Specific Sites of Metastases
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Local Approaches to Metastatic Disease

- **Version 2002:**
  Dall / Fersis / Friedrich

- **Versions 2003–2014:**
  Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Fehm / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Maass / Oberhoff / Rezai / Schaller / Seegenschmiedt / Solomayer / Souchon

- **Version 2015:**
  Bischoff / Diel
Specific Sites of Metastases

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

Consider also chapter „CNS Metastases“ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“
## General Aspects of Metastases Surgery or Ablation

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- **Histological / cytological verification**
- **Systemic treatment preferred**
- **Consider surgery only in case of good response to palliative treatment**
- **Metastases surgery is an option in good condition pts. with late onset oligometastases**
- **Surgical treatment in the case of pain, exulceration, persistance after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression**
- **Systemic treatment after surgery**

* See chapters with systemic treatment recommendations
Breast Surgery in Primary Metastatic Disease

- Local treatment (R0) of primary tumor
- Axillary surgery for cN1
- Sentinel in cN0
Liver Metastasis
Local Therapy

- **Resection of liver metastasis (R0)**
  - Individual cases (liver function) with resectable metastases
    - HR positive; chemotherapy sensible
- **Regional chemotherapy**
- **Regional radiotherapy**
  - (SIRT, radiochemoembolization, other modalities)
- **Thermoablation**
  - (RFA, LITT, cryotherapy)
Pulmonary Metastases
Local Therapy

- VATS or conventional resection 3b C +/-
- Thermoablation (CT-guided RFA, LITT) 3b C +/-
Malignant Pleural Effusions (MPE)

Incidence:
- ~ 10 % of all breast cancer patients
- ~ 50 % of pat. with advanced breast cancer
- ~ 30 % of all MPE are caused by breast cancer

Clinical presentation:
- Extensive MPE are mostly due to malignancy
- The majority of MPE are symptomatic
- Survival is related to the presence of additional metastases, age and extent of involving the pleural surface

Diagnostic procedures:
- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion (cytology, histology by thoracoscopy)
Malignant Pleural Effusion (MPE) Local Therapy

- VATS and Talcum-pleurodesis*  1b B  ++
- Chemical pleurodesis
  - Talcum slurry  1a B  +
  - Bleomycin, Doxycycline, Mitoxantrone  2b C  +/-
  - Povidone iodide  3b C  +/-
- Continuous pleural drainage  2a B  +
- Systemic treatment after pleurodesis  3b C  +/-
- Local antibody therapy (i.e. Catumaxomab)  3b C  -
- Repeated pleural drainage  5 D  +/-

* Adequate pain-relief
VATS: video-assisted thoracoscopic surgery
Malignant Ascites
Local Therapy

Treatment according to:
Symptoms
Clinical manifestations
Anticipated response to systemic therapy

Ascites:
- Puncture, drainage
- Local chemotherapy
- Systemic therapy
- Local antibody therapy (i.e. Catumaxomab)

Oxford / AGO LoE / GR

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Symptomatic pericardial effusion:

- Drainage, fenestration
  - Oxford / AGO LoE / GR: 3b B ++
- VATS (video-assisted thorac. surgery)
  - Oxford / AGO LoE / GR: 4 D +
- US-guided puncture + instillation of mitoxantron, cisplatin
  - Oxford / AGO LoE / GR: 4 D +/-
Bone Marrow Involvement
Associated with Pancytopenia

Weekly chemotherapy with*:
  Epirubicin, Doxorubicin, Paclitaxel

Capecitabine

HER2 pos.: add anti-HER2

Treatment

* Consider pre-treatment
Soft Tissue Metastasis
Local Therapy

Radiotherapy (if no immediate surgery is indicated or even after surgery):

- Paresis, spinal cord compression
  - Oxford / AGO LoE / GR: 2b C ++
- Plexus infiltration
  - Oxford / AGO LoE / GR: 3b C ++
- Soft tissue metastasis
  - Oxford / AGO LoE / GR: 3b C +
Specific Sites of Metastases (2/13)

Further information:


Screened guidelines:
NCI (National Cancer Institute, 2013): http://www.cancer.gov
CMA (Canadian Medical Association, 2013): http://www.cmaj.ca

No references
Specific Sites Of Metastases (3/13)

Further information:

Specific sites of metastases are liver, lung, pleura, pericard, ascites, bone marrow, soft tissue (muscle, subcutaneous fatty tissue, fascia etc.). Breast cancer metastases in the orbita, adrenals, ovaries, uterus, stomach, colon, gall bladder a.s.o. are very seldom seen clinically. So there are only case reports or series. In such cases treatment options must discussed individual.

