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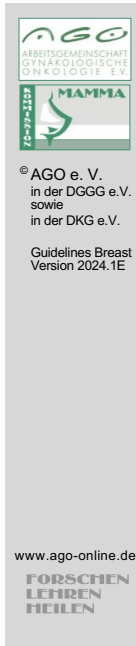
Guidelines Breast
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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Sites of Metastases



Sites Of Metastases

Specific Approaches to Metastatic Disease

- **Versions 2002–2023:**

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

1. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.



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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)“ and „Osteo-oncology“

General Treatment Aspects of Metastases

	Oxford		
	LoE	GR	AGO
▪ Histological verification	3	B	++
▪ Cytological verification, if histology not possible	3	B	+
▪ Systemic therapy preferred	2a	B	++*
▪ Consider surgery of metastases in case of good response to palliative treatment, oligometastases (cave: no clear definition available)	2b	C	+/-
▪ Stereotatic Radiotherapy for patients with oligometastases	2b	B	+/-
▪ Local-interventional ablative procedure	3b	C	+/-
▪ 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

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

1. Warschkow R, Güller U, Tarantino I et al. Improved Survival After Primary Tumor Surgery in Metastatic Breast Cancer: A Propensity-adjusted, Population-based SEER Trend Analysis. Ann Surg. 2016 Jun;263(6):1188-98.

2. Yoo TK, Chae BJ, Kim SJ et al. Identifying long-term survivors among metastatic breast cancer patients undergoing primary tumor surgery. *Breast Cancer Res Treat.* 2017 Aug;165(1):109-118
3. Barinoff J, Schmidt M, Schneeweiss A et al.: Primary metastatic breast cancer in the era of targeted therapy - Prognostic impact and the role of breast tumour surgery. *Eur J Cancer.* 2017 Sep;83:116-124.
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12. Soran A, Ozmen V, Ozbas S et al. MF07-01 Study Group. Primary Surgery with Systemic Therapy in Patients with de Novo Stage IV Breast Cancer: 10-year Follow-up; Protocol MF07-01 Randomized Clinical Trial. *J Am Coll Surg.* 2021 Dec;233(6):742-751.
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14. Chen YQ, Xu JW, Xu XF et al. Predicting the survival benefit of local surgery in patients aged 70 years or older with stage IV breast cancer: A population-based analysis. *Breast.* 2021 Oct;59:124-134.

Radiotherapy in oligometastatic breast cancer

1. Trovo M, Furlan C, Polesel J et al.: Radical radiation therapy for oligometastatic breast cancer: Results of a prospective phase II trial. *Radiother Oncol.* 2018 Jan;126(1):177-180.
2. Thelen WSME, Peulen HMU, Lalezari F et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non—small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol* 2019; 5:1276–1282
3. Weykamp F, König L, Seidensaal K et al. Extracranial Stereotactic Body Radiotherapy in Oligometastatic or Oligoprogressive Breast Cancer. *Front Oncol.* 2020 Jun 26;10:987.
4. Palma DA, Olson R, Harrow S et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet.* 2019 May 18;393(10185):2051-2058.
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9. Chmura S, Winter KA, Robinson C et al. Evaluation of Safety of Stereotactic Body Radiotherapy for the Treatment of Patients With Multiple Metastases: Findings From the NRG-BR001 Phase 1 Trial. *JAMA Oncol.* 2021 Jun 1;7(6):845-852.
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13. Chmura SJ, Winter KA, Woodward WA, et al. : NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557). *J Clin Oncol* 40, 2022. (suppl 16; abstr 1007)

Overviews

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2. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in survival in metastatic breast cancer with treatment advances: meta-analysis and systematic review. 2018. <https://doi.org/10.1093/jncics/pky062>.
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Combined surgery of the primary side and metastasis

1. Bilani N, Yaghi M, Singh Jabbal I et al. Survival benefit of a combined surgical approach in patients with metastatic breast cancer. *J Surg Oncol*. 2021 Dec;124(8):1235-1241.
2. Bilani N, Elson L, Liang H et al. Effect of Surgery at Primary and Metastatic Sites in Patients With Stage IV Breast Cancer. *Clin Breast Cancer*. 2021 Jun;21(3):170-180.

