Guidelines Breast
Version 2021.1D

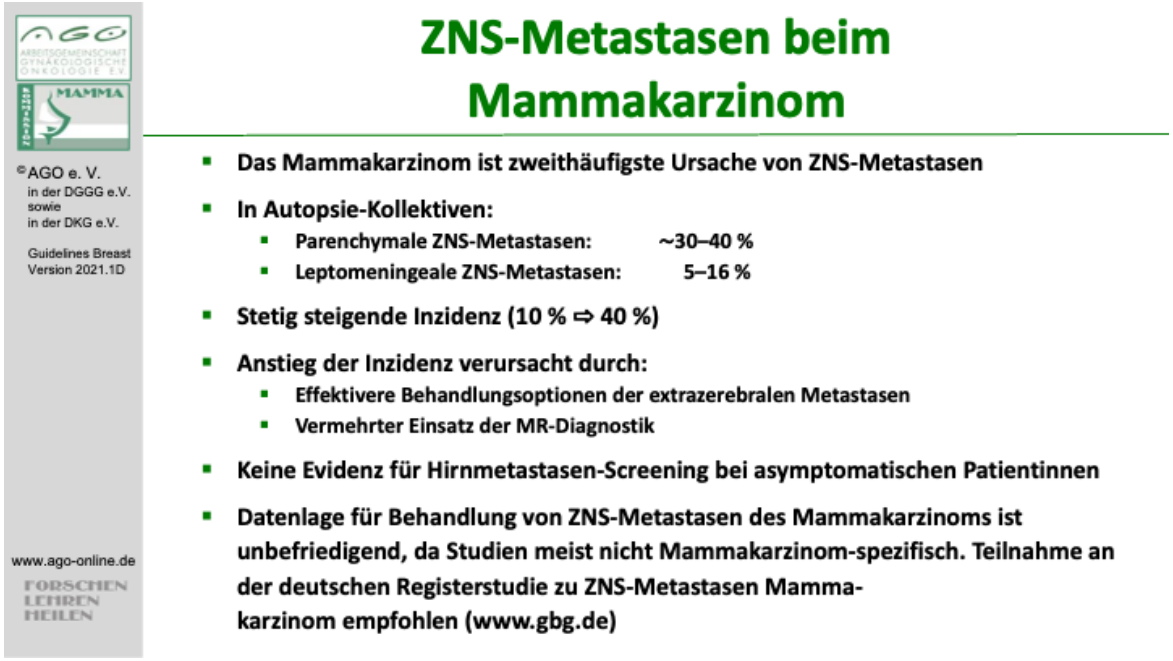
FORSCHEN
LEHREN
HEILEN

ZNS-Metastasen beim Mammakarzinom

ZNS-Metastasen beim Mammakarzinom

- **Versionen 2003–2020:**
  Bauerfeind / Bischoff / Diel / Ditsch / Fehm / Friedrich / Gerber / Huober / Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz / Solbach / Stickeler / Witzel

- **Version 2021:**
  Huober / Rody



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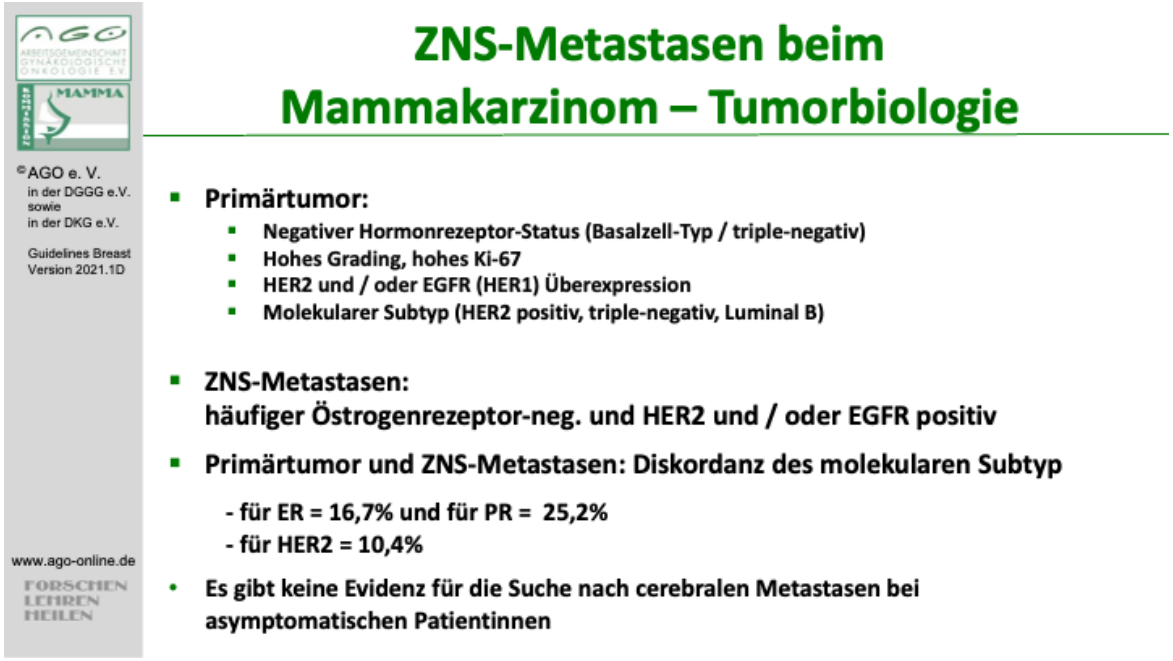

Risk factors (see also references slide CNS incidence)

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Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR

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Molekulare Diskordanz Primärtumor – Metastase:

1. Hulsbergen AFC, Claes A, Kavouridis VK, et al. Subtype switching in breast cancer brain metastases: a multicenter analysis. Neuro Oncol. 2020 Jan 23. pii: noaa013. doi: 10.1093/neuonc/noaa013. [Epub ahead of print]

