EBreast II

Management of Metastatic breast cancer

Co-funded by the
Erasmus+ Programme
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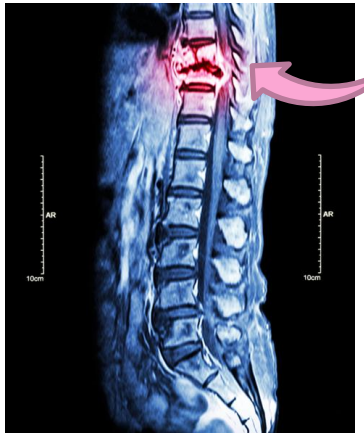
In this lecture about metastatic breast cancer (MBC):

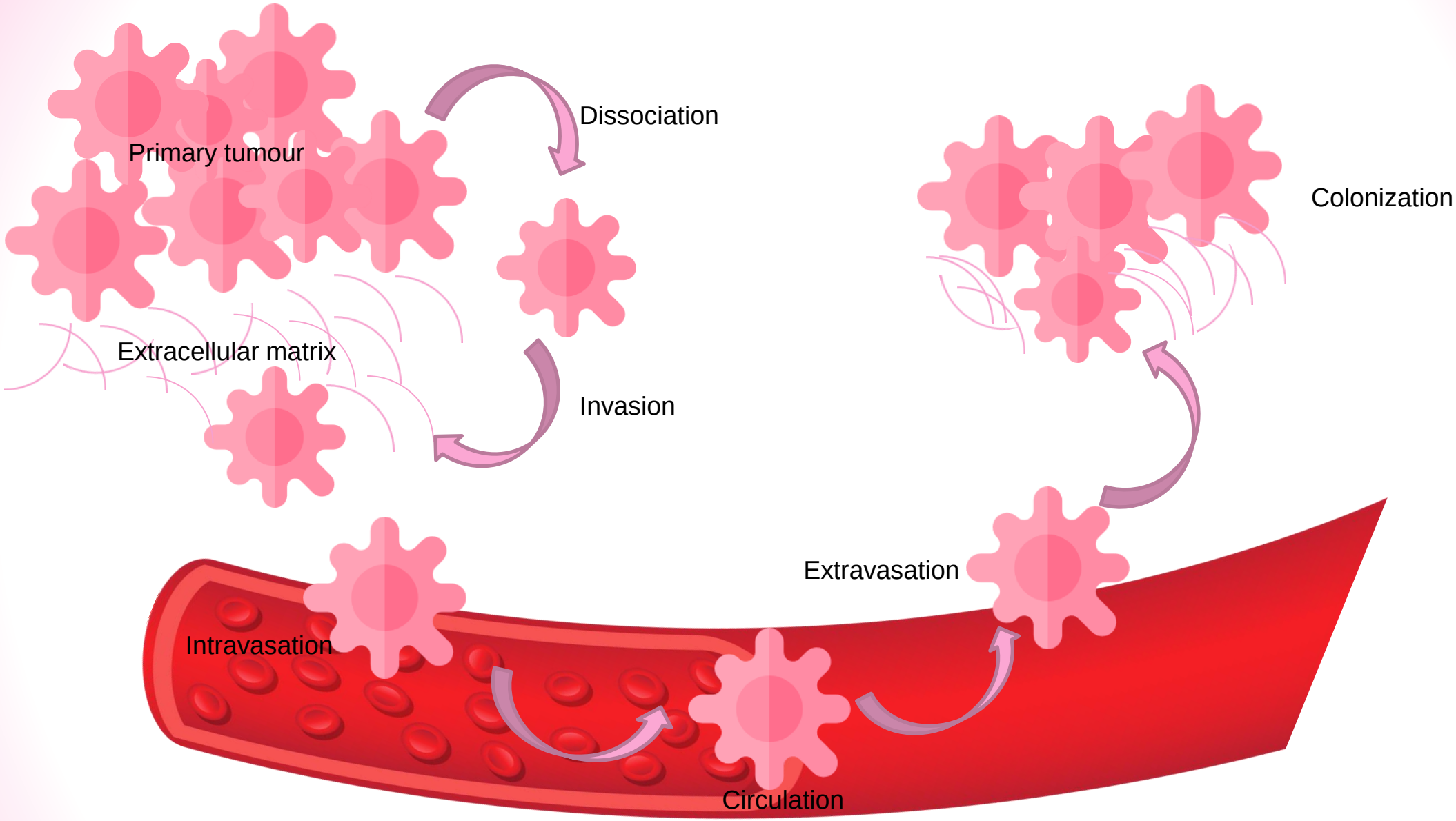
1. What is metastasis?
2. Key facts of MBC
3. Common symptoms of MBC
4. Epidemiology of MBC
5. Treatment options for MBC
6. Staging and risk assessment
7. Tests on tumour biology
8. Treatment pathway and factors underpinning the treatment choice
9. Assessment of disease status
10. Treatment side-effects, patient support and palliative care
11. Prognosis