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. oligopersistence, oligopersistence vs. oligopersistence, 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



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1. Gennari A, André F, Barrios CH, et al.: ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021; 32: 1475-1495.
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4. ABC-7 consensus: Cardoso F et al., *Breast* 2024 (in preparation)

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) 	<p>1b</p> <p>1b</p> <p>3b</p> <p>5</p> <p>3a</p> <p>2c</p>	<p>B</p> <p>B</p> <p>B</p> <p>D</p> <p>C</p> <p>B</p>	<p>+/-</p> <p>-</p> <p>+/-</p> <p>-</p> <p>+/-</p> <p>+/-</p>

Surgery of the primary tumor (R0)

1. Xiao W, Zou Y, Zheng S et al. Primary tumor resection in stage IV breast cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2018 Oct;44(10):1504-1512.
2. Tosello G, Torloni MR, Mota BS et al. Breast surgery for metastatic breast cancer. Cochrane Database Syst Rev. 2018 Mar 15;3:CD011276. doi: 10.1002/14651
3. Soran A, Ozmen V, Ozbas S et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol. 2018 Oct;25(11):3141-3149.
4. Fitzal F, Bjelic-Radisic V, Knauer M et al. Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIIVE Trial Ann Surg. 2019 Jun;269(6):1163-1169.
5. Khan SA Plenary Session ASCO 2020 Late Breaking Abstract 2
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8. Kahn SA. Educational Session SABCS 2021, Thursday 9th Dec; Session: Local Therapy of the Primary and Beyond in Patients with Advanced Disease, Presentation: Local therapy of the primary tumor in de novo Stage IV breast cancer.

9. Peng P, Chen JY, Han YT et al. Impact of surgery on survival in breast cancer with bone metastases only: a SEER database retrospective analysis. BMC Surg. 2021 Oct 26;21(1):378.

Axillary surgery

1. Bitencourt A, Rossi Saccarelli C, Morris EA et al. Regional Lymph Node Involvement Among Patients With De Novo Metastatic Breast Cancer. JAMA Netw Open. 2020 Oct 1;3(10):e2018790.
2. De Wit A, Arbion F, Desille-Gbaguidi H et al. Role of surgery in patients with synchronous metastatic breast cancer: Is there a need for axillary lymph node removal? J Gynecol Obstet Hum Reprod. 2021 Apr;50(4):101771.

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

1. Choi SH, Kim JW, Choi J et al. Locoregional Treatment of the Primary Tumor in Patients With De Novo Stage IV Breast Cancer: A Radiation Oncologist's Perspective . Clin Breast Cancer. 2018 Apr;18(2):e167-e178.
2. Pons-Tostivint E, Kirova Y, Lusque A. Survival Impact of Locoregional Treatment of the Primary Tumor in De Novo Metastatic Breast Cancers in a Large Multicentric Cohort Study: A Propensity Score-Matched Analysis. Ann Surg Oncol. 2019 Feb;26(2):356-365.
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5. Stahl K, Wong W, Dodge D et al. Benefits of Surgical Treatment of Stage IV Breast Cancer for Patients With Known Hormone Receptor and HER2 Status. Ann Surg Oncol. 2021 May;28(5):2646-2658.
6. Kim YJ, Kim YJ, Kim YB et al. Effect of Postoperative Radiotherapy after Primary Tumor Resection in De Novo Stage IV Breast Cancer: A Multicenter Retrospective Study (KROG 19-02). Cancer Res Treat. 2021 Jul 13.



