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

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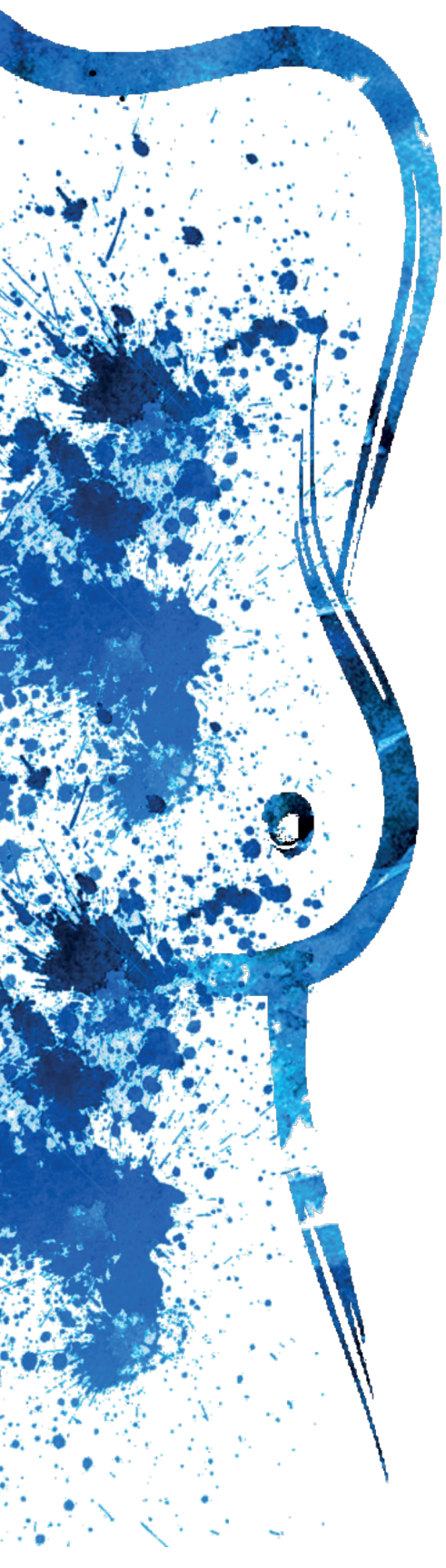

CHAPTER 1

INTRODUCTION AND OUTLINE OF THIS THESIS

Breast cancer is the most common type of invasive cancer among women worldwide with almost 15.000 newly diagnosed patients in the Netherlands in 2019 (1, 2). Extensive treatment (i.e. surgery, radiation-, hormone-, chemotherapy and/or immunotherapy) resulted in an increased and excellent five-year overall survival (OS) of 99% for stage I and 91% for stage II breast cancer patients (2). Potential downside is overtreatment of breast cancer patients and the presence of (lifetime) morbidity in breast cancer survivors. As a result, breast cancer research shifted to reducing overtreatment while remaining disease control and survival, thereby reducing morbidity and improving quality of life (QoL) of breast cancer survivors. This thesis will focus on the road towards less (extensive) axillary treatment in early breast cancer patients.

Axillary lymph node dissection

For years, axillary lymph node status in breast cancer patients was assessed by axillary lymph node dissection (ALND). This procedure consists of the removal of all axillary lymph nodes and aimed to treat regional disease, improve OS, provide information on breast cancer prognosis and nodal outcome was used as one of the clinicopathological indicators for the recommendation of adjuvant chemotherapy. Though in most patients, the ALND specimen contained no nodal metastases. ALND is associated with short- and long-term morbidities, such as nerve injury (55-75%), seroma (15-75%), lymphedema (20%), reduced shoulder function (16%) and can therefore result in a reduced QoL of breast cancer survivors (3-6).

The road towards less extensive axillary treatment started by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-04) trial in 1970 (7). This trial randomized 1.079 clinically node negative breast cancer patients to mastectomy with ALND, mastectomy with axillary radiotherapy (RT), or mastectomy-only. None of these patients received adjuvant systemic therapy. Forty percent of the patients randomized to mastectomy with ALND were diagnosed with lymph node metastases. Delayed ALND was performed in only 18.6% of the mastectomy-only patients who developed clinically node positive disease during follow-up. After 25-years of follow-up, regional recurrence (RR) rate was 4% in patients randomized to mastectomy with ALND, 4% in patients randomized to mastectomy with axillary RT, and 6% in patients randomized to mastectomy-only ($p = 0.002$). There was no significant difference in disease-free survival (DFS) or OS between the patient groups after 25 years of follow-up ($p = 0.65$ and $p = 0.68$) (7).
Despite these results, ALND remained standard of care in clinically node negative patients, due to newly discovered benefit of adjuvant systemic therapy in patients with lymph node metastases.

Sentinel lymph node biopsy

The sentinel lymph node biopsy (SLNB) was introduced in 1994, as a less invasive alternative to assess the axillary lymph node status in clinically node negative breast cancer patients (8, 9). Based on the pattern of lymphatic drainage of the breast, the sentinel lymph node (SLN) is most likely the first lymph node(s) to which cancer cells spread to. Based on this principle, it is assumed that if the SLN contains no lymph node metastasis, all other regional lymph nodes are negative as well.

Safety of omitting completion ALND in SLNB negative patients was studied in the NSABP B-32 trial (10). Clinically node negative breast cancer patients (n = 5.611) were randomized to SLNB only in case of absence of SLN metastases, or SLNB followed by immediate completion ALND (independent of SLNB results). The overall node positive rate was 29.2% (n = 766). Of the patients with negative SLN randomized to immediate completion ALND, 75 patients had nodal metastases in the completion ALND specimen, resulting in a false negative rate (FNR) of the SLNB of 9.8%. Additional lymph node metastases were identified in 38.6% of the patients with a positive SLN. After median follow-up of eight years, OS was 91.8% in the SLNB only group and 90.3% in the SLNB and completion ALND group (p = 0.12). RR occurred in eight patients (0.4%) in the SLNB only group, compared to 14 patients (0.7%) in the SLNB and completion ALND group (p = 0.22) (10).

Based on these results, the performance of ALND was omitted in case of a negative SLN, an important step towards less invasive axillary treatment. Though, in patients undergoing completion ALND in case of a positive SLN, approximately 60% have no additional lymph node metastases, and thus no clinical benefit of the completion ALND (11,12).
Bilimoria et al. retrospectively compared SLN positive patients (n = 97.314) who underwent SLNB only (20.8%, n = 20.217) to SLN positive patients treated with completion ALND (79.2%, n = 77.097) (13). Results showed that SLNB followed by completion ALND did not improve RR rate (HR 0.58, 95%CI, 0.32-1.06) compared to SLNB only, after a median follow-up of 63 months. The RR rate was 0.6% in the SLNB only group compared to 0.2% in the SLNB with completion ALND group for patients with a micrometastasis in the SLN (p = 0.063) and 1.2% and 1.0% for patients with a macrometastasis in the SLN, respectively (p = 0.40). For the overall group, OS was not improved by completion ALND (HR 0.89, 95%CI, 0.76-1.04). Five-year OS was 98.5% for patients with micrometastasis in the SLN undergoing completion ALND, compared to 98.2% in case of SLNB only (p = 0.72), and 91.7% and 88.7% in case of a macrometastasis, respectively (p = 0.010). This study concluded that RR and OS were comparable for clinically node negative patients with positive SLN treated with SLNB only and led to several randomized controlled trials (RCTs) to support this hypothesis (13).

Omission of axillary lymph node dissection

The American College of Surgeons Oncology Group (ACOSOG) Z0011 multicenter trial included clinically node negative T1-2 breast cancer patients (n = 856) treated with breast conserving therapy (BCT) with one or two macrometastases in the SLNB. Patients were randomized to completion ALND (n = 420) or SLNB only (watchful waiting) (n = 436) (14). BCT consisted of breast conserving surgery followed by whole breast irradiation therapy (WBRT). Adjuvant systemic therapy was administered in 96%. Additional lymph node metastases beyond the SLNB were detected in 27.3% of the patients randomized to completion ALND, with range of total number of lymph node metastases between one and 22. Five-year RR, OS and DFS were respectively, 0.5%, 91.8% and 82.8% in the patients randomized to completion ALND, and 0.9%, 92.5% and 83.9% in the patients randomized to SLNB only (p = 0.45, p = 0.25, p = 0.14) (15). Long-term results of the Z0011 trial were published in 2016 and showed a ten-year cumulative locoregional recurrence (LRR) of 6.2% in the patients randomized to completion ALND and 5.3% in the patients randomized to SLNB only (p = 0.36). Ten-year cumulative incidence of RR was 0.5% in completion ALND group and 1.5% in the SLNB only group (p = 0.28) The 10-year OS was 83.6% in the completion ALND group compared to 86.3% in the SLNB only group (p = 0.40), and DFS was 78.3% compared to 80.3%, respectively (p = 0.30) (16). The Z0011 trial showed that 10-year survival for patients treated with SLNB only (besides BCT and adjuvant systemic treatment) was noninferior to patients treated with completion ALND.

In addition to the Z0011 trial, two multicenter RCTs confirmed the safety of omitting completion ALND in early breast cancer patients. The International Breast Cancer Study Group (IBCSG) 23-01 included clinically node negative T1-2 breast patients treated with BCT or mastectomy with micrometastases in the SLN (n = 931). Patients were randomized to completion ALND (n = 464) or SLNB only (watchful waiting) (n = 467) (17). Adjuvant systemic therapy was administered in 96% of the patients. Additional lymph node metastases beyond the SLN were detected in 13% in the completion ALND group. Among the patients who received completion ALND, 59 (13%) had at least one additional lymph node metastases: 37 (8%) had one, 13 (3%) had two, and nine (2%) had three or more additional lymph node metastases. After a median follow-up of five-years, RR occurred in only one patient (0.2%) in the completion ALND group and five patients (1.1%) in the watchful waiting group. Five- and 10-year DFS were respectively 87.8% and 74.9% in the completion ALND group, and 84.4% and 76.8% in the watchful waiting group, (p = 0.16, p = 0.24) (17, 18). Therefore, results of the IBCSG 23-01 trial support the results of the Z0011 trial, however only patients with SLN micrometastases were included.

The Agència d' Avaluació de Tecnologia i Recerca Mèdiques (AATRM) 048/13/2000 trial included clinically node negative breast cancer patients with a tumor size up to 3.5 cm who

were treated with BCT or mastectomy and who were diagnosed with micrometastasis in the SLNB. Of the included 233 patients, 112 were randomized to the completion ALND and 121 to SLNB only (watchful waiting) (19). Adjuvant systemic therapy was administered in 92.1% of the patients. Additional lymph node metastases beyond the SLNB were detected in 13% in the completion ALND group. Only four patients experienced recurrence, one had a distant recurrence and three had LRR: one after completion ALND and three patients after SLNB only (p = 0.348). There was no difference in five-year DFS between both groups (p = 0.325) (14). The AATRM 048/13/2000 trial also support results of the Z0011 trial in patients with a tumor up to 3.5cm with micrometastases in the SLN (19).

In conclusion, these three studies (ACOSOG Z0011, IBCSG 23-01, AATRM 048/13/2000) showed that completion ALND could be safely omitted in selected clinically node negative patients with limited SLN metastases who are treated with BCT and adjuvant systemic therapy.

Alternative axillary treatment

Two RCTs examined axillary RT as an alternative for conventional additional axillary treatment in early breast cancer patients (20-24). The After Mapping of the Axilla, Radiotherapy or Surgery? (AMAROS) multicenter trial randomized clinically node negative T1-2 breast cancer patients (n = 4.806) treated with BCT or mastectomy to completion ALND (n = 2.402) or axillary RT after a positive SLNB (n = 2.404) (20). Axillary RT included all three levels of the axilla and the medial part of the supraclavicular fossa with a prescribed dose of 25 fractions of 2 Gray to all levels. Additional lymph node metastases beyond the SLN were detected in 33% of the patients treated with completion ALND. RR occurred in 0.5% (4/744) of the patients treated with completion ALND and 1.0% (7/681) of the patients treated with axillary RT. Five-year RR was 0.43% in the completion ALND group and 1.19% in the axillary RT group (p = 0.09). Five-year DFS was 86.9% in the completion ALND group compared to 82.7% in the axillary RT group (HR 1.18, 95%CI 0.93–1.51, p = 0.18). Five-year OS was 93.3% and 92.5%, respectively (HR 1.17, 95%CI 0.85–1.62, p = 0.34). Less lymphedema in the ipsilateral arm was seen in patients treated with axillary RT compared to patients treated with completion ALND after one year (15% versus 28%), three years (14% versus 23%), and five years of follow-up (11% versus 23%) (p <0.0001, p = 0.003, p <0.0001). This did not impact QoL (20, 21). After 10-years of follow-up, the RR rate was 0.93% (7/744) in the completion ALND group compared to 1.82% (11/681) in the axillary RT group (p = 0.37). There was no significant difference in 10-year OS: 84.6% in the completion ALND group versus 81.4% in the axillary RT group (p = 0.26) and no significant difference in 10-year DFS: 81.7% and 78.2% (p =0.19), respectively. However, contralateral breast cancer more frequently occurred in patients treated with axillary RT (3.1%, 21/681) compared to patients treated with completion ALND (1.5%, 11/744) (p = 0.035) (22).

The AMAROS trial showed that completion ALND and axillary RT provided comparable regional control and survival rates for clinically node negative patients with T1–2 breast cancer and limited SLN metastases.

The single center Optimal Treatment Of the Axilla Surgery Or Radiotherapy (OTOASOR) trial randomized stage I-II (tumor size ≤3cm, N0) breast cancer patients with a positive SLN (n = 2.106) to completion ALND (n = 1.054) or axillary RT (n = 1.052) (23). Axillary RT included all three levels of the axilla and the medial part of the supraclavicular fossa with a prescribed dose of 25 fractions of 2 Gray. Additional lymph node metastases beyond the SLN were detected in 38.5% in the completion ALND group. After eight years of follow-up, RR occurred in 2.0% in completion ALND group and 1.7% in the axillary RT group (p = 1.00). Eight-year OS and DFS were 77.9% and 72.1% in the completion ALND group compared to 84.8% and 77.4% in the axillary RT group (p = 0.060, p = 0.51) (23, 24). After one year of follow-up, patients treated with completion ALND (15.3%) showed higher rates of lymphedema, paresthesia, swelling, arm pain, and shoulder immobility compared to patients treated with axillary RT (4.7%). There was no significant difference in QoL between both groups (23, 24). These results showed that axillary RT instead of completion ALND did not increase the risk of RR, OS and DFS and is therefore an alternative treatment for selected patients with limited SLN metastases.

The AMAROS and OTOASOR trials both showed that axillary RT has an equally good disease control and a lower rate of lymphedema compared to completion ALND in early breast cancer patients with limited SLN metastases treated with BCT (AMAROS and OTOASOR) and mastectomy (AMAROS). On the contrary, axillary RT could be considered as overtreatment of the axilla, especially when compared in light of the ACOSOG Z0011, IBCSG 23-01 and AATRM 048/13/2000 studies who showed that completion ALND could be safely omitted in BCT treated patients with limited SLN metastases. We further should take note of the increased incidence of contralateral breast cancer in patients treated with axillary RT.

Axillary treatment in mastectomy patients

Majority of the patients in previous mentioned trials were treated with BCT. It is known that WBRT is associated with a significantly lower RR rate, most likely by incidental radiation therapy to the axilla (25). Results can therefore not just be extrapolated to mastectomy patients.

The IBCSG 23-01 trial included 931 clinically node negative breast cancer patients with one or more micrometastases in the SLN, of whom 845 (91.0%) were treated with BCT and only 86 (9.0%) with mastectomy (17). Ten-year DFS was 76.4% in the BCT group and 70.5% in the mastectomy group (p = 0.19). Breast-cancer events occurred in 132 patients (16%) treated

with BCT compared to 17 patients (20%) treated with mastectomy (p = 0.71). The number of RR was low; only two mastectomy patients (2%) experienced RR compared to seven BCT patients (0.8%) (18). Subgroup analysis suggested that omission of completion ALND might be acceptable for patients undergoing mastectomy with micrometastasis in the SLN.

In the AMAROS trial, 17.4% of the patients (248 of 1.425) were treated with mastectomy, of whom 127 underwent completion ALND and 121 received axillary RT (20). In the AATRM 048/13/2000 trial, only 8% of the patients (18 of 233) were treated with mastectomy: ten patients were randomized to completion ALND and eight to SLNB only (watchful waiting) (19). The OATASAR trial included 74 patients treated with mastectomy (22%), 44 were treated with completion ALND and 30 with axillary RT (23, 24). In summary, early breast cancer patients treated with mastectomy and positive SLN were either excluded (ACOSOG Z0011) (14), or underrepresented in previous mentioned trials (IBCSG 23-01, AMAROS, AATRM 048/13/2000 and OATASAR) (17, 20, 19, 23). Currently, several trials are investigating whether completion ALND can be omitted in mastectomy treated patients as well (e.g. POSNOC, SENOMAC, and SINODAR trial) (26-28).

Introduction of axillary ultrasound

All clinically node negative patients in previous mentioned trials were selected by physical examination of the axilla only. Accuracy of physical examination of the axilla for pre-operative nodal staging is low, with a sensitivity of 25 - 32.3% (29-31). In the Netherlands, physical examination is combined with axillary ultrasound (US) to clinically assess axillary lymph node status prior to axillary surgery (SLNB or ALND). If physical examination and axillary US show no signs of nodal metastases, SLNB is performed. Otherwise, an ALND is often indicated.

Sensitivity of axillary US combined with biopsy is 79.6% with a specificity of 98.3% (32). Adding axillary US to physical examination improves the pre-operative nodal staging of clinically node negative patients. A negative US selects patients with a more favorable tumor load and excludes advanced nodal disease (≥4 metastatic nodes) in 4.4% (33). This could be favorable in case of omission of extensive axillary treatment in clinically node negative patients.

On the contrary, most previous mentioned RCTs, such as the ACOSOG Z0011 trial, used only physical examination to select clinically node negative patients. Using standard axillary US could withheld some patients with negative physical examination but positive US from omitting completion ALND in case of one or two SLN metastases. However, offering neoadjuvant systemic therapy to patients with positive axillary US will allow lymph node metastases to convert to axillary pathologic complete response and potentially adjust the extent of axillary treatment strategy in this subset of patients.

Omitting sentinel lymph node biopsy

Currently, there is an ongoing debate on the role of SLNB in future management of the axilla. The ACOSOG Z0011, IBCSG 23-01 and AATRM 048/13/2000 studies showed that omission of completion ALND in clinically node negative breast cancer patients with positive SLN did not affect survival rates and RR rates were low. As mentioned, all clinically node negative patients in these trials were selected by physical examination only and addition of axillary US further promotes the pre-operative selection of node negative patients or with low tumor load. Also, adjuvant systemic therapy and WBRT reduces the risk of possible lymph node metastases left in situ that require treatment during follow-up. Subsequently, several RCTs are currently investigating whether the SLNB can be safely omitted in clinically node negative (including axillary US) T1-2 patients treated with BCT (SOUND, BOOG 2013-08, and INSEMA) (34-36).

Follow-up time in randomized controlled trials

Topic of debate in recent and ongoing RCTs investigating the safety of reducing axillary treatment is the required follow-up duration for adequate safety analyses. Endpoints of RCTs are now usually reported after five-, 10- or 25-years (NSABP B-04) of follow-up. These long follow-up durations prevent early implementation of study results, while it has been suggested that most recurrences occur in the first years after diagnosis. This questions whether results can be published earlier and also questions the yield of longer follow-up.

Another topic of debate in these RCTs is whether different subtypes might need patient tailored treatment, since they have different patterns of disease presentation (37), metastatic spread (38) and response to treatment (39-41).

Aim and outline of thesis

The aim of this thesis is to specify a subset of early breast cancer patients in whom axillary treatment can be reduced while remaining disease control and survival, thereby reducing axillary morbidity and improve QoL of these early breast cancer survivors (Part I and II). The second aim of this thesis is to optimize follow-up period for trials in early breast cancer patients and to investigate different staging systems based on tumor biology (Part III).

Part I – Omission of the completion axillary treatment

Studies showed that completion ALND can be safely omitted in a specific subset of clinically node negative breast cancer patients. Completion ALND can be omitted in BCT treated patients but is still standard care for patients treated with a mastectomy.
Chapter 2 determines the proportion of patients who could avoid completion ALND by choosing BCT instead of mastectomy. **Chapter 3** evaluates whether extracapsular extension (ECE) in the SLN is associated with involvement of more than or equal to four lymph node metastases at completion ALND and its effect on five-year DFS and 10-year OS.

Part II – Omission of the sentinel lymph node biopsy

In **Chapter 4** the design of the BOOG 2013-08 trial is described. Clinically node negative T1-2 breast cancer patients treated with BCT will be randomized to SLNB or watchful waiting. In context of the BOOG 2013-08 study, **Chapter 5** evaluates whether the diagnostic performance of axillary ultrasound for nodal staging differs per breast cancer subtype.

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

Topic of debate in RCTs omitting axillary treatment is adequate follow-up time.
Chapter 6 shows the five-year regional recurrence in different breast cancer subtypes. The effect of event-free years on the risk of five-year local recurrence is described in **Chapter 7.** The Bioscore is a novel prognostic staging system for breast cancer patients treated with primary surgery, combining traditional pathological TNM staging with tumor biology (i.e. grade and receptor status). **Chapter 8** investigates the prognostic stage group of the AJCC TNM system and the Bioscore staging system, as novel staging systems, combining the traditional AJCC with tumor biology for ER+HER2- breast cancer patients with a 10-year follow-up period.

