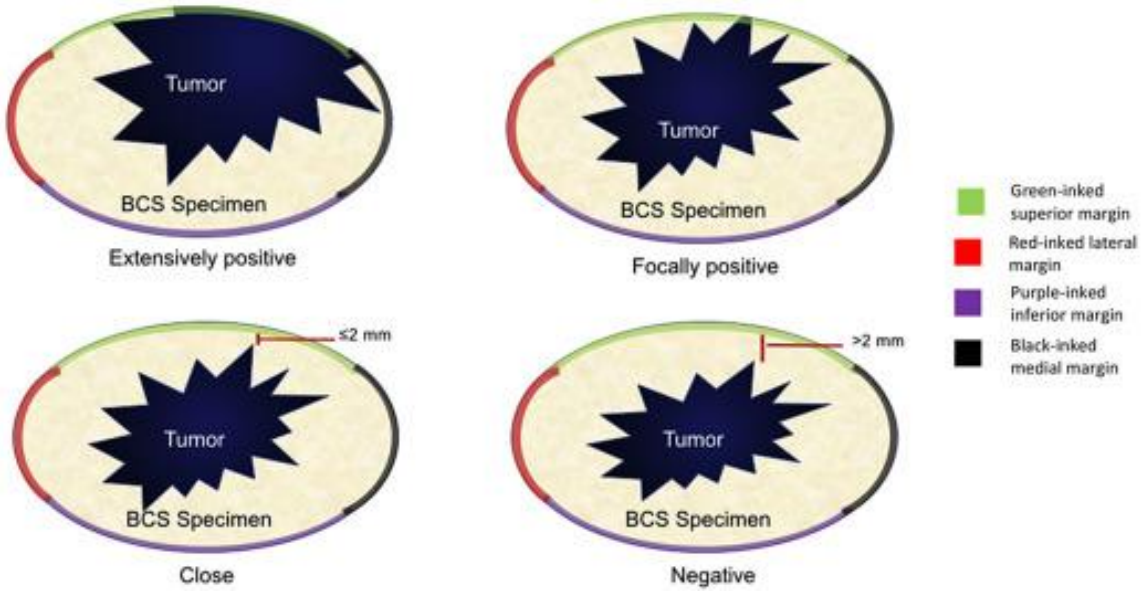
Pleomorphic LCIS (PLCIS)





Margin status at breast-conserving surgery

- Negative Margin: No cancer cells at the outer inked edge of the tissue
- Positive Margin: Cancer cells or tumor extends to the edge of the sample
- Close Margin: Any situation in between negative and positive



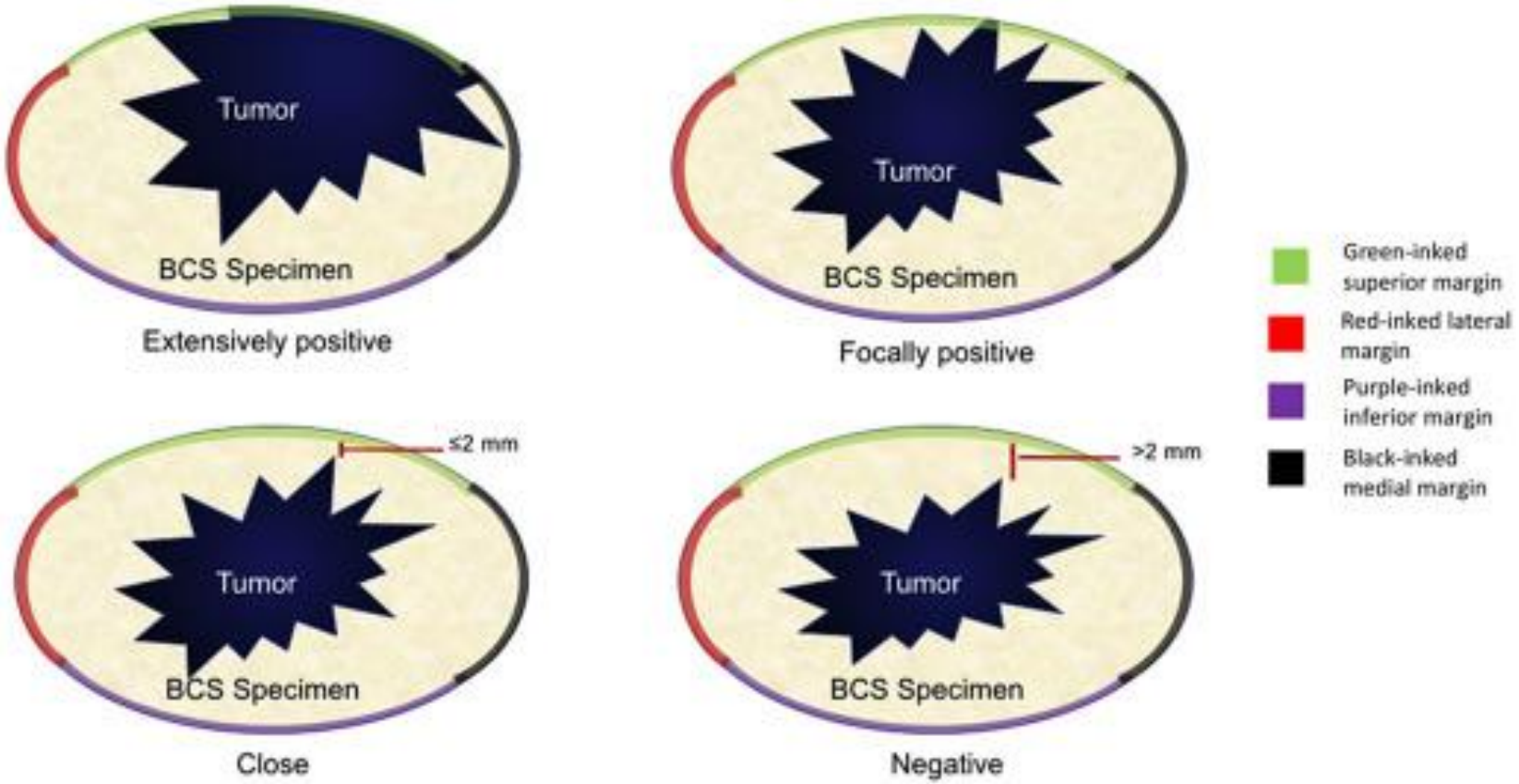
- Nayyar at el. Definition and management of positive margins for invasive breast cancer. Surg Clin N Am 2018;98:761-771

Surgical Margin: How close is too close?

