The Surgeon`s Perspective:

Local Treatment in the Age of Neoadjuvant Therapy

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Disclosures

No relevant disclosures to this presentation

However, I am surgical oncologist with a passion for reducing morbidity of our patients

- Performing SNB for 18 years
- Routinely using intraoperative ultrasound
- Try to avoid mastectomies by using oncoplastic surgery
- Extensive use of neoadjuvant therapies
- Co-PI in the European Axilla trial – TAXIS

Outline of this presentation

- Adaption of surgery according to response:
  → Is it safe?

- Principles of surgery after neoadjuvant treatment
  → What`s different from primary surgery?

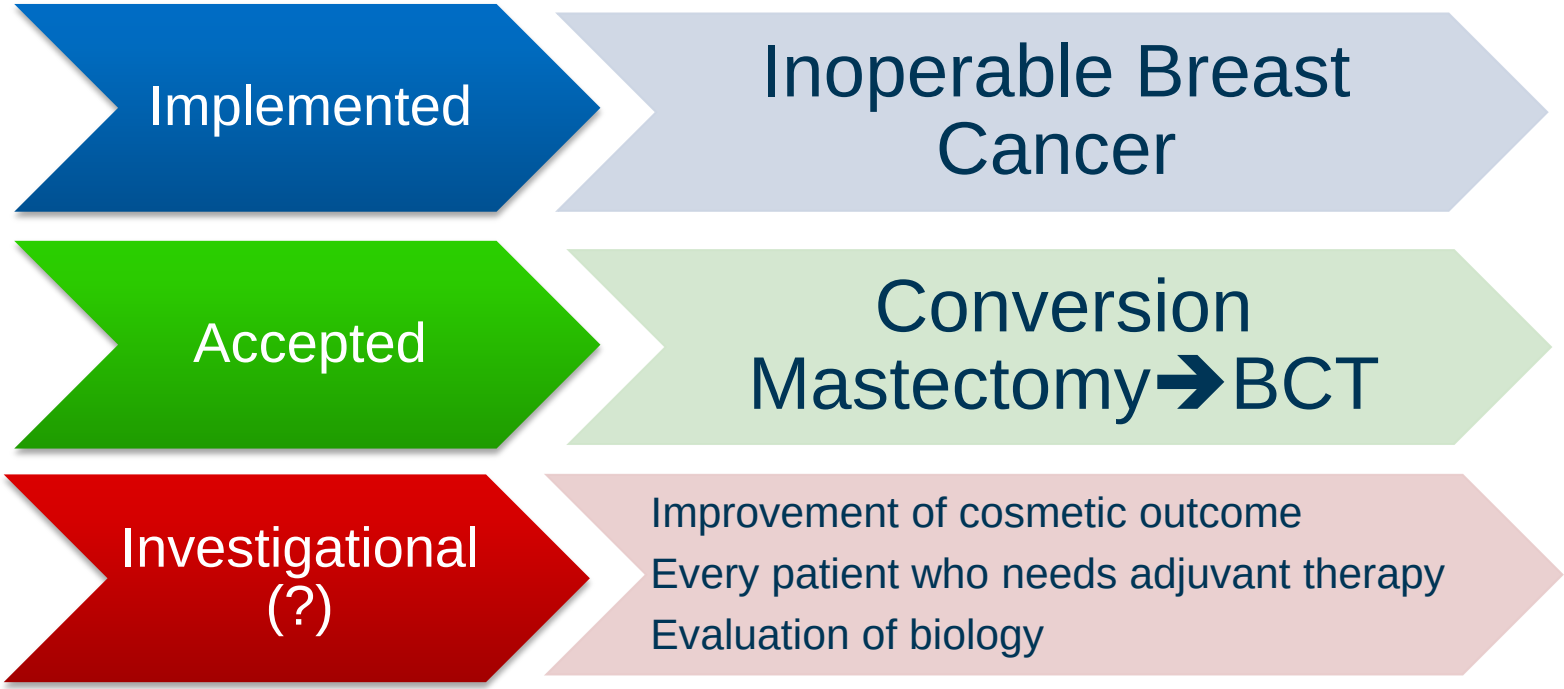
- Axillary surgery after neoadjuvant therapy

Oppositional trends in breast surgery

- BRCA-Testing
- Contralateral mastectomies (US)
- Improvements in reconstructive surgery

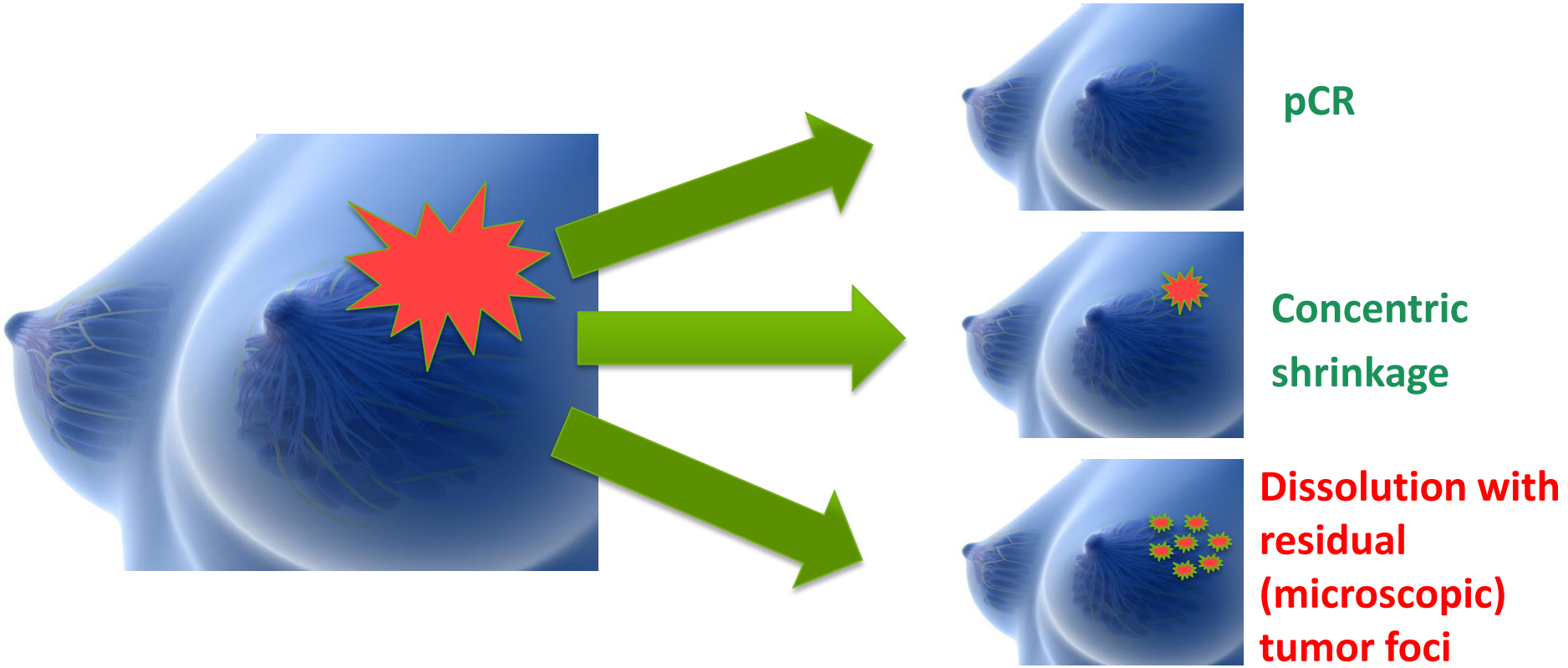
- Screening
- Oncoplastic surgery
- Neoadjuvant therapy