There is no evidence for BM-screening in asymptomatic BC-patients

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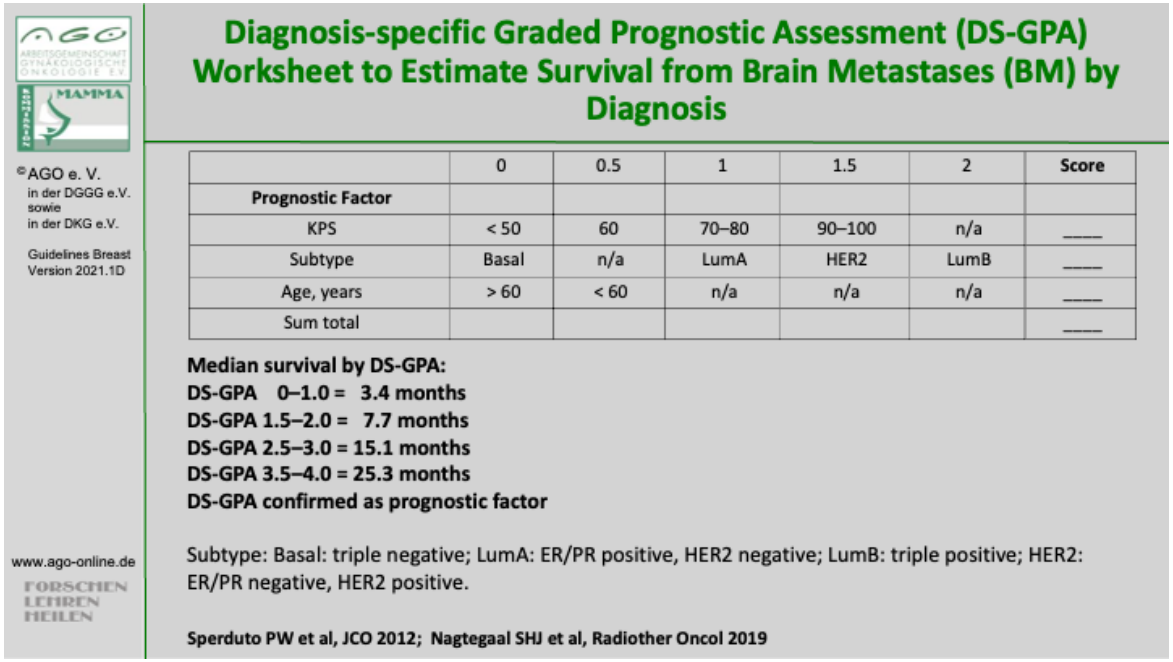

Diagnosis-specific Graded Prognostic Assessment (DS-GPA) Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

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	0	0.5	1	1.5	2	Score
Prognostic Factor						
KPS	< 50	60	70–80	90–100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	> 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival by DS-GPA:
DS-GPA 0–1.0 = 3.4 months
DS-GPA 1.5–2.0 = 7.7 months
DS-GPA 2.5–3.0 = 15.1 months
DS-GPA 3.5–4.0 = 25.3 months
DS-GPA confirmed as prognostic factor

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive.

Sperduto PW et al, JCO 2012; Nagtegaal SHJ et al, Radiother Oncol 2019

Breast-GPA

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Prognostic Factors for Survival

1. Castaneda CA, Flores R, Rojas KY et al.: Prognostic factors for patients with newly diagnosed brain metastasis from breast cancer. CNS Oncol 2015;4:137-145.
2. Huttenlocher S, Dziggel L, Hornung D et al.: A new prognostic instrument to predict the probability of developing new cerebral metastases after radiosurgery alone. Radiation oncology 2014;9:215.
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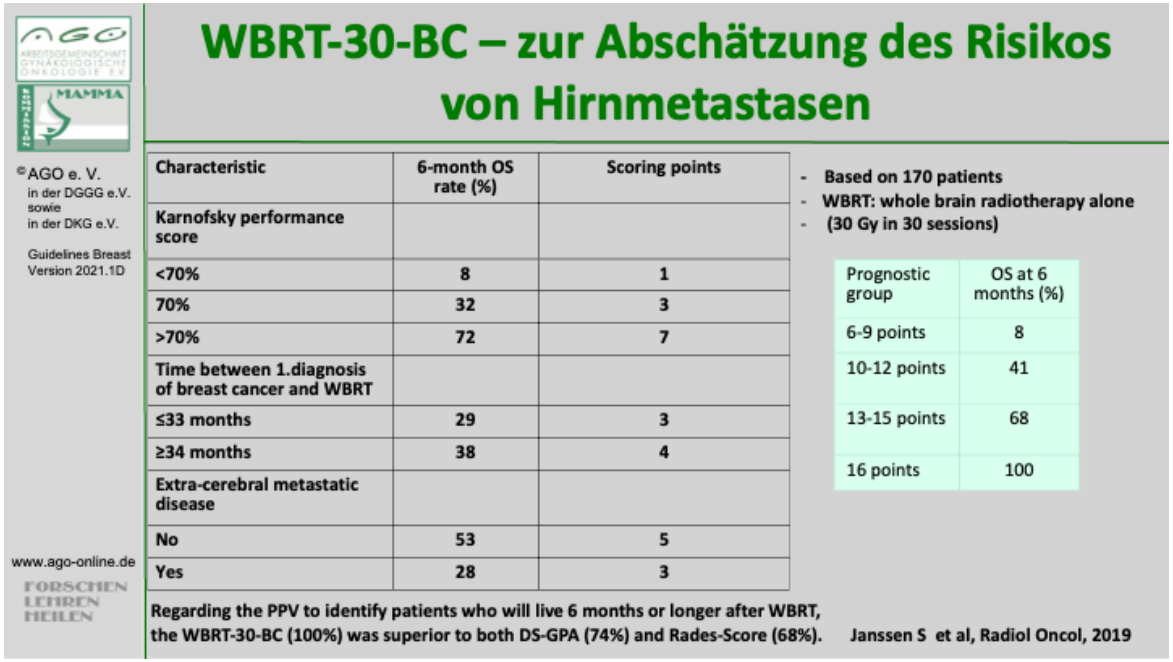

