RESEARCH PROTOCOL

The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy.

A Dutch randomized controlled multicentre trial

This study is developed in collaboration with the Dutch Breast Cancer Trialists´ Group (BOOG): BOOG 2013-07

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1. ABBREVIATIONS AND RELEVANT DEFINITIONS

ALND	Axillary lymph node dissection
BCT	Breast conserving therapy: i.e. lumpectomy followed by whole breast radiotherapy
cN0	Clinically node negative: no signs of axillary lymph node metastases at physical examination and preoperative axillary ultrasound (or negative cyto-/histopathology)
cT1	Clinical (physical examination and imaging) tumour 2 cm or less in greatest dimension
cT2	Clinical (physical examination and imaging) tumour more than 2 cm but not more than 5 cm in greatest dimension
ER	Oestrogen receptor
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
pN0i+	Only isolated tumour cells (<0.2 mm), no regional lymph node metastasis
pN1mi	Micrometastasis (0,2 - 2,0 mm)
pN1	1-3 ipsilateral axillary lymph node metastases
pN>2	4 or more ipsilateral axillary lymph node metastases
SLN	Sentinel lymph node
TNM	TNM classification 7th edition. T: Primary tumour, N: Regional lymph nodes, M: Distant metastases
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

2. SUMMARY

Rationale - The diagnostic work-up and treatment of axillary lymph nodes in breast cancer patients is an ongoing topic of research. The ACOSOG Z0011 study demonstrated no additional value of a completion axillary lymph node dissection in case of limited sentinel lymph node metastases in breast cancer patients undergoing breast conserving therapy. This emphasizes what was already suggested many years ago by the NSABP B-04; axillary lymph node dissection does not contribute to survival nor disease control and can therefore be considered as overtreatment. As a result of the axillary lymph node dissection, many patients suffer from significant morbidity, such as seroma, lymph oedema, nerve injury and arm- and shoulder pain. Study results of the ACOSOG Z0011 could not be implemented in all sentinel node positive patients, because the study only concerned patients undergoing breast conserving therapy. It has been suggested that the results of the Z0011 trial might be ascribed to accidental irradiation of part of the axilla by the tangential breast irradiation. Therefore, this study investigates whether completion axillary treatment can also be safely omitted in sentinel node positive breast cancer patients undergoing a mastectomy.

Objectives - The primary objective of this study is to determine whether omitting completion axillary treatment is not inferior to the current axillary treatment regimen in sentinel node positive breast cancer patients undergoing a mastectomy, in terms of regional recurrence rate.

Study design - A prospective non-inferiority randomized multicentre trial.

Study population - Women aged 18 years or older diagnosed with unilateral invasive cT1-2N0 (clinically node negative based on physical examination and preoperative axillary ultrasound (+/- cyto-/histology)) breast cancer treated with mastectomy, who have limited axillary sentinel lymph node metastases (pN1mi(sn) or pN1(sn): 1 micro- to 3 macrometastatic sentinel lymph nodes).

Intervention - Eligible patients will be randomized for one of the following treatment groups:
- Arm A (control arm): mastectomy with completion axillary treatment
- Arm B (study arm): mastectomy without completion axillary treatment

Main study endpoints - Regional recurrence rate is the primary endpoint. Distant-disease free survival, overall survival, number of delayed axillary lymph node dissections, axillary morbidity rate, quality of life, local recurrence rate, contralateral breast cancer and administration of chest wall radiotherapy are secondary endpoints. All are measured during a follow-up period of 10 years. Prior data indicate a 5-year regional recurrence free survival rate of 98% among controls and 96% for study (as considered acceptable), resulting in a sample size of 399 per arm, to be able to reject the null hypothesis that the rate for experimental and control subjects is inferior by at least 5% (delta = -5%) with probability of 0.8.

Hypothesis - Completion axillary treatment can be safely omitted in sentinel node positive breast cancer patients undergoing a mastectomy. This will lead to a decreased axillary morbidity rate and to an increased quality of life, with non-inferior regional control, distant-disease free- and overall survival rates.

Nature and extend of the burden, risks and benefit associated with participation - Treatment procedures are all performed according to the Dutch breast cancer guideline. No patient will encounter any delay in their treatment as a result of inclusion. No additional interventions will be performed, only less if randomized for the study arm. Possible burden and risks for patients in study arm: worse regional recurrence rate, overall survival or distant-disease free survival and performance of delayed axillary lymph node dissection. Possible benefit for patients in study arm: lower axillary morbidity rate, less axillary surgery, shorter recovery time and improved quality of life.

3. INTRODUCTION

Breast cancer is the most common cancer in women worldwide with rising survival rates thanks to more extensive (adjuvant) treatment regimens [1, 2]. Consequently, more attention is warranted for the lifetime morbidity of breast cancer survivors resulting from overtreatment. The introduction of breast conserving therapy and especially the sentinel lymph node procedure significantly improved the quality of life of breast cancer patients. However, a recent study showed that the current treatment of the axillary lymph nodes following positive sentinel lymph node procedure is debatable.

Axillary lymph node dissection

For a long time the standard procedure to assess the axillary lymph node status in breast cancer patients was an axillary lymph node dissection (ALND), since the lymph node status was the most important indicator for adjuvant systemic therapy. Since the now known important role of patient and tumour related factors and even more recently gene expression profiling, the lymph node status is no longer the only indicator for adjuvant systemic therapy, but has become mostly a prognostic factor in breast cancer patients. An ALND is associated with significant short- and long-term morbidity. Most reported are seroma (15-75%), lymph oedema (20%), nerve injury (55-75%) and reduced shoulder function (16%) [3-5].

The supposed therapeutic effect of the ALND - improving overall survival and maintaining regional control - has been questioned for a long time, substantiated among others by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial with 25 years of follow-up, which was initiated in 1971. This trial aimed to determine whether clinically node negative breast cancer patients who received local or regional treatments other than radical mastectomy (total mastectomy plus ALND) would have outcomes similar to those achieved with radical mastectomy. A total of 1079 breast cancer patients, who were clinically node negative (based purely on physical examination) with a mean tumour size of 3.3 cm (± 2 cm), were randomly assigned to undergo radical mastectomy, or mastectomy with postoperative axillary radiotherapy, or mastectomy followed by delayed ALND for those patients who subsequently develop clinically apparent nodes. None of the patients received adjuvant systemic therapy [6].

In the radical mastectomy group, the ALND specimen contained lymph node metastases in about 40% of the women. Because all women were randomly assigned to the different treatment groups, about 40% of those who underwent mastectomy alone are also estimated to have had positive nodes not removed at the time of initial surgery. During follow-up of the mastectomy only group, involved ipsilateral nodes became clinically apparent in only 68 of 365 women (18.6%). Thus, occult lymph node metastases never became clinically positive in 53.5% of patients (21.4% of 40%). The clinically detected metastatic nodes were removed by a delayed ALND within 2 years in 75.0%, in year 2-5 in 14.7%, in year 5-10 in 8.8% and in year 10-25 in 1.5% (mean 14.8 months [3.0-134.5 months]).
After 25 years of follow-up, the (actual) regional recurrence rate (including supra- and subclavicular, internal mammary and ipsilateral axillary nodes) was significant different (p=0.002) between the three groups, with 4% (15/362) in the radical mastectomy group, 4% (15/352) in the mastectomy with postoperative irradiation group and 6% (23/365) in the mastectomy only group. Despite the need for a delayed ALND in 18.6% of patients in the mastectomy only group and the significantly different regional recurrence rate, no significant differences were observed among the three groups with respect to overall survival and disease-free survival (p=0.68 and 0.65 respectively).

In conclusion, the NSABP B-04 randomized controlled trial revealed that omitting primary axillary treatment of occult positive lymph nodes in clinically node negative breast cancer patients does not affect survival, even after 25 years of follow-up and without the use of adjuvant systemic or radiation therapy. The performance of a delayed ALND in case axillary lymph nodes become clinically positive does not affect survival and prevents axillary overtreatment in the majority of patients. Despite these favourable results, the ALND remained to be the standard procedure to assess the axillary lymph node status. Partly due to the in that time newly recognised value of adjuvant systemic therapy that appeared to be mainly beneficial for node-positive breast cancer patients.

