Guidelines Breast
Version 2021.1E

CNS Metastases in Breast Cancer

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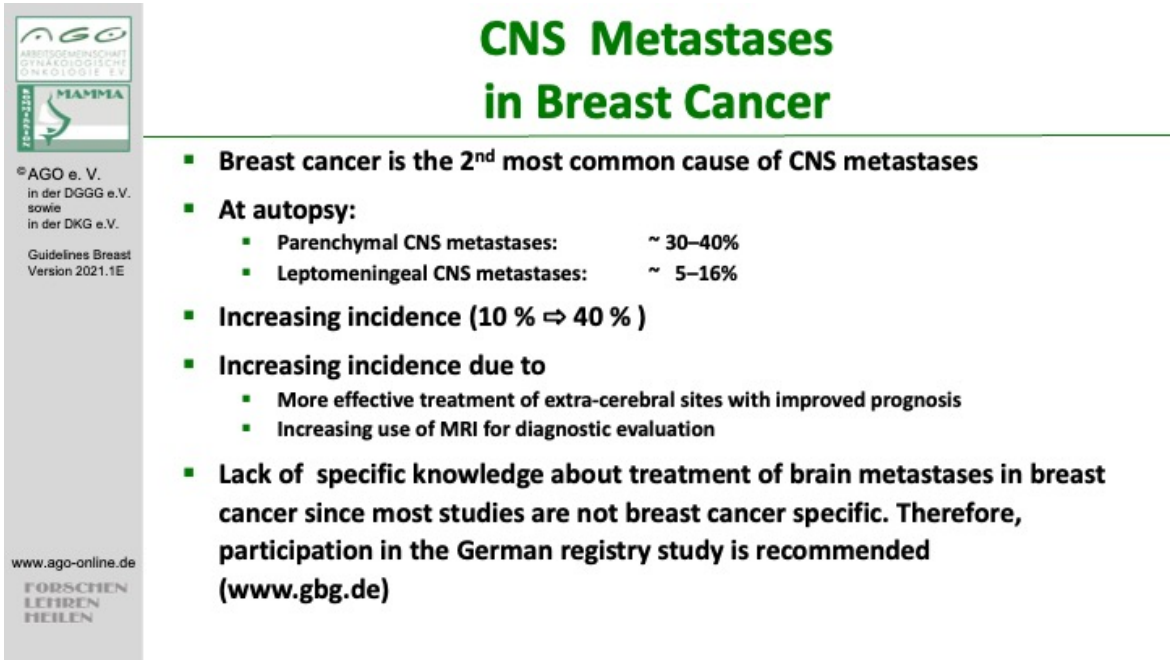

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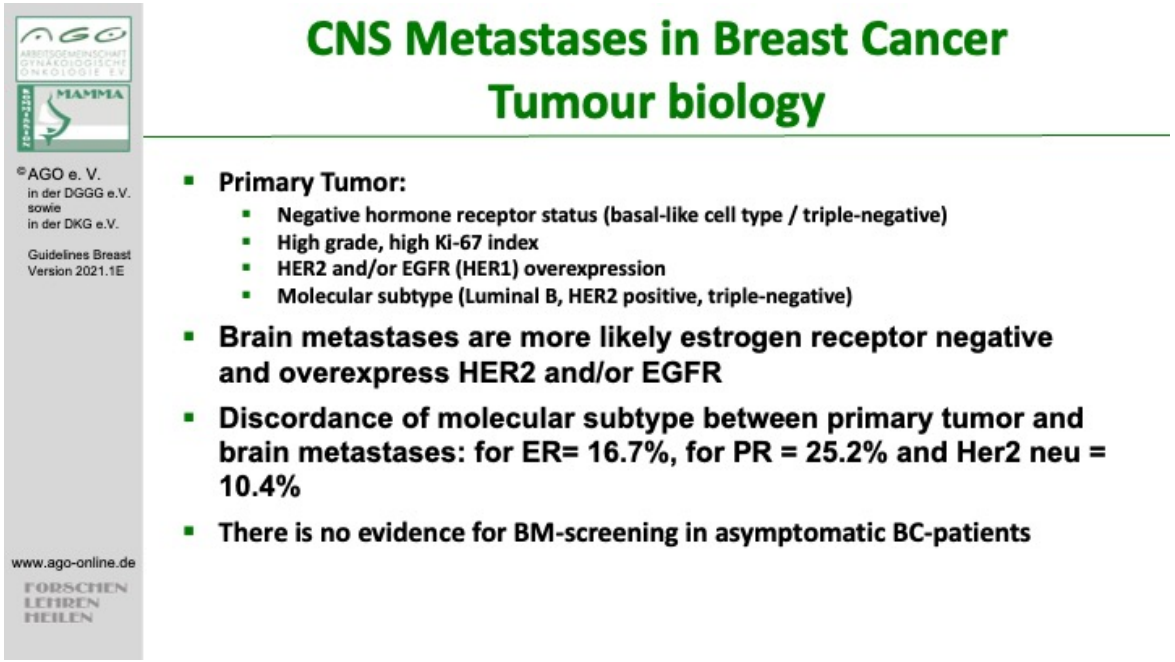