No references
The systemic treatment of metastatic disease is standard. In general, surgery of distant metastases of breast cancer should be considered in patients with a good health condition, oligometastases and a long distance between primary treatment and the occurrence of metastases.(1-5). Good response to palliative treatment may also indicate patients who will benefit from breast surgery. Reported improved overall survival might be the result of patients selection. Before surgery is done metastases should be confirmed as such one by histology. By that a secondary malignancy can be excluded. A re-evaluation of receptor- and HER2-status in metastases is mandatory, because a receptor-shift occurs in nearly 20% with an impact on systemic treatment. Other indications for surgical intervention are symptoms like pain, exulceration or persistence after systemic treatment.

Because no data from prospective studies are available, clinicians must weigh retrospective experiences and clinical judgment in deciding whether to offer surgery or techniques for tumor disturbance to these patients. An ongoing trial, E2108 (http://clinicaltrials.gov/show/NCT01242800) has been designed to assess the effect of breast surgery in metastatic patients responding to first-line systemic therapy.

References:

17. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) SABCS [S2-03], 2013
**Breast Surgery in Primary Metastatic Disease (5/13)**

*Further information:*

The management of primary stage IV (metachronous or primary metastatic) breast cancer focuses on systemic therapy for distant sites. The impact of local treatment extent on overall survival is still under discussion. However retrospective data on more than 30,000 women from North America and Europe have now been published, showing a robust association between surgery or radiotherapy for the primary tumor and prolonged survival.\(^{(1)}\) Many questions remain, most importantly, whether this observed association reflects a selection of women with good prognosis for primary site therapy; others relate to the fraction of women in published studies who were diagnosed with metastatic disease postoperatively, whether specific subsets of metastases and biological subtypes would derive greater benefit, and the appropriate timing and extent of local therapy. Depending on the extent of metastatic disease, a local excision of primary tumor or mastectomy with sufficient health margins is recommended.\(^{(2-6)}\) An axillary surgery is only indicated for bulky disease. The impact of local radiotherapy on survival is unknown. It should be mentioned, that there are reports, which could not find an advantage regarding overall survival for local surgery in this situation.

*References:*


9. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) SABCS [S2-03], 2013


Liver Metastasis - Local Therapy (6/13)

Further information:

Resection of liver metastases should only be performed if histological verification was done, if R0-resection is feasible and no extrahepatic metastases were present. Other procedures like regional radiotherapy as well as thermoablation are indicated in individual cases. The efficacy of the last ones is primarily determined by preablation tumor size and location in relation to the hilum. There are no data to legitimate a regional chemotherapy of liver alone. Mostly a survival benefit for surgery or other ablation techniques have been reported. However this could be the result of patients selection. Diagnostic laparoscopy in combination with intraoperative ultrasound should be planned in future experience.

References:

Resection of liver metastases:


Systemic Reviews:


Regional chemotherapy: (TACE= transarterial chemoembolization)

**SIRT (selective internal radiation therapy):**


**RFA (Radiofrequency ablation):**


**LITT (Laser-induced Thermotherapy):**


**Cyrotherapy:**


*Target Therapy*

Pulmonary Metastases Local Therapy (7/13)

Further information:

For proven pulmonary metastases, the level of evidence for a curative approach is low, but some patients might benefit from a metastasectomy followed by an appropriate systemic treatment. In accordance with treatment of liver metastases resection of lung metastases should only be performed if R0-resection is feasible and if histological verification was done. Other procedures like thermoablation are indicated in individual cases.