Sentinel lymph node procedure

In the past 10 years, the sentinel lymph node (SLN) procedure has become the standard, less invasive technique to evaluate the nodal status in clinically node negative breast cancer patients. This procedure is based on the pattern of lymphatic drainage to one or more regional lymph nodes (the sentinel lymph nodes), assuming that if these sentinel lymph nodes contain no metastatic disease, all other regional lymph nodes are negative as well. High accuracy, low false-negative rates and safety of the SLN procedure were proven by several studies and randomized controlled trials [4, 7]. Complications known from ALND occur due to SLN procedure as well, though less frequently [8-10]. Severe lymphoedema occurs in still 8% after a follow-up of only 3 years [11].

In case an SLN contains metastatic disease, a completion ALND was standardly performed in all patients. However, about 60% of the completion ALND-patients appeared to have no additional metastases [12, 13]. In these patients the completion ALND provided no additional prognostic information and it neither had a therapeutic effect. Despite several studies, it appeared not possible to predict the absence of additional metastases after a positive SLN, to select a group of SLN-positive patients in whom the completion ALND can be omitted [14]. Before the SLN-era, research already proved that axillary radiotherapy is equal to ALND in clinically node negative patients in terms of local and regional disease control [15]. Arm oedema is observed in approximately 11% of the patients in case of axillary radiotherapy and impaired shoulder function in 17% of the patients after a 5 year follow-up [16].

Bilimoria et al. retrospectively assessed the differences in recurrence and survival for SLN procedure alone versus SLN procedure with completion ALND in 97,314 patients from the American National Cancer Data Base [17]. Of these 97,314 patients, 20.8% underwent the SLN procedure alone and 79.2% underwent the SLN procedure with completion ALND. After a median follow-up of 63 months, neither the regional recurrence rate nor overall survival was significantly improved in the completion ALND group. The regional recurrence rate in patients with a micrometastasis in the SLN and treated with an SLN procedure only was 0.6% (95%CI 0.0-1.3) compared to 0.2% (95%CI 0.0-0.4) when treated with completion ALND. The regional recurrence rate in patients with a macrometastasis in the SLN and treated with an SLN procedure only was 1.2% (95%CI 0.5-1.8) compared to 1.0% (95%CI 0.8-1.1) when treated with axillary clearance. Several recent studies showed a similar low regional recurrence rate after a positive SLN procedure alone of 0-3% [18-23].

In contrast, in the MIRROR study, omission of completion axillary treatment in patients with micrometastases resulted in a significantly higher 5-year regional recurrence rate (1.2% versus 6.2%, HR4.45 95%CI 1.46-13.54) [24]. However these data should be interpreted with caution since the regional recurrence rate of > 5% after 5 years seems extra-ordinary high and is not in accordance with other series.

In a meta-analysis, the false negative rate for the SLN procedure ranges from 0-40%, with a median of 7% [25]. So in theory, lymph node metastases are left in situ in 2.8% of clinically node negative breast

cancer patients (7% of 40%). This rate however, did not result in the expected regional recurrence rate of 4.45% (2.8% / 62.8%) after a negative SLN procedure. In contrast, after a negative SLN procedure the regional recurrence rate amounts only 0.3% (median follow-up was 34 months; median time interval to the recurrence was 20 months (range 4-63 months)) [12]. So, the true regional recurrence rate is 14.86 times lower (4.45% / 0.3%) than expected. So only a small amount of patients with false negative SLN's will develop clinically positive nodes.

Results of the ACOSOG Z0011 trial: omitting ALND following positive sentinel lymph nodes

Recently, the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial were published. This randomized controlled trial aimed to determine the effects of omitting completion ALND on overall survival in patients with SLN metastases. The study included patients undergoing breast conserving therapy (i.e. lumpectomy plus whole breast radiotherapy), who were clinically node negative (based on physical findings only), had a primary tumour size of less than 5 cm and one or two metastatic SLN´s. Patients with SLN metastases only identified by immunohistochemical staining were excluded [26].

Patients were randomly assigned to undergo completion ALND (control arm) or watchful waiting (study arm). In the control arm, 97 of 355 patients (27.3%) had additional lymph node metastases removed by ALND. At a median follow-up of 6.3 years (range 5.2-7.7), the overall survival and disease-free survival rate was 91.8% and 82.8% in the completion ALND arm, and 92.5% and 83.9% in the watchful waiting arm. A regional recurrence rate of 0.5% (2 events) was observed in the completion ALND arm and of 0.9% (4 events) in the SLN procedure only arm. All differences between groups were non-significant. It was concluded that omitting the completion ALND in this population does not result in inferior survival results nor a higher regional recurrence rate.

After publication in JAMA February 2011, criticisms followed. It was suggested that the radiotherapists may have enlarged their radiation fields [27]. The principal investigator, Giuliano is revising the radiotherapy-part of the ACOSOG Z0011 at this moment. Furthermore, it was claimed that the study was not representative for the standard breast cancer population. The share of oestrogen receptor negative (ER-) patients was low and consequently the share of oestrogen receptor positive (ER+) patients high. Regional recurrences in ER+ patients were said often to appear later than the 5 year follow-up period. Besides, it was commented that the number of young patients was relatively low.

Giuliano (Cidars-Sinai Medical Centre) and Morrow (Memorial Sloan-Kettering Cancer Centre) reacted in the 2011 June edition of Annals of Surgical Oncology [28]. Both substantiated that the mean time to regional recurrence for ER+ tumours amounts 33-36 months. Regional recurrence after 5 years occurs only in 1-2%. The follow-up period of at least 5 years (median 6.3) should therefore suffice. Contrarily, ER- patients often do not have more than two involved nodes. Chances for retained lymph node metastases are therefore reduced. Targeted therapy is a powerful method for reducing local and regional recurrences and the addition of trastuzumab to chemotherapy even diminishes local and regional recurrences by 50%. Young age is a risk factor for local and regional recurrences. Though, is emphasized that the bigger share of locoregional recurrences consists of solitary local recurrences.

The article concludes with: "surgeons must ask themselves whether they are more comfortable using their own clinical impressions and retrospectively derived nomograms to make the decision about performing an axillary dissection for a positive sentinel node than they are with the use of criteria employed in a prospective, randomized trial. Meanwhile, there is ample opportunity for critics to rectify the limitations of Z11 in the next generation of trials, which should address the role of axillary dissection in patients excluded from Z11 - those undergoing mastectomy, those who have received neoadjuvant therapy and those having breast conservation without whole breast radiotherapy" [28].

Findings of the ACOSOG Z0011 trial are supported by the results of the International Breast Cancer Study Group (IBCSG) 23-01 trial. This randomized controlled trial investigated whether no axillary dissection was non-inferior to axillary dissection in clinically node negative patients with one or more micrometastatic sentinel nodes and a primary tumour of 5 cm or less. Both patients treated with breast conserving therapy and mastectomy were included. In the ALND group, 13% of patients had additional nodal disease in the ALND specimen. However, the 5-year regional recurrence rate was only 1% and overall survival was not affected, in accordance to other studies [29].

MD Anderson and Memorial Sloan-Kettering Cancer Centre openly changed their protocol at least for cN0 breast cancer patients undergoing breast conserving therapy in case of a maximum of two involved SLN's [30]. The current Dutch breast cancer guideline 2012 also implemented the results of the ACOSOG-Z0011, describing that omitting completion ALND may be considered in these patients, with the limitation that adjuvant systemic therapy should be indicated and breast conserving therapy is performed [31].

Recently, the results of the After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial were presented at ASCO 2013. This trial randomized clinically node negative, sentinel node positive patients to ALND or axillary radiotherapy. Both patients treated with breast conserving therapy and mastectomy were included. The 5-year regional recurrence rate was low in both randomization groups: 0.43% in the ALND group and 1.19% in the radiotherapy group. Also, disease-free and overall survival rates were similar for both groups. Fewer side effects were seen in the radiotherapy group; lymphoedema rates of 28% in the ALND group and 14% in the radiotherapy group after 5 years ($p<0.0001$) [32]. However, it is uncertain whether this advantage for radiotherapy will persist over time, as side effects of radiotherapy evolve over a more prolonged time course than surgical side effects. Therefore, clinicians should be cautious for a widespread adoption of radiotherapy in sentinel node positive patients.

