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METASTATIC BREAST CANCER

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Journal Pre-proof

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer[†]

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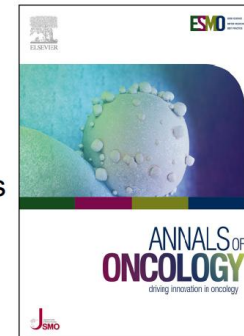
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- ▶ For women diagnosed with EBC, the 5-year survival probability is around 96% in Europe.
 - ▶ However, when MBC is diagnosed, the 5-year survival rate is in the range of 38%.
 - ▶ MBC was still the leading cause of death from all cancers in women, accounting for ~3.6% of all deaths in women and 1.8% of all deaths in Europe in 2015.

DEFINITIONS


Advanced Breast Cancer (ABC)

Denovo Breast Cancer

Subsequent Metastatic Breast Cancer

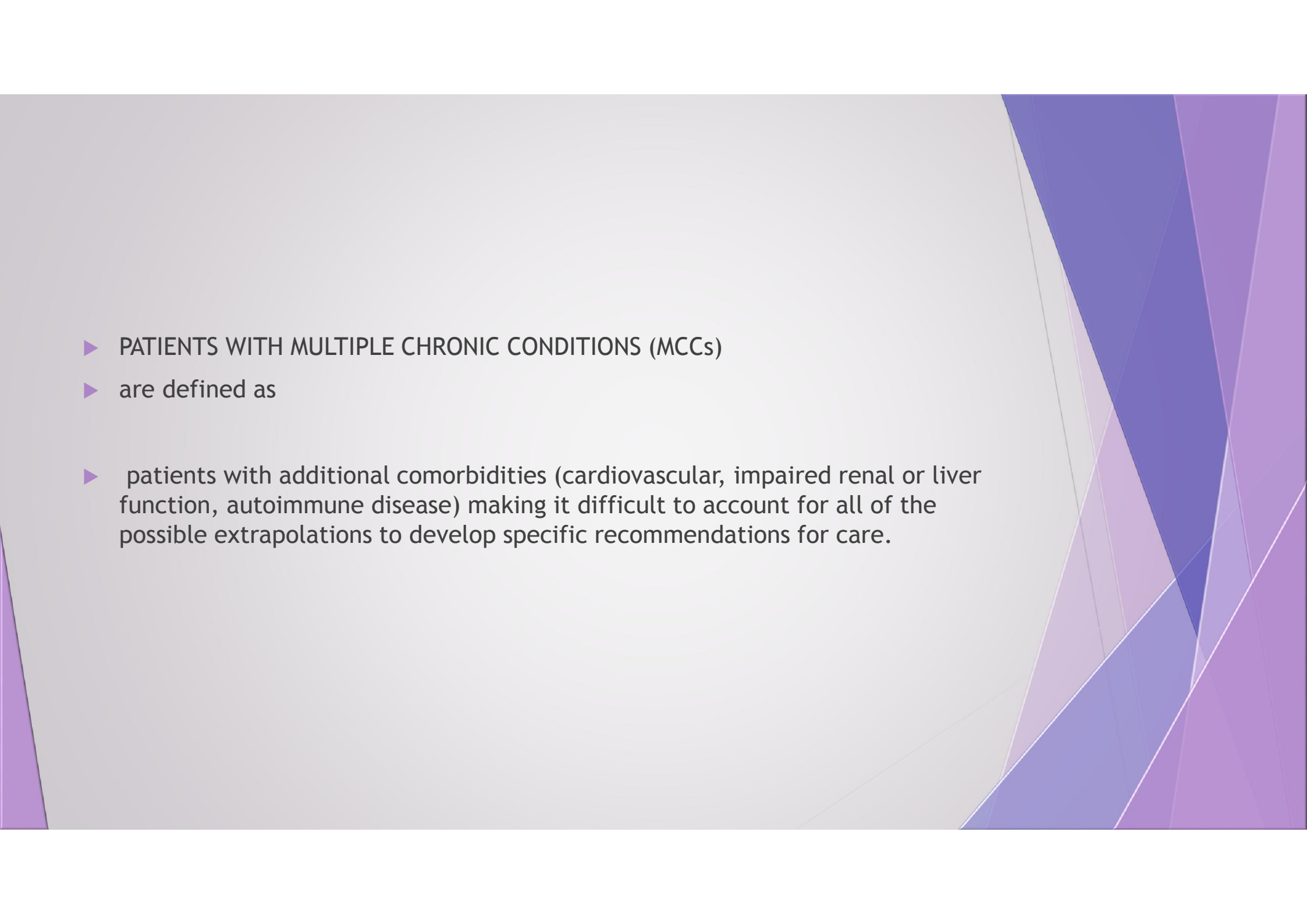



- ▶ MBC subsequent to therapy for EBC tends to have a more aggressive tumour biology and a worse outcome compared with de novo MBC.
- ▶ denovo MBC incidence rates remained constant whereas subsequent MBC decreased.
- ▶ Yet, 5-year disease specific survival (DSS) of de novo MBC improved over time from 28% to 55% whereas subsequent MBC worsened from 23% to 13%

