Lokoregionäre Therapie des Mammakarzinoms - Review of the year 2021-22

B. Gerber (Rostock)

Conflict of Interest: Kein

2019-2021

AB / Honorare / Kongresse : AZ, Pfizer, Novartis, Roche, Pierre Fabre, Lilly, MSD

Aktien: keine

Inhalte

- SINODAR One
- Re-BET nach BET und in-Brust-Rezidiv
- Intraoperativer Ultraschall
- Verzicht auf SLNE
- OP bei primär metastasiertem MaCa
- NAST: Wieviel OP zur Prediktion pCR erforderlich?
- Zusammenfassung

SINODAR-ONE = 1. Confirmation of ACOSOG Z0011

SAN ANTONIO BREAST CANCER SYMPOSIUM®

SABCS 2021 SAN ANTONIO BREAST CANCER SYMPOSIUM

December 7-10, 2021

HENRY B. GONZALEZ CONVENTION CENTER

SAN ANTONIO, TEXAS

HUMANITAS UNIVERSITY

Preservation of axillary lymph nodes compared to complete dissection in T1-2 breast cancer patients presenting 1-2 metastatic sentinel lymph nodes: A multicenter randomized clinical trial. SINODAR-ONE

Damiano Gentile, MD; *Wolfgang Gatzemeier, MD; Erika Barbieri, MD; Andrea Sagona, MD; Alberto Bottini, MD; Valentina Errico, MD; Alberto Testori, MD; Marta Scorsetti, MD, PhD; Giuseppe Canavese, MD; Corrado Tinterri, MD*

Breast Unit, Humanitas Research Hospital, Milan, Italy

HUMANITAS CANCER CENTER

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Study design

SINODAR ONE

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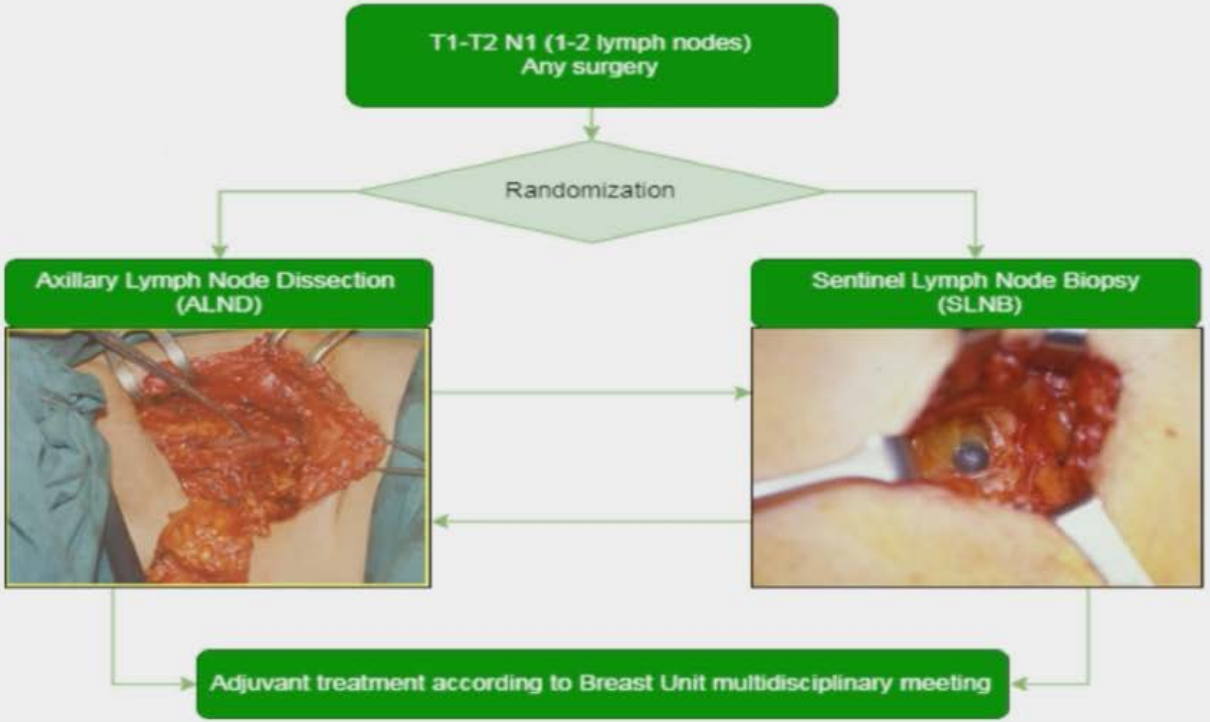

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T surgery

Standard arm N = 443	
Surgery type	**%**
BCS	75.9
BCS followed by mastectomy	1.0
Mastectomy (total or nipple-sparing)	23.1

Experimental arm N = 446	
Surgery type	**%**
BCS	76.9
BCS followed by mastectomy	3.0
Mastectomy (total or nipple-sparing)	20.1

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Follow-up: Events and survival

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Standard arm N = 439	p value	Experimental arm N = 440
Events (N = 16) (1 py recurrence + death)		**Events (N = 20) (2 py recurrence + death)**
Mortality = 4 (2 py no breast cancer related death)	0.984	Mortality = 4 (1 py no breast cancer related death)
Axillary recurrence = 1	0.489	Axillary recurrence = 1
Ipsilateral breast cancer recurrence = 0	0.169	Ipsilateral breast cancer recurrence = 3
Distant recurrence = 7	0.815	Distant recurrence = 8
Second primary tumor = 5	0.779	Second primary tumor = 6

No statistically significant difference in terms of survival and recurrence was found between the two different groups of treament

Follow-up: Events and survival

Timing of axillary recurrence?