References:

Resection:


**Thermoablation:**


**Radio Frequency Ablation:**

Malignant Pleural Effusion (8/13)

Further information:

Metastatic breast cancer is the second-ranking cause of malignant pleural effusion (MPE), resulting in dyspnoea and reduced subjective well-being. About 10% of all patients develop this clinical complication, in almost 50% of these cases malignant pleural effusion is the first sign of metastatic disease. Median time from primary diagnosis of the cancer to the appearance of pleural effusion is 42 months. It should be treated in symptomatic cases exclusively. Tumor type, extent of involving the pleural surfaces, age and extra-pleural metastases influences the success of a pleurodesis, regardless of the sclerosing agent used. Malignant effusions due to mesothelioma and lung cancer are particularly prone to a failed procedure. (2)

References:

Further information:

Thoracoscopy with Talcum pleurodesis is the treatment option of choice for malignant pleural effusion. The main procedure for chemical pleurodesis is talcum slurry. Bleomycin, Doxycycline and Mitoxantrone are individual options. Povidone-iodine can be considered as a good alternative to TTP to ensure effective pleurodesis for patients with malignant pleural effusion due to MBC. The drug is available, cost effective and safe, can be given through a thoracostomy tube and can be repeated if necessary. There is no approval for povidone iodide in Germany.

The CALGB trial 9334 showed that bedside talcum pleurodesis was equivalent to thorascopic pleurodesis. Two randomized studies could show that indwelling pleural catheter or tunneled catheter (versus thorascopic pleurodesis) for palliation of malignant pleural effusion is a therapeutic and quality of life sustaining alternative. Retrospectively study confirmed a higher efficacy of pleurodesis followed by systemic treatment may be superior to that of systemic treatment alone with respect to local control of pleural effusions (8.5 versus 4.1 months) in breast cancer patients. Indwelling pleural catheters are indicated in individual cases. Catumaxomab is not recommended because of its side effects.

References:

VATS and talcum-pleurodesis


**Indwelling catheter/pleural drain**


**Antibody therapy:**

**Malignant Ascites - Local Therapy (10/13)**

*Further information:*

Malignant ascites are the cancer-associated accumulation of fluids in the peritoneal cavity. The cancers most commonly associated to ascites are ovarian (37%), pancreato-biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%). After histological confirmation and re-evaluation of receptors the most effective treatment consist in adequate systemic treatment. Management of malignant ascites takes place in the context of palliative care and aims at improving the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab remains an option in individual cases. It has to be payed attention to the side effects.

*References:*

Further information:

Malignant pericardial effusion and cardiac tamponade remains a rarity, which are known complications of many advanced malignancies such as breast cancer, lung cancer, lymphomas and leukemias. In general overall survival is low, due to other metastatic localizations. The standard treatment of malignant effusion and cardiac tamponade has not yet been defined. Physicians should consider the status and the prognosis of each case. In symptomatic patients drainage and fenestration are the treatment options of choice. VATS is an alternative treatment option. In individual cases US-guided puncture with instillation of mitoxantrone is possible.

References:

Bone Marrow Involvement Associated with Pancytopenia (12/13)

Further information:

The choice between supportive care or specific anticancer treatment for poor performance status (PS) breast cancer patients with multimetastatic disease and pancytopenia due to bone marrow involvement (BMI) often remains a clinical dilemma. If hormonal treatment options have been exhausted, concomitant weekly low-dose chemotherapy (anthracycline, paclitaxel or cabecitabine) and either bisphosphonates or RANK-Ligands antibodies are indicated. Low-dose chemotherapy with epirubicin or paclitaxel as well as treatment with anti-HER2-therapy is the therapy of choice for patients with bone marrow involvement and pancytopenia. Otherwise it has been reported that even in patients with severe BMI-associated cytopenia, aggressive combination treatment regimens were effective, since most patients show improved marrow function after chemotherapy and long-lasting survival is possible.

References:

Soft Tissue Metastasis - Local Radiotherapy (13/13)

Further information:

Local radiotherapy is the most important treatment for patients with paresis or spinal cord compression, who cannot be operated or have failed to systemic treatment. Even after surgery a concomitant radiotherapy and a systemic treatment is indicated. Plexus infiltration and other inoperable soft tissue metastasis should be treated by radiotherapy.

References: