3. Leipziger Post SABCS
Neues zur lokoregionären Therapie – operative Therapie
22.01.2020

Susanne Briest

Klinik und Poliklinik für Frauenheilkunde
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Universitätsklinikum Leipzig
Anstalt öffentlichen Rechts

Offenlegung der möglichen Interessenskonflikte

Honoraria für Vorträge, Teilnahme an adboards und Reiseunterstützung von folgenden Firmen:

Pfizer, Teva, Novartis, AstraZeneca, Roche, Janssen, Pierre Fabre, Amgen, Daiichi Sankyo, Lilly, MSD, Eisai, genomic health

Evaluation of Pathologic Response after Neoadjuvant Chemotherapy

K.P. Siziopikou, MD, PhD
Professor of Pathology
Director of Breast Pathology
Director of Breast Pathology Fellowship Program
Northwestern University
Robert H. Lurie Comprehensive Cancer Center
Chicago, IL

SAN ANTONIO BREAST CANCER SYMPOSIUM®

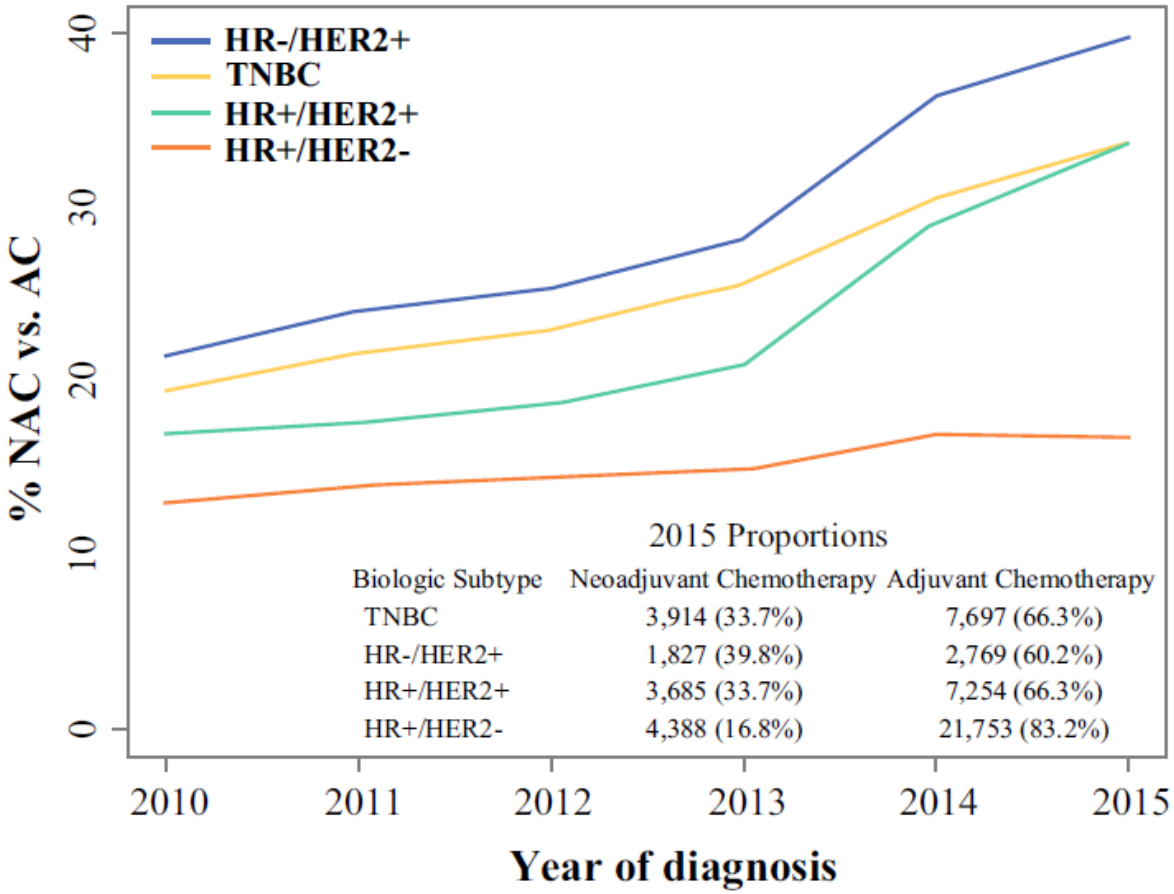
Ziele der neoadjuvanten Chemotherapie

Downstaging
Inoperabel – operabel
Mastektomie – Brusterhaltung
Vermeidung der ALND

Erfassung des Ansprechens

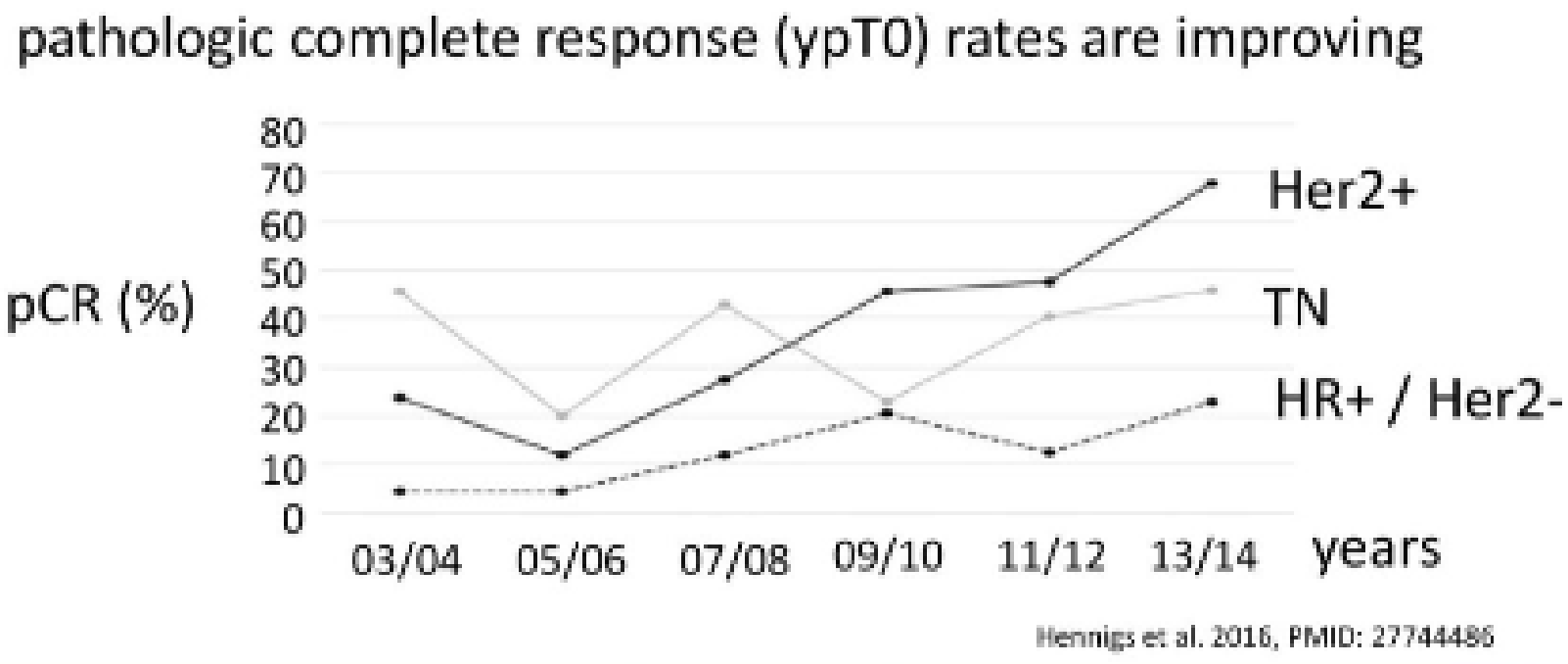
Evaluierung des Ansprechens als Prognosefaktor