Indications for neoadjuvant systemic therapy – a surgeon`s view...



Kaufmann et al., JCO 2006
Gralow et al., JCO 2008

Tumor response patterns



No improvement in breast conservation rates in study arms with better pCR rates

- **NSABP B-27:** pCR in taxane arm 26% vs. 14%

  BCT rate in AC-T: 64%

  BCT rate in AC: 62%

- **CHER-LOB:** pCR in dual blockade 47% vs 25%

  BCT rate in T+L: 69%

  BCT rate in T alone: 67%

- **NeoALTTO:** pCR in dual blockade 51% vs. 30%

  BCT rate in T+L: 41% (*26%)

  BCT rate in T alone: 39% (*28%)

*Rate of BCT in women deemed to be candidates of mastectomy at diagnosis

Bear et al., J Clin Oncol 2003 and 2006
Guarneri et al., J Clin Oncol 2012
Baselga et al., Lancet 2012

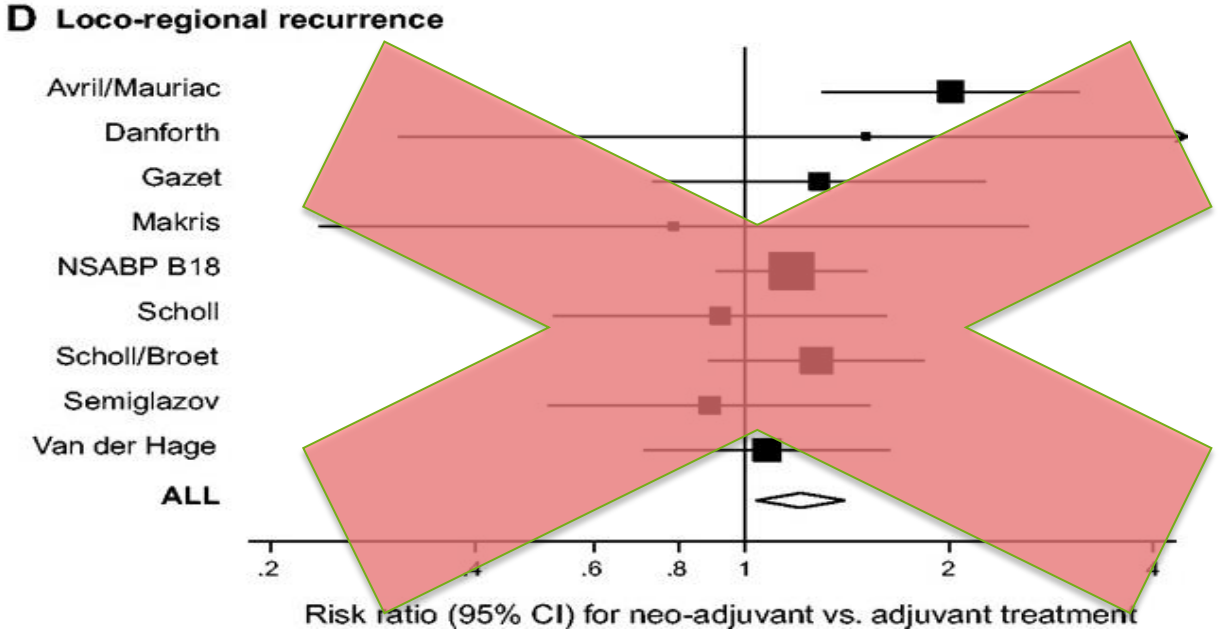
No Improvement in BCT rates in study arms with better pCR rates: Neo-ALTTO

Risk factors for mastectomy	p-value
Mastectomy planned before NAC	p<0.001
Patients treated in developing countries	p<0.001
Tumor size >5cm	p<0.001
Tumor still palpable after NAC	p<0.001
Multifocal / Multicentric tumor	p=0.007
ER-negative	p=0.005
Unknown grade	p=0.02

53% of patients with pCR and 55% with partial response still underwent mastectomy!

Criscitiello et al., Ann Oncol 2013

Higher risk of local recurrence after NAC?



- 3946 patients
- 22% increase
- RR 1.22
  p=0.015

Mauri et al., JNCI 2005

Higher risk of local recurrence after NAC?