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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

1. Khan SA Plenary Session ASCO 2020 Late Breaking Abstract 2
2. Kahn SA. Educational Session SABCS 2021, Thursday 9th Dec; Session: Local Therapy of the Primary and Beyond in Patients with Advanced Disease, Presentation: Local therapy of the primary tumor in de novo Stage IV breast cancer.
3. Badwe R, Hawaldar R, Nair N et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet 2015 Oct;16(13):1380-8.
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reported quality-of-life outcomes of the prospective randomized multicenter ABCSG-28 Positive Trial. BMC Cancer. 2020 May 6;20(1):392.



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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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
<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	+/-
▪ Interventional regional chemotherapy (TACE)*	3b	C	+/-
▪ Interventional regional radiotherapy (SIRT/TARE)*	3a	B	+/-
▪ 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	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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Local surgery

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8. Rangarajan K, Lazzereschi L, Votano D, Hamady Z. Breast cancer liver metastases: systematic review and time to event meta-analysis with comparison between available treatments. *Ann R Coll Surg Engl.* 2023 Apr;105(4):293-305. doi: 10.1308/rcsann.2021.0308. Epub 2022 Feb 17. PMID: 35175853; PMCID: PMC10066639.

Statement: Regional chemotherapy

1. Liberchuk AN, Deipolyi AR. Hepatic Metastasis from Breast Cancer. *Semin Intervent Radiol* 2020; 37(5): 518-526.
2. Duan XF, Dong NN, Zhang T et al. Treatment outcome of patients with liver-only metastases from breast cancer after mastectomy: a retrospective analysis. *J Cancer Res Clin Oncol* 2011; 137: 1363-1370.
3. Vogl TJ, Nour-Eldin NA, Hammerstingl RM et al. Microwave Ablation (MWA): Basics, Technique and Results in Primary and Metastatic Liver Neoplasms – Review Article. *Rofo* 2017; 189: 1055-1066.
4. Lin YT, Médioni J, Amouyal G et al. Doxorubicin-Loaded 70-150 µm Microspheres for Liver-Dominant Metastatic Breast Cancer: Results and Outcomes of a Pilot Study. *Cardiovasc Intervent Radiol* 2017; 40: 81-89.
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Statement: Regional radiotherapy

1. Chang J, Charalel R, Noda C et al. Liverdominant Breast Cancer Metastasis: A Comparative Outcomes Study of Chemoembolization Versus Radioembolization. *Anticancer Res* 2018; 38: 3063-3068.
2. Trovo M, Furlan C, Polesel J et al. Radical radiation therapy for oligometastatic breast cancer: Results of a prospective phase II trial. *Radiother Oncol.* 2018 Jan;126(1):177-180.
3. Onal, C.; Guler, O.C.; Yildirim, B.A. Treatment outcomes of breast cancer liver metastasis treated with stereotactic body radiotherapy. *Breast* 2018, 42, 150–156.
4. Mahadevan, A.; Blanck, O.; Lanciano, R et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis-clinical outcomes from the international multi-institutional RSSearch(R) Patient Registry. *Radiat. Oncol.* 2018, 13, 26.
5. Weykamp F, König L, Seidensaal K et al. Extracranial Stereotactic Body Radiotherapy in Oligometastatic or Oligoprogressive Breast Cancer. *Front Oncol.* 2020 Jun 26;10:987.
6. Franzese C, Comito T, Viganò L et al. Liver Metastases-directed Therapy in the Management of Oligometastatic Breast Cancer. *Clin Breast Cancer.* 2020 Dec;20(6):480-486.
7. Ridouani F, Soliman MM, England RW et al. Relationship of radiation dose to efficacy of radioembolization of liver metastasis from