WBRT-30-BC – zur Abschätzung des Risikos von Hirnmetastasen

Characteristic	6-month OS rate (%)	Scoring points
Karnofsky performance score		
<70%	8	1
70%	32	3
>70%	72	7
Time between 1.diagnosis of breast cancer and WBRT		
≤33 months	29	3
≥34 months	38	4
Extra-cerebral metastatic disease		
No	53	5
Yes	28	3

- Based on 170 patients
- WBRT: whole brain radiotherapy alone
- (30 Gy in 30 sessions)

Prognostic group	OS at 6 months (%)
6-9 points	8
10-12 points	41
13-15 points	68
16 points	100

Regarding the PPV to identify patients who will live 6 months or longer after WBRT, the WBRT-30-BC (100%) was superior to both DS-GPA (74%) and Rades-Score (68%).

Janssen S et al, Radiol Oncol, 2019

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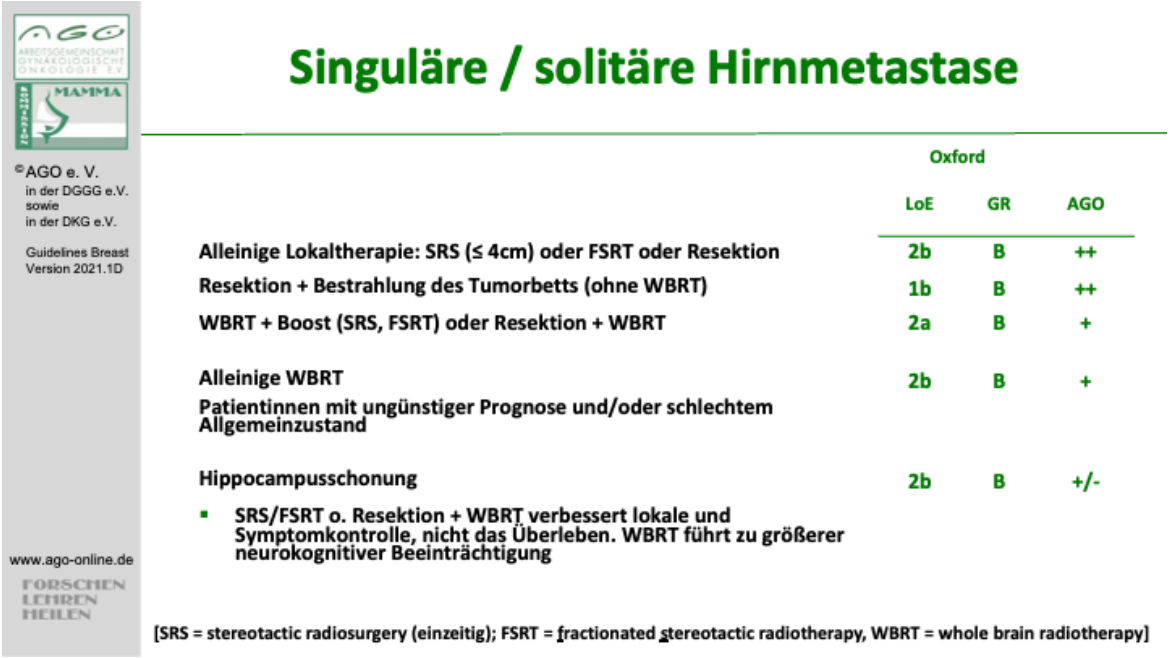

Singuläre / solitäre Hirnmetastase

	Oxford		
	LoE	GR	AGO
Alleinige Lokaltherapie: SRS (≤ 4cm) oder FSRT oder Resektion	2b	B	++
Resektion + Bestrahlung des Tumorbetts (ohne WBRT)	1b	B	++
WBRT + Boost (SRS, FSRT) oder Resektion + WBRT	2a	B	+
Alleinige WBRT Patientinnen mit ungünstiger Prognose und/oder schlechtem Allgemeinzustand	2b	B	+
Hippocampusschonung	2b	B	+/-

- SRS/FSRT o. Resektion + WBRT verbessert lokale und Symptomkontrolle, nicht das Überleben. WBRT führt zu größerer neurokognitiver Beeinträchtigung

[SRS = stereotactic radiosurgery (einzeitig); FSRT = fractionated stereotactic radiotherapy, WBRT = whole brain radiotherapy]

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7. Kocher M, Soffietti R, Abacioglu U et al.: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011, 29:134-141.
8. Ling DC, Vargo JA, Wegner RE et al.: Postoperative stereotactic radiosurgery to the resection cavity for large brain metastases: Clinical outcomes, predictors of intracranial failure, and implications for optimal patient selection. Neurosurgery 2015;76:150-156; discussion