In conclusion, the AMAROS trial revealed that axillary radiotherapy instead of completion ALND provides similar regional recurrence, disease-free and overall survival rates in clinically node negative, sentinel node positive patients, with lower lymphoedema rates. The ACOSOG Z0011 and the IBCSG 23-01 randomized controlled trials revealed that completion ALND can even be safely omitted in clinically node negative breast cancer patients with metastatic sentinel nodes. The ALND specimen of patients in the control arm of the trials contained additional nodal metastases beyond the SLN metastasis in 13-27%. Patients randomized to the SLN only arm were therefore likely to have residual nodal disease that was not surgically removed. Nevertheless, survival rates were not affected and regional recurrence rates low.

Preoperative axillary ultrasound

As highlighted before, about 40% of newly diagnosed breast cancer patients have nodal metastases. Physical examination and the axillary ultrasound are performed routinely in the Netherlands to assess the axillary lymph node status prior to SLN procedure or ALND. If a suspicious lymph node is detected by ultrasound, this node will be sampled and if pathology shows a metastasis, the SLN procedure is omitted and an ALND is indicated. The ALND can then be performed simultaneously with the tumour excision. This approach prevents 19.8% of breast cancer patients from having to undergo an additional operation [33].

Clinically node negative breast cancer patients in the NSABP B-04 and the ACOSOG Z0011 trial were selected by physical examination. The accuracy of physical examination of the axilla for pre-operative staging is low, with a sensitivity of 25-32.3% for detecting axillary metastases [34-37]. Preoperative

staging with axillary ultrasound selects node negative patients more accurately. The sensitivity of axillary ultrasound combined with biopsy is 79.6%, with a specificity of 98.3% [33]. Furthermore, it selects patients with a more favourable tumour load, as the total number of lymph node metastases per patient is significantly lower after a negative axillary ultrasound compared to when the clinically node negative status is based solely on physical examination [38, 39]. Besides, a negative axillary ultrasound accurately excludes advanced axillary nodal disease (≥4 lymph node metastases), with a negative predictive value of 93-96% [40, 41]

Low regional recurrence rate

In the NSABP B-04 trial, less than half of the patients with nodal metastases (based on the incidence of metastases in the ALND arm) developed clinically apparent regional recurrence [6]. None of these patients received adjuvant systemic or radiation therapy. It is therefore likely that the biology of lymph node metastases plays an important role in the growth of metastases in the axilla.

In the NSABP B-04 trial, none of the patients received adjuvant systemic treatment. At present, adjuvant systemic therapy (i.e. chemo-, endocrine- and immunotherapy) is administered in both node positive and increasingly in node negative patients due to the development of more effective and targeted systemic therapy. Adjuvant systemic therapy is known to decrease local and regional recurrence rates [42]. Reported pathologic complete response rates for axillary lymph node metastases following primary systemic therapy of about 20-40% demonstrate that systemic therapy eradicates lymph node metastases left in situ [43-47].

Conclusion

In conclusion, the NSABP B-04 randomized controlled trial showed us that omitting primary axillary treatment of occult positive lymph nodes in clinically node negative breast cancer patients does not affect survival, even after 25 years of follow-up and without the use of adjuvant systemic or radiation therapy. The performance of a delayed ALND in case axillary lymph nodes become clinically positive does not affect survival and prevents axillary overtreatment in the majority of patients. The AMAROS trial revealed that axillary radiotherapy instead of completion ALND can be safely performed in clinically node negative breast cancer patients with metastatic sentinel nodes, who are treated with mastectomy or breast conserving therapy, providing lower lymphoedema rates. The ACOSOG Z0011 and the IBCSG 23-01 randomized controlled trial revealed that completion ALND can be safely omitted in clinically node negative breast cancer patients with metastatic sentinel nodes, who are treated with breast conserving therapy. Patients randomized for watchful waiting were likely to have residual nodal disease (13-27%) that was not surgically removed. Nevertheless, survival rates were not affected and regional recurrence rates low. Clinically node negative patients in these trials were selected by physical examination. Adding axillary ultrasound will improve the preoperative selection of node negative patients, as it selects patients with a more favourable tumour load and accurately excludes advanced nodal disease (≥4 metastatic nodes). Biology and adjuvant systemic therapy are factors that most likely diminish the risk that possible metastases left in situ develop into clinically detectable lymph nodes.

The study

Therefore, we propose a randomized controlled trial to prove that completion axillary treatment can be safely omitted in breast cancer patients with a negative axillary ultrasound, who have positive sentinel lymph nodes and who are treated with a mastectomy. This study will significantly decrease the number of breast cancer patients receiving overtreatment of the axilla, thereby diminishing the risk of complications and improving quality of life, while maintaining excellent regional control and not affecting survival.

4. OBJECTIVES

Primary objective
The primary objective of this study is to investigate whether omitting completion axillary treatment is not inferior to the current axillary treatment regimens in sentinel node positive breast cancer patients undergoing a mastectomy, in terms of regional recurrence rate.

Secondary objectives
Secondary objectives of this study are to investigate whether omitting completion axillary treatment is not inferior to the current axillary treatment regimes in sentinel node positive breast cancer patients undergoing a mastectomy, in terms of distant-disease free survival, overall survival rate, the local recurrence rate and the occurrence of contralateral breast cancer. Other secondary objectives are the administration of postoperative radiotherapy and the influence of omitting completion axillary treatment on the number of delayed axillary lymph node dissections, the axillary morbidity rate and quality of life.

All objectives are measured during a follow-up of 10 years.

Hypothesis
Completion axillary treatment can be safely omitted in sentinel node positive breast cancer patients undergoing a mastectomy and results in a significantly lower axillary morbidity rate and an improved quality of life.

5. STUDY DESIGN

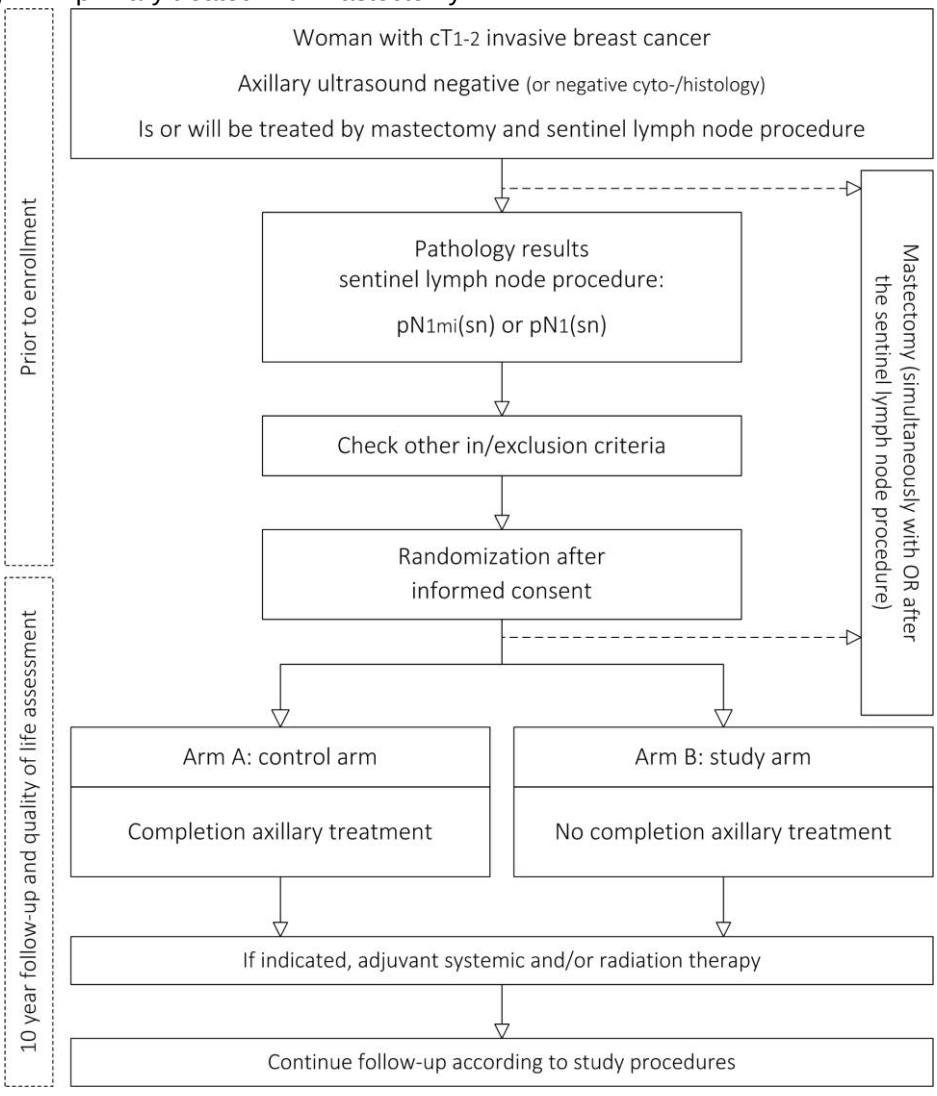
a. Description of the study design

Study design: a prospective non-inferiority randomized multicentre trial. Patient group:
cT1-2N0* invasive breast cancer patients undergoing a mastectomy with a minimum of 1 micro- and a maximum of 3 macrometastatic axillary sentinel lymph nodes (pN1mi / pN1).
- Randomization:
Arm A - control arm: mastectomy with completion axillary treatment
Arm B - study arm: mastectomy without completion axillary treatment
* cT1-2N0: tumour not larger than 5 cm and clinically node negative based on a negative axillary ultrasound (or negative cyto-/histology).