What is metastasis?

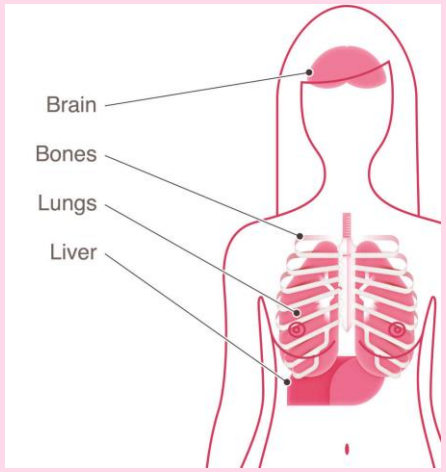
A multistep process in which cancer cells escape and migrate from the primary tumour to other locations of the body to form a new, secondary tumour



Canva.com


Primary tumour
Dissociation
Extracellular matrix
Invasion
Colonization
Extravasation
Intravasation
Circulation

Key facts of metastatic breast cancer



www.nationalbreastcancer.org

Metastatic breast cancer (MBC) or stage IV breast cancer is cancer that has spread (metastasized) from the breast to another part of the body. Breast cancers most often metastasize to bones, lungs, liver and brain in some cases. It happens when breast cancer cells break off a breast tumor and move through the body in the bloodstream or lymphatic system.

It is important to understand that metastasized cancer cells are still breast cancer cells not that for example bone metastasis become bone cancer.

1/3 De Novo

2/3 Have been treated for earlier stage before

Most commonly, recurrence appears in the first 3 years after treatment, yet some 15-20 year cases

There is always a risk! Maintaining healthy lifestile and being aware of the common symptoms.

Continuing with hormonal treatment

But if the cancer was considered cured, why is it even a possibility that it ever comes back?

It is always possible that some cancer cells have survived initial treatment being resistant to radiation or systemic therapies. They have travelled to other parts of the body but remain dormant or in other cases, will spread, grow and become metastatic lesions.

Roughly 30% (considering all earlier stages) of the women treated for breast cancer will develop distant metastases at some time.

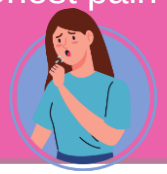
Why the cancer cells become active again after even so many years? →Stress?!

The risk of recurrence is also tied to the stage of initial diagnosis. Stage III→ Risk of recurrence in the next 15y is around 40%, Stage I→around 10%