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9. Liu Y, Alexander BM, Chen YH et al.: Salvage whole brain radiotherapy or stereotactic radiosurgery after initial stereotactic radiosurgery for 1-4 brain metastases. J Neurooncol 2015;124:429-437.
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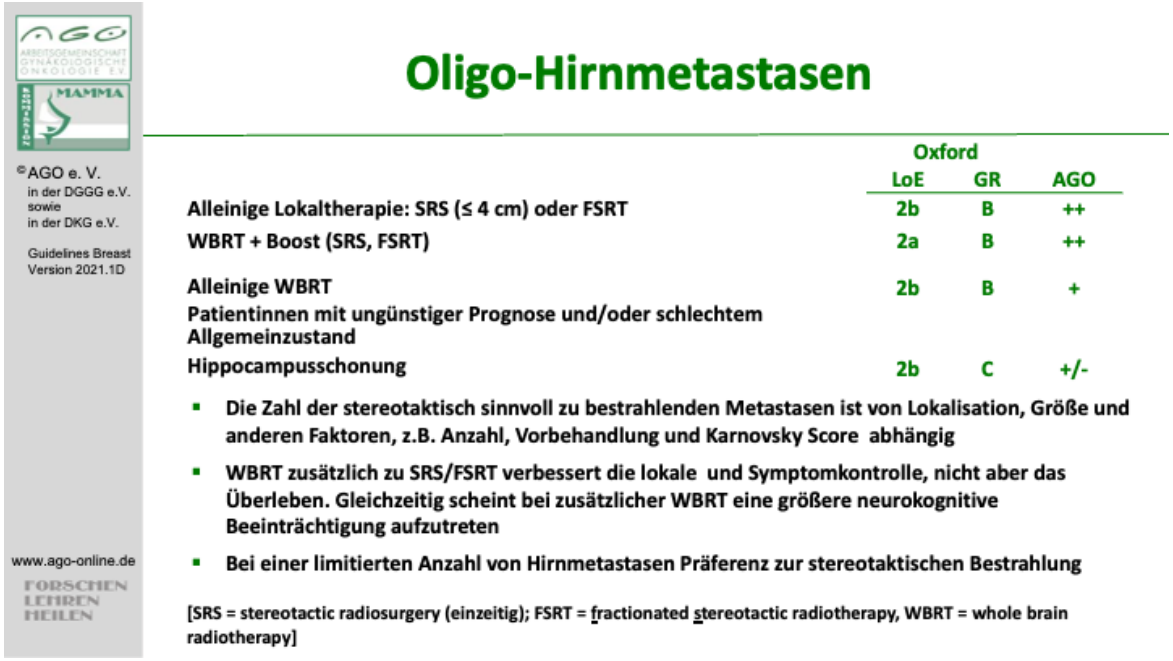

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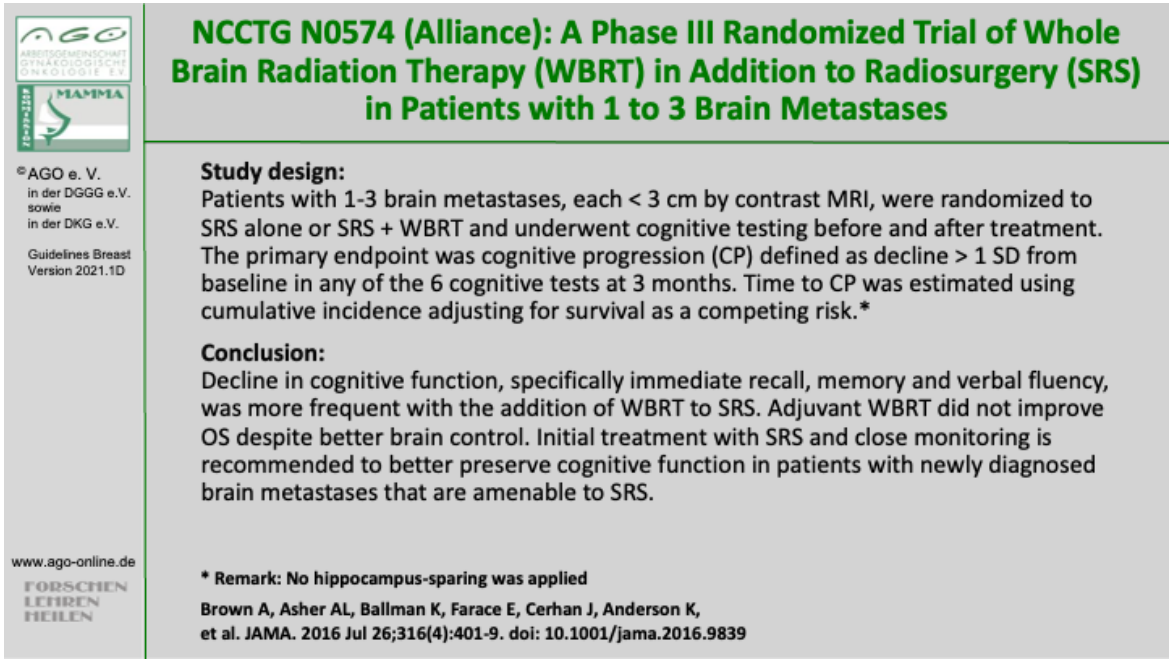