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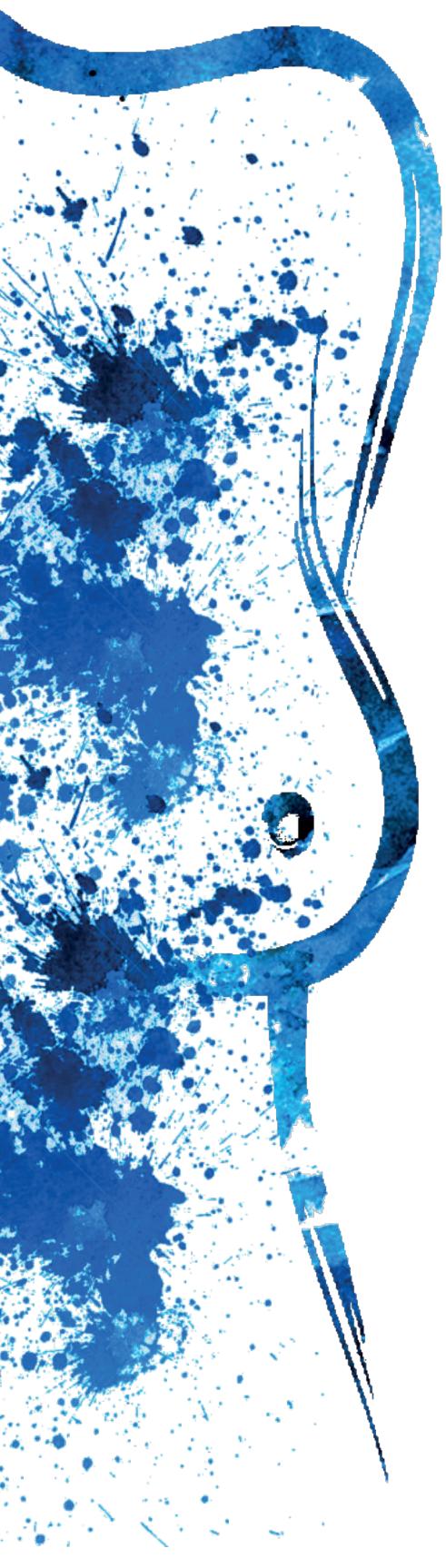
PART I

OMISSION OF COMPLETION AXILLARY TREATMENT



CHAPTER 2

WOMEN COULD AVOID AXILLARY LYMPH NODE DISSECTION BY CHOOSING BREAST-CONSERVING THERAPY INSTEAD OF MASTECTOMY

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Abstract

Background The ACOSOG Z0011 trial showed that completion axillary lymph node dissection (cALND) can be safely omitted for some patients with T1-2 clinically node-negative breast cancer with one to two involved sentinel lymph nodes (SLNs) treated with breast conserving therapy (BCT). There is little evidence for the safety of omitting cALND for mastectomy treated patients. Consequently, cALND is often recommended for sentinel node-positive patients treated with mastectomy. The aim of this study was to determine the proportion of patients who could avoid cALND by choosing BCT instead of mastectomy at a tertiary cancer center.

Methods All T1-2 clinically node-negative breast cancer patients treated with BCT or mastectomy between 2012-2017 with metastases in the SLN(s) were selected from a prospectively maintained database. Clinical factors and outcomes were evaluated between the two groups. Differences were compared using Wilcoxon rank-sum test, chi-square test or Fisher's exact test as appropriate. Significance was set at the 0.05 level for all analyses.

Results A total of 306 patients were included, 199 (65.0%) patients were treated with BCT and 107 (35.0%) with mastectomy. Patients treated with mastectomy were more often treated with cALND compared to those treated with BCT (71.0% versus 26.6%, $p<0.0001$). Overall, 52 of the mastectomy patients (68.4%) could have avoided cALND if they had chosen BCT.

Conclusions Patients treated with mastectomy are more likely to receive cALND than those treated with BCT. Axillary management should be addressed during discussion of primary tumor therapy, and cALND may be avoided when patients choose BCT instead of mastectomy.

Introduction

Sentinel lymph node biopsy (SLNB) is a less invasive technique for nodal staging in clinically node negative breast cancer patients. Numerous prospective trials have shown that completion axillary lymph node dissection (cALND) can be safely omitted for some early breast cancer patients with a negative sentinel lymph node biopsy (SLN) (1-5). The ACOSOG Z0011 trial showed that cALND can also be omitted in early breast cancer patients with limited tumor burden in the SLN. That trial randomized T1-2 clinically node negative breast cancer patients treated with breast conserving therapy (BCT) with one or two SLN with metastases to cALND or no additional specific axillary treatment (SLNB alone) (6). There was no statistically significant difference in 5- and 10-year locoregional recurrence (LRR), overall (OS) and disease-free survival (DFS) between patients treated with cALND and SLNB alone (6-8).

Currently, there is little evidence for the safety of omitting cALND for node-positive patients treated with mastectomy. Traditionally, BCT consists of breast conserving surgery followed by whole breast radiation therapy (WBRT). Since WBRT partly irradiates the axilla as well, results of the Z0011 cannot be directly extrapolated to mastectomy treated patients (9). The AMAROS study by the EORTC randomized patients who had a positive sentinel node to axillary lymph node dissection or nodal irradiation (10). This study included only 121 patients treated with mastectomy without axillary dissection, too few to permit generalization of the results. Overall, the study showed no significant difference in outcome between axillary dissection or radiation for patients with an involved sentinel node. Similarly, the study of patients with sentinel node micrometastases by Galimberti had few sentinel-node positive patients treated with mastectomy (11, 12).

Several randomized controlled trials (RCTs) are currently investigating whether cALND can be omitted in mastectomy treated patients (e.g. POSNOC, SENOMAC and SINODAR trial) (13-15). Until publication of these results, cALND is likely to remain standard for SLN positive patients treated with mastectomy. However, some of these patients could perhaps avoid cALND if they had chosen BCT instead of mastectomy. The aim of this study was to determine the proportion of patients who could avoid cALND by choosing BCT instead of mastectomy. This information could be of value in counseling patients preoperatively and should be discussed.

Material and Methods

This study was approved by the institutional review board of Cedars-Sinai Medical Center. Women treated between January 2012 and December 2017 with T1-2 clinically node negative breast cancer with one or two SLN with micro- or macrometastases were identified from a prospectively maintained database. A clinically node negative axilla was defined as no palpable adenopathy to suggest spread of disease to the axilla. Patients were excluded if no SLNB was performed or if they had distant metastasis, history of ipsilateral axillary surgery, and/or treatment with neoadjuvant systemic therapy.

Clinical data were obtained from a prospectively maintained database and electronic medical records and included patient demographics (i.e. age, menopausal status), tumor characteristics (tumor size, tumor type, tumor grade, multifocality/multicentricity, number of lesions, concomitant ductal carcinoma in situ (DCIS), estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor (HER2) status, Ki-67, presence of lymphovascular invasion, nodal extracapsular extension), and breast surgical procedure.

The SLN was identified using the various common techniques: radioisotope and/or dye. SLN was defined as positive if carcinoma cells were identified by frozen section, hematoxylin and eosin (H&E) staining or immunohistochemistry (IHC). Micro metastatic disease was defined as tumor cells > 0.2 - 2.0 mm (N1mic) and macro metastatic disease as tumor cells > 2.0 mm (N1). Patients with isolated tumor cells in the SLN were categorized as N0 (16). ECE was defined as extension of neoplastic cells through the nodal capsule into perinodal adipose tissue of the axilla regardless of the extent (17).

Continuous variables were described using medians and ranges and compared with the Wilcoxon rank-sum test. Differences in categorical variables were described in numbers and percentages and compared using the Pearson chi-square test or Fisher's exact test as appropriate. The primary outcome of this study is to estimate the number of node-positive patients who could have avoided cALND if they had chosen BCT instead of mastectomy. All statistical analyses were performed using SPSS software version 25.0 (SPSS Inc, Chicago, IL). Significance was set at the 0.05 level for all analyses.

Results

A total of 306 patients were eligible for this study, 107 (35.0%) were treated with mastectomy and 199 (65.0%) treated with BCT (Figure 1). Median tumor size was 1.8 cm (range 0.3 – 4.9 cm). The most common type of breast cancer was invasive ductal carcinoma in 78.8% of the patients, followed by lobular carcinoma (15.0%), mixed type (5.2%), and other types of breast cancer (1.0%). ER positive breast cancer was detected in 92.5%, and in 4.6% of the patients HER2 was amplified. Mastectomy treated patients were younger (51 versus 63 years), more often were premenopausal (35.0% versus 12.1%), had multifocal/multicentric tumors (56.9% versus 26.5%) compared to patients treated with BCT. Patient and tumor characteristics are summarized in Table 1.

Sentinel lymph node and completion axillary lymph node outcomes

From the overall population, 228 (74.5%) patients contained macrometastases and 78 (25.5%) contained micrometastases in the SLN. There was no significant difference in the status of the SLN between patients treated with mastectomy compared to those treated with BCT. Of the mastectomy treated patients, 76.6% (82/107) contained macrometastases and 23.4% (25/107) micrometastases compared to 73.4% (146/199) and 26.6% (53/199) in the BCT group ($p = 0.53$). Mastectomy treated patients (76/107) more often were treated with a cALND after positive SLN compared to BCT patients (53/199) (71.0% versus 26.6%, $p<0.001$). Of the mastectomy patients with macrometastases in the SLN, 79.3% (65/82) received cALND compared to 34.2% (50/146) of the BCT patients with macrometastases in the SLN ($p<0.001$). For patients with micrometastases in the SLN, this difference was even more pronounced; 44.0% (11/25) of the mastectomy treated patients received cALND compared to 5.7% (3/53) patients treated with BCT ($p<0.001$).

Approximately 43% (33/76) of the mastectomy patients treated with cALND contained macrometastases in non-SLN, 5.3% (4/76) contained micrometastases in non-SLN, and 51.3% (39/76) contained no positive non-SLN compared to 50.9% (27/53), 5.7% (3/53), and 43.4% (23/53) respectively in the BCT-treated patients ($p=0.641$) (Table 2).
Presence of ECE in the SLN was seen in 28.8% (85 of the 306) patients with a positive SLN (27.2% in the mastectomy group versus 29.7% in the BCT group, $p = 0.651$).
Of the patients treated with a cALND after detecting metastases in the SLN, 31.6% (24/76) of the mastectomy treated patients contained ECE in the SLN, in BCT treated patients, this was 54.7% (29/53).

Table 1. Baseline characteristics of the overall population (n = 306) and separately for patients treated with mastectomy (n = 107) and BCT (n = 199)

Characteristic	Overall n = 306	Mastectomy n = 107	BCT n = 199	p-value
Age, years				
median	58.5	51	63	
range	28 - 91	35 - 86	28 - 91	<0.001
Menopausal status, n (%)				
premenopausal	48 (15.7)	28 (35.0)	20 (12.1)	
perimenopausal	16 (6.5)	5 (6.3)	11 (6.7)	
postmenopausal	181 (73.9)	47 (58.7)	134 (81.2)	<0.001
Genetic mutation, n (%)				
BRCA 1	1 (0.3)	1 (0.9)	0 (0)	
BRCA 2	7 (2.3)	6 (5.6)	1 (0.5)	0.0279
Radiologic tumor size, cm				
median	1.8	1.9	1.7	
range	0.3 - 4.9	0.3 - 4.9	0.3 - 4.6	0.055
Location, n (%)				
bilateral	9 (2.9)	1 (0.9)	8 (4.0)	
unilateral	297 (97.1)	106 (99.1)	191 (96.0)	0.035
Number of lesions, n%				
1	255 (83.3)	86 (80.4)	169 (84.9)	
2	44 (14.4)	15 (14.0)	29 (14.6)	
3	6 (1.97)	5 (4.7)	1 (0.5)	
4	1 (0.3)	1 (0.9)	0 (0)	0.030
Tumor type, n (%)				
ductal	241 (78.8)	80 (74.8)	161 (80.9)	
lobular	46 (15.0)	17 (15.9)	29 (14.6)	
mixed	16 (5.2)	8 (7.5)	8 (4.0)	
other	3 (1.0)	2 (1.9)	1 (0.5)	0.289
Multicentric/multifocal				
no	136 (64.1)	28 (43.1)	108 (73.5)	
yes	76 (35.8)	37 (56.9)	39 (26.5)	<0.001
Grade (Bloom-Richardson), n (%)				
I	46 (15.1)	13 (12.3)	33 (16.7)	
II	155 (51.0)	52 (49.1)	103 (52.0)	
III	99 (32.6)	41 (38.7)	58 (29.3)	
missing	4 (1.3)	0 (0)	4 (2.0)	0.193
Pathologic tumor size, mm				
median	2.1	2.0	2.2	
range	0.1 – 8.0	0.3 – 7.0	0.1 – 8.0	0.314
ER status, n (%)				
negative	23 (7.5)	8 (7.5)	15 (7.5)	
positive	282 (92.5)	98 (92.4)	184 (92.5)	0.998
PR status, n (%)				
negative	62 (20.4)	22 (20.7)	40 (20.2)	
positive	242 (79.6)	84 (79.2)	158 (79.8)	0.909
HER2 status (FISH), n (%)				
equivocal	13 (4.6)	8 (8.4)	5 (2.7)	
negative	256 (90.8)	82 (86.3)	174 (93.0)	
positive	13 (4.6)	5 (5.2)	8 (4.3)	0.095

N = number, BCT breast conserving therapy, DCIS ductal carcinoma in situ, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, FISH Fluorescence In Situ Hybridization.

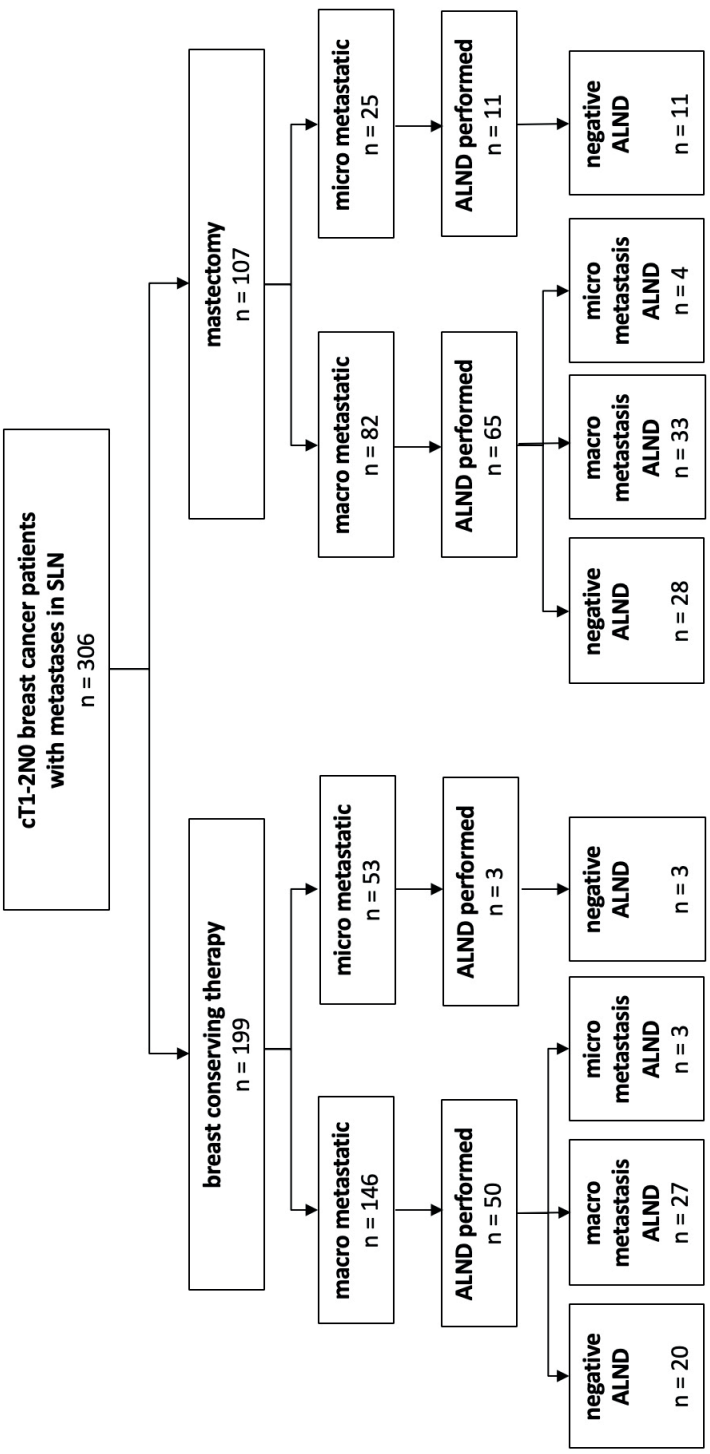

Figure 1. Flowchart of the included T1-2 clinically node negative breast cancer patients and SLN outcome

cT clinical tumor stage, n number of cases, SLN sentinel lymph node, AlND axillary lymph node dissection

Table 2. Sentinel lymph node and completion axillary lymph node outcomes for the overall population (n = 306) and separately for patients treated with mastectomy (n = 107) and breast conserving therapy (n = 199)

Characteristic	Overall n = 306	Mastectomy n = 107	BCT n = 199	p-value
SLN outcome, n (%)				
macrometastases	228 (74.5)	82 (76.6)	146 (73.4)	
micrometastases	78 (25.5)	25 (23.4)	53 (26.6)	0.532
Number of SLN with macrometastasis				
median	1	1	1	
range	0 - 2	0 - 2	0 - 2	0.803
Number of SLN with micrometastasis				
median	0	0	0	
range	0 - 2	0 - 2	0 - 2	0.459
Number of lymph nodes in SLN biopsy				
median	2	2	2	
range	1 - 9	1 - 7	1 - 9	0.841
Presence of ECE in SLN, n (%)				
no	210 (71.2)	75 (72.8)	135 (70.3)	
yes	85 (28.8)	28 (27.2)	57 (29.7)	0.651
Size of ECE in SLN, in mm				
median	2	2	2	
range	0.1 - 18	0.1 - 17	0.1 - 18	0.572
cALND performed, n (%)				
no	177 (57.8)	31 (29.0)	146 (73.4)	
yes	129 (42.2)	76 (71.0)	53 (26.6)	<0.001
cALND outcome, n (%)				
macrometastasis in non-SLN (>2mm)	60 (46.5)	33 (43.4)	27 (50.9)	
micrometastasis in non-SLN (>0.2-2mm)	7 (5.4)	4 (5.3)	3 (5.7)	
negative	62 (48.1)	39 (51.3)	23 (43.4)	0.641
Number of non-SLN with macrometastases in cALND				
median	0	0	1	
range	0 - 16	0 - 16	0 - 16	0.399
Number of non-SLN with micrometastases in cALND				
median	0	0	0	
range	0 - 13	0 - 2	0 - 13	0.029
Number of non-SLN retrieved in cALND				
median	4	11	3	
range	1 - 35	1 - 35	1 - 30	<0.001

N number, BCT breast conserving therapy, SLN sentinel lymph node, ECE extracapsular extension, cALND completion axillary lymph node dissection.

Discussion

This study included 306 T1-2 clinically node-negative breast cancer patients with metastases in the SLN, of these 35.0% were treated with mastectomy and 65.0% with BCT. Mastectomy patients were more often treated with a cALND after the detection of metastases in the SLN compared to BCT patients (71.0% versus 26.6%, p<0.001). Overall, 24 of the 76 patients (31.6%) treated with mastectomy and cALND after metastases in the SLN contained ECE in the SLN. Often their ECE was minimal. The remaining 52 patients (68.4%) did not contain ECE in the SLN and could, therefore, have avoided cALND if they initially had chosen BCT. This number would be even greater if ALND were not performed for minimal ECE.

Mastectomy and BCT are equivalent surgical treatment in early breast cancer patients in terms of 10-year survival (18), however, mastectomy rates have increased over time (18-21). Highest increase in mastectomy rates were observed in clinically node-negative breast cancer patients as well as in patients with carcinoma in situ (19). Reasons for choosing a mastectomy or BCT are mostly based on patients' preference (e.g. concerns for breast cancer recurrence, avoidance of radiation therapy, impact of surgery on body image and femininity) and/or recommendation of physician. In this present study, mastectomy patients were younger (51 versus 63 years, p<0.001) and more often had multifocal/multicentric tumors (56.9% versus 26.5%, p<0.001) compared to BCT patients. Seven of the mastectomy patients who could have avoided cALND if they initially opted for BCT had a multifocal or multicentric tumor. Rosenkranz et al. showed that multifocal or multicentric tumors could be treated with BCT; in that study 67.6% of the included patients achieved a margin-negative excision and 7.1% of the included patients required conversion to mastectomy due to positive margins (22). Furthermore, three out of 52 mastectomy patients who could have avoided cALND if they initially opted for BCT had a BRCA mutation. BCT may be used as treatment in some patients such as the elderly or by choice in patients with a BRCA mutation as well. Other known factors are larger tumor size, presence of lymphovascular invasion and inherited genetic mutation (19,20).

Since the Z0011 trial, two RCTs (International Breast Cancer Study Group (IBCSG) 23-01 and Agència d' Avaluació de Tecnologia i Recerca Mèdiques (AATRM)) examined less extensive axillary treatment (11, 23). Both studies were not designed to extrapolate the Z0011 results but did include patients treated with a mastectomy. The International Breast Cancer Study Group (IBCSG) 23-01 trial included 931 clinically node negative breast cancer patients with one or more micrometastases in the SLN, whereof 845 (91.0%) were treated with BCT and only 86 (9.0%) with mastectomy (11). Ten-year disease-free survival (DFS) was 76.4% in the BCT group and 70.5% in the mastectomy group [HR 1.39, 95%CI

0.85-2.26, p=0.19]. Two mastectomy treated patients (2%) experienced RR compared to seven BCT patients (0.8%) (12).

The AATRM trial included clinically node negative breast cancer patients treated with BCT or mastectomy with micrometastases in the SLN. In total 233 patients were included, of these 112 were randomized to cALND and 121 to no further axillary surgery. From the 233 included patients, four experienced an axillary recurrence: one in the cALND group and three in the observative group. There was no difference in five-year DFS between both groups (p = 0.325). Only 18 patients were treated with a mastectomy: 10 patients were randomized to cALND and eight to the SLNB alone (23). Both RCTs suggest that omission of cALND after mastectomy may be appropriate for selected patients. However, the number of patients treated with mastectomy was small.

Additionally, three single center studies examined the omission of cALND in mastectomy patients with a positive SLN (24-26). Milgrom et al. included early breast cancer patients who underwent mastectomy (n = 210) or BCT (n = 325) with a positive SLN in whom either cALND was or was not performed. There was no significant difference in four-year LR (1.7% versus 1.4%, p = 0.85) and RR in mastectomy patients compared to BCT patients (1.2% versus 1.0%, p = 0.51). Higher survival rates were seen in mastectomy patients compared to BCT (four-year DFS 94.8% versus 90.1%, p = 0.02 and four-year OS 97.8% versus 92.6%, p = 0.002) (24).

In the study of Fitz-Sullivan et al., 642 mastectomy patients with positive SLN with no cALND (n = 70), cALND alone (n = 292), cALND followed by radiotherapy (RT) (n = 254) and RT alone (n = 26) were included. The 10-year recurrence rates did not significantly differ; 3.8% for patients treated without cALND, 1.6% for cALND alone, 1.8% for cALND followed by RT and 0.0% for RT alone (p = 0.45). Ten-year recurrence-free survival and OS were not significantly different among different groups as well (p = 0.22 and p = 0.111, respectively) (25).