Risk factors (see also references slide CNS incidence)

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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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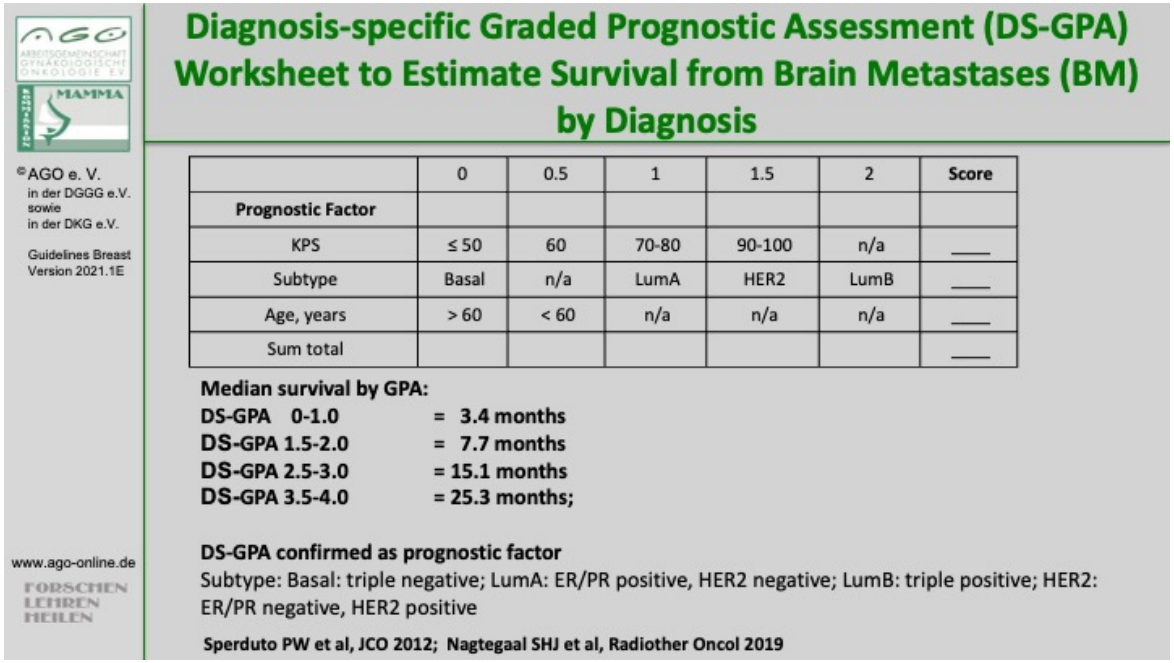

Diagnosis-specific Graded Prognostic Assessment (DS-GPA) Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

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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 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

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Breast-GPA

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Prognostic Factors for Survival

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3. Laakmann, E., K. Riecke, Y. Goy et al.: (2016). "Comparison of nine prognostic scores in patients with brain metastases of breast cancer receiving radiotherapy of the brain." J Cancer Res Clin Oncol 142(1): 325-332.

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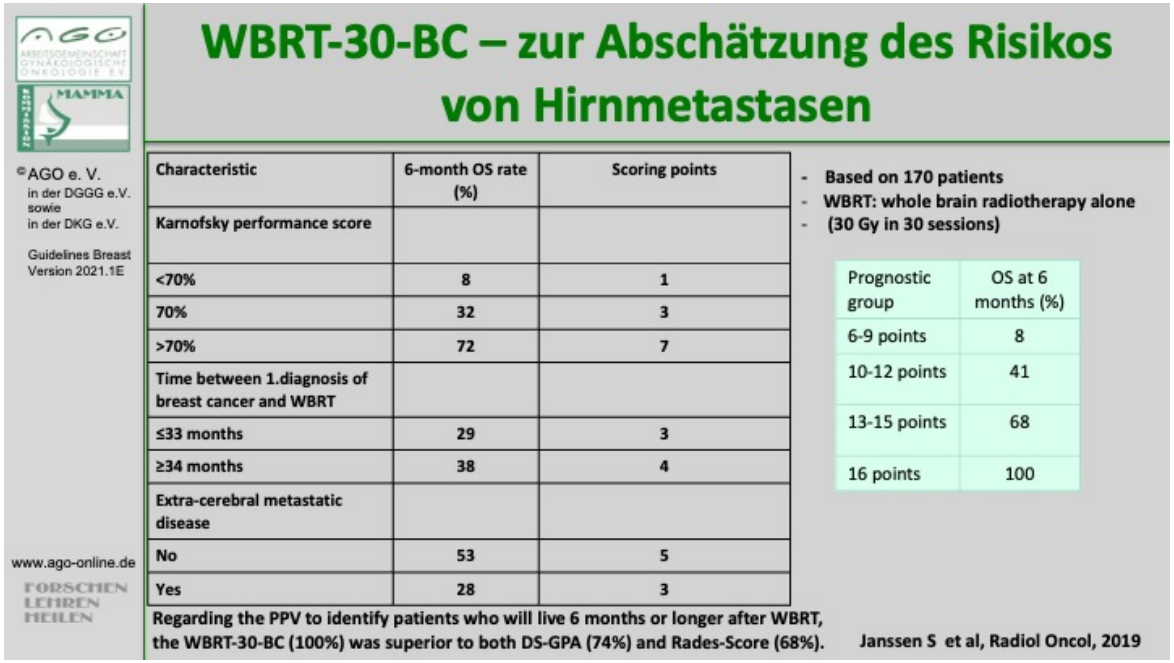