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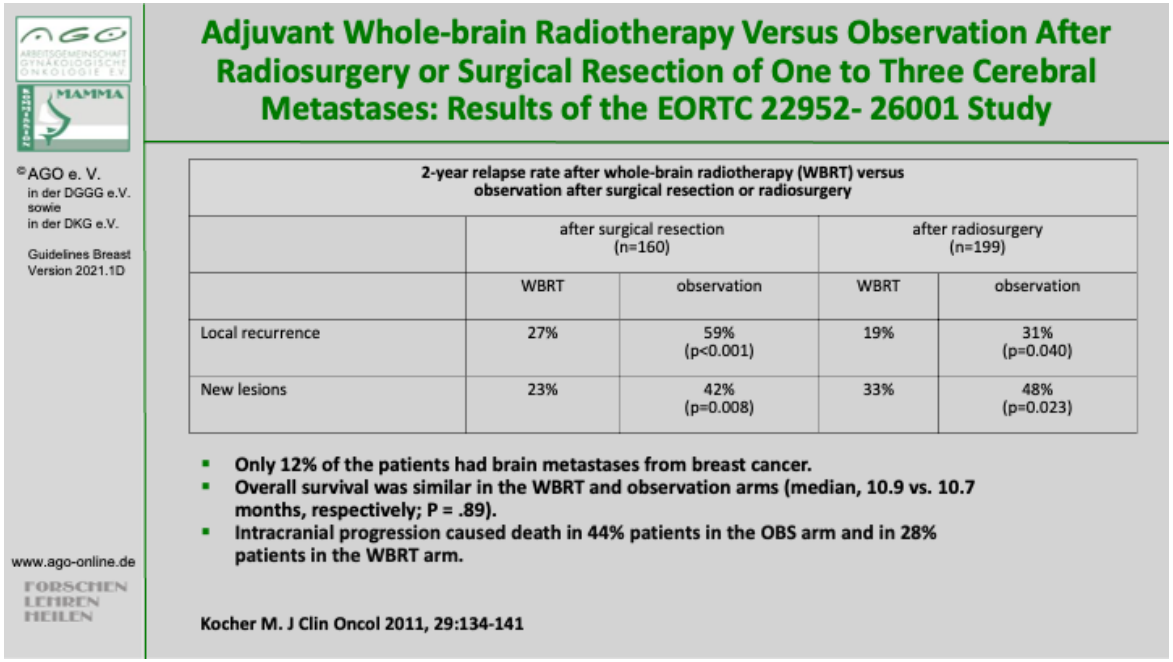

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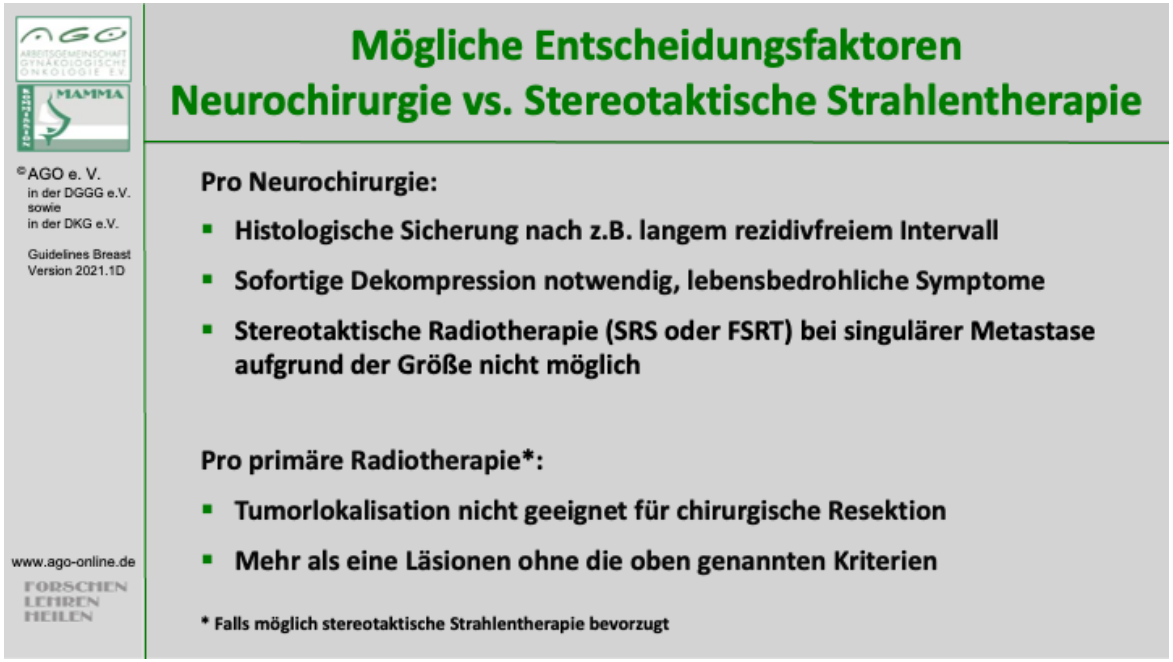

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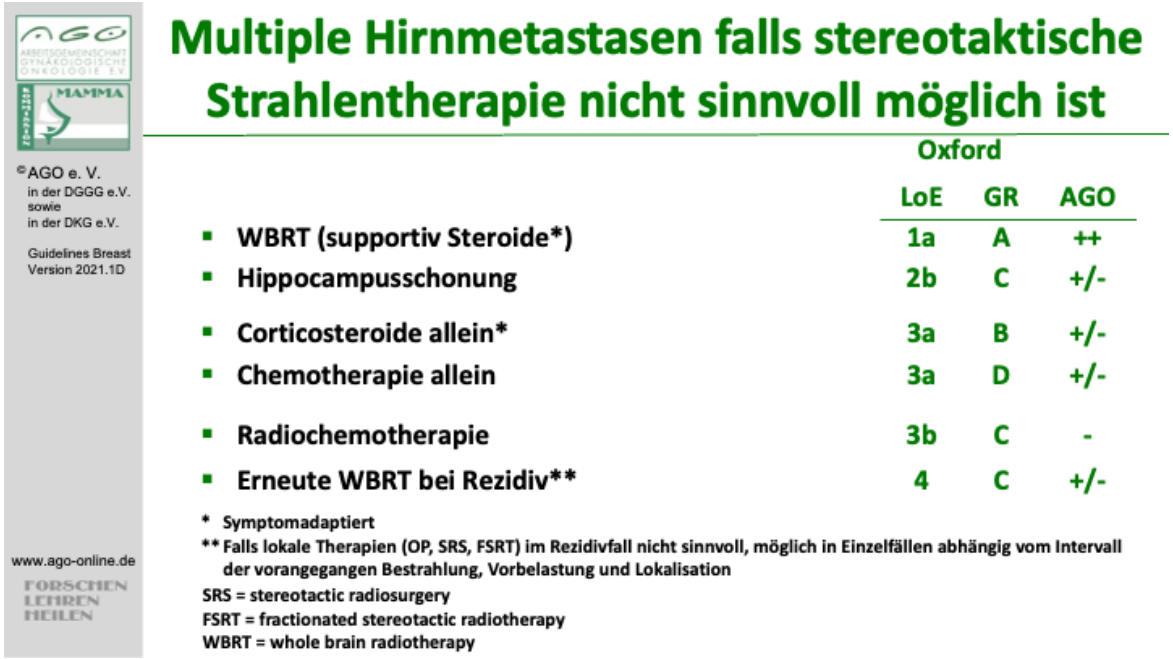