- breast cancer. *Eur J Radiol*. 2021 Mar;136:109539.
8. Helmberger T, Golfieri R, Pech M et al. On behalf of the CIRT Steering Committee; On behalf of the CIRT Principal Investigators. Clinical Application of Trans-Arterial Radioembolization in Hepatic Malignancies in Europe: First Results from the Prospective Multicentre Observational Study CIRSE Registry for SIR-Spheres Therapy (CIRT). *Cardiovasc Intervent Radiol*. 2021 Jan;44(1):21-35.
 9. Schatka I, Tschernig M, Rogasch JMM et al. Selective Internal Radiation Therapy in Breast Cancer Liver Metastases: Outcome Assessment Applying a Prognostic Score. *Cancers (Basel)*. 2021 Jul 27;13(15):3777.
 10. Lehrer EJ, Singh R, Wang M et al. Safety and Survival Rates Associated With Ablative Stereotactic Radiotherapy for Patients With Oligometastatic Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2021 Jan 1;7(1):92-106.
 11. Viani GA, Gouveia AG, Alexander V Louie AV et al. Stereotactic body radiotherapy to treat breast cancer oligometastases: A systematic review with meta-analysis. *Meta-Analysis Radiother Oncol*. 2021 Nov; 164:245-250.
 12. Liu C, Tadros G, Smith Q, Martinez L, Jeffries J, Yu Z, Yu Q. Selective internal radiation therapy of metastatic breast cancer to the liver: A meta-analysis. *Front Oncol*. 2022 Nov 24;12:887653. doi: 10.3389/fonc.2022.887653. PMID: 36505832; PMCID: PMC9729947.
 13. Rangarajan K, Lazzereschi L, Votano D, Hamady Z. Breast cancer liver metastases: systematic review and time to event meta-analysis with comparison between available treatments. *Ann R Coll Surg Engl*. 2023 Apr;105(4):293-305. doi: 10.1308/rcsann.2021.0308. Epub 2022 Feb 17. PMID: 35175853; PMCID: PMC10066639.

Statement: Thermoablation

1. Xiao YB, Zhang B, Wi YI. Radiofrequency ablation versus hepatic resection for breast cancer liver metastasis: a systematic review and meta-analysis *J Zhejiang Univ-Sci B (Biomed & Biotechnol)* 2018 19(11):829-843
2. Bale R, Richter M, Dünser M et al. Stereotactic Radiofrequency Ablation for Breast Cancer Liver Metastases. *J Vasc Interv Radiol*. 2017 Dec 19. pii: S1051-0443(17)30911-9
3. Bai XM, Yang W, Zhang ZY et al. Long-term outcomes and prognostic analysis of percutaneous radiofrequency ablation in liver metastasis from breast cancer. *Int J Hyperthermia*. 2019 Jan 1;35(1):183-193.
4. Franzese C, Comito T, Viganò L et al. Liver Metastases-directed Therapy in the Management of Oligometastatic Breast Cancer. *Clin Breast Cancer*. 2020 Dec;20(6):480-486.

Pulmonary Metastases

Local Therapy

	Oxford		
	LoE	GR	AGO
▪ Before any local therapy: staging and biopsy, histology for exclusion of second tumor	3a	B	+
▪ Resection of pulmonary metastases by VATS or conventional resection			
▪ In case of multi-locular metastatic disease	3a	B	-
▪ In case of single / few unilateral metastasis	3a	B	+/-
▪ Thermoablation (CT-guided RFA, LITT)	3b	C	+/-
▪ Regional radiotherapy	2a	B	+/-
(stereotactic radiotherapy with volumetric intensity modulated arc therapy (SRS-VMAT))			

* VATS = video-assisted thoracic surgery

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.
2. Soh J, Komoike Y, Mitsudomi T. Surgical therapy for pulmonary metastasis of breast cancer. Transl Cancer Res. 2020 Aug;9(8):5044-5052. doi: 10.21037/tcr.2020.03.63. PMID: 35117870; PMCID: PMC8798234.