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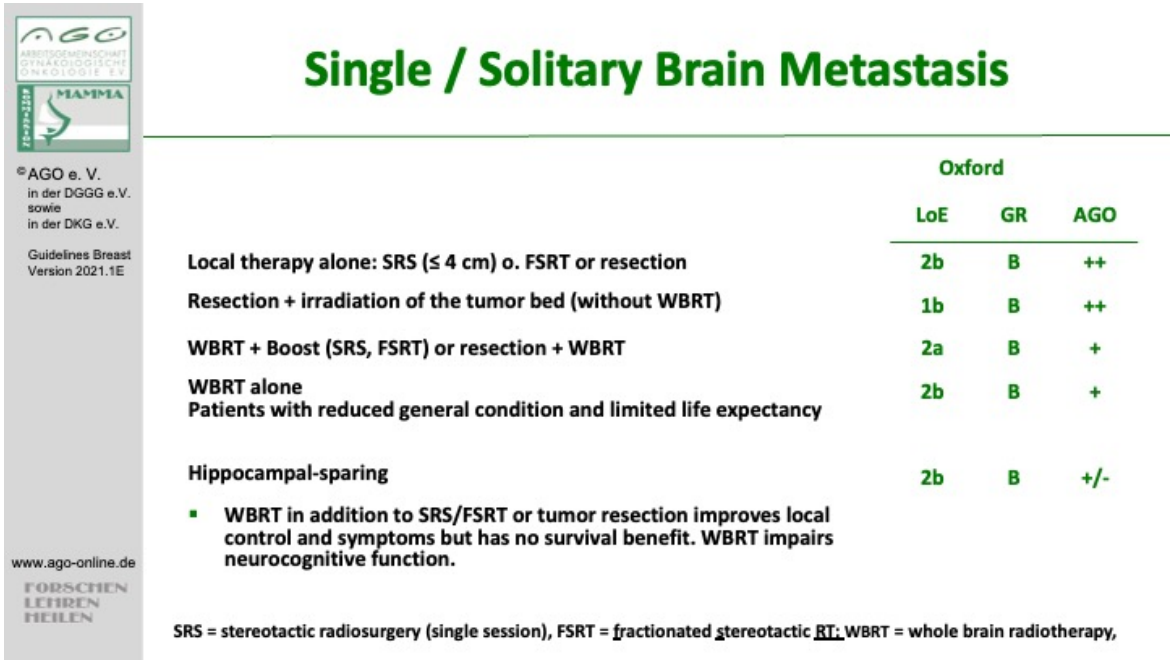

Single / Solitary Brain Metastasis

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (≤ 4 cm) o. FSRT or resection	2b	B	++
Resection + irradiation of the tumor bed (without WBRT)	1b	B	++
WBRT + Boost (SRS, FSRT) or resection + WBRT	2a	B	+
WBRT alone Patients with reduced general condition and limited life expectancy	2b	B	+
Hippocampal-sparing	2b	B	+/-

- WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms but has no survival benefit. WBRT impairs neurocognitive function.

SRS = stereotactic radiosurgery (single session), FSRT = fractionated stereotactic RT; WBRT = whole brain radiotherapy,