8 Studies	LRR in NACT	LRR in ACT		HR (95%CI)	p
Optimal local treatment	208/1870	199/2328		1.12 (0.92-1.37)	0.25
3 Studies					
Inadequate local treatment	97/429	66/417		1.45 (0.85-2.13)	0.02

Mieog et al., Br J Surg 2007

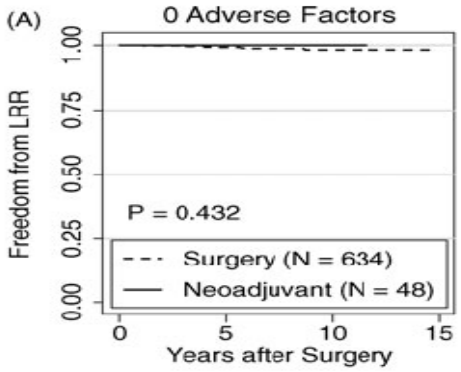
Local recurrence risk and neoadjuvant therapy

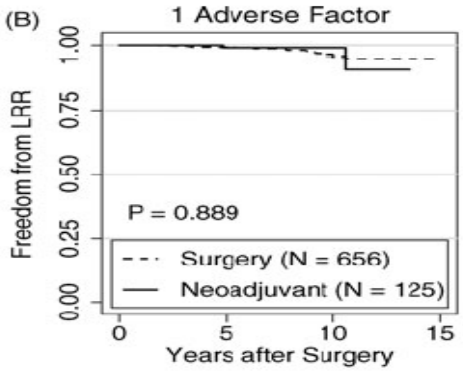
- MD Anderson 1987 – 2005, 2.983 patients
- 52% downstaging from stage II/III to stage 0/I
- Univariate: 6% vs. 10% LRR after primary surgery vs. NACT
- Multivariate: NO DIFFERENCE after correction for clinical stage

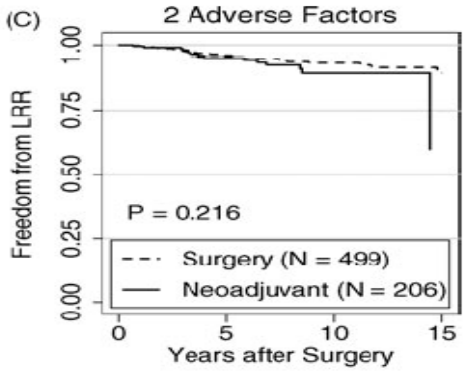
- 8 risk factors for local recurrence:
  - Age <50, stage III, grade 3, LVI, ER-, ER+ without ET, multifocal cancer, positive margins
  - NOT: neoadjuvant therapy

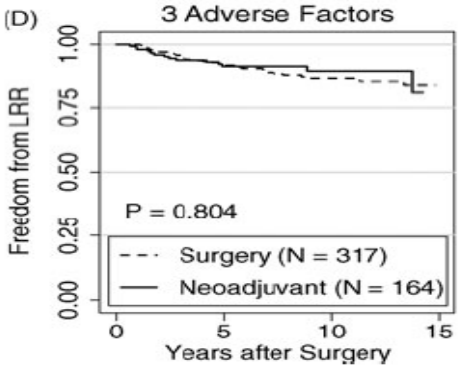
Mittendorf et al., Ann Surg 2013

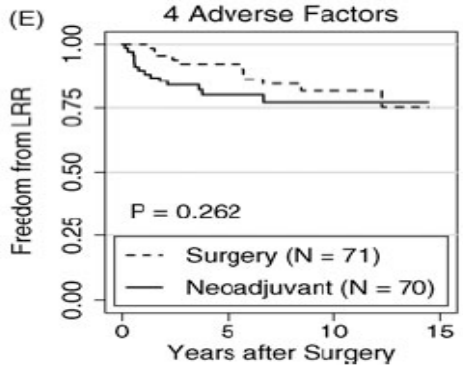
Adjustment for risk factors











Neoadjuvant chemo
is no risk factor
for local recurrence

Mittendorf et al., Ann Surg 2013

Surgical margins – is it the same for surgery after neoadjuvant therapy?

- Consensus conference SSO and ASTRO 2014
  - Meta-analysis 33 studies – 28.000 patients – 1.500 local recurrences
  - LRR: 5.3% after 6.6 years

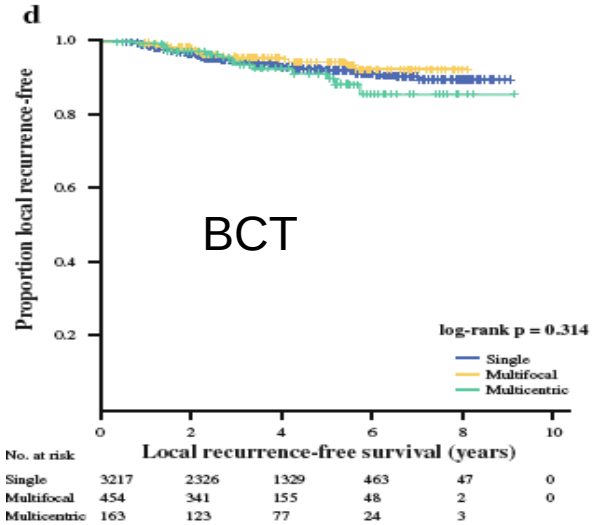
- Positive margins: > 2-fold higher risk
  - Not mitigated by: good biology, endocrine therapy, radiotherapy boost

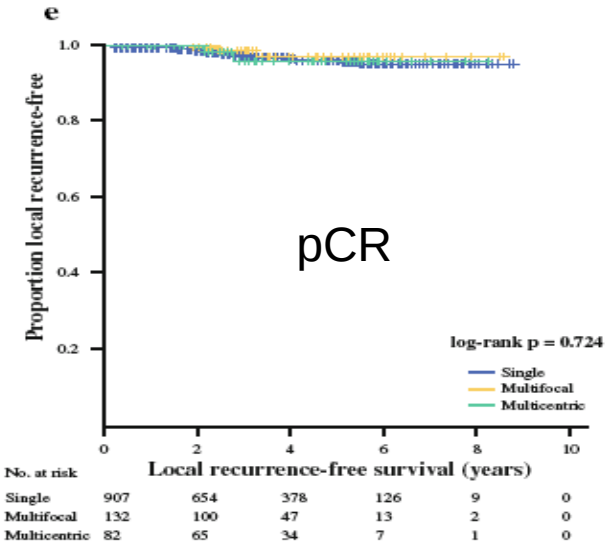
- No Tumor on Ink: WIDER MARGINS do not reduce risk further
  - NOT EVEN: poor biology, young age, lobular cancer, EIC

Mittendorf et al., Ann Surg 2013

Multifocality and Multicentricity – BCS
GBG database: 6134 patients

- Local recurrence rates are not increased after breast conserving therapy in MF and MC cancer