Snow et al. randomized breast cancer patients with one to three macrometastases in the SLN to BCT and SLNB alone (n = 28), mastectomy and SLNB alone (n = 32), BCT and SLNB followed by ALND (n = 101) and mastectomy and SLNB followed by ALND (n = 157). The overall rate of recurrences (LR, RR and distant metastasis) after 44.4 months in mastectomy patients was not significantly different in patients treated with mastectomy and SLNB compared to patients treated with mastectomy and SLNB followed by ALND, with a 10-year estimated recurrence-free survival of 81% (p = 0.10) (26).

These studies suggest that omission of cALND might be acceptable in patients treated with a mastectomy. However, this applies for a very specific subset of early stage breast cancer patients treated with mastectomy and positive SLN, since patients usually were older (24-27), contained more favorable tumor characteristics, such smaller tumor size (24-27), fewer positive SLN(s) (25, 27), smaller size of SLN metastasis (24), ER positive tumors (24, 27), no evidence of lymphovascular invasion (25), no evidence of extracapsular extension (25), and poorly differentiated tumors (27).

This present study shows T1-2 clinically node-negative breast cancer patients with a positive SLN treated with mastectomy are more likely to receive cALND than BCT treated patients. The majority of the clinically node-negative breast cancer patients with a positive SLN treated with a mastectomy could avoid cALND if they initially opt for BCT. Until publication of the POSNOC, SENOMAC and SINODAR results, cALND will remain commonly utilized for mastectomy-treated T1-2 clinically node negative breast cancer patients with a positive SLN. For clinical practice, this means that patients choosing a mastectomy should be made aware of the additional risk of ALND and increased axillary morbidity which patients could avoid if they choose BCT.

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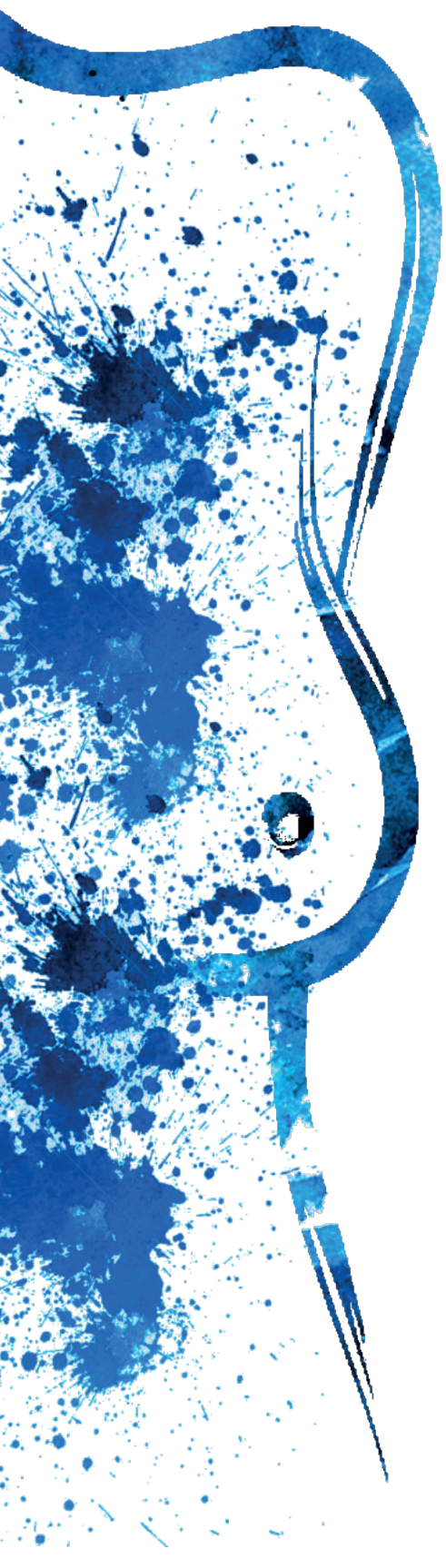

CHAPTER 3

EXTRACAPSULAR EXTENSION IN THE POSITIVE SENTINEL LYMPH NODE: A MARKER OF POOR PROGNOSIS IN CT1-2N0 BREAST CANCER PATIENTS?

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Abstract

Objective This study aims to evaluate whether extracapsular extension (ECE) in the sentinel lymph node (SLN) is associated with involvement of ≥4 lymph node metastases at completion axillary lymph node dissection (ALND) and the effect on 5-year disease-free survival (DFS) and 10-year overall survival (OS).

Summary background data ECE in a SLN is usually a contraindication for omitting completion ALND in *c*T1-2N0 breast cancer patients treated with breast conserving therapy and 1-2 positive SLN(s).

Methods All *c*T1-2N0 breast cancer patients with 1-3 positive SLN(s) who underwent ALND between 2005-2008 were selected from the Netherlands Cancer Registry. Logistic regression analysis was used to determine the association between ECE and ≥4 lymph node metastases. Five-year DFS and 10-year OS were analysed using Kaplan-Meier survival analysis. Cox regression analysis was performed to correct for other prognostic factors.

Results A total of 3.502 patients were included. Information on ECE was available for 2.111 (60.3%) patients, consisting of 741 (35.1%) patients with and 1.370 (64.9%) without ECE. The incidence of ≥4 lymph node metastases was 116 (15.7%) in the ECE group versus 80 (5.8%) in the group without ECE ($p < 0.001$). Five-year DFS rate was 86.4% in the ECE group compared to 88.8% in the group without ECE ($p = 0.065$). 10-year OS rate was 78.6% compared to 83.0% ($p = 0.018$), respectively. Cox regression analysis showed that ECE was not an independent prognostic factor for both DFS and OS.

Conclusions ECE was significantly associated with involvement of ≥4 lymph node metastases in the completion ALND group. ECE was not an independent prognostic factor for both DFS and OS.

Introduction

Extension of neoplastic cells through the nodal capsule into perinodal adipose tissue in sentinel lymph node (SLN) positive patients is called extracapsular extension (ECE) (Appendix 1) (1). Previous studies showed that presence of ECE is associated with presence of additional non-sentinel lymph node metastases (2-9). Additionally, ECE is associated with other prognostic factors, such as lymphovascular invasion and macrometastases (4, 9). Earlier, presence of ECE had no consequences for axillary treatment. All cT1-2N0 breast cancer patients with micro or macro metastases in the SLN were treated with an axillary lymph node dissection (ALND) or radiotherapy of the axilla, irrespective of the presence of ECE.

Currently, the value of completion axillary treatment is being questioned. The ACOSOG Z0011 and IBCSG 23-01 trials have shown that ALND can be safely omitted in cT1-2N0 breast cancer patients treated with breast conserving therapy (BCT) and 1-2 macrometastases in the SLN (10, 11). In both studies (macroscopic) ECE was an exclusion criterion and therefore it remains unclear whether completion axillary treatment can also be safely omitted in patients with ECE. Gooch et al. showed that presence of ECE larger than 2mm was significantly correlated with increased nodal tumor burden and therefore ALND might be indicated for patients with ECE >2mm (12).

Ongoing trials (e.g. BOOG 2013-07, POSNOC, SINODAR and SENOMAC trial) randomize cT1-2N0 patients treated with mastectomy or BCT with a maximum of three macrometastases in the SLN to completion axillary treatment (consisting of ALND or radiotherapy of the axilla) or watchful waiting, irrespective of the presence of ECE (13-15). The most important question remains whether omission of completion axillary treatment in patients with ECE affects disease-free survival (DFS) and overall survival (OS).

The aim of the present study was to determine whether ECE in the SLN is associated with involvement of ≥4 axillary lymph node metastases after completion of an ALND in a large cohort of breast cancer patients. The secondary aim was to investigate whether patients with ECE have an inferior prognosis, with respect to local (LR), regional recurrence (RR), distant metastasis (DM), five-year DFS and ten-year OS.

Material and methods

Data collection

For this population-based study, the Netherlands Cancer Registry (NCR) and the Pathological Anatomical National Automated Archive (PALGA) was used. The NCR contains data on all newly diagnosed malignancies in the Netherlands. Trained data managers of the Comprehensive Cancer Organisation the Netherlands (IKNL) gather data from patients' records in all hospitals based on a notification by PALGA.
Data on patient and tumor characteristics, surgical, radiation, and systemic treatment were obtained, as well as follow-up data on first breast cancer events and survival.
First breast cancer event was registered as new primary ipsilateral breast cancer, contralateral breast cancer, LR, RR or DM. The vital status was obtained through linkage to the Municipal Personal Records Database. Data on pathology, e.g. presence of ECE, size (micro- or macrometastasis), number of positive SLN(s) and/or ALND and total number of removed axillary lymph nodes during sentinel lymph node biopsy (SLNB) and/or ALND were retrieved from the PALGA. This is a nationwide network, which registers all histo- and cytopathology reports generated by all pathology laboratories in the Netherlands (16).

Study population

This study focused on study populations similar to the previously mentioned randomized controlled trials, involving breast cancer patients with a clinically T1-2 tumor, clinically node negative status and positive SLN(s) treated BCT or mastectomy. From the NCR, all patients diagnosed between 2005 and 2008 with primary invasive epithelial cT1-2N0 breast cancer were included, with one to three micro/macro metastases at SLNB, who underwent completion ALND. Patients with distant metastasis at diagnosis (or within 91 days), an incomplete five-year follow-up, or patients treated with primary systemic treatment were excluded. Subsequently, selected patients were linked to data of the PALGA. In case of incomplete registered SLN and/or ALND results (e.g. presence of ECE, number of positive SLN/ALND and total number of removed axillary lymph nodes) patients were excluded.

Locoregional treatment

All patients were treated according to the Dutch breast cancer guidelines of 2005 (17). Locoregional treatment consisted of BCT (lumpectomy and whole breast radiotherapy) or mastectomy combined with a SLNB in clinically node negative breast cancer. Clinically node negative was based on physical examination (axillary ultrasound was common but not mandatory). Contraindications for SLNB were previous axillary surgery and multiple tumors. Patients with a positive SLN were treated with either ALND or axillary radiotherapy, in context of the AMAROS trial. For this present study, patients treated with axillary radiotherapy were excluded. If indicated, patients received adjuvant systemic

treatment (e.g. chemotherapy, hormone therapy, and/or immunotherapy) or adjuvant radiotherapy (17).

Endpoints

ECE was defined as extension of neoplastic cells through the nodal capsule into perinodal adipose tissue of the axilla (1). DFS was defined as the absence of any first LR, RR, or contralateral recurrence, DM or death within five years. OS was defined as the time interval between date of diagnosis and date of death or date of emigration.

LR was defined as any invasive breast cancer in the ipsilateral breast (including skin, biopsy tract and surgical scar) or on the ipsilateral thoracic wall including the mastectomy scar, i.e. both LR and new primary ipsilateral breast cancer were counted for the analysis. RR was defined as recurrence in an ipsilateral axillary, infraclavicular, supraclavicular, internal mammary/parasternal or intramammary lymph node. DM was defined as breast cancer in any organ other than breast, excluding LR and RR and second primary breast cancer (18). Events after 91 days were regarded as a recurrence (LR, RR, DM, new primary ipsilateral breast cancer or contralateral breast cancer). Events between 0 and 91 days after diagnosis were regarded as synchronous with the primary tumor. Patients were censored at the date of their first event, at the date of last follow-up, or at the date of death. Data about recurrences were up-to-date for five years of follow-up.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY, USA). Baseline characteristics between subgroup with and without ECE were compared using Chi-squared test for categorical data and Mann Whitney U-test/ independent t-test for continuous data.

LR, RR, DM, DFS and OS for both subgroups were calculated with Kaplan-Meier curves and compared with the log-rank test. Prognostic factors of DFS and OS were examined using univariable and multivariable Cox proportional hazards regression, to estimate crude and adjusted Hazard Ratios (HR's) and corresponding 95% confidence intervals. P-values (two-sided) ≤ 0.05 were considered statistically significant.

Results

A total of 3.502 patients with clinically T1-2N0 breast cancer and 1-3 positive SLN(s) who underwent a completion ALND were included. Of these, information on ECE was available for 2.111 patients (60.3%), consisting of 741 patients with ECE (35.1%) and 1.370 without ECE (64.9%) (Figure 1). Patient and tumor characteristics of patients with and without ECE were compared (Table 1). Compared to patients without ECE, patients with ECE had more

often a macrometastasis in the SLN (63.4% vs. 53.2%, p <0.001), ≥4 additional lymph node metastases at completion ALND (15.7 vs. 5.8, p <0.001) and received more often hormone therapy in case of estrogen receptor positive (93.9% vs. 89.8%, p <0.001). Presence of ECE was a predictor of ≥4 additional lymph node metastases in the ALND (OR 2.8 95%CI 1.936 - 4.270, p <0.001) (Table 2). Other predictors of ≥4 additional lymph node metastases in the ALND were clinical tumor size (OR 1.652 95% CI 1.119 - 2.438, p = 0.012) and SLN size (macro vs. micrometastases) (OR 3.262 95%CI 1.611 - 6.605, p = 0.001).

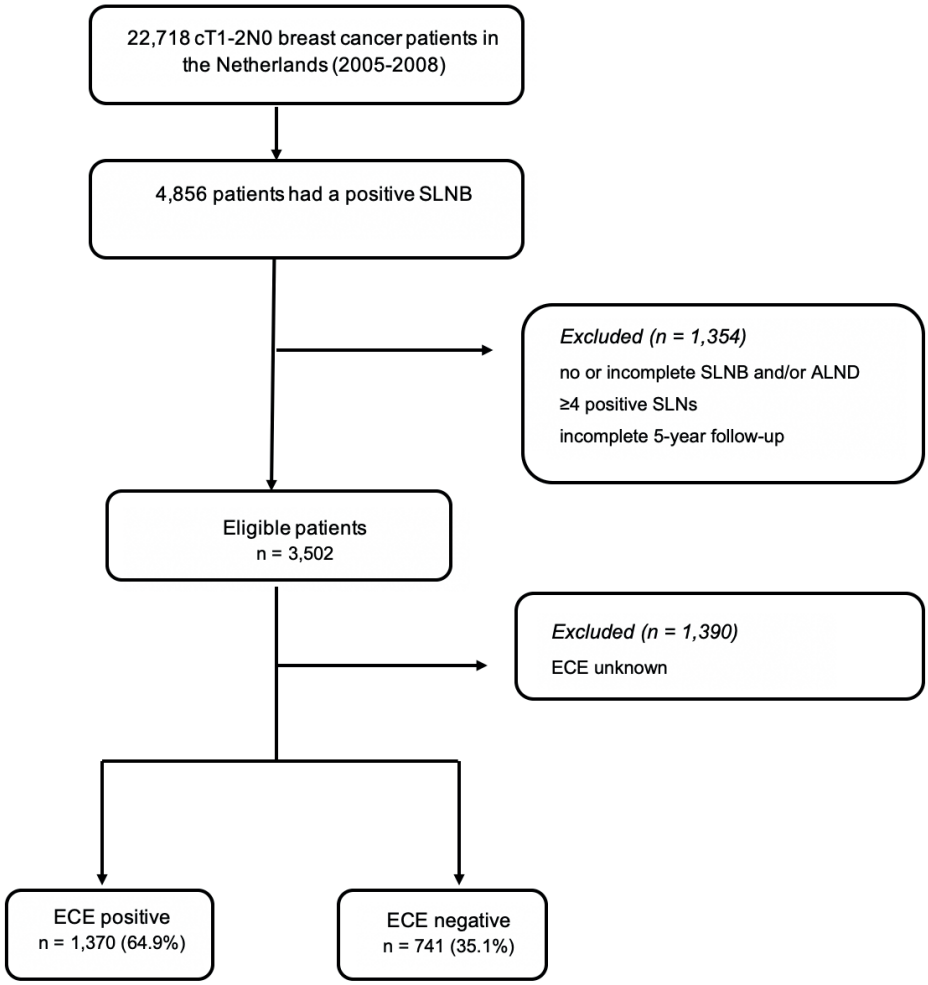


Figure 1. Flowchart included patients

cT clinical tumor stage, n = number of cases, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, ECE extracapsular extension

Table 1. Patient demographics and tumor characteristics (n = 2.111)

Characteristic	ECE negative n = 1.370	ECE positive n = 741	p-value
Age, years			
mean	56	57	0.073
range	24-91	25 - 88	
Tumor type, n (%)			
invasive carcinoma of NST	1.034 (75.5)	591 (79.8)	0.130
lobular	173(12.6)	78 (10.5)	
mixed or other	90 (6.6)	44 (5.9)	
unknown	73 (5.3)	28 (3.8)	
Grade (Bloom-Richardson), n (%)			
I	276 (20.1)	179 (24.2)	0.053
II	630 (46.0)	341 (46.0)	
III	417 (30.5)	198 (26.7)	
unknown	47 (3.4)	23 (3.1)	
cT-stage, n (%)			
cT1	924 (67.4)	490 (66.1)	0.539
cT2	446 (32.6)	251 (33.9)	
pT-stage, n (%)			
pT1	759 (55.4)	355 (47.9)	0.011
pT2	576 (42.0)	370 (49.9)	
pT3	30 (2.2)	12 (1.6)	
pT4	2 (0.2)	2 (0.3)	
unknown	3 (0.2)	2 (0.3)	
Subtype, n (%)			
ER+PR+Her2-	789 (57.6)	484 (65.3)	<0.001
ER+PR-Her2-	143 (10.4)	77 (10.4)	
ER+Her2+	109 (7.9)	59 (8.0)	
ER-Her2+	68 (5.0)	18 (2.4)	
triple negative	120 (8.8)	34 (4.6)	
unknown	141 (10.3)	69 (9.3)	
Surgical treatment, n(%)			
mastectomy	594 (43.4)	338 (45.6)	0.319
lumpectomy	776 (56.6)	403 (54.4)	
Outcome SLN, n(%)			
micrometastasis	343 (25.0)	50 (6.8)	**<0.001**
macrometastasis	729 (53.2)	470 (63.4)	
unknown	298 (21.8)	221 (29.8)	
Number of positive additional lymph nodes in ALND, n (%)		625 (84.3)	**<0.001**
1-3	1.290 (94.2)	116 (15.7)	
≥4	80 (5.8)		
Radiotherapy in case of lumpectomy, n (%)			
yes	769 (99.1)	397 (98.8)	0.403
no	7 (0.9)	6 (0.2)	
Chemotherapy, n (%)			
yes	865 (63.1)	483 (65.2)	0.351
no	505 (36.9)	258 (34.8)	
Hormone therapy in case of ER+, n (%)			
yes	1.033 (89.8)	630 (93.9)	<0.001
no	117 (10.2)	41 (6.1)	
Trastuzumab and chemotherapy in case of HER2+, n (%)			
yes	134 (89.3)	54 (87.1)	0.125
no	16 (10.7)	8 (12.9)	

N number of cases, NST invasive carcinoma of no special type, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, cT clinical tumor stage, pT pathological tumor stage.

Table 2. Logistic Regression Analysis ≥4 positive lymph nodes in the ALND

	OR (95%CI)	P-value
ECE vs no ECE	2.875 [1.936 – 4.270]	<0.001
Age (per year increment)	1.003 [0.987 – 1.018]	0.755
Grade III vs I-II	1.005 [0.648 – 1.559]	0.982
cT-stage cT2 vs cT1	1.652 [1.119 – 2.438]	0.012
SLN size macro vs micrometastasis	3.262 [1.611 – 6.605]	0.001
Triple negative subtype yes vs no	1.552 [0.785 – 3.071]	0.207

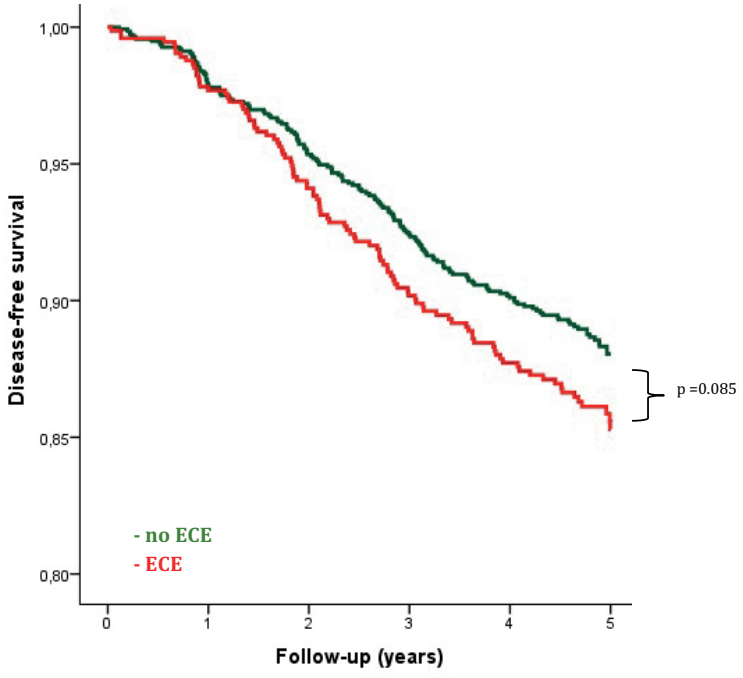
ECE extracapsular extension, cT clinical tumor stage, SLN sentinel lymph node, OR odds ratio, CI confidence interval

Recurrence

Locoregional recurrence (LRR) occurred rarely within five years after diagnosis.
Only 2.2% (47/2.111) of the patients was diagnosed with LR as a first event and RR occurred in only 1.0% (22/2.111) of the patients. Subgroup analyses showed that LR occurred in 1.6% (12/741) of the patients with ECE and in 2.6% (35/1.370) of the patients without ECE (p = 0.196). RR occurred in 0.9% (7/741) and in 1.1% (15/1.370) (p = 0.788), respectively. Distant metastasis was diagnosed in 9.0% (190/2.111) of the patients, whereof 12.2% (83/741) in patients with ECE and 7.8% (107/1.370) of the patients without ECE (p = 0.008).

Disease-free survival

Within five years after diagnosis, 12.1% (255/2.111) of the patients was diagnosed with LR, RR, DM or were deceased. This resulted in a five-year DFS of 87.9% (1.856 of 2.111) for all patients. Subgroup analyses showed a 5-year DFS of 86.4% (640/741) with ECE and 88.8% (1,216/1.370) in patients without ECE (p = 0.085) (Figure 2).
In multivariable Cox regression analyses, the effect of ECE on DFS was not significant (HR 1.302, 95%CI 0.930 – 1.823, p = 0.125). Grading (HR 1.998, 95%CI 1.439 – 2.772, p <0.001), clinical tumor stage (HR 2.155, 95%CI 1.572 – 2.953, p <0.001) and ≥4 additional lymph node metastases in the ALND (HR 1.983, 95%CI 1.277 – 3.078, p = 0.002) were identified as significant predictors for decreased DFS and endocrine therapy for increased DFS (HR 0.473, 95%CI 0.305 – 0.732, p = 0.001) (Table 3).