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156-157; quiz 157.
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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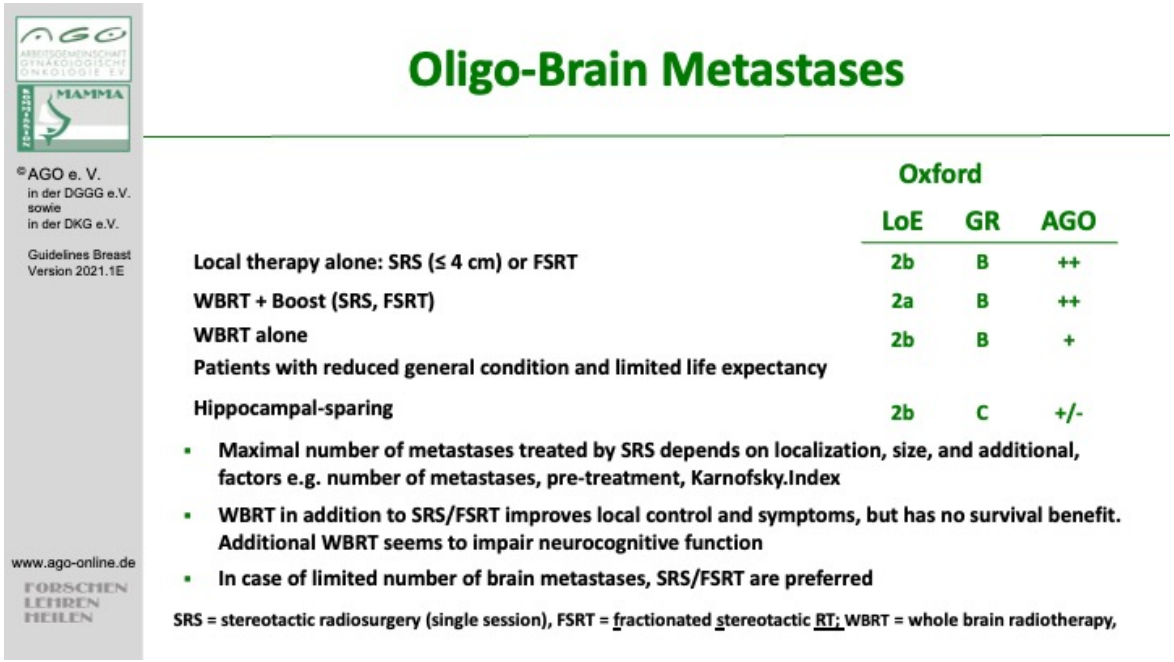

Oligo-Brain Metastases

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (≤ 4 cm) or FSRT	2b	B	++
WBRT + Boost (SRS, FSRT)	2a	B	++
WBRT alone	2b	B	+
Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing	2b	C	+/-

- Maximal number of metastases treated by SRS depends on localization, size, and additional, factors e.g. number of metastases, pre-treatment, Karnofsky.Index
- WBRT in addition to SRS/FSRT improves local control and symptoms, but has no survival benefit. Additional WBRT seems to impair neurocognitive function
- In case of limited number of brain metastases, SRS/FSRT are preferred

SRS = stereotactic radiosurgery (single session), FSRT = fractionated stereotactic RT; WBRT = whole brain radiotherapy,

1. Brown A, Asher AL, Ballman K et al.: A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839Soon YY1,
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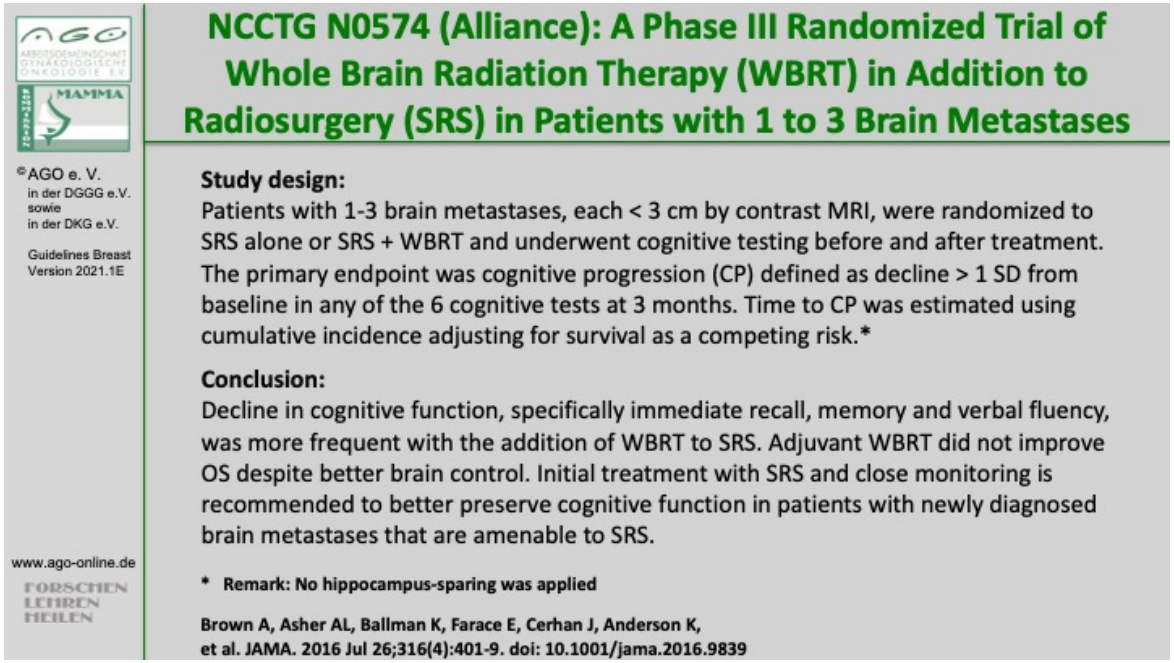

