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CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer

- **Versions 2003–2017:**
  Bischoff / Diel / Friedrich / Gerber / Huober / Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz / Fehm / Witzel

- **Version 2018:**
  Müller / Stickeler

  unter Mitarbeit von:
  Petra Feyer und Dirk Rades (DEGRO)

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CNS Metastases in Breast Cancer – Incidence

- **Breast cancer is the 2nd most common cause of CNS metastases**
- **At autopsy:**
  - **Parenchymal CNS metastases: ~ 30–40%**
  - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (10 % ⇨ 40 %)**
- **Increasing incidence due to**
  - **More effective treatment of extracerebral sites with improved prognosis**
  - **Increasing use of MRI in diagnostic evaluation**
- **Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de)**

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CNS Metastases in Breast Cancer (BC)
Risk Factors

- **Primary Tumor:**
  - **Negative estrogen receptor status (basal-like cell type / triple-negative)**
  - **High grading, high Ki-67 index**
  - **HER2 and/or EGFR (HER1) overexpression**
  - **Molecular subtype (Luminal B, HER2 positive, triple-negative)**

Brain metastases are more likely to be estrogen receptor negative and overexpress HER2 and/or EGFR

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

Graded Prognostic Assessment (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:
GPA 0-1.0 = 3.4 months
GPA 1.5-2.0 = 7.7 months
GPA 2.5-3.0 = 15.1 months
GPA 3.5-4.0 = 25.3 months

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases;
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

Sperduto PW, J Clin Oncol 2012, 30:419-425

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Rades Score* - Worksheet to Estimate Survival from Brain Metastases (BM) by plus chemotherapy Diagnosis

Prognostic Factor	6-months survival rate(%)	Score
age		
≤ 60 Jahre	43	4
≥ 61 Jahre	25	3
Karnofsky-Index		
< 70	8	1
≥ 70	53	5
Extracranial metastases		
no	51	5
yes	24	2
Interval from first diagnosis to WBRT		
≤ 8 months	32	3
> 8 months	36	4

Median survival by Rades-Score:
Rades-Score 9-10 = 2 months
Rades-Score 11-13 = 3 months
Rades-Score 14-16 = 5 months
Rades-Score 17-18 = 12 months

* **Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed, validated in 350 new patients**

Rades et al., STO 2008
Dziggel et al., STO 2013

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Single / Solitary Brain Metastasis

	Oxford LoE	Oxford GR	AGO
Local therapy alone: SRS (≤ 4 cm) o. FSRT o. Resection	2b	B	++
WBRT + Boost (SRS, FSRT) o. Resection + WBRT	2a	B	++
Resection + Irradiation of the tumor bed (without WBRT)	2b	B	+
WBRT alone*	2b	B	+
Hippocampal-sparing	2b	C	+/-

- **WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms, but has no survival benefit. WBRT impaires neurocognitive function.**
- **In case of resection of the tumor the tumorbed has to be irradiated (either local RT or boost in case of WBRT). In general there is no advantage of surgical resection over RT.**

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

* **Patients with reduced general conditions and limited life expectancy**

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Oligo-Brain Metastases

	Oxford LoE	Oxford GR	AGO
Local therapy alone: SRS (≤ 4 cm) or FSRT	**2b**	**B**	**++**
WBRT + Boost (SRS, FSRT)	**2a**	**B**	**++**
WBRT alone *	**2b**	**B**	**+**
Hippocampal-sparing	**2b**	**C**	**+/-**

- **Maximal number of metastases treated by SRS depends on localization, size and additional factors**
- **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 preferred**

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

* **Patients with reduced general conditions and limited life expectancy**

NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy (WBRT) in Addition to Radiosurgery (SRS) in Patients with 1 to 3 Brain Metastases

Study design:
Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.*

Conclusion:
Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.

*** Remark: No hippocampus-sparing was applied**

Brown A, Asher AL, Ballman K, Farace E, Cerhan J, Anderson K, et al. JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839

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

Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

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Factors in favor of neurosurgery:

- Histological verification e.g. after a long recurrence-free interval
- Need for immediate decompression, life-threatening symptoms
- Tumor size not allowing stereotactic radiotherapy

Factors in favor of primary radiotherapy:

- Tumor location poorly amenable to surgery
- More than four lesions

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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	+/-
▪ Radiochemotherapy for control intracerebral	3b	C	-
▪ WBRT in case of recurrence**	4	C	+/-

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

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

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Systemic and Symptomatic Therapy of Brain Metastases*

	Oxford		
	LoE	GR	AGO
▪ Continuation of the actual systemic therapy if first diagnosis of brain metastases and stable extracranial disease	2c	C	+
▪ Lapatinib + Capecitabine as initial treatment (HER2 pos. disease)	1b	B	+/-
▪ Chemotherapy alone as primary treatment	3	D	-
▪ Anticonvulsants only if symptoms of seizures	3	C	+
▪ Glucocorticoids only when symptoms and / or mass effect	3	C	++

* In addition to local therapy

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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