Improving radical resection rates in patients with breast cancer by intraoperative imaging using bevacizumab-IRDye800CW - the MARGIN-2 study

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Primary objectives -To determine whether real-time tumor visualization using targeted fluorescent imaging during breast conserving therapy in breast cancer patients can be achieved intraoperatively and results in adequate assessment of the tumor...

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

Summary

ID

NL-OMON53445

Source
ToetsingOnline

Brief title
Improving breast cancer radical resection rates using fluorescence imaging.

Condition

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

Synonym
Breast cancer, carcinoma of the breast

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KRF grant UMCG

Intervention

Keyword: Bevacizumab-IRDye800CW, Breast conserving therapy, Fluorescence-guided surgery, Intraoperative imaging

Outcome measures

Primary outcome

Tumor-positive margin detection rate in breast cancer patients undergoing

breast conserving therapy of real-time, intraoperative, ex-vivo and in-vivo

fluorescence imaging measurements using bevacizumab-IRDye800CW.

Secondary outcome

Presence of tumor-positive margins as assessed by ex-vivo imaging of the

resected tissue specimen.

Presence of residual tumor as assessed by in-vivo imaging of the cavity

intraoperatively.

Tumor margins as obtained following standard histopathological practice.

Histopathological analysis of biopsies taken from region of interest in the

cavity and resected specimen.

Number and percentage of patients with radical resection after taking biopsy

based on fluorescence guided surgery.

Study description

Background summary

Breast conserving therapy combined with radiotherapy has become the gold standard in breast cancer patients with limited tumor size. BCT consists of local tumor resection with a small rim of healthy tissue. A major limitation in breast conserving therapy is the challenging differentiation between benign and malignant breast tissue intraoperatively, thereby increasing the risk of tumor-positive margins and incomplete resection of the tumor on the one hand and removing too much healthy tissue on the other. A tumor-positive margin results in higher rates of local recurrence and decrease in survival compared to a radical resection. Current postoperative workflows to assess surgical margins by microscopy take up to several days, which excludes the possibility of altering the operative plan (performing a wider local excision) immediately during surgery. Direct tumor-margin assessment and immediate intervention could possibly reduce the number of TPMs and thereby the need for additional therapy. Previously, our multidisciplinary research group Optical Molecular Imaging Groningen (OMIG) performed a phase-1 fluorescence-guided surgery study investigating breast cancer surgery (MARGIN-1). This study showed that using the fluorescent tracer bevacizumab-IRDye800CW tumor-positive margins could be adequately detected. However, this was a proof-of-concept study in which the fluorescent images were analyzed and correlated to pathology months after the initial operation. Strikingly, the study found tumor-positive margins in 30% of the cases, which potentially could have been detected using fluorescence guided surgery. This current study aims to obtain real-time tumour visualization and tumour margin assessment using fluorescence guided surgery with bevacizumab-IRDye800CW intraoperatively.

Study objective

Primary objectives
-To determine whether real-time tumor visualization using targeted fluorescent imaging during breast conserving therapy in breast cancer patients can be achieved intraoperatively and results in adequate assessment of the tumor margin.

Secondary objectives
-To determine whether ex-vivo fluorescence imaging can adequately show tumor-positive margins in resected tissue samples.
-To determine whether in-vivo fluorescence imaging can adequately show residual tumor in the cavity.
-To determine whether one of the above-mentioned imaging techniques is superior to the other in assessing tumor margin or that both techniques should be used together.
-To determine whether the fluorescence images do correlate with pathology and fluorescence shows the presence of tumor-positive margins as hypothesized.
-To investigate the potential feasibility of novel 3D (microscopic) imaging techniques on 3D depth assessment of the obtained biopsies out of resected tissue, if available
-To analyze whether patients that in standard-of-care would have tumor-positive

margins and needed additional treatment postoperatively, had a radical resection after biopsy using fluorescence guided surgery (number and percentage).

Study design

This study is a non-randomized, prospective, multi-center, interventional and diagnostic accuracy study. The interventional character of this study is explained by the fact that an extra biopsy can be performed based on fluorescence imaging and possible tumor-positive margins. Patients with limited size breast cancer scheduled for breast conserving therapy will be included. The total number of included patients will be 60, if at least 9 of these patients will have tumor-positive margins. Otherwise, the total number of included patients will be expanded to 70. After written informed consent is obtained, the tracer bevacizumab-IRDye800CW (10 mg) is intravenously administered two to three days prior to surgery. On the day of surgery, standard-of-care procedure is performed, and the tumor is resected. After resection of the tumor, first the resected specimen will be analyzed ex-vivo and imaged by an ex-vivo fluorescence imaging system, screening for possible tumor-positive margins. Then the surgical cavity will be imaged in-vivo by the other, in-vivo fluorescence imaging system, screening for residual tumor tissue in the patient. This imaging should not take more than 5-10 minutes. The fluorescence images will be analyzed directly and if no tumor-positive margin is suspected, the procedure is ended. However, if a tumor-positive margin is suspected, the in-vivo fluorescence imaging system will be used to image the resected tissue specimen as well and biopsies will be taken from the region of interest of both the cavity and resected tissue specimen (if applicable). After obtaining the biopsies, the procedure is ended. If feasible determined by the pathologist team member, biopsies of fluorescent areas will be taken from the already standard of care resected tissue specimen to further study fluorescent tracer distribution on novel (3D) imaging techniques. The fluorescence images will be postoperatively correlated to the histopathology (i.e. hematoxylin and eosin, H&E staining).

Intervention

According to current standard-of-care workflow, patients with limited size breast cancer eligible for breast conserving therapy according to the multidisciplinary tumor board will be informed about the intended surgery. During this outpatient clinic visit the patient will be informed about this study as well. After written informed consent patients will receive intravenous administration of the fluorescent tracer bevacizumab-IRDye800CW two or three days prior to surgery. At day of surgery, surgery will be performed according to standard-of-care. After resection of the tumor, this whole tumor sample will be imaged ex-vivo screening for possible tumor-positive margins. Using another imaging device in-vivo cavity imaging screening for possible tumor-positive

margins will be performed. When a tumor-positive margin is suspected, a biopsy will be obtained from the region of interest in the patient before the procedure is ended. This way the fluorescence images can be correlated to pathology results afterwards. The study will extend the whole procedure approximately by 10-15 minutes. We hypothesize that tumor-positive margins can be detected by real-time fluorescence imaging, paving the way for future implementation of fluorescence imaging in standard-of-care and improving radical resection rates.

Study burden and risks

Burden: Time investment: Generally, patients visit the hospital (30 minutes) two or three days day prior to surgery for tracer administration. Operation duration is extended by max. 15 minutes. Additional procedures: First additional procedure is the intravenous administration of bevacizumab-IRDye800CW two or three days prior to surgery. The second procedure is in-vivo imaging of the cavity after resection of the tumor, screening for a possible tumor-positive margin. The third procedure is only performed if a tumor-positive margin is suspected based on ex-vivo and/or in-vivo imaging and consists of tissue biopsy of the region of interest for correlation of the fluorescence images to pathology results afterwards. Considering the size of a possible biopsy, no harm to the patients is expected.
Risk: No allergic reactions or other adverse events related to administration of bevacizumab-IRDye800CW were seen in previous studies containing more than 200 patients in the Martini Hospital and UMCG, even in higher dose-cohorts. The fluorescence imaging system used for cavity imaging is CE-approved for clinical use. Therefore, this study is considered low risk.
Benefit: For now, no clear benefit is expected for patients included in this study. The study is mostly focused on proof-of-concept of real-time fluorescence imaging for implementation and reducing tumor-positive margins (thereby lowering additional treatments) in future patients. Yet, current patients might benefit by acquiring radical resection after biopsy (and thereby complete removal) of tumor-positive lesions. However, this is not the aim of this study, but will be the subject of subsequent studies in the future.

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

To be eligible to participate in this study, the subject must meet all the following criteria:
-Patients are females with histologically proven carcinoma of the breast
-The carcinoma of the breast is a local disease with limited size (but tumor size >= 0.5cm) and in the multidisciplinary tumor board meeting breast conserving therapy is advised
-Age >= 18 years
-Written informed consent has been obtained
-Women of childbearing potential (premenopausal women with intact reproductive organs and women less than two years after menopause) require use of effective contraception at least 3 months before administration of the tracer (if not, a negative serum pregnancy test has to be submitted), and they need to be willing to ensure that she or her partner uses effective contraception during the trial and for 3 months thereafter.

Exclusion criteria

-Medical or psychiatric conditions that compromise the patient*s ability to give informed consent -Prior surgery of this breast -Received an investigational drug within 30 days prior to bevacizumab-IRDye800CW -Received neo-adjuvant therapy with (near) complete response -History of myocardial

infarction, cerebrovascular accident, uncontrolled cardiac heart failure or unstable angina within 6 months prior to enrollment -Inadequately controlled hypertension with or without current antihypertensive medication -Significant renal or hepatic impairment (grade II or higher deviations by CTCAE) -History of allergy or infusion reactions bevacizumab or other monoclonal antibodies -Pregnant or lactating women -Patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents -Life expectancy < 12 weeks -Preoperatively undetectable lymph nodes using SPECT-scan, requiring the use of patent blue.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-03-2024
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bevacizumab-IRDye800CW
Generic name:	Bevacizumab-IRDye800CW

Ethics review

Approved WMO

Date:	25-10-2022

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-12-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2022-002804-19-NL
ClinicalTrials.gov	NCT05939310
CCMO	NL82299.042.22