Greco 2000 [1]
Objective: to evaluate the impact of breast carcinoma (T1–2N0) surgery without axillary dissection on axillary and distant relapses (**401** patients)
Median axillary-free relapsed time: **30.6** months (6–72)

Fischer 2002 (NSABP B-04) [2]
Objective: to determine whether less extensive surgery with or without radiation therapy was as effective as the Halsted radical mastectomy (**1079** patients)
Median axillary-free relapsed time: **14.8** months (3-134)

Sinodar-1: 33 Monate

Hwang 2007 [3]
Objective: review patients with invasive BC who underwent SLNB with a positive SLN without ALND (**196** patients)
Median axillary-free relapsed time: **32** months (8–44)

Sekine 2019 [4]
Objective: review **1056** women who underwent SLNB without ALND
Median axillary-free relapsed time: **23** months (8–92)

1. Greco M, Agresti R, Cascinelli N, Casalini P, Giovanazzi R, Maucione A, Tomasic G, Ferraris C, Ammatuna M, Pilotti S, Menard S. Breast cancer patients treated without axillary surgery: clinical implications and biologic analysis. Annals of surgery 2000;232(1):1-7.
2. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. New England Journal of Medicine 2002;347(8):567–75.
3. Hwang RF, Gonzalez-Angulo AM, Yi M, Buchholz TA, Meric-Bernstam F, Kuerer HM, Babiera GV, Tereffe W, Liu DD, Hunt KK. Low locoregional failure rates in selected breast cancer patients with tumor-positive sentinel lymph nodes who do not undergo completion axillary dissection. Cancer 2007;110(4):723-30.
4. Sekine C, Nakano S, Mibu A, Otsuka M, Oinuma T, Takeyama H. Breast cancer hormone receptor negativity, triple-negative type, mastectomy and not receiving adjuvant radiotherapy were associated with axillary recurrence after sentinel

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Position statement and conclusions

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The overlap between the results of SINODAR-ONE trial and those of the Z0011 is very convincing

Ethical problem: is it correct to continue to propose complete axillary dissection to patients who meet the study selection criteria?

Inhalte

- SINODAR One
- **Re-BET nach BET und in-Brust-Rezidiv**
- Intraoperativer Ultraschall
- Verzicht auf SLNE
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RE-BET bei in-Brust-Rezidiv

Author	MRM	RE-BET +Radiatio	Follow-up (months)	OAS
Alpert 2005	116	50	>120	64 vs. 58%
Wu 2020	1600	475	>120	42 vs. 48%
Baeck 2020	245	90	>120	HR 1.08 (95% CI 0.49–2.39)[BET vs MRM]
Su 2019	4048	1050	>120	HR 1.15 (95% CI 0.87–1.52)
Yoshida 2016	122	149	>120	HR 1.11 (95% CI 0.77–1.44)
Caiqin-Mo 2021 Metaanalyse	1224	431	-	HR 0.65 (95% CI 0.39–1.08)[MRM vs BET]

- Bias (time interval to first surgery, tumor size, nodal status, biology, patient wishes etc.)
- LRR (Re-BET > MRM) ↗
- OAS vergleichbar, **WENN** Radiatio der Restbrust erfolgte

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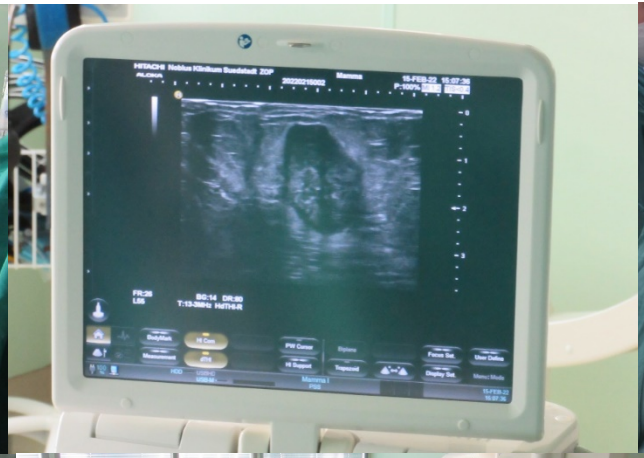
GBG
GERMAN BREAST GROUP

Intraoperativer Ultraschall (IOUS)



Intraoperativer Ultraschall (IOUS)

- **Sonographisch detektierbare Läsion**
- ***Konventionelle*** **Drahtmarkierung erfolgt am Morgen des Op-Tages:**
  - OP häufig erst nach Stunden → Belastung für Patn.
  - Verrutschen des Drahtes
- **Vorteile IOUS[1]**
  - Verringerung der Rate an R1-Resektionen und somit an 2. OP´s
  - Kleineres Resektionsvolumen
  - Unabhängigkeit von der radiologischen Abteilung
  - Präparate-Sono im OP-Saal →Transport (Personal, Kosten Zeit) entfällt
  - IOUS kann bei ca. Hälfte nicht tastbarer Brusttumore angewandt werden
- **Nachteil: US-Gerät im OP**
- **AGO 2022?**

1. Zhang QX: Eur Rev Med Pharm Sci 2021;25:1387

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SLNE - Standard für alle MaCa Patn.?