Multiple Hirnmetastasen falls stereotaktische Strahlentherapie nicht sinnvoll möglich ist

	Oxford		
	LoE	GR	AGO
▪ WBRT (supportiv Steroide*)	1a	A	++
▪ Hippocampusschonung	2b	C	+/-
▪ Corticosteroide allein*	3a	B	+/-
▪ Chemotherapie allein	3a	D	+/-
▪ Radiochemotherapie	3b	C	-
▪ Erneute WBRT bei Rezidiv**	4	C	+/-

* Symptomadaptiert

** Falls lokale Therapien (OP, SRS, FSRT) im Rezidivfall nicht sinnvoll, möglich in Einzelfällen abhängig vom Intervall der vorangegangen Bestrahlung, Vorbelastung und Lokalisation

SRS = stereotactic radiosurgery

FSRT = fractionated stereotactic radiotherapy

WBRT = whole brain radiotherapy

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Radiochemotherapy

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Re-Bestrahlung bei Rezidiv

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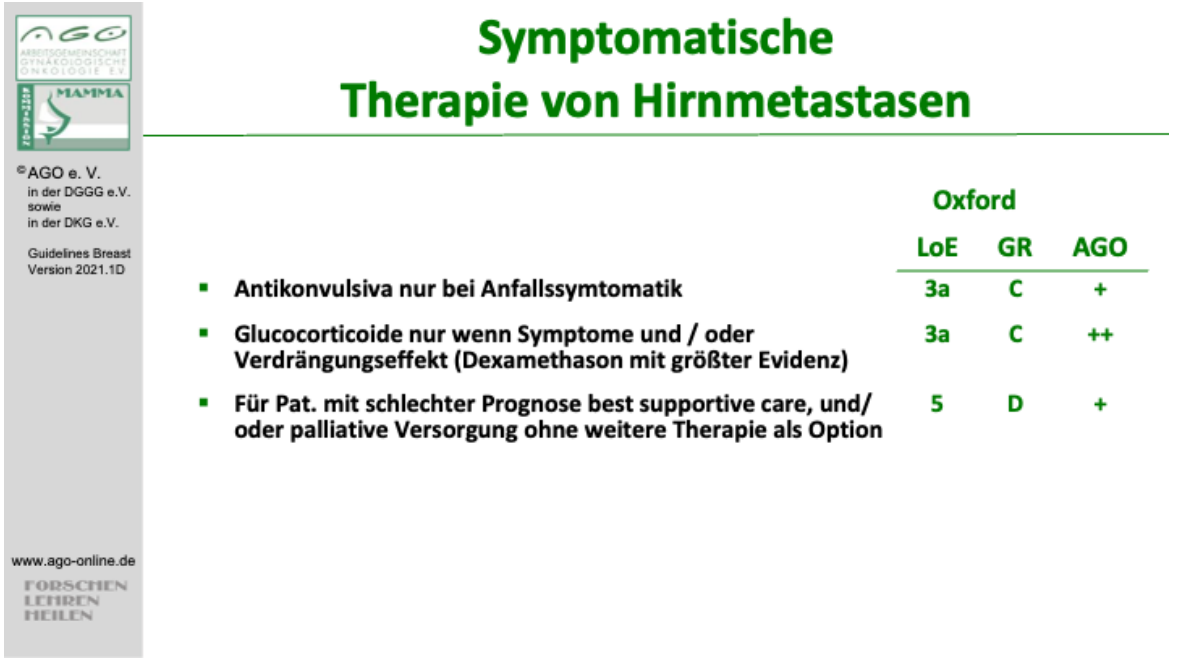

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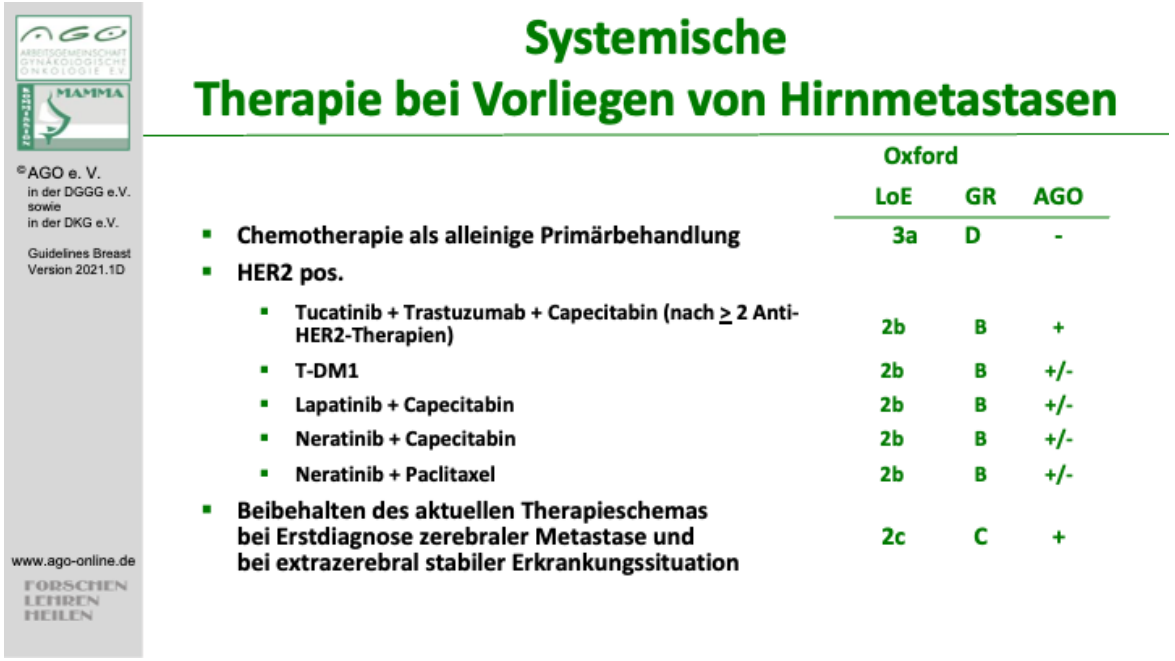

