Systemic therapy with or without Up front surgery of the primary tumor in Breast cancer patients with distant Metastases at Initial presenTation (SUBMIT, BOOG 2010-05)

Published: 01-06-2011
Last updated: 27-04-2024

Up front breast surgery in patients with primary distant metastatic breast cancer, will result in an improvement of the 2-year survival compared to the survival achieved with systemic therapy and delayed local treatment or systemic therapy alone.The...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON39378

Source
ToetsingOnline

Brief title
SUBMIT

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Breast disorders
- Breast therapeutic procedures

Synonym
breast cancer

Research involving

Human

Sponsors and support

Primary sponsor: Jeroen Bosch Ziekenhuis
Source(s) of monetary or material Support: KWF (datamanagement voor klinische studies);sanofi-aventis (financiering 'opstartkosten' onderzoek),Sanofi-aventis

Intervention

Keyword: Breast cancer, Overall survival, Stage IV, Surgery

Outcome measures

Primary outcome

Primary endpoint:

Overall survival

Secondary outcome

Secondary endpoints:

Quality of life

Two-year survival

Number of unplanned local therapies, i.e. surgery or radiotherapy

Number of axillary lymph node dissections or axillary radiotherapy

Determination of pathological resection margin (margin status) in patients

treated by surgery of the primary tumor

Type of chemotherapy, immunotherapy and endocrine therapy and number of

regimens of systemic therapy during the first 2 years

Study description

Background summary

Patients with breast cancer are treated with surgery of the breast tumor if there is no evidence of distant metastases. However, 5% of all patients with breast cancer present with primary distant metastases (metastases at initial presentation). Because metastatic breast cancer is considered to be an incurable disease, the aim of the treatment is to provide palliation. Therefore systemic therapy is used. Breast surgery is only performed if the tumor is symptomatic. Until recently, it is believed that, once distant metastases have occurred, (aggressive) local therapy provides no survival advantage and should not be the aim of the treatment. Nevertheless, women who have primary metastatic disease and survive several years following this diagnosis may benefit from elimination of the primary tumor as a source of re-seeding of distant sites.

Recent retrospective studies have demonstrated that (complete) resection of the primary tumor significantly improves the outcome of patients with primary metastatic breast cancer. The hazard ratios for overall survival vary from 0,47 to 0,71. Furthermore, in studies taking into account surgical resection margins, better survival was only observed in patients whose primary breast lesion had been removed with free surgical margins.

It has to be mentioned that in several studies potential confounders can be identified: age, site of metastases and surgical margins. Most retrospective studies adjusted for age, hormone receptor status and site of metastases, but hardly any study adjusted for factors such as comorbidity or selection criteria for surgical treatment.

Also, three recent studies showed that different forms of bias may explain the observed survival benefit in patients who underwent surgery. This concerns stage migration bias, case selection bias and coding errors based on the retrospective character of the studies.

Given the results of these retrospective studies, it is not possible to answer the question whether up front surgery of the primary tumor does improve overall survival. A randomized controlled trial (RCT) should therefore be performed.

In a randomized controlled trial effective local therapy, meaning a resection

with free surgical margins, should be performed (in case of randomization for surgical treatment) and at the same time the study protocol should allow flexibility in the choice of systemic therapy regimens.

Study objective

Up front breast surgery in patients with primary distant metastatic breast cancer, will result in an improvement of the 2-year survival compared to the survival achieved with systemic therapy and delayed local treatment or systemic therapy alone.

The objective of the study is to test the following hypotheses:

I Up front breast surgery in patients with primary distant metastatic breast cancer, will result in a significant improvement of the 2-year survival compared to the survival achieved with palliative systemic therapy followed by delayed local treatment or systemic therapy alone.

II Local tumor control in these patients will be superior in case of up front breast surgery compared to patients who receive systemic treatment with delayed local therapy or systemic therapy alone.

III Better local control, by the use of up front breast surgery, results in a better quality of life in patients with Stage IV breast cancer, compared to patients who receive systemic treatment with delayed local therapy or systemic therapy alone.

In a separate side study the association of HER2 status on CTCs with outcome on hormonal treatment and chemotherapy will be assessed.

Study design

This study is a multicenter, open-label, randomized controlled trial of 516 patients.

Patients with primary distant metastatic breast cancer, diagnosis confirmed with biopsy, including estrogen- and progesteronreceptor status and HER2Neu status, can be included in the study.

