Tailored treatment in Older Patients

TOP-1: Omission of radiotherapy in elderly patients with low risk breast cancer

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ANTONI VAN LEEUWENHOEK NEDERLANDS KANKER INSTITUUT

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KWF KANKER BESTRIJDING

TOP-1: OMISSION OF RADIOTHERAPY IN ELDERLY PATIENTS WITH LOW RISK BREAST CANCER

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PROTOCOL SIGNATURE SHEET

I declare that I have read and familiarized myself with the following protocol:

Tailored treatment in Older Patients

TOP-1: Omission of radiotherapy in elderly patients with low risk breast cancer

Version: 1.3

I agree to conduct the study as described in the protocol.

Name	Site	Signature	Date
Principal Investigators (PI):			
G.J. Liefers	**LUMC**		**October 2016**
A.N. Scholten	**NKI-AvL**		**October 2016**
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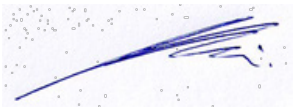
S.G. Elias	**UMCU**		**October 2016**
Local Investigator (LI):			

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
BC	**Breast Cancer**
BCSS	**Breast Cancer-Specific Survival**
BCS	**Breast Conserving Surgery**
BOOG	**Dutch Breast Cancer Trialists'-Group**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DMFS	**Distant Metastases Free Survival**
eCRF	**Electronic Case Report Form**
ER	**Estrogen Receptor**
EU	**European Union**
GCP	**Good Clinical Practice**
IC	**Informed Consent**
IKNL	**Integraal Kankercentrum Nederland**
LI	**Local Investigator**
LR	**Local Recurrence**
LRR	**Local Recurrence Rate**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NBCA	**NABON Breast Cancer Audit**
NKR	**Netherlands Cancer Registry; in Dutch: Nederlands Kanker Registratie**
OS	**Overall Survival**
PI	**Principal Investigator**
QoL	**Quality of Life**
RCT	**Randomized Controlled Trial**
RT	**Radiotherapy**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
TOP	**Tailored treatment in Older Patients**

WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Breast cancer is the most common cancer type in women of 70 years and older, accounting for over 4.000 patients per year in the Netherlands(1). The benefit of standard adjuvant treatments in older patients with breast cancer are limited and influenced by both patient related factors as well as tumor related factors(2). Preventing over-treatment is therefore pivotal for these patients, allowing reduced treatment burden, improved quality of life and cost efficacy(2, 3). However, in clinical practice, older women are mostly treated according to general standards, not taking into account age specific factors(4). The Dutch TOP consortium (Tailored treatment in Older Patients) aims at tailoring treatment of older women with breast cancer by allocating treatment to those patients who will benefit and to prevent overtreatment in all others.

Previous studies, including the recent PRIME-II study, showed that omitting radiotherapy after breast conserving surgery in older patients is safe and does not result in decreased survival(5-7). Despite these results, currently, 98% of older patients with low risk breast cancer (obviating the need for adjuvant systemic therapy) in the Netherlands, still receive adjuvant radiotherapy after breast conserving surgery(8).

Objective: The main focus of the present trial is a first step towards treatment de-escalation in older breast cancer patients. For this, we initiate the first TOP consortium study (TOP-1).

Primary aim: to assess whether radiotherapy can be safely omitted after breast conserving surgery in elderly patients with a very low risk of local recurrence.

Secondary aim: assessment of: quality of life, toxicity, geriatric assessment, overall- and breast cancer specific survival, distant metastasis free survival, relating biomarkers to outcome (tumor characteristics, at least: IHC ER, PR, HER2 and Ki-67), additional state of the art molecular analysis if possible, development and validation of local recurrence rate prediction models, (cost) efficacy (comparison with historical control group) and implementation of findings into standard care.

Study design: TOP-1 is a national, multicenter, non-randomized, single-arm, prospective cohort study.

Study population: 800 Patients ≥70 years of age, with estrogen receptor positive disease without axillary nodal involvement and without indication for adjuvant hormonal therapy.

Intervention: Omitting adjuvant radiotherapy.

Main study parameters/endpoints: The primary endpoint is the local recurrence rate (LRR) at 5 years. Secondary determinants are the distant metastases free survival (DMFS), breast cancer-specific survival (BCSS) and overall survival (OS), quality of life, side-effects, costs, cosmetic outcome, geriatric assessment and biomarkers.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The immediate impact for 95% of the TOP-1 participants is to be spared intensive radiotherapy and subsequent risk of side effects (such as fatigue, possible lung and cardiac damage). The other 5% will develop a local recurrence, which would not have happened with standard radiotherapy (3-fold of this risk, from 2.5% to 7.5% at five years). The majority of these local recurrences can however effectively be treated with salvage surgery and previous studies showed that patient survival will likely not be affected(9, 10). This limited risk of local recurrence increase for this particular patient population was deemed acceptable following consultation with patient advocates.

All TOP studies will be performed in a nationwide, multidisciplinary consortium, in close collaboration with Dutch Breast Cancer Trialists' Group (BOOG) together with patient advocates. Due to the nationwide character of this study and the involvement of all stakeholders, the findings can be easily implemented into national guidelines as a standard treatment. Because of this study, tools can be developed to predict a local recurrence in absence of any adjuvant therapy (providing a globally unique opportunity). Altogether, this will contribute to optimal therapy for elderly patients with BC without excessive treatment or under treatment. Eventually, this strategy can potentially be implemented in all breast cancer patients in the future.

Keypoints: elderly breast cancer patients, low risk tumors, multicenter implementation study, omitting radiotherapy after breast conserving surgery, first study TOP consortium, BOOG .

1. INTRODUCTION AND RATIONALE

Breast cancer (BC) is the most common cancer type in women of 70 years and older, accounting for over 4.000 patients per year in the Netherlands(1). With ageing of the population and the increasing life expectancy, the incidence of BC will rapidly increase in the Netherlands for the coming decades(11). Older patients with BC differ from younger patients in many aspects. Older women are more likely to have BC with estrogen receptor (ER) expression and less likely to have HER-2 positive tumors(2, 12). In addition, with increasing age the number of comorbidities will increase as well: multimorbidity (having two or more comorbidities) is present in 65% of patients of 65 to 84 years(13). A previous study showed that in contrast to outcome in younger counterparts, survival of older patients with BC has not improved over the last decades(14).

There is a lack of evidence on treating older patients with (breast)cancer. Despite comprising more than 40% of newly diagnosed BC, older patients are rarely included in randomized trials(15, 16). De Glas et al. showed that only 2% of current breast cancer trials are focused on the elderly(17). Necessitated by lack of evidence for the older patients with BC, results of trials in younger patients are often extrapolated to the older patient population and age specific aspects of older women are not taken into consideration(18, 19). In response to this current critical need the American Society of Clinical Oncology (ASCO) recently gave several recommendations on improving the evidence for treating older patients with cancer.(20)

Obviously overall survival deteriorates with increasing age among unselected older BC patients(21). Analysis of the TEAM study pointed out this was for a great part due to competing risk of mortality. We know that the benefit of standard adjuvant treatments in older patients with BC is therefore limited by both patient related factors (e.g. more co-morbidity) as well as tumor related factors (e.g. more often hormone receptor positive disease)(2). Preventing overtreatment is therefore pivotal for these patients, allowing reduced treatment burden, improved quality of life (QoL) and cost efficacy(2, 3).

However, among postmenopausal women with hormone receptor-positive BC, increasing age was also associated with a higher disease-specific mortality(22). This leads to both *overtreatment* as *undertreatment* of older patients with BC. Therefore, the Dutch **TOP** (**T**ailored treatment in **O**lder **P**atient) consortium has been established. The TOP consortium aims at tailoring treatment for older women with BC. This national consortium will provide the evidence needed for such change in practice, by initiating a series of multicenter national studies in women 70 years or older.

Adjuvant radiation therapy (RT) is one of the essential modalities in BC treatment. Previous studies, including the recent PRIME-II study, showed that omitting radiotherapy (RT) after breast conserving surgery (BCS) in older patients is safe and does not result in decreased survival(5-7). Despite these results, currently, 98% of older patients with low risk BC (obviating the need for adjuvant systemic therapy) in the Netherlands, still receive adjuvant RT after BCS(8). Therefore, the aim of TOP-1 study is to change this in clinical practice. This first TOP consortium study aims to assess whether RT can be safely omitted after BCS in patients ≥70 years of age, with ultra low risk, ER-positive disease without axillary nodal involvement, who would otherwise receive RT (and without indication for adjuvant systemic treatment). These patients will *not* receive adjuvant RT in the TOP-1 study, which may be regarded as the new standard. By improved tailoring, treatment burden (toxicity, hospital visits) will probably be reduced in clinical practice, QoL and presumably cost efficacy may improve. Extensive biomarker- and geriatric assessment studies will accompany all TOP studies.

The current trial therefore focuses on reducing overtreatment of BC, taking into consideration age and clinicopathological factors. This TOP-1 study is performed in close collaboration with patient advocates, as well as the Dutch Breast Cancer Trialists' Group (BOOG). This study is embedded in a nationwide, multidisciplinary consortium, which will allow rapid implementation of findings into national guidelines and standard treatment.

2. OBJECTIVES

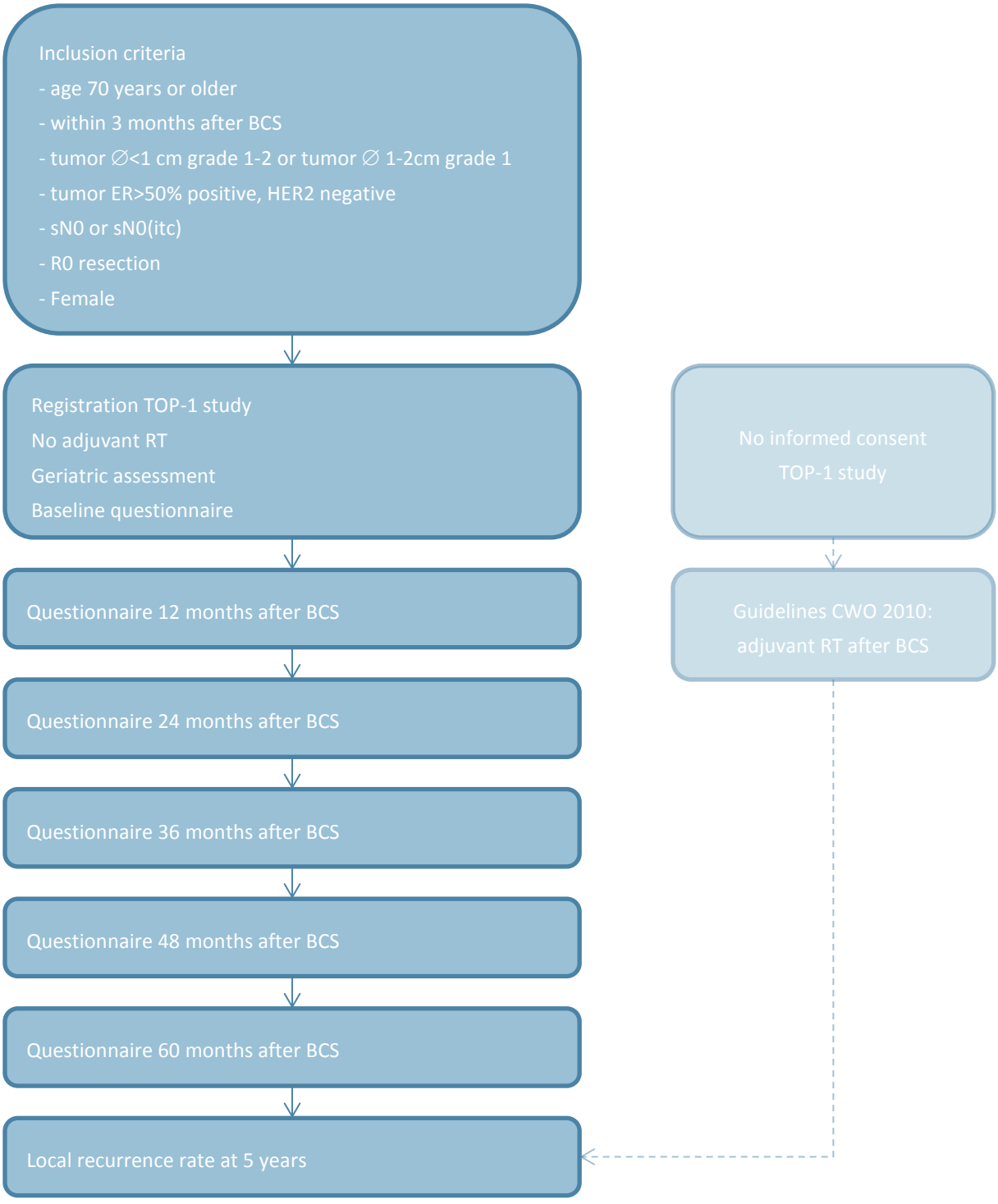
Primary Objective: To determine if radiotherapy (RT) can safely be omitted after breast conserving surgery (BCS) in elderly patients at low risk of developing a local recurrence (LR)

Secondary Objectives:

1. To determine the DMFS, BCSS, and OS rates in this study population.
2. To determine the QoL of patients after they received treatment regarded as new standard practice, directly after BCS and at 12, 24, 36, 48 and 60 months after BCS.
3. To determine the geriatric status of the study population.
4. To determine the cosmetic outcome of the study population.
5. To determine if omitting RT after BCS in elderly patients with a low local recurrence rate (LRR) is cost efficacious.
6. To determine if poor outcome of the study population can be predicted at diagnosis by clinicopathological factors including IHC, ER, PR, HER2 and Ki-67 and emerging omics technology.

3. STUDY DESIGN

TOP-1 is a multicenter, prospective cohort study, in which all patients do not receive RT. The convincing evidence from RCT's support this nationwide implementation study in a low-risk population. The non-randomized design will enhance the participation rate and thereby the generalizability compared to an RCT. Furthermore, the primary focus is to determine whether the absolute LRR during a treatment regimen without RT is acceptable by itself in a representative cohort of older BC patients. The schematic design is given below.



Furthermore, the primary focus is to determine whether the absolute LRR during a treatment regimen without RT is acceptable by itself in a representative cohort of older BC patients. In contrast to the previous mentioned studies (CALBG 9343 trial, PRIME II), this study is an observational cohort with the focus on implementation in clinical practice, showing the uniqueness of this study.

The TOP-1 study is conducted in collaboration with the BOOG. The supervision of TOP-1 will be performed by PI's and the LUMC Datacenter.

4. STUDY POPULATION

4.1 Population (base)

The TOP-1 study will be conducted in collaboration with the BOOG. All hospitals in the Netherlands have shown interest in the concept of TOP. We expect therefore to accrue patients from most Dutch hospitals. After a kick-off meeting all patients that meet the inclusion criteria and consent to participate will be treated according to the TOP-1 study. An enrolment log will be used to keep track of patients that receive RT despite this implementation study.

The duration of the TOP-1 study is estimated to consist of 48 months recruitment with a minimum of 60 months of follow-up.
In view of the fact that 338 TOP-1 eligible patients are treated with BCS yearly in The Netherlands, and a further 133 patients with ablative surgery, possibly to avoid RT (for a total of n=471/year; NCR data 2008-2012), it should be feasible to include this number of patients within the time span of 48 months.

4.2 Inclusion criteria

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

- age 70 years or older;
- within 3 months after BCS;
- tumor ∅ <1 cm grade 1-2 or tumor ∅ 1-2cm grade 1;
- tumor ER>50% positive, HER2 negative;
- sN0 or sN0(itc);
- R0 resection;
- Female.

4.3 Exclusion criteria

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

- Indication for hormonal therapy;
- Bilateral.

In case of a multifocal tumour: only the diameter of the largest lesion counts.

TNM Classification according to AJCC Cancer Staging Manual 7th edition (2010).

4.4 Sample size calculation

Data of the Netherlands Cancer Registry (NKR) of 2003-2008 showed a LRR of 1.3% after 5 years following RT in patients representative for those eligible for the TOP-1 study, with a 99% CI of 0.6-2.5%. A 5 years LRR greater than 2.5% after RT can therefore be excluded in this group of patients. This worse-case LRR risk of 2.5% at 5-years in current practice was used to determine the necessary sample size for TOP-1. Omitting RT will triple the risk of LRR, thus from 2.5% to 7.5%. In close collaboration with Dutch Breast Cancer Trialists' Group (BOOG) and together with patient advocates, it was concluded that a 5-years LRR risk of 10% or more would be unacceptable in this patient population. A sample size of 800 patients is required to achieve a power of >80% to exclude a LRR at 5 years of 10% or more, if the actual 5-year LRR risk is 7.5% (at a one-side alpha of 0.05 and taking into account competing risks of death). The actual power will likely be higher as the actual LRR risk without RT will probably be lower (considering above data of NKR and previous RCT's like the PRIME-II study and CALBG-study which resulted considerably lower risk of LRR).

This conservative approach was chosen so that:

1) the study still has enough power to conclude that omitting RT is acceptable in this patient group, even if the 5-year risk of LRR is unexpectedly high (i.e. 7.5%).

2) that with the most likely LRR risk increase (i.e. from 1.3% in current practice to 3.9% in TOP-1), we will be able to exclude a 5-year LRR risk of even less than the acceptability boundary of 10% following omission of RT, which will improve implementation;

3) that LRR risk estimations are sufficiently precise and the number of LR will be enough to answer secondary research questions in a meaningful way (i.e. costs efficacy and developing and validating risk models for LRR);

4) also with even lower LR risk numbers than currently anticipated, this study design will prove that LR risk is increased in the predefined acceptable range (omitting RT is considered to be acceptable if an absolute 5-year LRR risk exceeding 10% can be ruled out).

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

LRR at 5 years

5.1.2 Secondary study parameters/endpoints

LRR at 10 years
DMFS, BCSS and OS at 5 years and 10 years

QoL

Side-effects

Costs

Cosmetic outcome

Geriatric assessment

Biomarkers

5.2 Registration procedure

After having properly checked all eligibility criteria and having obtained patients informed consent by the local study team, patients will be registered online through the ProMISe program or by phone, fax or email at the LUMC Datacenter.

Online registration
Registration can be performed online 24 hours per day through the ProMISe registration program.
Go to:
www.clinicalresearch.nl/PROMISE/S/HEIT/S_O_LUMC_C_HEELK_TOP_/LOGON/INDEX.HEI.

Investigators, datamanagers or research nurses can apply to the LUMC Datacenter for a username and password. E-mails with the answered questions and the patient number will be automatically sent to the local and central study team.

Registration by email, phone or fax
Registration can be done by email datacenter@lumc.nl, telephone +31 71 526 3500; Monday-Friday; 9:00-17:00 or fax +31 71 526 6744. During the registration procedure eligibility criteria will be checked.

After registration, a sequential identification number will be assigned. This number has to be recorded on the registration form, along with the registration date. The registration form must be signed by the local investigator (in case of faxed registration, the confirmation of

the data manager/research nurse also has to be signed by the local investigator) and filed with the eCRFs. An automatic e-mail will be sent to the local and central study team (see online registration).

5.3 Study procedures

Current practice consists of adjuvant RT after BCS. The new standard practice will be no adjuvant RT after BCS. The primary endpoint (the LRR at 5 years) and the secondary endpoints: LRR at 10 years, DMFS, BCSS and OS will be determined according to standard clinical care by local datamanagers from Integraal Kankercentrum Nederland (IKNL). An electronic case report form (eCRF) will be used to collect the necessary data. The treating health care provider can delegate the filling out the eCRF.
Baseline data will be derived from the NABON Breast Cancer Audit (NBCA) (see 5.7).

The other secondary endpoints will be determined by assessments. This data will be collected in the local hospital where patient is treated. After BCS, a geriatric assessment will be done. These assessments focus on the elderly and their mental- and physical status.

At 0, 12, 24, 36, 48 and 60 months after BCS patients will be followed up by collecting questionnaires. The 0 moment is defined as 0 days to 2 weeks after registration. This allows patient a considerable time to withdraw from the study and still receive the regular care (adjuvant radiotherapy) within 6 weeks after surgery. After informed consent is obtained by the health care provider, the patient will be asked if they would prefer to receive a link to the questionnaires provided by e-mail or receive the questionnaires by post. A stamped envelope will be provided to return the filled out questionnaires if patient's preference is to fill out the questionnaire in hardcopy. If patients do not complete the digital version of the questionnaire or do not return the hardcopy, patients will be contacted again by the local study team. The LUMC Datacenter will inform the local study team about the incomplete or missing questionnaire.

The geriatric assessment and the questionnaires used, correspond to those used in the CLIMB study. The aim of this ongoing prospective non-randomized longitudinal study is to gain knowledge on the prevalence and consequents of functional, cognitive, psychological and social restraints in elderly with breast cancer in comparison to elderly without breast cancer. The study population consists of 650 breast cancer patients of 70 years and older who underwent loco-regional treatment in different hospitals in the Leiden/The Hague area. These patients were treated according to guidelines, meaning patients that had

breast-conserving surgery will have been treated with radiotherapy. Including the same geriatric assessment and questionnaires in our study, allows us to compare our patients to patients that underwent radiotherapy as part of their loco-regional treatment.

The geriatric assessment and QoL will be assessed by the following instruments:
Just after the BCS the following assessments will take place in the hospital:

- Malnutrition Universal Screening Tool (MUST)
- Mini Mental State Examination
- Timed up and Go test

These questionnaires will be given to the patient at 0, 12, 24, 36, 48 and 60 months after BCS:

- Groningen Activiteiten Restrictie Schaal (GARS) questionnaire
- EORTC QLQ-C30 questionnaire
- EORTC QLQ-BR23 questionnaire
- Cantrils Ladder
- De Geriatric Depression Scale (GDS)
- Apathy scale of Starkstein (AS)
- Lonelyness questionnaire of De Jong-Gierveld
- The Nurses' Health Study II Activity and Inactivity Questionnaire

Prior to using the geriatric assessment and questionnaires for the CLIMB study, a pilot study was performed to define the burden of the geriatric assessment and the questionnaires. In cooperation with the patient's advocacy group BVN, a handful of elderly breast cancer patients filled out the questionnaires. The burden deems acceptable according the BVN.

<u>Tumor tissue for future biomarker research</u>
The tumour tissue is routinely stored by the pathologists. For future purposes we will ask patients informed consent to send this tumour tissue to the LUMC for biomarker research if a research question relates to this study.

5.4 Withdrawal of individual subjects

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Patients will not be contacted for filling out the questionnaires.

5.5 Follow-up of subjects withdrawn from treatment

Not applicable. Patients will have no adjuvant treatment.

5.6 Data retrieval from the NABON Breast Cancer Audit (NBCA)

The NBCA registers every (operated) breast cancer patient. Data on co-morbidity, tumour characteristics and treatment are collected. One question in the NBCA is about trial participation. If answered with yes, into TOP-1 trial, data without any patient identifier, will be automatically transferred to the TOP-1 database in Leiden on the basis of the unique TOP-1 patient number. This number will also be registered on the baseline CRF to assure a correct merge of data.

Explicit permission for the LUMC to import data from the NBCA into the TOP-1 database is required from every participating hospital board.

6. SAFETY REPORTING

Since this is a prospective de-escalation, cohort study, without treatment intervention, safety reporting is not applicable.

7. STATISTICAL ANALYSIS

7.1 Primary study parameter

For the primary research question, the 5-year LRR risk together with the one-sided upper bound of its 95% confidence interval is estimated using the cumulative incidence function according to Gray, and variance estimation according to Aalen. The upper bound of the confidence interval will be compared with the set limit of 10% 5-year LRR risk, which is deemed acceptable and safe. Follow-up time is defined as time from registration into ProMISe to date of LR or end of follow-up. Death from any cause is treated as a competing risk.

7.2 Secondary study parameters

For the second endpoints, distant recurrence rates and BC specific survival will be calculated with the same methodology. QoL will be measured according to the methodology provided by several questionnaires and compared with the available mean scores of the general population. The change of QoL over time will be evaluated and specific aspects of QoL (e.g. fear and fatigue) will be taken into account as well. Geriatric status will be measured by a complete geriatric assessment.

In this unique study of primary BC patients that will only receive surgical treatment, we will validate and develop adverse outcome risk prediction models, according to state-of-the-art methodology suitable for small datasets. All these analyses will take the competing risk of death into account, and we will specifically focus on the (added) value of biomarkers to predict patient outcome.

By using our study data and data of previous studies, we will develop markov models to determine costs-efficacy of omission of adjuvant RT for quality adjusted life years gained from a societal perspective.

7.3 Interim analysis

There are two reasons why interim analysis is not considered necessary or appropriate.

Firstly, an interim analysis is not considered of value for the study population. We expect to have included most of the participants by the time an interim analysis could be performed. Delayed radiotherapy after breast conserving therapy is not considered effective. Therefore we cannot offer this treatment to this study population even when we find the local recurrence rate at 2,5 years higher than expected.

Secondly, this study is designed as an implementation study because there is enough evidence (see introduction/rationale) that it is safe to omit radiotherapy in this study population. This is also the reason for not involving a control group. By using this study design we can gain extra information on quality of life and create robust evidence for safely omitting radiotherapy. A local recurrence rate exceeding 10% after five years is not expected. If it does exceed this number, we cannot directly conclude it would be unsafe to omit radiotherapy because of the past research that has been done on this topic.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

8.2 Recruitment and consent

Each patient will receive oral information at the patients' out clinic and written information which empowers her to give informed consent to TOP-1. The written registration for informed consent will be obtained in accordance with Good Clinical Practice (GCP).

8.3 Benefits and risks assessment, group relatedness

The advantage of this study consists of omitting RT after BCS. The immediate impact for 95% of the study participants is to be spared unnecessary RT whereby less burden for the patients (e.g. no multiple visits to the hospital for RT) and no side-effects of the RT itself, such as redness of the skin, fatigue, fibrosis and possible lung- and/or cardiac damage.
The disadvantage of this study is the slightly increased risk of a LR. The other 5% of the study participants are expected to develop a LR, which would not have happened with standard RT (3-fold of this risk, from 2.5% to 7.5% at 5 years). LR's are usually treated with salvage surgery and will not affect survival in these patients. The boundaries of accepted risk increase and inclusion criteria are determined in close collaboration with patient advocates.

8.4 Compensation for injury

Participation in TOP-1 is completely voluntary. Participants of the TOP-1 study will not receive adjuvant RT after BCS. Because of omitting of the adjuvant RT possible side-effects or injury of this intervention will not occur; therefore there is no compensation for injury.

8.5 Incentives

There will be no incentives (compensation) for the participants.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Electronic Case Report Forms

Data must directly be entered on site into the webbased TOP-1 database. Local investigators and/or authorized staff members should read the manual carefully and apply for a username and password at the LUMC Datacenter.

All forms must be dated and signed by the responsible local investigator or one of his/her authorized staff members (see signature log) as soon as the requested information is available. The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the LUMC Datacenter by the responsible local investigators before the start or the study.

In all cases, it remains the responsibility of the local investigator to check that original case report forms are entered into to the webbased TOP-1 database and that they are completely and correctly filled out.

If a local investigator needs to modify a eCRF after the original has been saved to the database, he/she should change the item in the database and describe the reason of the change. Date, time and user are automatically tracked for each modification.

To contact the LUMC Datacenter: by email datacenter@lumc.nl, telephone +31 71 526 3500; Monday-Friday; 9:00-17:00 or fax +31 71 526 6744.

The LUMC Datacenter will perform extensive consistency checks on the eCRFs and issue Query Forms in case of inconsistent data that will be sent to the local investigator. Those Query Forms must be answered and signed by the local investigator (or an authorized staff member).

9.2 Handling and storage of data and documents

For this study it is necessary that medical and personal information is collected. Information of each participating patient will be coded by the local datamanagers of the IKNL. All the information from the questionnaires will be handled most confidentially. This data will be stored and handled by the LUMC Datacenter. The key to the code is safeguarded by the contact of the participating center itself.

Patient's name and address (and email) for the purpose of hardcopy questionniares, will be stored via a Trusted Third Party (TTP) server, and stored encrypted into the database.

9.3 Monitoring and Quality Assurance

On-site monitoring of the conduct of the study will not take place.

9.4 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.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

9.5 Annual progress report

The sponsor/investigator 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, other problems, and amendments.

9.6 Temporary halt and (prematurely) end of study report

The investigator/sponsor 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 submission of the last patient's last questionnaire.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.7 Public disclosure and publication policy

The final publication of the trial results will be written by the PI on the basis of the final analysis performed at the LUMC Datacenter. A draft manuscript will be submitted to the Datacenter for review no later than six months after receiving the Datacenter Report. After revision by the Datacenter and other co-authors the manuscript will be sent to a major scientific journal. Authors of the manuscript will include at least the Project Manager and the members of the Datacenter team who have contributed to the trial. All publications,

abstracts or presentations including date from the present trial will be submitted for review to the Datacenter prior to submission.

All manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the trial, as well as supporting bodies. The Group Chairman and the Datacenter must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered/randomised in the trial, or any subgroup of the trial patients.

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