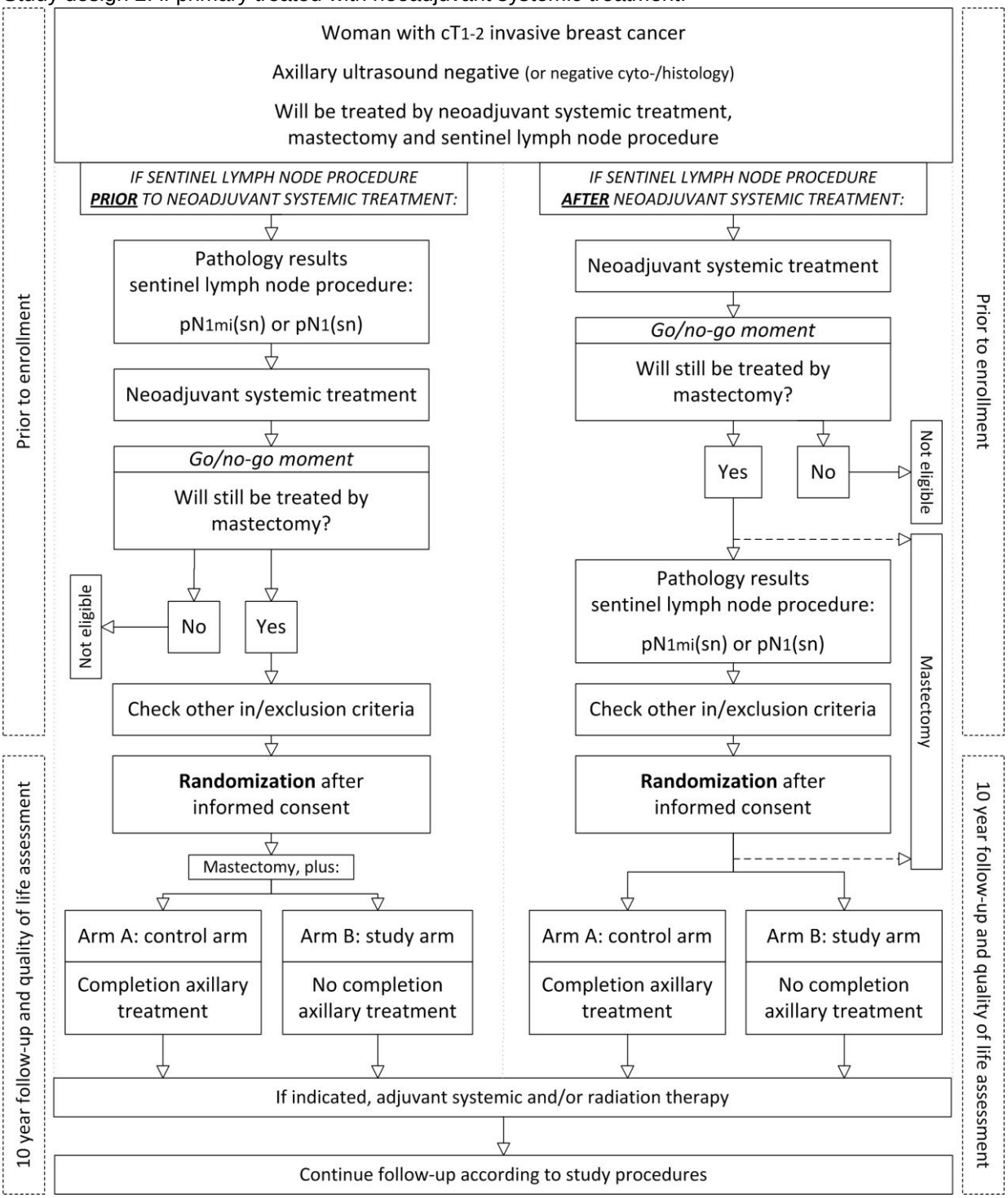
Stratification for the randomization arm
Patients will be stratified by: age (≤50, 50≤75, >75), oestrogen receptor status (positive vs. negative), HER2neu status (amplified vs. not-amplified), lymph node metastasis (micro vs. macrometastasis), clinical tumour size prior to any treatment (<3cm vs. ≥3cm), grading (grade I-II vs. III - according to modified Bloom-Richardson grading system), neoadjuvant systemic therapy and participating centre.

b. Schematic study design

Study design 1: if primary treated with mastectomy:



Study design 2: if primary treated with neoadjuvant systemic treatment:



c. Timeline

Oct 2013	**-**	**Mar 2014**	Review of the study by one central METC
Apr 2014	**-**	**May 2017**	Inclusion of patients (878; 36 months)
			Start of 10 year follow-up
May 2017	**-**	**May 2022**	Completion of 5 year follow-up of every patient
May 2022	**-**	**May 2027**	Completion of 10 year follow-up of every patient

6. STUDY POPULATION

a. Population

The incidence of invasive breast cancer in female patients in the Netherlands was approximately 14.000 in 2011.

b. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all the following criteria:

1. Female
2. Aged 18 years or older
3. Pathologically confirmed invasive unilateral breast carcinoma
4. A clinical T1-2 tumour (including multifocal or multicentric breast cancer)
5. Will be or is treated with mastectomy
6. Clinically node negative: no signs of axillary lymph node metastases at physical examination and preoperative axillary ultrasound (or negative cyto-/histopathology)
7. SLN procedure and its pathologic evaluation should be performed according to the Dutch breast cancer guideline
8. pN1mi(sn) or pN1(sn): at least one and a maximum of three axillary sentinel lymph nodes containing micro- and/or macrometastases.
9. Written informed consent

Furthermore, neoadjuvant systemic therapy and primary and secondary breast reconstructions are also allowed.

c. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participating in this study:

1. Clinically node positive pre-operative
2. Sentinel lymph nodes only containing isolated tumour cells (<0.2mm)
3. Solitary parasternal sentinel lymph node metastasis (pN1b)
4. Bilateral breast cancer
5. Irradical resection of primary tumour at time of randomization (applicable in case the mastectomy is performed before randomization)
6. Evidence of metastatic disease
7. History of invasive breast cancer
8. Previous treatment of the axilla with surgery or radiotherapy (except surgery for hidradenitis suppurativa or for other superficially located skin lesions, such as naevi)
9. Pregnant or nursing
10. Other prior malignancies within the past 5 years (except successfully treated basal cell and squamous cell skin cancer, carcinoma in situ of the cervix or carcinoma in situ of the ipsilateral or contralateral breast) or unsuccessfully treated malignancies > 5 years before randomization
11. Unable or unwilling to give informed consent

d. Sample size calculation

Sample size calculation for a non-inferiority design including sentinel node positive breast cancer patients treated with mastectomy, who will be randomized between follow-up versus completion axillary treatment is as follows: Our hypothesis is that patients with limited positive SLN´s who do not undergo completion axillary treatment will have a non-inferior regional recurrence rate compared to patients in the control group and should therefore be treated as such.

Prior data indicate a 5-year regional recurrence free survival rate of 98% for the control patient group. A regional recurrence free survival rate of 96% is considered acceptable for the experimental patient group, when taking in account the higher morbidity rate caused by axillary treatment in the control arm. The expected regional recurrence free survival rates result in a sample size of 399 per arm. Therefore, we will need to study 399 experimental subjects and 399 control subjects to be able to reject the null hypothesis that the rate for experimental and control subjects is inferior by at least 5% (delta = -5%) with a probability of 0.8.

	p1	**p2**	**alpha (type I error)**	**Power (1-beta)**	**epsilon (p1-p2)**	**delta (non-inferiority margin)**	**Sample Size (per arm)**
Non-Inferiority	0,96	0,98	0,05	0,8	-0,02	-0,05	399

When taking in account a lost to follow-up rate of 10 %, **878** patients need to be randomized. Every year **14.000** female patients are diagnosed with invasive breast cancer. About 80 % is operated on primarily (excluding patients treated with chemo- or hormonal therapy only, or with metastatic disease and frail elderly).