Screening for metastases should take place in patients with a T2 tumor > 3 cm, patients with a T3 or T4 tumor and/or patients with clinical pathological axillary lymph nodes.

Patients with a T1-T3 tumor and a resectable T4 tumor can be included.

Patients either randomize for up front surgery of the breast tumor (UFS)

followed by systemic therapy or they randomize for systemic therapy (ST) possibly followed by local treatment of the breast tumor.
1. Up front breast surgery (UFS) followed by systemic therapy (group A)
2. Systemic therapy (ST) possibly followed by local treatment of the breast tumor (group B)

Patients who randomize for surgery are treated with the intent of a radical resection of the breast tumor. Furthermore, all patients will be treated with systemic treatment according to local practice.

In case of local progression, all patients can be treated with local treatment (surgery/radiotherapy) to establish local control.

Intervention

The aim of this study is to determine the effect of up front surgery of the primary tumor on survival in patients with primary metastatic breast cancer. According to randomization, half of the patients will undergo up front surgery of the primary tumor.

Randomization:
A. Up front breast surgery (UFS) followed by systemic therapy
B. Systemic therapy (ST) potentially followed by delayed local treatment of the breast tumor

Up front breast surgery:
Depending on patient and tumor characteristics a lumpectomy or mastectomy of the breast will be performed. Both types of surgery may be conducted as long as the intention is a radical operation. The definition of radical resection in this trial is free resection margins for the invasive component of the tumor.

In case of involved margins there are several options; perform a re-excision or mastectomy (preferred options in UFS group), treat the patient with radiotherapy or accept that a non-radical resection has been performed. This decision is the responsibility of the treating physician; he or she is not bound by restrictions in the protocol. Of note, radiotherapy can be postponed after first-line chemotherapy has been delivered. Concurrent radiotherapy and chemotherapy is not allowed because of expected excessive toxicity.

The choice to perform an axillary lymph node dissection is left to the discretion of the treating physician, but is highly recommended if palpable (and tumor positive) lymph nodes in the axillary region are present.

In case of local progression at any time, local treatment at another point than scheduled (= up front or after 5-6 months of systemic therapy) to gain local control is allowed. Local progression is defined as progression of the primary tumor during systemic therapy, in which case the tumor can cause wound problems

or ulceration. To prevent this, local treatment should be considered.

Surgical treatment or (stereotactic) radiotherapy of oligometastases can be considered after systemic therapy (after 5-6 months).

Last but not least, breast surgery is an accepted treatment for patients without distant metastases; it is a relatively safe operation, without chance of major complications.

Study burden and risks

The extent of the burden regarding the visits to the out-patient clinic and completing quality of life questionnaires is estimated below:

Visits to out-patient clinic; questions about trial,
inclusion, baseline criteria, randomization 30 min.

1/2e of all patients: preoperative assessment,
surgery, visit for check-up after surgery, result
of pathologic examination tissue 60 min. + admission in hospital for surgery (72 hours)

8 x Quality of life questionnaire 80 min.

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Total: 170 min. + possible admission in hospital for surgery (72 hours)

Additional visits to the out-patient clinic are comparable with patients with primary metastatic breast cancer who do not participate in this trial.

If patients give their informed consent an additional 20 ml of blood will be collected during a standard vena punction.

The risks associated with participation of this trial are the risks caused by surgery. The patients randomized for surgery have the same risks as breast cancer patients without distant metastases, who undergo surgery as a standard part of their treatment. These risks include postsurgical bleeding, wound infection and the development of a hematoma or a seroma. Risks associated with anesthesia should also be considered. Breast surgery is in medical terms a relative minor operation with little chance of complications, and it is very unlikely that severe complications occur.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Newly diagnosed primary distant metastatic breast cancer (M1)
Anticipated survival of at least 6 months
Histological proven breast cancer, hormonal and HER2Neu status should be known
T1-T3, resectable T4 status, N0-N3
Performance status of the patient should allow surgery/systemic therapy
Age 18 years, or older
Informed consent

Exclusion criteria

Primary invasive breast cancer in medical history
Other malignancy within the last 10 years, besides basal cell carcinoma of the skin or early stage cervical cancer
Surgical treatment / radiotherapy of this breast tumor before randomization

Irresectable T4 breast tumor
Synchronous bilateral breast cancer

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-02-2012
Enrollment:	516
Type:	Actual

Ethics review

Approved WMO Date:	01-06-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	18-01-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-02-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-05-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-08-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01392586
CCMO	NL30331.028.11