Nact -Histopatologi og Biomarkører

- Eva
  - Håndtering af præparater efter neoadjuverende terapi
- Tomasz
  - Estimering af resttumor

    -nuværende og kommende vejledninger

    -fordele og ulemper
- Anne- Vibeke
  - Biomarkører
  - Prognostiske og prædiktive markører

  - Anne Marie og Eva
    - Cases

Vejledninger til patologi

-i overensstemmelse med førende gruppers erfaringer og anbefalinger

J Clin Pathol. 2019 Feb;72(2):120-132. doi: 10.1136/jclinpath-2018-205598.

Breast specimen handling and reporting in the post-neoadjuvant setting: challenges and advances

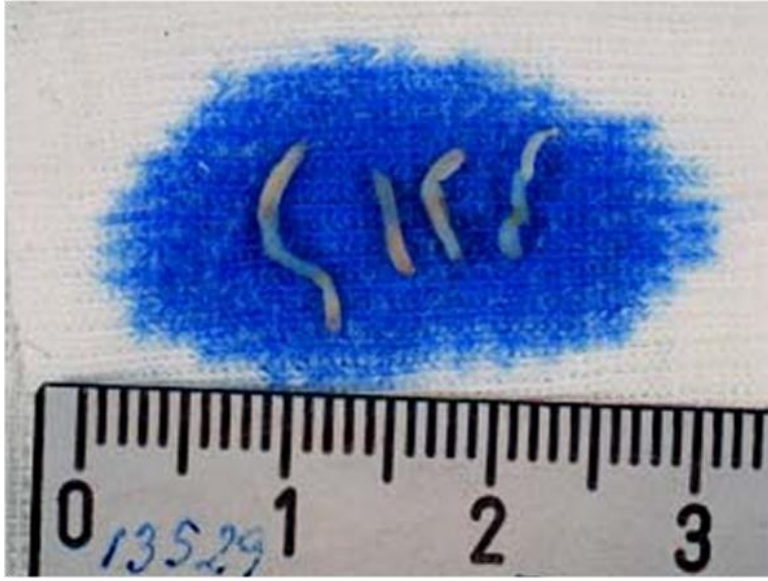
Histopathology. 2015 Sep;67(3):279-93. doi: 10.1111/his.12649. Epub 2015 Mar 8.

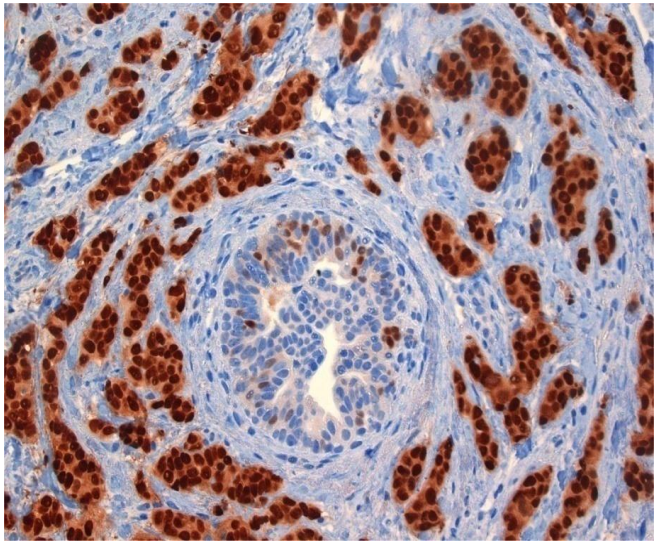
Macroscopic handling and reporting of breast cancer specimens pre- and post-neoadjuvant chemotherapy treatment: review of pathological issues and suggested approaches.

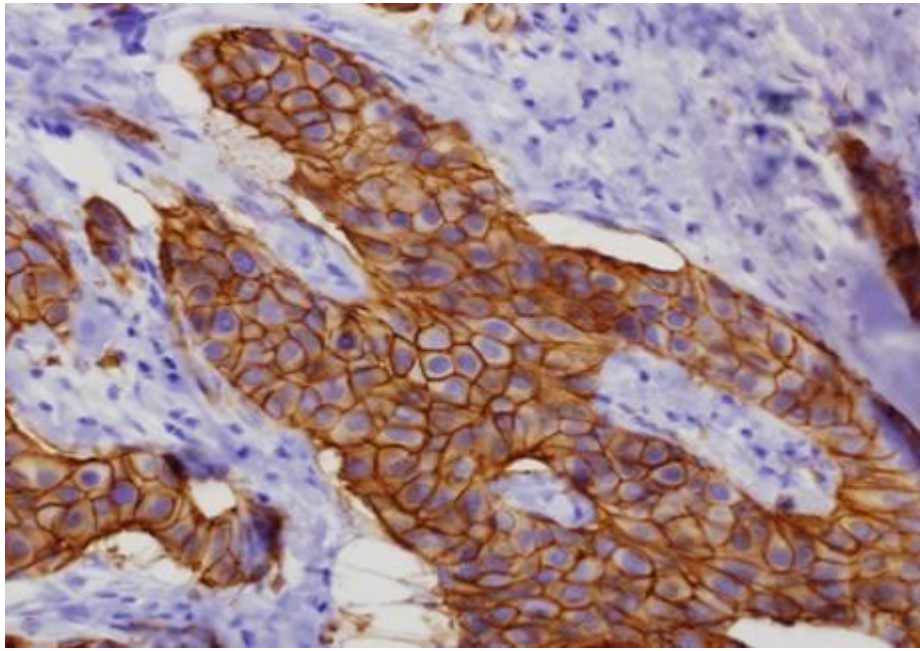
Pinder SE[1], Rakha EA[2], Purdie CA[3], Bartlett JM[4], Francis A[5], Stein RC[6], Thompson AM[7], Shaaban AM[8]; Translational Subgroup of the NCRI Breast Clinical Studies Group

Før behandling- Nålebiopsi

- Histologisk tumor type (Ecadherin, p120)
- Malignitetsgradering
- Receptor ER, HER2
- Ki67
- DCIS tilstede/fraværende
- Cellularitet (% tumor)







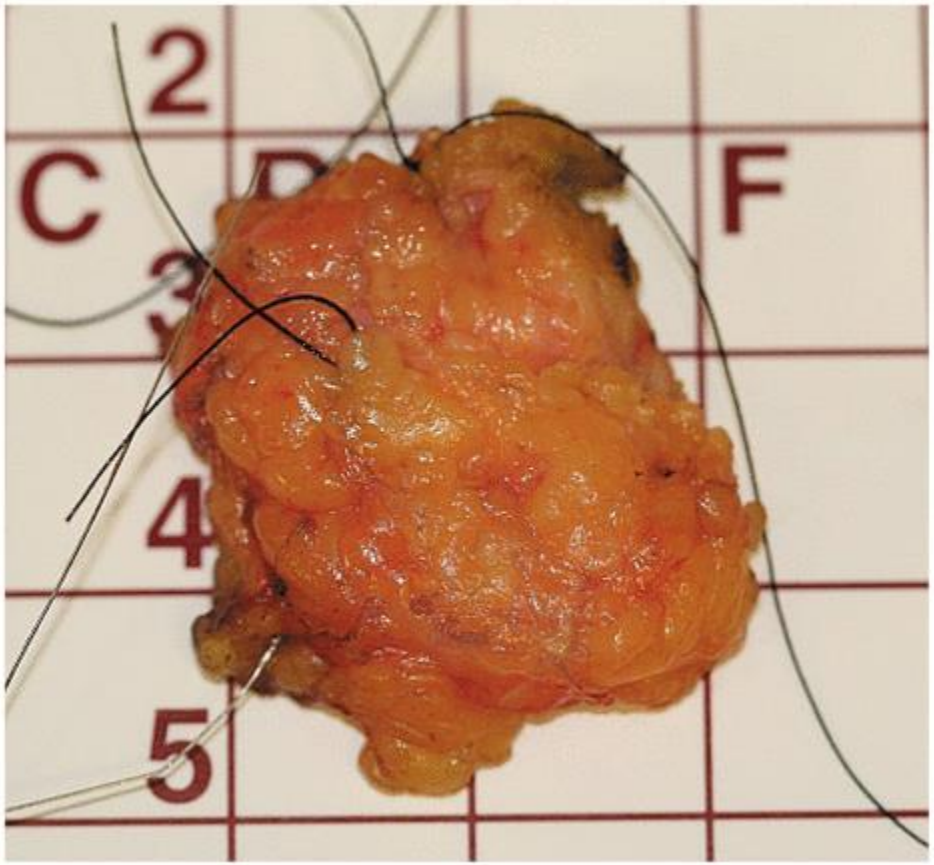
Hvordan håndterer vi operationsvæv?