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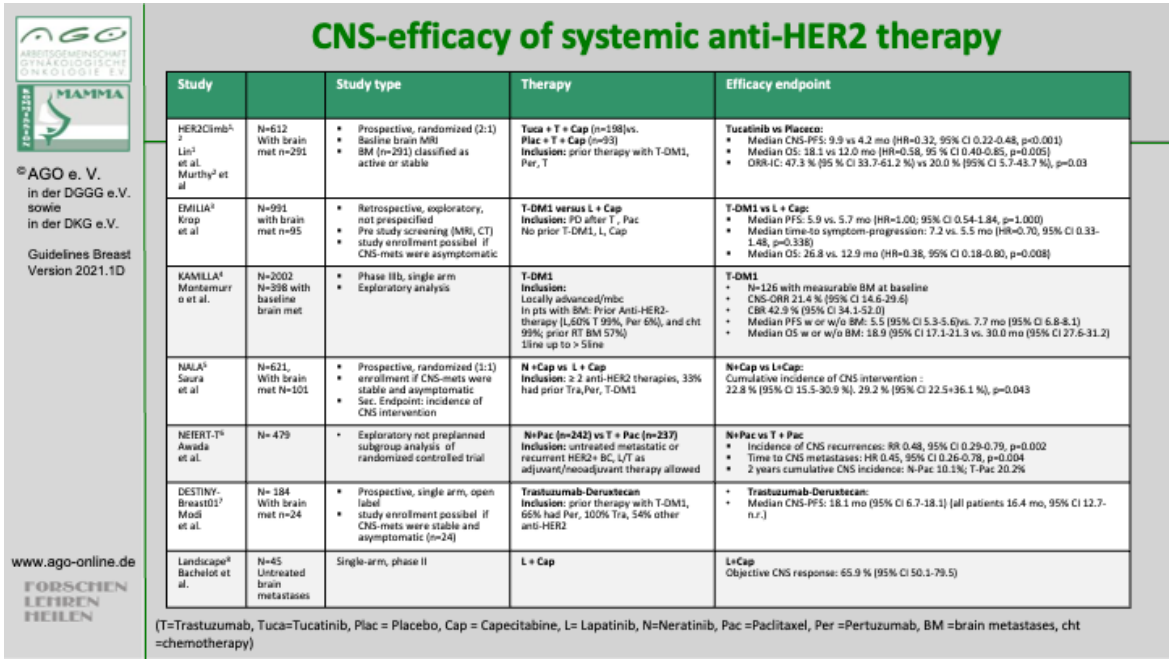

CNS-efficacy of systemic anti-HER2 therapy

Study		Study type	Therapy	Efficacy endpoint
HER2Climb[1,2] Lin[1] et al. Murthy[2] et al	N=612 With brain met n=291	• Prospective, randomized (2:1) • Baseline brain MRI • BM (n=291) classified as active or stable	**Tuca + T + Cap** (n=198)vs. **Plac + T + Cap** (n=93) **Inclusion:** prior therapy with T-DM1, Per, T	**Tucatinib vs Placeco:** • Median CNS-PFS: 9.9 vs 4.2 mo (HR=0.32, 95% CI 0.22-0.48, p<0.001) • Median OS: 18.1 vs 12.0 mo (HR=0.58, 95 % CI 0.40-0.85, p=0.005) • ORR-IC: 47.3 % (95 % CI 33.7-61.2 %) vs 20.0 % (95% CI 5.7-43.7 %), p=0.03
EMILIA[3] Krop et al	N=991 with brain met n=95	• Retrospective, exploratory, not prespecified • Pre study screening (MRI, CT) • study enrollment possibel if CNS-mets were asymptomatic	**T-DM1 versus L + Cap** **Inclusion:** PD after T , Pac No prior T-DM1, L, Cap	**T-DM1 vs L + Cap:** • Median PFS: 5.9 vs. 5.7 mo (HR=1.00; 95% CI 0.54-1.84, p=1.000) • Median time-to symptom-progression: 7.2 vs. 5.5 mo (HR=0.70, 95% CI 0.33-1.48, p=0.338) • Median OS: 26.8 vs. 12.9 mo (HR=0.38, 95% CI 0.18-0.80, p=0.008)
KAMILLA[4] Montemurro et al.	N=2002 N=398 with baseline brain met	• Phase IIb, single arm • Exploratory analysis	**T-DM1** **Inclusion:** Locally advanced/mbc In pts with BM: Prior Anti-HER2-therapy (L,60% T 99%, Per 6%), and cht 99%; prior RT BM 57%) 1line up to > 5line	**T-DM1** • N=126 with measurable BM at baseline • CNS-ORR 21.4 % (95% CI 14.6-29.6) • CBR 42.9 % (95% CI 34.1-52.0) • Median PFS w or w/o BM: 5.5 (95% CI 5.3-5.6)vs. 7.7 mo (95% CI 6.8-8.1) • Median OS w or w/o BM: 18.9 (95% CI 17.1-21.3 vs. 30.0 mo (95% CI 27.6-31.2)
NALA[5] Saura et al	N=621, With brain met N=101	• Prospective, randomized (1:1) • enrollment if CNS-mets were stable and asymptomatic • Sec. Endpoint: incidence of CNS intervention	**N +Cap vs L + Cap** **Inclusion:** ≥ 2 anti-HER2 therapies, 33% had prior Tra,Per, T-DM1	**N+Cap vs L+Cap:** Cumulative incidence of CNS intervention : 22.8 % (95% CI 15.5-30.9 %). 29.2 % (95% CI 22.5+36.1 %), p=0.043
NEfERT-T[6] Awada et al.	N= 479	• Exploratory not preplanned subgroup analysis of randomized controlled trial	**N+Pac (n=242) vs T + Pac (n=237)** **Inclusion:** untreated metastatic or recurrent HER2+ BC, L/T as adjuvant/neoadjuvant therapy allowed	**N+Pac vs T + Pac** • Incidence of CNS recurrences: RR 0.48, 95% CI 0.29-0.79, p=0.002 • Time to CNS metastases: HR 0.45, 95% CI 0.26-0.78, p=0.004 • 2 years cumulative CNS incidence: N-Pac 10.1%; T-Pac 20.2%
DESTINY-Breast01[7] Modi et al.	N= 184 With brain met n=24	• Prospective, single arm, open label • study enrollment possibel if CNS-mets were stable and asymptomatic (n=24)	**Trastuzumab-Deruxtecan** **Inclusion:** prior therapy with T-DM1, 66% had Per, 100% Tra, 54% other anti-HER2	• **Trastuzumab-Deruxtecan:** • Median CNS-PFS: 18.1 mo (95% CI 6.7-18.1) (all patients 16.4 mo, 95% CI 12.7-n.r.)
Landscape[8] Bachelot et al.	N=45 Untreated brain metastases	Single-arm, phase II	**L + Cap**	**L+Cap** Objective CNS response: 65.9 % (95% CI 50.1-79.5)