	0	1	2	3	4	5
no ECE	1,370	1,353	1,307	1,268	1,238	1,216
ECE	741	712	698	670	653	640

Figure 2. Kaplan Meier curve of five-year DFS

Table 3. Uni- and multivariable analysis for predictors of five-year DFS

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**
ECE vs no ECE	1.246 [0.970 – 1.602]	0.086	1.302 [0.930 – 1.823]	0.125
Age (per year increment)	1.00 [0.989 – 1.010]	0.959	-	-
Type lobular vs invasive carcinoma NST	1.131 [0.785 – 1.628]	0.509	-	-
Grade III vs I-II	3.341 [2.595 – 4.302]	<0.001	1.998 [1.439 – 2.772]	<0.001
Triple negative subtype yes vs no	5.001 [3.772 – 6.721]	<0.001	1.684 [0.998 – 2.843]	0.051
cT-stage cT2 vs cT1	2.068 [1.618 – 2.644]	<0.001	2.155 [1.572 – 2.953]	<0.001
SLN size macro vs micrometastasis	1.418 [0.981 – 2.050]	0.063	1.337 [0.889 – 2.010]	0.163
ALND ≥4 vs 1-3	2.446 [1.782 – 3.357]	<0.001	1.983 [1.277 – 3.078]	0.002
Radiation therapy Yes vs No	1.271 [1.124 – 1.437]	<0.001	1.007 [0.710 – 1.428]	0.969
Chemotherapy Yes vs No	1.110 [0.854 – 1.443]	0.434	-	-
Endocrine therapy Yes vs No	1.596 [1.396 – 1.824]	<0.001	0.473 [0.305 – 0.732]	0.001
Targeted therapy Yes vs No	0.932 [0.781 – 1.112]	0.434	-	-

ECE extracapsular extension, NST invasive carcinoma of no special type, cT clinical tumor stage, SLN sentinel lymph node, ALND axillary lymph node dissection

Overall survival

After ten years of follow-up, 81.6% (1.722/2.111) of all patients were alive. This concerned 78.9% (585/741) of patients with ECE and 83.0% (1.137/1.370) without ECE (p = 0.018). In multivariable cox regression analyses, the effect of ECE on OS was not statistically significant (HR 1.168, 95%CI 0.881 - 1.548, p = 0.281). Significant predictors for decreased OS were age (HR 1.047, 95%CI 1.031 – 1.063, p < 0.001), grading (HR 2.158, 95%CI 1.616 – 2.881, p < 0.001), triple negative breast tumors (HR 2.564, 95%CI 1.195 – 5.499, p =0.016), clinical tumor size (HR 1.594, 95%CI 1.204 -2.110, p < 0.001), and ≥4 positive lymph node metastasis in the ALND (HR 1.992, 95%CI 1.368 – 2.901, p < 0.001) (Table 4).

Table 4. Uni- and multivariable analysis for predictors of ten-year OS

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**
ECE vs no ECE	1.277 [1.0443 – 1.564]	0.018	1.168 [0.881 – 1.548]	0.281
Age (per year increment)	1.047 [1.038 – 1.056]	<0.001	1.047 [1.031 – 1.063]	<0.001
Type lobular vs ductal	1.009 [0.740 – 1.377]	0.953	-	-
Grade III vs I-II	2.235 [1.822 – 2.742]	<0.001	2.158 [1.616 – 2.881]	<0.001
Triple negative subtype yes vs no	3.646 [2.790 – 4.765]	<0.001	2.564 [1.195 – 5.499]	0.016
cT-stage cT2 vs cT1	1.656 [1.355 – 2.024]	<0.001	1.594 [1.204 – 2.110]	0.001
SLN size macro vs micrometastasis	1.306 [0.976 – 1.747]	0.072	1.263 [0.907 – 1.759]	0.167
ALND ≥4 vs 1-3	2.279 [1.752 – 2.966]	<0.001	1.992 [1.368 – 2.901]	<0.001
Radiation therapy Yes vs No	1.559 [1.280 – 1.898]	<0.001	0.772 [0.104 – 5.722]	0.800
Chemotherapy Yes vs No	0.533 [0.437 – 0.651]	<0.001	0.922 [0.613 – 1.387]	0.696
Endocrine therapy Yes vs No	1.354 [1.206 – 1.521]	<0.001	0.508 [0.220 – 1.170]	0.111
Targeted therapy Yes vs No	1.108 [0.936 – 1.311]	0.232	-	-

ECE extracapsular extension, NST invasive carcinoma of no special type, cT clinical tumor stage, SLN sentinel lymph node, ALND axillary lymph node dissection

Discussion

This large population-based study of more than 2.000 breast cancer patients showed that presence of ECE in the SLN is associated with the presence of ≥4 additional lymph node metastases in the ALND (15.7% vs. 5.8%, p <0.001), which is in agreement with several studies, which showed that presence of ECE was a predictor for the presence of non-SLN metastases (2, 5, 7, 19). Previous studies also investigated that presence of ECE was significantly associated with a higher incidence of N2 disease (20 - 47.6%) compared to the group without ECE (2.7 - 9.2%) (6, 12, 20). Gooch et al. also showed that size of ECE was important, where > 2mm had significantly more often N2 disease compared to ECE ≤2 mm (33% vs. 9%, p < 0.001) (12).

The association of ECE to an increased nodal tumor burden is however, less important than its potential relation to disease recurrence and survival. The present study showed that LR (2.2%) or RR (1.0%) rarely occurred during the first five years following diagnosis, and did not significantly differ between the group with ECE and without ECE (1.6% vs. 2.6%, p = 0.196 and 0.9% vs. 1.1%, p = 0.788), respectively. DM was more often diagnosed in patients with ECE compared to patients without ECE (12.2% vs. 7.8%, p = 0.008). These results are consistent with Choi et al. that showed presence or absence of ECE did not influence LR and RR (5.3% vs. 3.4% and 0% vs. 3.4% respectively). Distant metastasis did occur more often in patients with ECE, but not statistically significant (10.5% vs. 2.7%, p = 0.19) (20). In contrast, Neri et al. showed that presence of ECE was significantly related to an increased risk of both RR (13.4% vs. 6.6%; p = 0.037) and distant (43% vs. 16.2%; p < 0.001) recurrence (21).

The five-year DFS rate in this study was 86.4% in the group with ECE compared to 88.8% in the group without ECE (p = 0.085) and the 10-year OS rate was 78.6% and 83.0%, retrospectively, respectively (p = 0.018). Cox regression analysis showed that ECE is not an independent prognostic factor for both five-year DFS and OS. Other studies investigating the effect of ECE on DFS and OS are inconsistent. Neri et al. demonstrated that presence of ECE resulted in a negative prognostic effect on DFS (HR = 2.34, 95%CI 1.64 – 3.32, p < 0.001) and OS (HR = 2.98, 95%CI 1.89 – 4.66, p < 0.001) (21). Gruber et al. demonstrated that ECE was associated with worse OS and DFS, but did not remain significant when the number of positive nodes was added in the multivariable analyses (22). Despite the increased nodal tumor burden, results regarding survival remain contradictory.

The strength of the present study is the large nationwide multicenter cohort of 2.111 *c*T1-2N0 breast cancer patients with 1-3 positive SLN(s). This is one of the first studies reporting both the association between ECE and ≥4 additional lymph node metastases and its effect on recurrence risk and DFS and OS. A limitation of this study is its retrospective design, which may have caused many incomplete pathology reports (39.1%). A possible explanation is the lack of a standard definition and method of reporting the presence or absence of ECE. The incidence of ECE was 35.1%, within the range of 24-57% of previous studies. As a result, selection bias could have occurred since ECE is probably more often registered in the pathology report if present and not registered if not present, resulting in incomplete pathology reports. Therefore, it is likely that the incidence of ECE in this study population is overestimated, compared to the incidence in current (Dutch) breast cancer population. Furthermore, axillary ultrasound was not part of standard preoperative nodal staging then. This could have contributed to an overestimation of the presence of nodal tumor burden in the ALND, since a negative axillary ultrasound excludes the presence of advanced axillary disease (pN2-pN3), and potentially could also have led to an overestimation of ECE (23).

A second limitation of this study is that we were not able to distinction between ECE ≤2mm or >2mm, as this not used in the Dutch clinical setting and therefore not available. However, results of Choi et al. already showed that results of both groups were comparable (20). Furthermore, there is not yet a consensus regarding the definition of ECE. Finally, lymphovascular invasion (LVI) and multifocality of the primary tumor are other known prognostic factors for non-SLN metastases and survival. These factors were not included in our multivariable analyses, due to a large number of missing data. Yajima et al. investigated the effect of ECE in combination with other clinicopathological factors (i.e. age, tumor type, grade and size, positive lymph nodes, lymphvascular invasion, ER, PR and Her2 status) and demonstrated that patients with a combination of ECE and vascular invasion decreased their DFS (24).

In conclusion, this study showed that ECE in the SLN is associated with the presence of ≥4 additional lymph node metastases. Despite the increased nodal tumor burden, *c*T1-2N0 breast cancer patients with a positive SLN treated with either BCT or mastectomy and an ALND, did not have an inferior prognosis in multivariable analysis, in terms of inferior five-year LR, RR, DFS and OS. Based on results, it seems justified to include patients with ECE in the ongoing trials in order to demonstrate if omitting axillary treatment is safe in this subgroup of patients.

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Appendix

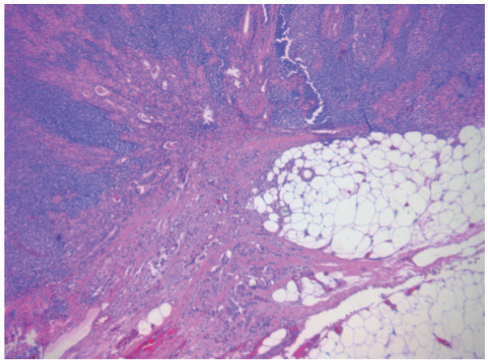


Figure 1A.

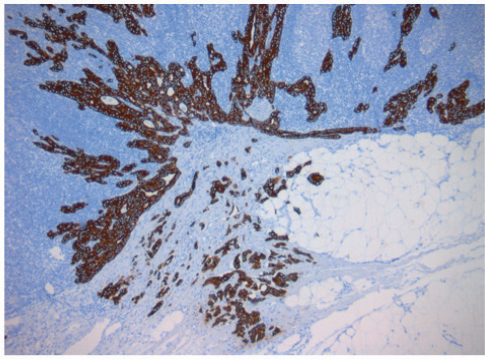


Figure 1B.

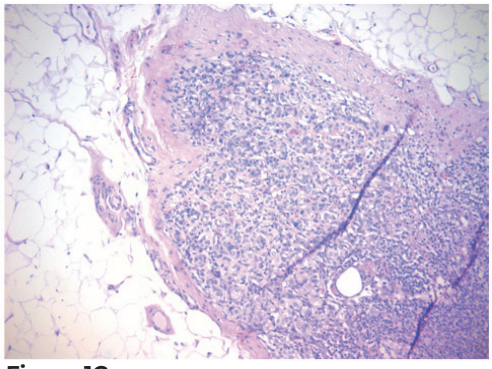


Figure 1C.

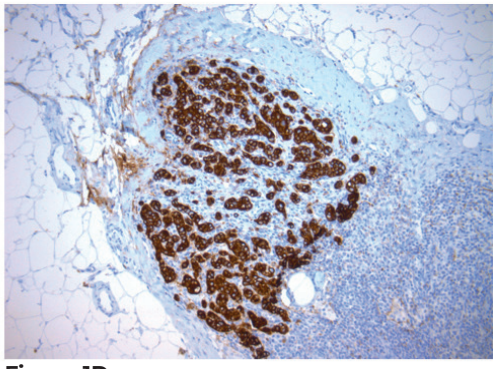


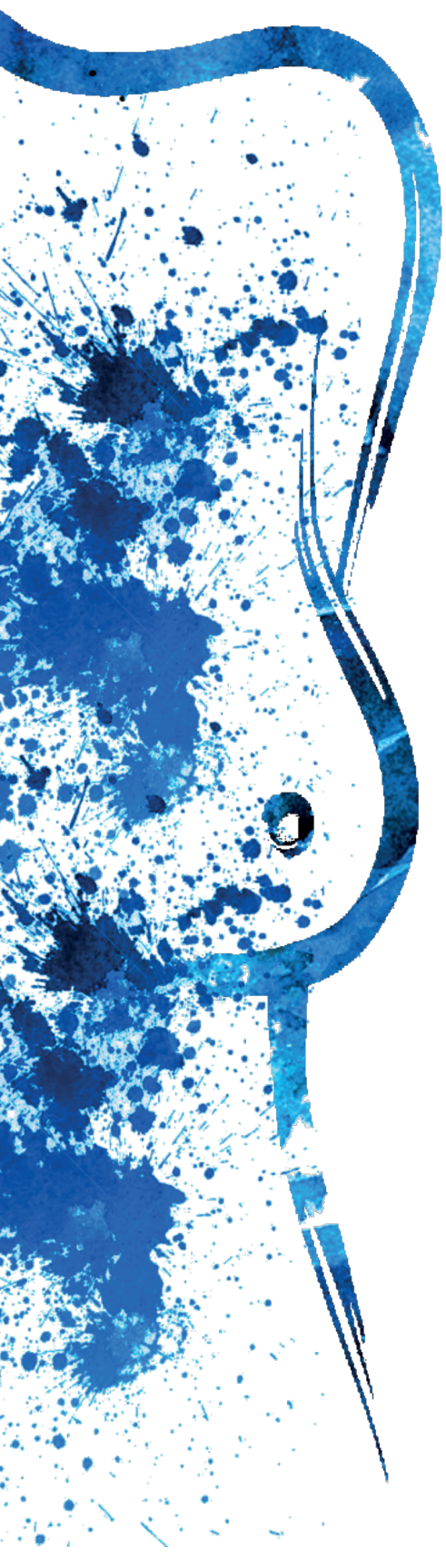
Figure 1D.

Figure 1. Extracapsular extension in sentinel lymph node

Figure 1A. SLN metastasis with extracapsular extension; hematoxylin and eosin stain (HE) marker
Figure 1B. SLN metastasis with extracapsular extension; pankeratin (epithelial) marker (CK MNF116).
Figure 1C. SLN metastasis without extracapsular extension; hematoxylin and eosin stain (HE) marker
Figure 1D. SLN metastasis without extracapsular extension; pankeratin (epithelial) marker (CK MNF116).

PART II

OMISSION OF THE SENTINEL LYMPH NODE BIOPSY



CHAPTER 4

CLINCALLY NODE NEGATIVE BREAST CANCER PATIENTS UNDERGOING BREAST CONSERVING THERAPY: SENTINEL LYMPH NODE PROCEDURE VERSUS FOLLOW-UP: A DUTCH RANDOMIZED CONTROLLED MULTICENTRE TRIAL (BOOG 2013-08)

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Abstract

Background Studies showed that axillary lymph node dissection can be safely omitted in presence of positive sentinel lymph node(s) in breast cancer patients treated with breast conserving therapy. Since the outcome of the sentinel lymph node biopsy has no clinical consequence, the value of the procedure itself is being questioned. The aim of the BOOG 2013-08 trial is to investigate whether the sentinel lymph node biopsy can be safely omitted in clinically node negative breast cancer patients treated with breast conserving therapy.

Methods The BOOG 2013-08 is a Dutch prospective non-inferiority randomized multicentre trial. Women with pathologically confirmed clinically node negative T1-2 invasive breast cancer undergoing breast conserving therapy will be randomized for sentinel lymph node biopsy versus no sentinel lymph node biopsy. Endpoints include regional recurrence after five (primary endpoint) and 10 years of follow-up, distant-disease free and overall survival, quality of life, morbidity and cost-effectiveness. Previous data indicate a 5-year regional recurrence free survival rate of 99% for the control arm and 96% for the study arm. In combination with a non-inferiority limit of 5% and probability of 0.8, this result in a sample size of 1.644 patients including a lost to follow-up rate of 10%. Primary and secondary endpoints will be reported after five and 10 years of follow-up.

Discussion If the sentinel lymph node biopsy can be safely omitted in clinically node negative breast cancer patients undergoing breast conserving therapy, this study will cost-effectively lead to a decreased axillary morbidity rate and thereby improved quality of life with non-inferior regional control, distant-disease free survival and overall survival.

Trial registration The BOOG 2013-08 study is registered in ClinicalTrials.gov since October 20, 2014, Identifier: NCT02271828.

Introduction

More than fifteen years ago, the sentinel lymph node biopsy (SLNB) was introduced in clinically node negative breast cancer patients to evaluate their lymph node status for diagnostic purposes. In case of a negative sentinel lymph node (SLN) an axillary lymph node dissection (ALND) was omitted. The SLN is negative in approximately 74% of patients in a general breast cancer population [1, 2]. Although SLNB is less invasive compared to ALND, short-term complications still occur in 25% of the patients. Most reported complications are axillary seroma, wound infections, hematoma, anaphylactic reaction, axillary paresthesia, and lymphedema, which is described in 8% of patients after a follow-up of only three years, resulting in significant reduction of quality of life (QoL) of breast cancer survivors [3-7].

Ever since the National Surgical Adjuvant Breast and Bowel Project (NSABP B-04) trial, the need for completion axillary treatment for clinically node negative patients has been questioned. This trial revealed that omitting ALND in clinically node negative patients did not affect disease-free survival (DFS) and overall survival (OS) [8]. Patients were randomized for mastectomy-only, mastectomy with ALND or mastectomy with axillary radiotherapy (RT). About 40% of the patients who underwent mastectomy-only had lymph node metastases that were not removed at the time of initial surgery. During follow-up, ipsilateral lymph nodes became clinically apparent in less than half of these patients (18.6%). Nevertheless, omitting ALND in clinically node negative patients did not affect DFS and OS, even after 25 years of follow-up and without adjuvant RT or systemic therapy.

The more recent American College of Surgeons Oncology Group (ACOSOG) Z0011 and International Breast Cancer Study Group (IBCSG) 23-01 trials investigated whether completion ALND can be safely omitted in patients with a metastasis in the SLN. The ACOSOG Z0011 trial included patients with one to two macrometastatic SLN(s) who were treated with breast conserving therapy (BCT) [9]. The IBCSG 23-01 trial only included patients with a micrometastasis in the SLN, but gave no restriction on type of breast surgery [10]. Most patients were treated with adjuvant systemic treatment (both 97%). Patients in these trials were randomized to completion ALND or watchful waiting. Additional lymph node metastases beyond the SLN were detected in 27% (ACOSOG Z0011) and 11% (IBCSG 23-01) in the ALND groups [9, 10]. Despite the fact that nodal metastases remained in situ in a considerable percentage of patients in the 'watchful waiting' groups, omitting completion ALND did not result in inferior regional recurrence (RR) rates, DFS and OS after five-years of follow-up. These studies indicated that completion ALND can be safely omitted in presence of positive SLN(s) in patients treated with BCT and adjuvant systemic treatment. Since the outcome of the SLNB has no clinical consequence, the value of the SLNB itself is being questioned.

Clinically node negative status in the NSABP B-04, ACOSOG Z0011 and IBCSG 23-01 trials was based on negative physical examination of the axilla. Preoperative nodal staging with physical examination has a low accuracy, with a sensitivity of only 32% [11-14]. In the Netherlands, axillary ultrasound is part of standard preoperative axillary work-up. The sensitivity of axillary ultrasound (in combination with tissue sampling where deemed necessary) is approximately 80% [15]. Furthermore, a negative axillary ultrasound excludes the presence of four or more lymph node metastases, with a negative predictive value of 93-96% in the general breast cancer population [16-18]. Therefore, axillary ultrasound improves preoperative selection of node negative patients, as it selects patients with a more favourable tumor load and confidently excludes advanced nodal disease.

Several factors besides surgery have proven to decrease RR rates. For instance, it is assumed that biology plays an important role in dormancy of nodal metastases. Less than half of the patients with occult nodal metastases in the NSABP B-04 trial, developed clinically detectable lymph nodes during follow-up, none of these patients received adjuvant systemic or RT [8]. Adjuvant systemic therapy is known to decrease RR rates [19]. Primary systemic therapy can eradicate lymph node metastases with a reported pathologic complete response rates of 20 - 40% [20-23].

Lack of knowledge on the pathological lymph node status is nowadays hardly influencing systemic therapy indication [24]. Low RR rates in the ACOSOG Z0011 (and IBCSG 23-01) trial might be due to whole breast irradiation (WBI) following lumpectomy [25-28]. RT of the breast may contribute to the elimination of (occult) lymph node metastases by including part of the axilla [25]. A recent study has shown that, even with contemporary 3D radiation techniques, the SLN receives an elective radiation dose in 76% of patients [29]. Biology, adjuvant systemic and RT most likely diminish the risk that possible lymph node metastases left in situ develop into clinically detectable lymph nodes.

This randomized controlled BOOG 2013-08 trial proposes to demonstrate that the SLNB can be safely omitted in breast cancer patients with a clinically node negative T1-2 status undergoing BCT. This trial aims to decrease the number of breast cancer patients receiving an invasive axillary procedure, to decrease the axillary morbidity rate, thereby improving QoL and reducing the costs of SLNB without affecting regional control and survival.

Main study objectives

Primary objective of this study is to investigate whether watchful waiting (i.e. no SLNB) is not inferior in terms of five and 10-year RR rate to the current axillary staging regimen in breast cancer patients with a clinically node negative T1-2 status undergoing BCT. Secondary objectives are distant-DFS, OS, local recurrence (LR) rate, contralateral breast

cancer, number of delayed axillary treatment, adjuvant RT, QoL, axillary morbidity rate, and cost-effectiveness after five- and 10-years of follow-up.

Methods

Study design

The BOOG 2013-08 is a Dutch prospective non-inferiority randomized controlled multicentre trial. Women with pathologically confirmed unilateral clinically node negative T1-2 invasive breast cancer undergoing BCT are randomized to SLNB or watchful waiting (i.e. no SLNB). Primary and secondary endpoints will be reported after five and 10 years of follow-up. The BOOG 2013-08 is a multicentre trial and will be performed in 35 participating centres (Table 1). This study design was based on the BOOG 2013-07 trial of the same research group [30].