Sentinel-Lymphknoten-Exzision (SLNE) Indikationen I

	Oxford		
	LoE	GR	AGO
▪ Klinisch / sonographisch neg. Axilla (cN0)	1b	A	++
▪ Zusätzliche CNB bei cN1 um eine SLNE zu ermöglichen	2a	B	+
▪ cT 1–2	2b	A	++
▪ cT 3–4c	3b	B	+
▪ Multifokales / multizentrisches MaCa	2b	B	+
▪ DCIS			
▪ Mastektomie	3b	B	+
▪ BET	3b	B	-
▪ DCIS beim Mann	5	D	+/-
▪ MaCa des Mannes	2b	B	+
▪ Bei der älteren Patientin	3b	B	+

Guidelines Breast
Version 2021.1D

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

SLNE - Standard für alle Ma-Ca Patn.?

ASCO special art

Management of the Axilla in Early-Stage Breas Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline

Muriel Brackstone, MD, PhD[1]; Fulvia G. Baldassarre, MSc[2]; Francisco E. Perera, MD[1]; Tulin Cil, MD, MEd[3]; Mariana Chavez Mac Gregor, MD, MSc[4]; Ian S. Dayes, MD[5]; Jay Engel, MBBCh[6]; Janet K. Horton, MD[7]; Tari A. King, MD[8]; Anat Kornecki, MD[9]; Ralph George, MD[10]; Sandip K. SenGupta, MD[11]; Patricia A. Spears, BS[12]; and Andrea F. Eisen, MD[13]

Recommendations

Objective 1

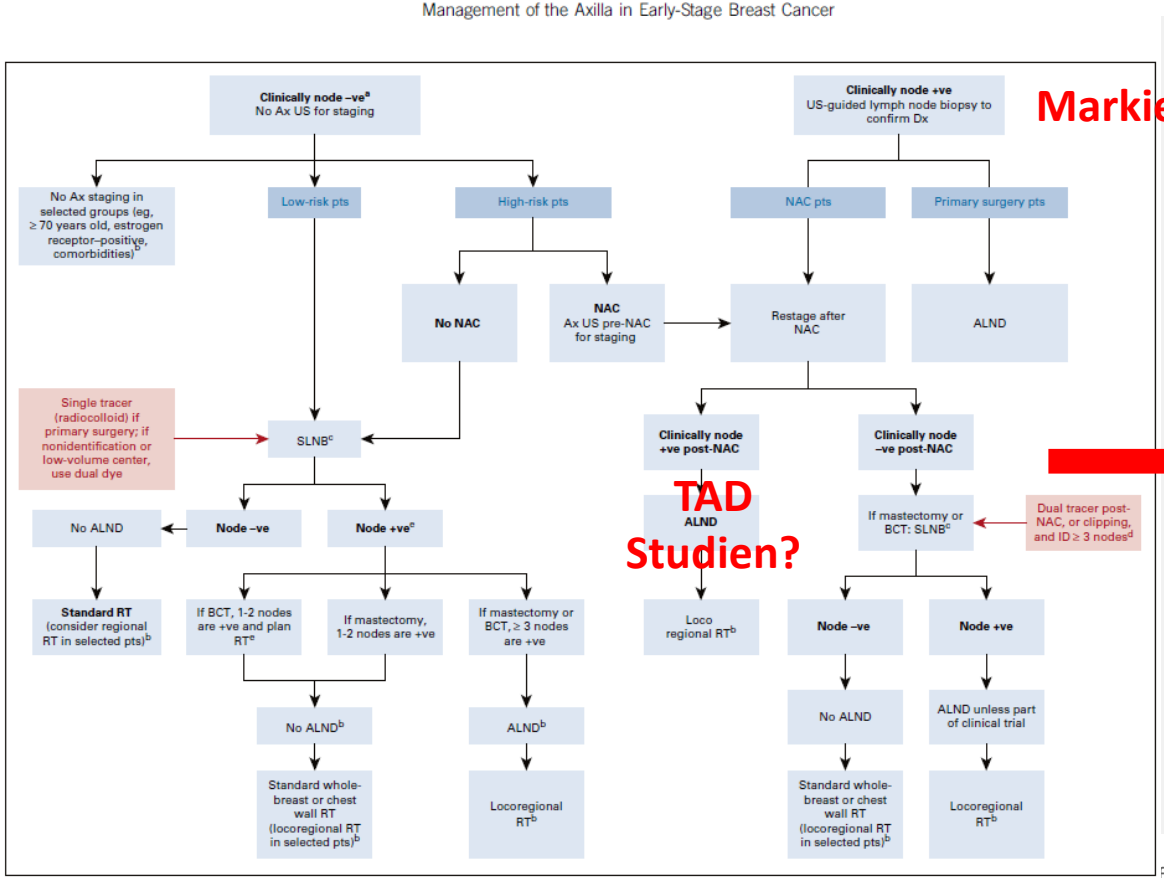
To determine which patients with early-stage breast cancer require axillary staging.

Recommendation 1

- For patients age ≥ 70 years with clinically node-negative (T1N0) early-stage invasive breast cancer, that is hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative, SLNB is not required. This is supported by the Choosing Wisely statement released on July 12, 2016, and updated on June 20, 2019, by the Society of Surgical Oncology[8] that stated, "Don't routinely use sentinel node biopsy in clinically node negative women ≥ 70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer" if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery to discuss hormonal therapy (Type: informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
- For patients age < 70 years without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate to high for staging by ALND *v* no ALND; insufficient for staging by SLNB *v* no staging; Strength of recommendation: strong).