Hintergrund I



Murphy et al. 2018, Heil et al. SABCS 2019

Hintergrund II



Hennigs et al. 2016, Heil et al. SABCS 2019

Hintergrund III

Die Bildgebung ist nicht zuverlässig geeignet, die Remission nach einer neoadjuvanten Chemotherapie zu beurteilen.

Kuerer et al. 2017, Rauch et al. 2017, Fowler et al. 2017, Schaefgen et al. 2016, Heil et al. SABCS 2019

pCR

abhängig vom Tumortyp

höher für TNBC und HER2 positive Tumore

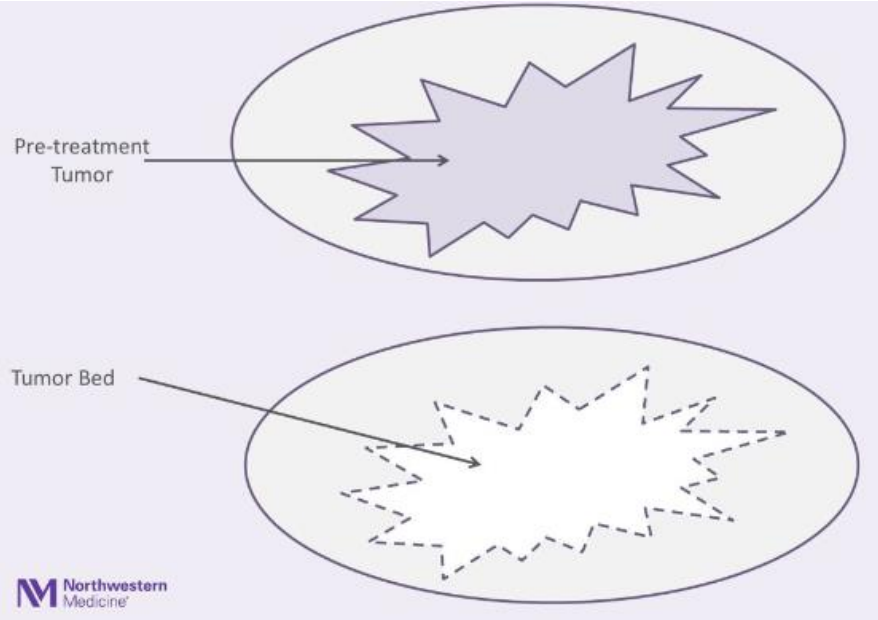
geringer für HR positive Tumore und lobuläre Ca

	HR-/HER-	HR-/HER2+	HR+/HER2+	HR+/HER2-
pCR rates	30-40%	35-50%	15-30%	<10%
LN conversion	50%	45-65%	35%	10-20%

Mrkonjic et al. J lin Pathol, 2019

Arten der Veränderung des Tumors unter neoadjuvanter Chemotherapie

1. pCR – pathologische komplette Remission



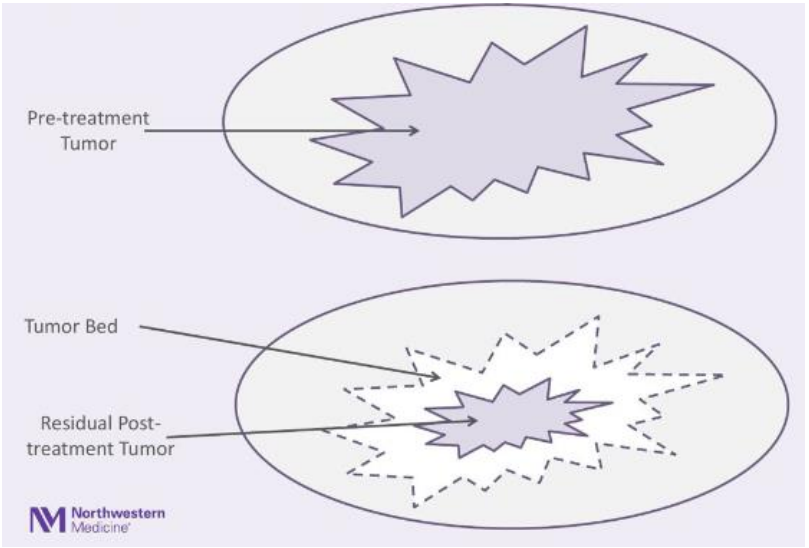
Tumorbett:
Fibrose, Ödem
Chronische Entzündung
Schaumzellen
Ablagerung von Hämosiderin
Erhöhte Vaskularisierung
Mikroverkalkungen

Siziopikou SABCS 2019

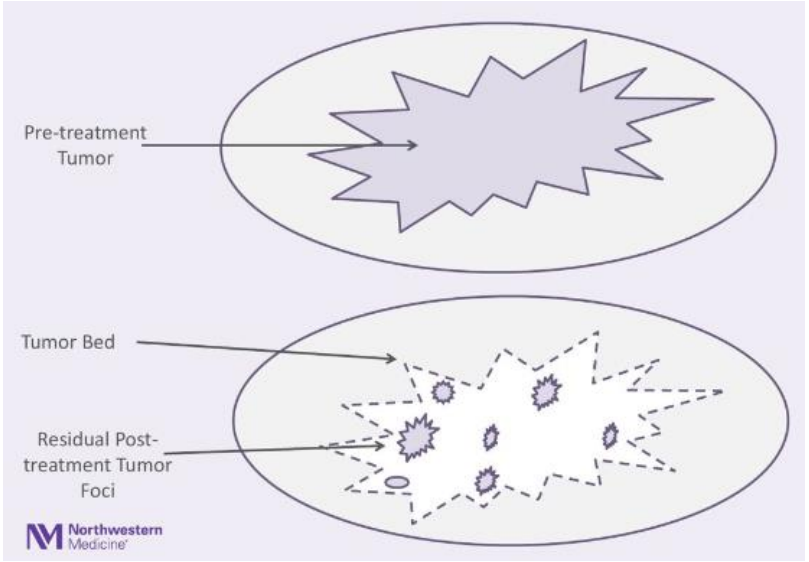
Arten der Veränderung des Tumors unter neoadjuvanter Chemotherapie