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- ▶ . Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time
 - ▶ (many years in some circumstances).
 - ▶ There has been an increase in liver and central nervous system (CNS) metastases and a decline in bone metastases


- ▶ **OLIGO-METASTATIC DISEASE** is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status.
- ▶ The concept of oligometastases represents a condition midway between locoregionally confined cancer and disseminated disease, in which tumor burden is low and the number of affected organs is limited, typically with 1 to 5 secundarisms

- ▶ VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.
- ▶ **Liver** visceral crisis: rapidly increasing bilirubin $>1.5\times$ ULN, in the absence of Gilbert's Syndrome or biliary tract obstruction.
- ▶ **Lung** visceral crisis: rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion

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- ▶ PATIENTS WITH MULTIPLE CHRONIC CONDITIONS (MCCs)
 - ▶ are defined as
 - ▶ patients with additional comorbidities (cardiovascular, impaired renal or liver function, autoimmune disease) making it difficult to account for all of the possible extrapolations to develop specific recommendations for care.



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- ▶ A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time.
 - ▶ Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible.

- ▶ To date, the removal of the primary tumor in patients with de novo stage IV breast cancer has not been associated with prolongation of survival, with the possible exception of the subset of patients with bone only disease.
- ▶ However, it can be considered in selected patients, with controlled systemic disease, particularly to improve quality of life, always taking into account the patient's preferences.

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- ▶ A small but very important subset of patients with MBC, for example those with oligo-metastatic disease or low volume metastatic disease that is highly sensitive to systemic therapy, can achieve complete remission and a long survival.
 - ▶ A multimodal approach, including local-regional treatments with curative intent, should be considered for these selected patients.

Review

Oligometastatic Breast Cancer: How to Manage It?

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Oligometastatic Breast Cancer: How to Manage It?

- ▶ ECOG-ACRIN E 2108: 258 MBC
- ▶ Retrospective analyses demonstrate that patients who underwent surgery on the primitive tumor show a better prognosis compared to those who received only systemic therapy.

- ▶ an increase of 2.5 times in the risk of locoregional progression in patients who received systemic therapy without locoregional treatment.
- ▶ So that the predominant prognostic role is given by medical treatments, histopathologic features, and tumor burden.
- ▶ Conclusively, in patients with de novo MBC, the surgery approach has a palliative role
- ▶ (**ulceration, pain, bleeding, infection, and poor wound healing lesions**).