14.000 * 80 % = **11.200** patients
Of these patients, 30 % will have N+ and no N2 nodal status.
11.200 * 30 % = **3.360** patients
In the Netherlands 44% of the cT1-2 patients undergo a mastectomy.
3.360 * 44 % = **1.478** patients
With the now known interest in participating of 43 hospitals in the Netherlands, 73 % of the patients will visit a study hospital.
1.478 * 73 % = **1079** patients
We expect an accrual rate of 30 %
1079 * 30 % = **324** patients yearly
This means that **3 years** will suffice to include **878 patients** (incl. 10% lost to follow-up)

For the interim analysis the sample size was recalculated with a doubled delta from 5% to 10%.

	p1	**p2**	**alpha (type I error)**	**Power (1-beta)**	**epsilon (p1-p2)**	**delta (non-inferiority margin)**	**Sample Size (per arm)**
Non-Inferiority	0,96	0,98	0,05	0,8	-0,02	-0,1	57

When taking into account a lost to follow-up rate of 10 %, 125 patients need to be included for the interim analysis.

7. METHODS

a. Study endpoints

Main study endpoints

- *Regional recurrence rate*

Regional recurrence is defined as tumour recurrence and as residual tumour that became clinically apparent in ipsilateral axillary, infraclavicular and supraclavicular lymph nodes (pathologically proven).

Secondary study endpoints

- *Regional recurrence free survival*

Regional recurrence free survival is defined as the time interval between the date of randomization and the date of first suspicion of regional recurrence or date of death, whichever comes first, measured in days. Patients who did not experience regional recurrence and are still alive are censored at the date of last follow-up.

- *Number of delayed axillary lymph node dissections*

This is defined as the number of patients in in whom a delayed ALND (>6 months after randomization) was performed in case of regional recurrence, with the time interval between the date of randomization and the date of the delayed ALND, measured in days.

- *Distant-disease free survival*

Distant-disease free survival is defined as the time interval between the date of randomization and the date of first suspicion of distant recurrence or death, whichever comes first, measured in days. Patients in whom a distant recurrence was not observed and are still alive are censored at the date of last follow-up.

Included are: distant recurrence (distant metastasis), death from breast cancer and its treatment, death from second primary invasive (nonbreast) cancer, death from unknown cause. N.B.: lymph node recurrence in cervical lymph nodes or in contralateral internal mammary lymph nodes or in the contralateral axilla is coded as distant metastasis.

Excluded are: ipsilateral breast tumour recurrence, regional invasive recurrence, contralateral breast cancer, and all in situ carcinomas, as these events are potentially nonlethal.

- *Overall survival*

Overall survival is defined as the time interval between the date of randomization until death from any cause. Patients who are still alive are censored at the date of last follow up.

Included are: death from breast cancer, death from nonbreast invasive cancer cause, death from unknown cause.

- *Local recurrence rate*

Local recurrence is defined as pathologically proven recurrence after breast surgery in the skin or soft tissue of the chest wall (within the anatomical area bounded by the midsternal line, the clavicle, the posterior axillary line and the costal margin). The local recurrence free interval is defined as the time interval between the date of randomization and the date of first clinical suspicion of local recurrence, measured in days.

- *Other-regional recurrence rate*

Other-regional recurrence is defined as pathologically proven recurrence in the region of the ipsilateral internal mammary lymph node chain (lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia). Other-regional recurrence free interval is defined as the time interval between the date of randomization and the date of first clinical suspicion of other regional recurrence, measured in days.

- *Contralateral breast cancer rate*

The occurrence of (pathologically proven) contralateral invasive breast cancer will be registered. Contralateral breast cancer free interval is defined as the time interval between the date of randomization and the date of first clinical suspicion of contralateral breast cancer, measured in days.

- *Percentage difference in the administration of postoperative radiotherapy*

This is defined as the percentage difference in the administration of chest wall radiotherapy between both study arms.

- *Diagnosis of recurrence outside the axillary region*

One or more of the following must be positive for the diagnosis of tumour recurrence to be accepted:

I. Histology or cytology
II. Autopsy examination

Diagnosis based on radiological findings can be considered if I or II is not possible/available (these cases will be presented to the DSMB for an independent review).

- *Axillary morbidity rate*

The axillary morbidity rate will be assessed using a validated questionnaire, as shown in chapter 7, section e ‘Axillary morbidity rate and quality of life’ on page 24.

- *Quality of life*

Quality of life will be assessed using validated questionnaires, as shown in chapter 7, section e ‘Axillary morbidity rate and quality of life’ on page 24.

b. Study procedures - diagnosis and randomization

Diagnosis

The study population will be selected from the group of patients visiting the hospital with breast complaints or patients referred by the breast cancer screening program. Eligibility for the study should be verified in every patient with invasive breast cancer. According to the standard care and work-up of breast cancer patients, general patient information and medical history will be obtained, and all patients will undergo standard preoperative physical, radiological and pathological examination (which may include mammography, ultrasound of the breast and axillary region, MRI of the breast, cytological and/or histological biopsies) according to the Dutch breast cancer guideline. Screening for axillary lymph node metastases with physical examination and an axillary ultrasound is obligatory.

Axillary ultrasound

The axillary ultrasound is standard of care in the preoperative diagnostic work-up of breast cancer patients according to the Dutch breast cancer guideline. The performance of the axillary ultrasound is standardized in this study to ensure its quality. Therefore the radiologist should perform the axillary ultrasound according to the following method:

Preferably, the patient is positioned with the ipsilateral hand placed behind the head. The entire axilla is examined in a standardized fashion, starting at the low axilla (level I: inferior and lateral to the pectoralis minor muscle), and continuing upwards toward mid-axilla (level II: medial and lateral to the pectoralis minor muscle and interpectoral) and apical axilla (level III: superior and medial to the pectoralis minor muscle with apical lymph nodes).

The following criteria are used during ultrasound to identify positive lymph nodes: long to short axis ratio of <2 (i.e. round), diffuse or focal cortical thickening, effacement or replacement of the fatty hilum, and/or nonhilar blood flow (using Doppler ultrasound, if detectable). As described in the Dutch breast cancer guideline, cortical thickening of more than 2.3 mm is considered as the optimal cut-off point to perform fine-needle aspiration biopsy. Additionally, a subjective assessment of thickening can be made by the radiologist during real-time imaging, similar to the studies by Koelliker et al, Abe et al, and Neal et al [41, 48, 49]. Fine-needle aspiration biopsy or core biopsy is recommended when suspicious lymph nodes are identified. Preferably, a core biopsy of a suspicious lymph node is performed instead of fine-needle aspiration biopsy, because core biopsy is more sensitive, as described by Rautiainen et

al. [50]. In case of two or more abnormal lymph nodes, the lymph node with the most suspicious findings is selected for tissue sampling.

Randomization

In case a patient meets the inclusion criteria and mastectomy is the choice of treatment (according the considerations of the surgeon and the patients' preference), the patient will be asked to participate in the study by the attending surgeon. We will start the inclusion of patients immediately after the approval of the METC and the Executive Board.

- *Written informed consent pre-SLN procedure*

This section is applicable in cases where frozen section during the SLN procedure is performed to assess the sentinel lymph nodes peroperative.

These patients must be informed before the sentinel lymph node procedure about the goal, the randomization procedure and the consequences. So, written informed consent must be obtained preoperative before the SLN procedure. In case these patients turn out to be eligible for inclusion, randomization will take place peroperative. Randomization is performed centrally.

- *Written informed consent post-SLN procedure*

This section is applicable in all other cases than the one described in the section above.

These patients will be informed after the sentinel lymph node procedure, in case the sentinel lymph nodes turn out to contain one micrometastasis or a maximum of three macrometastases. So in these cases, written informed consent will be obtained postoperative after the SLN procedure when final histopathology results are known and when a mastectomy is performed or will be performed on short notice. For example when a patient is treated with neoadjuvant systemic treatment and the sentinel lymph node procedure is performed before start of this treatment: randomisation should take place after completion of the neoadjuvant systemic treatment when the decision is made that the patient is treated with mastectomy. Randomization is performed centrally.