- Mastektomi med/uden lymfeknuder
- Lumpektomi
- Resektat
- Lymfeknuder (sn, andre lymfeknuder, aksilrømning)

Operationspræparat
status i DK

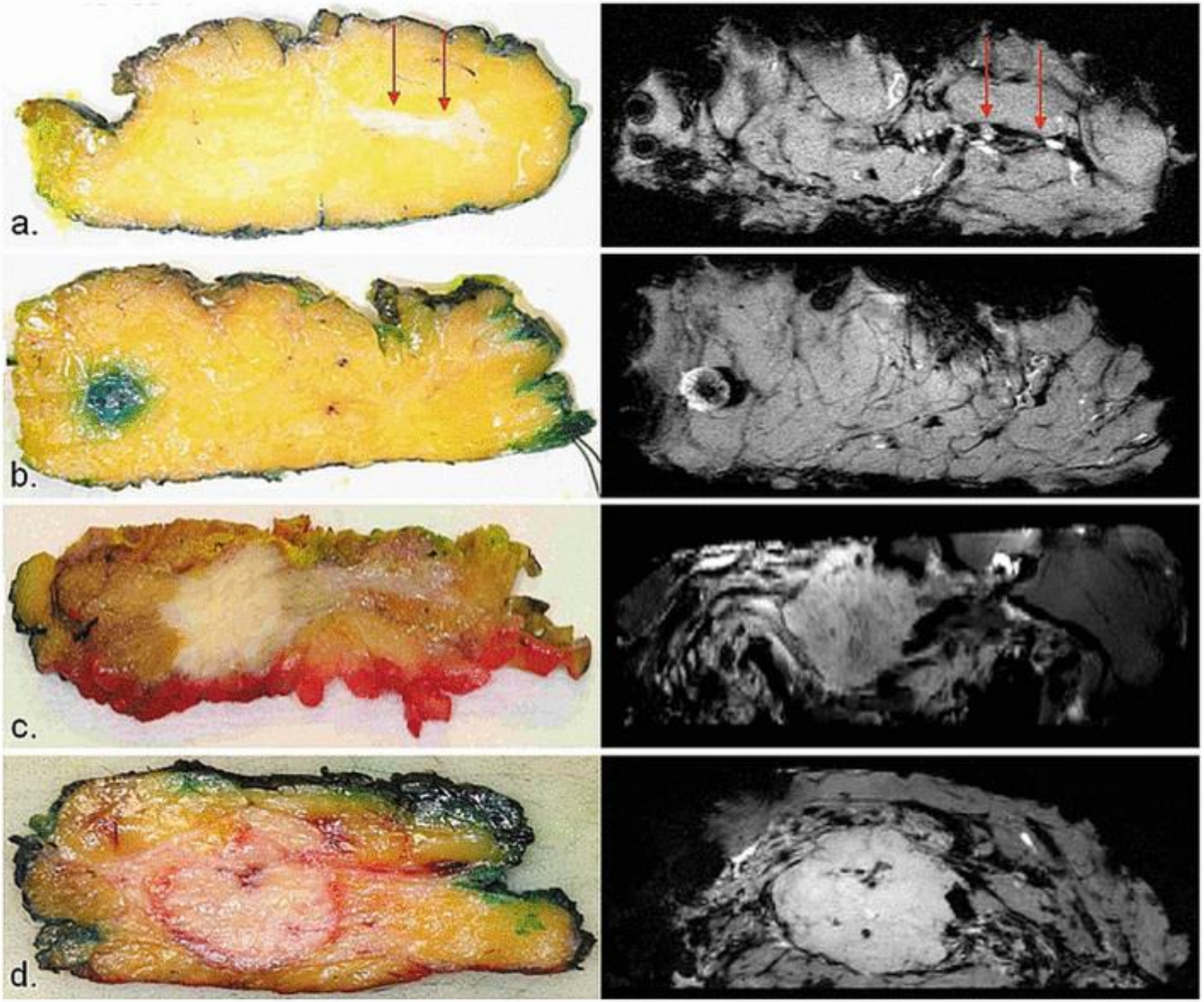
- Resttumor måles
- Diameter af største fokus angives i mm
- Antal foci angives
- Modificeret Miller Payne- responsgrad
- Vurdering af respons i lymfeknuder
- Ved patologisk komplet respons (pCR), indstøbes det oprindelige tumorområde i sin helhed

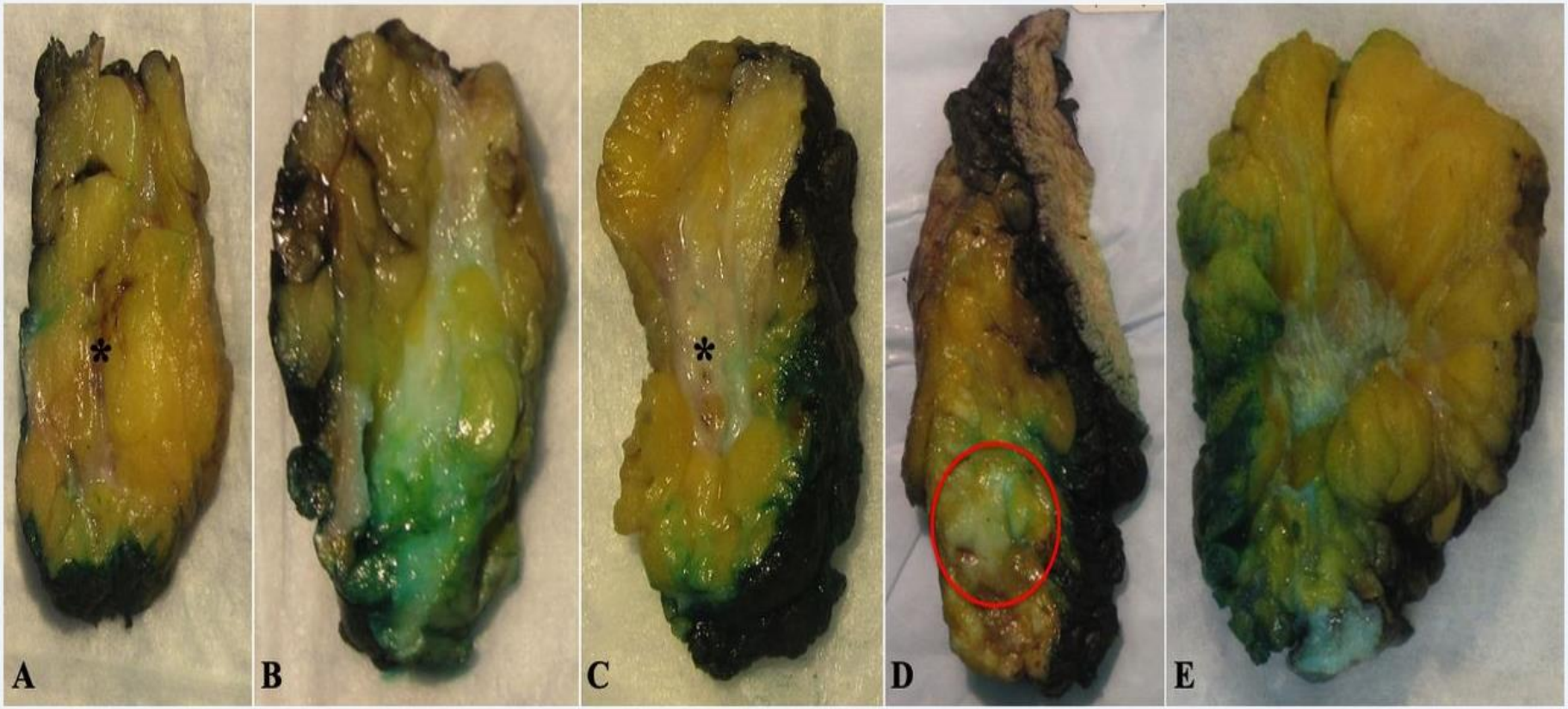
Nålemarkeret lumpektomi



Lumpektomi med coil

Farves med 6 forskellige, let genkendelige farver


a.
b.
c.
d.