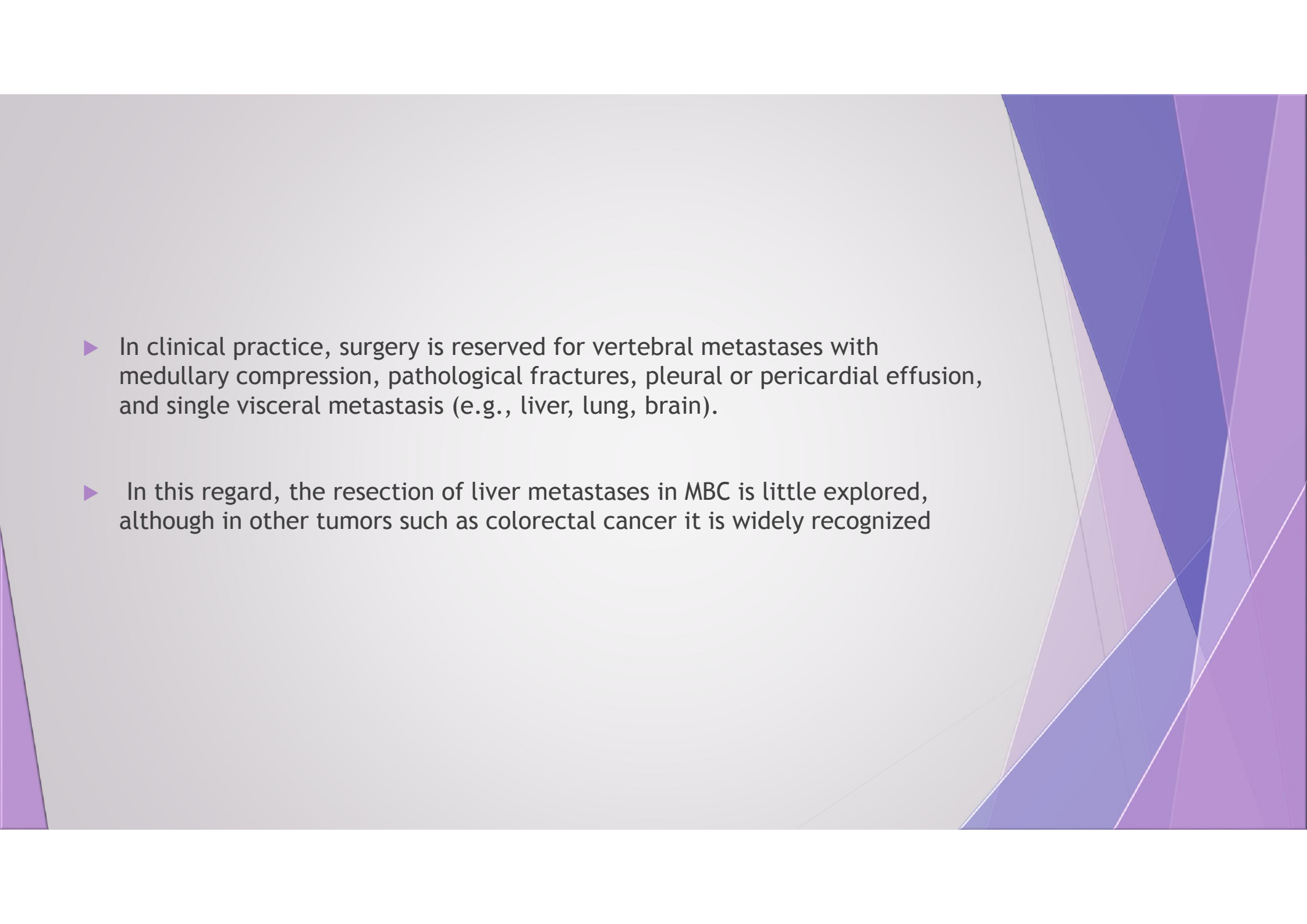
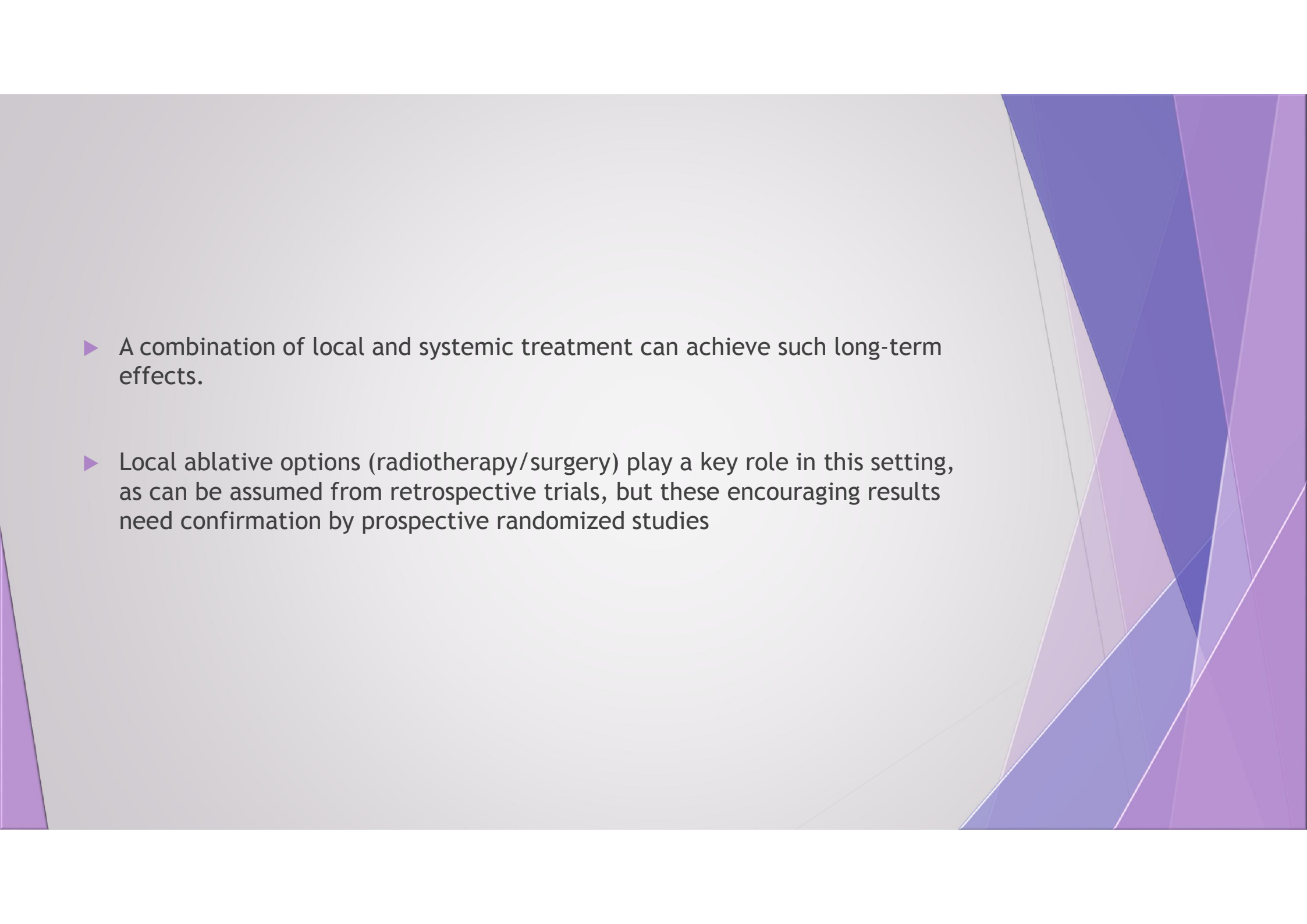
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- ▶ In clinical practice, surgery is reserved for vertebral metastases with medullary compression, pathological fractures, pleural or pericardial effusion, and single visceral metastasis (e.g., liver, lung, brain).
 - ▶ In this regard, the resection of liver metastases in MBC is little explored, although in other tumors such as colorectal cancer it is widely recognized