Brackstone M: JCO 2021; 39(27):3056

SLNE - Standard für alle Ma-Ca Patn.?



Markierung?

TAD Studien?

Brackstone M: JCO 2021; 39(27):3056

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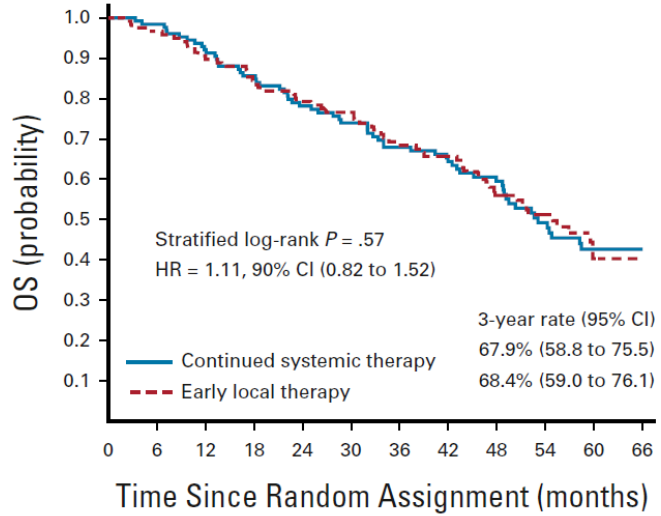
OP bei primär metastasiertem MaCa (de novo Stage IV)

Khan et al

Systemic therapy for 4-8 months

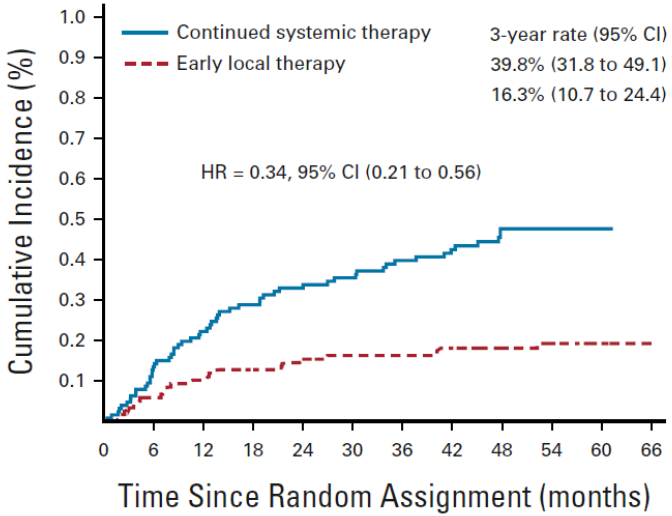
A = OAS



No. at risk:

Continued systemic therapy	131	125	115	105	93	87	77	71	58	40	12	3
Early local therapy	125	112	103	97	91	85	75	70	54	36	8	2

B = Local recurrence free survival



No. at risk:

Continued systemic therapy	131	108	89	75	67	59	50	44	30	21	3	1
Early local therapy	125	107	95	89	80	74	67	61	47	33	9	3

Khan S: JCO 2022, Jan 7; epub ahead

OP bei primär metastasiertem MaCa (de novo Stage IV)

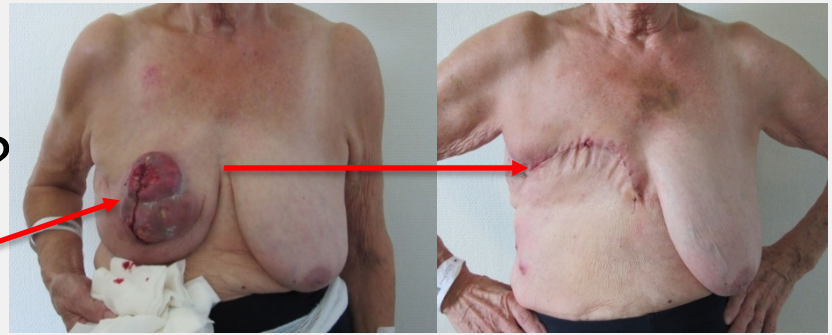
	Tata Memorial[1] 2015	Turkey MF 07-01[2] 2021	TBCRC 013[3] (USA) 2016	POSYTIVE[4] (Austria) 2020	EA2108[5] (USA) 2022	National Cancer Database[6] 2021
N **foll-up mo**	350 23	274 40	127 54	90 37,5	256 42	12,838 -
Design: locoregion. treatment or none	CAF+Tam →1:1	Systemic therapy → 1:1	Systemic therapy TPC; Elective surgery after discussion with pts.	Systemic therapy →1:1	Systemic therapy for 4-8 months; 256 of 390 random.	Systemic therapy (ST) alone vs. ST + surgery (S) vs. ST+S+RadioT
OAS	Median: 19 vs 20mo 2-y-OAS: 42 vs 43%	40-mo-OAS: 77 vs 55 % (p=0.005) Bone only met´s: Median: 56 vs 42 mo	3-y-OAS: 70 % Responder 78% Non-responder 24%	HR 0.69; 95% CI, 0.36 to 1.33	3-y-OS 68 vs 68% HR 1.11 (90% CI 0.82 - 1.52; P=.57) LRFS: HR 0.34; P < .001	5-y-OAS: ST vs. ST+S HR 0.72; 95% CI 0.67-0.79) ST+S+RT:HR 0.64 95% CI 0.59-0.69 (both p < 0.0001)
Conclusio	Responders to 1th line Chemo: no benefit from sur-gery; no modern systemic treatm., very low OAS	Signif improvement in survival with surgery in pts with indolent PMBC (ER+, HER2-, bone met, <55 y)	Elective surgery had no impact on OAS in responders (77% vs. 76%)	Non-significant OAS improvement favored systemic therapy; did not reach full accrual	Improved local PFS in pts who received early locoregional therapy; QOL =	Greatest survival advantage in pts with HR+ and/or HER2+ after ST before surgery