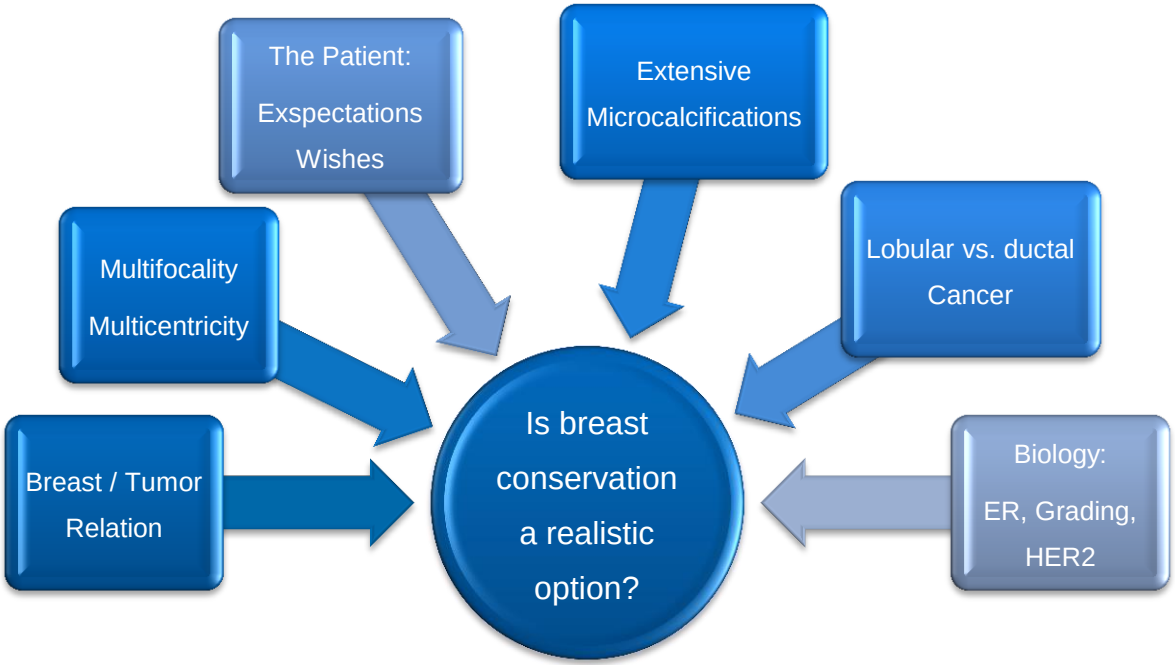


Ataseven, et al., Ann. Surg. Oncol. 2015

How to perform surgery in the context of NAC

- 3 essential time points in multidisciplinary treatment
  - Diagnostics BEFORE neoadjuvant therapy
  - Assessment of treatment response
  - Pre-/Intraoperative marking and assessment

Factors influencing BCS vs. Mastectomy



How to safely perform BCT after NAC

- Exact documentation of tumor spread
  BEFORE, DURING and AFTER neoadjuvant therapy
- Clip-Marking at Biopsy:
  multifocality, DCIS, small tumors

MRI – the surgeon`s view

- Meta-analysis 44 studies – 2050 patients
- Good assessment, if residual tumor is present
- Overestimation of residual tumor spread
- Better accuracy than mammography
- Comparable accuracy to ultrasound

- Combination of clinical examination, mammography and ultrasound is sufficient for planning of surgery in most cases
- Key to optimal planning ist multidisciplinary assessment – and probably not MRI for all

Marinovich et al., BJC 2013
Marinovich et al., JNCI 2013

Target volume for resection – recommendations from BIG-NABCG

- Multidisciplinary care is essential – before, during, after NAT
- Preoperative imaging according to stage at presentation, use the method(s), that were initially helpful
- Surgical resection is planned and conducted according to imaging immediately before surgery
- All detectable residual disease should be removed
- In case of pCR: remove the center of the tumorbed including any clips…and place new clips for radiotherapy

Bossuyt et al., Ann Oncol 2015
Chagpar et al., Ann Surg 2006

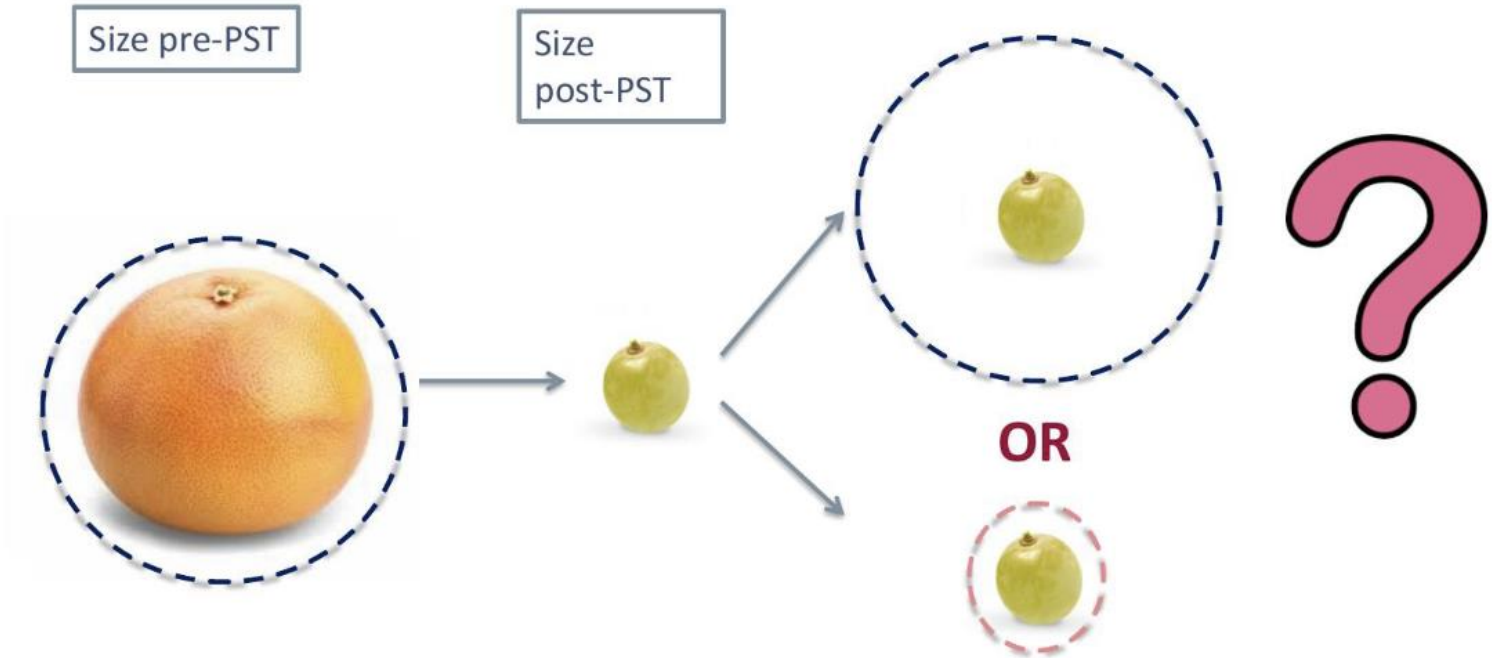
Preoperative and intraoperative Localization