Table 1. Randomized trials that evaluate the efficacy of surgery in MBC.

Trial	Number of Patients	Site of Metastases	Biological Subtype		Site of Surgery	Outcome
Tata Memorial, NCT00193778	350	Bone and/or visceral	HR+ /HER2– HR+/HER2+	- - -	Modified radical mastectomy Breast-conserving surgery Palliative surgery upon progression	1. No differences in OS 2. Better locoregional PFS FOR surgery 3. Worse DPFS for surgery
MF0701, NCT00557986	274	Bone and/or lung and/or liver	HR+ 85.5% HER2+ 30.4% TN 7.3%	- - -	Breast conserving surgery Metastasectomy Axillary lymph node dissection	1. Increase in median survival for surgery upfront 2. Superior survival for locoregional treatment in women with luminal tumors, age < 55 years, and solitary bone metastases
ECOG-ACRIN E 2108, NCT01242800	258	Bone and/or any organ system, including CNS	HR+/HER2– 60% HER2+ 26% TN 15%	- - -	Breast-conserving therapy Total mastectomy Palliative surgery	1. No difference in OS and PFS 2. Possible detrimental effect of locoregional treatment in TN mBC 3. Increase of 2.5x risk of locoregional progression in patients who received systemic therapy without locoregional treatment
TBCRC 013, NCT00941759	127	Bone and/or any organ system, including CNS	HR+/HER2– HR+/HER2+ HR– /HER2+ HR– /HER2–	- -	Elective breast surgery Palliative breast surgery	1. No improvement of PFS and OS for surgery in patients who have responded to first-line treatment

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- ▶ A combination of local and systemic treatment can achieve such long-term effects.
 - ▶ Local ablative options (radiotherapy/surgery) play a key role in this setting, as can be assumed from retrospective trials, but these encouraging results need confirmation by prospective randomized studies