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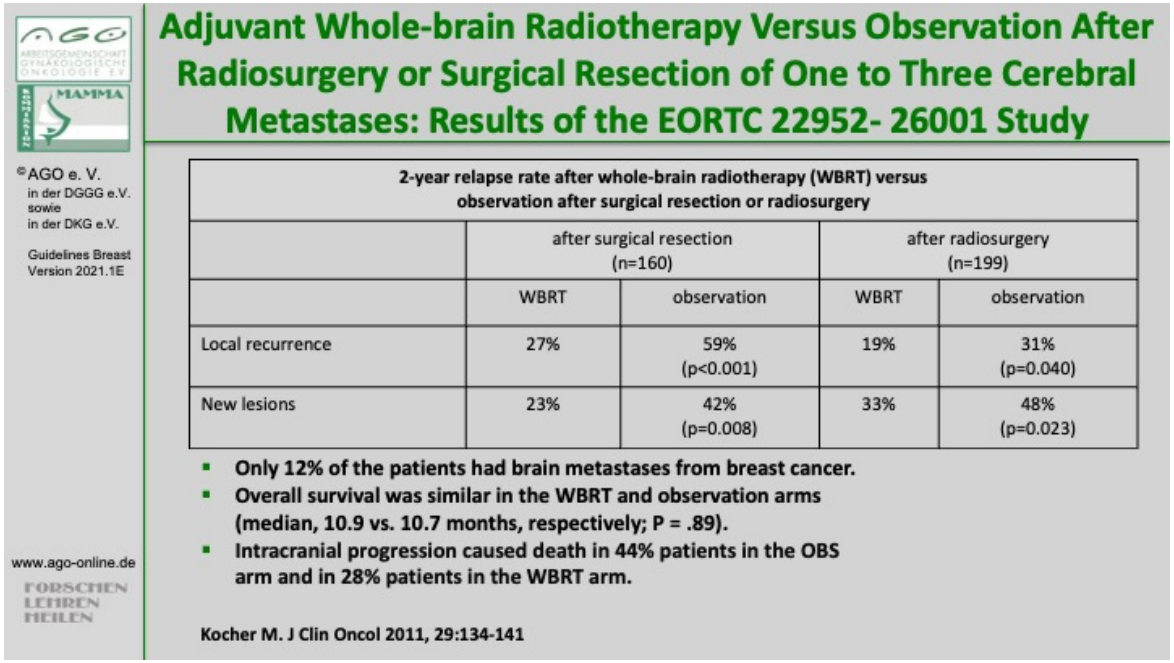

Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

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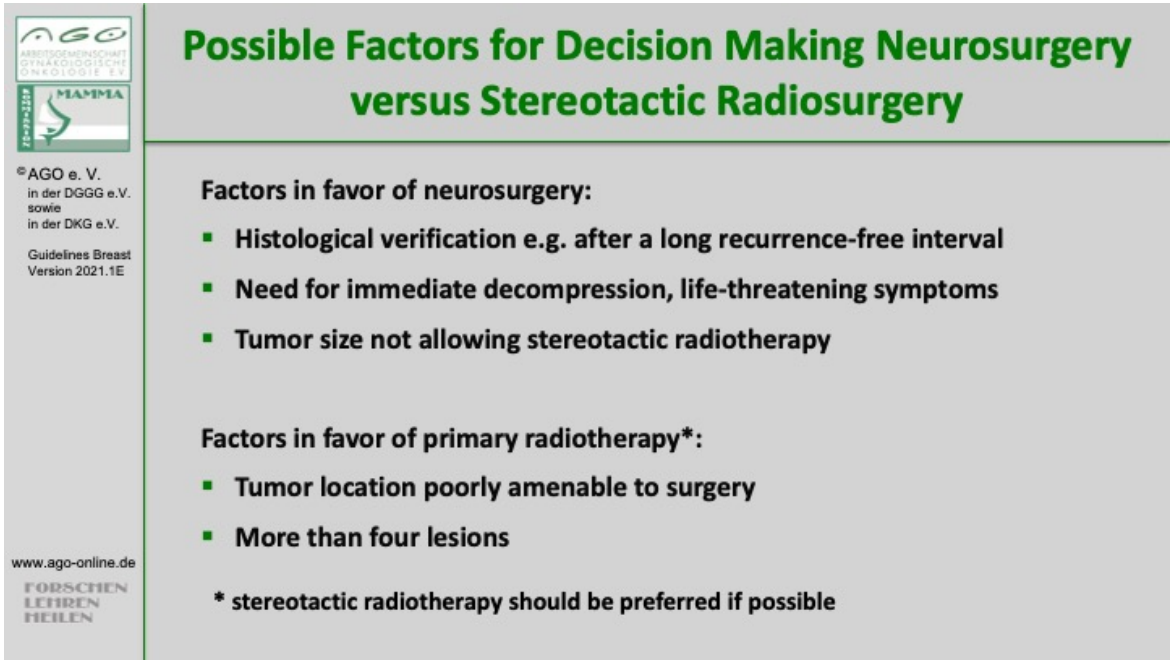
2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation after surgical resection or radiosurgery

	after surgical resection (n=160)		after radiosurgery (n=199)	
	WBRT	observation	WBRT	observation
Local recurrence	27%	59% (p<0.001)	19%	31% (p=0.040)
New lesions	23%	42% (p=0.008)	33%	48% (p=0.023)

- **Only 12% of the patients had brain metastases from breast cancer.**
- **Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; P = .89).**
- **Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.**

Kocher M. J Clin Oncol 2011, 29:134-141

1. 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;29:134-41.