Nayyar A. et al. Surg Clin North Am 2018;98:761-771

Extensively positive margin:
tumor at the inked margin **> 4 mm**

Focally positive margin:
tumor at the inked margin **≤ 4 mm**



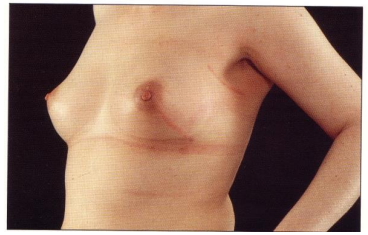
Negative, but close margin **≤ 2 mm**

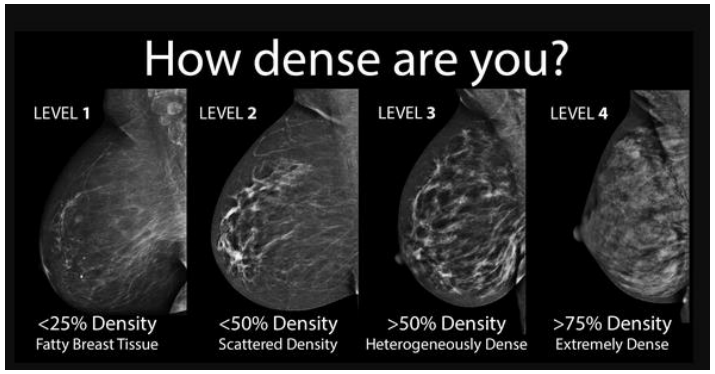
Negative margin **> 2mm**

Factors with higher risk of positive margin status

Manhoobi I et al. BMC Research Notes (2025) 18:36

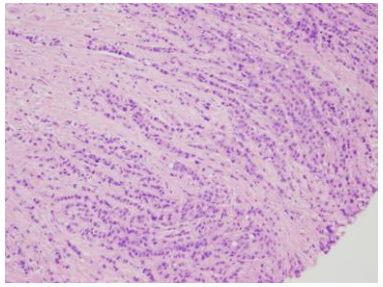
- Younger age
- Increased breast density



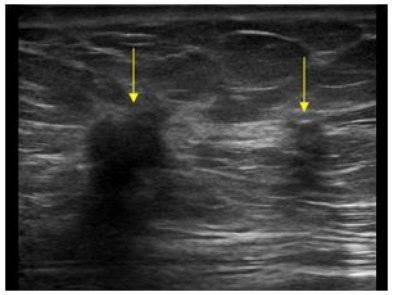


- Large tumor size

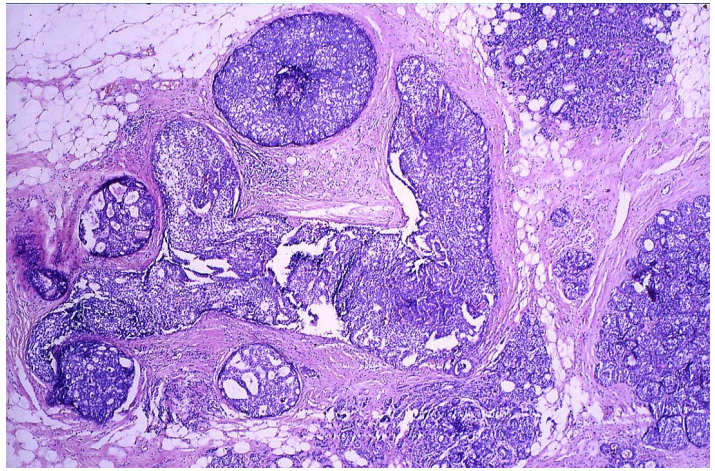
- Lobular histology



- Tumor multifocality



- Extensive in situ component



- Smaller breast size

Breast-conservative surgery with close or positive margins: can the breast be preserved with high-dose-rate brachytherapy boost?

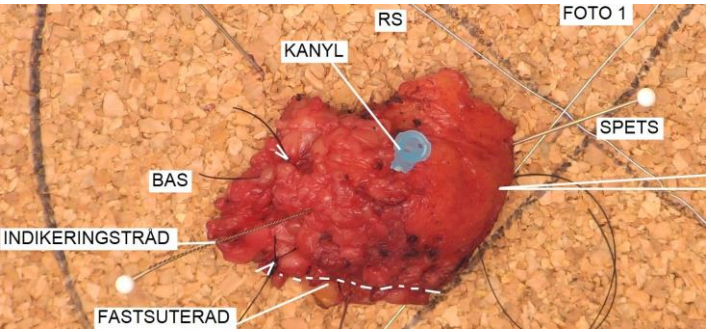
Guinot et al. 2007;68:1381-1387

- Close or positive-margin breast cancer
  can be well managed with a high dose boost
  in a wide tumor bed
  by means of high-dose-rate brachytherapy

Re-excision of positive margins might be **omitted** in selected patients with low-risk breast cancers (pT1, N0, Luminal A)

- **64%** of re-excised patients **had no residual disease** on specimen after re-operation
- Margins incorrectly considered positive after handling of the specimen for histopathol analysis, **misinterpretation due to specimen shrinkage**
- **Dutch guidelines** do not recommend re-excision for focally positive margin
- Vos et al. 492 parients without re-intervention: locoregional recurrence rate was 2.9% versus 1.1% in case of re-excision (Breast Cancer Res treat 2017;164:157-167)

Sorrentino L et al. Involved margins after lumpectomy for breast cancer: Always to be re-excised? Surg Oncol 2019;30:141-146



Update of the American Society of Breast Surgeons Toolbox to address the lumpectomy reoperation epidemic