Study population

Women ≥18 years with pathologically confirmed clinically node negative T1-2 invasive breast cancer, treated with BCT (lumpectomy and WBI) are eligible for inclusion. Clinically node negative is defined as no signs of axillary lymph node metastases, consisting of a negative physical examination of the axilla and preoperative axillary ultrasound (or negative cyto-/histopathology in case of a suspicious axillary lymph node) [30].
Exclusion criteria are: metastatic disease; bilateral breast cancer; history of invasive breast cancer; previous surgical treatment or RT of the ipsilateral axilla (except surgery for superficially skin lesions, such as naevi or hidradenitis suppurativa); other prior malignancies, except successfully treated malignancies >5 years before inclusion, successfully treated basal cell and squamous cell skin cancer, and carcinoma in situ of the ipsilateral, contralateral breast or cervix; and pregnancy or lactation [30]. Primary systemic therapy and breast reconstructions are no exclusion criteria.

Axillary ultrasound

In the Netherlands, axillary ultrasound is standard care for preoperative nodal staging of breast cancer patients [30]. The following criteria are used to identify axillary lymph node metastases during an axillary ultrasound: cortical thickening, long to short axis ratio of <2 (i.e. round), effacement or replacement of the fatty hilum, and/or nonhilar blood flow [30]. If cortical thickening is >2.3 mm, fine-needle aspiration biopsy is performed [31]. Further, the radiologist can make a subjective assessment of cortical thickening during real-time imaging [16, 32, 33]. When suspicious lymph nodes are observed during an axillary ultrasound, fine-needle aspiration cytology or core needle biopsy is recommended. If more than one suspicious lymph node is present, the most suspicious lymph node is sampled [30].

Breast conserving therapy

BCT is defined as lumpectomy followed by WBI. The primary tumor size is determined during pathological assessment. Immunohistochemical (IHC) staining is used to determine the hormone receptor status and is considered positive if ≥10% of the cells stain positive. HER2neu status is determined by IHC, or in case of 2+ by Chromogenic In Situ Hybridization (CISH) or Fluorescence In Situ Hybridization (FISH) [30].
World Health Organization is used to define the histological tumor type. The modified Bloom-Richardson grading system is used to assess histological tumor grading. Multifocality is defined as foci or carcinoma separate from the primary breast tumor. Lymphovascular invasion is defined as ≥1 tumor cells in a lymphatic or vascular structure [30].

Sentinel lymph node biopsy

The SLN procedure is performed using technetium-99m Nanocolloid as a radioactive tracer and blue dye for lymphatic mapping. Both are injected into breast parenchymal tissue surrounding the tumor, biopsy cavity or periareolar. The SLN is identified using the following triple technique: lymphoscintigraphy, intraoperative use of the gamma probe, and intraoperative detection of the blue lymphatic vessels. After removal of the SLN(s), palpation of the axilla is performed to identify and remove additional suspicious (non-) SLN(s) [30].

Each SLN is examined at three histological levels (500-µm intervals) as a minimal requirement for pathological assessment. Two parallel sections on each level are performed, one for haematoxylin and eosin (H&E) staining and one for IHC staining [30]. When H&E staining is negative IHC staining is done. Lymph nodes marked by the surgeon as non-SLNs are also examined with H&E and if negative with cytokeratin IHC staining. The diameter of each metastasis and the presence of extranodal growth must be determined. Isolated tumor cells (<0.2mm) are considered as SLN negative [30].

Radiation therapy

Dose and fractionation for whole breast radiation

A fractionation scheme equivalent to 25 x 2 Gray (Gy), 5 fractions per week is applied. Most Dutch RT centers use a scheme of 15 -16 x 2.67 Gy, 5 fractions per week. In case of focal irradical resection, a higher boost dose is recommended (equivalent to 10-13 x 2 Gy) [30]. Partial breast irradiation is not allowed.

Delineation of whole breast radiation

The European Society for Radiotherapy and Oncology (ESTRO) guidelines of Offersen et al. are used to perform delineation of target volumes and organs at risk [34]. Delineation of tumor bed, including a clinical target volume (CTV) and a planning target volume (PTV) is obligatory. In addition, delineation of axillary nodal regions, axilla level 1, 2, Rotter nodes and 3 is obligatory, even when there is no indication for axillary radiation. In case of left-sided breast cancer, delineation of the heart and lungs is obligatory [30].

Radiation technique and dose distribution

The dose in the target volume (whole breast, with or without axillary and periclavicular nodes irradiation) must be between 95%-107% of the prescribed dose [30]. The Central Lung Distance must be < 3 cm (in case of tangential fields) and mean lung dose should be < 7.5 Gy. The Maximum Heart Distance (in case of tangential fields) must be < 1 cm, and the heart volume receiving > 10 Gy should be < 15%. If lung or heart constraints cannot be met, some underdose in the breast can be accepted to reach the constraints, provided that the PTV of the tumor bed is adequately covered. Breath holding techniques to reduce heart dose are highly recommended for left sided breast cancer patients. For evaluation purposes, the minimum, maximum and mean dose of the axilla level 1, 2, Rotter nodes, and 3 must be recorded [30].

Consent and randomization

Eligible patients will be informed about the study aim, randomization procedure, consequences of participating (i.e. possible adverse events), and their rights and responsibilities by the attending surgeon. Written informed consent must be obtained and randomization will be performed preoperatively. Patients will be randomized between SLNB (control arm) and no SLNB (study arm).

Patients will be stratified by: clinical tumor size (<3 cm vs. ≥3 cm), grading (grade I-II vs. III), oestrogen receptor status (positive vs. negative), HER2neu status (positive vs. negative), age (≤50, 50≤75, >75 years), primary systemic therapy (yes vs. no) and participating centre.

Systemic therapy

According to the Dutch breast cancer guideline and multidisciplinary approach, indication for systemic therapy is determined for each individual patient [30, 31]. Adjuvant! Online can be used to estimate the 10-years breast cancer specific survival and the risk reduction by systemic therapy, with or without knowledge of the pathological nodal status. Validated gene expression profiling can be used as an addition to clinicopathologic characteristics, in case of doubt about the indication for adjuvant systemic therapy based on the traditional prognostic factors. Primary systemic therapy is allowed, if the patient has a clinically node negative T1-2 status that is amenable to BCT surgery pre-systemic therapy.

Follow-up

The first five years of follow-up consists of outpatient clinic visits once yearly, including a physical examination of the axilla and a full-field digital mammography (FFDM). Year six to ten of follow-up, consists of a FFDM annually in patients aged ≤60 years or once every two years in patients aged >60 years [30].

Additional diagnostic imaging is only performed on indication. Axillary ultrasound is performed, in case of a clinical suspicion of axillary lymph node metastases. Staging for distant metastatic disease is performed, if an axillary lymph node metastasis is confirmed (cyto-/histopathology) or in case of a clinical suspicion of distant metastatic disease [30].

Quality of life

A Dutch version of two validated QoL questionnaires of the European Organization for the Research and Treatment of Cancer (EORTC QLQ-C30 and QLQ-BR23) are used to assess the QoL of breast cancer patients. To assess the subjective morbidity the validated Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF) is used. A validated short version of the Spielberger State-*Trait* Anxiety Inventory (STAI-trait) and Neuroticism Extraversion Openness Five Factor Inventory (NEO-FFI) is used to measure if anxiety and personality traits influences the outcome of QoL [35-38]. The combination of these questionnaires will provide information on the general and breast cancer specific QoL, subjective morbidity, and anxiety and personality traits that might influence the outcome of QoL [39]. The first QoL questionnaires are provided pre-randomisation for baseline measurement, and the following are provided post-randomization at six months, and at one, two, three, five and 10 years. Patients are eligible for evaluation when at least the pre-randomisation questionnaire and the subsequent questionnaire are completed [30].

Adverse events

Any undesirable experience during the study, whether or not considered related to the protocol treatment is defined as an adverse events (AEs), including seroma, postoperative haemorrhage, wound complication/infection, lymphedema of the arm or chest wall, neuralgia, paraesthesia, decreased arm or shoulder motion, muscle weakness of the arm or shoulder, and pain in the arm or shoulder. NCI/CTCAE 4.0 grading criteria is used to grade the severity of the AE into mild, moderate, or severe, in combination with the degree of limitation in activities of daily living [30].

An untoward medical occurrence or effect related to protocol treatment that results in death, hospitalisation or prolongation of existing inpatients hospitalisation, or surgery is defined as a serious adverse event (SAE). Protocol treatment is defined as BCT of the primary tumor, WBI, SLNB or completion axillary treatment. Any other operation or adjuvant treatment is not considered protocol treatment [30].

The local investigator of the participating centre is responsible for reporting the SAE to the central data centre within 24 hours. The principal investigators of the study are responsible for SAE assessment and reporting to the accredited medical ethics committee within 15 days. For fatal or life threatening cases, the term is maximal seven days for a preliminary report with another eight days to completion the report. All SAEs 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 [30].

Statistics

Endpoints

Primary endpoint of this study is RR rate after five and 10-years of follow-up. Secondary endpoints are regional recurrence free survival (RRFS), number of delayed axillary treatment, distant-DFS, OS, LR rate, other-RR rate, contralateral breast cancer rate, diagnosis of recurrence outside the axillary region, percentage difference in the administration of postoperative RT, axillary morbidity rate, QoL and cost-effectiveness after 5- and 10-years of follow-up. RR, other-RR, LR and distant recurrence are defined according the Maastricht Delphi Consensus on Event Definition by Moossdorff et al [40, 41]. Pathological confirmation of a RR is mandatory. All suspected lesions for recurrence on imaging, which are not accessible for histology or cytology, are presented to the Data Safety Monitoring Board (DSMB) for an independent review.

Time to event endpoints are defined as the time interval between the date of randomization and the date of first suspicion of the predefined recurrence, or the date of death, whichever comes first, measured in days. Patients in whom recurrence is not observed and are still alive are censored at the date of last follow-up. Death from breast cancer and its treatment, death from a second primary invasive non-breast cancer, and death from other- or an unknown cause are recorded [30].

Administration of (neo)adjuvant systemic therapy is registered and the percentage difference between both study arms is recorded. Axillary morbidity rate is assessed using a validated questionnaire and by predefined AE that are recorded by the treating physician. QoL is assessed using validated questionnaires. Cost-effectiveness is assessed using the EQ-5D health questionnaire [30].

Sample size

Previous data indicate a five year regional recurrence free survival rate of 99% for the control arm and 96% for the study arm. The expected regional recurrence free survival rate and non-inferiority limit of 5% (delta) with a probability of 0.8, result in a sample size of 747 per arm. When taking in account a lost to follow-up rate of 10%, 1.644 patients need to be randomized. An annual accrual of 856 patients can be achieved, when taking into consideration the incidence of women diagnosed with invasive breast cancer in the Netherlands, the rate of patients that is primarily operated (when excluding patients treated systemic therapy only, or patients with metastatic disease and frail elderly), treatment with BCT, the 35 participating hospitals, and an expected accrual rate of 30%. Therefore, two years will suffice to include the 1.644 patients.

Data Safety Monitoring Board

An independent DSMB is established comprising an independent surgeon, medical oncologist, radiation oncologist and a statistician [30]. The independent DSMB will meet annually to discuss RR, other events, occurrence of AEs, and the percentage difference in administration of adjuvant systemic therapy between both study arms [30]. The DSMB can decide to alter the frequency of discussion. All suspected lesions for recurrence on imaging, which are not accessible for histology or cytology, are presented to the Data Safety Monitoring Board (DSMB) for an independent review. An interim analysis is performed by a statistician, results will be presented to the DSMB for further interpretation. The principal investigators will receive the DSMB recommendations. Should the principle investigators decide not to fully implement the DSMB recommendations, then the principle investigators have to send the recommendation to the accredited medical ethics committee, including a note to substantiate why (part of) this recommendation will not be followed [30].

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; in case of a percentage difference in the administration of adjuvant systemic therapy of more than 5% between both study arms; or disappointing accrual so that the total enrolment of 1.644 patients seems not feasible [30].

Final analysis

Per protocol and in the intention to treat population will be used to analyse the primary and secondary endpoints after five and 10 years of follow-up. To evaluate the null hypothesis, uncorrected chi-squared statistics will be used. In case of censored data, chi-square test will be based on the Kaplan-Meier estimator. 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, using stratification factors. All statistical tests are 1-sided and a p value of 0.05 or less is considered statistically significant [30].

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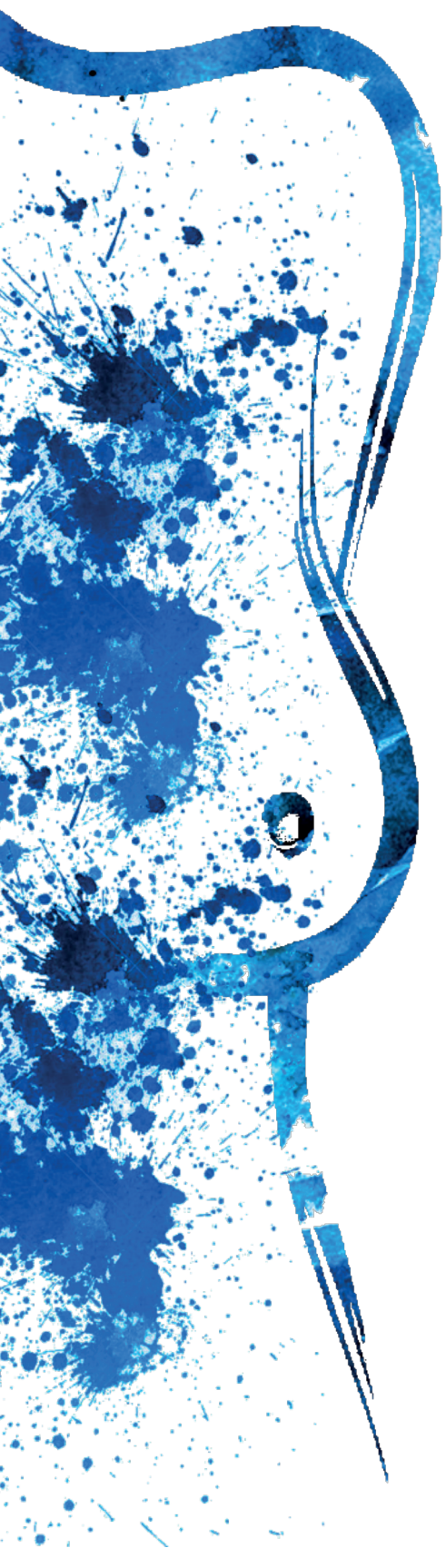

CHAPTER 5

DOES THE SUBTYPE OF BREAST CANCER AFFECT THE DIAGNOSTIC PERFORMANCE OF AXILLARY ULTRASOUND FOR NODAL STAGING IN BREAST CANCER PATIENTS?

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Abstract

Introduction Imaging findings can be affected by histopathological characteristics, such as breast cancer subtypes. The aim was to determine whether the diagnostic performance, in particular negative predictive value (NPV), of axillary US differs per subtype of breast cancer.

Methods All patients diagnosed between 2008-2016 in our hospital with primary invasive breast cancer and an axillary US prior to axillary surgery were included. Histopathology of axillary surgery specimens served as gold standard. The NPV, sensitivity, specificity, positive predictive value (PPV) and accuracy of the axillary US were determined for the overall population and for each subtype (ER+/PR+HER2-, HER2+, triple negative tumors). The Chi-square test was used to determine the difference in diagnostic performance parameters between the subtypes.

Results A total of 1,094 breast cancer patients were included. Of these, 35 were diagnosed with bilateral breast cancer, resulting in 1,129 cancer cases. Most common subtype was ER+/PR+HER2- in 858 cases (76.0%), followed by 150 cases of HER2+ tumors (13.3%) and 121 cases of triple negative tumors (10.7%). Sensitivity, specificity and accuracy of axillary US did not significantly differ between the subtypes. There was a significant difference for NPV between triple negative tumors and HER2+ tumors (90.3% vs. 80.2%, $p = 0.05$) and between HER2+ and ER/PR+HER2- tumors (80.2% vs. 87.2%, $p = 0.04$).

Conclusion There was no significant difference in the diagnostic performance of axillary US between the subtypes, except for NPV. This was highest in triple negative subtype and lowest in HER2+ tumors. This can be explained by the difference in prevalence of axillary lymph node metastases in our cohort.

Introduction

According to current European guidelines, physical examination followed by axillary ultrasound (US) is routinely performed to assess the preoperative axillary lymph node status in newly diagnosed breast cancer patients (1). In case of suspicious axillary lymph node(s), axillary US is combined with ultrasound-guided tissue sampling. Preoperative axillary US combined with ultrasound-guided tissue sampling has a pooled sensitivity of 50.0% (95%CI 43.0 - 57.0), specificity of 98.3% (95%CI 97.2 - 99.0), positive predictive value (PPV) of 100.0% (95%CI 100.0 - 100.0) and negative predictive value (NPV) of 67.4% (95%CI 60.0 - 76.2) (2, 3). These results imply that prior to surgery, only half of the patients with axillary lymph node metastases can be identified with axillary US. Otherwise, one in four patients with a negative axillary US appear to have axillary lymph node metastases after axillary surgery at pathology.

Imaging findings can be affected by histopathological characteristics, such as (invasive carcinoma of no special type (NST) versus invasive lobular carcinoma), tumor size, and size of axillary lymph node metastases (4, 5). For instance, preoperative breast magnetic resonance imaging (MRI) is more likely to detect axillary lymph node metastases in luminal B (35.6%) and HER2+ (34.6%) tumors compared to luminal A (17.3%) and basal like tumors (24.7%) ($p = 0.014$) (6). The influence of breast cancer subtypes on the diagnostic performance of axillary US is unknown. Therefore, the aim of this study was to determine whether the diagnostic performance (sensitivity, specificity, PPV, accuracy), and in particular the NPV of axillary US differs per subtype of breast cancer.

Material and methods

Data collection and study population

All patients diagnosed between 2008 and 2016 in our hospital with primary invasive breast cancer and an axillary US prior to surgery were included. Exclusion criteria were: ductal carcinoma *in situ*, recurrent breast cancer, patients without any surgical nodal staging (i.e. sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND)), and patients who were primarily treated with neoadjuvant systemic therapy. Data on patient and tumor characteristics, diagnostic work-up, surgical procedures and data on the histopathological outcome of the axillary lymph nodes were retrospectively collected.
Due to the retrospective design of this study, the necessity to acquire informed consent from the study subjects was waived by the local medical ethics committee. We wish to disclose that a subset of this cohort (n = 577) has been included in earlier publications on the accuracy of axillary ultrasound to predict final pN status in terms of the total number

of metastatic lymph nodes (7, 8). However, these studies did not separate the different subtypes of breast cancer.

Clinical and nodal status

Pre-operative nodal staging consisted of physical examination combined with an axillary US. The axillary US was performed by dedicated breast radiologists using an iU-22-xMATRIX ultrasound system in combination with a linear 2 to 17 MHz array transducer. Prior to 2011, an ATL-HDI5000 system was used (both Philips Healthcare, Best, the Netherlands). The following criteria were used to identify suspicious axillary lymph nodes: diffuse cortical thickening, focal cortical mass and/or effacement or replacement of the fatty hilum (9). Tissue sampling was performed in case of suspicious axillary lymph node(s) using 16-18 Gauge core needle biopsy. Fine needle aspiration cytology was performed when core needle biopsy was deemed technically challenging. In case multiple axillary lymph nodes were suspicious, only one of these lymph nodes was sampled. In patients with bilateral breast cancer, axillary lymph nodes in both cases were assessed. Clinical nodal status was defined as cN0 in case of no evidence for axillary lymph node metastases and cN+ in case of ≥ 1 axillary lymph node metastases.

Sentinel lymph node procedure

In clinically node negative patients an SLNB was performed. The SLNB procedure was performed using the following triple technique: lymphoscintigraphy (using 80MBq Technetium-99 m nanocolloid injected peri-areolar), blue dye to detect lymphatic vessels (Bleu Patente®; Guerbet Aaulnaysous-Bois, France) and intraoperative use of a gamma probe to detect radioactivity. In case of one or more SLN metastases, a completion ALND or radiotherapy of the axilla was performed. In clinically node positive patients, an ALND was performed directly.

Pathological assessment sentinel lymph node

Sentinel lymph node(s) were mostly lamellated and paraffin embedded for histological evaluation. Each sentinel lymph node was examined at three histological levels at 500-µm intervals and were stained with haematoxylin and eosin (H&E). If H&E staining was negative, cytokeratin immunohistochemical (IHC) staining was done. All ALND lymph nodes were paraffin embedded after at least 16h of fixation for histological evaluation.
Isolated tumor cells (clusters <0.2 mm and/or less than 200 cells) and micrometastasis (≥0.2 and/or or more than 200 cells, but ≤2.0mm) were considered as negative, and macrometastasis (>2.0mm) as positive. Pathological nodal staging was based on the number of malignant axillary lymph nodes: pN0 is none or micrometatasis, pN1 is 1-3 (at least one larger than 2.0 mm), pN2-3 ≥4 (at least one larger than 2.0mm) axillary lymph node metastases. In this study, non-axillary lymph node metastases are not taken into account.

Receptor status

Biomarker status was determined by immunohistochemical (IHC) staining and was considered positive if ≥10% of the cells stain positive, according to Dutch guidelines (10). HER2neu status was determined by IHC or FISH according to ASCO-CAP guidelines (11). Three subtypes of breast cancer were distinguished, namely ER/PR+HER2-, HER2+ and triple negative (ER/PR-HER2-).

Statistical analysis

Data were summarized as proportion with 95% confidence intervals or means with standard deviations (SD). For both the overall population and subtypes of breast cancer the sensitivity, specificity, PPV, NPV, and accuracy was determined. Accuracy was calculated as the sum of true positives and true negatives divided by total number of cases. The Chi square test was used to determine the difference in sensitivity, specificity, NPV, and accuracy between the breast cancer subtypes. Statistical analyses were performed using the statistical Package for the Social Sciences (version 22, IBM, Armonk, New York, USA). P-value ≤ 0.05 was considered statistically significant.

Results

Between 2008 and 2016, 1,094 patients were diagnosed with primary invasive breast cancer patients and underwent an axillary US. Of these, 35 were diagnosed with bilateral breast cancer, resulting in 1,129 examined axillae (Figure 1). Most common subtype was ER/PR+HER2- in 858 tumors (76.0%), followed by HER2+ in 150 tumors (13.3%) and triple negative tumors in 121 examined axillae (10.7%). Grade III was most common in triple negative tumors (80.2%) compared to HER2+ tumors (60.7%) and ER/PR+HER2- tumors (18.9%). Patient and tumor characteristics are summarized in Table 1.