Survival rates have increased! Average in some regions even around 25%

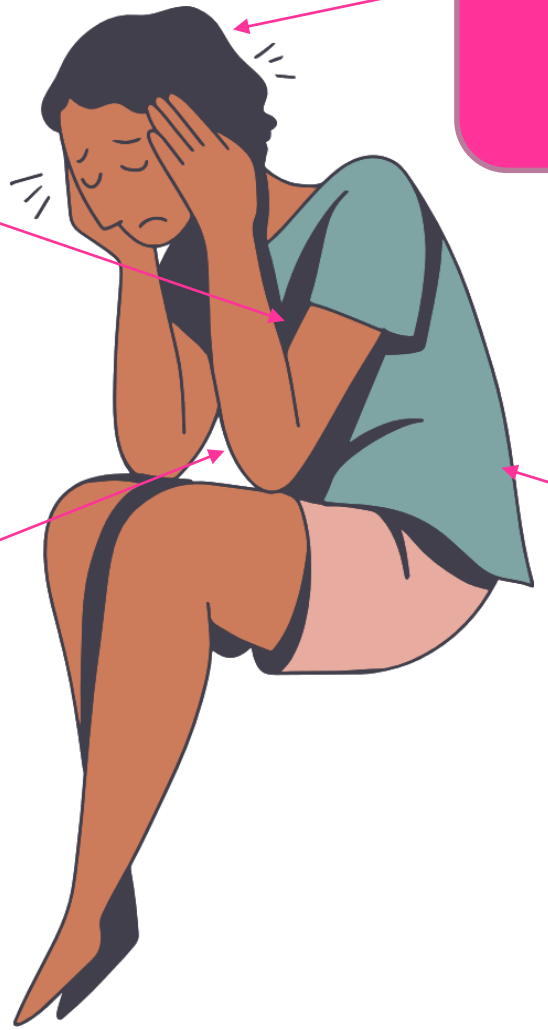
Common symptoms of MBC

Pneumonia
Chest pain



Shortness of breath

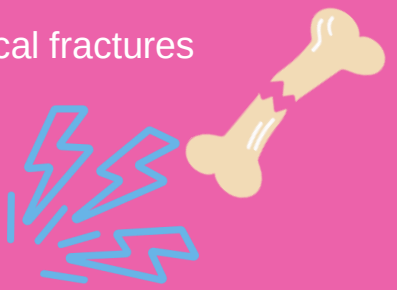
Seizures
Headache
Double vision



Jaundice

Abdominal pain, nausea

Pathological fractures



Sudden
new bone
pain

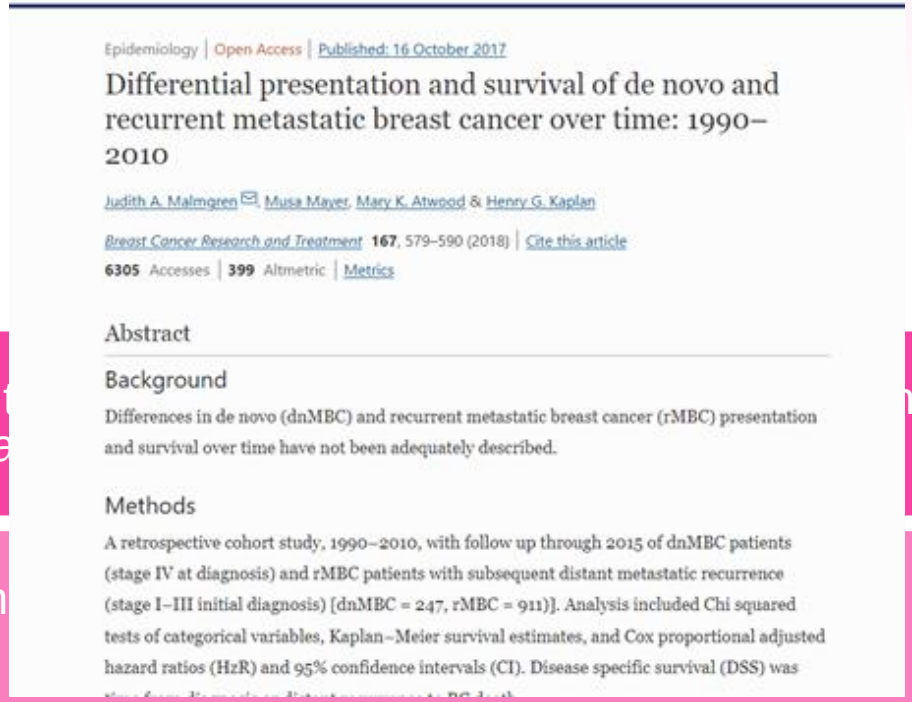
Epidemiology of MBC

In Europe in 2018, in terms of absolute numbers, MBC was t
women, accounting for approx. 4 % of all deaths in women a

MBC after therapy for early breast cancer tends to have a m
outcome compared with de novo MBC.