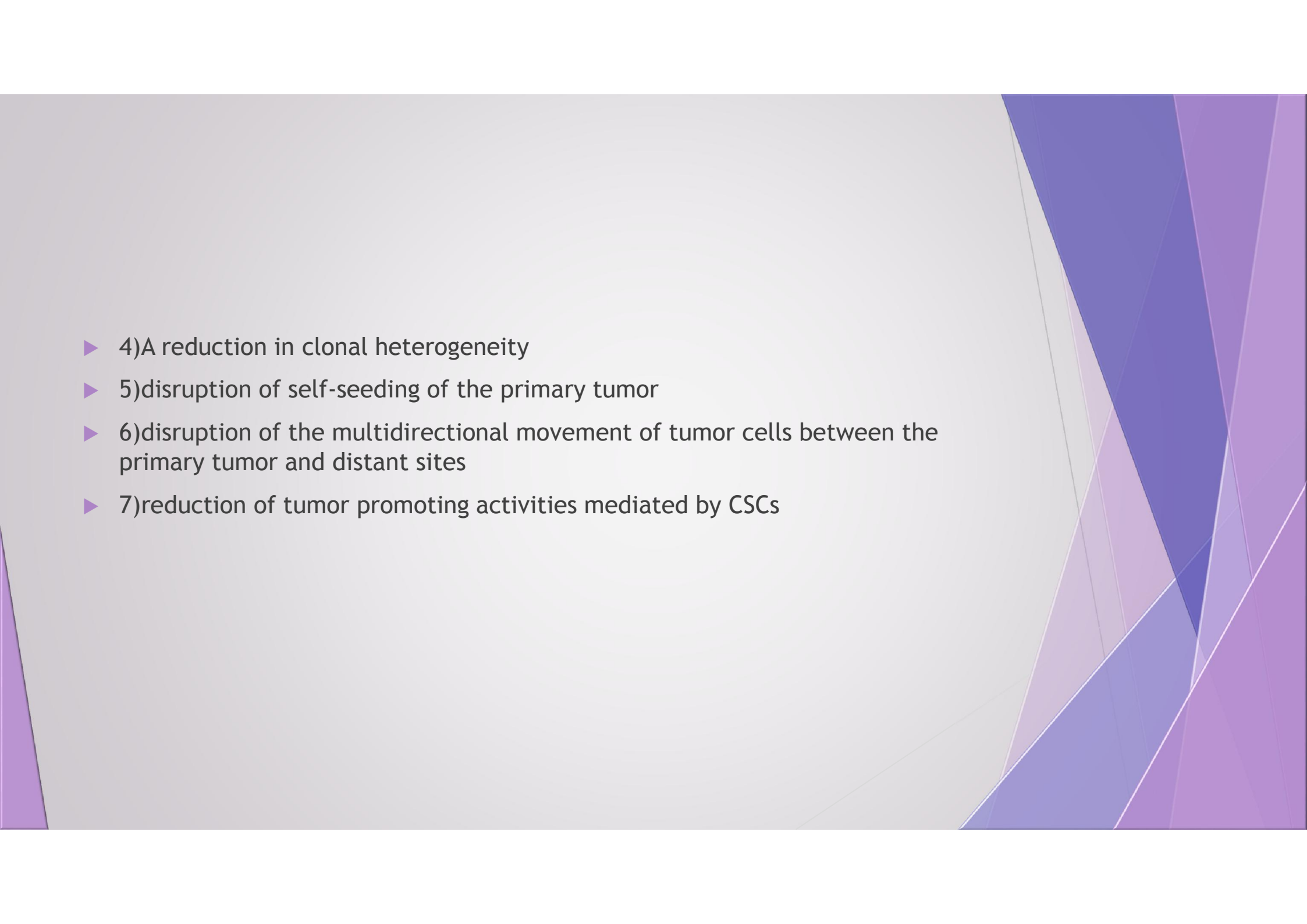
OPEN

Locoregional therapy of the primary tumour in *de novo* stage IV breast cancer in 216 066 patients: A meta-analysis

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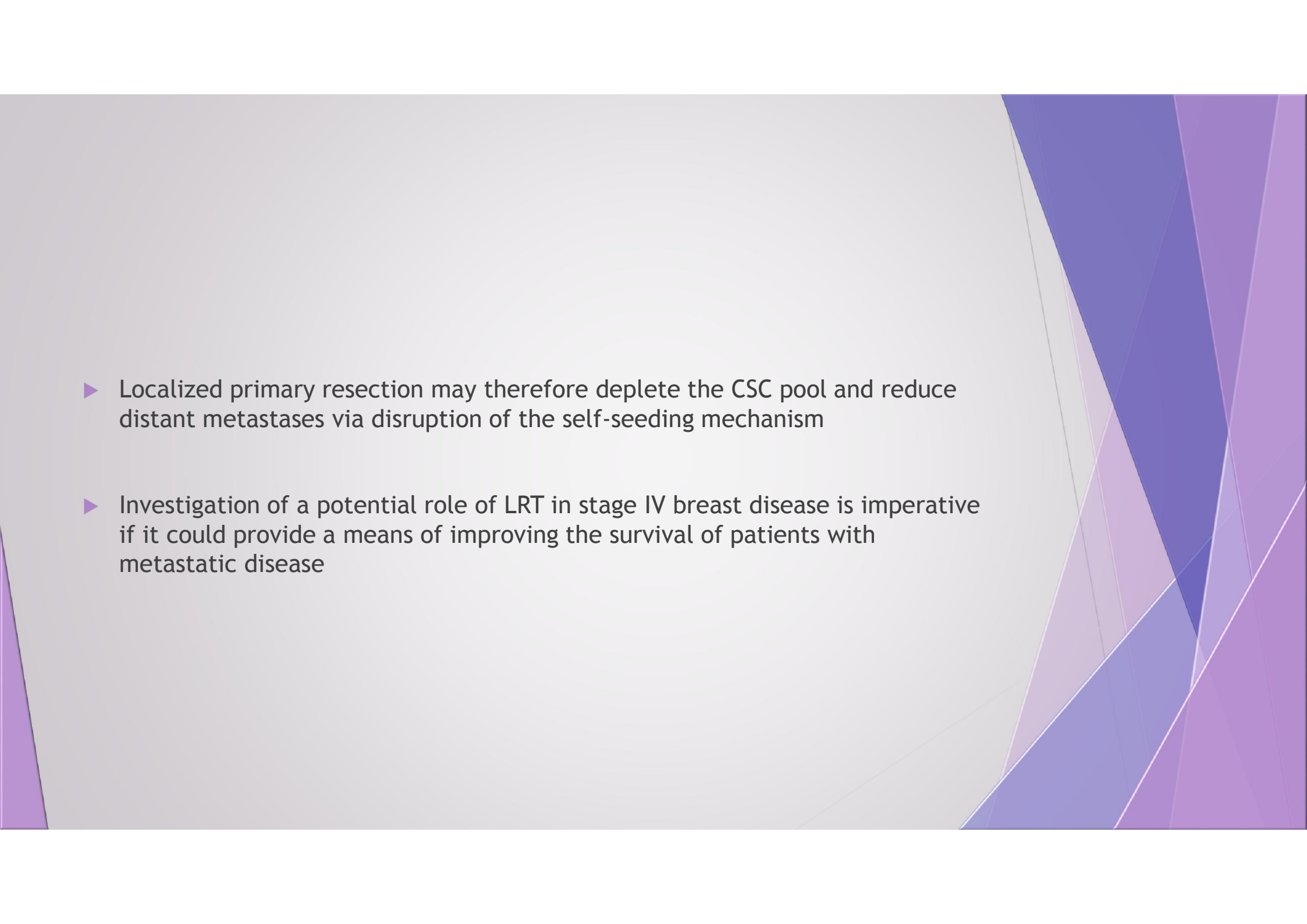
Patients presenting with *de novo* stage IV metastatic breast cancer have a complex disease which is normally treated with palliative intent and systemic therapy. However, there is mounting evidence that resection of the primary tumour and/or localised radiotherapy (locoregional therapy; LRT) could be associated with overall survival improvements. We aimed to conduct a meta-analysis to inform decision making. Using the PubMed, Cochrane and Ovid SP databases, a literature review and meta-analysis were conducted to assess the effect of LRT on overall survival. Studies were analysed for the impact of LRT on survival. All forms of LRT resulted in a significant 31.8% reduction in mortality ($N = 42$; $HR = 0.6823$ (95% CI 0.6365; 0.7314)). Surgical resection resulted in a significant 36.2% reduction in mortality ($N = 37$; $HR = 0.6379$ (95% CI 0.5974; 0.6811)). The prospective trials reported a 19.23% reduction in mortality which was not statistically significant ($N = 3$, $HR = 0.8077$ (95% CI 0.5704; 1.1438)). 216 066 patients were included. This is the largest meta-analysis regarding this question to