2. Partielle Remission

konzentrisches Schrumpfen



„Schweizer-Käse“ Muster



Siziopikou SABCS 2019

Arten der Veränderung des Tumors unter neoadjuvanter Chemotherapie

Residueller Tumor:
Keine Änderung des intrinsisches Subtyps
Verminderung der Zellularität
Größere Zellen, reichlich Zytoplasma
Größere Zellkerne, zahlreiche und polymorphe Zellkerne
Chronische Entzündung
Retraktion des Stromas um den residuellen Tumor

Zusätzlich:
Rezeptorstatus kann sich ändern unter neoadjuvanter Chemotherapie
ER bis 15%, PR bis 30%, HER2 bis zu 10% Jabbour et al. BCRT 2012, Zhang et al. Cancer Invest 2011

Tumorheterogenität, Technische Probleme, Therapieeffekt – clonale Selektion, Plastizität des residuellen Tumor bedingt durch den Therapiedruck

Siziopikou SABCS 2019

Klassifikation der Tumorremission unter neoadjuvanter Chemotherapie

	Definition of pCR	Is presence of DCIS only OK for pCR?	Requirement for pre/post comparison
Sinn et al, 1994	Breast and LNs	No	Yes
Sataloff et al, 1995	Breast and LNs	Yes	Yes
Chevallier et al,1995	Breast and LNs	No	No
NSABP B-18, 2001	Breast Only	Yes	No
Miller-Payne, 2003	Breast Only	Yes	Yes
Pinder et al, 2007	Breast and LNs	Yes	Yes
Residual Cancer Burden (RCB), 2007	Breast and LNs	Yes	No
RDBN, 2008	Breast and LNs	Yes	No
AJCC ypTNM, 2017	Breast and LNs	Yes	No

Siziopikou SABCS 2019

De-escalating Surgery: Use of core biopsies to evaluate possible pCR after NAC; SABCS 2019 General Session 5

- **GS5-03. Diagnosing residual disease and pathologic complete response after neoadjuvant chemotherapy in breast cancer patients by image-guided vacuum-assisted breast biopsy: results of a prospective multicenter trial;** Heil J, Pfob A, Sinn H, Rauch G, Bach P, Schaefgen B, Weber W, Kuemmel S, Reimer T,Hahn M, Thill M, Blohmer J, Golatta M, RESPONDER Investigators. Department of Gynecology, University Hospital Heidelberg, Heidelberg, Germany; Department of Pathology, University Hospital Heidelberg, Heidelberg, Germany; Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute of Biometry and Clinical Epidemiology, Berlin, Germany; Department of Surgery, University Hospital Basel, Basel, Switzerland; Kliniken Essen Mitte (KEM), Breast Unit, Essen, Germany; Department of Gynecology, University Hospital Rostock, Rostock, Germany; Department of Gynecology, University Hospital Tuebingen, Tuebingen, Germany; Department of Gynecology, Agaplesion Markus Hospital Frankfurt, Frankfurt, Germany; Department of Gynecology, University Hospital Berlin, Berlin, Germany **(NO)**

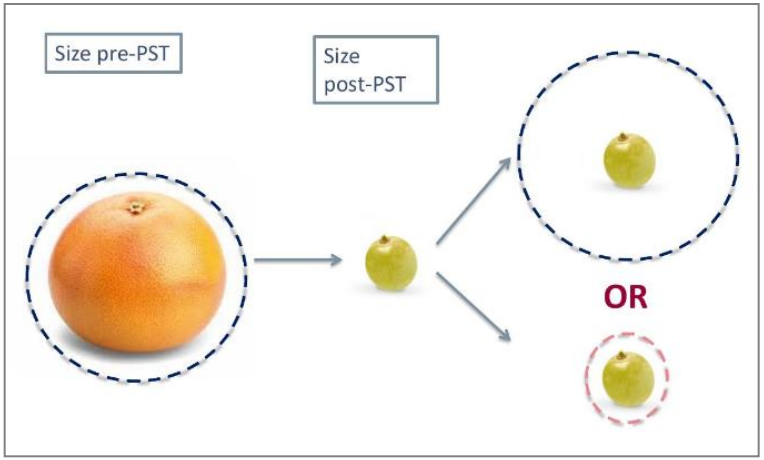
- **GS5-04. Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict the presence of residual cancer: A multi-institutional pooled analysis;** Tasoulis M, Lee H, Yang W, Pope R, Krishnamurthy S, Kim S, Cho N, Teoh V, Rauch GM, Smith BD, Valero V, Han W, Royal Marsden Hospital MDT, MacNeill F, Kuerer HM. The Royal Marsden NHS Foundation Trust, London, United Kingdom; Seoul National University Hospital, Seoul, Republic of Korea; The University of Texas MD Anderson Cancer Center, Houston, TX **(YES)**