Resection of pulmonary metastases by VATS or conventional resection

1. Patrini D, Panagiotopoulos N, Lawrence D et al. Surgical management of lung metastases. Br J Hosp Med (Lond). 2017 Apr 2;78(4):192-198.
2. Meng D, Fu L, Wang L et al. Video-assisted thoracoscopic surgery versus open thoracotomy in pulmonary metastasectomy: a meta-analysis of observational studies. Interact Cardiovasc Thorac Surg. 2016 Feb;22(2):200-6.
3. Endoh M, Shiono S, Yamauchi Y et al. Pulmonary metastasectomy for pulmonary metastasis of breast cancer has a limited prognostic impact: a multi-institutional retrospective analysis. J Thorac Dis. 2020 Nov;12(11):6552-6562.
4. Bilani N, Yaghi M, Main O et al. Metastasectomy versus radiation of secondary sites in stage IV breast cancer: Analysis from a national cancer registry. Breast. 2021 Dec;60:185-191.

Statement: Thermoablation (CT-guided RFA, LITT)

1. Vogl TJ, et al: Microwave ablation therapy: clinical utility in treatment of pulmonary metastases. Radiology. 2011 Nov;261(2):643-51.
2. Ewert R, Opitz C. Pulmonary function testing before ablative methods] Radiologe. 2004 Jul;44(7):708-10. 4.
3. Diederich S, Hosten N: Percutaneous ablation of pulmonary tumours: state-of-the-art 2004 Radiologe. 2004 Jul;44(7):658-62.

Statement: Regional Radiotherapy

1. Ricco A, Davis J, Rate W et al. Lung metastases treated with stereotactic body radiotherapy: the RSSearch® patient Registry's experience. Radiation Oncology (2017) 12: oi: 10.1186/s13014-017-0773-4
2. Lehrer EJ, Singh R, Wang M et al. Safety and Survival Rates Associated With Ablative Stereotactic Radiotherapy for Patients With Oligometastatic Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2021 Jan 1;7(1):92-106.
3. Viani GA, Gouveia AG, Alexander V Louie AV et al. Stereotactic body radiotherapy to treat breast cancer oligometastases: A systematic review with meta-analysis. Meta-Analysis Radiother Oncol. 2021 Nov; 164:245-250.

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	+
▪ Intrathoracic chemotherapy	2b	C	+/-
▪ Povidone-iodine (20 ml of 10% solution)	1b	B	+
▪ 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. Thomas R, Fysh ETH, Smith NA et al. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. JAMA. 2017 Nov 21;318(19):1903-1912.
2. Bibby AC, Dorn P, Psallidas I, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur J Cardiothorac Surg. 2019 Jan 1;55(1):116-132.
3. Kapp CM, Lee HJ. Malignant Pleural Effusions. Clin Chest Med. 2021 Dec;42(4):687-696. Review
4. Dipper A, Jones HE, Bhatnagar R, et al. Interventions for the management of malignant pleural effusions: an updated network meta-

analysis. Eur Respir Rev 2021; 30: 210025.

Statement: Continuous pleural drainage

1. 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.
2. 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.

Statement: Intrathoracic chemotherapy

1. Karampinis I, Dionysopoulou A, Galata C, Almstedt K, Grilli M, Hasenburger A, Roessner ED. Hyperthermic intrathoracic chemotherapy for the treatment of malignant pleural effusion caused by breast and ovarian cancer: A systematic literature review and pooled analysis. Thorac Cancer. 2022 Apr;13(7):883-888. doi: 10.1111/1759-7714.14361. Epub 2022 Feb 22. PMID: 35194945; PMCID: PMC8977169.

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. Korpi S, Salminen VV, Piili RP et al. Therapeutic Procedures for Malignant Ascites in a Palliative Care Outpatient Clinic. J Palliat Med. 2018 Jun;21(6):836-841.
2. Lew M, Cantley R, Heider A et al. Diagnosis and categorization of malignant effusions: A 6-year review from a single academic institution. Diagn Cytopathol. 2021 May;49(5):615-621.