In a retrospective cohort study covering the period 1990-2010 de novo MBC incidence rates remained constant whereas subsequent (recurrent) MBC decreased. Yet, 5-year disease-specific survival of de novo MBC improved over time from 28% to 55% whereas subsequent MBC worsened from 23% to 13%.

Improvements in EBC therapies seem to have led to an alteration in tumour biology and metastasis presentation in subsequent MBC, presumably resulting from a molecular selection process.



Epidemiology | Open Access | Published: 16 October 2017

Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990–2010

Judith A. Malmgren, Musa Mayer, Mary K. Atwood & Henry G. Kaplan

Breast Cancer Research and Treatment **167**, 579–590 (2018) | Cite this article

6305 Accesses | **399** Altmetric | Metrics

Abstract

Background

Differences in de novo (dnMBC) and recurrent metastatic breast cancer (rMBC) presentation and survival over time have not been adequately described.

Methods

A retrospective cohort study, 1990–2010, with follow up through 2015 of dnMBC patients (stage IV at diagnosis) and rMBC patients with subsequent distant metastatic recurrence (stage I–III initial diagnosis) [dnMBC = 247, rMBC = 911)]. Analysis included Chi squared tests of categorical variables, Kaplan–Meier survival estimates, and Cox proportional adjusted hazard ratios (HzR) and 95% confidence intervals (CI). Disease specific survival (DSS) was

Treatment options for MBC

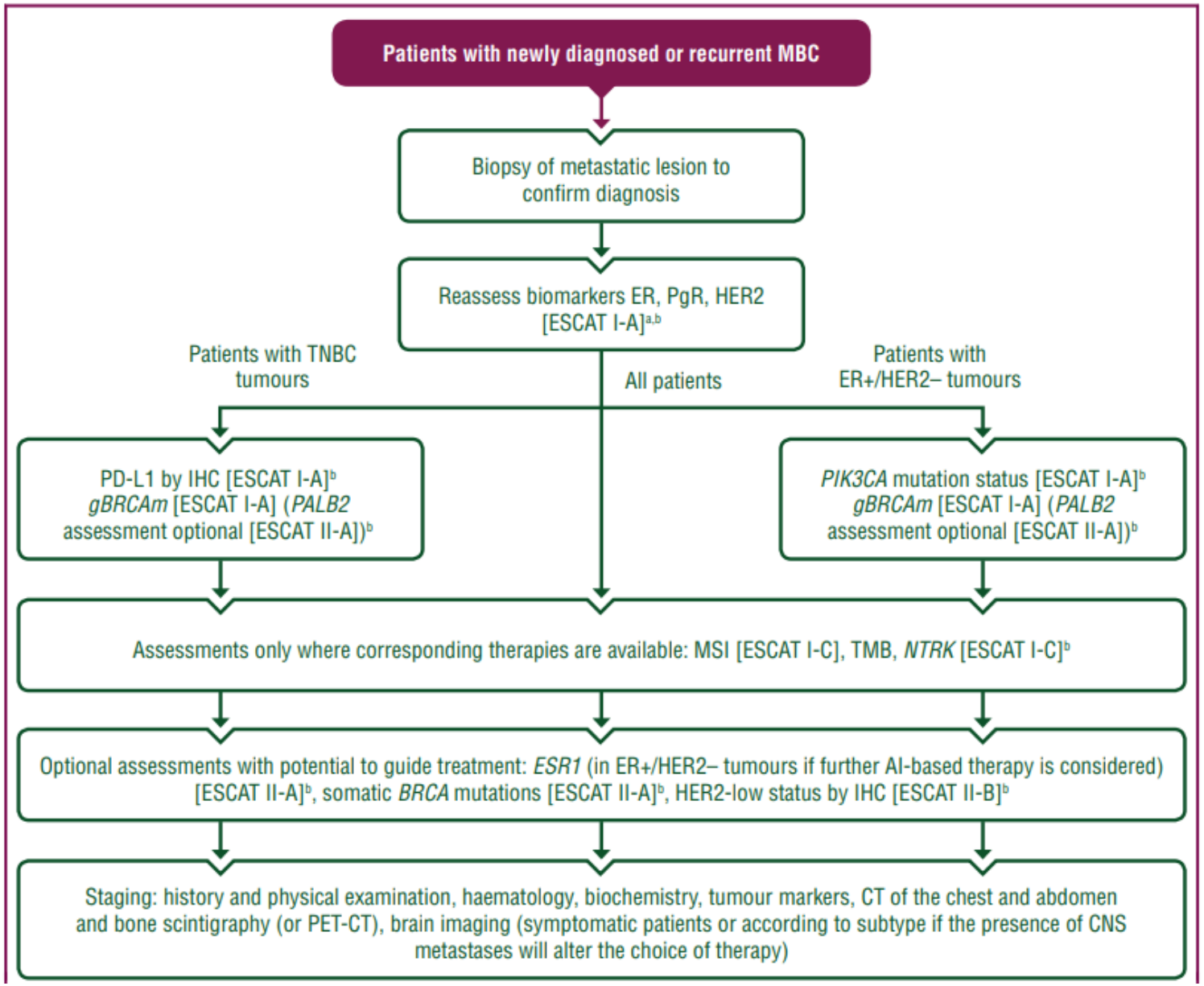
While there is no cure for MBC, there are a variety of treatment options that may prolong lives.