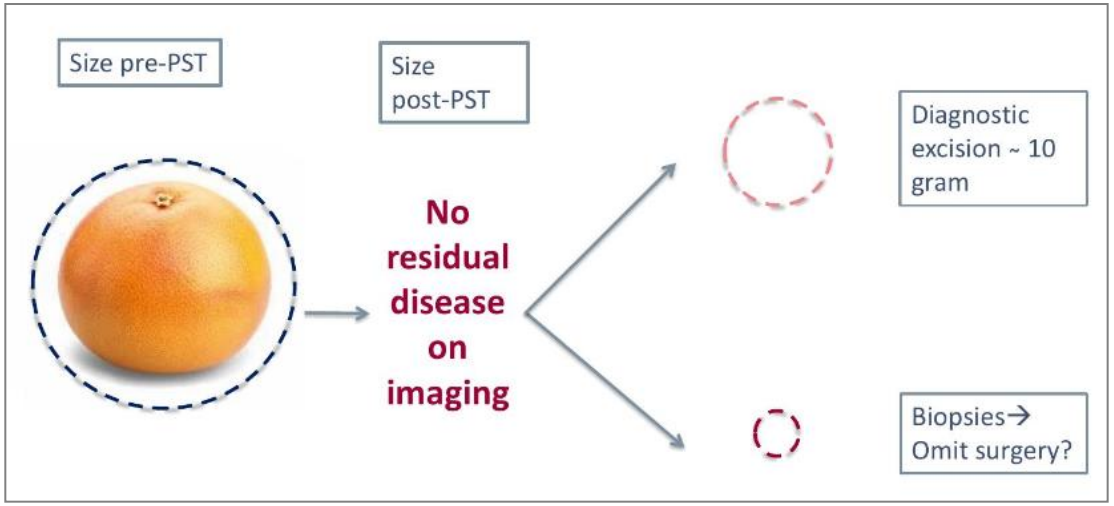
- **GS5-05. Primary analysis of NRG-BR005, a Phase II trial assessing accuracy of tumor bed biopsies in predicting pathologic complete response (pCR) in patients with clinical/radiological complete response after neoadjuvant chemotherapy (NCT) to explore the feasibility of breast-conserving treatment without surgery;** Basik M, Cecchini RS, De Los Santos JF, Umphrey HR, Julian TB, Mamounas EP, White J, Lucas PC, Balanoff C, Tan A, Weber JJ, Edmonson D, Brown-Glaberman U,Diego E, Teshome M, Matsen CB, Andrews Seaward S, Wapnir I, Wagner JL, Tjoe JA,Thompson AM, Wolmark N. NRG Oncology, Philadelphia, PA; University of New Mexico Comprehensive Cancer Center, Albuquerque, NM; ALLIANCE, and The University of Kansas Medical Center, Kansas City, MO; ECOG-ACRIN. and Advocate Aurora Health, Aurora Research Institute, Milwaukee, WI; SWOG, and Baylor College of Medicine, Houston, TX **(NO)**

- **GS5-06. Toward omitting breast surgery in patients with a pathologic complete response after neoadjuvant systemic treatment: interim analysis of the MICRA trial (Minimally Invasive Complete Response Assessment;** Vrancken Peeters MTFD, van Loevezijn A, van der Noordaa MEM, van Duijnhoven FH,Loo CE, van Werkhoven E, van de Vijver KK, Wiersma T, Winter-Warnars HAO, SonkeGS., Netherlands Cancer Institute **(NO)**

Northwestern Medicine

GS5-06 Toward omitting breast surgery in patients with a pathologic complete response after neoadjuvant systemic treatment: interim analysis of the MICRA trial (Minimally Invasive Complete Response Assessment)