Malignant Pericardial Effusion

Local Therapy

Symptomatic pericardial effusion:	Oxford		
	LoE	GR	AGO
▪ Drainage, fenestration	3b	B	++
▪ Combination with optimized systemic therapy	4	C	++
▪ VATS (video-assisted thoracic surgery)	4	C	+
▪ Ultrasound-guided puncture and instillation of cytotoxic / targeted compounds			
▪ Bleomycin, cisplatin, mitomycin C, mitoxantrone etc., Bevacizumab	4	C	+/-

1. Strobbe A, Adriaenssens T, Bennett J et al. Etiology and Long-Term Outcome of Patients Undergoing pericardiocentesis. J Am Heart Assoc. 2017 Dec 23;6(12). pii: e007598.
2. Numico G, Cristofano A, Ocelli M et al. Prolonged Drainage and Intrapericardial Bleomycin Administration for Cardiac Tamponade Secondary to Cancer-Related Pericardial Effusion. Medicine (Baltimore). 2016 Apr;95(15):e3273
3. Lambert A, Salleron J, Kieffer A, Raymond P, Geoffrois L, Gavaille C. Intrapericardial instillation of bleomycin prevents recurrence of malignant pericardial effusions: Series of 46 cases and comprehensive literature review. Bull Cancer. 2020 Jul-Aug;107(7-8):756-762.
4. Kotake M, Imai H, Kaira K, Fujisawa T, Yanagita Y, Minato K. Intrapericardial carboplatin in the management of malignant pericardial effusion in breast cancer: a pilot study. Cancer Chemother Pharmacol. 2019 Sep;84(3):655-660. .
5. Chen D, Song X, Shi F et al. Greater efficacy of intracavitary infusion of bevacizumab compared to traditional local treatments for patients with malignant cavity serous effusion. Oncotarget. 2017 May 23;8(21):35262-35271.
6. Lew M, Cantley R, Heider A et al. Diagnosis and categorization of malignant effusions: A 6-year review from a single academic institution. Diagn Cytopathol. 2021 May;49(5):615-621.

Bone Marrow Infiltration Associated with Pancytopenia

	Oxford		
	LoE	GR	AGO
▪ Weekly chemotherapy with*:			
▪ Epirubicin, Doxorubicin, Paclitaxel	4	D	++
▪ Capecitabine	4	D	++
▪ HER2-positive:			
▪ anti-HER2-treatment	5	D	++
▪ Hormone receptor-positive:			
▪ Endocrine-based therapy	3b	C	+

* Consider pre-treatment

1. 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.
2. 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.
3. Pahouja G, Wesolowski R, Reinbolt R et al. Stabilization of bone marrow infiltration by metastatic breast cancer with continuous doxorubicin. Cancer Treat Commun. 2015;3:28-32.
4. Yamaguchi T, Masumoto M, Sakurai U et al. Disseminated Carcinomatosis of the Bone Marrow from Occult Breast Cancer Responding to a Sequence of Endocrine Therapy. Case Rep Oncol. 2020 Feb 24;13(1):193-199.

Soft Tissue Metastasis Local Therapy

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Surgery of limited locoregional metastasis (e.g. skin, muscular, nodal) with complete resection (R0) after exclusion of further metastases 	4	C	+/-
<ul style="list-style-type: none"> ▪ Radiotherapy in*: <ul style="list-style-type: none"> ▪ Soft tissue metastases ▪ Paresis, spinal cord compression ▪ Plexus infiltration 	3b	C	+/-
	2b	C	++
	3b	C	++

* Exception: acute indication for surgery

1. Kong JH, et al: Patterns of skin and soft tissue metastases from breast cancer according to subtypes: relationship between EGFR overexpression and skin manifestations. *Oncology*. 2011;81(1):55-62. Epub 2011 Sep 16.
2. 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.



Oligo-Metastases Contralateral Axillary Metastasis

“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%)

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
5. ABC-7 consensus: Cardoso F et al., *Breast* 2024 (in preparation)