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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Sites of Metastases



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Sites Of Metastases

Specific Approaches to Metastatic Disease

- **Versionen 2002–2021:**
 Albert / Bauerfeind / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm /
 Fersis / Friedrich / Friedrichs / Gerber / Hanf / Janni / Kolberg-Liedtke /
 Kreipe / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Park-Simon
 / Rezai / Rody / Schaller / Schütz / Seegenschmiedt / Solomayer /
 Souchon / Thomssen

- **Version 2022:**
 Kolberg-Liedtke / Solbach

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Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Contralateral axillary metastasis

See also chapters „CNS Metastases “ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“



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Distribution of Breast Cancer Metastases

Risk of breast cancer metastases

- is approx. 20%
- is dependent on molecular breast cancer subtype (i.e., lower in luminal A and higher in HER2-enriched and basal-like breast cancer)
- is decreasing due to more efficacious therapeutic regimens
- about 6% of new breast cancer diagnosis are stage IV and have an estimated 5-y OS rate of 27%

Pattern of breast cancer metastases

- Bone metastases are most common metastases (30-40%), followed by lung (20%) pleura (8%) and liver metastases (isolated liver metastases approx. 5%). Other locations are rare
- Breast cancer is the most common origin of cutaneous metastases and is considered to be the most prevalent primary tumor of all metastases to the orbit
- Metastatic pattern strongly depends on breast cancer molecular biology and efficacy of (targeted) therapy (i.e., compared with luminal A tumors, luminal/HER2 and HER2-enriched tumors are associated with a significantly higher rate of brain, liver, and lung metastases, while Basal-like tumors show a higher rate of brain, lung, and distant nodal metastases but a significantly lower rate of liver and bone metastases)
- Pattern of breast cancer metastases is one of several factors determining disease prognosis

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General Treatment Aspects of Metastases			
	Oxford		
	LoE	GR	AGO
■ Histological / cytological verification	3	B	+
■ Systemic therapy preferred	2a	B	++*
■ Consider surgery of metastases only in case of good response to palliative treatment, oligometastases	2b	C	+
■ Stereotatic Radiotherapy for patients with oligometastases	2a	B	+
■ Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression	5	D	+/-
■ Systemic treatment after surgery	2c	B	++

* See chapters with systemic treatment recommendations



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Wording

Stereotactic Therapy can be referred to as:

SBRT

Stereotactic Body Radiation Therapy

SABR

Stereotactic Ablative Radiotherapy

IGRT

Image Guided Radiation Therapy

Histology

1. Kasraeian S, Allison DC, Ahlman ER et al. A comparison of fine-needle aspiration, core biopsy, and surgical biopsy in the diagnosis of extremity soft tissue masses. Clin Orthop Relat Res. 2010;468:2992-3002.

Local surgery

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Combined surgery of the primary side and metastasis

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Local Therapy in Primary Metastatic Disease			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Surgery (R0) of the primary tumor (individualized procedure in case of oligometastatic disease) <ul style="list-style-type: none"> ■ In case of bone metastases only ■ In case of visceral metastases ■ Axillary surgery for cN1 ■ Sentinel biopsy if cN0 ■ Radiotherapy of the primary tumor <ul style="list-style-type: none"> ■ Alone (without surgery) ■ After local surgical treatment with BCS or mastectomy (according to adjuvant indication) 	1b	B	+/-
	1b	B	-
	3b	B	+/-
	5	D	-
	3a	C	+/-
	2c	B	+

Surgery of the primary tumor (R0)

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Axillary surgery

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Primary metastatic breast cancer - Locoregional therapy (local RT vs. surgery + RT vs. surgery)


