

The road towards less axillary treatment in early breast cancer patients and faster implementation of study results

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Impact Paragraph

The survival rates of breast cancer patients have increased tremendously over the past decades due to screening programs, improved diagnosis and extensive treatments (i.e. surgery, radiation-, hormone-, chemotherapy and/or immunotherapy). For the increasing number of breast cancer survivors, breast cancer research shifted to reducing (axillary) overtreatment while remaining disease control and survival, thereby reducing morbidity and improving quality of life (QoL) of breast cancer survivors.

Relevance of the scientific results in this thesis

Part I – Omission of completion axillary treatment

Axillary lymph node dissection (ALND) is associated with short- and long-term morbidities, such as nerve injury, seroma, lymphedema, reduced shoulder function and can therefore result in a reduced quality of life (QoL) of breast cancer survivors. Several randomized controlled trials (RCTs) showed that completion ALND can be safely omitted in clinically node negative breast cancer patients with limited sentinel lymph node (SLN) metastases treated with breast conserving therapy (BCT). This has led to a reduction of axillary overtreatment and axillary morbidity, and improvement of QoL in these breast cancer patients.

Mastectomy and BCT are equivalent concerning the oncologic safety of surgical treatment of the breast. Nevertheless, there is little evidence for the safety of omitting completion ALND for mastectomy treated patients (mastectomy patients were not included in previous mentioned RCTs). Consequently, completion ALND is often recommended for SLN positive patients undergoing a mastectomy. This thesis showed that patients treated with mastectomy, more often underwent a completion ALND compared to those treated with BCT. Majority of the mastectomy patients could have avoided completion ALND if they had chosen BCT if possible.

ECE in the SLN is associated with presence of additional non-SLN metastases and other less favorable prognostic factors, such as lymphovascular invasion and macrometastases. Therefore, patients with ECE in the SLN were excluded in previous mentioned RCTs investigating the omission of completion ALND. This thesis showed that although ECE in the SLN was associated with involvement of more than three lymph node metastases, patients did not have an inferior five-year disease-free survival and 10-year overall survival.

Part II – Omission of the sentinel lymph node biopsy

Since several RCTs showed that completion ALND can be safely omitted in breast cancer patients treated with BCT and limited SLN metastases, the value of pathological lymph node status and consequently the sentinel lymph node biopsy (SLNB) is also being questioned. Although morbidity rates of SLNB are lower compared to ALND, it still is an invasive staging method leading to symptoms like numbness, paresthesia or impairment of arm mobility, and could even result to (chronic) lymphedema and decreased QoL. In this thesis the rationale and study design of a Dutch prospective multicenter RCT, the BOOG 2013-08, is described. Clinically node negative T1-2 breast cancer patients treated with BCT are randomized to SLNB or watchful waiting (no SLNB).

In the BOOG 2013-08 trial, preoperative axillary lymph node assessment consists of physical examination followed by axillary ultrasound (US). The influence of breast cancer subtypes on the diagnostic performance of axillary US was unknown. This thesis showed that there was a significant difference for negative predictive value (NPV) between ER-PR-HER2- tumors and HER2+ tumors, and between HER2+ and ER+PR+HER2- tumors. This difference can be explained by the different prevalence of axillary lymph node metastases among the breast cancer subtypes, which was highest in HER2+ tumors and lowest in ER-PR-HER2- tumors. Therefore, this difference in NPV has no clinical consequence.

Part III – Adequate follow-up time in axillary treatment trials

Topic of debate in previous mentioned RCTs omitting axillary treatment is the optimal duration of follow-up. Results showed that the risk of local (LR) and regional recurrence (RR) is low. Different patterns were seen between different breast cancer subtypes: with the highest recurrence risk in triple negative and lowest in ER+PR-HER2- tumors. Furthermore, patients with highest risk at baseline showed proportionally the highest decrease (i.e. triple negative tumors). This thesis showed that the absolute yield of follow-up to detect LR and RR beyond three years is low, suggesting that follow-up longer than three years is of limited value for detecting LR and RR both in clinical and research setting.

Breast cancer is usually staged according to the TNM system based on tumor size, lymph node status, and presence or absence of distant metastasis. Novel staging systems for breast cancer patients, such as the prognostic stage group of the 8th AJCC TNM and Bioscore, combine the traditional AJCC TNM system with tumor biology. All systems similarly discriminated groups according to the risk of recurrence. However, the prognostic stage group (IIIC) identified a group with a very poor prognosis which could not be identified using the other staging systems.

Target population

Results of this thesis apply to all newly diagnosed early breast cancer patients.

The first part of this thesis includes clinically node negative T1-2 breast cancer patients with one to three SLN metastases (with or without ECE in the SLN) treated with a mastectomy and completion ALND. Part two of this thesis focused on the omission of the SNLB in early breast cancer patients, and included clinically node negative T1-2 breast cancer patients undergoing BCT (lumpectomy followed by whole breast irradiation). The third part is focused on the optimal duration of follow-up in RCTs regarding axillary treatment in early breast cancer patients. Therefore, early breast cancer patients with all different subtypes were included.

Implementation

Results of this thesis were published in international cancer related journals. Furthermore, these results were presented during national and international (breast) cancer meetings and conferences. The goal of this thesis is the implementation of its outcome in clinical guidelines to optimize axillary lymph node treatment in the breast cancer management.

Part I – Omission of completion axillary treatment

Until publication of the RCTs investigating whether completion ALND can be safely omitted in clinically node negative T1-2 breast cancer patients with limited SLN metastases in mastectomy patients, completion ALND will be standard of care. Meanwhile, majority of these patients could avoid completion ALND if they initially opt for BCT instead of mastectomy. For clinical practice, this means that patients choosing a mastectomy should be made aware of the almost threefold higher risk for a completion ALND and increased axillary morbidity which could be avoided in case of choosing BCT. For these patients the outcome of the current RCTs investigating whether completion ALND could be omitted in mastectomy patients (POSNOG, SINODAR ONE and SENOMAC trial) is very important.

ECE is usually a contraindication for omitting completion ALND in clinically node negative T1-2 breast cancer patients treated with BCT. Even in current RCTs, patients with ECE in the SLN are often excluded. This thesis showed that patients with ECE in the SLN did not have an inferior five-year disease-free survival and 10-year overall survival.

Therefore, it is important that current ongoing RCT include patients with ECE in the SLN, in order to increase external validity and demonstrate if omission of completion axillary treatment is safe in this subgroup of patients as well.

Part II – Omission of the sentinel lymph node biopsy

Recently, the BOOG 2013-08 finished patient inclusion of 1.735 clinically node negative breast cancer patients treated with BCT to SLNB or no SLNB. First follow-up results of the BOOG 2013-08 trial are expected in 2026. Until publication of final follow-up results, SLNB will be standard of care in clinically node negative T1-2 breast cancer patients undergoing BCT (lumpectomy followed by whole breast irradiation).

If results will confirm the hypothesis of the BOOG 2013-08, clinically node negative T1-2 breast cancer patients treated with BCT will no longer need invasive staging with the SLNB. Omission of the SLNB will reduce axillary (over)treatment, decrease (axillary) morbidity, and improve QoL of early breast cancer patients. Besides the patient gain, this will result in omission of preoperative lymphoscintigraphies, resulting in a reduced operation time, and consequently reduced health care costs.

Part III – Adequate follow-up time in axillary treatment trials

This part of the thesis showed that longer follow-up in RCTs (five- or 10-year) investigating axillary treatment in early breast cancer patients is of limited value for LR and RR. Outcomes of these RCTs could therefore be published and implemented in clinical practice earlier than the standard five- or 10-year follow-up period. For instance, the primary objective of the BOOG 2013-08 is to investigate whether omitting the SLNB is not inferior to the current axillary staging regimen in clinically node negative breast cancer patients undergoing BCT, in terms of five-year RR rate. This means that after five years of patient inclusion, another five years of follow-up is needed before the publication of the first safety results. This thesis showed that follow-up longer than three years is of limited value for detecting LR and RR. First results can therefore be published after three instead of five years of follow-up.

Furthermore, this thesis suggested that clinicians (who have access to analysis of biological factors) should use the prognostic stage group in addition to the anatomic stage group of the 8th edition of AJCC TNM staging system to determine a more patient-tailored prognosis.