Most common treatments for stage IV breast cancer are:

- Hormonal therapies such as tamoxifen, fulvestrant (Faslodex) or aromatase inhibitors (Letrozole)
- Chemotherapy agents (paclitaxcel, doxirubicin)
- Targeted therapies including antibodies (trastuzumab, pertuzumab, pembrolizumab) which use the patient`s own immune system to destroy cancer cells
- PARP- inhibitors (olaparib) which target an enzyme involved in DNA repair
- CDK4/6 inhibitors (palbociclib) which interrupt specific enzymes to slow or stop cancer cells from growing

Also, surgery and radiotherapy as local treatment methods may be used to alleviate pain or orher symptoms. For example, stereotactic radiotherapy is used to treat brain metastasis, bone metastasis, lung or liver metastasis.

Diagnostic workup of MBC



ESMO Clinical Practice Guideline (3)

Staging and risk assessment

The minimum imaging work-up for staging includes computed tomography (CT) of the chest and abdomen and bone scintigraphy.

18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)CT may be used instead of CT and bone scans.

There is no evidence that any staging or monitoring approach provides an OS benefit over another.

The imaging modality chosen at baseline should be applied for disease monitoring to ensure comparability.

The interval between imaging and treatment start should be 4 weeks.

Evaluation of response should generally occur every **2-4 months** depending on disease dynamics, location, extent of metastasis and type of treatment.

Disease monitoring intervals should not be shortened as there is no evidence of an OS benefit but potential for emotional and financial harm.

Less frequent monitoring is acceptable, particularly for indolent disease.

If progression is suspected, additional tests should be carried out in a timely manner irrespective of planned intervals.

Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases, but image interpretation may be confounded by a possible **flare** during the first few months of treatment.

Brain imaging should not be routinely carried out in all asymptomatic patients at initial MBC diagnosis or during disease monitoring.

Patients with asymptomatic HER2- positive BC or TNBC have higher rates of brain metastases (BMs) at initial MBC diagnosis, even as the first site of recurrence.

Symptomatic patients should always undergo brain imaging, preferably with MRI.

Tests on tumour biology

Which tumors are tested?	What does the tumor test determine?	How do the test results guide treatment?
All tumors	Hormone receptor status (estrogen and progesterone receptor status)	If the cancer is hormone receptor-positive, the first treatment is usually hormone therapy, often with a CDK 4/6 inhibitor
All tumors	HER2 status	If the cancer is HER2-positive, HER-2 targeted therapies, such as trastuzumab (Herceptin), are included in the treatment plan.
Tumors that are both hormone receptor-positive and HER2-negative	Whether the tumor has a *PIK3CA* gene mutation	If the tumor has a *PIK3CA* gene mutation, the cancer may be treated with the PI3 kinase inhibitor alpelisib and the hormone therapy fulvestrant.
Triple-negative breast cancers (tumors that are both hormone receptor-negative and HER2-negative)	PD-L1 status	If the cancer is PD-L1-positive, the first treatment may be the immunotherapy drug pembrolizumab (Keytruda) in combination with chemotherapy.
Adapted from NCCN, 2021		

The National Comprehensive Cancer Network (NCCN) recommend everyone diagnose with metastatic brea cancer get genetic testing for BRCA1 a BRCA2 inherited ge mutations.