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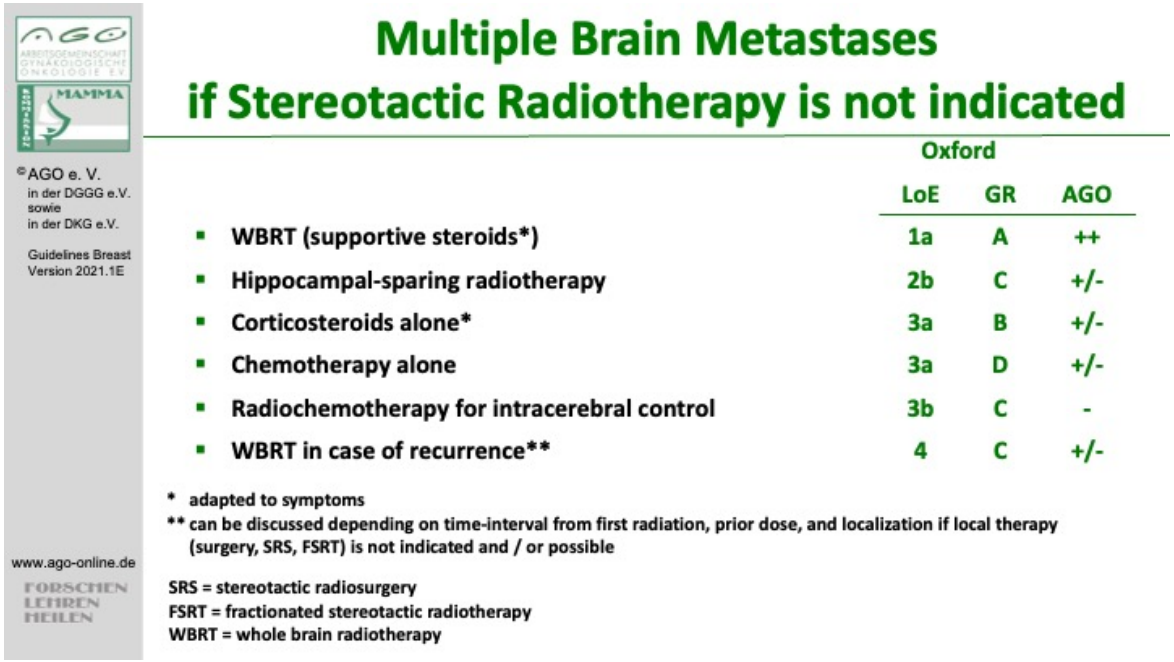

Multiple Brain Metastases if Stereotactic Radiotherapy is not indicated

	Oxford LoE	GR	AGO
▪ WBRT (supportive steroids*)	1a	A	++
▪ Hippocampal-sparing radiotherapy	2b	C	+/-
▪ Corticosteroids alone*	3a	B	+/-
▪ Chemotherapy alone	3a	D	+/-
▪ Radiochemotherapy for intracerebral control	3b	C	-
▪ WBRT in case of recurrence**	4	C	+/-

* adapted to symptoms
** can be discussed depending on time-interval from first radiation, prior dose, and localization if local therapy (surgery, SRS, FSRT) is not indicated and / or possible

SRS = stereotactic radiosurgery
FSRT = fractionated stereotactic radiotherapy
WBRT = whole brain radiotherapy

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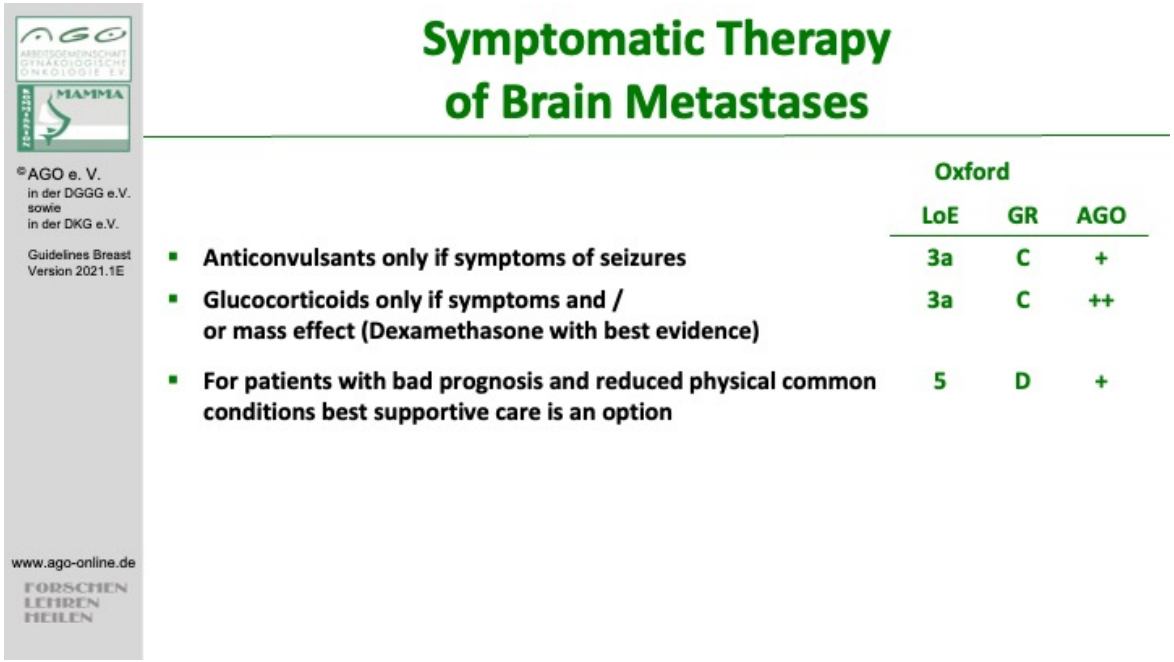