(T=Trastuzumab, Tuca=Tucatinib, Plac = Placebo, Cap = Capecitabine, L= Lapatinib, N=Neratinib, Pac =Paclitaxel, Per =Pertuzumab, BM =brain metastases, cht =chemotherapy)

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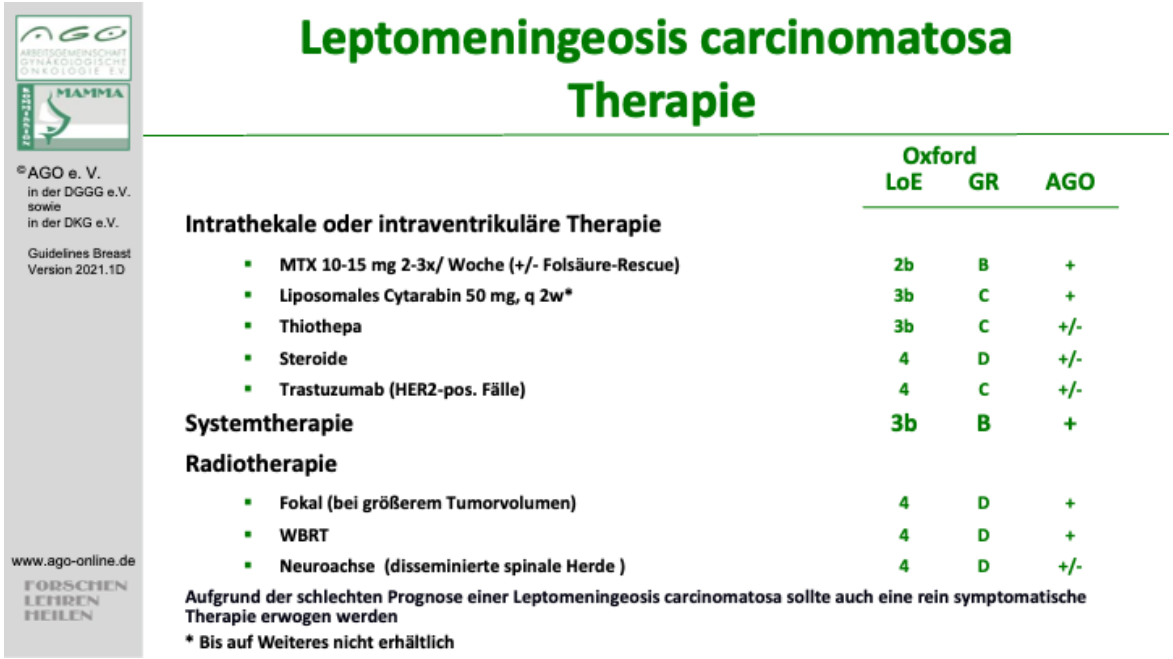

Leptomeningeosis carcinomatosa
Therapie

	Oxford LoE	Oxford GR	AGO
Intrathekale oder intraventrikuläre Therapie			
▪ MTX 10-15 mg 2-3x/ Woche (+/- Folsäure-Rescue)	2b	B	+
▪ Liposomales Cytarabin 50 mg, q 2w*	3b	C	+
▪ Thiothepa	3b	C	+/-
▪ Steroide	4	D	+/-
▪ Trastuzumab (HER2-pos. Fälle)	4	C	+/-
Systemtherapie	**3b**	**B**	**+**
Radiotherapie			
▪ Fokal (bei größerem Tumorvolumen)	4	D	+
▪ WBRT	4	D	+
▪ Neuroachse (disseminierte spinale Herde)	4	D	+/-

Aufgrund der schlechten Prognose einer Leptomeningeosis carcinomatosa sollte auch eine rein symptomatische Therapie erwogen werden

*** Bis auf Weiteres nicht erhältlich**

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MTX high dose

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