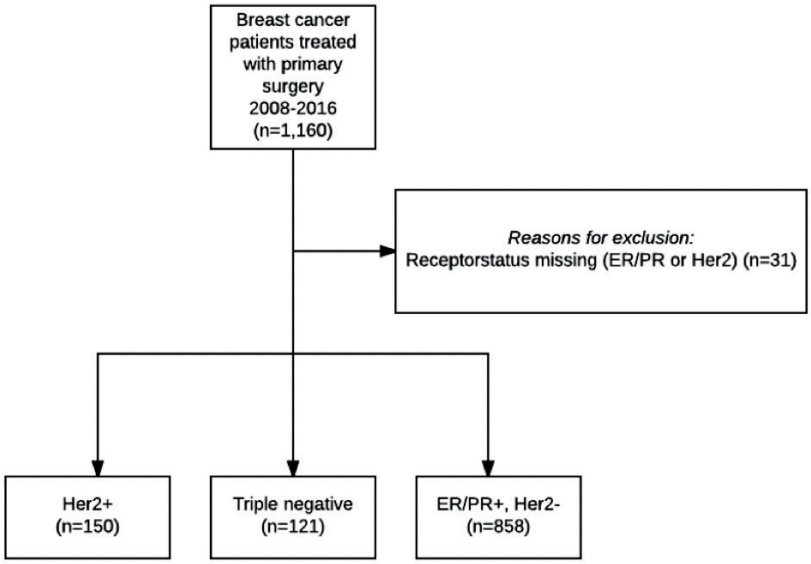

Figure 1. Flowchart patient inclusion

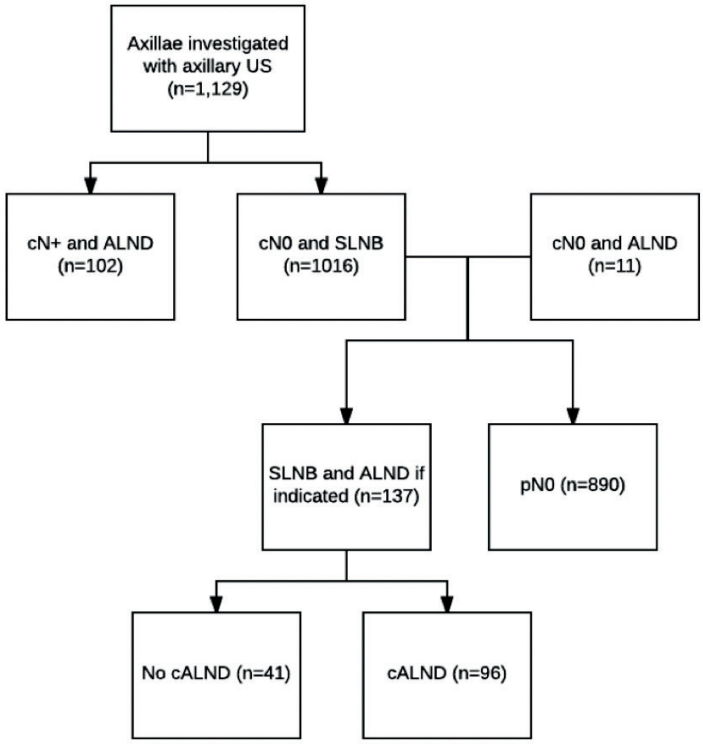

Figure 2. Flowchart of axillary nodal staging

N number of cases, US ultrasound, cN+ positive clinical nodal stage, cN0 negative clinical nodal stage, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, pN0 negative pathological nodal stage, cALND completion axillary lymph node dissection.

Table 1. Patient and tumor characteristics

Characteristic	Total	ER/PR+HER2-	HER2+	Triple negative
Number of cases evaluated, n	1,129	858	150	121
Mean age (y) (range)	61 (21-90)	62 (31-90)	59 (21-84)	60 (26-86)
Mean cT-size, mm (range)	22 (1-100)	21 (2-100)	28 (3-100)	24 (0-78)
Uni-/Multifocal tumors, n (%)				
Unifocal	936 (82.9)	707 (82.4)	123 (82.0)	106 (87.6)
Multifocal	193 (17.1)	151 (17.6)	27 (18.0)	15 (12.4)
Tumor type, n (%)				
Invasive carcinoma NST	911 (80.7)	679 (79.1)	133 (88.7)	99 (81.8)
Lobular	144 (12.8)	127 (14.8)	12 (8.0)	5 (4.1)
Other	62 (5.5)	42 (4.9)	5 (3.3)	15 (12.4)
Missing	12 (1.0)	10 (1.2)	0 (0)	2 (1.7)
Tumor grade, n (%)				
1	241 (21.3)	228 (26.7)	7 (4.6)	6 (5.0)
2	537 (47.6)	468 (54.4)	52 (34.7)	17 (14.0)
3	350 (31.0)	162 (18.9)	91 (60.7)	97 (80.2)
Missing	1 (0.1)	0 (0)	0 (0)	1 (0.8)
cN stage, n (%)				
cN0	1027 (91.0)	788 (91.8)	126 (84.0)	113 (93.4)
cN+	102 (9.0)	70 (8.2)	24 (16.0)	8 (6.6)
pN stage, n (%)				
pN0	890 (78.8)	687 (80.1)	101 (67.3)	102 (84.3)
pN+	239 (21.2)	171 (19.9)	49 (32.7)	19 (15.7)
pT stage, n (%)				
T1	765 (67.8)	612 (71.3)	84 (56.0)	69 (57.0)
T2	319 (28.3)	209 (24.4)	61 (40.7)	49 (40.5)
T3	39 (3.4)	31 (3.6)	5 (3.3)	3 (2.5)
T4	6 (0.5)	6 (0.7)	0 (0)	0 (0)
Axillary surgery, n (%)				
SLNB	890 (78.9)	694 (80.9)	97 (64.7)	99 (81.9)
SLNB with completion ALND	127 (11.2)	88 (10.3)	26 (17.3)	13 (10.7)
ALND	112 (9.9)	76 (8.8)	27 (18.0)	9 (7.4)

N number of cases, cT clinical tumor stage, cN clinical nodal stage, pN pathological nodal stage, pT pathological tumor stadium, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection.

Diagnostic performance axillary US – overall population

The prevalence of axillary lymph node metastasis, based on histopathological examination, was 21.2% (239 of 1,129 cases) in the overall population. Using pre-operative axillary US, 1,027 of 1,129, (91.0%) cases were clinically node negative (cN0) (Figure 2). Of the 1,027 cases preoperatively staged as cN0, 890 (86.7%) were true negative and 137 cases (13.3%) were false negative; 113 with pN1 (11.0%), and 24 with pN2-3 (2.3%). Based on pre-operative axillary US, 102 of 1,129 (9.0%) cases were clinically node positive (cN+). The sensitivity, specificity, PPV, NPV, and accuracy in the overall population were 42.7% (102/239), 100% (8890/890), 100% (102/102), 86.7% (890/1027), and 87.9% (992/1129), respectively (Table 2).

Table 2. Diagnostic performance axillary ultrasound per subtypes

	All cases % [95%CI]	HER2+ % [95%CI]	Triple negative % [95%CI]	ER/PR+HER2- % [95%CI]
Sensitivity	42.7 [36.6 - 49.0] (102/239)	49.0 [35.6 - 62.5] (24/49)	42.1 [23.1 - 63.8] (8/19)	40.9 [33.8 - 48.4] (70/171)
Specificity	100.0 [100.0-100.0] (890/890)	100.0 [100.0-100.0] (101/101)	100.0 [100.0-100.0] (102/102)	100.0 [100.0-100.0] (687/687)
PPV	100.0 [100.0-100.0] (102/102)	100.0 [100.0-100.0] (24/24)	100.0 [100.0-100.0] (8/8)	100.0 [100.0-100.0] (70/70)
NPV	86.7 [84.4-88.6] (890/1027)	80.2 [72.3-86.2] (101/126)	90.3 [83.3-94.6] (102/113)	87.2 [84.7-89.3] (687/788)
Accuracy	87.9 [85.8-89.7] (992/1129)	83.3 [76.5-88.5] (125/150)	90.9 [84.3-95.0] (110/121)	88.2 [85.9-90.2] (757/858)

CI confidence interval, PPV positive predictive value, NPV negative predictive value, HER2+ human epidermal growth factor receptor 2, ER estrogen receptor, PR progesteron receptor

Diagnostic performance axillary US – subtypes

The prevalence of axillary lymph node metastases differed between breast cancer subtypes. The prevalence was highest in HER2+ tumors with 32.7% (49/150), followed by 19.9% (171/858) in ER/PR+HER2- tumors and 15.8% (19/121) in triple negative tumors.
Triple negative tumors were most often (93.4%) preoperatively staged as cN0 (113 of 121 cases). Of these, 102 (90.3%) were true negative and 11 (9.7%) false negative. In ER/PR+HER2- tumors, 788 of 858 cases (91.8%) were staged as cN0, whereof 687 (87.1%) were true negative and 102 (12.9%) false negative. In HER2+ tumors 126 of 150 (84.0%) were staged as cN0, whereof 101 (80.2%) were true negative and 25 (19.8%) false negative.

NPV was highest in triple negative tumors with 90.2%, followed by 87.2% in ER/PR+HER2- tumors and 80.6% in HER2+ tumors. The difference in NPV was statistically significant for triple negative and HER2+ subtype ($p = 0.05$), as well as for HER2+ and ER/PR+HER2- subtype ($p = 0.04$). There was no significant difference between triple negative and ER/PR+HER2- tumors ($p = 0.36$). Sensitivity was highest for HER2+ subtype (49.0%), followed by triple negative tumors (42.1%) and ER/PR+HER2- tumors (40.9%), but these differences were not statistically significant ($p = 0.60$, $p = 0.90$ and $p = 0.30$, respectively). The accuracy was highest for triple negative tumors (90.9%), followed by ER/PR+HER2- tumors (88.2%) and lowest for HER2+ tumors (88.3%), but were not statistically significant ($p = 0.40$, $p = 0.10$ and $p = 0.07$, respectively). There was no difference between the breast cancer subtypes for the specificity and PPV (Table 2).

Discussion

In the current era, breast cancer subtypes have become more important for patient tailored treatment, since they have different patterns of disease presentation (12), metastatic spread (13) and response to treatment (14-16). The panel of the eighth edition of the TNM classification of the American Joint Commission of Cancer (AJCC) for breast recognized the need to incorporate breast cancer subtypes (17). It is therefore arguable whether breast cancer subtypes should be kept in mind while interpreting results in the diagnostic pre-operative work-up. No prior study investigated the diagnostic performance of axillary US for different subtypes among breast cancer patients. Current randomized controlled trials (e.g. BOOG 2013-08, SOUND, INSEMA and NCT01821768 trial) investigate whether SLNB can be safely omitted in clinically node negative patients treated with BCT (18-21). Most important for these trials, is to accurately select true negative patients since patients are randomized for omission of the SLNB.

The NPV in the overall population was 86.7% compared to the pooled NPV of 67.4% in the meta-analysis of Houssami et al. and Diepstraten et al. (2, 3). This present study showed that there is a significant difference for NPV between triple negative tumors and HER2+ tumors (90.3% vs. 80.2%, $p<0.05$) and between HER2+ and ER/PR+HER2- tumors (80.2% vs. 87.2%, $p = 0.04$). This can be explained by the difference in prevalence of axillary lymph node metastases between breast cancer subtypes. Highest prevalence of axillary lymph node metastases and thus lowest NPV was seen in HER2+ tumors and highest NPV and thus highest NPV for triple negative tumors. Triple negative tumors often have the lowest prevalence of axillary lymph node metastases compared to other breast cancer subtypes (22-24). Other diagnostic performance parameters, sensitivity, specificity and accuracy of axillary US did not significantly differ between the breast cancer subtypes.

Besides breast cancer subtypes, other histopathological characteristics could affect the diagnostic performance of axillary US as well (e.g. tumor size, tumor type, and size of lymph node metastases). Stachs et al. showed that the diagnostic performance of axillary US depends on the size of axillary lymph node metastases. Only 9.8% (4 of 41) axillary lymph node metastases were identified with a preoperative axillary US in metastases ≤5 mm versus 72.4% (55 of 76) in metastases >10mm (4). Schipper et al. previously demonstrated with a subset of this cohort that none of the patients with isolated tumor cells or micrometastases were identified by axillary US (7). In this present study, isolated tumor cells and micrometastasis were considered as node negative. Results on the influence of tumor type, (invasive carcinoma NST versus invasive lobular carcinoma) on the diagnostic performance of axillary US are inconsistent. Choi et al. and Schipper et al. showed no significantly difference between invasive carcinoma NST and lobular carcinoma (25).

In contrast, Neal et al. and Johnson et al. reported a significantly higher NPV invasive carcinoma NST (96%) compared to invasive lobular carcinoma (83%, $p < 0.01$) (9, 26).

Despite the difference in NPV between breast cancer subtypes, the clinical consequence remains questionable. The axillary US has a NPV of 96% to exclude advanced nodal disease (i.e. pN2-3) in the overall breast cancer population (7). Potential metastases that are preoperatively not diagnosed with axillary US are therefore limited (1-3 metastases). Additionally, in these clinically node negative patients with limited axillary lymph node metastases in the SLNB; completion axillary treatment can be safely omitted (27, 28).
Triple negative tumors have generally the worst prognosis at baseline compared to other breast cancer subtypes. For current randomized controlled trials it can be reassuring that the risk of metastases in patients with negative axillary US is lower than 10% triple negative tumors, because NPV is 90.3% due t rather relatively low prevalence of axillary lymph node metastases. Prevalence is higher and NPV lower in HER2+ tumors compared to the other breast cancer tumors. However, potential axillary lymph node metastases that are left in situ in HER2+ tumors can be diminished by (neo)adjuvant treatment with chemotherapy and trastuzumab (with or without pertuzumab). The review of Moja et al. showed that adjuvant treatment with trastuzumab led to a significant improvement in disease-free and overall survival in HER2+ breast cancer patients (HR 0.66, 95%CI 0.57 - 0.77, $p < 0.0001$; and HR 0.60, 95%CI 0.50-0.71, $p < 0.00001$ (29).

To our knowledge, this is the first study assessing the effect of breast cancer subtypes on the diagnostic performance of the axillary US. Another strength is that these results are based on a large single center study and an extensive study period. This study has several limitations. First, reporting diagnostic performance of axillary US highly depends on prevalence of nodal tumor burden (2). The median prevalence of histology proven axillary lymph node metastases in this present study is low compared to the meta-analyses of Houssami et al. and Diepstraten et al. (21.0% versus 47.2%). Diepstraten et al. also demonstrated that the sensitivity of axillary US increased with an increasing prevalence of histology proven axillary lymph node metastases, 0.62 (95%CI 0.55 - 0.68) in the group with a high prevalence compared to 0.38 (95%CI 0.3 - 0.46) in the group with low prevalence (2). High prevalence was defined as ≥40% and low prevalence as <40% of the patients with axillary lymph node metastases. The lower sensitivity in this present study can be explained by the low prevalence of axillary lymph node metastases in this cohort. Interpreting results of the present study should therefore incorporate the prevalence of axillary lymph node metastases in this cohort. Most of the clinically node positive breast cancers patients within our institution were treated with neoadjuvant systemic therapy and therefore excluded in the present study. This results in a lower prevalence of patients with axillary lymph node metastases. Final limitation of the present study is that information on

size of the axillary lymph node metastases from axillary US was not available. Therefore, it is unknown whether the size of the axillary lymph node metastases could also have affected the diagnostic performance of axillary US.

In conclusion, there was no significant difference in sensitivity of axillary US between the subtypes of breast cancer. However, the NPV was highest in triple negative subtype and lowest for HER2+ tumors. This difference can be explained by the different prevalence of axillary lymph node metastases among the breast cancer subtypes.

The clinical consequence of the difference in NPV between breast cancer subtypes remains questionable. Recruitment of patients of all different breast cancer subtypes remains important for the current randomized controlled trials that investigate whether the SLNB can be safely omitted in all breast cancer subtypes.

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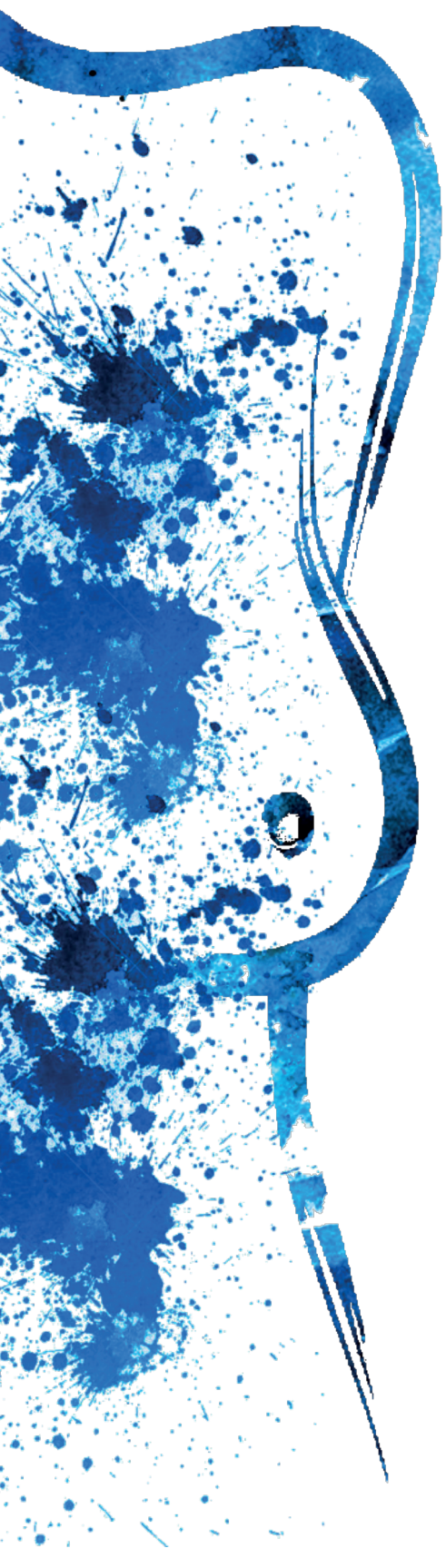
PART III

ADEQUATE FOLLOW-UP TIME IN AXILLARY TREATMENT TRIALS



CHAPTER 6

CONDITIONAL REGIONAL RECURRENCE RISK: THE EFFECT OF EVENT-FREE YEARS IN DIFFERENT SUBTYPES OF BREAST CANCER

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Abstract

Background Regional recurrence (RR) is an endpoint in several trials concerning reducing axillary treatment in *c*T1-2N0 breast cancer patients. The risk of RR may decrease with each subsequent event-free year, affecting the yield and consequently usefulness of long(er) follow-up. The aim of this study is to determine the risk of RR as a first event within five years after diagnosis in subtypes of breast cancer, conditional to being event-free for one, two, three and four years.

Methods From the Netherlands Cancer Registry, *c*T1-2N0 breast cancer patients diagnosed from 2005-2008 were analyzed. Subgroup analysis was performed for pT1-2N+(sn) patients. RR risk was calculated with Kaplan-Meier analysis. Conditional RR (assuming x event-free years) was determined by selecting patients without an event at x years, and calculating the remaining risk for RR within five years after diagnosis.

Results A total of 18.009 *c*T1-2N0 (all pN stages) breast cancer patients were included. RR occurred in 1.3% of *c*T1-2N0 and 1.5% of pT1-2N+(sn) patients. The risk of RR varied between subtypes; it was highest for triple negative tumors and lowest for ER+PR+Her2- and ER+Her2+ tumors. After event-free years, the risk of RR decreased subsequently in both groups and in all subtypes. After two event-free years, the risk of RR was 0.8%.

Conclusion The absolute yield of follow-up to detect RR beyond two years is low; for every 125 event-free patients, one RR can be expected until five years. This suggests that follow-up longer than two years is of limited value for detecting RR in both clinical and research setting.

Introduction

As a result of several recent randomized controlled trials, the extent of axillary treatment in breast cancer patients is being reduced (1-6). Since a complete axillary dissection is replaced by radiotherapy, sentinel node only or no axillary treatment at all, regional recurrence (RR) is an important endpoint in these different trials. Endpoints are standardly reported as rates after five and ten-years of follow-up. However, these rates improve when patients remain event-free during follow-up for each consecutive year.

Conditional survival is defined as the probability of surviving an additional x years given that a patient has already survived a number of years after diagnosis (7). Previous studies assessed conditional OS and DFS among breast cancer patients (8-11) and showed that conditional survival improves over time, in particular among patients with worst prognosis at baseline (e.g. stage III versus stage I-II) (11). This is in accordance with ovarian, colorectal, endometrial, and testicular cancer and melanoma patients, in which prognosis for cancer survivors generally improves with each event-free year (10, 12, 13). It is conceivable that in line with OS and DFS the risk for RR might decrease after a number of event-free years.

Adequate duration of follow-up in both clinical and research setting remains controversial. Most studies report their first results after five years, but it has been suggested that most RRs occur in the first few years after diagnosis. This questions the yield and therefore use of longer follow-up for this purpose. Another topic of debate in these randomized controlled trials is whether different subtypes of breast cancer might require a different approach. The benefit of computing an individual's RR rate is gaining more tailored prognostic information and follow-up time for breast cancer survivors.
The aim of this study is to determine the risk of RR as a first event within five years after diagnosis, conditional to being event-free for one, two, three, and four years. This study will focus on clinically node negative breast cancer patients in general, and additionally on patients with sentinel node involvement. Conditional RR will be presented separately for ER+PR+Her2-, ER+PR-Her2-, ER+Her2+, ER-Her2+, and triple negative tumors.

Methods

Data collection

The Netherlands Cancer Registry (NCR) data is based on all new breast cancer patients from all Dutch hospitals. Data on patient-, tumor-, and treatment-related characteristics, prospectively retrieved from patients' records by trained data managers of the Netherlands

Comprehensive Cancer Organisation (IKNL). For patients diagnosed between 2005 and 2008, an active follow-up was conducted in which data on first breast cancer event within five years after diagnosis were gathered directly from patient files. First breast cancer event was registered as new primary ipsilateral breast cancer, contralateral breast cancer, local recurrence (LR), RR or distant recurrence.