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BRCA1- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer

Synonym: *BRCA1*- and *BRCA2*-Associated HBOC

Nancie Petrucelli, MS, Mary B Daly, MD, PhD, and Tuya Pal, MD.

Author Information

Initial Posting: September 4, 1998; Last Update: February 3, 2022.

Estimated reading time: 47 minutes

Summary

Go to:

Clinical characteristics. *BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) is characterized by an increased risk for female and male breast cancer, ovarian cancer (including fallopian tube and primary peritoneal cancers), and to a lesser extent other cancers such as prostate cancer, pancreatic cancer, and melanoma primarily in individuals with a *BRCA2* pathogenic variant. The risk of developing an associated cancer varies depending on whether HBOC is caused by a *BRCA1* or *BRCA2* pathogenic variant.

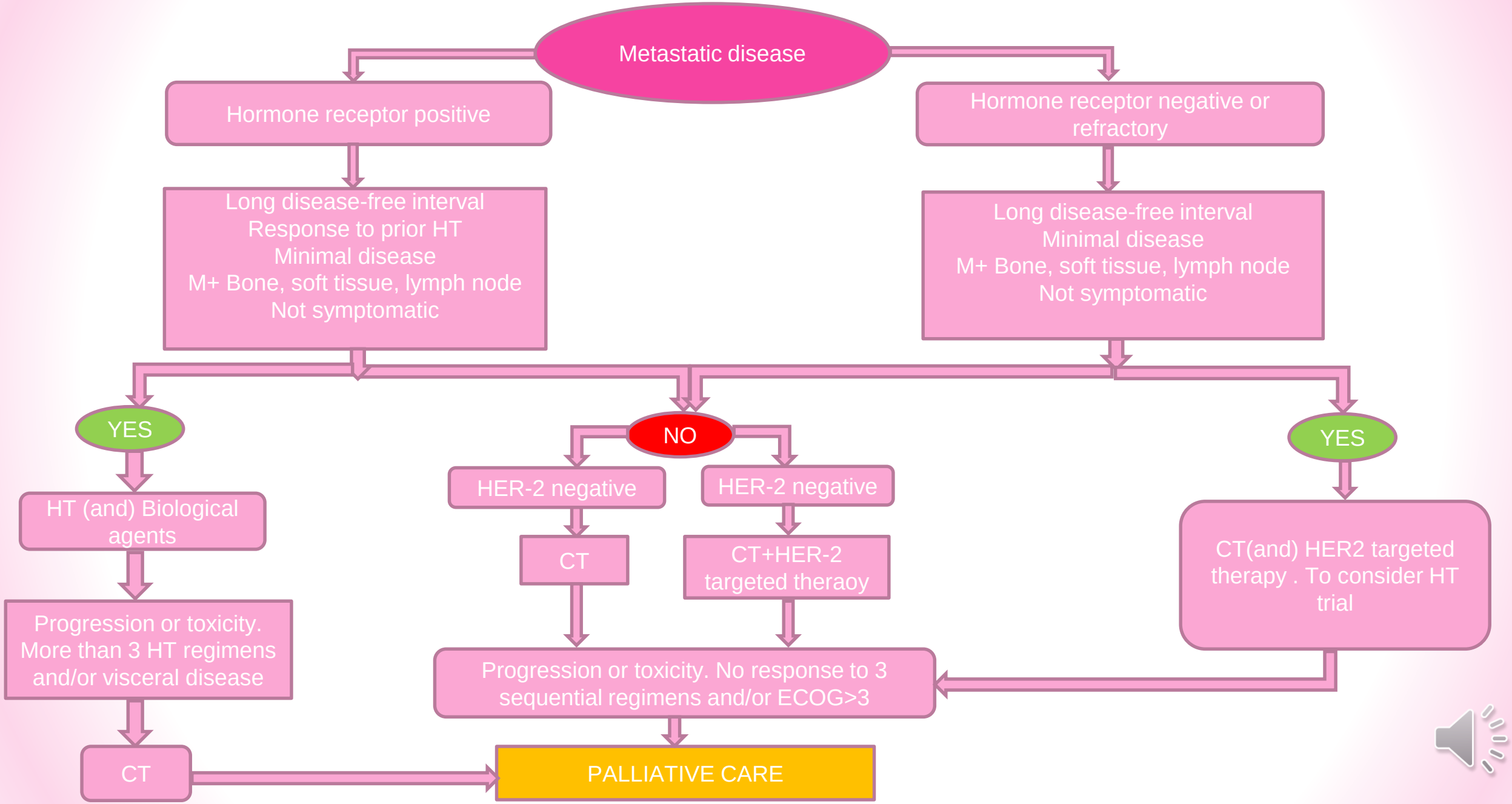
Diagnosis/testing. The diagnosis of *BRCA1*- and *BRCA2*-associated HBOC is established in a proband by identification of a heterozygous germline pathogenic variant in *BRCA1* or *BRCA2* on molecular genetic testing.