1. Badwe R: Lancet Oncol. 2015;16:1380; 2. Soran A: J Am Coll Surg. 2021;233:742; 3.) King TA: JCO 34, 2016 (suppl; abstr 1006); 4. Bjelic-Radisic V: BMC Cancer 2020;20:392; 5. Khan S: JCO 2022, Jan 7; epub ahead; 6. Stahl K: Ann Surg Oncol 2021;28:2646

OP bei primär metastas. MaCa: Wie Vorgehen?

1. Bias in allen Studien!
2. Prognose hängt von Meta-Lokalisation / Anzahl ab; ist aber besser gegenüber sekundär metastasierten MaCa
3. OP keine Verbesserung des OAS (Subgruppen !!!)
4. Lokale R0-Resektion nach Systemtherapie kann lokalen Progress verhindern
5. Stellenwert Axilla-Op ist unklar
6. Systemtherapie → Op + Radiatio?

… Palliative lokale OP bei M1



Hartmann, Gerber, Reimer et al: Breast Care 2014;9:87
Fitzal F: Ann Surg. 2019;269:1163
Reinhorn D: Breast 2021;58:173
Pons-Tostivent E: Crit Rev Oncol Hematol 2021;58:173

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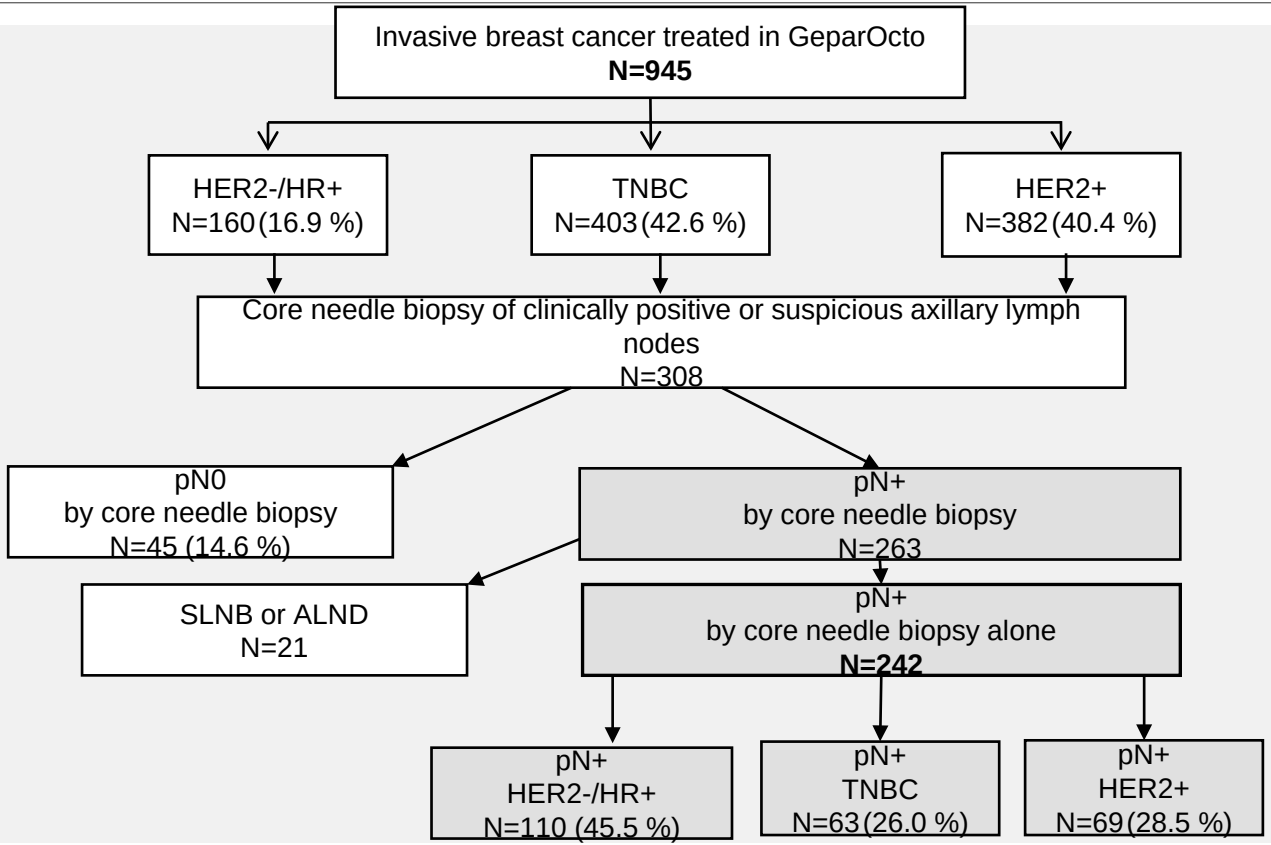
Vorteile der NAST

- pCR ist mit einem besseren Überleben assoziiert
- Operabilität kann bei primär inoperablen Tumoren erreicht werden
- Verbessert die Optionen für eine BET
- Senkt die Rate an axillären Lymphonodektomien / TAD
- **Prognoseverbesserung durch Individualisierung der post-NAST-Therapie**

pCR → **Deeskalieren**
Radiotherapie Brust (Axilla?)

