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

Specific Sites of Metastases

Specific Sites Of Metastases

Local Approaches to Metastatic Disease

- **Versions 2002–2020:**

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

- **Version 2021:**

Mundhenke / Park-Simon / Thomssen

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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Specific Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Any other organs

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

General Treatment Aspects of Metastases

	Oxford		
	LoE	GR	AGO
▪ Histological / cytological verification	3	B	+
▪ Systemic therapy preferred	2a	B	++*
▪ Consider surgery only in case of good response to palliative treatment, oligometastases	2b	C	+
▪ Radiation for patients in good physical condition with late onset of oligometastases	3a	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	5	D	++

* See chapters with systemic treatment recommendations

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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2. Cameron D. Removing the primary tumour in metastatic breast cancer. Lancet Oncol. 2015 Oct;16(13):1284-5.
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4. Soran A et al. A randomized controlled trial evaluating resection of the primary tumor in women presenting with de novo stage IV breast cancer; Turkish study (MF07-01). J Clin Oncol 34, 2016 (suppl; abstr 1005)
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12. 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 POSYTIME Trial *Ann Surg*. 2019 Jun;269(6):1163-1169.
13. Khan SA Plenary Session ASCO 2020 Late Breaking Abstract 2
14. Lopez-Tarruella S, Escudero MJ, Pollan M et al. Survival impact of primary tumor resection in de novo metastatic breast cancer patients (GEICAM/El Alamo Registry). *Sci Rep*. 2019 Dec 27;9(1):20081.
15. Amabile MI, Frusone F, De Luca A et al. Locoregional Surgery in Metastatic Breast Cancer: Do Concomitant Metabolic Aspects Have a Role on the Management and Prognosis in this Setting? *J Pers Med*. 2020 Nov 13;10(4):227.

Radiotherapy in oligometastatic breast cancer

1. Scorsetti M, Franceschini D, De Rose F et al.: Stereotactic body radiation therapy: A promising chance for oligometastatic breast cancer. *Breast*. 2016 Apr;26:11-7.
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. 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.
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Overviews

1. Bale R, Putzer D, Schullian P. Local Treatment of Breast Cancer Liver Metastasis. *Cancers (Basel)*. 2019 Sep; 11(9): 1341.
2. Kent CL, McDuff SGR, Salama JK. Oligometastatic breast cancer: where are we now and where are we headed?-a narrative review. *Ann Palliat Med*. 2020 Sep 10:apm-20-1128.
3. Liberchuk AN, Deipolyi AR. Hepatic Metastasis from Breast Cancer. *Semin Intervent Radiol*. 2020 Dec;37(5):518-526.

Local Therapy in Primary Metastatic Disease

	Oxford		
	LoE	GR	AGO
▪ Surgery (R0) of the primary tumor (no OS Benefit)*	1b	B	-
▪ In case of symptoms by primary tumor	5	D	+/-
▪ In case of bone metastases only	2b	B	+/-
▪ In case of visceral metastases	2b	B	-
▪ Axillary surgery for cN1	5	D	+/-
▪ Sentinel if cN0	5	D	-
▪ Radiotherapy of the primary tumor			
▪ Alone (without surgery)	3a	C	+/-
▪ After local surgical treatment with BCS or mastectomy (according to adjuvant indication)	3a	C	+

* Individualized procedure in case of oligometastatic disease


Operation (R0) des Primärtumors

1. 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.
2. Headon H, Wazir U, Kasem A et al. Surgical treatment of the primary tumour improves the overall survival in patients with metastatic breast cancer: A systematic review and meta-analysis. Molecular and Clinical Oncol. 2016;4;863-867
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5. 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.
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Lokoregionäre Therapie (alleinige Bestrahlung vs OP+Bestrahlung vs OP) bei primär metastasiertem Mammakarzinom

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.
3. Wang W, Liu J, Wang J et al. Impact of Locoregional Treatment on Prognosis of de novo Stage IV Breast Cancer: A Retrospective Long-Term Study of Chinese Population. Gynecol Obstet Invest. 2019;84(3):248-258.
4. Bourgier C, Khodari WA, Vataire AL et al. Breast radiotherapy as part of loco-regional treatments in stage IV breast cancer patients with oligometastatic disease. Radiother Oncol. 2010 Aug;96(2):199-203



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Randomized Phase III Trials

Trial	n	Prior to Randomization	Local Control	Improved OS Primary Endpoint	QoL
ECOG-Acrin 2108	256	4-8 months systemic therapy	yes	no	ns
Tata Memorial Hospital	350	chemotherapy	yes	no	-
MF07-01	278	no systemic therapy	yes	no in post analysis evaluation improved OS (notably in solitary bone mets.)	-
ABCSG-28*	90	no systemic therapy	yes	no	ns
JCOG 1017	410	completed, results not reported so far			

ns not significant *trial terminated due to poor recruitment



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1. 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.
2. 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 POSYTIVE Trial Ann Surg. 2019 Jun;269(6):1163-1169.
3. Khan SA Plenary Session ASCO 2020 Late Breaking Abstract 2
4. 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.