Maureen P. et al. Gland Surg 2018;7:536-553

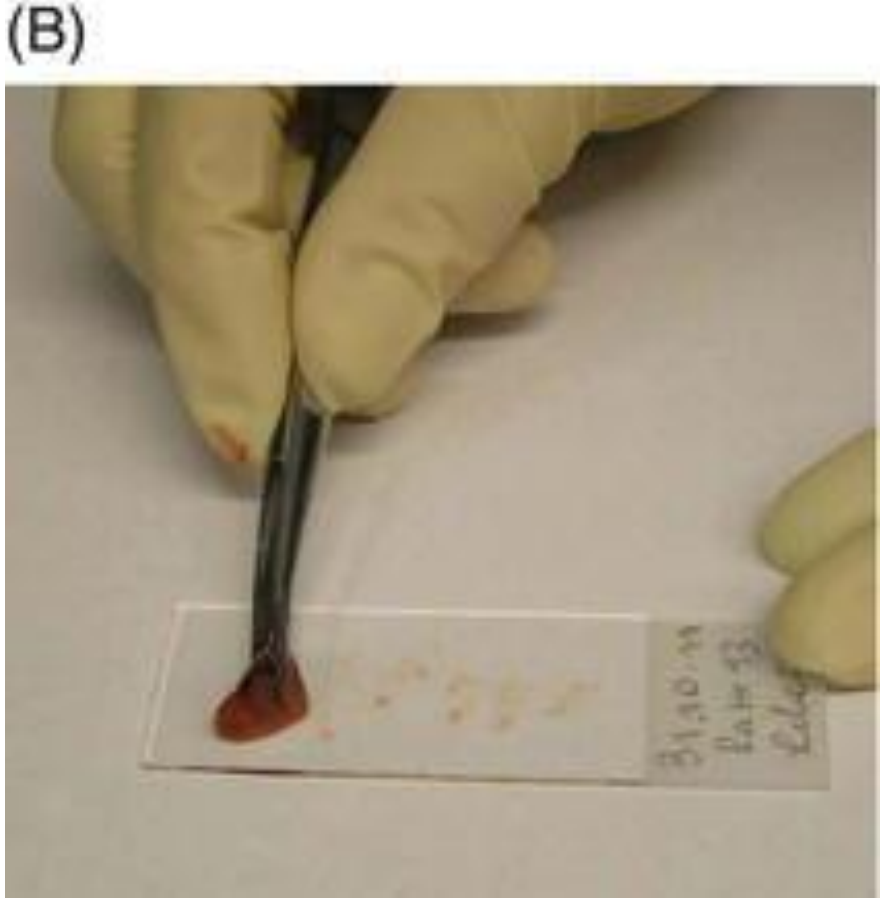
- **Tool 1**: **preoperative diagnostic imaging** should include full-field digital mammography and supplementary imaging to include ultrasound as needed
- **Tool 2**: **minimally invasive breast biopsy** (MIBB) for breast cancer diagnosis
- **Tool 3**: **multidisciplinary discussions** to include radiology, pathology, surgery, and radiation and medical oncology
- **Tool 4**: for nonpalpable breast lesions, the **use of radioactive seeds**, intraoperative US, or wire localization to direct lesion excision is recommended
- **Tool 5**: **oncoplastic techniques** can reduce the need for reoperation in anatomically suitable patients
- **Tool 6**: **specimen orientation of 3 or more margins**
- **Tool 7**: **specimen radiograph** with surgeon **intraoperative** review
- **Tool 8**: consider **cavity shave margins** in patients with T2 or greater tumor size or Ti with extensive intraductal carcinoma (EIC).
- **Tool 9**: **intraoperative pathology assessment of lumpectomy margins** may help decrease re-excision when feasible
- **Tool 10**: **compliance with the SSO-ASTRO margin guideline** to not routinely re-operate for close margins with no tumor on ink in patients with invasive cancer

Intraoperative margin assessment

Time-consuming and inaccurate

- Frozen section

- Imprint cytology



- Nowikiewicz T et al. Scientific reports 2019;9:13441

Novel techniques for intraoperative assessment of margin involvement

Dumitru D et al. *e*cancer 2018;12:795

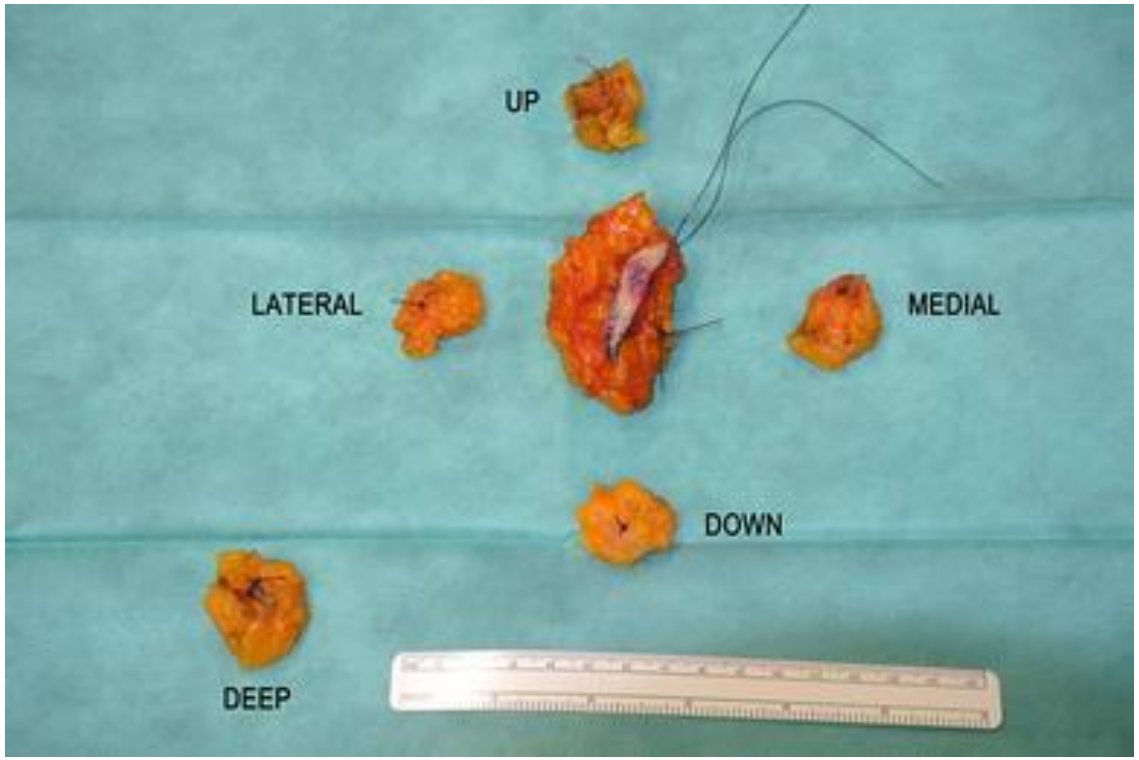
- Routine cavity shaves and intraoperative margin pathology
- Intraoperative ultrasound
- Faxitron
- MarginProbe: based on reflection of radiofrequency waves that measure local electrical properties of breast tissue
- ClearEdge: bioimpedance spectroscopy
- Optical coherence tomography images using deep neural networks
- Intelligent knife

Cavity Shaving Reduces Involved Margins and Reinterventions Without Increasing Costs in Breast-Conserving Surgery:

Corsi F. et al. Annals of Surgical Oncology 2017;24:1516–1524

- Clear margins were found in 98.3% of patients in the cavity shaving margin group
- versus 74.4% of patients in the simple lumpectomy group

The reoperation rate was 18.9% in the simple lumpectomy group and 1.9% in the cavity shave margin group

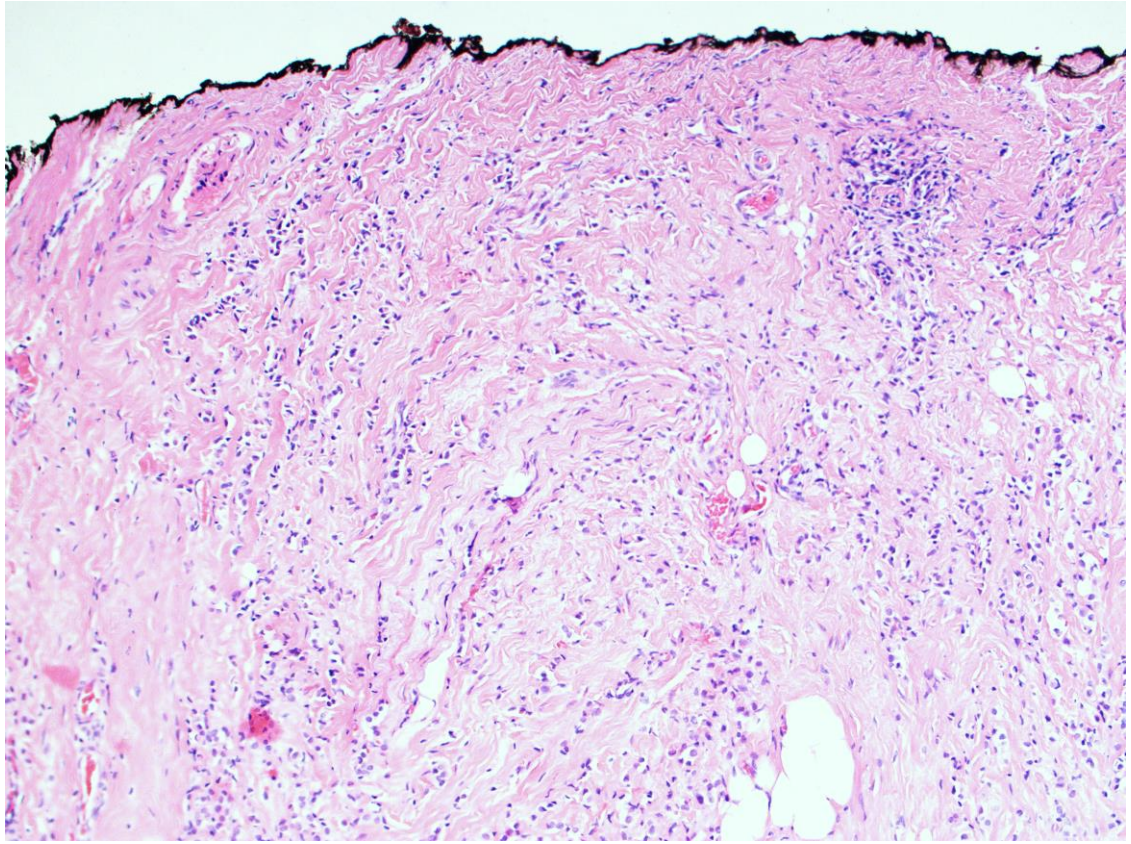


Cavity shave margins technique;
all margins were separately shaved

Breast conservation and negative margins in **invasive lobular carcinoma**: the impact of oncoplastic surgery and **shave margins** in 358 patients

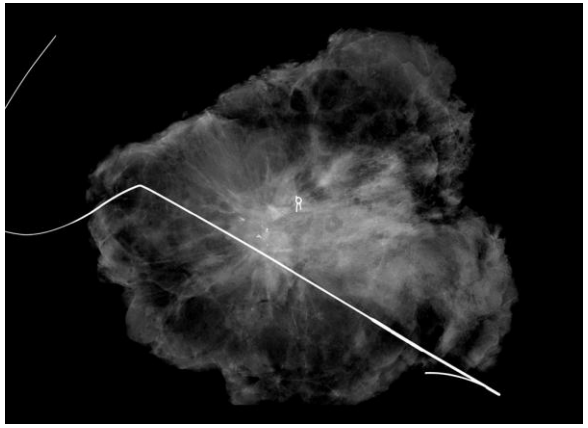
Mukhtar RA et al. Ann Surg Oncol 2018;25:3165-3170

- 358 patients with breast conservation:
- 25% conversion rate to mastectomy
- Shave margin: 61% lower odds of positive margin and re-operation



Faxitron intraoperative specimen X-ray

- Faxitron did not improve the effectiveness of intraoperative selective margin excision, nor did it reduce reoperation
- Routine cavity shave has been proposed



Philpott A et al. Factors influencing reoperation following breast-conserving surgery.
ANZ J Surg 2018;88:922-927

The MarginProbe® System:

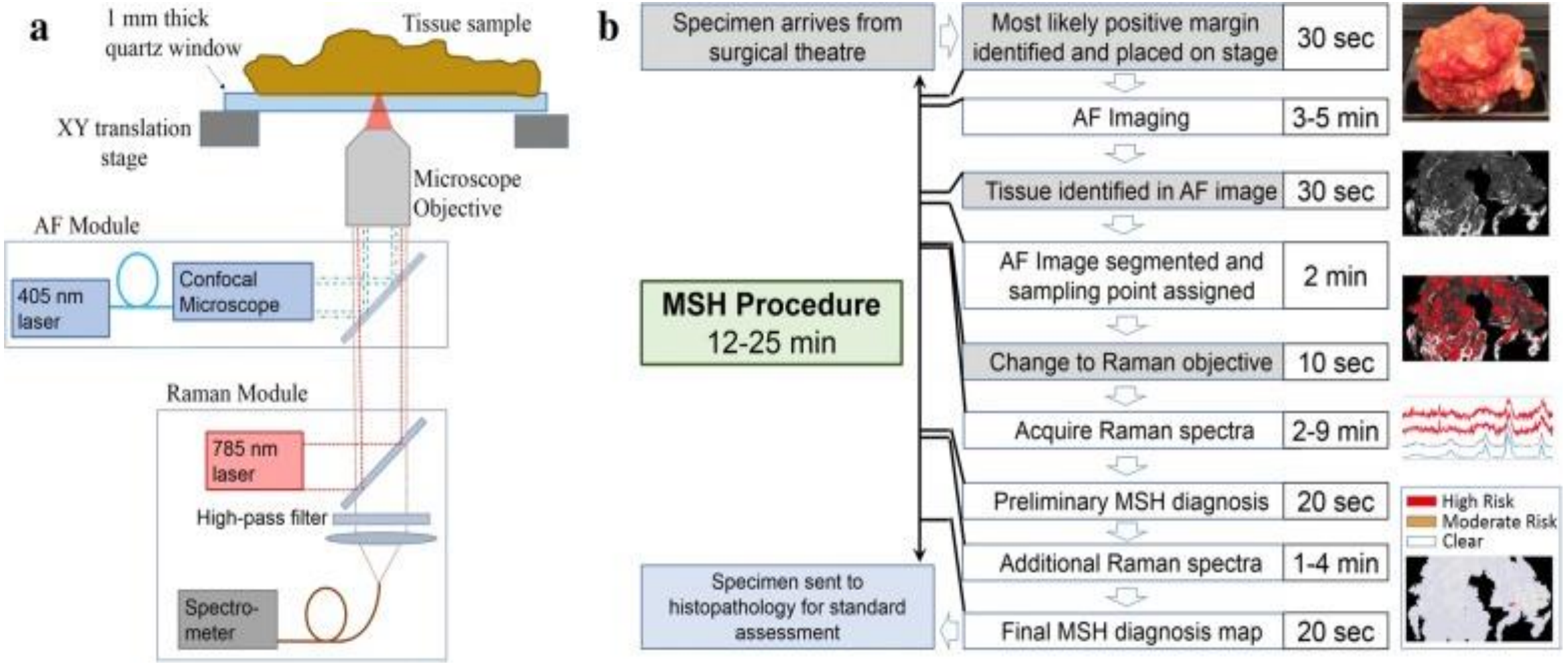
an innovative approach to reduce the incidence of positive margins found after lumpectomy

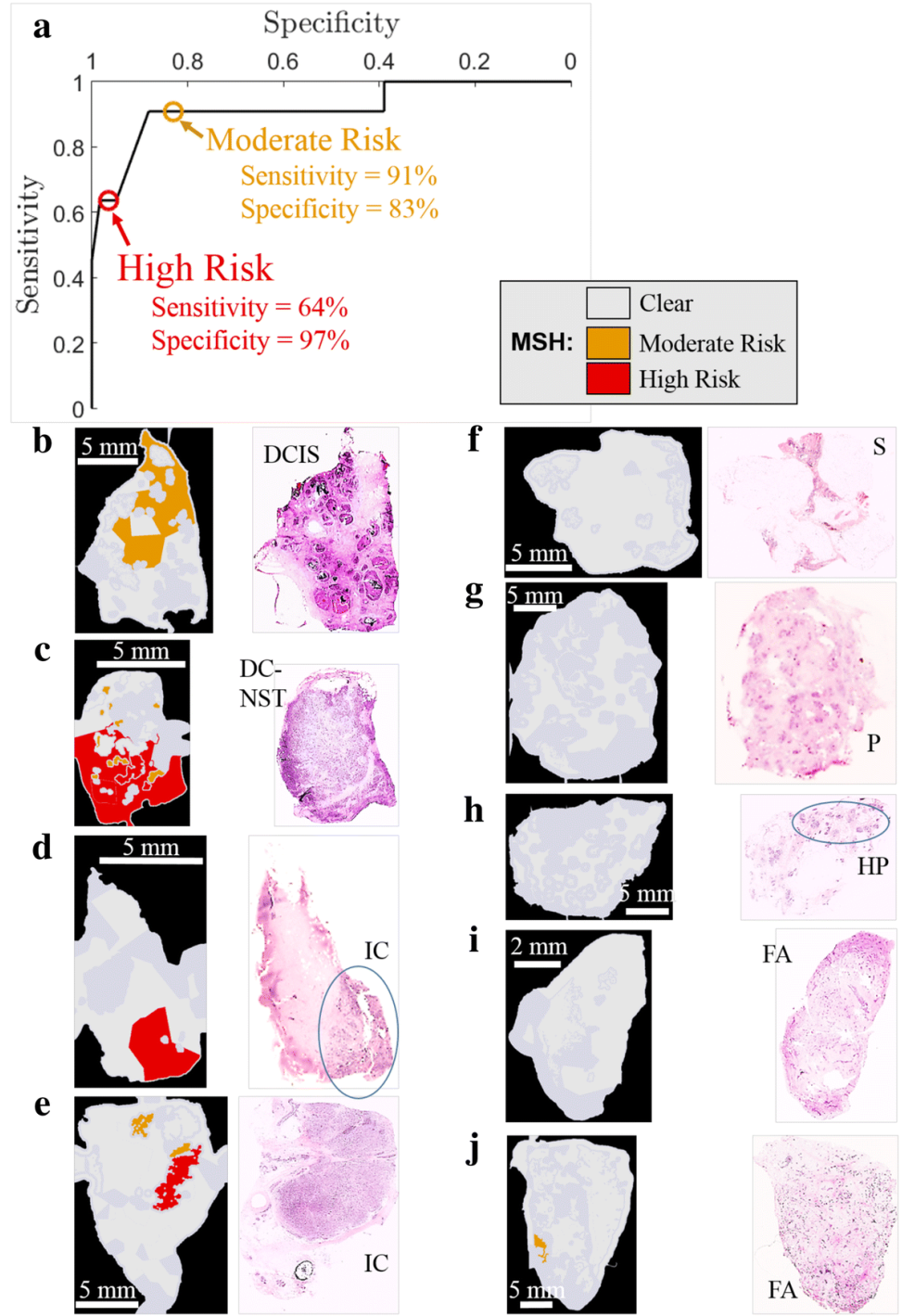
Gola S., Doyle-Lindrud S. Clin J Oncol Nursing 2016;20:598-599

Radiofrequency spectroscopy
measuring
the local electrical properties
of breast tissue to detect
normal or malignant cells

Intraoperative spectroscopic assessment of surgical margins during breast conserving surgery