- *Stratification*

Patients will be stratified by: age (≤50, 50≤75, >75), oestrogen receptor status (positive vs. negative), HER2neu status (amplified vs. not-amplified), lymph node metastasis (micro- vs. macrometastasis), clinical tumour size prior to any treatment (<3 cm vs. ≥3 cm), grading (grade I-II vs. III - according to modified Bloom-Richardson grading system), neoadjuvant systemic therapy and participating centre.

c. Study procedures - treatment

Sentinel lymph node procedure

The SLN procedures will be performed using technetium-99m Nanocolloid as a radioactive tracer and blue dye / patent blue for lymphatic mapping. Both are injected into breast parenchymal tissue surrounding the tumour, biopsy cavity or periareolar. The tracer will search its way through draining lymph vessels to the first receiving lymph node. This SLN will be identified and harvested by use of the following triple technique: lymphoscintigraphy, intraoperative use of the gamma probe, and intraoperative detection of the blue lymphatic vessels. Palpation of the axilla through the incision after removal of tracer-labelled SLN's should be performed to identify and remove firm suspicious nodes. These nodes are called non-SLN's.

Frozen section during surgery is allowed, with the requirement that all SLN's and possible non-SLN's identified are pathologically assessed peroperative. Eligibility for randomization should be (re)considered if the definitive pathology results differ from the frozen section results. A patient is eligible for randomization in case a (non-)SLN is negative on frozen section, but turns out to be positive after definitive pathology. A patient is not eligible (anymore) for randomization if four (non-)SLN's are harvested of which three are positive and one negative on frozen section, but the negative turns out to be positive after definitive pathology. This patient will be excluded from the study (off-study) and will be treated according to the Dutch breast cancer guideline.

- *Pathological assessment - the sentinel node*

As a minimal requirement three histological levels (500 micron distance) for each SLN are examined. On each level two parallel sections are performed, one for immunohistochemistry and one for haematoxylin and eosin (H&E) staining. Immunohistochemical staining is performed for markers containing at least cytokeratin 8 and 18 (e.g. CAM 5.2, NCL5D3). Cytokeratin immunohistochemical (IHC) staining is done only when H&E staining is negative. Lymph nodes submitted for pathological examination which are marked by the surgeon as non-sentinel nodes are examined with H&E and if negative with cytokeratin IHC staining.
The exact diameter of every SLN must be determined, as well as describing the occurrence of extranodal growth. Isolated tumour cells (<0.2mm) are considered as SLN negative and not included in this study.
Patients with solitary parasternal sentinel lymph node metastases, classified as pN1b (TNM classification) are excluded from this study.

Randomization arm A - control arm: mastectomy with completion axillary treatment
Patients randomized for arm A will undergo completion axillary treatment. Completion axillary treatment can consist of an ALND or axillary radiotherapy in accordance to the Dutch breast cancer guideline. Axillary radiotherapy can be either level 1 and 2, or level 1, 2 and 3, including the supraclavicular nodes. Each centre should state beforehand which radiation strategy they will follow.

Randomization arm B - study arm: mastectomy without completion axillary treatment
Patients randomized for arm B will be registered instead of undergoing completion axillary treatment. During follow-up the axilla will be accurately assessed by physical examination. In case of the suspicion of an axillary lymph node metastasis at physical examination, an axillary ultrasound (+/- tissue sampling) is indicated. When metastasis is cyto- or histopathologically confirmed, accurate staging for distant metastases is performed. A delayed ALND is performed if indicated by the multidisciplinary team.

Local treatment primary tumour - mastectomy
A mastectomy is defined as the surgical removal of the entire breast tissue of the breast.

Radiation therapy (if applicable)

- Chest wall

Radiation therapy of the thoracic wall after a mastectomy is indicated in specific circumstances depending on the Dutch and local protocol and therefore not an exclusion criterion in this study.
According to the Dutch breast cancer guideline, postoperative radiation therapy after mastectomy can be considered in patients with 1-3 axillary lymph nodes containing metastatic disease with at least one risk factor*. The indication for radiation therapy must be clearly defined for each participating centre to prevent a low-threshold for initiating chest wall irradiation in study arm B.
Quality assurance (QA) for chest wall irradiation in the BOOG 2013-07 trial will be performed to analyze inter-observer variation. Each participating radiotherapy center will be asked to provide their chest wall radiation treatment plan of three representative cases of breast cancer patients, as if these were patients included in the BOOG 2013-07 trial.
* Risk factors: angioinvasive growth, grade III tumours, tumour size of ≥3 cm and/or age ≤ 40 years.

- Axilla

In case the patient is randomized for axillary treatment, this can consist of an ALND, radiation therapy of axilla level 1 and 2 (i.e. the regions that would be operated upon if an ALND would be performed), or radiation therapy of axilla level 1-3 including the supraclavicular nodes (i.e. conform the regions that were irradiated in the AMAROS trial).

- *Radiation therapy details (if applicable)*

<u>Dose and fractionation for both chest wall and axilla</u>

A fractionation scheme equivalent to 25 x 2 Gy, 5 fractions per week must be applied; i.e. schemes of 15 -16 x 2.67 Gy, 5 fractions per week are allowed as well. In case of an irradical resection a boost should be given to the tumour bed, equivalent to 7-13 x 2 Gy. A simultaneous integrated boost is recommended, with high fraction size not exceeding 2.67 Gy.

Delineation of chest wall and axillae

Delineation or target volumes and organs at risk should be performed using the European Society for Radiotherapy & Oncolology (ESTRO) guidelines of v. Offeresen et al. [51]. Delineation of the target volume, i.e. the thoracic wall, is optional. Delineation of the heart and the lungs is obligatory. Delineation of other normal structures is optional. To allow adequate evaluation of the radiation in the axillary nodal regions, delineation of axilla level 1, 2, Rotter and 3 is obligatory, even if axillary radiation is not applied. In case a patient is irradiated on the axilla level 1-3, including the supraclavicular nodes, this latter region should be delineated as well, according to the DBCG guidelines [51].

Technique/ dose distribution

The dose in the (Planning Target Volume (PTV) of the) thoracic wall with or without the axillary and periclavicular nodes must be between 95%-107% of the prescribed dose. If the distance between the skin and the pectoral muscle is < 5 mm, it is recommended to place at least 5 mm tissue-equivalent material. The Central Lung Distance (CLD) must be < 3 cm (in case of tangential fields) and/or the mean lung dose < 5 Gy in case of tangential fields only, and < 7.5 Gy in case of locoregional radiation. The Maximum Heart Distance (in case of tangential fields) must be < 1 cm, or the heart volume receiving > 25 Gy should be < 20%; the Mean Heart Dose should preferably be below 3 Gy, but should not exceed 5 Gy. If lung or heart constraints cannot be met, some underdose in the thoracic wall can be accepted to reach the constraints, provided that the quadrant where the tumour was localized is adequately covered. Breath holding techniques to reduce heart dose are highly recommended for left sided breast cancer patients. The dose in the brachial plexus should be kept below an equivalent of 60 Gy in 30 fractions. The minimum, maximum and mean dose of the axilla level 1, 2, Rotter and 3 should always be recorded for evaluation purposes, even in case no axillary radiotherapy is indicated.

Pathological assessment - the primary tumour

The pathological size of the primary tumour must be assessed. The hormone receptor status must be determined by immunohistochemical staining and is considered positive if ≥10% of the cells stain positive. HER2neu status is determined by immunohistochemistry and in case of 2+ determined by CISH or FISH. Histological tumour grading will be assessed according to the modified Bloom-Richardson grading system. The presence of multifocality is defined as foci or carcinoma separate from the primary tumour. The histological tumour type must be defined according to the World Health Organization. Presence of lymphovascular invasion is defined as one or more tumour cells in a lymphatic or vascular structure.

- *Modified Bloom-Richardson grading system*

The grading system consists of three components of the tumour morphology: the extent of tubule formation, the nuclear polymorphism and mitotic activity defined as the number of mitoses per 2 mm^2. A score of 1, 2 of 3 is assigned to each of these components. The histological grade is determined by the sum of these scores.