A
B
C
D
E

Resttumor- makroskopi

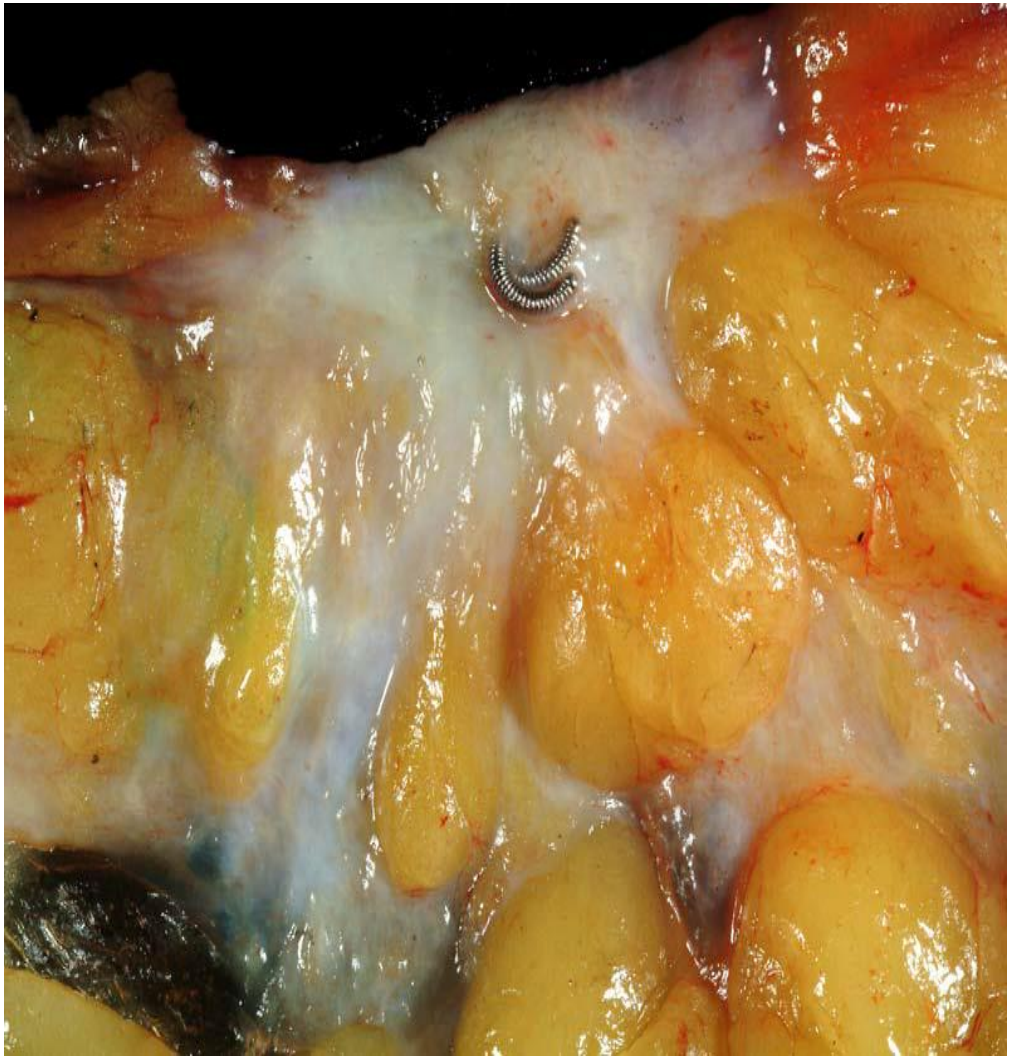
Tumor tilstede ja/ nej

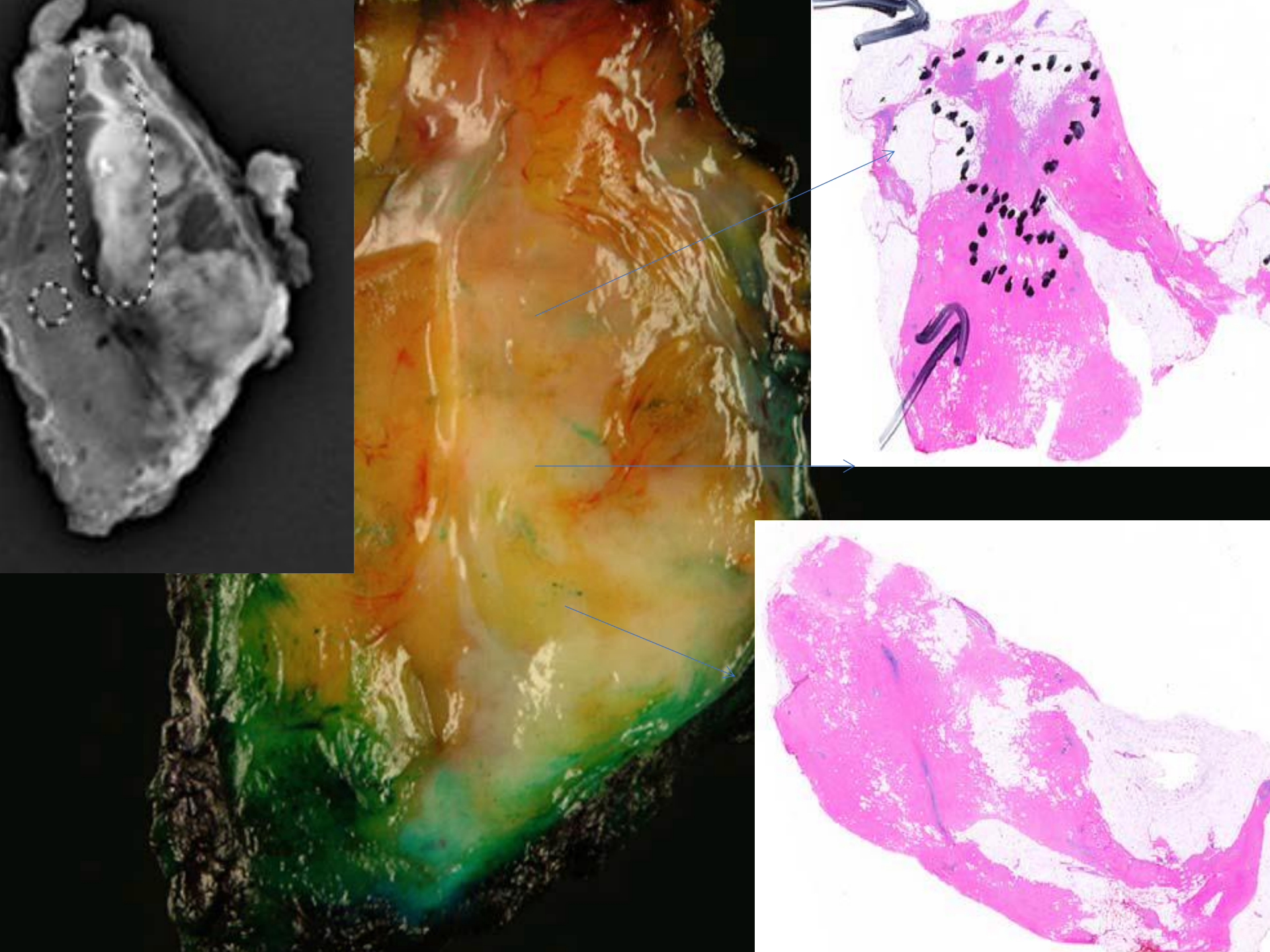
Coil JA/NEJ

Udmåling til resektionsrand

Hvis ingen tumorrest måles oprindelige tumorområde?

Sammenligning med MR?





Udfordringer Lobulært karcinom

Ikke Palpabel og meget lidt synlig efter neoadjuverende terapi.
Falsk negative marginer ved makroskopi

