

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Sites of Metastases

Sites Of Metastases

Specific Approaches to Metastatic Disease

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

■ Version 2024:

Bauerfeind / Reimer

Sites of Metastases

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

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General Treatment Aspects of Metastases

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- **Histological verification**
- **Cytological verification, if histology not possible**
- **Systemic therapy preferred**
- **Consider surgery of metastases in case of good response to palliative treatment, oligometastases (cave: no clear definition available)**
- **Stereotatic Radiotherapy for patients with oligometastases**
- **Local-interventional ablative procedure**
- **Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression**
- **Systemic treatment after surgery**

	Oxford		
	LoE	GR	AGO
	3	B	++
	3	B	+
	2a	B	++*
	2b	C	+/-
	2b	B	+/-
	3b	C	+/-
	5	D	+/-
	2c	B	++

* See chapters with systemic treatment recommendations

Different Definitions of Oligometastatic Disease (OMD)

Societies / Organisations or inclusion criteria of prospective clinical trials (selection)

ESMO	limited or low-volume metastatic disease; up to five lesions in total, not necessarily in the same organ; all potentially amenable to receive local treatment
ESTRO/ASTRO	1-5 metastatic lesions; controlled primary tumor optional, all metastatic sites must be safely treatable
ESTRO/EORTC OligoCare project	Different clinical scenarios of OMD: synchronous vs. metachronous, repeat vs. de novo OMD, oligorecurrence vs. oligoprogression, oligopersistence vs. oligoprogression, induced vs. genuine OMD.
ABC-7	Low volume metastatic disease (up to 5 lesions and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status; highly dependent on the imaging method used. Note: OMD sites need to be solid; excludes pleural effusions, ascites, leptomeningeal disease.
SABR-COMET trial (NCT05784428)	≤ 5 metastatic sites; small subset for breast cancer patients (n = 18)
NRG-BR002 trial (NCT02364557)	controlled locoregional disease and ≤ 4 metastases (standard imaging), ≤ 12 months systemic therapy without progression
OLIGOMA trial (NCT04495309)	up to 5 clinically manifest metastases, maximum of 3 cerebral metastases known

Local Therapy in Primary Metastatic Disease

Oxford

LoE GR AGO

	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 	1b	B	+/-
<ul style="list-style-type: none"> Axillary surgery for cN1 	1b	B	-
<ul style="list-style-type: none"> Axillary surgery for cN1 	3b	B	+/-
<ul style="list-style-type: none"> Sentinel biopsy if cN0 	5	D	-
<ul style="list-style-type: none"> 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) 	3a	C	+/-
	2c	B	+/-

Randomized Phase III Trials ST +/- Surgery of the Primary Tumor

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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		

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



Prospective Registry Study (Bone only)

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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	-

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FORSCHEN
LEHREN
HEILEN

ST = systemic therapy, LRT = locoregional therapy,

Liver Metastases

Local Therapy

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	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ 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 	3a	B	+/-
<ul style="list-style-type: none"> ▪ Interventional regional chemotherapy (TACE)* 	3b	C	+/-
<ul style="list-style-type: none"> ▪ Interventional regional radiotherapy (SIRT/TARE)* 	3a	B	+/-
<ul style="list-style-type: none"> ▪ Stereotactic Radiotherapy with VMAT (SRS-VMAT), other modalities* 	2a	B	+/-
<ul style="list-style-type: none"> ▪ Regional ablative procedures (RFA, MWA) <ul style="list-style-type: none"> ▪ IRE, LITT, HIFU ▪ Cryoablation 	3b 5 3b	C D C	+/- - -

* interdisciplinary decision

Pulmonary Metastases

Local Therapy

Oxford

LoE GR AGO

- | | LoE | GR | AGO |
|---|-----|----|-----|
| <ul style="list-style-type: none"> Before any local therapy: staging and biopsy, histology for exclusion of second tumor | 3a | B | + |
| <ul style="list-style-type: none"> Resection of pulmonary metastases by VATS or conventional resection <ul style="list-style-type: none"> In case of multi-locular metastatic disease In case of single / few unilateral metastasis | 3a | B | - |
| <ul style="list-style-type: none"> In case of single / few unilateral metastasis | 3a | B | +/- |
| <ul style="list-style-type: none"> Thermoablation (CT-guided RFA, LITT) | 3b | C | +/- |
| <ul style="list-style-type: none"> Regional radiotherapy
(stereotactic radiotherapy with volumetric intensity modulated arc therapy (SRS-VMAT)) | 2a | B | +/- |

* VATS = video-assisted thoracic surgery

Malignant Pleural Effusion (MPE)

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■ 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	+
■ Intrathoracic chemotherapy	2b	C	+/-
■ Povidone-iodine (20 ml of 10% solution)	1b	B	+
■ Serial thoracentesis	4	C	+/-

* Adequate pain-relief

VATS: video-assisted thoracoscopic surgery

Malignant Ascites

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Ascites:

- Puncture, drainage in symptomatic patients
- Continuous drainage of ascites
- Systemic therapy
- Local chemotherapy

	Oxford		
	LoE	GR	AGO
Puncture, drainage in symptomatic patients	4	D	++
Continuous drainage of ascites	3b	D	+
Systemic therapy	3b	D	++
Local chemotherapy	3b	D	-

Malignant Pericardial Effusion

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Symptomatic pericardial effusion:

- Drainage, fenestration
- Combination with optimized systemic therapy
- VATS (video-assisted thoracic surgery)
- Ultrasound-guided puncture and instillation of cytotoxic / targeted compounds
 - Bleomycin, cisplatin, mitomycin C, mitoxantrone etc., Bevacizumab

Oxford		
LoE	GR	AGO
3b	B	++
4	C	++
4	C	+
4	C	+/-

Bone Marrow Infiltration Associated with Pancytopenia

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Weekly chemotherapy with*: <ul style="list-style-type: none"> ■ Epirubicin, Doxorubicin, Paclitaxel ■ Capecitabine ■ HER2-positive: <ul style="list-style-type: none"> ■ anti-HER2-treatment ■ Hormone receptor-positive: <ul style="list-style-type: none"> ■ Endocrine-based therapy 	4 4 5 3b	D D D C	++ ++ ++ +

* Consider pre-treatment

Soft Tissue Metastasis

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- **Surgery of limited locoregional metastasis (e.g. skin, muscular, nodal) with complete resection (R0) after exclusion of further metastases**
- **Radiotherapy in*:**
 - **Soft tissue metastases**
 - **Paresis, spinal cord compression**
 - **Plexus infiltration**

Oxford		
LoE	GR	AGO
4	C	+/-
3b	C	+/-
2b	C	++
3b	C	++

* Exception: acute indication for surgery

Oligo-Metastases

Contralateral Axillary Metastasis

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“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”

ABC-7 (2023): LoE: Expert opinion/NA (85%)