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Randomized Phase III Trials ST +/- Surgery of the Primary Tumor					
Trial	n	Therapy prior to randomization	Local Control	Improved OS Primary Endpoint	QoL
ECOG 2108 * ^{1,2} (USA/Kanada) 2001-2016	256	4-8 months systemic therapy	yes	no	ns
Tata Memorial Hospital * ³ (India) 2005-2012	350	chemotherapy	yes	no	-
MF07-01 * ^{4,5,6,7} (Turkey) 2008-2012	278	no systemic therapy	no 10 y LRP: LRT 1% vs 14% ST, s	10 y fu OS: LRT 19% vs. ST 5%, s (HR+, Her2-, < 55 y, solitary bone only metastasis)	ns
ABCSG-28#* ^{8,9} (Austria) 2010-2019	90	no systemic therapy	yes	no	ns
JCOG 1017 (Japan) 2011-2018	410	primary ST	Completed, results not reported so far		

ns not significant, s: significant #trial terminated due to poor recruitment
ST = systemic therapy, LRT= locoregional therapy, LRP = locoregional progression

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Prospective Registry Study (Bone only)

Trial	n	Randomization	Local Control	Improved OS Primary Endpoint	QoL
BOMET MF 14-01# 2014-	505	ST vs LRT (LRT+ST vs. ST+LRT)	yes	3 y fu: improved OS in the LRT group (HR 0.40) HR+, Her2-; Her2+ subgroups, no benefit in triple neg. patients	-

ST = systemic therapy, LRT = locoregional therapy,

1. Soran A, Dogan L, Isik A et al. The Effect of Primary Surgery in Patients with De Novo Stage IV Breast Cancer with Bone Metastasis Only (Protocol BOMET MF 14-01): A Multi-Center, Prospective Registry Study. Ann Surg Oncol. 2021;28(9):5048-5057.

Liver Metastases Local Therapy			
	Oxford		
	LoE	GR	AGO
<p> Resection of liver metastases (R0) <ul style="list-style-type: none"> HR-positive: chemotherapy-sensitive, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases HER2-positive: age < 50 y, metastases < 5 cm, no further metastases </p>	3a	B	+/-
Interventional regional chemotherapy (TACE)*	3b	C	+/-
Interventional regional radiotherapy (SIRT/TARE)*	3b	C	+/-
Stereotactic Radiotherapy with VMAT (SRS-VMAT), other modalities*	2a	B	+/-
Regional ablative procedures (RFA, MWA) <ul style="list-style-type: none"> IRE, LITT, HIFU Cryoablation 	3b	C	+/-
	5	D	-
	3b	C	-

* interdisciplinary decision

CA = cryoablation
 HIFU = high-intensity focused ultrasound
 IRE = irreversible electroporation
 LITT = laser-induced interstitial thermotherapy
 MWA = microwave ablation
 RFA = radiofrequency ablation
 SIRT = selective internal radiotherapy = TARE
 SRS = stereotactic radiosurgery with volumetric modulated arc therapy (VMAT)
 TACE = transarteriel chemoembolization
 TARE = transarteriel radioembolization

Statements:

Resection of liver metastasis (R0)
 HR positive: chemotherapy sensible, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases
 Her2 positive: age < 50 y., metastasis < 5 cm, no further metastases

Diagnostics

1. van Dam PJ, van der Stok EP, Teuwen LA et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. Br J Cancer. 2017 Nov 7;117(10):1427-1441.

Overview

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Statement: Regional radiotherapy

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Statement: Thermoablation

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Pulmonary Metastases Local Therapy			
	Oxford		
	LoE	GR	AGO
<p>■ Before any local therapy: staging and biopsy (CT-guided FNA / CNB or transbronchial FNA, EBUS, VATS)</p>	3a	B	+
<p>■ Resection of pulmonary metastases by VATS or conventional resection</p>			
■ In case of multi-locular metastatic disease	3a	B	-
■ In case of single / few unilateral metastasis with curative intent	3a	B	+/-
■ Thermoablation (CT-guided RFA, LITT)	3b	C	+/-
<p>■ Regional radiotherapy (stereotactic radiotherapy with volumetric intensity modulated arc therapy (SRS-VMAT))</p>	2a	B	+/-

* VATS = video-assisted thoracic surgery

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Overview

1. Lin S, Mo H, Li Y et al. Clinicopathological characteristics and survival outcomes in patients with synchronous lung metastases upon initial metastatic breast cancer diagnosis in Han population. BMC Cancer. 2021 Dec 14;21(1):1330.