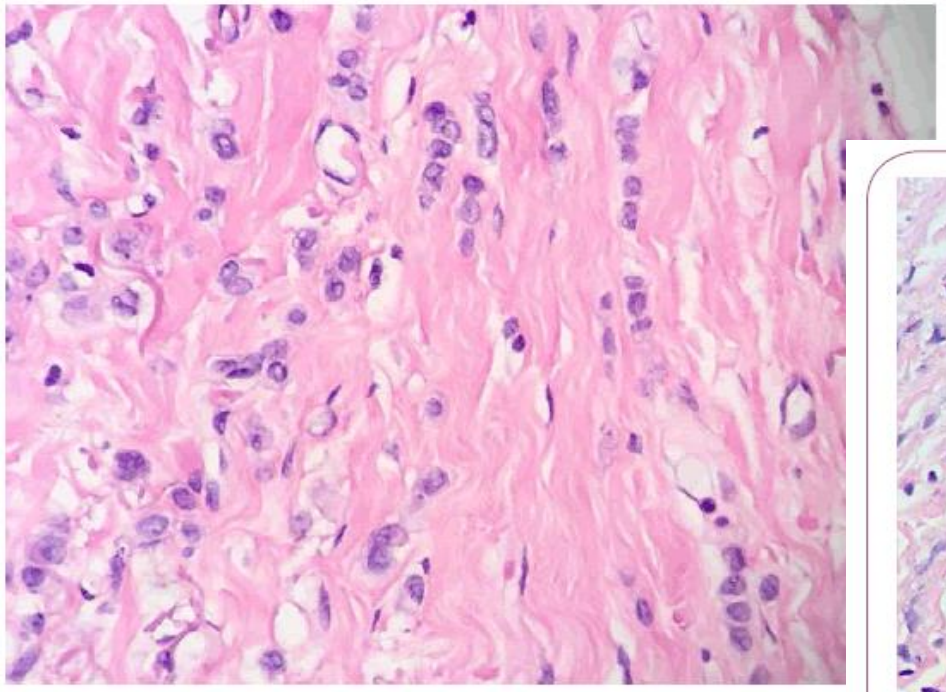


Figure 1 Invasive lobular carcinoma - infiltration in a "single

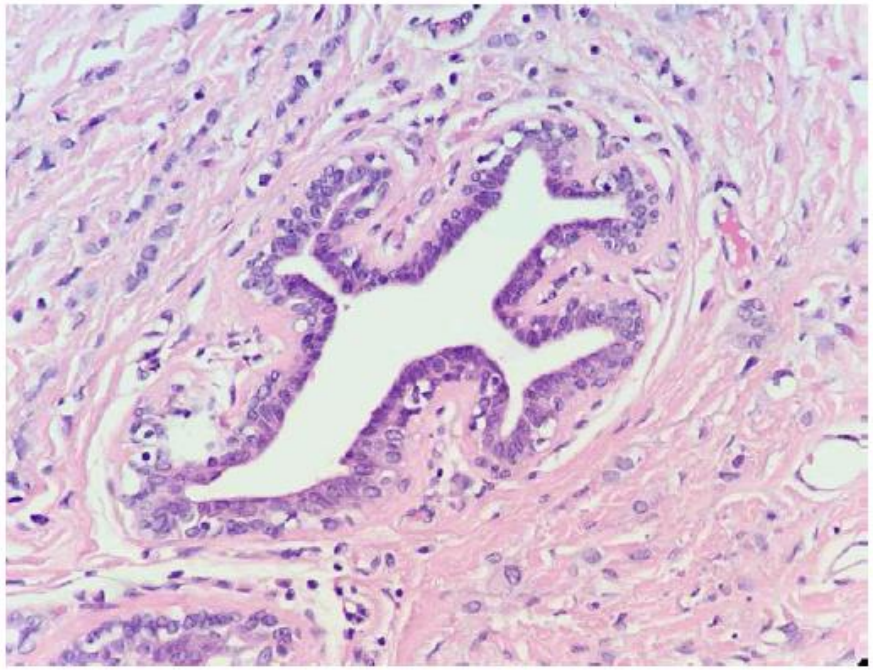
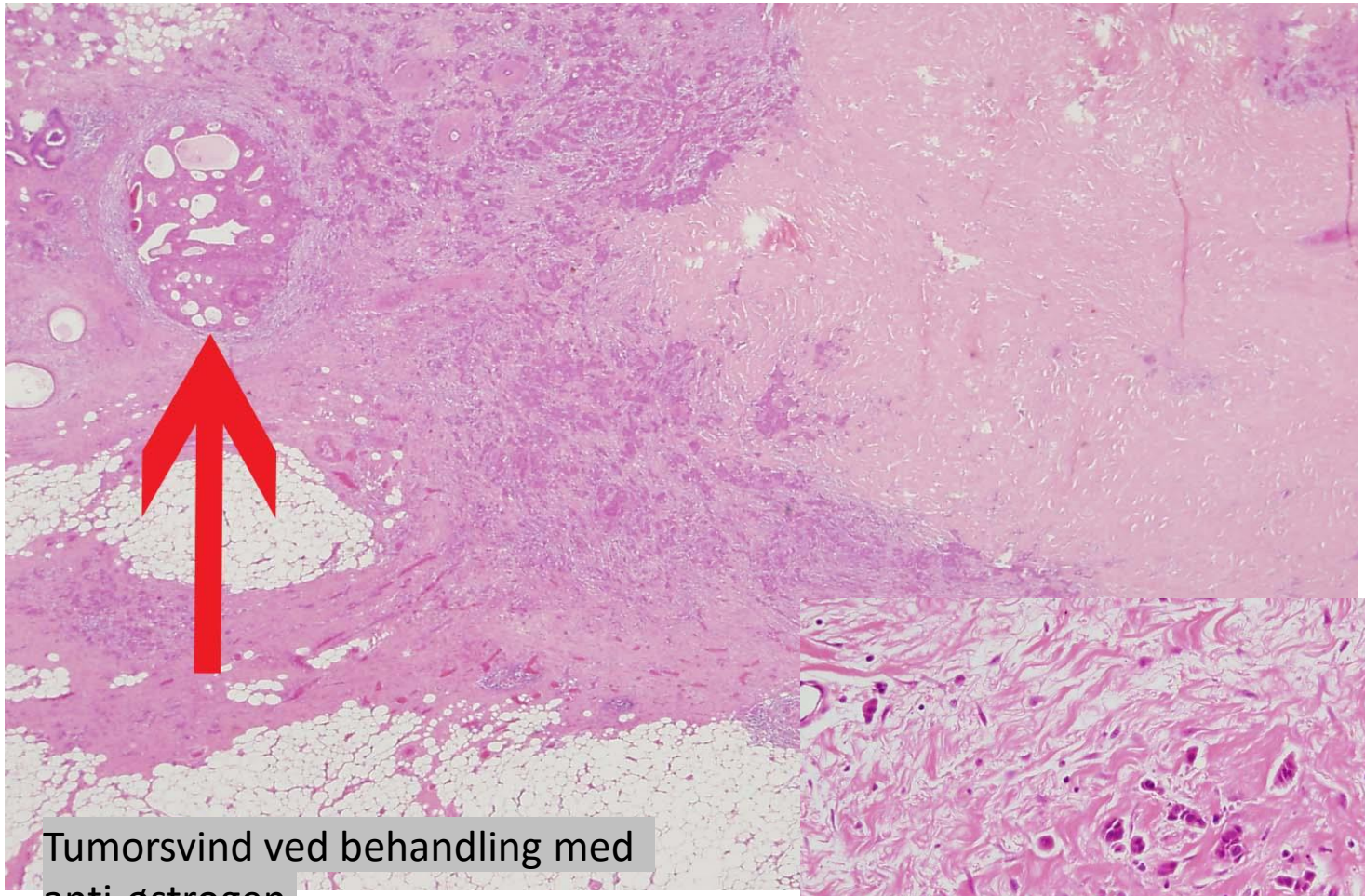
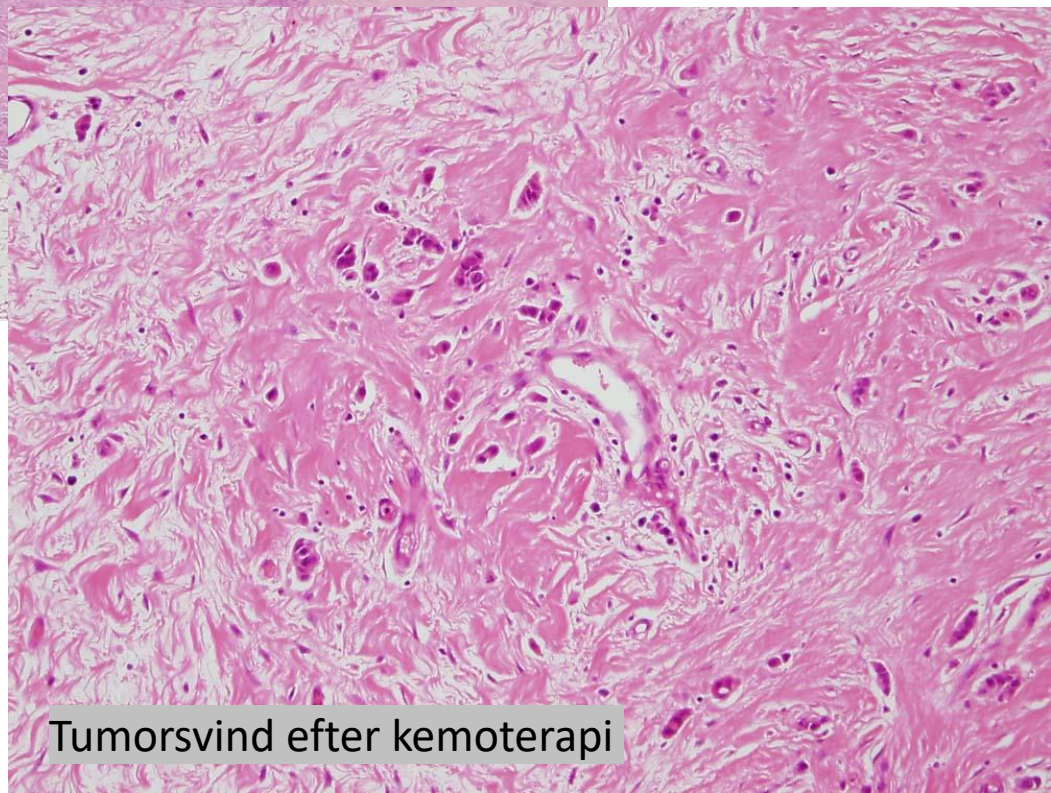


Figure 2 Invasive lobular carcinoma - arrangement of neoplastic cells "on target".



Tumorsvind ved behandling med anti-østrogen

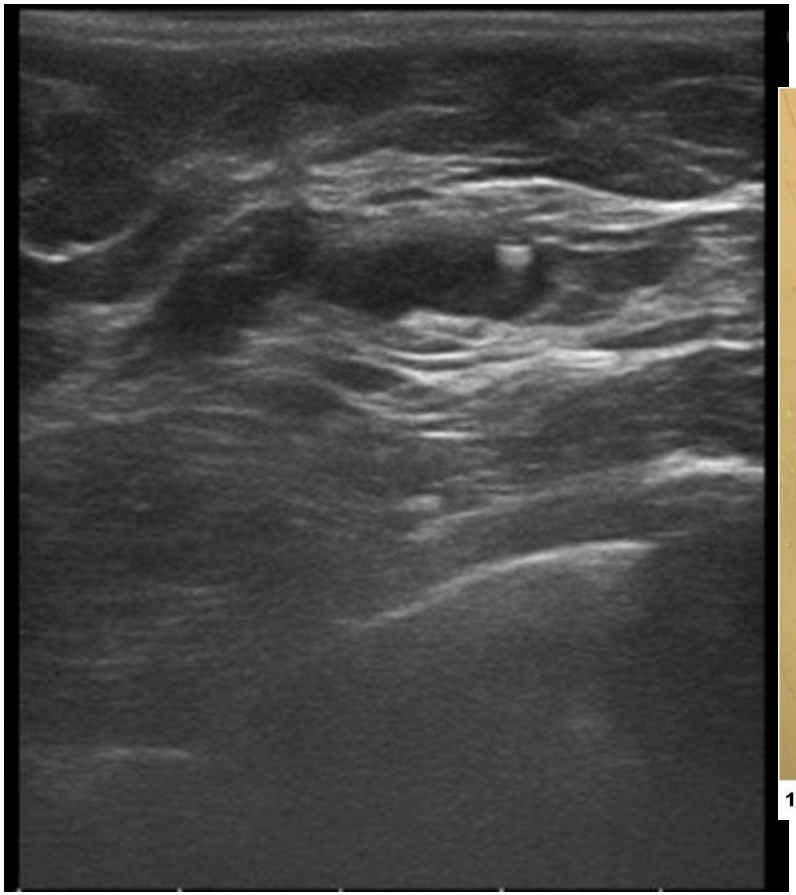


Tumorsvind efter kemoterapi

Udfordringer bryst

- Finde coil efter udtagning
- RTG fast coil kan blive usynlig på RTG
- Skal Coil findes ?
- Responsgradering
- Måle størrelse af tumorrest