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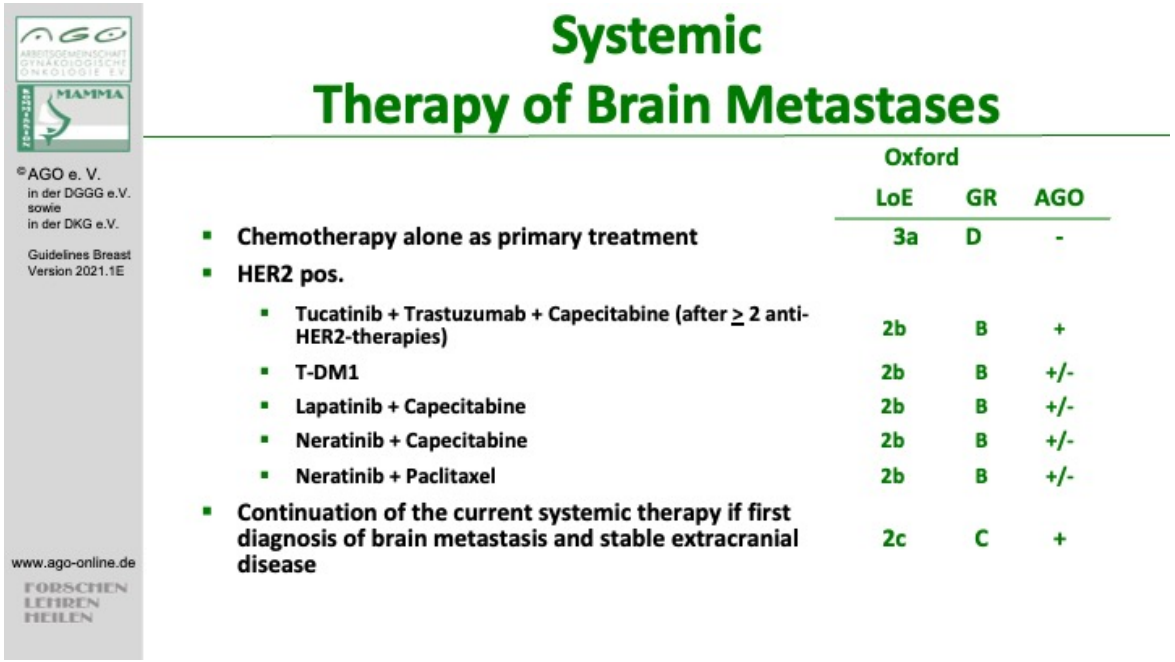

Systemic Therapy of Brain Metastases

	Oxford LoE	GR	AGO
▪ Chemotherapy alone as primary treatment	3a	D	-
▪ HER2 pos.			
▪ Tucatinib + Trastuzumab + Capecitabine (after ≥ 2 anti-HER2-therapies)	2b	B	+
▪ T-DM1	2b	B	+/-
▪ Lapatinib + Capecitabine	2b	B	+/-
▪ Neratinib + Capecitabine	2b	B	+/-
▪ Neratinib + Paclitaxel	2b	B	+/-
▪ Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease	2c	C	+