Resection of pulmonary metastases by VATS or conventional resection

1. García-Yuste M, Pulmonary metastasectomy in breast cancer. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S170-1.
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Metastasectomy.

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Statement: Thermoablation (CT-guided RFA, LITT)

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Malignant Pleural Effusion (MPE) Local Therapy			
	Oxford		
	LoE	GR	AGO
▪ If short life expectancy, less invasive procedures should be considered	4	C	++
▪ VATS and Talcum-pleurodesis*	1b	B	++
▪ Continuous pleural drainage	2a	B	++
▪ Chemical pleurodesis*			
▪ Talcum powder	1a	B	+
▪ Bleomycin, Doxycycline, Mitoxantrone	2b	C	+/-
▪ Povidone-iodine (20 ml of 10% solution)	1b	B	+
▪ Systemic treatment after pleurodesis	3b	C	+/-
▪ Serial thoracocentesis	4	C	+/-
* Adequate pain-relief VATS: video-assisted thoracoscopic surgery			

If expected survival is short, less invasive procedures should be considered

1. Zamboni MM, da Silva CT Jr, Baretta R et al. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulm Med. 2015 Mar 28;15:29.

VATS and Talcum-pleurodesis

Chemical pleurodesis

Talcum powder

Bleomycin, Doxycycline, Mitoxantrone

Povidone-iodine (20 ml of 10% solution)

Serial thoracocentesis

1. Hirata T et al: Efficacy of pleurodesis for malignant pleural effusions in breast cancer patients. Eur Respir J. 2011 Dec;38(6):1425-30
2. Mohsen TA et al: Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial. Eur J Cardiothorac Surg. 2011 Aug;40(2):282-6.
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Statement: Continuous pleural drainage

1. Cases E, et al: Use of indwelling pleural catheter in the outpatient management of recurrent malignant pleural effusion Arch Bronconeumol. 2009 Dec;45(12):591-6.
2. Demmy TL, Gu L, Burkhalter JE et al. Cancer and Leukemia Group B. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Canc Netw. 2012 Aug;10(8):975-82.
3. Davies HE et al., Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012 Jun 13;307(22):2383-9.
4. Warren WH, Kalimi R, Khodadadian LM et al. Management of malignant pleural effusions using the Pleur(x) catheter. Ann Thorac Surg. 2008 Mar;85(3):1049-55.
5. Hak CC, Sivakumar P, Ahmed L. Safety of indwelling pleural catheter use in patients undergoing chemotherapy: a five-year retrospective evaluation. BMC Pulm Med. 2016 Mar 11;16:41.

Malignant Ascites Local Therapy			
	Oxford		
	LoE	GR	AGO
Ascites:			
▪ Puncture, drainage in symptomatic patients	4	D	++
▪ Continuous drainage of ascites	3b	D	+
▪ Systemic therapy	3b	D	++
▪ Local chemotherapy	3b	D	+/-

1. Saâda E, et al: Pathogenesis and management of refractory malignant ascites. Bull Cancer. 2011 Jun;98(6):679-87.
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Malignant Pericardial Effusion Local Therapy			
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	LoE	GR	AGO
	3b	B	++
	4	C	++
	4	C	+
Symptomatic pericardial effusion:			
<ul style="list-style-type: none"> Drainage, fenestration Combination with optimized systemic therapy VATS (video-assisted thoracic surgery) Ultrasound-guided puncture and instillation of cytotoxic / targeted compounds <ul style="list-style-type: none"> Bleomycin, cisplatin, mitomycin C, mitoxantrone etc., Bevacizumab 			
	4	C	+/-

1. Pokieser W, Cassik P, Fischer G et al. Malignant pleural and pericardial effusion in invasive breast cancer: impact of the site of the primary tumor. Breast Cancer Res Treat. 2004 Jan;83(2):139-42.
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Bone Marrow Infiltration Associated with Pancytopenia			
	Oxford		
	LoE	GR	AGO
Weekly chemotherapy with*:			
▪ Epirubicin, Doxorubicin, Paclitaxel	4	D	++
▪ Capecitabine	4	D	++
HER2-positive:			
▪ Add anti-HER2-treatment	5	D	++
Hormone receptor-positive:			
▪ Endocrine-based therapy	4	C	+
* Consider pre-treatment			