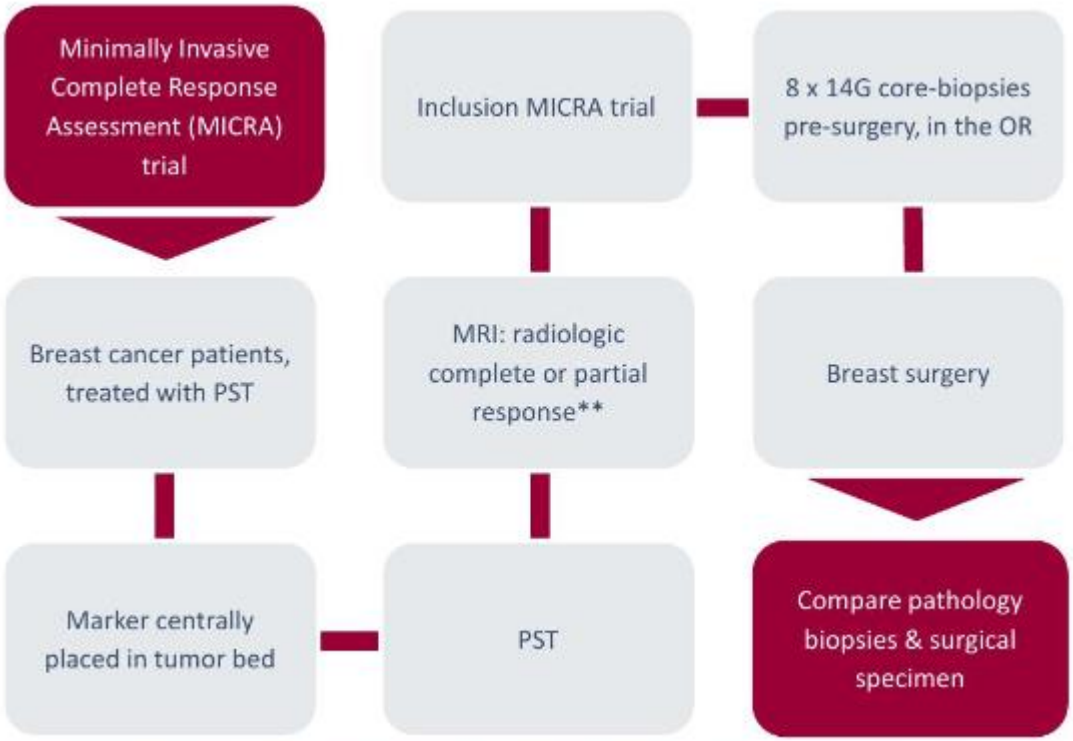




Peeters et al. SABCS 2019

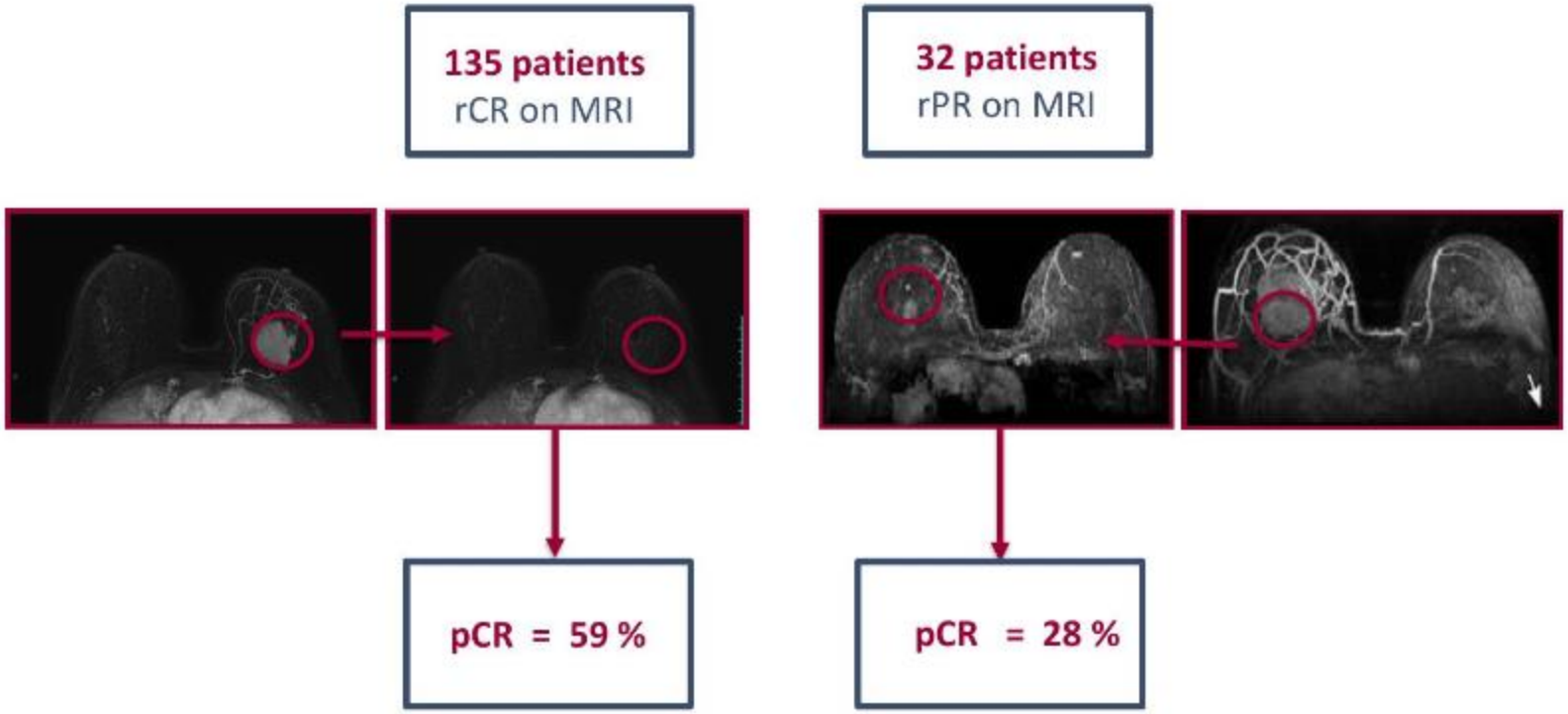
MICRA

Design:
Prospektive Beobachtungsstudie
525 Pat 371 mit kompletter Remission in der Bildgebung (rCR)
150 Pat mit rPR
Ziel:
Definition der Falsch negative Rate für die Biopsiemethoden



Peeters et al. SABCS 2019

MICRA - Ergebnisse



Peeters et al. SABCS 2019

MICRA - Ergebnisse

	Complete response MRI (n = 135)	Partial response MRI (n = 32)	Total (n = 167)
Pathological response surgical specimen*			
no residual carcinoma	80 (59%)	9 (28%)	89 (53%)
no residual invasive but DCIS	8 (6%)	0	8 (5%)
minimal residual disease, <10%	31 (23%)	8 (25%)	39 (23%)
10-50% of tumour remaining	11 (8%)	12 (38%)	23 (14%)
>50% of tumour remaining	3 (2%)	3 (9%)	6 (4%)
no-evidence of response	1 (1%)	0	1 (1%)
Only LVSI present	1 (1%)	0	1 (1%)

* Miller-Payne classification Breast 2003;12(5):320-327

Peeters et al. SABCS 2019

MICRA - Ergebnisse

	specimen neg	specimen pos				
biopsy neg	89	29	118	FNR=	29/78	37%
biopsy pos	0	49	49	FOR=	29/118	24%
	89	78	167			

False negative rate (FNR) = 1 - Sensitvity:

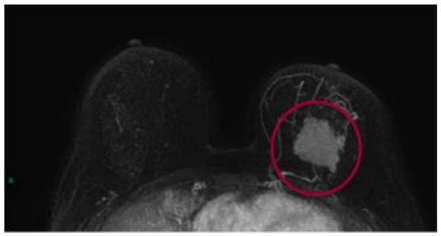
Σ False negative/Σ Condition positive = **37% (29/78)**

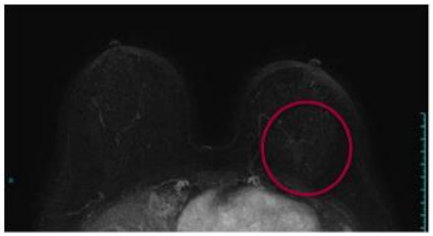
Relative chance of a negative test when residual disease in present in the specimen

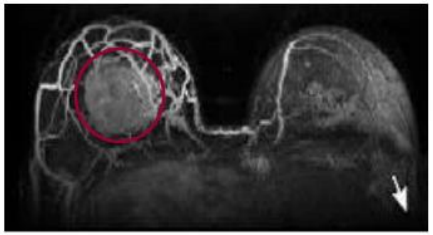
False omission rate (FOR) = 1 - NPV:

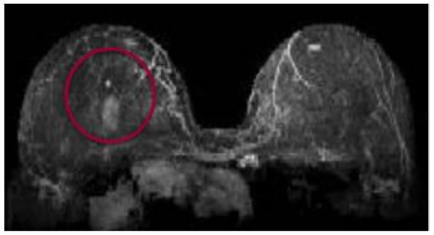
Σ False negative/Σ Predicted condition negative = **24 % (29/118)**

Relative chance of residual tumor in the specimen when the biopsie is negative









	specimen neg	specimen pos				
biopt neg	80	26	106	FNR=	26/55	45 %
biopt pos	0	29	29			
	80	55	135			

	specimen neg	specimen pos				
biopt neg	9	3	12	FNR=	3/23	13 %
biopt pos	0	20	20			
	9	23	32			

Peeters et al. SABCS 2019

MICRA – Zusammenfassung

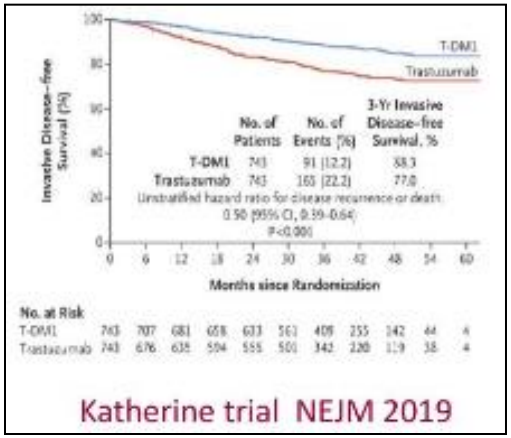
MRT ist nicht genau genug, um eine pCR vorauszusagen
14G Nadel ist nicht ausreichend

Residueller Tumor wird häufig übersehen

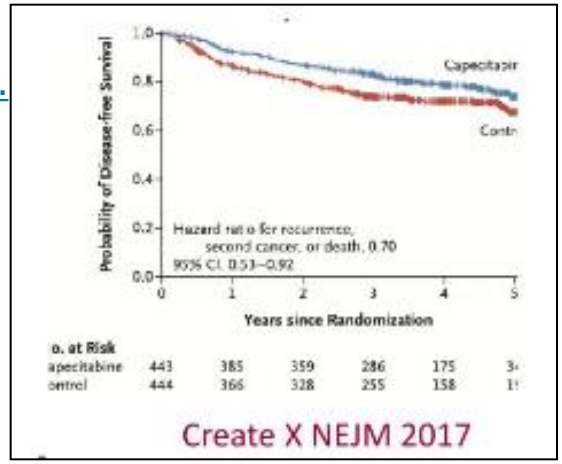
Die Ergebnisse unterstützten nicht den Verzicht auf die brusterhaltende Therapie auf der Basis der Ergebnisse der Bildgebung und der Tumorbettbiopsie.