Study population

We analyzed the risk of RR in women between 2005 and 2008 diagnosed with primary invasive breast cancer in the Netherlands. This study focused on the study populations of previous mentioned randomized controlled trials, involving breast cancer patients with a clinically T1-2 tumor and clinically node negative status. First, the overall clinically T1-2N0 population (consistent with the study population of BOOG 2013-08, SOUND, INSEMA and NCT01821768) was analyzed (6). Second, patients from this population with a positive sentinel lymph node (SLN) (consistent with the study population of ACOSOG Z0011, IBCSG 23-01, AMAROS, POSNOC, SENOMAC and SINODAR) were analyzed separately (1, 3-6). These patients will be further referred to as the pT1-2N+(sn) subpopulation. Patients were excluded in case of distant metastasis at (or within 91 days of) diagnosis, an incomplete five-year follow-up, treatment with primary systemic therapy, or in case of no sentinel lymph node biopsy (SLNB) or incomplete registered results.

Locoregional treatment

Patients were treated according to the Dutch breast cancer guidelines of 2005 (14). All patients had clinically T1-2 tumors and were clinically node negative (based on physical examination, axillary ultrasound was common but not mandatory). Locoregional treatment consisted of breast conserving therapy (lumpectomy and whole breast radiotherapy) or mastectomy, both combined with an SLNB. Patients with a positive SLN were treated with an axillary lymph node dissection (ALND) or axillary radiotherapy, in context of the AMAROS trial.

Systemic treatment

Adjuvant systemic treatment was recommended for all pN+ breast cancer patients. Adjuvant systemic treatment for N0 patients was recommended for patients <35 years and for patients ≥35 years with risk factors. Risk factors were tumor ≥3cm, or tumor ≥1cm and grade III, or tumor ≥2cm and grade II. Chemotherapy regimen consisted of five courses 5 Fluorouracil, Epirubicin, Cyclophosphamide (FEC) or six courses of Taxotere, Adriamycin and Cyclophosphamide (TAC). Endocrine therapy (Tamoxifen and/or Luteinizing hormone-releasing hormone agonist) was recommended for ER+ and/or PR+ tumors. In case of Her2Neu receptor (Her 2) amplification, targeted therapy (trastuzumab) was recommended in addition to chemotherapy.

Endpoints

The primary endpoint was conditional RR, defined as the risk of RR as a first event within five years after diagnosis, conditional to being event-free for one, two, three, and four years. RR included recurrence in an ipsilateral axillary-, infraclavicular-, or supraclavicular lymph node, internal mammary/parasternal or intramammary lymph node (15). Events within 91 days following diagnosis were regarded as synchronous with the original tumor. Patients were censored at the date of their first event, at the date of last follow-up, or at the date of death. If another event (new primary ipsilateral breast cancer, contralateral breast cancer, local recurrence, RR or distant recurrence) occurred within 91 days of the first recurrence, this was considered synchronous to the first event, and also counted as a first recurrence.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY, USA). RR was determined for the overall population and for the subgroup of clinically node negative patients with positive lymph nodes. Kaplan-Meier analysis was used to determine the probability of RR over time. Missing values were disregarded, not imputed. Significance of the difference between the subtypes (ER+PR+Her2-, ER+PR-Her2-, ER+Her2+, ER-Her2+, and ER-PR-Her2-) was tested with the log-rank test. Univariable and multivariable Cox regression was used to determine the effect of subtype corrected for several prognostic variables that may differ among the groups. The risk of conditional RR was calculated by selecting patients who were event free (i.e. no local recurrence, RR, distant recurrence, second primary breast cancer, or death) at one, two, three, and four years. The risk of RR within five years of diagnosis was calculated for each time point and for five approximate subtypes of breast cancer. A p-value ≤0.05 was considered as statistically significant.

Results

Patient demographics and primary tumor characteristics

A total of 18.009 primary clinically T1-2N0 breast cancer patients were included. Patient and tumor characteristics are summarized in Table 1. Median age was 59 years (range 22-98). The most prevalent subtype was ER+PR+Her2- in 9.929 patients (55.1%), followed by ER+PR-Her2- in 2.032 patients (11.3%), triple negative tumors in 1.701 patients (9.5%), ER+Her2+ in 1,231 patients (6.8%) and ER-Her2+ in 667 patients (3.7%). Subtype was unknown in 2.449 of the patients (13.6%). All patients underwent SLNB for determining axillary lymph node status. Patient and tumor characteristics per subtype are shown in Appendix 1.

Table 1. Patient demographics and tumor characteristics of the cT1-2N0 population (N = 18.009)

Age, years		**pT-stage, n (%)**	
median	59	pT0	1 (0.0)
range	22 - 98	pT1	12.332 (68.5)
		pT2	5.422 (30.1)
		pT3	157 (0.9)
		pT4	18 (0.1)
		unknown	79 (0.4)
cT-stage, n (%)		**pN-stage, n (%)**	
cT1	13.809 (76.7)	pN0	13.177 (73.2)
cT2	4.200 (23.3)	pN1mi	1.211 (6.7)
		pN1a	2.813 (15.6)
		pN1b	29 (0.1)
		pN2	519 (2.9)
		pN3	177 (1.0)
		unknown	36 (0.2)
Surgical treatment, n (%)		**Radiotherapy for breast conserving treatment, % (n)**	
	12.173 (67.6)		1.1935 (98.0)
breast conserving	5.836 (32.4)	yes	238 (2.0)
mastectomy		no	
Tumor type, n (%)		**Chemotherapy, n (%)**	
ductal	13.640 (75.7)	yes	5.767 (32.0)
lobular	1.858 (10.3)	no	12.242 (68.0)
mixed or other	2.511 (14.0)		
Grade (Bloom-Richardson), n (%)		**Hormone therapy for ER+, n (%)**	
			7.102 (47.2)
I	4.730 (26.3)	yes	7.935 (52.8)
II	7.774 (43.2)	no	
III	4.872 (27.0)		
unknown	663 (3.5)		
Subtypes, n (%)		**Trastuzumab and chemotherapy for HER2+, n (%)**	
ER+PR+Her2-	9.929 (55.1)		933 (49.3)
ER+PR-Her2-	2.032 (11.3)	yes	974 (50.7)
ER+Her2+	1.231 (6.8)	no	
ER-Her2+	667 (3.7)		
triple negative	1.701 (9.5)		
unknown	2.449 (13.6)		

N number of cases, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, cT clinical tumor stage, pT pathological tumor stage.

The effect of x-event-free years on risk of regional recurrence within five years

The incidence of RR as a first event within five years of diagnosis was 1.3% in the overall cT1-2N0 group, and 1.5% in the subpopulation of pT1-2N+(sn) patients. These results were corrected for confounders, for both the overall cT1-2N0 group and subpopulation of pT1-2N+(sn) (Appendix 2). After one, two, three, and four event-free years, the risk of developing RR in the remaining period decreased in both groups. In the overall cT1-2N0 group, the risk of RR decreased with additional event-free years to 1.1%, 0.8%, 0.6%, and 0.3%, respectively (Table 2). In the pT1-2N+(sn) subpopulation, the risk of RR decreased to 1.2%, 0.8%, 0.6%, and 0.4%, respectively (Table 3). In both the overall cT1-2N0 group and in the pT1-2N+(sn) subpopulation, the risk of RR as a first event, after 2 event-free years was 0.8%.

Regional recurrence as a first event between different subtypes

The risk of RR at diagnosis in the overall cT1-2N0 group varied between subtypes, and was highest for triple negative (3.7%) and lowest for ER+PR+Her2- tumors (0.8%) (Table 2). The difference between the subtypes ER+PR+Her2- and ER+PR-Her2- (0.8% vs 1.5%, p = 0.001); and between ER-Her2+ and triple negative were significant (1.8% vs 3.7%, p = 0.029) (Figure 1). In the subpopulation of pT1-2N+(sn), the risk of RR at diagnosis also varied between subtypes, and was highest for triple negative (10.7%) and lowest for ER+Her2+ tumors (0.4%) and ER+PR+Her2- (0.5%) (Table 3). The difference between the subtypes in the pT1-2N+(sn) subpopulation were significant in ER+PR+Her2- and ER+PR-Her- (0.5% vs 1.9% p = 0.011), ER+PR-Her- and ER+Her2+ (1.9% vs 0.4%, p = 0.077), ER+Her2+ and ER-Her2+ (0.4% vs 3.4%, p = 0.006) and ER-Her2+ and triple negative (3.4% vs 10.7%, p = 0.015) (Figure 2).

The effect of x-event-free years on risk of regional recurrence between subtypes

The risk of RR as a first event within five years after diagnosis decreased in all subtypes from both the overall and subgroup, when more event-free years had passed. Triple negative tumors had the worst prognosis at baseline, but showed proportionally the largest decrease (3.7% to 0.4%) in the cT1-2N0 group and (10.7% to 1.2%), respectively in the pT1-2N+(sn) subgroup. Tumors with the best prognosis at baseline, ER+PR+Her2- in the overall cT1-2N0 group (0.8% to 0.2%), and ER+Her2+ tumors (0.4% to 0.4%) and ER+PR+Her2- (0.5% to 0.2%) in the pT1-2N+(sn) subgroup, showed proportionally the least decrease. After 2 event-free years, the overall risk of developing RR within five years, was less than 1% in the cT1-2N0 group and pT1-2N+(sn) patients (Table 2 and 3). In the subgroup of pT1-2N+(sn) patients, the risk of developing RR within five years was less than 1% after three event-free years, except for ER-Her2+ (1.5%) and triple negative tumors (5.2%) (Table 3).

Table 2. Impact of a number of event-free years on the risk of RR as a first event within five years after diagnosis in clinically node negative patients (cT1-2N0)

			Risk of regional recurrence within five years after diagnosis, after x event-free years			
	N	Risk of 5-year RR at diagnosis	After 1 event-free year	After 2 event-free years	After 3 event-free years	After 4 event-free years
All patients	18.009	1.3% (206/18.009)	1.1% (163/17.460)	0.8% (117/16.693)	0.6% (77/15.891)	0.3% (35/14.749)
Breast cancer subtypes						
ER+PR+Her2-	9929	0.8% (67/9.929)	0.8% (61/9.695)	0.7% (51/9.346)	0.4% (34/8.967)	0.2% (16/8.316)
ER+PR-Her2-	2032	1.5% (27/2.032)	1.2% (21/1.958)	0.9% (15/1.873)	0.4% (7/1.765)	0.3% (4/1.644)
ER+Her2+	1231	1.4% (15/1.231)	1.3% (14/1.204)	1.1% (11/1.155)	0.7% (7/1.098)	0.3% (2/1.031)
ER-Her2+	667	1.8% (11/667)	1.3% (8/641)	0.7% (4/601)	0.6% (3/568)	0.2% (1/525)
Triple negative	1701	3.7% (54/1.701)	2.6% (36/1.594)	1.4% (17/1.449)	0.9% (10/1.351)	0.4% (3/1.255)

N number of cases, RR regional recurrence, ER estrogen receptor, PR progesteron receptor, HER2 human epidermal growth factor receptor 2

Table 3. Impact of a number of event-free years on the risk of RR as a first event within five years after diagnosis in clinically node negative patients with a positive SLN (pT1-2N+(sn))

			Risk of regional recurrence within five years after diagnosis, after x event-free years			
	N	Risk of 5-year RR at diagnosis	After 1 event-free year	After 2 event-free years	After 3 event-free years	After 4 event-free years
All patients	4348	1.5% (58/4.348)	1.2% (45/4.194)	0.8% (27/4.002)	0.6% (19/3.798)	0.4% (12/3.559)
Breast cancer subtypes						
ER+PR+Her2-	2630	0.5% (13/2.630)	0.4% (9/2.558)	0.3% (7/2.472)	0.2 (5/2.372)	0.2% (4/2.244)
ER+PR-Her2-	480	1.9% (7/480)	1.5% (5/457)	1.0% (3/438)	0.8% (2/406)	0.8% (2/371)
ER+Her2+	366	0.4% (1/366)	0.4% (1/328)	0.4% (1/312)	0.4% (1/298)	0.4% (1/279)
ER-Her2+	336	3.4% (5/157)	3.4% (5/152)	1.5% (2/143)	1.5% (2/137)	0.0% (0/126)
Triple negative	293	10.7% (24/293)	8.7% (18/257)	5.2% (9/220)	2.8% (4/191)	1.2% (1/173)

N number of cases, RR regional recurrence, ER estrogen receptor, PR progesteron receptor, HER2 human epidermal growth factor receptor 2

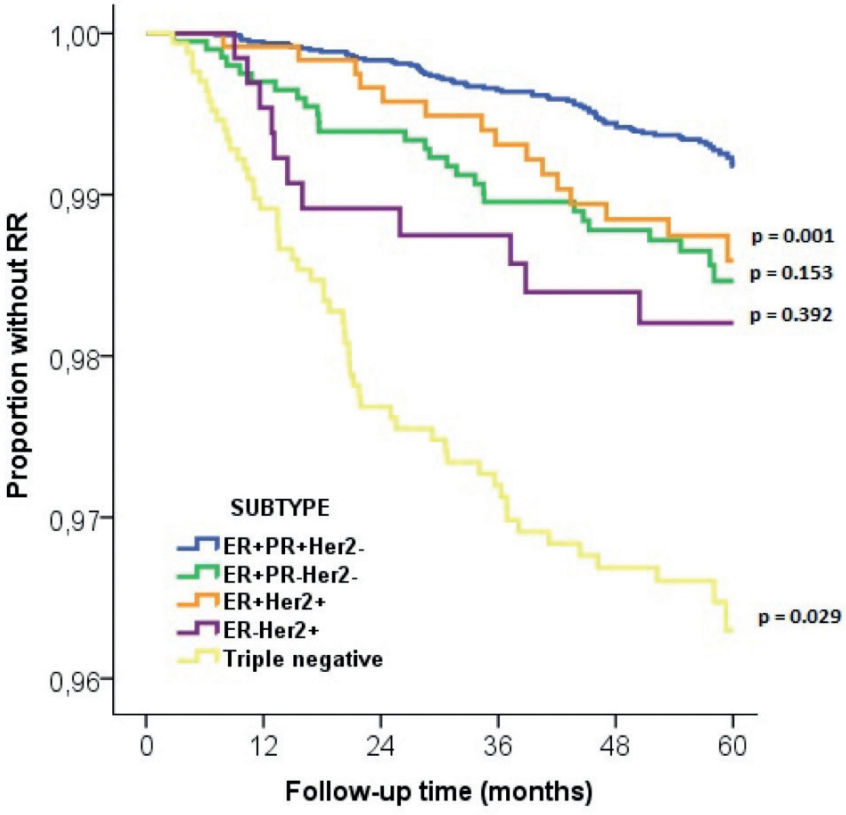

Figure. 1 Kaplan Meier curves for regional recurrence as a first event between different subtypes (ER+PR+Her2-, ER+PR-HER2-, ER+Her2+, ER-Her2+ and triple negative) in cT1-2N0 breast cancer after five years

Time (months)	0	12	24	36	48
N at risk	18.009	17.460	16.693	15.814	14.749

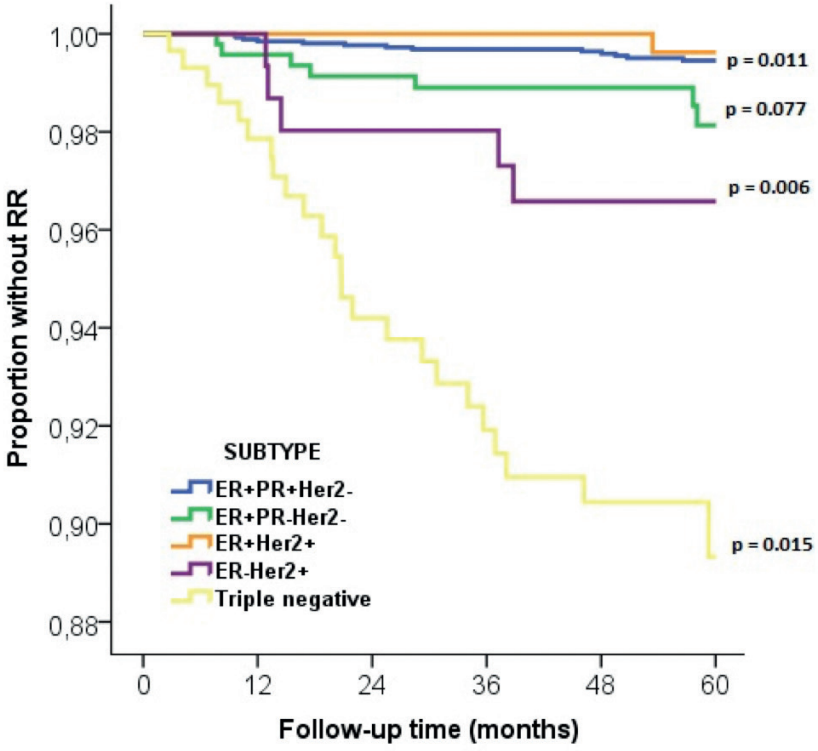

Figure 2. Kaplan Meier curves for regional recurrence as a first event between different subtypes (ER+PR+Her2-, ER+PR-HER2-, ER+Her2+, ER-Her2+ and triple negative) in pT1-2N+(sn) breast cancer after five years

Time (months)	**0**	**12**	**24**	**36**	**48**
N at risk	4.0348	4.194	4.002	3.798	3.559

Discussion

In a large cohort of patients from the national cancer registry in the Netherlands the RR as a first event within five years after diagnosis was determined. Moreover, conditional survival, being event-free for every consecutive year during follow-up, was calculated. In the overall *c*T1-2N0 group, and in the pT1-2N+(sn) subpopulation the risk of RR was 1.3%, and 1.5% respectively. In the overall group and subpopulation, the risk of RR significantly differed between subtypes. The risk of RR decreased in both groups and in all subtypes when more event-free years passed.

Previous studies showed that conditional DFS and OS improves as time elapses since breast cancer diagnosis (8, 9, 11). Janssen-Heijnen et al. showed a clear difference in conditional survival between stage (favorable for stage III versus stage I-II) and between age groups (favorable for age groups 45-54 and 55-64 years). These differences in conditional survival remained significant, but decreased in time (10, 11). Only one study reported the impact of subtype as a prognostic factor on conditional survival. Ten-year RR declined over time, the risk changed from 1.7 – 0.5% for luminal A subtypes and from 4.9 – 0.2% for triple negative tumors (16). In the current era, subtypes of breast cancer have become more important in addition to traditional prognostic factors, such as age and stage.

The strength of the present study is the large cohort of 18.009 breast cancer patients. All new Dutch breast cancer patients diagnosed between 2005 and 2008 were included. Therefore, all subtypes, including ER+PR+Her2-, ER+PR-Her2-, ER+Her2+, ER-Her2+, and even triple negative tumors are adequately represented in this cohort. Although triple negative breast cancer patients were less frequently diagnosed with a positive SLN at diagnosis compared to other subtypes, these tumors had the highest risk of RR as a first event within five years after diagnosis (3.7% in the overall group and 10.7% in the subpopulation of sentinel node positive patients). The systematic review of Lowery et al. concluded that locoregional recurrence was significantly higher in triple negative tumors compared with other subtypes (17). Metzger et al. also observed an increased incidence of RR in triple negative tumors compared to other subtypes (18). In contrast, van Roozendaal et al. showed that RR occurred in only 2.9% of the triple negative *c*T1-2N0 breast cancer patients (19).

This study showed that the decrease in risk of RR was most explicit in the subtype with the highest risk at baseline (triple negative tumors). This is consistent with previous studies, which suggested that improvement with event-free years is greatest for tumors with the worst prognosis at baseline (11).

Based on these results, physicians can use conditional RR for more patient tailored information after one, two, three and four event-free years classified on subtype. In the clinical setting, follow-up is continued to at least five years after diagnosis. However, after two event-free years, only one in 125 patients will have a RR in the remaining three years of follow-up. This suggests that longer follow-up is of limited value for detection of RR, although this may be required for other reasons. Furthermore, this study showed that most patients with highest risk of RR at baseline (triple negative pT1-2N+(sn) tumors) will develop RR early during follow-up. So even in these tumors, follow-up after three years is of limited value for detection of RR. The information on conditional RR can also be used to determine follow-up duration and calculate sample sizes in clinical research using RR as an endpoint, although longer follow-up may be required for other outcomes. Cost-effectives of reducing the follow-up period could be the subject of future investigations.

A limitation of this study is the lack of follow-up beyond five years. However, Matsen et al. showed that the majority of RR in node negative patients occurred within the first five years after surgery (20). They reported late RR, defined as RR after more than five years of surgery, occurring in only five of the 1.529 included patients. The recently published ten-year results of the ACOSOG Z0011 trial showed that from five to ten years of follow-up, only two patients developed a RR in the ALND group versus five in the SLNB alone group (21). These results imply that late RR after a negative SLNB are extremely rare. The question remains whether this is also applicable to ER+ tumors treated with at least five years of hormone therapy, since RR in this subtype continue to occur through 10 years (22, 23).

Further, this analysis includes all patients with a positive SLN, i.e. 1-3 and 4 or more, as only the total number of positive nodes was registered and not the number of positive SLNs. Another limitation of this study is that only the first event (RR) within five years after diagnosis was registered, which could have resulted in an underestimated number of events. Finally, patients were treated according to the Dutch breast cancer guideline of 2005. This differs from current guideline concerning that axillary ultrasound was common but not mandatory and indication changed chemo-, hormone and immunotherapy regimens.

In conclusion, the overall risk of RR as a first event was low in cT1-2N0 breast cancer patients (1.3%). After one, two, three and four event-free years, the risk of RR decreased in both groups and all subtypes. The absolute yield of follow-up beyond two years concerning RR is low (0.8%); for every 125 event-free patients, one RR can be expected until five-years. This suggests that follow-up longer than two years is of limited value for detecting RR in both clinical and research setting.