Level of tubule formation:	1 = > 75%
	2 = 10-75%
	3 = < 10%
Nuclear polymorphism:	1 = comparable to normal epithelium
	2 = enlarged, vesicular, small nucleoli
	3 = polymorphic, vesicular, large nucleoli

Mitotic activity: 1 = 0 through to 7 mitoses per 2 mm^2
2 = 8 through 12 mitoses per 2 mm^2
3 = 13 or more mitoses per 2 mm^2
The histological grade is I for the scores 3-5, II for 6-7, and III for 8-9.

Neoadjuvant chemo- or hormonal therapy
Neoadjuvant systemic therapy in clinically T1-2 (pre-systemic therapy) patients is no exclusion criterion. Patients will be excluded from this study (off-study) if a mastectomy is not performed after the neoadjuvant systemic therapy.

Adjuvant systemic therapy
The indication for adjuvant systemic therapy is determined for the individual patient according to the current Dutch breast cancer guideline and multidisciplinary approach.

d. Study procedures - follow-up

After inclusion a follow-up period of 10 years follows.
Year 1 - 5: outpatient clinic visits with physical examination of the axilla and a mammography once yearly
Year 6 - 10: outpatient clinic visits once yearly with physical examination of the axilla
≤ 60 years: mammography once yearly
> 60 years: mammography once every two years
Additional imaging techniques for detecting possible recurrence will only be performed on indication.

- An axillary ultrasound is performed in patients with a clinical suspicion (physical examination) of axillary lymph node metastases during follow-up. If an axillary lymph node metastasis is confirmed (cyto-/histology), staging for distant metastatic disease is mostly performed according to the Dutch breast cancer guideline.
- Staging for metastatic disease is mostly performed (according to the Dutch breast cancer guideline) in patients with a clinical suspicion of distant metastatic disease during follow-up. Physical examination of the axilla must then always be performed for the detection of possible axillary lymph node metastases. An axillary ultrasound is only performed in patients with a clinical suspicion (physical examination) of axillary lymph node metastases.

Required Investigations	**Prestudy**	**Follow-up in years**										
		0,5	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Mammography	X		Once yearly					≤ 60 years: once yearly > 60 years: once in two years				
FNA/core biopsy primary tumour	X											
Receptor status	X											
Physical examination axilla	X		Once yearly - outpatient clinic									
Axillary ultrasound	X		On indication									
Sentinel lymph node procedure	X											
Staging for distant metastatic disease			On indication									
QoL and morbidity	X	X	X	X			X					X

assessment												

e. Axillary morbidity rate and quality of life

Introduction

Breast cancer is the most common cancer in women worldwide, with rising disease free and overall survival rates due to more extensive treatment regimens. Until recently it was unknown whether completion axillary treatment like completion ALND following a positive SLN contributed to survival and regional control. The recently published ACOSOG Z0011 study showed that omitting completion ALND in patients undergoing breast conserving therapy did not result in inferior results, in case of limited sentinel lymph node metastases. As axillary treatment is associated with significant morbidity, this axilla-conserving treatment is thought to lead to a reduction in the occurrence of morbidity with an improvement of quality of life, while maintaining equivalent overall and distant-disease free survival. However, limitations of the ACOSOG Z0011 study prevent implementation of the treatment protocol in all breast cancer patients, as they did not investigate omitting completion ALND in patients treated with mastectomy. Therefore, this study aims to investigate whether completion axillary treatment can be safely omitted in clinically node negative breast cancer patients undergoing mastectomy.

If this study concludes that completion axillary treatment can be safely omitted in clinically node negative breast cancer patients undergoing a mastectomy, this will lead to a striking reduction of the number of completion axillary treatments performed. This treatment will then only affect women with advanced axillary metastatic disease. The incidence of axillary treatment-associated morbidity will consequently decrease impressively. A reduction in morbidity will affect both mental and physical health of the patient and will most likely increase quality of life.

Improvement of quality of life seems logical, but is not guaranteed. Less extensive axillary treatment and possibly leaving supposed tumour load behind could negatively influence patient's well-being, with more insecurity and anxiety towards their future. Van der Steeg however concluded in 2006 that trait anxiety rather than the diagnosis breast cancer determined whether patients experienced a low quality of life [52]. Another study of Pieterse in 2011 showed that shared-decision making in patients about to undergo adjuvant therapy, with a relatively favourable prognosis are more likely to choose a better quality of life over the chance for additional survival [53]. The goal of this study is to demonstrate whether anxiety is not worsened and whether quality of life is positively affected by less extensive axillary treatment.

Hypothesis

Omitting completion axillary treatment in clinically node negative breast cancer patients undergoing a mastectomy in case of limited axillary sentinel lymph node metastases will positively influence the axillary morbidity rate and quality of life.

Patient selection

All patients eligible for the study will be asked to complete the questionnaires once pre-operative and on regular basis post-operative, as shown in the timeline, until a total of 700 patients is reached, equally divided over both treatment arms. Patients are eligible for evaluation only when at least two following questionnaires are completed, of which a completed preoperative questionnaire is mandatory. No patient selection will be performed in order to accomplish a representative study population in accordance to the general breast cancer population.

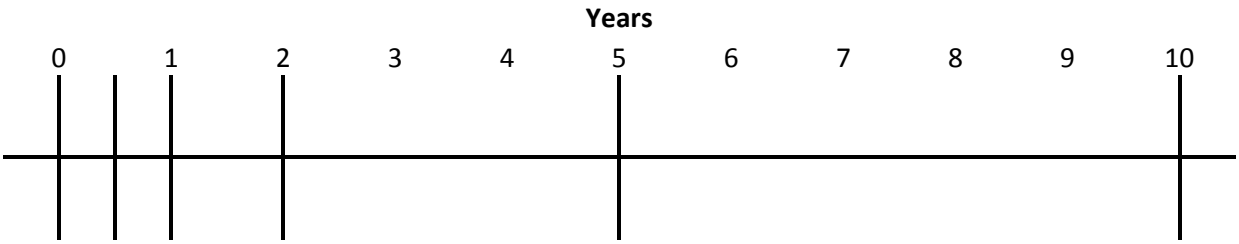
Organisation

The surgeons of the participating centres are responsible for inclusion of patients and handing out the first (preoperative) questionnaire. IKNL Clinical Trial Centre is responsible for the transmission of the questionnaires during follow-up to all included patients. Addresses are collected on the informed consent form. Study patients also give consent that their address can be collected from their general practitioner during the follow-up period, in order to prevent lost to follow-up due to migration. Patients can return the completed questionnaires in self-addressed envelopes.

Methods

To assess the Quality of Life of breast cancer patients in this study, we will use the Dutch version of two validated Quality of Life questionnaires of the EORTC, QLQ-C30 and QLQ-BR 23 (developed specifically for the use in breast cancer patients) [54, 55]. To assess the subjective morbidity we will use the validated "Lymph oedema Functioning, Disability and Health" (Lymph-ICF) questionnaire, which assesses the impairments in function, activity limitations and participation restrictions of patients with arm lymph oedema [56]. A validated short Dutch version of the Spielberger State-Trait Anxiety Inventory (STAI-trait) and the NEO Five Factor Inventory (NEO-FFI) is used to measure if anxiety and personality traits influence the outcome of Quality of Life [57].

These questionnaires are provided at the day of randomization and sequentially post randomization at 6 months 1, 2, 5 and 10 years, as shown in the timeline below.



T = 0 is moment of randomization.