Liver Metastases Local Therapy

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Resection of liver metastases (R0) HR-positive: chemotherapy-sensitive, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases HER2-positive: age < 50y, metastasis < 5 cm, no further metastasis 	3a	B	+/-
<ul style="list-style-type: none"> Regional chemotherapy 	3b	C	+/-
<ul style="list-style-type: none"> Regional radiotherapy [SIRT, stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT), radiochemo-embolization, other modalities] 	3b	C	+/-
<ul style="list-style-type: none"> Thermoablation (RFA, LITT, cryotherapy) 	3b	C	+/-

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

1. Bale R, Putzer D, Schullian P. Local Treatment of Breast Cancer Liver Metastasis. Cancers (Basel). 2019 Sep; 11(9): 1341.
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3. Liberchuk AN, Deipolyi AR. Hepatic Metastasis from Breast Cancer. Semin Intervent Radiol. 2020 Dec;37(5):518-526.

Local surgery

1. van Walsum GA, de Ridder JA, Verhoef C et al. Dutch Liver Surgeons Group Resection of liver metastases in patients with breast cancer: survival and prognostic factors. *Eur J Surg Oncol*. 2012 Oct;38(10):910-7. doi: 10.1016/j.ejso.2012.04.015. Epub 2012 Jun 7.
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3. Sadot E, Lee SY, Sofocleous CT et al. Hepatic Resection or Ablation for Isolated Breast Cancer Liver Metastasis: A Case-control Study with Comparison to Medically Treated Patients. *Ann Surg*. 2016 Jul;264(1):147-154.
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9. Wen J, Ye F, Xie F, Liu D et al. The role of surgical intervention for isolated breast cancer liver metastasis: Results of case-control study with comparison to medical treatment. *Cancer Med*. 2020 Jul;9(13):4656-4666.
10. 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.

Statement: Regional chemotherapy

1. Martin RC et al. Optimal outcomes for liver-dominant metastatic breast cancer with transarterialchemoembolization with drug-eluting beads loaded with doxorubicin. *Breast Cancer Res Treat*. 2012;132(2):753-63.
2. Petrelli F, Borgonovo K, Lonati V et al. Regression of liver metastases after treatment with intraperitoneal catumaxomab for malignant ascites due to breast cancer. *Target Oncol*. 2012 Nov 30
3. Eichler K et al. Transarterial chemoembolisation (TACE) with gemcitabine: phase II study in patients with liver metastases of breast

cancer. *Eur J Radiol.* 2013;82(12):e816-22

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Statement: Regional radiotherapy

1. Hoffmann RT, et al: Radiofrequency ablation after selective internal radiation therapy with Yttrium90 microspheres in metastatic liver disease-Is it feasible? *Eur J Radiol.* 2010 Apr;74(1):199-205
2. Vogl TJ, Farshid P, Naguib NN et al. Thermal ablation therapies in patients with breast cancer liver metastases: A review. *Eur Radiol.* 2012 Oct 13. [Epub ahead of print]
3. Akhlaghpour S, Aziz-Ahari A, Amoui M et al. Short-term effectiveness of radiochemoembolization for selected hepatic metastases with a combination protocol. *World J Gastroenterol.* 2012 Oct 7;18(37):5249-59.
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8. 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.
9. 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.
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11. 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.

Statement: Thermoablation

1. Dwivedi DN, Pal S, Pande GK. Management of liver metastases: cut, cryo, coagulate or chemotherapy. Trop Gastroenterol. 2001 Apr-Jun;22(2):57-64. Review
2. Seifert JK, et al. Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature. Technol Cancer Res Treat. 2004 Apr;3(2):151-63.
3. Vogl TJ, et al. MR-guided laser-induced thermotherapy (LITT) of liver tumours: experimental and clinical data. Int J Hyperthermia. 2004 Nov;20(7):713-24
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5. Vogl TJ, et al. Magnetic resonance-guided laser-induced interstitial thermotherapy of breast cancer liver metastases and other noncolorectal cancer liver metastases: an analysis of prognostic factors for long-term survival and progression-free survival. Invest Radiol. 2013;48(6):406-12.
6. Xiao YB, Zhang B, Wi YL. 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
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8. 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.
9. 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 surgery: staging and biopsy (CT-guided FNA / CNB or transbronchial FNA, EBUS)	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 with curative intent	3a	B	+/-
▪ Thermoablation (CT-guided RFA, LITT)	3b	C	+/-
▪ Regional radiotherapy (e.g. stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT))	3a	B	+/-

* VATS = video-assisted thoracic surgery

Vor Operation: Staging und Biopsie (fine-needle aspiration with CT-guidance or transbronchial needle aspiration)

Resektion pulmonaler Metastasen (VATS oderr konventionelle Resektion García-Yuste M, Pulmonary metastasectomy in breast cancer. J

Thorac Oncol. 2010 Jun;5(6 Suppl 2):S170-1.