- ▶ several studies have suggested a survival benefit for patients who underwent resection of the primary tumor in de novo stage IV disease
- ▶ mechanisms of action:
 - ▶ 1) tumor burden reduction
 - ▶ 2) cancer stem cell (CSC) elimination
 - ▶ 3) A reversal of tumor-induced immunosuppression

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- ▶ 4) A reduction in clonal heterogeneity
 - ▶ 5) disruption of self-seeding of the primary tumor
 - ▶ 6) disruption of the multidirectional movement of tumor cells between the primary tumor and distant sites
 - ▶ 7) reduction of tumor promoting activities mediated by CSCs

CSCs

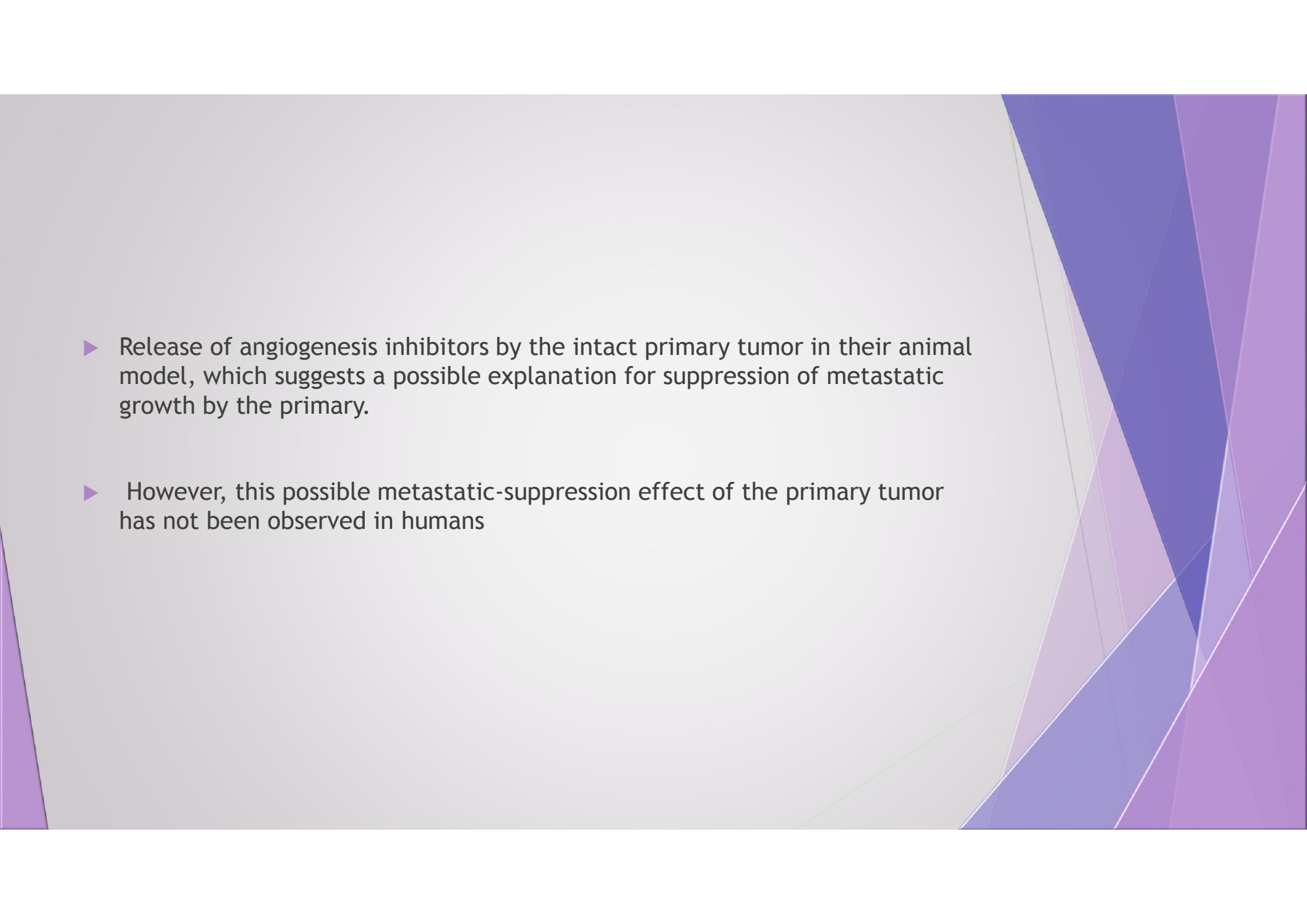
- ▶ Compared to the tumour bulk, CSCs are a small and dangerous subgroup of cells which are capable of self-renewal.
- ▶ CSCs can differentiate and cause tumorigenesis and are strongly implicated in haematogenous and lymphatic metastasis.
- ▶ CSCs localized in the primary tumor are likely to lend themselves to the development of metastatic disease