Informed consent for quality of life

All patients will be informed about the aims and procedure of the study. They will be informed about the strict confidentiality of their patient data. Axillary morbidity and quality of life assessment is part of the study procedures, therefore written informed consent is obtained simultaneously with the informed consent of the other study procedures, as described in chapter 7, section b 'Study procedures - diagnosis and randomization' on page 20. The informed consent form is part of the documents to be submitted to the METC for approval. It is the responsibility of the METC to guarantee that this form is conform ICH-GCP guidelines.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are randomized in the study. The written informed consent form should be signed and personally dated by the patient.

f. Withdrawal of individual subjects

Patients can leave the study at any time for any reason if they wish to do so without any consequences, and without having to specify the reason for withdrawal. The investigator can decide to withdraw a subject from the study for urgent medical reasons. In case of withdrawal within 3 months post randomization or when no mastectomy has been performed after neoadjuvant systemic therapy, new patients will be recruited to reach the total number of study subjects. Withdrawal of patients during the follow-up period will be counted to the 10% of lost to follow-up.

g. Premature termination of the study

After premature termination of the study, the investigators must contact all participating subjects within 4 weeks. No new patients are included in the trial. Follow-up of participating subjects will continue, following the study protocol. In case of premature termination of the study due to a higher regional recurrence rate than expected, this will not have a direct consequence for the treatment or follow-up of every study patient that has been randomized for study arm B. So in these patients, delayed axillary treatment is not standardly performed, but only if nodal metastases become clinically apparent.

h. Statistical analysis

An independent statistician will perform an interim analysis after a two-year follow-up of the first 125 included patients. For the sample size calculation see chapter 6, section d ‘Sample size calculation’ on page 17. The interim analysis is performed after a two-year follow-up period, because the total inclusion of patients is expected to be completed within 3 years. Most regional recurrences occur within two years after initial treatment. According to the Haybittle-Peto boundary, a P value of 0.001 or less is considered statistically significant for the interim analysis. Results of the interim analysis are reported to the Data Safety Monitoring Board.
The final analysis for the primary and secondary endpoints will be made per protocol and in the intention to treat population after 5 and 10 years of follow-up. Cox proportional hazards models and Kaplan Meier estimates will be used to analyse the outcome of both groups and to assess the univariable and multivariable association between prognostic variables, treatment and events. Chi-square tests will be used to compare categorical variables between groups and 2-sample t-tests will be used to compare continuous variables between groups. All statistical tests are 1-sided and a P value of 0.05 or less is considered statistically significant.

8. SAFETY REPORTING

a. Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO (In Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen), the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research protocol. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

b. Adverse events

Adverse events

Adverse events (AE's) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the protocol treatment. All AE's reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Serious adverse events

A serious adverse event (SAE) is defined as a untoward medical occurrence or effect related to mastectomy, SLN procedure, completion ALND or axillary radiotherapy, that results in:

- death;
- hospitalisation or prolongation of existing inpatients hospitalisation;
- surgery.

Other adjuvant treatment is not considered protocol treatment.

Information about SAE's that occur within 30 days after protocol treatment is collected and recorded on the Serious Adverse Report Form. The principal investigator of the participating centre where the SAE occurs is responsible to report the SAE by fax to the central data centre (IKNL Clinical Trial Centre) within 24 hours.

The Principal Investigators ("verrichter" in the terminology of the Dutch law) are responsible for SAE assessment and expedited reporting through the web portal *ToetsingOnline* to the accredited METC that approved the protocol. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

All SAE's will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated and/or referral to the general physician or a medical specialist.

c. Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established comprising one surgeon, one medical oncologist and one radiation oncologist. The DSMB will meet annually to discuss the occurrence and nature of AE's occurring during the study, initially at a 1-year interval. During the study, the DSMB may decide to change the frequency of discussion. All cases with a lesion that is highly suspicious for tumour recurrence on imaging, but not accessible for histology or cytology are presented to the DSMB for an independent review. An independent statistician informs the DSMB about the results of the interim analysis for further interpretation. Advice(s) of the DSMB are send to the Principal Investigators. Should the Principle Investigators decide not to fully implement the advice of the DSMB, the Principle Investigators will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

d. Stopping rule

The Principle Investigators reserved the right to discontinue the study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons such as; a negative advice for continuing the study by the DSMB; or disappointing accrual so that the total enrolment of 878 patients seems not feasible within the planned study period.

9. ETHICAL CONSIDERATIONS

a. Regulation statement

This study will be conducted in accordance to the standards of Good Clinical Practice, in agreement with the Declaration of Helsinki and with Dutch law in general and with the Medical Research Involving Human Subjects Act (In Dutch: *Wet Medisch-wetenschappelijk Onderzoek met mensen*) in particular. This protocol will be submitted for central approval to an authorized METC.

b. Recruitment and consent

The population being researched will be selected from the group of patients visiting one of the participating hospitals with breast complaints or after referral from the breast cancer screening program. The diagnostic work-up in these breast cancer patients will be performed according to the Dutch breast cancer guideline. Before they agree to participate in this trial, all patients will be provided with written information in the form of a Patient Information Folder.

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they will be exposed and the mechanism of treatment allocation. They will be informed that their identity will be protected. A sequential identification number will be allocated to each patient randomized in the study. The number will identify the patient and must be included in all case report forms including SAE forms. Patients must also be informed that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician and their study files and materials are being saved for 15 years as described in the patient information folder.

The informed consent form is part of the documents to be submitted to the METC for approval. It is the responsibility of the METC to guarantee that this form is conform ICH-GCP guidelines. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are randomized in the study. The written informed consent form should be signed and personally dated by the patient. The formal written consent of the patient must be obtained before initiation of any study-specific procedure.

c. Benefits and risk assessment

All treatment procedures will be performed according to the Dutch breast cancer guideline. No additional interventions will be performed, only less if randomized for arm B (no completion axillary treatment). When randomized for arm A (completion axillary treatment), patients will be treated according to the Dutch breast cancer guideline.

Possible advantages and disadvantages will depend on the treatment arm. Patients randomized for arm B have the possible advantages of less morbidity, less surgery and hospitalizations compared to patients randomized for arm A. Possible disadvantages for patients randomized for arm B are a worse regional recurrence rate. In case of regional recurrence during follow-up, delayed axillary treatment is performed if indicated.

No patient will encounter any delay in their treatment as a result of inclusion. Patients can leave the study at any time for any reason if they wish to do so without any consequences, and without having to specify the reason for withdrawal. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

d. Compensation for injury

The Principal Investigators have a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The Principal Investigators and the Local Investigators (also) have an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

a. Handling and storage of data

IKNL Clinical Trial Centre, is responsible for randomization of patients, supply of electronic Case Report Forms (eCRF), receipt of eCRF pages and generation of queries and SAE processing. Also, IKNL Clinical Trial Centre can give advice or perform audits in participating institutions, when requested by the Principal Investigators.

TRIAS is a web-based clinical data management system for automated and safe registration, administration and information service of patient data for clinical studies. A brochure of the system is attached to the protocol.

IKNL Clinical Trial Centre, is also responsible for the transmission of the questionnaires to all included patients.

The eCRF's must be completed, dated and signed as soon as the requested information is available. eCRF's will contain common information, but this information will be kept to a minimum. The time between the patient's visit and completion of eCRF pages should be kept to a reasonable minimum. The data managers are responsible for the correct completion of the eCRF's of all study patients.

To enable peer review and/or inspections from Health Authorities, the investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. hospital records), and all original signed Informed Consent Forms. To comply with international regulations, the Investigator should retain the records for 15 years, including assessments like mammographies.

A study initiation meeting to fully inform the investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation is strongly recommended and will be organized by the Principal Investigators.

The decision to perform monitoring visits on-site lies with the Principal Investigators, who may also decide who will perform the monitoring visits. Initial monitoring on informed consent, eligibility and safety will be performed by the data managers. Any major problems identified during monitoring will be reported to the Principal Investigators. All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality.

The investigator must assure that the subject's anonymity will be maintained on all documents submitted to the central data managers of IKNL Clinical Trial Centre. Each subject will be identified in the eCRF by a subject identification number and months and year of birth. The subject identification number will be a sequential number. To ensure that the subject identification number is linked to the right person, the subject identification log will be kept in the Investigator Site File on site.

b. Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

c. Annual Progression Report

The Principal Investigators will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems and amendments.

d. Final Report

The Principal Investigators will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case of a preliminary end of the study, the METC will be informed within 15 days, and the reason of the ending of the study will be provided. Within one year after the end of the study, the Principal Investigators will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

e. Public disclosure and publication policy

The publication guidelines of the Dutch CCMO (Central Committee for Research in Humans, www.ccmo.nl) will be adhered to the full. These guidelines consist of a number of basic principles. First of all the results of scientific research involving human subjects must be disclosed unreservedly. All parties concerned must justify their actions in this regard. Both positive and negative research results will be disclosed and submitted to peer-reviewed scientific journals. The Principal Investigators will prepare the manuscripts together with the statistician and other active writing committee members. Co-authorship is reserved for those investigators (one per centre) that enter more than 7% of the patients, in addition to those who constructively contributed to the study at the discretion of the Principal Investigators; all other participating centres/physicians will be acknowledged.

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12. ANNEX

The following attachments are enclosed:

- A0: Dutch Summary
- E1: Patient Information Folder
- E2: Consent Form
- F1: Quality of Life questionnaires
- K6: TNM Classification 7th edition
- K6: TRIAS brochure