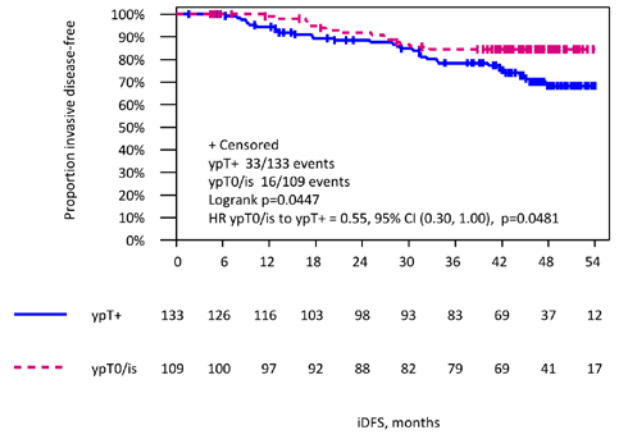
non-pCR → **Eskalieren**

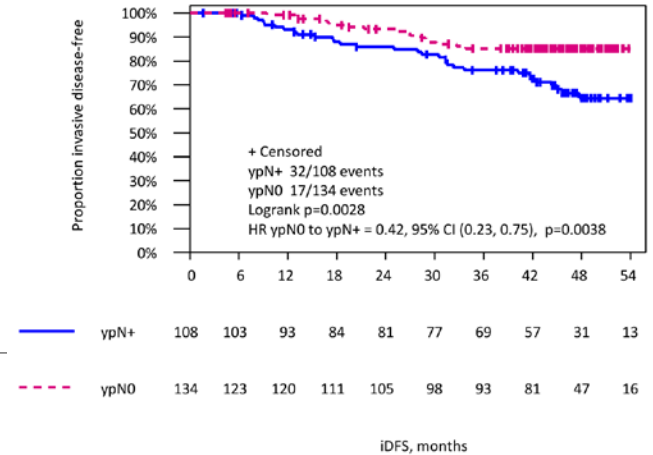
Prediction pcR nach NAST

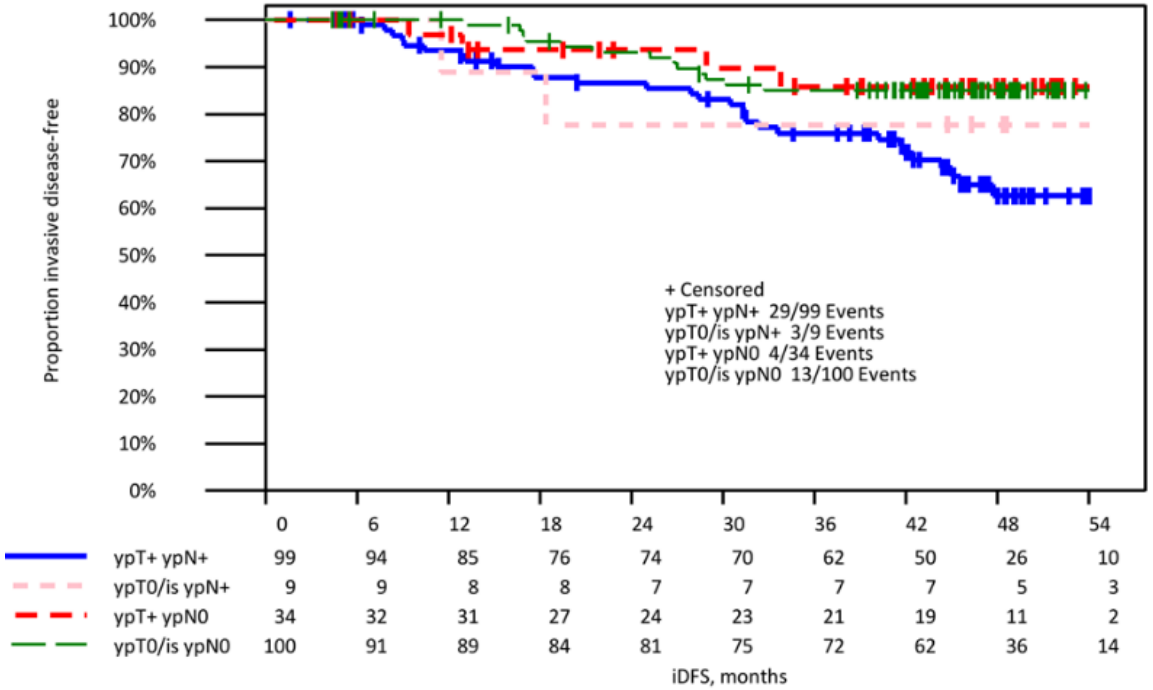


Gerber, B et al: Cancers 2022

GeparOcto: pCR - outcome





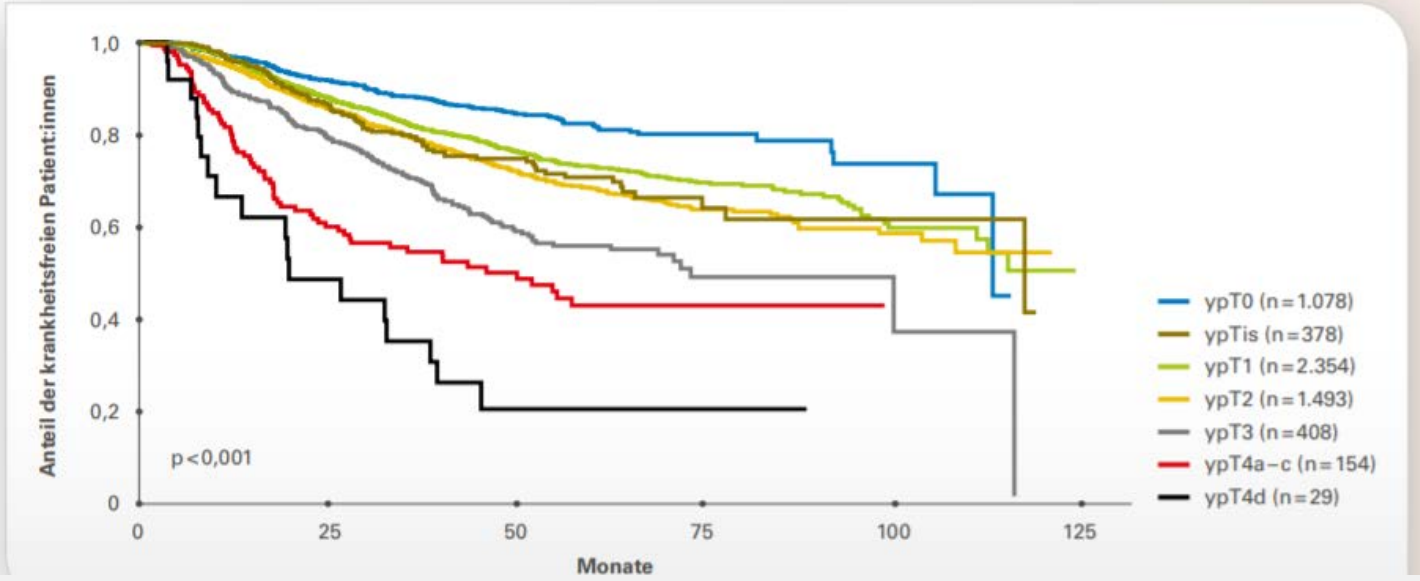


Gerber B et al: Cancers 2022

NAST : In-Brust-Resttumor und Rezidivrisko

ypT

Metaanalyse: DFS von Brustkrebspatient:innen nach Größe des Resttumors[6]



ypN

- **Vollständige Aufarbeitung aller Lymphknoten am Paraffinschnitt mit Schnittstufen von ≤ 500 µm** — **5** **D**
- **Immunhistochemie zum Nachweis von ITC** — **5** **D**

- **AGO 2022 ?**

Symmans WF: JCO 2017;35:1049

Prediction pCR-Breast nach NAST

Autoren	Inclusion Criteria	Method	Pats.-#	FNR
Heil J. Ann Surg. 2022;275:576	iPR, i-near-CR / iCR	VAB	398	17,8%
Tasoulis M JAMA Surg. 2020;155:e204103	cPR / cCR	VAB 86% CNB 14%	166	18,7%
Basik M SABCS 2019 GS5-05	i-near-CR / iCR (tri-mod. imaging)	CMB	98	22,5%
Vrancken-Peeters Ann Surg Oncol.2021;28:3243	rCR/rPR n MRI	US-CNB	167	37%