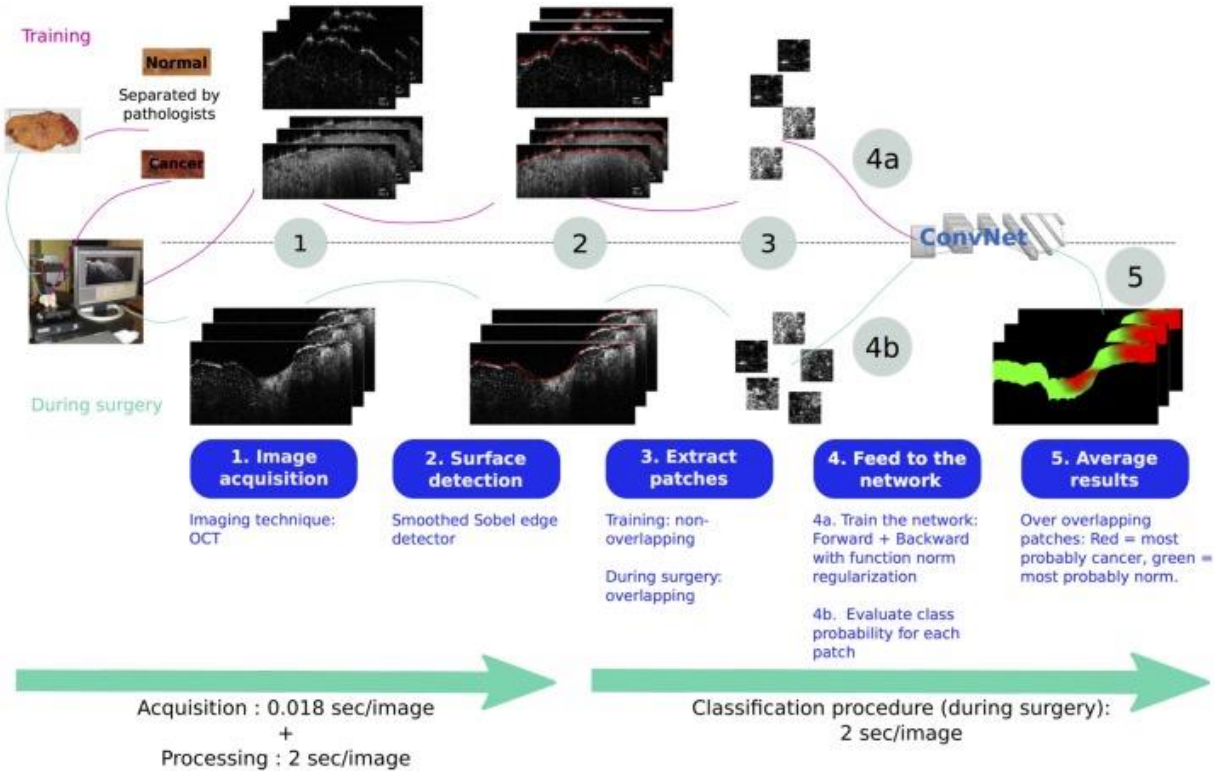
Shipp DW et al. Breast Cancer Research 2018;20:69

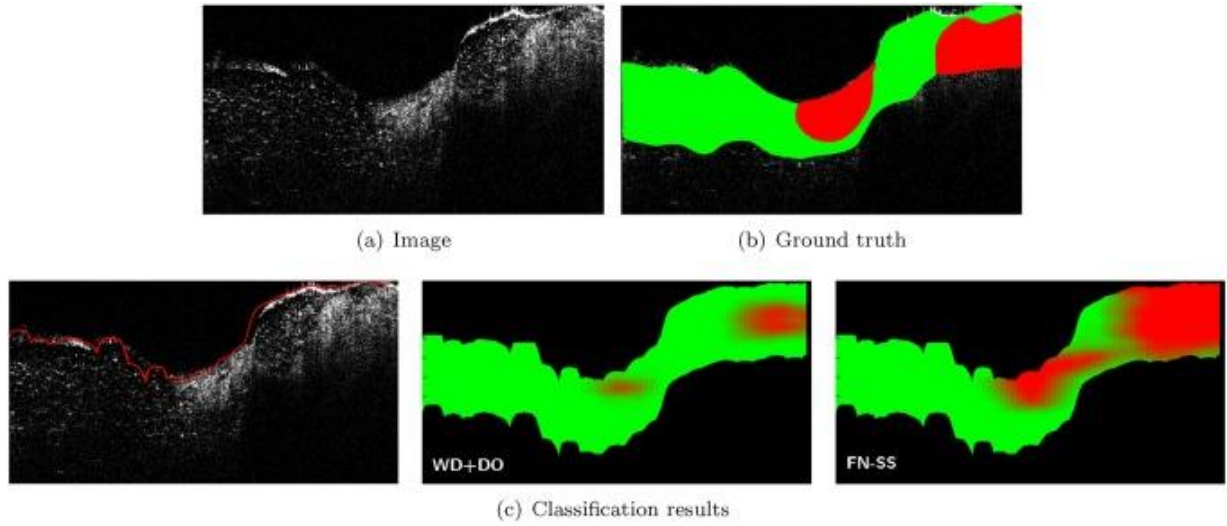



a
Specificity
1
0.8
0.6
0.4
0.2
0
Sensitivity
1
0.8
0.6
0.4
0.2
0
Moderate Risk
Sensitivity = 91%
Specificity = 83%
High Risk
Sensitivity = 64%
Specificity = 97%
MSH:
Clear
Moderate Risk
High Risk
b
5 mm
DCIS
c
5 mm
DC-
NST
d
5 mm
IC
e
5 mm
IC
f
5 mm
S
g
5 mm
P
h
5 mm
HP
i
2 mm
FA
j
5 mm
FA

Intraoperative margin assessment of human breast tissue in **optical coherence tomography** images using **deep neural networks**