- Localization Techniques
  - Wire guided techniques (intra- or preoperative)[1]
  - Radio guided occult lesion localization (ROLL)[1]
  - Carbon marking[2]
  - Clips with bio-resorbable material[3]
  - I^{125} seeds[4]
  - ……
  - **Intraoperative ultrasound[5]**

[1]Sajid et al, J. Surg. Oncol 2012
[2]Canavese et al., EJSO 1995
[3]Eby PR et al. , Acad. Radiol 2010
[4]Van der Noordaa et al., Eur J Surg Oncol 2015
[5]COBALT trial, Krekel et al Lancet Oncol. 2013

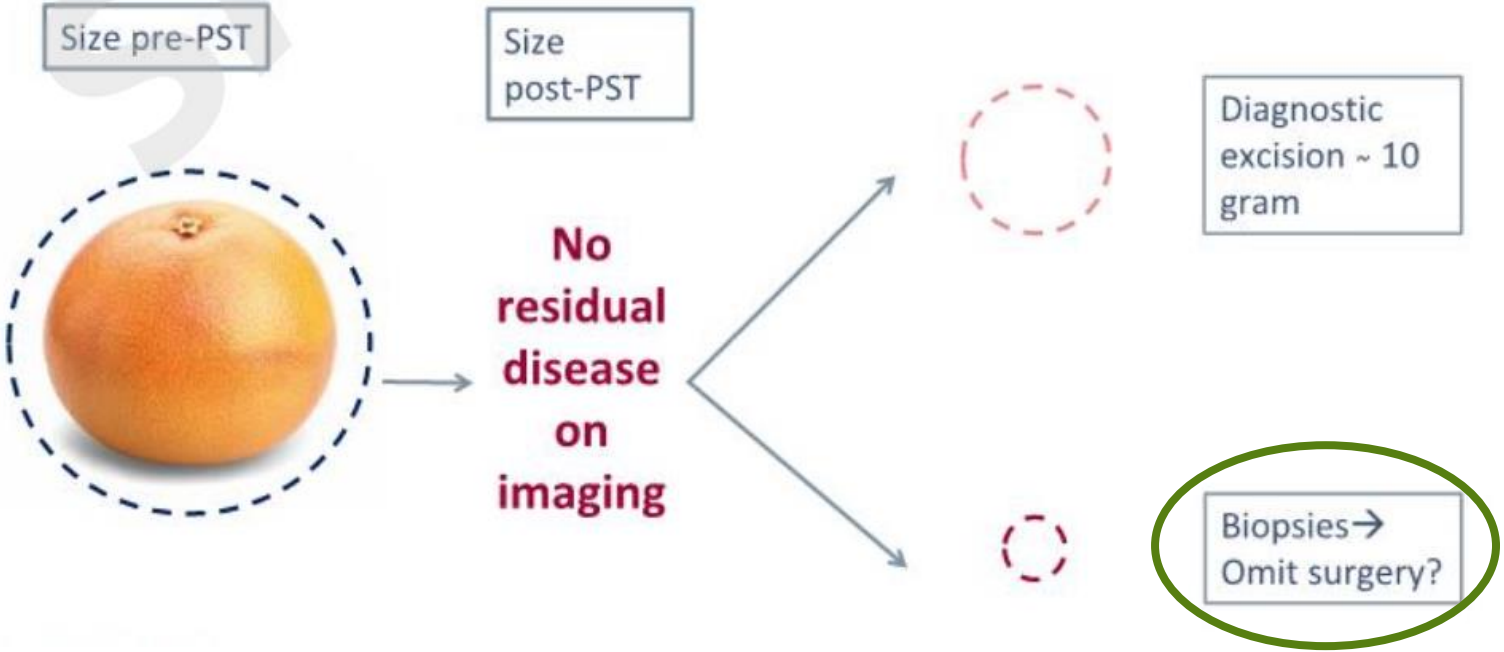
Can we omit surgery in the near future?

DE-ESCALATION OF LOCAL TREATMENT AFTER PST



Vrancken Peeters et al., SABCS 2019, GS5-06

DE-ESCALATION OF LOCAL TREATMENT AFTER PST



Vrancken Peeters et al., SABCS 2019, GS5-06

Biopsy instead of operation?

4 similar studies presented at SABCS 2019:

1. Responder Germany – Jörg Heil
2. London/Seoul/MD Anderson – Marios Tasoulis
3. NRG BR005 USA – Mark Basik
4. MICRA Amsterdam – Marie Jeanne Vrancken Peeters

Pilot studies VAB after NAC

Minimal invasive, image guided **vaccuum-assisted biopsies** showed promising results

Study site	women	FNR
Houston, MDACC	40	5%
Seoul	40	10%
London, RMH	53	0%
Heidelberg	50	5%

Heil et al., SABCS 2019, GS5-03

Primary endpoint: false-negative rate <10%

	image-guided VAB	
	VAB +	VAB -
surgery + (n=208)	171	37
surgery - (n=190)	28	162
FNR (95% CI)	17.8% (12.8-23.7)	

➡ Early trial discontinuation after 398/476 patients

Heil et al., SABCS 2019, GS5-03

Pooled Analysis – Royal Marsden/Seoul/MD Anderson

- Problematic patient population:
  - 17% T3 cancers
  - 23% multifocal or multicentric
  - 14% core needle biopsy
  - Number of biopsies: median 6 (2-18)

- False-negative rate: 18.7%

Tasoulis et al., SABCS 2019, GS5-04

NRG-BR005 – Results

Biopsy Findings	Residual Disease at Surgery		Total
	Yes (non-pCR)	No (pCR)	
Positive	18	0	18
Negative	18	62	80
Total	36	62	98

Negative Predictive Value (95% CI) = **77.5%** (66.8 to 86.1%)

Sensitivity (95% CI) = **50.0%** (32.9 to 67.1%)