Große R SABCS 2019 P4-03-01	all	MX-VAB	117	19%

“Intelligente“ Prediction pCR(-Breast) nach NAST

original reports

Intelligent Vacuum-Assisted Biopsy to Identify Breast Cancer Patients With Pathologic Complete Response (ypTO and ypNO) After Neoadjuvant Systemic Treatment for Omission of Breast and Axillary Surgery

André Pfob[1,2]; Chris Sidey-Gibbons, PhD[2,3]; Geraldine Rauch, PhD[4]; Bettina Thomas, MD[5]; Benedikt Schaefgen, MD[1]; Sherko Kuemmel, MD[6]; Toralf Reimer, MD[7]; Markus Hahn, MD[8]; Marc Thill, MD[9]; Jens-Uwe Blohmer, MD[10]; John Hackmann, MD[11]; Wolfram Malter, MD[12]; Inga Bekes, MD[13]; Kay Friedrichs, MD[14]; Sebastian Wojcinski, MD[15]; Sylvie Joos, MD[16]; Stefan Paepke, MD[17]; Tom Degenhardt, MD[18]; Joachim Rom, MD[19]; Achim Rody, MD[20]; Marion van Mackelenbergh, MD[20]; Maggie Banys-Paluchowski, MD[20,21]; Regina Große, MD[22]; Mattea Reinisch, MD[6]; Maria Karsten, MD[10]; Michael Golatta, MD[1]; and Joerg Heil, MD[1]