Triki AR et al. Comput Med Imaging Graph 2018;69:21-32



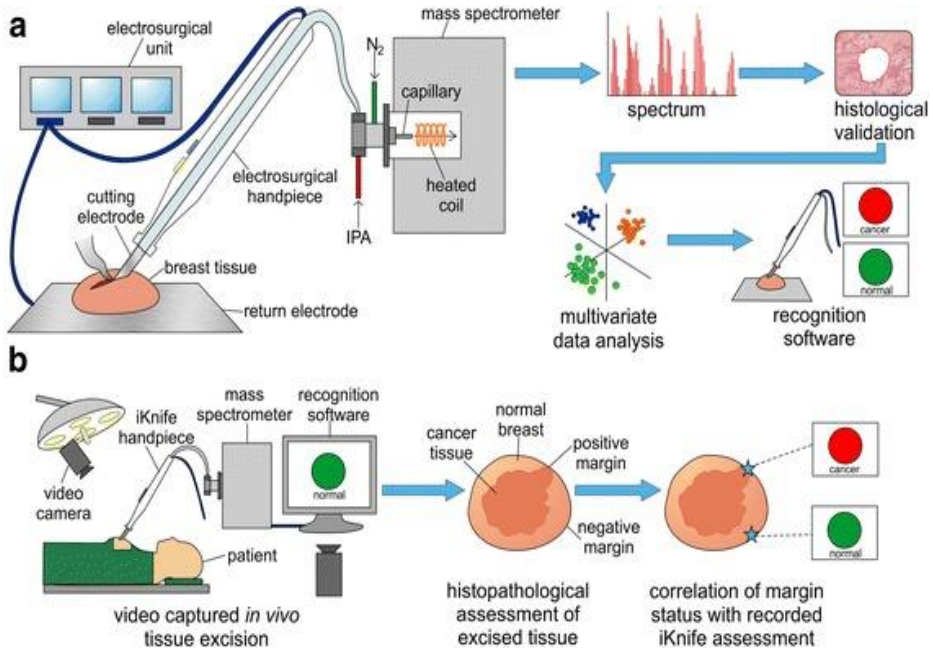


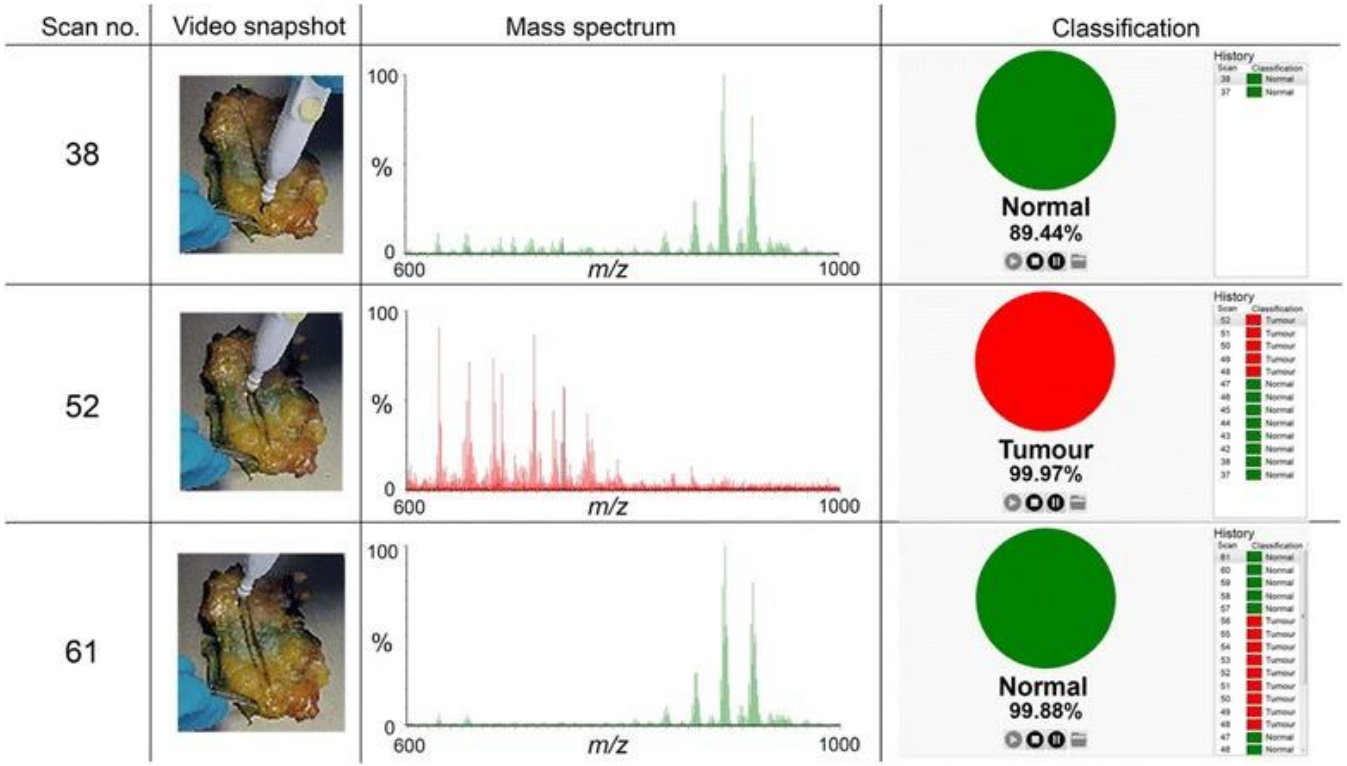
(a) Image (b) Ground truth

(c) Classification results

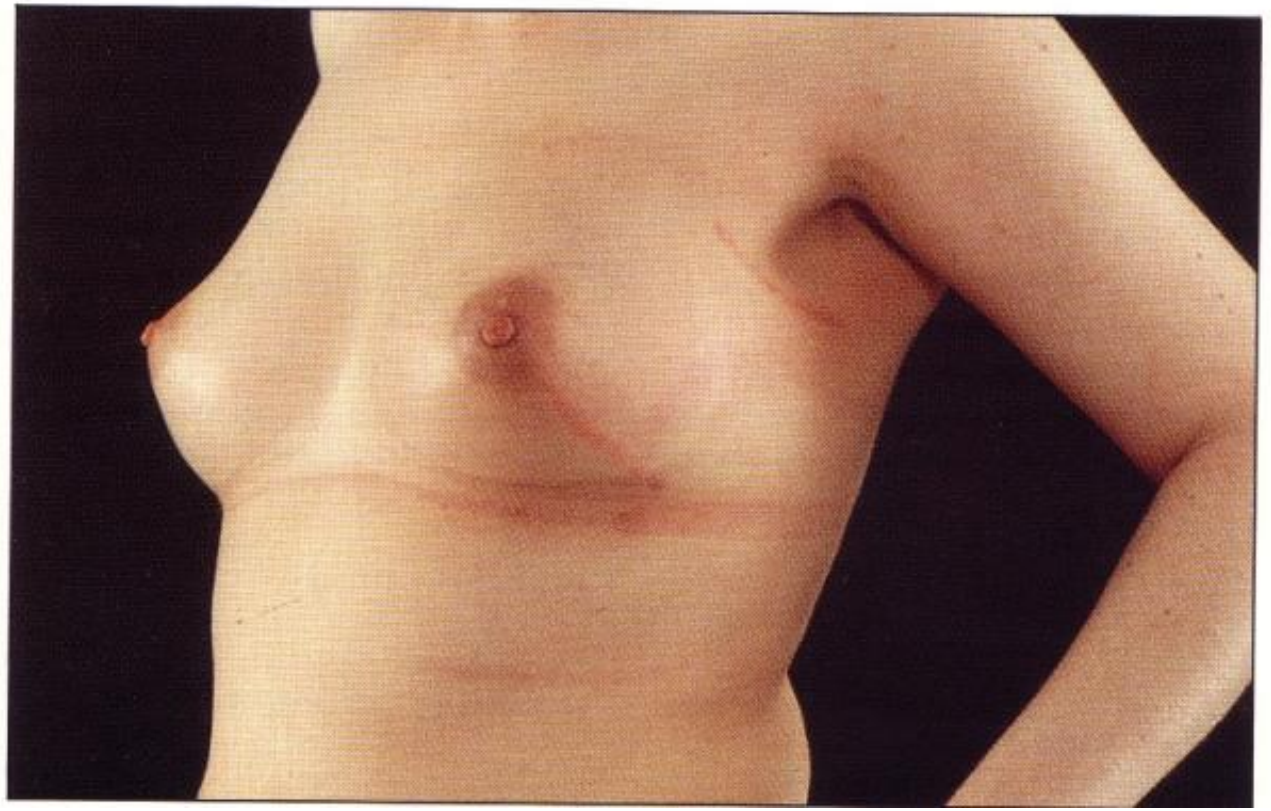
Intelligent knife

- Rapid evaporation ionisation mass spectrometry (REIMS) of electrosurgical vapours for identification of breast pathology: towards an intelligent knife for breast cancer surgery. St.John ER et al. Breast Cancer Research 2017;19:59

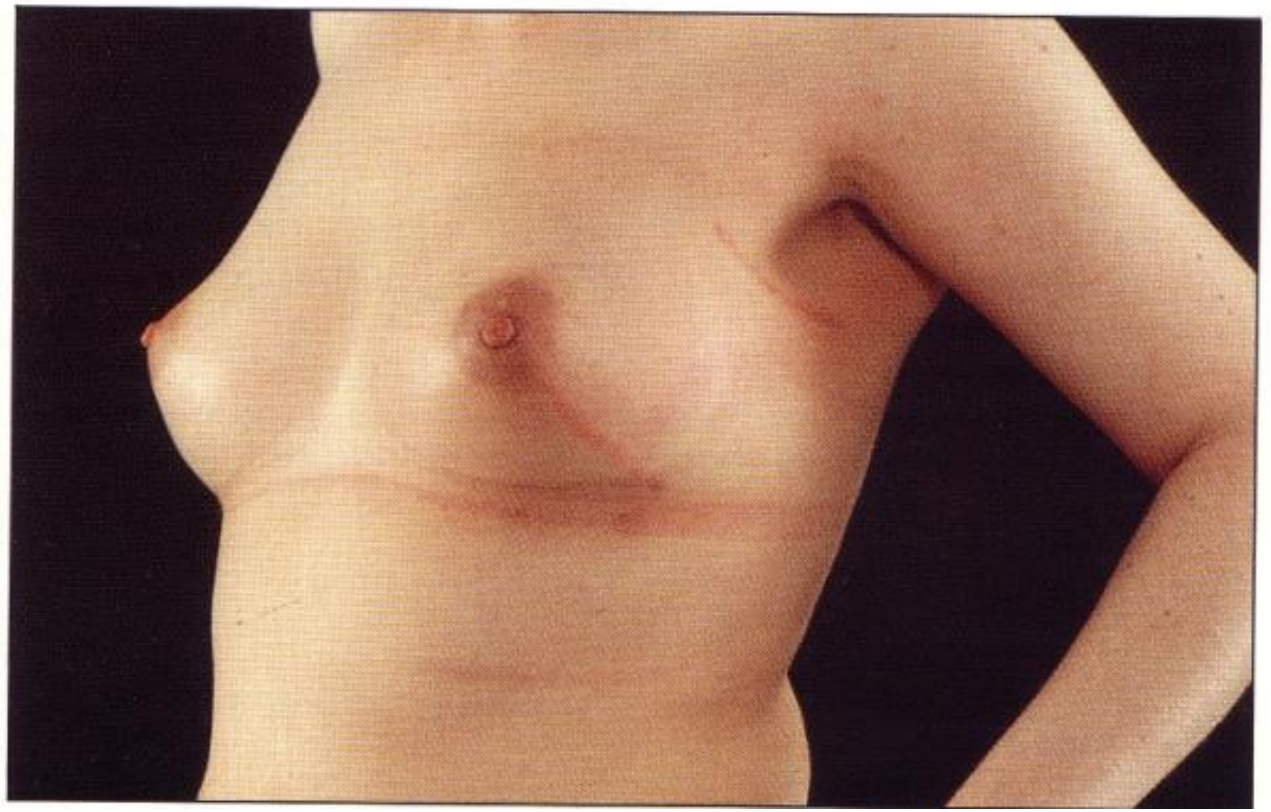




Future?



Future? Preoperative neoadjuvant treatment



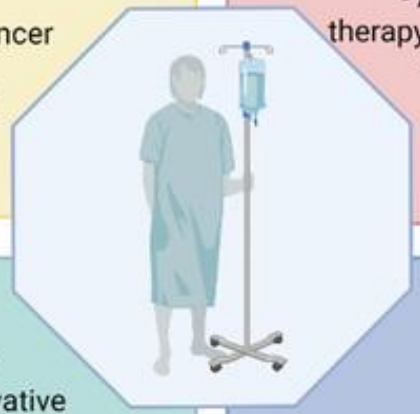
Preoperative neoadjuvant chemotherapy treatment (NACT) for triple negative and HER2+ breast carcinomas

Derouane F et al. Cancers 2022, 14(16), 3876

Aim: Complete pathology response (pCR): No residual invasive tumor

Neoadjuvant chemotherapy indications :
- Triple negative breast cancer >1cm
- HER2 positive breast cancer >3cm or node positive
- High risk luminal breast cancer
- Inflammatory breast cancer

Neoadjuvant regimens :
- Combination of anthracyclines and taxanes
- Addition of HER2-targeted therapy in HER2 positive subtype
- Addition of platinum and immunotherapy in triple negative subtype



Advantages :
- Evaluation of sensitivity
- Enabling breast conservative surgery
- Downstaging of lymph node status
- Micro-metastasis eradication
- Tailoring of adjuvant therapy

Disadvantages :
-Adverse events of NAC (*e.g.* cardiotoxicity, neuropathy)
-May delay surgery
- Healing difficulties after surgery
- Progression can occur during NAC

Main goal of neoadjuvant chemotherapy : achieving pathological complete response

Pathological complete response associated with better OS