Basik et al., SABCS 2019, GS5-05

NRG-BR005 – Discussion

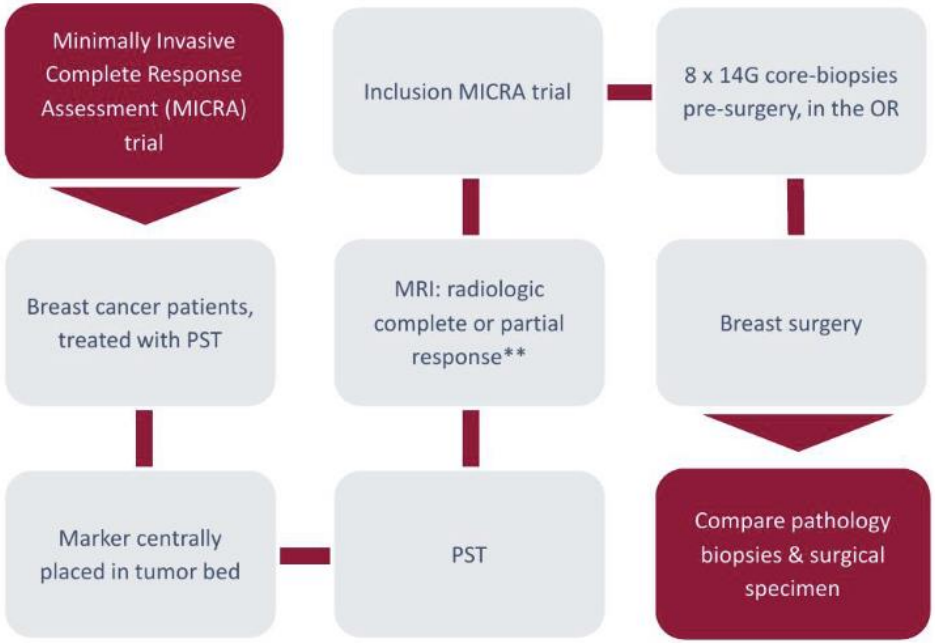
- Problematic patient population
  - 22% receptor-positive cancers (NPV 46%)
  - 10% multifocality
  - Often only 1-5 core needle biopsies

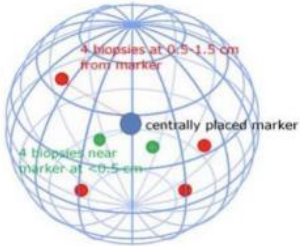
- False-negative rate 18.4%
- Discontinuation after 98/175 patients

Basik et al., SABCS 2019, GS5-05

MICRA - Amsterdam

- Target accrual: 525 patients
- 14G core biopsies after NAC





Vrancken Peeters et al., GS5-06

MICRA - Results

	specimen neg	specimen pos	
biopsy neg	89	29	118
biopsy pos	0	49	49
	89	78	167

- False-negative rate 37% - Discontinuation after 167/525 patients
- In 10% of patients the clip was not found

Vrancken Peeters et al., GS5-06

Problems of these 4 studies

	Responder	Poole Analys
Imaging without MRI	X	X
Any tumor biology (HR+)	X	X
Multifocality	X	X
Core needle biopsies		X
T3 tumors	X	X
Partial remission	X	X
Lobular cancers	X	X
Few biopsy cylinders	X	X

Has the question been answered definitely?

Vrancken Peeters et al., GS5-06

Can the Swiss and Austrian do better? SAKK 23/18 VISION I

- Protocol development included radiologists and pathologists
- No multicentricity allowed
- Only T1 and T2 cancers
- No Microcalcifications >2cm
- MRI is mandatory – no residual tumor
- Hydromark Clip recommended
- Correlation with response in the axilla
- Only complete remissions at MRI included for primary analysis
- Training workshops for all centers
- Vacuum-assisted biopsies only with strict QA-program:
  Number and technique of VAB standardized

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ABCSG
AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

PI: Christoph Tausch

What to do with the axilla after neoadjuvant therapy?

Sentinel Node Biopsy after Neoadjuvant Chemotherapy

ACOSOG Z1071:
SNB after NAC in cN1 – ycN0

- 649 patients: T0-4 N1-2 with neoadjuvant chemotherapy
  in 136 centers: 7/2009 – 6/2011: prospective **phase II** study
- 1.5 patients / year / center
- SLN identification rate 92.9%, pCR in lymph nodes: 41%
- False-negative rate in total: **12.6% = negative study**, goal: <10%

  FNR 31.5%

  FNR 21%

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Boughey et al., JAMA 2013

SENTINA: SNB after NAC in N1

	Arm B (n=64)	Arm C (n=226)
Overall false-negative rate (n/N; 95% CI)	51·6% (33/64; 38·7–64·2)	14·2% (32/226; 9·9–19·4)
False-negative rate, according to number of sentinel nodes removed		
1	66·7% (16/24)	24·3% (17/70)
2	53·8% (7/13)	18·5% (10/54)
3	50·0% (5/10)	7·3% (3/41)
4	50·0% (3/6)	0·0% (0/28)
5	18·2% (2/11)	6·1% (2/33)
False-negative rate, according to detection technique		
Radiocolloid alone	46·2% (18/39)	16·0% (23/144)
Radiocolloid and blue dye	60·9% (14/25)	8·6% (6/70)

Kühn et al., Lancet Oncol 2013

SNB only in cN1 – ycN0: a small note of caution

- Two studies: Z1071 and SENTINA: together 875 patients
- **BOTH studies were NEGATIVE:** false-negative rates 13 - 14%

- Sentina: not randomized, prospective cohort study
- Z1071: not randomized, phase II study
- Retrospective subgroup analyses

- [illegible] outcome and safety are not [illegible]hed!