Problem:
Vom pCR Status hängt die postneoadjuvante Chemotherapie ab

bei HER2 positiver Pat.



bei HER2 negativer Pat.

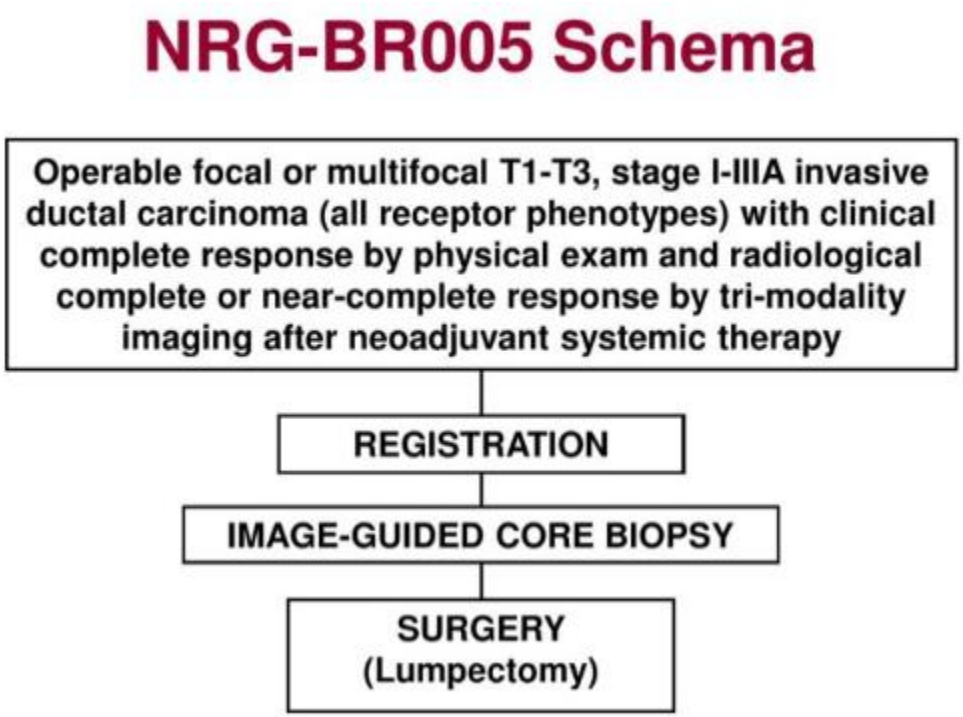


Peeters et al. SABCS 2019

GS5-05 Primary analysis of NRG-BR005, a Phase II trial assessing accuracy of tumor bed biopsies in predicting pathologic complete response (pCR) in patients with clinical/radiological complete response after neoadjuvant chemotherapy (NCT) to explore the feasibility of breast-conserving treatment without surgery

Basik et al. SABCS 2019

GS5-05 Primary analysis of NRG-BR005, a Phase II trial assessing accuracy of tumor bed biopsies in predicting pathologic complete response (pCR) in patients with clinical/radiological complete response after neoadjuvant chemotherap breast-conserving tr



Basik et al. SABCS 2019

Definitionen des primären Endpunktes

San Antonio Breast Cancer Symposium Dec. 10-14, 2019

Primary Endpoint Definitions

Biopsy Negative Predictive Value (NPV):

$$NPV = \frac{\text{number of patients with a negative biopsy and confirmed pCR at surgery}}{\text{total number of patients with a negative biopsy}}$$

Biopsy Sensitivity:

$$Sensitivity = \frac{\text{number of patients with a positive biopsy who had residual tumor at surgery}}{\text{total patients with residual tumor at surgery}}$$

NRG ONCOLOGY

Basik et al. SABCS 2019

NRG-BR005 – Ergebnisse

2017 – 2019
105 Pat eingeschlossen
98 Pat auswertbar (4 Pat lehnten CNB ab, 3 hatten noch keine CNB/Op)
36 Pat hatten eine non- pCR – zu hoch für die zuvor für die primäre Analyse festgelegte Zahl an non-pCR's

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%)

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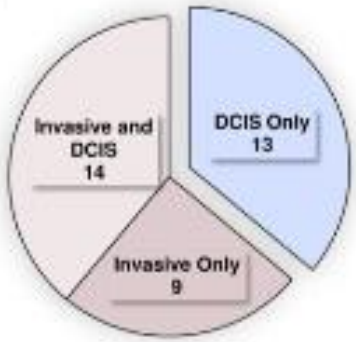
NRG-BR005 – Ergebnisse

NPV and Sensitivity of Biopsy by Baseline Tumor Subtype

Baseline Tumor Subtype*	# of Pts	# Patients with Residual Tumor	Negative Predictive Value (95% CI)	Sensitivity (95% CI)
Triple Negative	31	11	**74.1%** (53.7 to 88.9%)	**36.4%** (10.9 to 69.2%)
HR+/HER2–	21	15	**46.2%** (19.2 to 74.9%)	**53.3%** (26.6 to 78.7%)
HER+	44	10	**89.5%** (75.2 to 97.1%)	**60.0%** (26.2 to 87.8%)

*Two patients with equivocal HER2 are excluded

Type of Residual Disease



Comparison of Pathologic Findings from Biopsy and Surgery including only Invasive Disease as a Modified Endpoint for Residual Disease

Biopsy Findings	Residual Disease at Surgery: Yes (non-pCR)	Residual Disease at Surgery: No (pCR)	Total
Positive	14	1	15
Negative	9	74	83
Total	23	75	98

Negative Predictive Value (95% CI) = **89.2%** (80.4 to 94.9%)

Sensitivity (95% CI) = **60.9%** (38.5 to 80.3%)

Basik et al. SABCS 2019

NRG-BR005 – Zusammenfassung

Die Biopsie des Tumorbettes nach neoadjuvanter Chemotherapie erreichte nicht den negativen prädiktiven Wert von ≥90%.

Durch die Biopsie konnten 50% der Patientinnen identifiziert werden, die einen residuellen Tumorzum zum Zeitpunkt der Operation hatten.