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- ▶ Localized primary resection may therefore deplete the CSC pool and reduce distant metastases via disruption of the self-seeding mechanism
 - ▶ Investigation of a potential role of LRT in stage IV breast disease is imperative if it could provide a means of improving the survival of patients with metastatic disease

- ▶ The removal of the primary tumor reduces the tumor burden, thereby increasing response to systemic therapy.
- ▶ With reduced cancerous tissue, a complete response to therapy is more likely.
- ▶ Primary tumor is the main source of new clonal lines of cancer cells, which are implicated in the emergence of resistance to therapy and the appearance of more aggressive disease phenotypes.
- ▶ LRT would disrupt this process.

tumor-induced immunosuppression

- ▶ primary tumor encourages metastasis by induction of systemic inflammation via IL-1B, which leads to the expression of IL-17 from $\gamma\delta$ T cells.
- ▶ This results in tumor-induced neutrophils which would suppress cytotoxic CD8⁺ T cell effector function.

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- ▶ Release of angiogenesis inhibitors by the intact primary tumor in their animal model, which suggests a possible explanation for suppression of metastatic growth by the primary.
 - ▶ However, this possible metastatic-suppression effect of the primary tumor has not been observed in humans

- ▶ Data from British Columbia:
- ▶ Locoregional progression-free survival was 72% in those receiving any form of locoregional therapy (LRT) than in those who did not (72 vs. 46%, $p < 0.001$).
- ▶ The five-year overall survival (OS) for these groups was 22% and 14%, respectively.
- ▶ . Early surgical management of the primary site decreased symptomatic chest wall progression by 86% compared to delayed or no surgical management.

SURVIVORSHIP ISSUES

- ▶ ABC patients with stable disease, being treated as a “chronic condition”, should have the option to undergo breast reconstruction, if clinically appropriate.
- ▶ In ABC patients with long-standing stable disease or complete remission, breast imaging is an option.
- ▶ Breast imaging should also be performed when there is a suspicion of loco-regional progression.










Table 6.1 Prospective randomized trials investigating the role of local-regional treatment in Stage IV breast cancer