Management. *Treatment of manifestations:* Treatment of breast cancer per oncologist with consideration of bilateral mastectomy as a primary surgical treatment of breast cancer because of elevated rate of ipsilateral and contralateral breast cancer; PARP inhibitors may be considered in *BRCA1*- and *BRCA2*-related tumors. Melanoma treatment per dermatologist and oncologist.

Prevention of primary manifestations: Prophylactic bilateral mastectomy, prophylactic oophorectomy, and chemoprevention (e.g., tamoxifen) have been used for breast cancer prevention, but have not been assessed by randomized trials in high-risk women. Prophylactic salpingectomy followed by delayed oophorectomy or salpingo-oophorectomy for ovarian cancer prevention.

f patient has a utation in one of se genes, a PARP nhibitor may be ncluded in the reatment plan.

Treatment pathway for MBC patient



Factors underpinning the treatment approach of MBC

Sequential use of single agents is considered a standard approach for patients with MBC and is preferred mainly because of reduced toxicity compared with combination chemotherapy, with most women treated with multiple lines of therapy.

All therapeutic decisions are usually tailored, taking into account several variables such as:

- Tumor burden (oligometastasis?)
- Sites of the disease (visceral vs. nonvisceral)
- HER2 status
- Hormone receptor (HR) status
- Disease-free interval
- Age
- Menopausal status

Oligometastatic breast cancer

A distinctive subset of MB patients, who a most likely to benefit from intensified multidiscplina therapeutic approach.

Review > World J Clin Oncol. 2022 Jan 24;13(1):39-48. doi: 10.5306/wjco.v13.i1.39.

Role of radiotherapy in oligometastatic breast cancer: Review of the literature

Caglayan Selenge Beduk Esen [1], Melis Gultekin [2], Ferah Yildiz [2]

Affiliations + expand

PMID: 35116231 PMCID: PMC8790304 DOI: 10.5306/wjco.v13.i1.39

Free PMC article

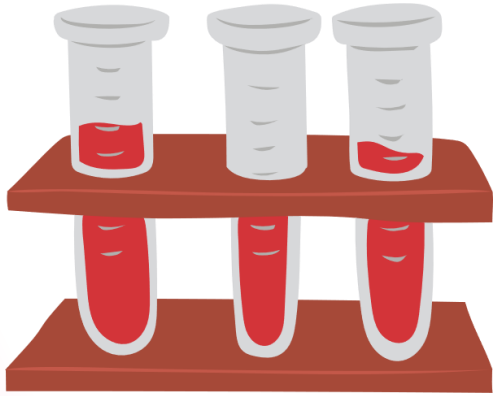
Abstract

Metastatic breast cancer has been historically considered as an incurable disease. Radiotherapy (RT) has been traditionally used for only palliation of the symptoms caused by metastatic lesions. However, in recent years the concept of oligometastatic disease has been introduced in Cancer Medicine as a clinical scenario with a limited number of metastases (≤ 5) and involved organs (≤ 2) with controlled primary tumor. The main hypothesis in oligometastatic disease is that locoregional treatment of primary tumor site and metastasis-directed therapies with surgery and/or RT may improve outcomes. Recent studies have shown that not all metastatic breast cancer patients have the same prognosis, and selected patients with good prognostic features as those younger than 55 years, hormone receptor-positive, limited bone or liver metastases, a low-grade tumor, good performance status, long disease-free interval (> 12 mo), and good response to systemic therapy may provide maximum