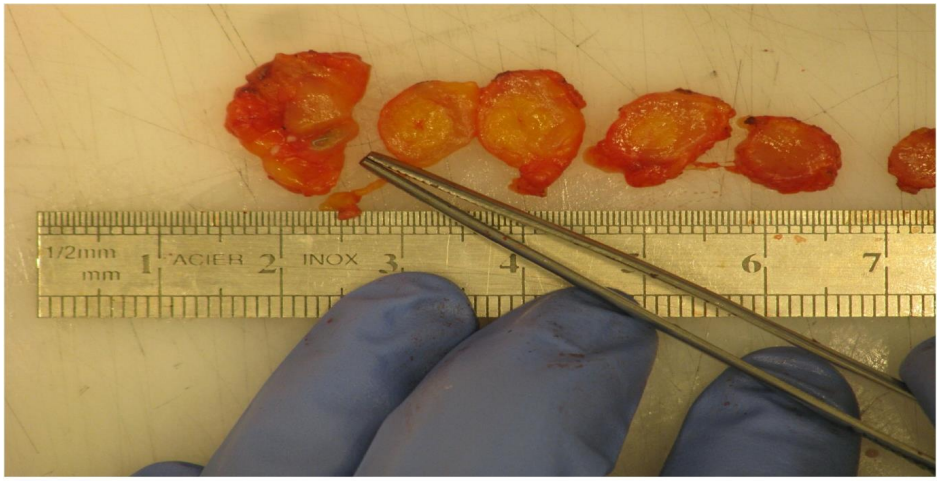
Coil i lymfeknude- jodkorn



Clips/ coil/ jodkorn i lymfeknude

- *Fordele*
- Sikker lokalisation af syg SN
- Kan genfinde metastasen UL eller RTG vejledt- jodkorn

- *Usikkerhed*
- Kan ikke findes ved RTG/gennemlysning
- Forsvinder ved udskæring
- Clips disloceres
- Forkert ”rask” lymfeknude udtages



1710644201 - 18 apr 2017 11:42

litteratur fund af Clips

- 91% af clips blev fundet i SN (Toan T. Nguyen, Breast Oncol 2018)
- In the ACOSOG Z1071 trial, the rate for missing the biopsy proven clipped lymph node was 17% for patients who underwent ALND, and when the clipped lymph node was removed during SLNB, the false negative rate fell to 6.6%.
- Sentina study 10/54 False Negative rate (< 3 SLN) 18,5%
- Forty-six patients had a clip placed in the positive node. In two (4.3%) cases, the clip could not be seen prior to surgery and the patient underwent ALND (Annals of Surgical Oncology March 2018, Volume 25, Issue 3, pp 784–791) ILINA trail
  - Er det vores procedure??

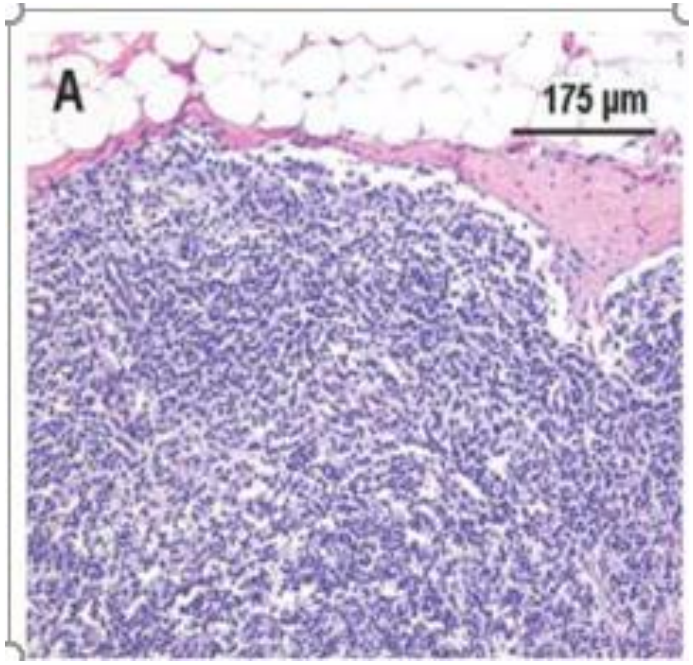
Forandringer i lymfeknuder

- *Tumorceller* bliver forstørrede med vakuoliserede kerner eller skrumper med pyknose
- Nekrose
- Eller ingen forandringer – ingen respons

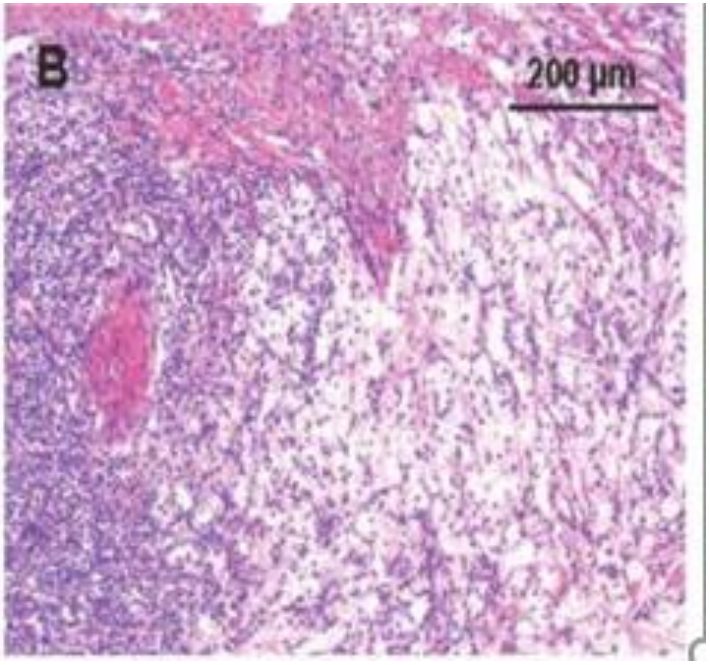
- *Granulationsvæv med mange nydannede kar*
- *Makrofager og jernpigment*
- *Stromaet* ses med fibrose, *arvæv,*
- Forkalkninger
- Hyalinisering af karvægge
- Lymfocyt depletering