Die Ergebnisse unterstützten nicht, die brusterhaltende Therapie auf der Basis der Ergebnisse der Bildgebung und der Tumorbettbiopsie zu indizieren.

Basik et al. SABCS 2019

GS5-04 Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict the presence of residual cancer: A multi-institutional pooled analysis

Tasoulis et al. SABCS 2019

The ROYAL MARSDEN NHS Foundation Trust

SNUH Seoul National University Hospital

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict residual cancer: a multi-institutional pooled analysis

Marios Konstantinos Tasoulis, Han-Byoel Lee, Wei Yang, Romney Pope, Savitri Krishnamurthy, Soo-Yeon Kim, Nariya Cho, Victoria Teoh, Gaiane M. Rauch, Benjamin D. Smith, Vicente Valero, Wonshik Han, Fiona MacNeill, Henry M. Kuerer

Universitätsklinikum Leipzig
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Results: diagnostic accuracy

% (95% CI)

	All histologic types (N=159)*	Invasive ductal carcinoma				
		All subtypes (N=153)	HR+/HER2- (N=25)	HR+/HER2+ (N=40)	HR-/HER2+ (N=29)	HR-/HER2- (N=59)
False Negative Rate	18.7 (9.8 – 26.8)	17.4 (8.4 – 25.4)	10 (0 – 32.2)	15 (0 – 30.6)	33.3 (2.5 – 53)	11.8 (0 – 23.5)
Negative Predictive Value	84.3 (76.7 – 91.8)	86.2 (79 – 93.4)	71.4 (38 – 100)	85 (69.3 – 100)	86.36 (72 – 100)	93.1 (83.9 – 100)

* 7 patients had non-representative image-guided biopsy and were excluded from the analysis

Tasoulis et al. SABCS 2019

Ergebnisse

Geplante Subgruppenanalyse:

N=76
Pat mit invasiv lobulärem Ca ausgeschlossen
Biospie bei allen Pat., die eine Auffälligkeit in der Bildgebung hatten, die ≤2 cm war
alle Pat erhielten eine VSB
mehr als 6 repräsentative Biopsien

Tasoulis et al. SABCS 2019

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Key Results

Planned Subgroup analysis

	All subtypes (N=76)	HR+/HER2- (N=10)	HR+/HER2+ (N=21)	HR-/HER2+ (N=11)	HR-/HER2- (N=34)	HER2+ and HR-/HER2- (N=66)
	% (95% CI)					
False Negative Rate	3.2 (0 – 8.8)	0 (0 – 0)	10* (0 – 29.6)	0 (0 – 0)	0 (0 – 0)	4.2 (0 – 10.7)
Negative Predictive Value	97.4 (84.6 – 99.6)	100 (100 – 100)	88.9 (68.4 – 100)	100 (100 – 100)	100 (100 – 100)	97.2 (83.6 – 99.6)
Sensitivity	96.8 (90.5 – 100)	100 (100 – 100)	90 (71.4 – 100)	100 (100 – 100)	100 (100 – 100)	95.8 (78.8 – 99.9)
Specificity	84.4 (73.8 – 95)	100 (100 – 100)	72 (46.4 – 99)	100 (100 – 100)	82.6 (67.1 – 98.1)	83.3 (68.6 – 93)
Overall Accuracy	89.5 (80.3 – 95.3)	100 (100 – 100)	80.9 (64.2 – 97.7)	100 (100 – 100)	88.2 (77.4 – 99.1)	87.9 (77.5 – 94.6)

* 1 patient missed (residual IDC < 1 mm)

Tasoulis et al. SABCS 2019

Zusammenfassung: Tasoulis et al.

Folgen Bildgebung und Biopsie nach neoadjuvanter Chemotherapie einem standardisierten Protokoll, kann residueller Tumor mit einer FNR von weniger als 5% vorausgesagt werden.

Ein standardisiertes Protokoll ist essentiell, um Studien zu entwerfen, die eine sichere Deeskalierung der chirurgischen Therapie untersuchen.

Tasoulis et al. SABCS 2019

GS5-03 Diagnosing residual disease and pathologic complete response after neoadjuvant chemotherapy in breast cancer patients by image-guided vacuum-assisted breast biopsy: results of a prospective multicenter trial

Heil et al. SABCS 2019


HEIDELBERG UNIVERSITY HOSPITAL
DFG Deutsche Forschungsgemeinschaft
December 13, 2019
SAN ANTONIO BREAST CANCER SYMPOSIUM
Diagnosing Complete Response in the Breast by Biopsy
Joerg Heil, André Pfob, Hans-Peter Sinn, Geraldine Rauch, Paul Bach, Bettina Thomas, Benedikt Schaefgen, Sherko Kuemmel, Toralf Reimer, Markus Hahn, Marc Thill, Jens-Uwe Blohmer John Hackmann,, Wolfram Malter, Inga Bekes, Kay Friedrichs, Sebastian Wojcinski, Sylvie Joos, Stefan Paepke, Nina Ditsch, Achim Rody, Regina Große, Marion van Mackelenbergh, Mattea Reinisch, Maria Karsten and Michael Golatta for the RESPONDER Investigators
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UK HD

Responder - Ergebnisse

N= 398

Ultrasound guidance	79%
Stereotactic guidance	21%
Mean number of samples	7
unclear representative biopsies by pathology	10%

VAB needles used	
• 10G	31%
• 9G	6%
• 8G	50%
• 7G	13%

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

Heil et al. SABCS 2019

Responder - Zusammenfassung

FNR der VSB war 17.8% im gesamten Kollektiv. Bei 37 von 208 Pat wurde der residuelle Tumor verpasst.

Aber: 51% hatten vermeidbare Gründe
Protokollverletzungen, (z.B. Pat mit Rezidiv randomisiert, multizentrischer Tumor mit unterschiedl Tumorbiologie)
Technische Probleme bei der Biopsie
Oder andere

Von den 37 Pat hatten 12 lediglich ein DCIS, bei 20 Pat war der Tumor kleiner 5 mm und bei 19 der 25 Patienten mit einem invasiven Tumor hatte der eine geringe Zellularität.

Heil et al. SABCS 2019

Zusammenfassung der 4 Studien

	MICRA Peeters et al	NRG-BR005 Basik et al.	Tasoulis et al.	Responder Heil et al.
NPV		77.5%	84.3%	
FNR	37%		18.7%	17.8%
Besonder-heiten		ypT0+ypTis	ypT0/is	

Es ist zu früh, auf eine Operation nach neoadjuvanter Chemotherapie zu verzichten.