1. Kopp HG, et al: Symptomatic bone marrow involvement in breast cancer-clinical presentation, treatment, and prognosis: a single institution review of 22 cases. Anticancer Res. 2011 Nov;31(11):4025-30.
2. Freyer G, et al: Palliative hormone therapy, low-dose chemotherapy, and bisphosphonate in breast cancer patients with bone marrow involvement and pancytopenia: report of a pilot experience. Eur J Intern Med. 2000 Dec 20;11(6):329-333.
3. Ardavanis A, et al: Low-dose capecitabine in breast cancer patients with symptomatic bone marrow infiltration: a case study. Anticancer Res. 2008 Jan-Feb;28(1B):539-41.
4. Krockenberger M, et al: Prolonged clinical benefit from platinum-based chemotherapy in a patient with metastatic triple negative breast cancer. Eur J Gynaecol Oncol. 2009;30(4):449-51. 2.
5. Pahouja G, Wesolowski R, et al: Stabilization of bone marrow infiltration by metastatic breast cancer with continuous doxorubicin. Cancer Treat Commun. 2015 ; 3: 28–32.
6. Artac M, Koral L, Toy H et al. Complete response and long-term remission to anti-HER2 combined therapy in a patient with breast cancer presented with bone marrow metastases. J Oncol Pharm Pract. 2014 Apr;20(2):141-5.
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Soft Tissue Metastasis Local Therapy			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Surgery of limited locoregional metastasis (skin, muscular, nodal) with complete resection (R0) after exclusion of further metastases 	4	C	+
<ul style="list-style-type: none"> ■ Radiotherapy (after surgery or, if immediate surgery is not indicated): <ul style="list-style-type: none"> ■ Soft tissue metastases ■ Paresis, spinal cord compression ■ Plexus infiltration 	3b 2b 3b	C C C	+ ++ ++

1. Wilson B, et al: Resolution of extensive leptomeningeal metastasis and clinical spinal cord compression from breast cancer using weekly docetaxel chemotherapy. Breast Cancer Res Treat. 2012 Jan;131(1):343-6. Epub 2011 Oct 26.
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5. Berlière M, Duhoux FP, Taburiaux L et al. The place of extensive surgery in locoregional recurrence and limited metastatic disease of breast cancer: preliminary results. Biomed Res Int. 2015;2015:782654. doi: 10.1155/2015/782654. Epub 2015 Mar 18.



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Oligo-Metastases

Contralateral Axillary Metastasis

“OLIGO-METASTATIC DISEASE in CONTRALATERAL AXILLA Contralateral axillary nodal metastasis (in the absence of contralateral primary) as initial diagnosis of recurrent disease is considered stage 4 metastatic breast cancer.

However, after prior local therapy to ipsilateral axilla for early breast cancer, subsequent metachronous contralateral axillary nodal metastasis, either alone or concurrent with an in-breast ipsilateral recurrence, could be considered and treated as a regional metastasis (due to altered lymphatic drainage), and has the potential for long survival or cure with a multidisciplinary approach”

ABC6 2021: LoE: Expert opinion/NA (85%)

1. Magnoni F, Colleoni M, Mattar D et al. Contralateral Axillary Lymph Node Metastases from Breast Carcinoma: Is it Time to Review TNM Cancer Staging? Ann Surg Oncol. 2020 Oct;27(11):4488-4499.
2. Díaz-Roldán J, Eguía-Larrea M, Rubio-Sánchez T et al. Systematic review of synchronous contralateral axillary metastases in breast cancer: really M1 disease? Breast Cancer. 2021 Oct 15. doi: 10.1007/s12282-021-01293-2. Online ahead of print. Review.
3. Nash AL, Thomas SM, Plichta JK et al. Contralateral Axillary Nodal Metastases: Stage IV Disease or a Manifestation of Progressive Locally Advanced Breast Cancer? Ann Surg Oncol. 2021 Oct;28(10):5544-5552.
4. SABCS 2021 Educational Session Local Therapy of the Primary and Beyond in Patients with Advanced Disease.