SN efter kemoterapi

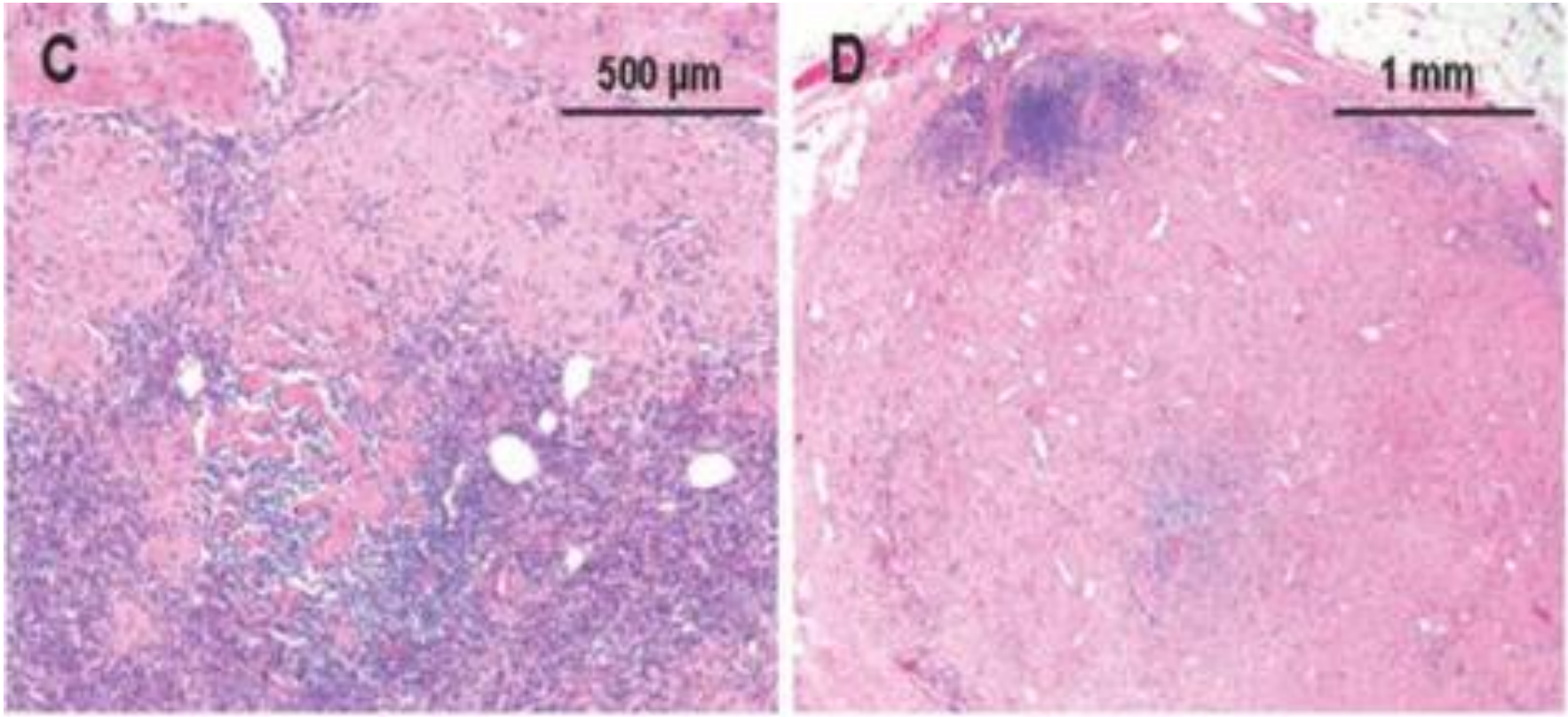
(A) no detectable histologic change,



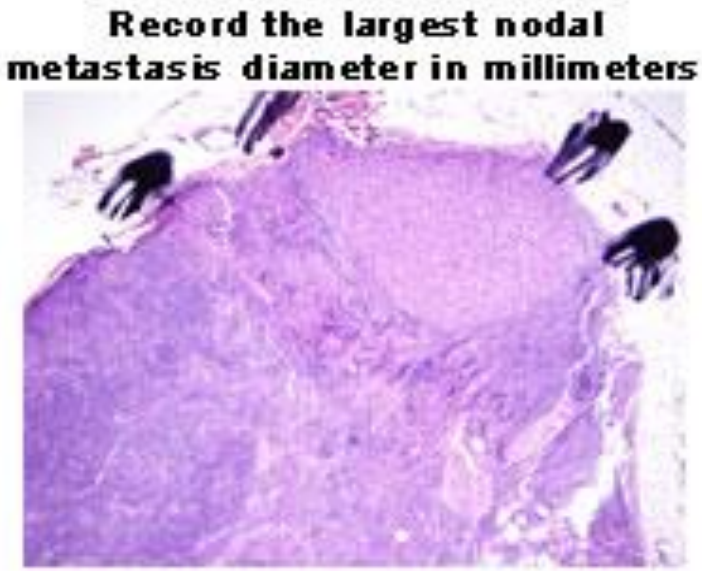
(B) a parenchymal histiocytic infiltrate,



Lymfeknude efter kemoterapi
(C) focal subcapsular fibrosis
(D) diffuse parenchymal fibrosis.

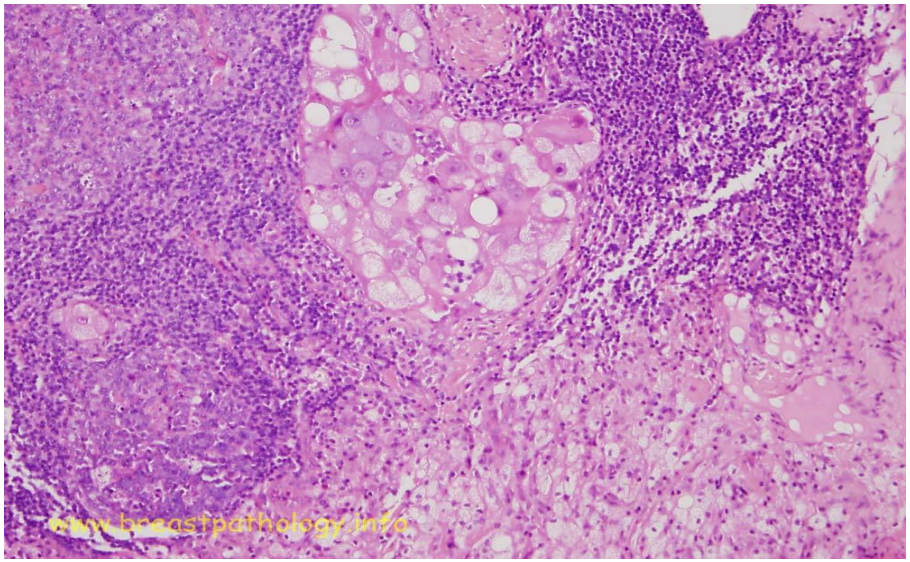


mikroskopi lymfeknude



- Den største metastase

  måles i mm
- Behandlings Effekt?
  - Antal med respons
  - Antal uden respons



udfordringer

- Klassifikation af resttumor
  - Miller Payne tager ikke højde for lymfeknude metastaser
  - Skal DCIS estimeres yderligere?

- Finde korrekt lymfeknude og SN
- Måling af tumorrest i lymfeknuder

Udfordringer ved lymfeknuderne

- Antal lymfeknuder udtages ved SN procedure
- Finde coils
- Er SN den samme som den coil markerede lymfeknude?
- Måling af restmetastase
- Måling af respons i mm?

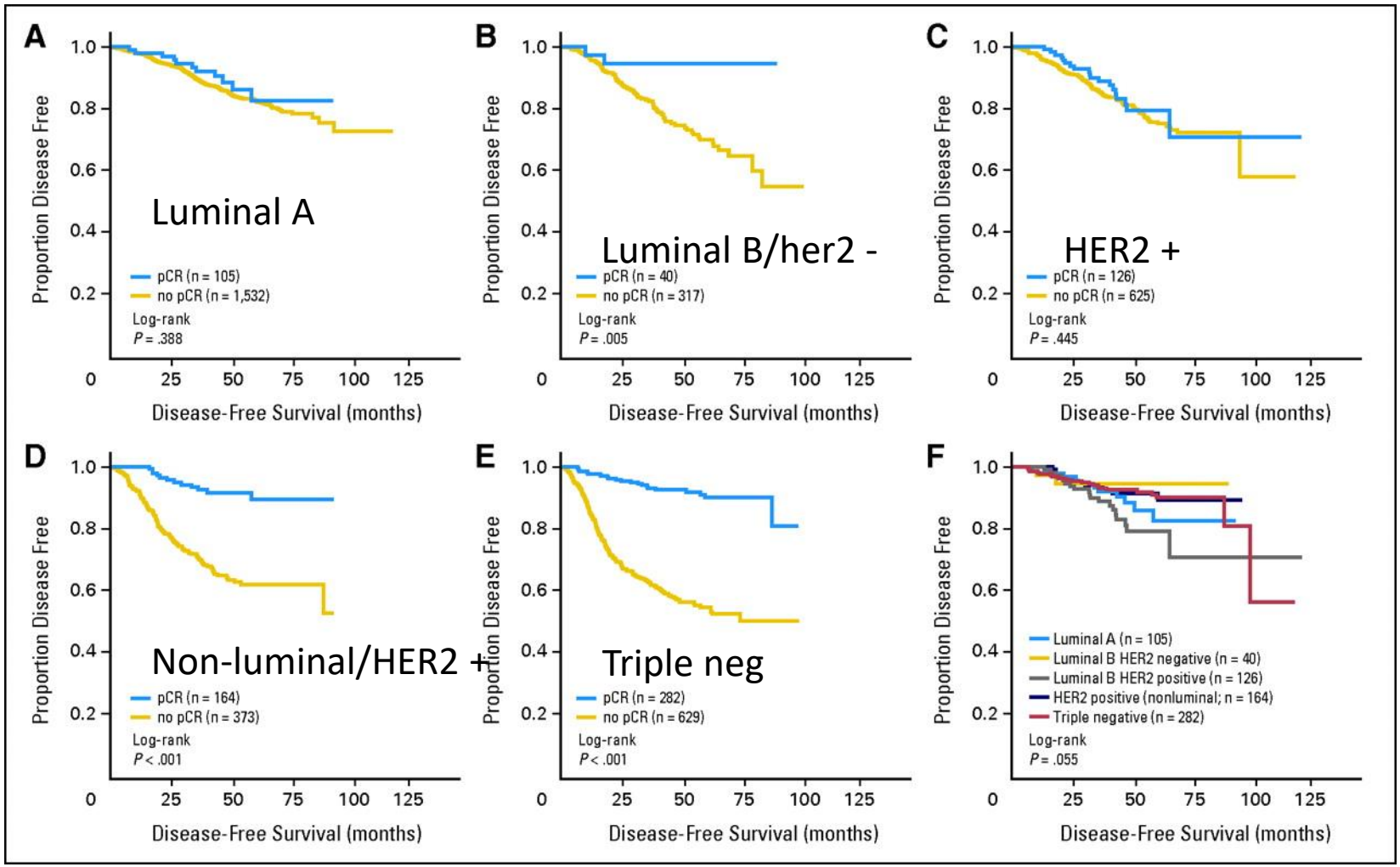
faktorer der har indflydelse på fund af korrekt lymfeknude

- Klips placering ved den biopterede lymfeknude
  - I kapsel
  - Ved siden af lymfeknude
  - Hvis klipsen ligger imellem flere lymfeknuder- hvilken er den rigtige
  - Er det SN?
- Vanskelighed ved at finde ”SN”
- Skip lesion-
- ----------
  - Patienter som har fået påvist aksilmetastase v. FNA fra lymfeknuden på diagnosetidspunktet. Denne lymfeknude markeres med coil eller iodkorn og kommer til undersøgelse efter NACT.
- Er det at betragte som en SN lymfeknude?

Andre faktorer der har indflydelse på prognose efter NACT

- pCR surrogat markør for lang overlevelse
- Luminal status af resttumor prognostisk udsagn
- Tumor-infiltrerende lymfocyter (TILs)(højt niveau)
  - Seminars in Cancer Biology 52 (2018) 16–25
- Måling af DCIS rest?
- DCIS i nålebiopsi og siderand har indflydelse på recidiv raten
  - Journal of Gynecology Obstetrics and Human Reproduction 48 (2019) 467–472

Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype.

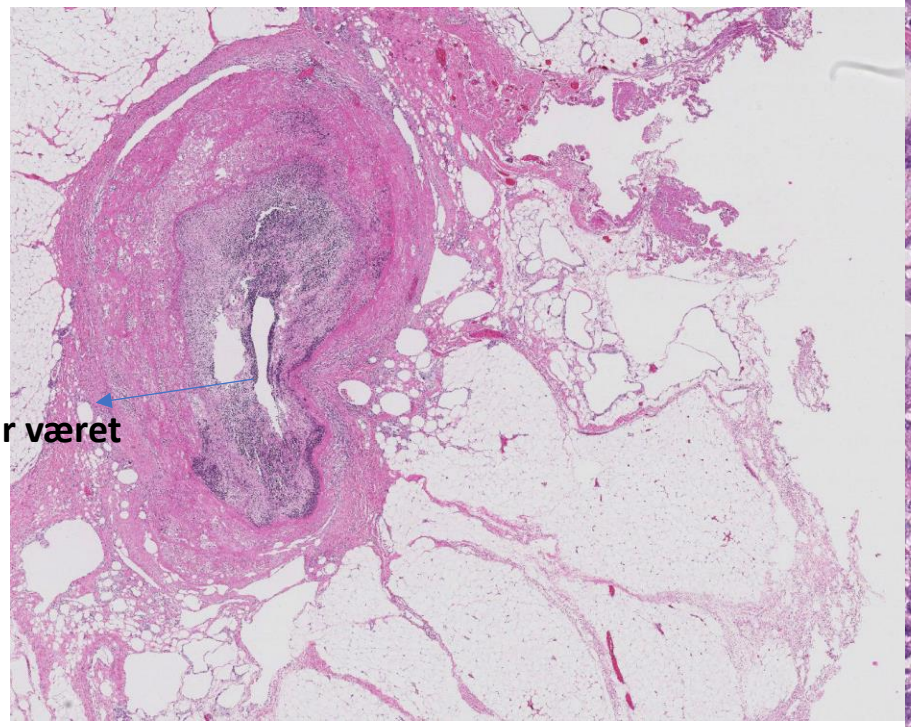


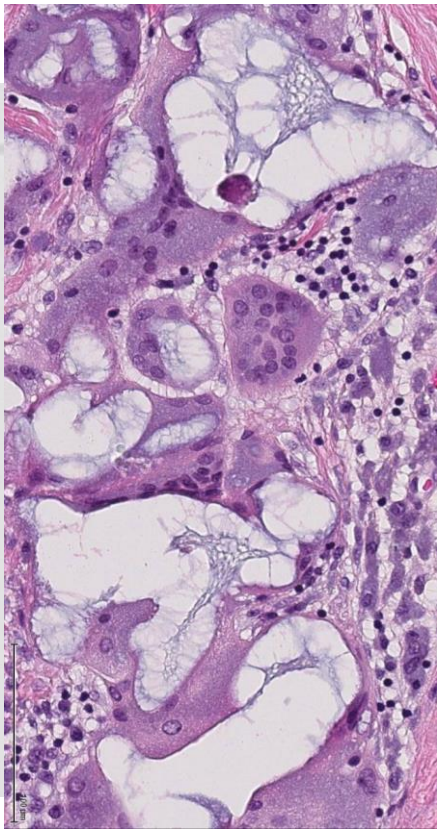
von Minckwitz G et al. JCO 2012;30:1796-1804

Tak

Komplet respons i lymfeknude

Hul hvor klips har været





Residual Cancer Burden RCB
MD Andersson, makroskopi

- Udtag snit der repræsenterer hele rest tumorområde (makrokapsler eller blokke hvor det er muligt at kende relation mellem snit)
- Hvis meget stor tumorrest udtages 5 kapsler til mikroskopi
- Væv omkring tumor udtages som led i opmåling af tumorrest

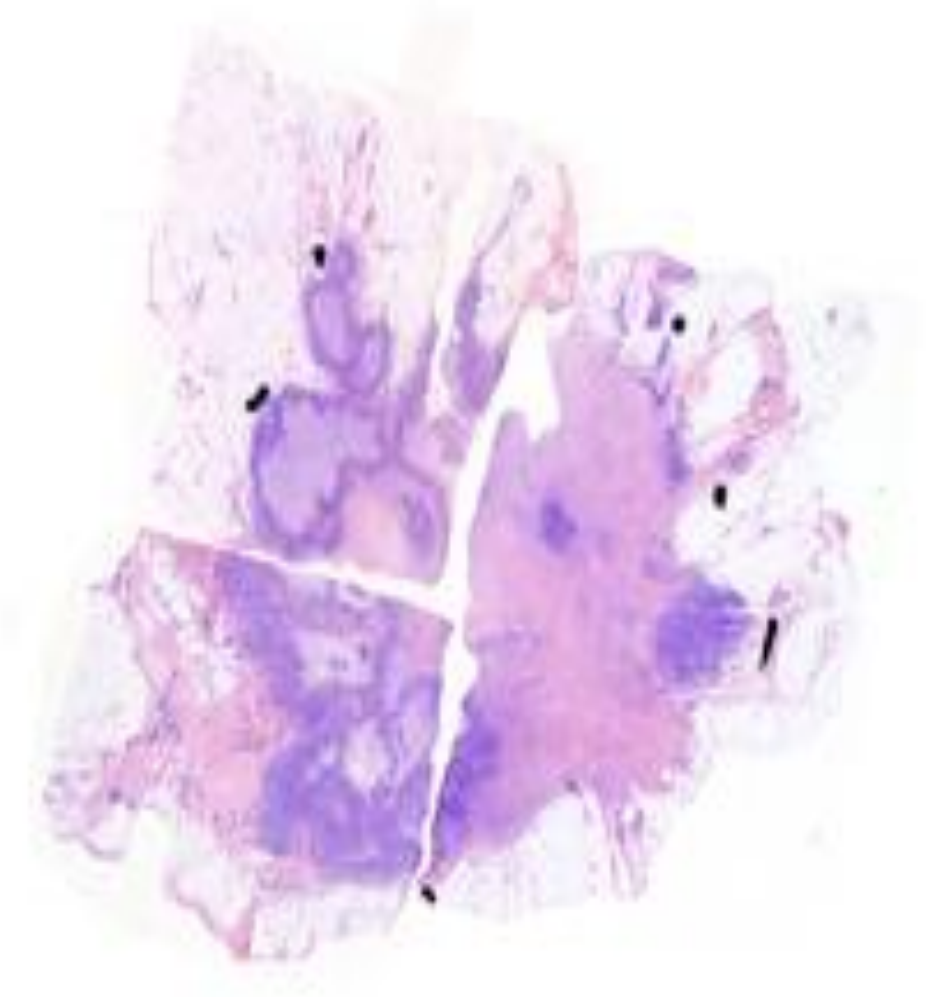
http://www.mdanderson.org/education-and-research/resources-for-professionals/clinical-tools-and-resources/clinical-calculators/index.html

Residual Cancer Burden RCB
MD Andersson

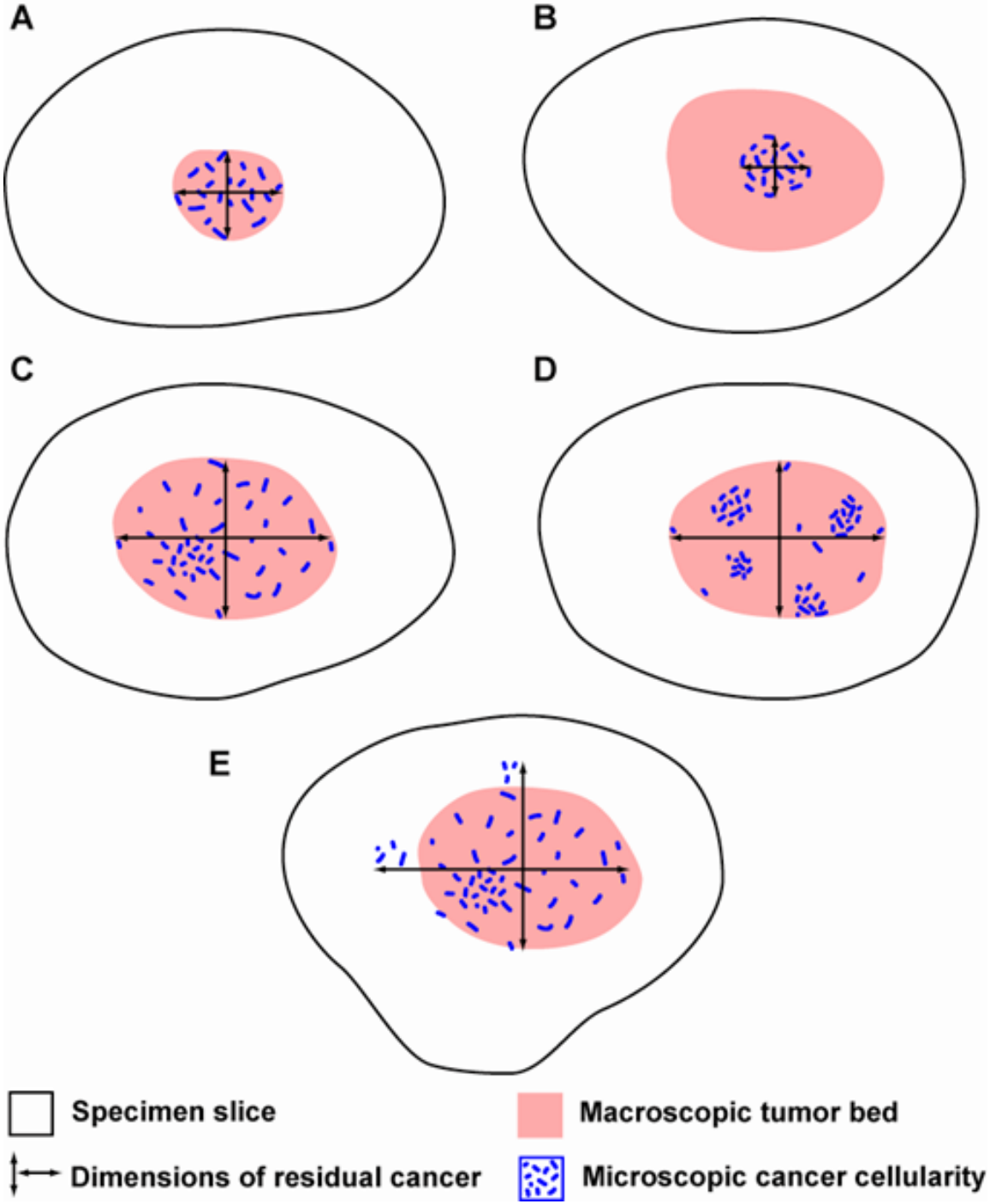
- Måling af resttumorområde
  - Hvis makroskopi og mikroskopi er ens i størrelse opretholdes målet i mm
- Cellularitet
  - På hvert snit, udtaget fra tumorområdet, opgøres tumorrest i % (fra 0-10% og nærmeste 10%)
  - Feks 6 snit med forskellige %´er lægges sammen og deles med 6, så der opnås et gennemsnit
- Det samme gøres for CIS, hvis det er tilstede