Locoregional therapy targeted at the primary tumour improves overall survival in patients presenting with de novo stage IV metastatic breast cancer: A systematic review and meta-analysis of real-world data with 201598 patients

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ABSTRACT

Background:
De novo stage IV metastatic breast cancer is a complex disease that is traditionally treated using systemic therapy. There is mounting evidence that locoregional therapy (LRT), defined as resection of the primary tumour and/or localised radiotherapy, could be associated with survival improvements. We aimed to conduct a meta-analysis to inform decision making.
Methods:
Using the PubMed, Cochrane and Ovid SP databases, a literature review and meta-analysis was undertaken to assess whether LRT of the primary tumour in metastatic breast cancer prolongs survival.
Results:
48 studies met the criteria for analysing the efficacy of all locoregional treatments (radiotherapy and/or surgery) and 44 studies were suitable for the analysis of surgery-only treatment of the primary. Studies were analysed for the impact of LRT on survival. All LRT resulted in a significant 32.9% reduction in mortality with LRT (N=48; HR=0.671: 95% CI 0.624-0.721). Primary resection alone resulted in a significant 36.9% mortality (N=44; HR=0.631: 95% CI 0.591-0.674).
Conclusions:
This is the largest meta-analysis regarding this question to date. LRT seems to improve overall survival in stage IV disease at initial diagnosis and should be considered in selected patients after a multidisciplinary discussion.

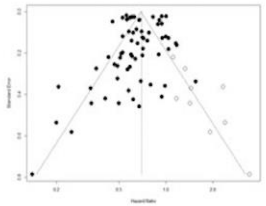
INTRODUCTION

De novo metastatic breast cancer has poor prognosis in affected patients and is commonly treated with palliative intent. However, the aim of this study was to determine whether locoregional surgery and/or irradiation of the breast could improve overall survival. We assessed combination locoregional therapy and surgical resection of the breast to determine the extent to which radiotherapy additionally influences overall survival outcomes. This is an update of a previously published meta-analysis by Mokbel et al (2016)[1], where analysis of sixteen studies resulted in the observation of a 37% mortality reduction associated with surgical resection of the primary tumour. We used a random effects model of statistical analysis to generate forest plots and also assessed for bias in included studies.

METHODS

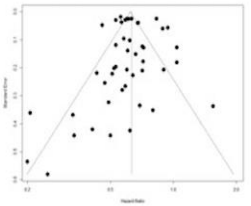
The PubMed, Cochrane, and Ovid SP databases were searched to find studies which were prospective clinical trials and retrospective studies examining adult patients diagnosed with histologically confirmed stage IV breast cancer and distant metastases. The study must have reported overall survival outcomes and 95% confidence intervals (CIs) of patients who had undergone surgical resection, radiotherapy, or no treatment of the primary tumour. Conservative and extended resections were also considered. Studies were excluded from the meta-analysis if: there was a failure to report hazard ratios (HRs) and 95% CIs for overall survival, the full text was not available for data extraction, and they were reviews/case reports/letters/commentaries. Cochran's Q test, $\chi 2$ test, and the I^2 statistic were used to assess and quantify statistical heterogeneity and the random effects model was used to report the overall HR.

RESULTS



Result 1: Funnel plot with Duval and Tweedie's trim and fill method to assess for bias in studies included in combined LRT of the breast vs no treatment analysis. There are a relatively large number of studies outside the 95% CI, indicating significant heterogeneity between reported results. **Duval and Tweedie's trim and fill suggests that 8 studies should be imputed to correct for asymmetry,** which are represented on the funnel plot using unpainted dots.

However, tests using Begg and Mazumdar Rank Correlation and Egger's calculations do not provide evidence for asymmetry or publication bias **(Begg and Mazumdar Rank Correlation Test, P=0.3007; Egger's test, P=0.6263)**. The Classic fail-safe N test (Rosenberg method) suggests that **as many as 48312 studies would be required to reduce the significance level of the pooled effect size to 5%.** Hence, **effect sizes were significant even in view of some publication bias.**



Result 2: Funnel plot with Duval and Tweedie's trim and fill method to assess for bias in studies included in surgery of the breast alone vs no treatment analysis. Although there are a relatively large number of studies outside the 95% CI, indicating significant heterogeneity between reported results, **Duval and Tweedie's trim and fill suggests that 0 studies need to be imputed** to correct for asymmetry.

Furthermore, tests using Begg and Mazumdar Rank Correlation and Egger's calculations do not provide evidence for asymmetry or publication bias **(Begg and Mazumdar Rank Correlation Test, P=0.2255; Egger's test, P=0.9120)**. The Classic fail-safe N test (Rosenberg method) suggests that **as many as 41173 studies would be required to reduce the significance level of the pooled effect size to 5%.** Hence, **effect sizes were significant even in view of some publication bias.**

RESULTS

Combined LRT of the breast results in a 32.9% risk reduction in mortality and surgery of the breast alone alone results in a 36.9% risk reduction in patients; both findings are highly significant. Patients with HER2/ER positive disease confined to the bone benefited more from LRT compared to patients with extensive visceral metastases and/or triple negative disease. Patients who respond well to systemic therapy derive greater benefit from LRT. Resectability of the tumor is also an important factor to take into consideration.

DISCUSSION

The underlying mechanisms that can explain our observations are most likely multifactorial and are likely related to the: removal of mammary circulating tumour cells (CTCs) within the primary tumour[2], interruption of the self-seeding process[3], and immunomodulation[4]. Although we found no evidence of publication bias, the selection bias of patients represents an important limitation in the studies included. We speculate that surgery alone shows a greater risk reduction because patients suffering from more aggressive disease, which is non-responsive to systemic therapy, are more likely to require breast irradiation along with/as an alternative to surgical resection. Prospective analyses from multiple clinical trials was not included due to their low accrual rate or paucity of data (NCT01906112, NCT01392586). As most of the data sets were retrospective, it is impossible to definitively state that no treatment to the axilla was administered.

CONCLUSIONS

LRT significantly improves overall survival of patients presenting with stage IV breast cancer at initial diagnosis. It should be considered in a multidisciplinary setting, particularly in patients with a good response to primary systemic therapy and a resectable tumor. Although the focus of this study was to examine the effect of LRT on the primary breast tumour, we recognize that surgery of non-primary sites is an important aspect of clinical care and it is unlikely that clinicians would operate on the breast in isolation. Greater investigation is required to determine the role of LRT in a palliative context. Another interesting avenue of future investigation would be to determine whether circulating tumour cells (CTCs) can be used to assess patient eligibility for LRT.

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P2-17-02

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OP des Primarius bei de novo disease

44/48 Studien

Surgery alone – no radiation

Unklar ist, ob eine axilläre Intervention durchgeführt wurde (retrospektive Studien)

Größter Vorteil bei HER2+/HR+

RESULTS

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