NCCN and ESMO guidelines list surgery, radiation and chemotherapy as possible therapeutic options for that type of localized disease.

These patients may achieve remission and long survival indicating also that more aggressive treatment options should be considered.

Assessment of disease status/Patient monitoring



In MBC, regular assessments of disease status and therapy toxicities should include clinical assessments, blood tests, imaging and patient-reported outcomes (PROs).

Side effects and recommendations

Decisions regarding the systemic treatment of MBC should be based on a balanced consideration of the predicted response to a particular treatment strategy and associated tolerability as well as adverse events.

Particular attention must be paid to the incidence and risk of side-effects in specific populations, such as elderly patients and those with comorbidities, in order to ensure therapy adherence.

Proactive symptom management and education helps to alleviate side-effects and improves quality of life. PRO measures capture the patient experience and perceived impact of treatment and toxicity on health status. PROs include areas of QoL as well as patient satisfaction with care.

An interdisciplinary approach is critical, including specialized oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities.

Careful assessment of side-effects should occur at each visit.

Electronic PROs may be useful in this context. QoL assessments should be incorporated into the evaluation of treatment efficacy.

Dose reduction and delay are effective strategies to manage toxicity in advanced disease.

Patient support

Patient preferences need to be considered as part of a shared decision-making process.

In elderly patients, a comprehensive geriatric assessment may add important information.

Supportive care should always be part of the treatment plan and early introduction of expert palliative care may help to better control symptoms.

Palliative care

Shared decision making between the patient and health care professionals, as well as good communication and relationship building with the patient, family members and caregivers, is therefore paramount to ensure a mutual understanding of treatment expectations and goals.

For patients with MBC, median OS is increasing with the introduction of new treatments and patients are more likely to experience metastases in many areas of the body.

As well as receiving the best available treatment, patients should be offered optimal symptom control, psychological, social and spiritual support.

Many areas of care need to be managed, including pain, dyspnea, cachexia, fatigue, depression and anxiety, which should also consider comorbidities, previous treatments, age and patient preferences.

The emotional toll of caring for patients who are dying also has an impact on health care staff, and processes should be in place to support their mental health, enabling them to continue to provide sensitive and effective care.

Prognosis of MBC

Estimating overall survival (OS) for wome
t oncologists have to face when dealing with this tumor type.

The median OS for women with MBC is a
of patients that have lived and live more than a decade with the disease.

BC is a highly heterogeneous disease co
khibiting specific histopathological and biological features, and variable clini
t treatments.

Based on these premises, it should come
understanding and treatment of these subtypes have been reached.

ESMO Open

Volume 7, Issue 2, April 2022, 100409

Review

Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival

F. Miglietta [1], M. Bottosso [1], G. Griguolo [1, 2], M.V. Dieci [1, 2], V. Guarneri [1, 2, 3]

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Referred to by F. Miglietta, M. Bottosso, G. Griguolo, M.V. Dieci, V. Guarneri

Erratum to 'Major advancements in metastatic breast cancer treatment: when expanding optio...

ESMO Open, Volume 7, Issue 3, June 2022, Pages 100472

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Highlights

- The treatment landscape of MBC has progressively widened in the last years.
- Several therapeutic strategies proved to be capable of prolonging survival of patients with MBC.
- We comprehensively reviewed practice-changing data on MBC treatment according to BC subtype.

HER2-positive disease is a stark example of this variability of outcomes: although a HER2-positive tumor used to be associated with poor prognosis, the development of anti-HER2 therapies has dramatically changed the prognosis of patients with HER2-positive disease

Author: Siret Kivistik
Tartu Healthcare College

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