Måling af resttumor

- Området kan være mærket (Franksnål, jodkorn, clips)
- Kan evt påvises ved rtg gennemlysning
- Måling af rest tumorområde i 2 dimensioner(d1 og d2)



Makroskopisk Måling af resttumor



Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area: _____ (mm) X _____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *In situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

Diameter of Largest Metastasis: _____ (mm)

Reset | Calculate

Residual Cancer Burden: _____

Residual Cancer Burden Class: _____

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

1. The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)
2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 – A9")
   - If the residual tumor is large (i.e. largest diameter >= 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative sections from the largest cross-sectional area of primary tumor bed were submitted in cassettes A5 - A9")
3. Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:

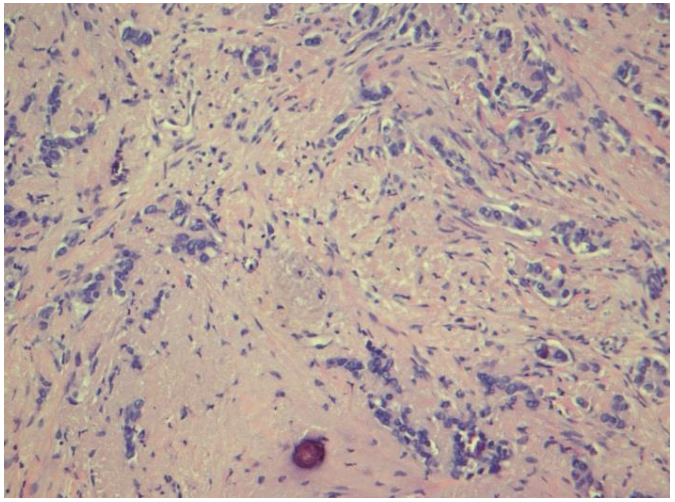
   ○ 0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%

   - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
   - When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.
   - Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.
   - e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.
4. Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following:

RESIDUAL TUMOR SIZE
”tumor bed”

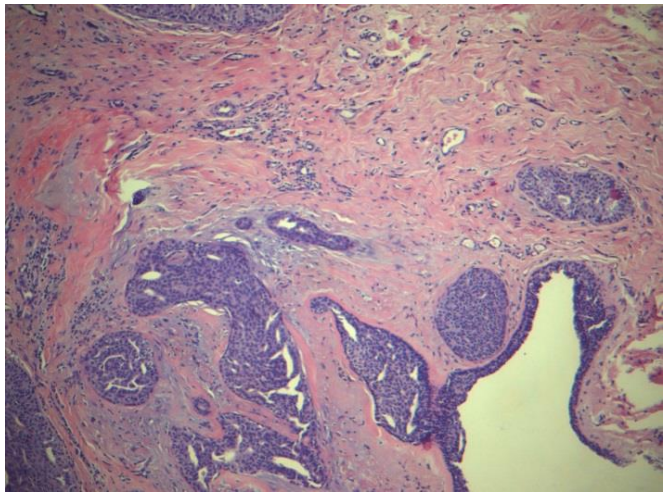
- **Microscopic response**
  Macroscopic response

Minor response

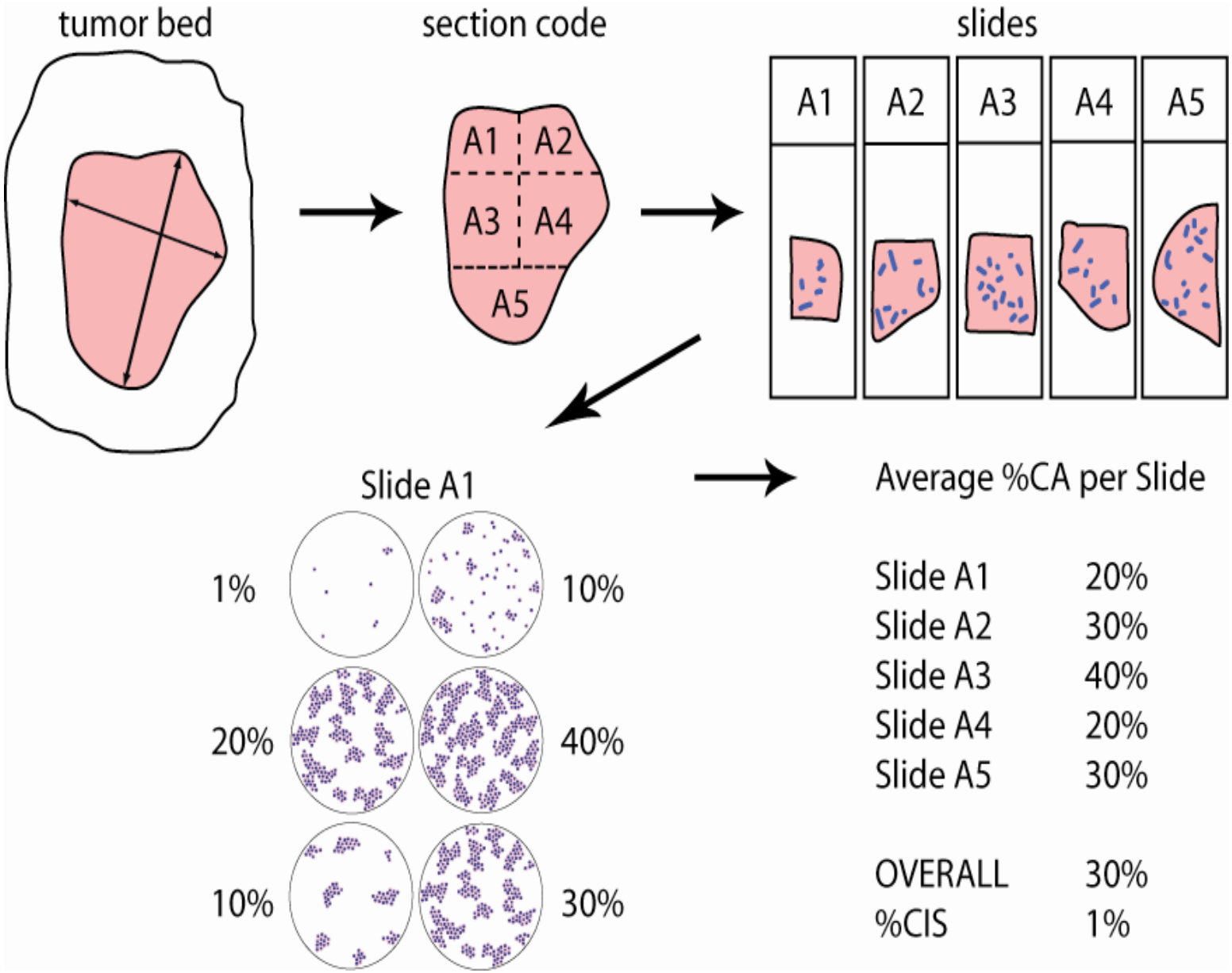


Tumor size, pretreatment: 50 mm
Tumor size, posttreatment: 35 mm

Complete response



Tumor size 50 mm, pre- treat- ,ment
inflam.carcinoma.
Tumor size, posttreatment:0
DCIS In the area


tumor bed
section code
slides
A1
A2
A3
A4
A5
A1
A2
A3
A4
A5
Slide A1
1%
10%
20%
40%
10%
30%
Average %CA per Slide
Slide A1 20%
Slide A2 30%
Slide A3 40%
Slide A4 20%
Slide A5 30%
OVERALL 30%
%CIS 1%

Respons til neo-adjuverende kemoterapi

Der er flere forskellige morfologiske forandringer i tumor og lymfeknuder

- Hvis den invasive komponent helt forsvinder
  - pCR- Pathologic complete response
- Partiel tumor respons
- Ingen respons
- Tumor vokser
  - Progressiv tumorvækst under behandling