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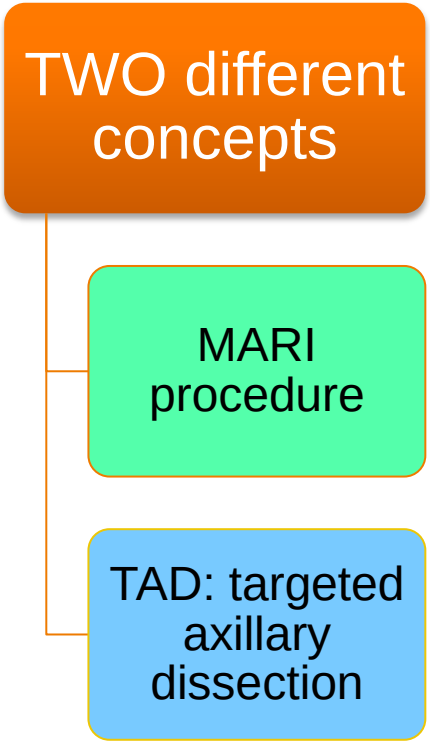
Methods to improve diagnostic accuracy: Clipping lymph nodes



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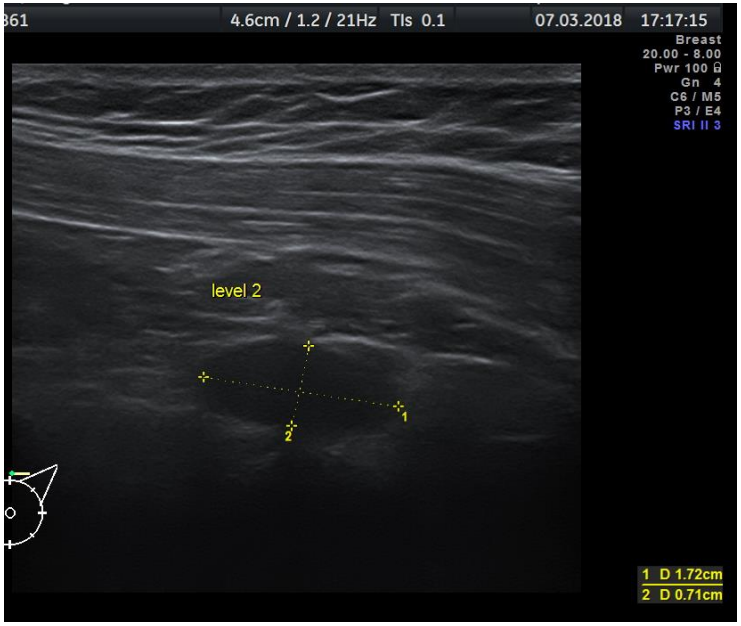
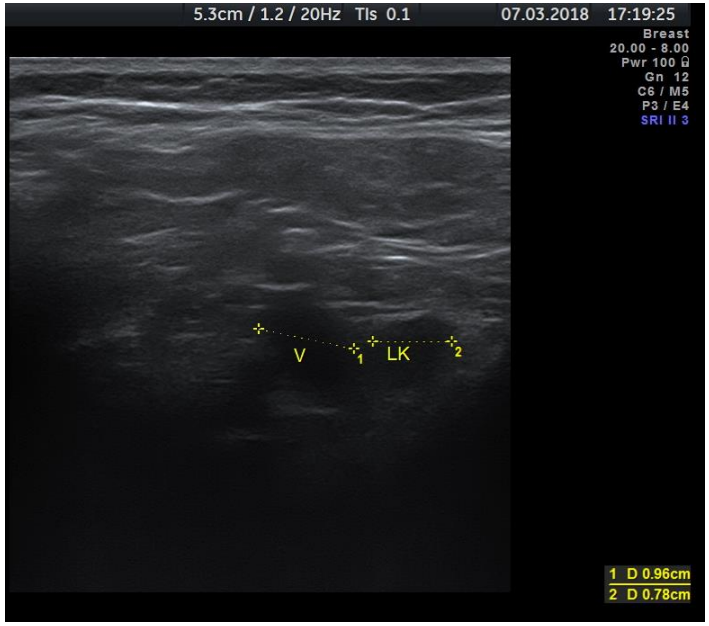
Biopsy and Clip placement in suspicious nodes





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07/09/17 17:19:36 ADM 1000511221, 08/11/66 Female Breast
FR 21
AO% 100
1 L 1.25 cm
LOGIQ S8
07/09/17 17:28:30 ADM 1000511221, 08/11/66 Female Breast
FR 21
AO% 100
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07/09/17 17:28:39 ADM 1000511221, 08/11/66 Female Breast
FR 21
AO% 100
SoS 1500
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LOGIQ S8
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1 L 0.99 cm
2 L 0.65 cm
1000511221 2.6cm / 1.1 / 28Hz TIs 0.1 27.12.2017 09:43:52
Breast
20.00 - 8.00
Pwr 100
Gn 12
Clip
L

Results MARI procedure – I^{125} seeds

MARI procedure

- 100 patients
- Duration of seed in place: 17 weeks (9 – 31)
- Detection rate: 97% (3% misplacement outside of lymph node)
- Activity at surgery: 0.006 – 0.06 mCi
- Operative time for MARI node: 6 min. (3 – 20)
- pCR rate of lymph nodes = downstaging: 26%
- Overall accuracy: 95%
- False-negative rate: 7%

Donker et al., Ann Surg 2015

Results TAD

TAD: targeted axillary dissection

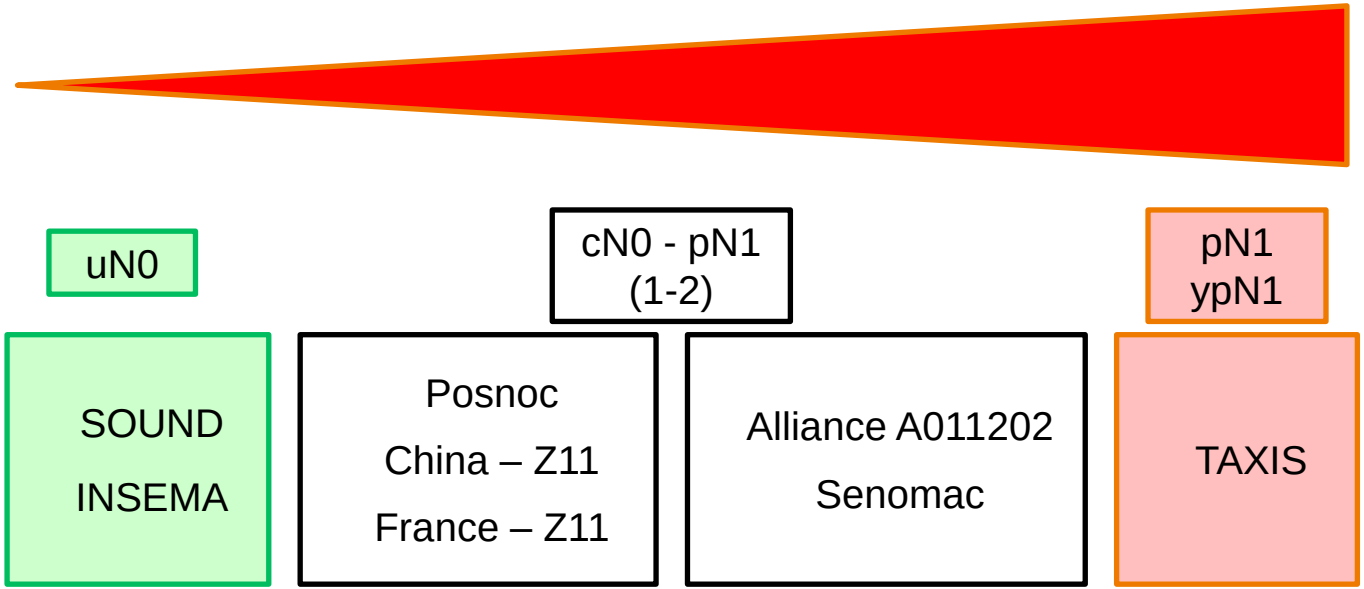
- pCR in lymph node: 37%
- If ≥ 4 nodes were abnormal on ultrasound, in 41% the clipped node was not among the sentinel nodes
- only sentinel node removed ≈ Z1071: FNR 10.6%
- only clipped node removed ≈ MARI: FNR 4.2%
- Sentinel + clipped node: FNR 2.0%

Caudle et al., JCO 2016

Critical comments

- Small single-center case-series
- Feasible in some centers of excellence
- Multiple interventions per patient
- Technical problems to identify or locate the clip

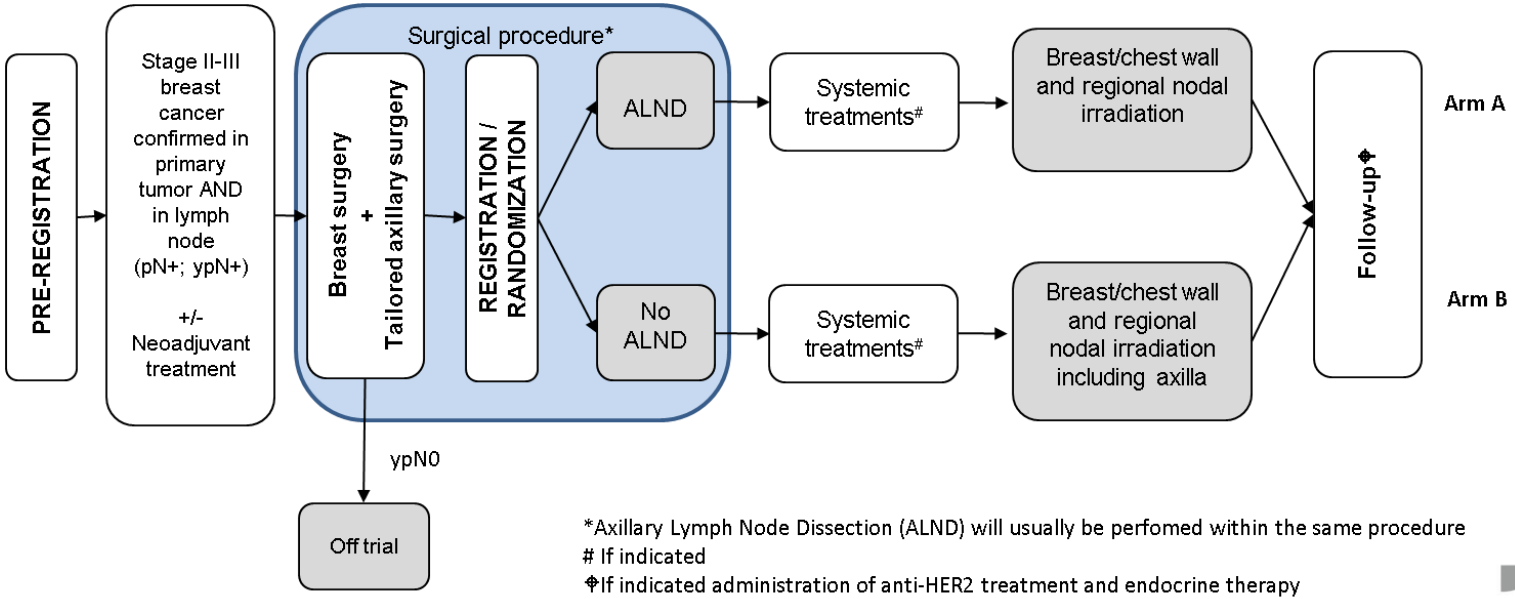
The whole spectrum of risk is being evaluated in clinical trials worldwide



SAKK 23/16: Tailored AXIllary Surgery with or without ALND followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS)
A multicenter randomized phase III trial

Coordinating investigator: Walter P. Weber

Supporting coordinating investigator: Michael Knauer



*Axillary Lymph Node Dissection (ALND) will usually be perfomed within the same procedure
If indicated
⌖If indicated administration of anti-HER2 treatment and endocrine therapy

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SAKK 23/16 – TAXIS: Design

- Non-inferiority study: Tailored axillary surgery and radiotherapy are equally effective as axillary dissection

Endpoints:

- 1. DFS
- QoL
- OS, BCSS, local recurrence, regional recurrence
- Morbidity (lymphedema, shoulder function etc.)
- Infections
- Radiotherapy-associated long-term morbidity
- TransTAXIS: translational portfolio

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Conclusions – Surgery of the primary tumor

- Neoadjuvant therapy is not a risk factor for local failure
- Resection within the new margins after NAC seems to be safe and is a major goal in multidisciplinary treatment
- No patient should be excluded from BCS, as long as negative margins can be obtained
- Surgeons have to learn to trust in the capabilities of neoadjuvant therapies to reduce the extent of surgery for better cosmetic outcomes without oncologic compromise.

Conclusions – Surgery of the primary tumor

Involvement of the surgical oncologist at 3 time points:

- Diagnostic assessment
- Response assessment
- Intraoperative assessment

- Surgical teams have to develop their “in-house standard” of localization and margin assessment

- (Very) Limited Level of Evidence
- Inclusion of surgical questions into clinical trial planning is necessary

Conclusions – Surgery of the Axilla

- Axillary staging is increasingly being recognized as a more diagnostic than therapeutic procedure
- SNB after NAC in cN0 – ycN0 is standard
- SNB after NAC in cN1 – ycN0 including targeted approaches has been implemented in most centers
- SNB after NAC in ypN1 (even micrometastases) is contraindicated in clinical routine
- Locoregional trials are ongoing

Thank You

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