Pfob A … Golatta M, Heil J: JCO 2022, February 4

“Intelligente“ Prediction pcR nach NAST

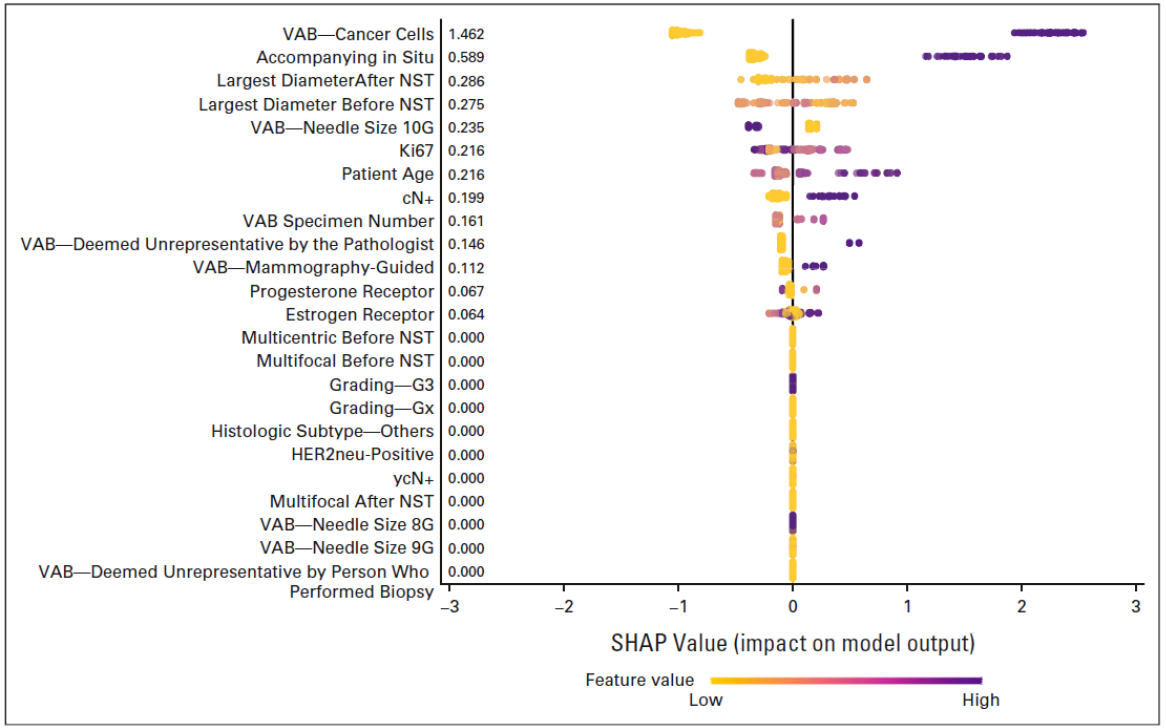


FIG 3. Insights into variable importance of the extreme gradient boosting tree model using local interpretation methods. SHAP value summary plot of the extreme gradient boosting tree model. Positive SHAP values on the *x*-axis indicate that the variable was important for predicting residual tumor in the breast or axilla. The values on the *y*-axis represent the overall global variable importance. HER2, human epidermal growth factor receptor 2; NST, neoadjuvant systemic treatment; SHAP, Shapley additive explanations; VAB, vacuum-assisted biopsy.

Axilla Lkn:
cN1: 28%
ycN1: 10%
ypN+: 18%

Pfob A … Golatta M,Heil J: JCO 2022, February 4

“Intelligente“ Prediction pcR nach NAST

CONTEXT

Key Objective

Neoadjuvant systemic treatment elicits a pathologic complete response in many women with breast cancer. These patients may not need therapeutic surgery as all local tumor has already been eradicated by neoadjuvant treatment. We evaluated whether a machine learning algorithm (intelligent vacuum-assisted biopsy [VAB]) can identify patients without residual cancer in the breast or axilla.

Knowledge Generated

In the development (n = 318) and external validation sets (n = 45), the intelligent VAB showed an false-negative rate of 0.0%-5.2%, a specificity of 37.5%-40.0%, and an area under the receiver operating characteristic curve of 0.91-0.92 to detect residual cancer (ypT+ or in situ or ypN+) after neoadjuvant treatment. The false-negative rate of the intelligent VAB was lower compared with imaging after neoadjuvant treatment, VAB alone, or combinations of both.

Relevance

An intelligent VAB algorithm can reliably exclude residual cancer after neoadjuvant treatment. These findings pave the way for the omission of breast and axillary surgery for these exceptional responders in future trials.

Pfob A … Golatta M,Heil J: JCO 2022, February 4

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Inhalte → Schlussfolgerungen aus 2021/22

- SINODAR One – **1. Bestätigungsstudie ACOSOG Z0011**
- Re-BET nach IBR – **mit Radiatio kein OAS-Nachteil (Cave: Bias)**
- Intraoperativer Ultraschall – **verbessert QOL und spart Kosten**
- Verzicht auf SLNE – **JA: bei "älterer" Patn, cT1N0, HR+, HER2- und HT**
- OP bei primär metast. MaCa – **Systemth.→OP+Radiatio kann in Subgruppen (HR+, HER2+, M1os …) OAS↗ (?); sonst OP keine OAS↗**
- NAST: Wieviel OP zur Prediktion pCR erforderlich? – **pCR-B und pCR-LN "noch" für Therapie-De-/Eskalation erforderlich; intelligente VAB-B/-LN?**
- …

HERZLICHEN DANK!