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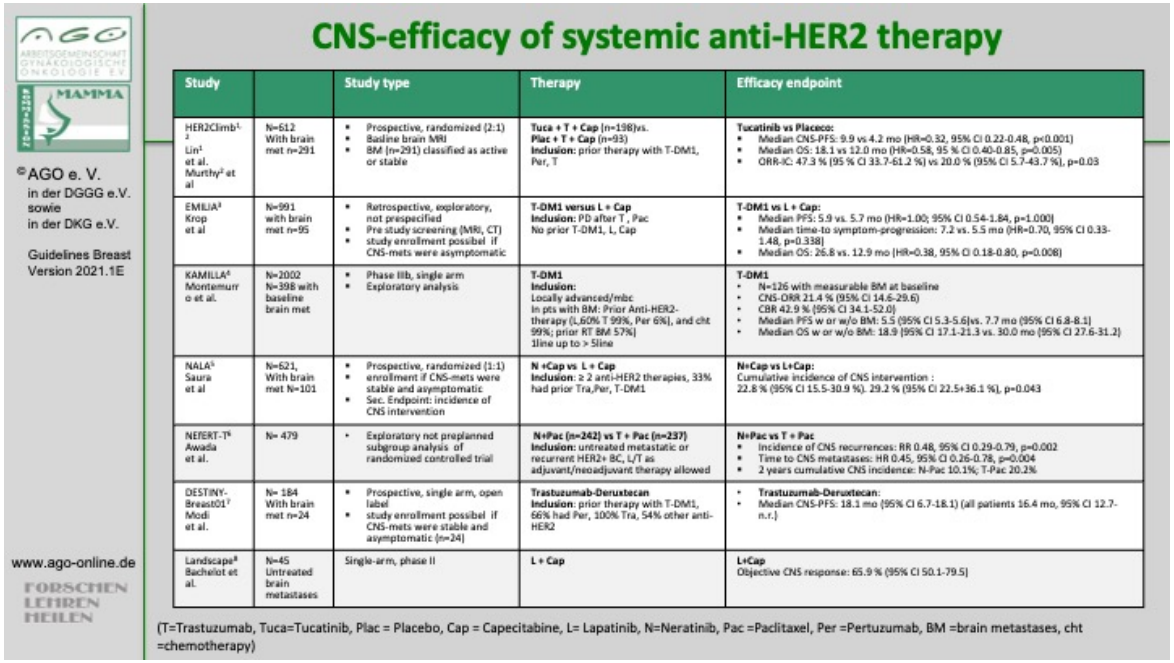

CNS-efficacy of systemic anti-HER2 therapy

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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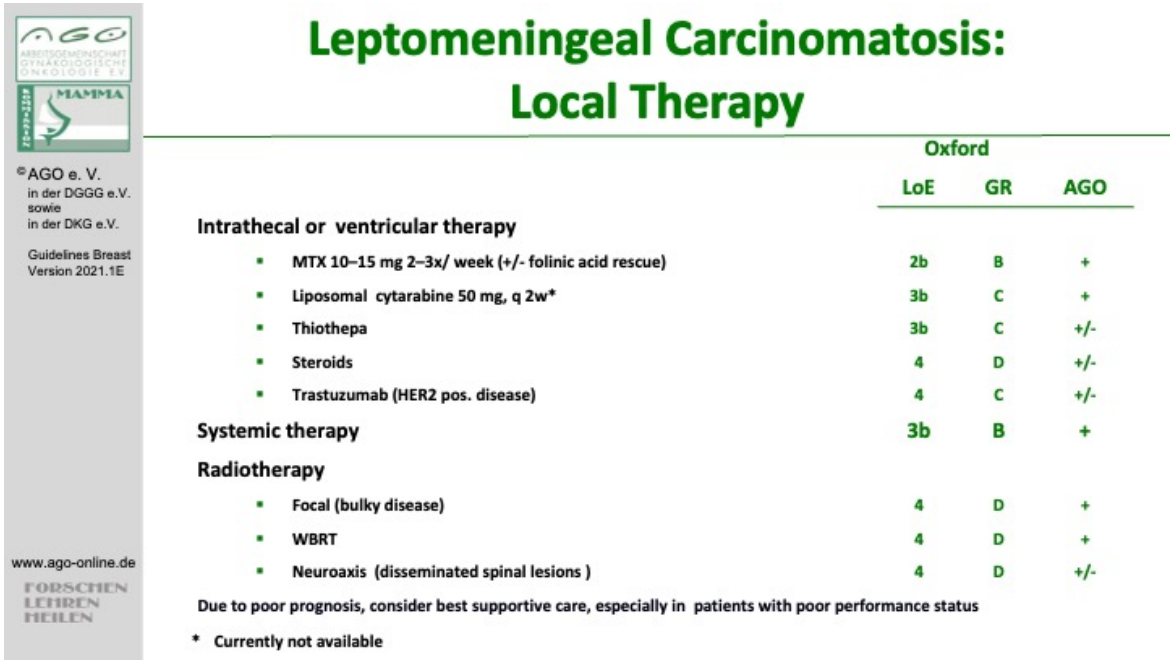

Leptomeningeal Carcinomatosis: Local Therapy

	Oxford LoE	Oxford GR	AGO
Intrathecal or ventricular therapy			
▪ MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)	2b	B	+
▪ Liposomal cytarabine 50 mg, q 2w*	3b	C	+
▪ Thiothepa	3b	C	+/-
▪ Steroids	4	D	+/-
▪ Trastuzumab (HER2 pos. disease)	4	C	+/-
Systemic therapy	3b	B	+
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis (disseminated spinal lesions)	4	D	+/-

Due to poor prognosis, consider best supportive care, especially in patients with poor performance status

* Currently not available

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MTX high dose

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