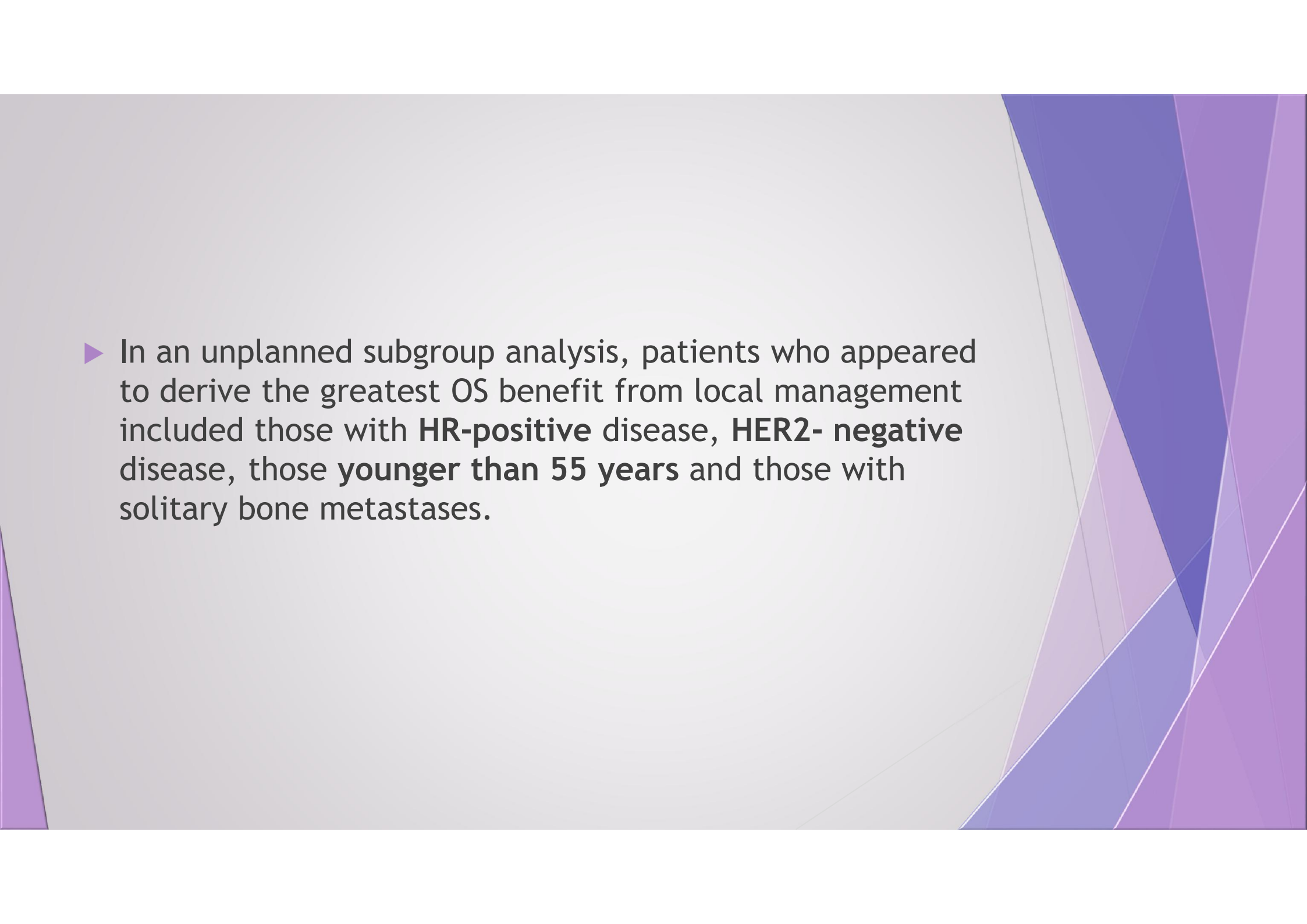
Study	Accrual period	Accrual goal	Systemic treatment before randomization	Status	Final number of randomized patients
India	2005–12	350	Yes	Published	350
Turkey	2008–12	271	No	Presented	274
USA, Canada	2011–15	368	Yes	Closed	Projected to be 268
Japan	2011–16	500	Yes	Open	Projected to be 400
Austria	2010–19	254	No	Presented	93

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- ▶ In one prospective trial, women (n =350) with de-novo metastatic breast cancer who achieved a partial or complete response to anthracycline-based chemotherapy were randomly assigned to either surgery of the primary tumor plus adjuvant radiation versus no locoregional treatment.
 - ▶ There was no difference in the overall survival (OS) between the group that received surgery and the group that did not .

- 
- ▶ However, another trial by the Turkish Federation, MF07-01 of women (n=274) with de-novo metastatic breast cancer randomized to local management (mastectomy, or BCS with radiation) followed by systemic therapy versus systemic therapy only, observed a benefit with surgery.
 - ▶ While no difference in survival was seen at 36 months, at 40 months, patients treated with local management showed an improvement in survival with locoregional treatment.

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- ▶ We may also do surgery in patients who are not symptomatic, but we are concerned may be symptomatic if they do not respond quickly, such as a primary breast mass that is amenable to resection and close to ulcerating.
 - ▶ However, the decision to proceed with local management in a similar situation should take into account patient preferences and should be made in a multidisciplinary setting

- ▶ The role of **axillary surgery** on overall survival has been difficult to evaluate in the published retrospective analyses.
- ▶ A meta-analysis by Hartmann and colleagues considered six retrospective studies that gave information about whether an axillary surgical procedure was performed in case of surgery .
- ▶ Only three studies investigated the impact of axillary surgery on survival, and did not find a benefit.

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- ▶ In an unplanned subgroup analysis, patients who appeared to derive the greatest OS benefit from local management included those with **HR-positive** disease, **HER2- negative** disease, those **younger than 55 years** and those with solitary bone metastases.