1. Nichols FC Pulmonary metastasectomy Thorac Surg Clin. 2012 Feb;22(1):91-9, REVIEW
2. Omar M. Rashid and Kazuaki Takabe The evolution of the role of surgery in the management of breast cancer lung metastasis. J Thorac Dis. 2012 August; 4(4): 420–424. REVIEW
3. Kyler W, Laski P: Surgical approach to pulmonary metastases from breast cancer. Breast J. 2012 Jan;18(1):52-7.
4. Meimarakis G et al. Prolonged overall survival after pulmonary metastasectomy in patients with breast cancer. Ann Thorac Surg. 2013;95(4):1170-80.
5. Fan J, Chen D, Du H et al. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. J Thorac Dis. 2015 Aug;7(8):1441-51. doi: 10.3978/j.issn.2072-1439.2015.08.10.
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2;78(4):192-198.


8. 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.
9. 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.

Statement: Thermoablation (CT-gesteuert 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: Regionale Radiotherapie

1. Macchia G, Deodato F, Cilla S et al. Volumetric intensity modulated arc therapy for stereotactic body radiosurgery in oligometastatic breast and gynecological cancers: feasibility and clinical results. *Oncol Rep*. 2014 Nov;32(5):2237-43.
2. 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



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Malignant Pleural Effusions (MPE)

Incidence:

- ~ 10 % of patients with metastatic breast cancer
- ~ 17-30 % of all MPE are caused by breast cancer

Clinical presentation:

- Extensive MPE are mostly due to malignancy
- The majority of MPE are symptomatic [dyspnea (80%), dull chest pain (30%), nonproductive cough (10%)]
- Survival is related to the presence of additional metastases, age, ECOG PS and extent of involving the pleural surface

Diagnostic procedures:

- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion [cytology (→ 50% false negative), histology by thoracoscopy]

1. Bielsa S et al: Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung. 2011 Apr;189(2):151-5.
2. Ried M, Hofmann HS.: The treatment of pleural carcinosis with malignant pleural effusion. Dtsch Arztebl Int. 2013 May;110(18):313-8.
3. 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..
4. Li Z, Pantanowitz L, Khalbuss WE et al. Challenges in diagnosing metastatic breast carcinoma in fluid cytology. Diagn Cytopathol. 2014 Nov;42(11):1006-8. doi: 10.1002/dc.23067. Epub 2014 Mar 8.
5. Guerrini GP, Lo Faso F, Vagliasindi A et al. The Role of Minimally Invasive Surgery in the Treatment of Lung Metastases. J Invest Surg. 2016 Oct 3:1-6.
6. Meyer C, Bartsch D, Mirow N et al. Video-Assisted Laser Resection of Lung Metastases-Feasibility of a New Surgical Technique. Thorac Cardiovasc Surg. 2017 Jan 22.
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9. Jany B, Welte T. Pleural Effusion in Adults—Etiology, Diagnosis, and Treatment. Dtsch Arztebl Int. 2019 May; 116(21): 377–386.

10. Ferreiro L, Suárez-Antelo J, Álvarez-Dobaño JM et al. Malignant Pleural Effusion: Diagnosis and Management. Can Respir J. 2020; 2020: 2950751

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	++
▪ Chemical pleurodesis*			
▪ Talcum powder	1a	B	+
▪ Bleomycin, Doxycycline, Mitoxantrone	2b	C	+/-
▪ Povidone-iodine (20 ml of 10% solution)	1b	B	+
▪ Continuous pleural drainage	2a	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

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VATS and Talcum-pleurodesis

Chemical pleurodesis

Talcum powder

Bleomycin, Doxycycline, Mitoxantrone

Povidone-iodine (20 ml of 10% solution)

Serial thoracocentesis

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Statement: Continuous pleural drainage

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Malignant Ascites Local Therapy

Ascites:

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

Oxford		
LoE	GR	AGO
4	D	++
3b	D	+
3b	D	++
3b	D	+/-

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Malignant Pericardial Effusion

Local Therapy

Symptomatic pericardial effusion:

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

	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 compounds			
▪ Bleomycin, cisplatin, mitomycin C, mitoxantrone etc.	4	C	+/-
▪ Bevacizumab	4	C	+/-

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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			

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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 metastasis 	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 metastasis ■ Paresis, spinal cord compression ■ Plexus infiltration 	3b 2b 3b	C C C	+ ++ ++

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