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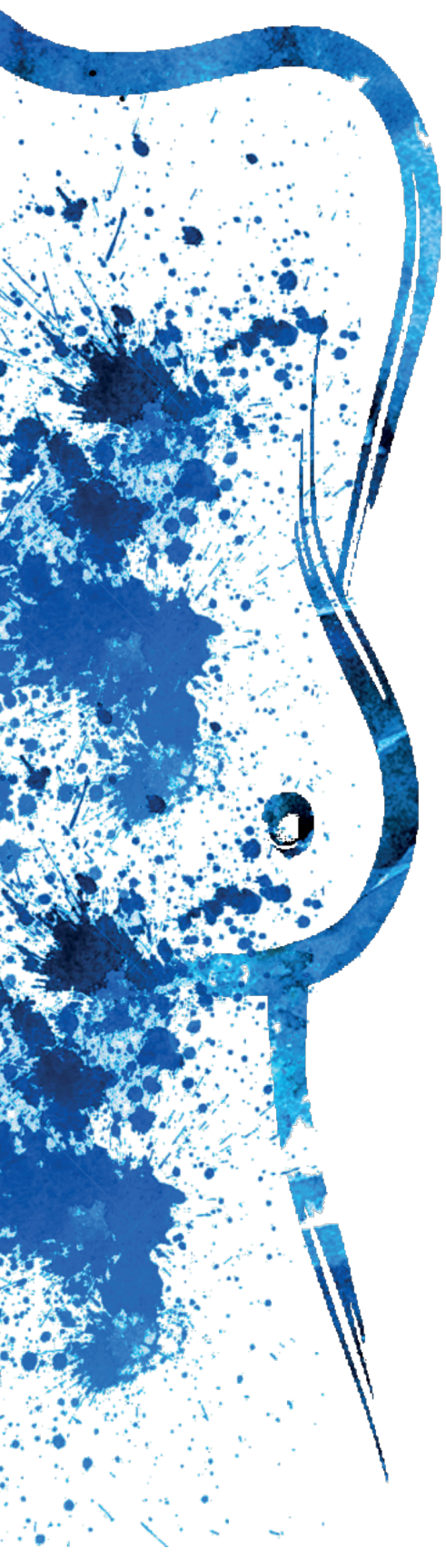
Appendix

Appendix 1. Patient demographics and primary tumor characteristics cT1-2N0 per subtype

	All patients (N = 18.009)	ER+PR+Her2- (N = 9.929)	ER+PR-Her2- (N = 2.032)	ER+Her2+ (N = 1.231)	ER-Her2+ (N = 667)	Triple negative (N = 1.701)
Age, in years						
median (range)	59 (22-98)	59 (22-95)	62 (23-91)	54 (24-88)	57 (30-89)	54 (30-89)
Tumor type, n (%)						
ductal	13640 (75.7)	7.299 (73.5)	1.454 (71.6)	1.064 (86.5)	606 (90.8)	1403 (82.5)
lobular	1.858 (10.3)	1.205 (12.1)	291 (14.3)	57 (4.6)	3 (0.5)	35 (2.1)
mixed or other	2.511 (14.0)	1.425 (14.4)	287 (14.1)	110 (8.9)	58 (8.7)	263 (15.4)
Grade, n (%)						
I	4.730 (26.3)	3.344 (33.7)	568 (28.0)	130 (10.6)	17 (2.6)	61 (3.6)
II	7.774 (43.2)	4.732 (47.6)	952 (46.9)	521 (42.3)	161 (24.1)	293 (17.2)
III	4.872 (27.0)	1.558 (15.7)	434 (21.3)	547 (44.4)	480 (72.0)	1.292 (76.0)
unknown	633 (3.5)	295 (3.0)	78 (3.8)	33 (2.7)	9 (1.3)	55 (3.2)
cT-stage, n (%)						
cT1N0	13.809 (76.7)	7.930 (79.9)	1.558 (76.7)	890 (72.3)	405 (60.7)	1.123 (66.0)
cT2N0	4.200 (23.3)	1.999 (20.1)	474 (23.3)	341 (27.7)	262 (39.3)	578 (34.0)
pT- stage, n (%)						
pT0	1 (0.0)	0 (0.0)	1 (0.05)	0 (0.0)	0 (0.0)	0 (0.0)
pT1	12.332 (68.5)	7.111 (71.6)	1.381 (68.0)	738 (63.6)	360 (54.0)	955 (56.1)
pT2	5.422 (30.1)	2.692 (27.1)	624 (30.7)	431 (35.0)	294 (44.1)	723 (42.5)
pT3	157 (0.9)	81 (0.8)	18 (0.9)	12 (1.0)	9 (1.3)	18 (1.1)
pT4	18 (0.1)	7 (0.1)	1 (0.05)	1 (0.1)	1 (0.1)	2 (0.1)
unknown	79 (0.4)	38 (0.4)	7 (0.3)	4 (0.3)	3 (0.5)	3 (0.2)
Surgical treatment, n (%)						
breast conserving	12.173 (67.6)	6.887 (69.4)	1.329 (65.4)	775 (63.0)	367 (55.0)	1.185 (69.7)
mastectomy	5836 (32.4)	3.042 (30.6)	703 (34.6)	456 (37.0)	300 (45.0)	516 (30.3)
SLN, n (%)						
negative	12.292 (68.3)	6.608 (66.6)	1.397 (68.8)	820 (66.6)	475 (71.2)	1.268 (74.5)
micrometastasis	1.322 (7.3)	826 (8.3)	136 (6.7)	87 (7.1)	47 (7.0)	83 (4.9)
macrometastasis	3.056 (17.0)	1.821 (18.3)	346 (17.0)	253 (20.5)	111 (16.7)	213 (12.5)
unknown	1.339 (7.4)	674 (6.8)	153 (7.5)	71 (5.8)	34 (5.1)	137 (8.1)
ALND performed if SLN+, n (%)						
yes	3.966 (90.6)	2.376 (89.8)	431 (89.4)	317 (93.2)	146 (92.4)	274 (92.6)
no	412 (9.4)	271 (10.2)	51 (10.6)	23 (6.8)	12 (7.6)	22 (7.4)
pN- stage, n (%)						
pN0	13.177 (73.2)	7.036 (70.9)	1.491 (73.4)	862 (70.0)	494 (74.1)	1.373 (80.7)
pN1mi	1.211 (6.7)	739 (7.4)	131 (6.4)	80 (6.5)	41 (6.2)	75 (4.4)
pN1a	2.813 (15.6)	1.716 (17.3)	319 (15.7)	208 (16.9)	95 (14.2)	183 (10.8)
pN1b	29 (0.1)	14 (0.1)	3 (0.2)	5 (0.4)	1 (0.1)	4 (0.3)
pN1c	47 (0.3)	30 (0.3)	6 (0.3)	1 (0.1)	1 (0.1)	2 (0.1)
pN2	519 (2.9)	292 (3.0)	51 (2.5)	53 (4.3)	23 (3.5)	41 (2.4)
pN3	177 (1.0)	83 (0.8)	27 (1.3)	21 (1.7)	11 (1.7)	16 (0.9)
unknown	36 (0.2)	19 (0.2)	4 (0.2)	1 (0.1)	1 (0.1)	7 (0.4)
Chemotherapy, n (%)						
yes	5767 (32.0)	2.578 (26.0)	463 (22.8)	600 (48.7)	453 (67.9)	1.095 (64.4)
no	12.242 (68.0)	7.351 (74.0)	1.569 (77.2)	631 (51.3)	214 (32.1)	606 (35.6)
Hormone therapy in case of ER+, n (%)						
yes	7.102 (47.2)	4.664 (47.0)	951 (46.8)	96 (64.7)	-	-
no	7.935 (52.8)	5.265 (53.0)	1.081 (53.2)	435 (35.3)	-	-
Trastuzumab and chemotherapy, in case of HER2+, n (%)						
yes	933 (87.7)	-	-	526 (87.7)	398 (87.9)	-
no	131 (12.3)	-	-	74 (12.3)	55 (12.1)	-

Subtype is missing is in 13.6%.
N number of cases, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, cT clinical tumor stage, pT pathological tumor stage, SLN sentinel lymph node, ALND axillary lymph node dissection.



CHAPTER 7

CONDITIONAL LOCAL RECURRENCE RISK: THE EFFECT OF EVENT-FREE YEARS IN DIFFERENT SUBTYPES OF BREAST CANCER

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Abstract

Background After breast cancer treatment, follow-up consists of physical examination and mammography for at least five years, to detect local and regional recurrence. The risk of recurrence may decrease after event-free time. This study aims to determine the risk of local recurrence (LR) as a first event until five years after diagnosis, conditional on being event-free for one, two, three and four years.

Methods From the Netherlands Cancer Registry, all M0 breast cancers diagnosed between 2005 and 2008 were included. LR risk was calculated with Kaplan-Meier analysis, overall and for different subtypes. Conditional LR (assuming x event-free years) was determined by selecting event-free patients at x years, and calculating their LR risk within five years after diagnosis.

Results Five-year follow-up was available for 34.453 patients. Overall, five-year LR as a first event occurred in 3.0%. This risk varied for different subtypes and was highest for triple negative (6.8%) and lowest for ER+PR+Her2- (2.2%) tumors. After one, two, three and four event-free years, the average risk of LR before five years after diagnosis decreased from 3.0% to 2.4%, 1.6%, 1.0%, and 0.6%. The risk decreased in all subtypes, the effect was most pronounced in subtypes with the highest baseline risk (ER-Her2+ and triple negative breast cancer). After three event-free years, LR risk in the next two years was 1% or less in all subtypes except triple negative (1.6%).

Conclusion The risk of five-year LR as a first event was low and decreased with the number of event-free years. After three event-free years, the overall risk was 1%. This is reassuring to patients and also suggests that follow-up beyond three years may produce low yield of LR, both for individual patients and studies using LR as primary outcome. This can be used as a starting point to tailor follow-up to individual needs.

Introduction

Outcomes such as local recurrence (LR) are usually expressed as five or ten-year probability from the time of breast cancer diagnosis. However, as time progresses and a patient remains event-free, this initial estimate of LR (or other outcomes) may have improved. Event-free time is usually not considered as a prognostic factor. An estimate of prognosis that takes the recurrence-free interval into account is called conditional survival or recurrence.
Earlier publications have addressed conditional overall and disease-free survival in breast cancer patients, however mostly without focus on LR (1-3). Furthermore, these studies were based on older cohorts that differed from current breast cancer patients in several ways: worse baseline prognosis, diagnosis in a time period when breast cancer screening was unavailable, incomplete information on intrinsic subtypes including Her2 status, incomplete use of modern (taxane-based) chemotherapy regimens, and incomplete use of trastuzumab for Her2 overexpressing tumors.

The advantage of calculating conditional LR risks is that individual patients can receive more tailored information about their prognosis, which could be reassuring. Furthermore, this information can also help to determine the optimal follow-up time, both for everyday practice and clinical research. After treatment for breast cancer, follow-up consists of physical examination and mammography for at least five years. Thereafter, recommendations vary with regard to frequency, duration, and required investigations. One of the goals of follow-up is to detect possible local and regional recurrences (4-7). Information on conditional LR risk may be used to tailor follow-up to individual needs. Although extended follow-up may be desirable for other goals such as monitoring endocrine therapy and reassurance, a low chance of events may be a reason to shorten follow-up in specific cases. Safely tailoring follow-up to individual patients could improve quality of care by reducing the number of hospital visits and stress. It can also save health care costs, and may also decrease the required time and financial resources for clinical trials if follow-up can be shortened. In order to preserve quality of care, we need to explore which patients may be eligible for this approach.

Earlier studies on conditional overall and disease-free survival demonstrated the greatest improvement of prognosis (in other words: greatest reduction of the chance of recurrence and death) for patients with the worst prognosis at baseline, which is in line with conditional survival studies for other types of cancer (8-11). As we hypothesize this may also be the case for LR risk in breast cancer, the role of biologic subtype as prognostic factor may be of interest, in addition to traditional prognostic factors such as tumor size and nodal status. Different subtypes show different patterns of recurrence (12). It is plausible that the prognostic differences between subtypes depend, among others, on contemporary

chemotherapy and trastuzumab. Knowing the effect of event-free years on LR risk in different subtypes could allow tailoring of follow-up, both for clinical practice and trials using LR as an endpoint.

This study aims to determine the risk of LR as a first event within five years after diagnosis, conditional on having no breast cancer event for one, two, three and four years. The results will be presented separately for ER+PR+Her2-, ER+PR-Her2-, ER+Her2+, ER-Her2+, and triple negative tumors.

Methods

Data collection

The Netherlands Cancer Registry (NCR) collects data on all newly diagnosed cancer patients in all hospitals in the Netherlands from 1989 onward. For the years 2005-2008, both five-year follow-up on recurrences and information on Her2 status and treatment with trastuzumab are available. Trained data managers of the Netherlands Comprehensive Cancer Organisation (IKNL) obtain data on patient-, tumor- and treatment-related characteristics prospectively from patients' records. Tumor topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O, 3rd edition (13)), and staging was coded according to the tumor, node and metastasis (TNM) classification system (AJCC/UICC, 6th edition (14)). For a period of five years after diagnosis, the first breast cancer event was registered (LR, new primary ipsilateral breast cancer, contralateral breast cancer, regional recurrence, or distant recurrence).

Included patients

From the NCR database, all new invasive epithelial breast cancers diagnosed between 2005 and 2008, of which five-year follow-up was complete, were included. Patients with distant metastasis at (or within 91 days of) diagnosis were excluded.

Treatment according to guideline

Patients were treated according to the Dutch national breast cancer guideline of 2005 (15). Local treatment consisted of breast conserving therapy (lumpectomy and whole breast irradiation) or mastectomy. Post-mastectomy chest wall irradiation was recommended for positive margins, involvement of the pectoralis muscle or skin (T4 tumors), and was considered individually for pT3 tumors. Locoregional radiation was performed for ≥pN2 or involvement of upper medial axillary nodes. Recommended dose was 45-50 Gy in 5 weeks, or 60-70 Gy in 6 or 7 weeks in case of residual tumor. Lymph node involvement was assessed with sentinel lymph node biopsy (SLNB) for clinically node negative patients

according to physical examination and biopsy/fine needle aspiration. Axillary ultrasound was common but not mandatory. Contraindications for SLNB at that time were multiple tumors, >T2, and previous axillary surgery. If SLNB was contraindicated, or if positive lymph nodes were identified either preoperatively or by SLNB, an axillary lymph node dissection (ALND) was performed.

The indication for systemic treatment depended on nodal involvement, tumor size, grade, receptor status, and age. In N+ breast cancer, endocrine therapy was recommended for all patients with ER+ and/or PR+ tumors. Chemotherapy was advised for N+ breast cancer in all premenopausal women and in women <70 years old with ER- and PR- tumors. In postmenopausal women aged 50-59 with ER+PR+ and N+ tumors, chemotherapy was considered if patients were in good physical condition, and in women aged 60-69 only if 4 or more of nodes were involved.

For N0 breast cancer, systemic therapy (both chemotherapy and endocrine therapy for ER+ or PR+ tumors and chemotherapy for ER-PR- tumors) was considered for patients ≤35 years (except grade I tumors ≤1cm), and for patients >35 years with tumors ≥ 3cm, or ≥1cm and grade III, or ≥2cm and grade II. Standard chemotherapy consisted of 5 courses of FEC (fluorouracil/epirubicin/cyclophosphamide) or 6 courses of TAC (docetaxel/doxorubicin/cyclophosphamide). If chemotherapy was indicated for a Her2 overexpressing tumor, patients were treated with trastuzumab for one year after chemotherapy.

Endocrine therapy consisted of tamoxifen for five years for premenopausal women, optionally including LHRH agonist if not postmenopausal after chemotherapy. For postmenopausal women, either an aromatase inhibitor was given for five years, or tamoxifen for two years, followed by an aromatase inhibitor.

Pathology and approximate subtypes

Five subtypes of breast cancer were distinguished, namely ER+PR+Her2-, ER+PR-Her2-, ER+Her2+, ER-Her2+, and triple negative tumours. Tumours were considered ER+ and PR+ then, if more than 10% of tumour cells showed nuclear staining on immunohistochemistry (IHC). Her2 status was evaluated with at least IHC, in which 3+ was considered positive (>10% of cells with strong intensity circumferential membrane staining) and 0 and 1+ were considered negative (<10% circumferential membrane staining, or >10% with weak intensity membrane staining). In case of a 2+ IHC score (>10% circumferential membrane staining with moderate intensity), fluorescence in situ hybridization (FISH) was mandatory in addition to IHC. If FISH was used, the result of FISH overruled the result of IHC.

Endpoints

The primary endpoint was (conditional) LR as a first event within five years after diagnosis. LR was defined as any invasive breast cancer in the ipsilateral breast (including skin, biopsy tract and surgical scar) or on the ipsilateral thoracic wall including the mastectomy scar, i.e. both LR and new primary ipsilateral breast cancer were counted as LR (16).

Events between 0 and 91 days after diagnosis were regarded as synchronous with the original tumour. Patients were censored at the date of their first event (see data collection above), at the last date of follow-up, or at the date of death. If another event occurred within 91 days of the first recurrence, this was considered synchronous with the first event, and also counted as a first recurrence.

Statistical analyses were performed using SPSS [IBM Corporation, version 23.0.0.0]. Kaplan-Meier analysis was used to determine five-year LR as a first event, for the overall population and separately for five approximate subtypes of breast cancer. To check whether there was an effect of subtype independent of tumor and treatment characteristics, multivariable Cox regression was performed. Variables that were significantly associated with LR on univariable analysis, as well as those known to influence the risk of LR were included in the multivariable analysis. Missing values were disregarded, not imputed. Conditional LR (assuming *x* event-free years) was determined by selecting patients without an event at *x* years, and calculating the risk of LR within five years after diagnosis for this selection.

Results

Baseline characteristics

In total, the database contained 34.453 new breast cancers diagnosed between 2005 and 2008, of which five-year follow-up was available. Median age was 59.0 years [range: 20-100]. Of these patients, 15.382 (44.6%) were treated with mastectomy, 19.071 (55.4%) with breast conserving therapy. The majority of tumors were ER+PR+Her2- (51.6%), 11.4% were ER+PR-Her2-, 7.8% were ER+Her2+, 5.5% ER-Her2+, and 10.5% triple negative. Of 4.548 (13.2%) tumors, subtype was unknown (Table 1).

Table 1. Baseline characteristics

Median age (range)		59.0 [20-100]	Morphology	Ductal	25.833 (75.0%)
pT-stage	T0	240 (0.7%)		Lobular	3.753 (10.9%)
	T1	20.759 (60.3%)		Mixed ductal/ lobular	2.122 (6.1%)
	T2	11.547 (33.5%)		Other	2.745 (8.0%)
	T3	1.036 (3.0%)	Positive margins	No	32.504 (94.3%)
	T4	343 (1.0%)		Microscopic	1.398 (4.1%)
	Tx	528 (1.5%)		Macroscopic	49 (0.1%)
pN-stage	N0	20.884 (60.6%)		Unknown	502 (1.5%)
	N1	9.157 (26.6%)	Breast surgery	Mastectomy	15.382 (44.6%)
	N2	2.533 (7.3%)		BCT	19.071 (55.4%)
	N3	1.403 (4.1%)	Radiation therapy	Yes	23.128 (67.1%)
	Nx	476 (1.4%)		No	11.325 (32.9%)
Grade	1	7.449 (21.6%)	Chemotherapy	Yes	13.392 (38.9%)
	2	14.275 (41.5%)		*Neoadjuvant#*	*1.708 (5.0%)*
	3	10.204 (29.6%)		No	21.061 (61.1%)
	Unknown	2.525 (7.3%)	Endocrine therapy for ER+ tumors	Yes	15.281/27.628 (55.3%)
ER	Positive	27.628 (80.2%)	Trastuzumab for Her2+ tumors	Yes	2.584/4.638 (55.7%)
	Negative	6.314 (18.3%)	Trastuzumab for Her2+ tumors receiving chemotherapy*	Yes	2.560/2.926 (87.5%)
	Unknown	511 (1.5%)	Subtype	ER+PR+Her2-	17.770 (51.6%)
PR	Positive	21.750 (63.1%)		ER+PR-Her2-	3.930 (11.4%)
	Negative	10.960 (31.8%)		ER+Her2+	2.689 (7.8%)
	Unknown	1.743 (5.1%)		ER-Her2+	1.897 (5.5%)
Her2	Positive	4.638 (13.5%)		Triple negative	3.619 (10.5%)
	Equivocal	1.092 (3.2%)		Unknown	4.548 (13.2%)
	Negative	26.693 (77.4%)			
	Unknown	2.030 (5.9%)	Total		34.453

ER: estrogen receptor, PR: progesterone receptor, BCT: breast conserving therapy
** If a patient with a Her2+ tumor was eligible for chemotherapy, this patient was also eligible for trastuzumab.*
 # Included in chemotherapy 'yes', percentage of total

Local recurrence as a first event within five years in different subtypes

The incidence of LR as a first event within five years of diagnosis varied between the subtypes of breast cancer (Table 2, Figure 1). Incidence was highest in triple negative tumors (5.6%) and lowest in ER+PR+Her2- tumors (1.9%). The difference between the subtypes was significant, except for the difference between ER+PR+Her2- and ER+PR-Her2- (2.2% vs 2.4%, p=0.329); and ER+PR-Her2- and ER+Her2+ (2.4% vs 2.8%, p=0.342). The difference between ER+PR+Her2- (2.2%) and ER+Her2+ (2.8%) was significant (p=0.046).

Table 2. Risk of local recurrence as a first event (Kaplan-Meier survival estimates) within 5 years after diagnosis in different subtypes of breast cancer

	N	5-year risk of LR at diagnosis	Significance of difference between the Kaplan-Meier curves
All patients	34.453	3.0%	
Approximate subtypes			
ER+PR+Her2-	17.770	2.2%	
			} p=0.329, χ^2=0.954
ER+PR-Her2-	3.930	2.4%	
			} p=0.342*, χ^2=0.902
ER+Her2+	2.689	2.8%	
			} p<0.001, χ^2= 12.599
ER-Her2+	1.897	4.7%	
			} p=0.006, χ^2=7.535
Triple negative	3.619	6.8%	

ER: estrogen receptor, PR: progesterone receptor, Her2: Her2Neu receptor
Log Rank (Mantel-Cox) was used to compare significance between the Kaplan-Meier curves
** ER+Her2+ (2.8%) tumors did not have significantly more LR than ER+PR-Her2- (2.4%), but ER+Her2+ did have significantly more LR than the most favorable subtype ER+PR+Her2- (2.2%), p=0.046, χ^2=3.978*

Local recurrence in different subtypes: differences significant on multivariable analysis

Factors that may influence the risk of LR in different subtypes were selected based on known prognostic significance and/or univariable analysis. When corrected for the selected factors using multivariable Cox regression, the difference in LR between ER+PR+Her2- tumors and the other subtypes was still significant (p-values < 0.05, HRs, CIs and p-values in Table 3), except for the difference between ER+PR+Her2- versus ER+PR-Her2- which has a HR of 0.954 with p=0.329. Additionally, after correction for these factors, there was no longer a significant difference in LR between patients treated with mastectomy and breast conserving therapy (HR 1.234, 95% CI 0.944-1.614, p=0.124).

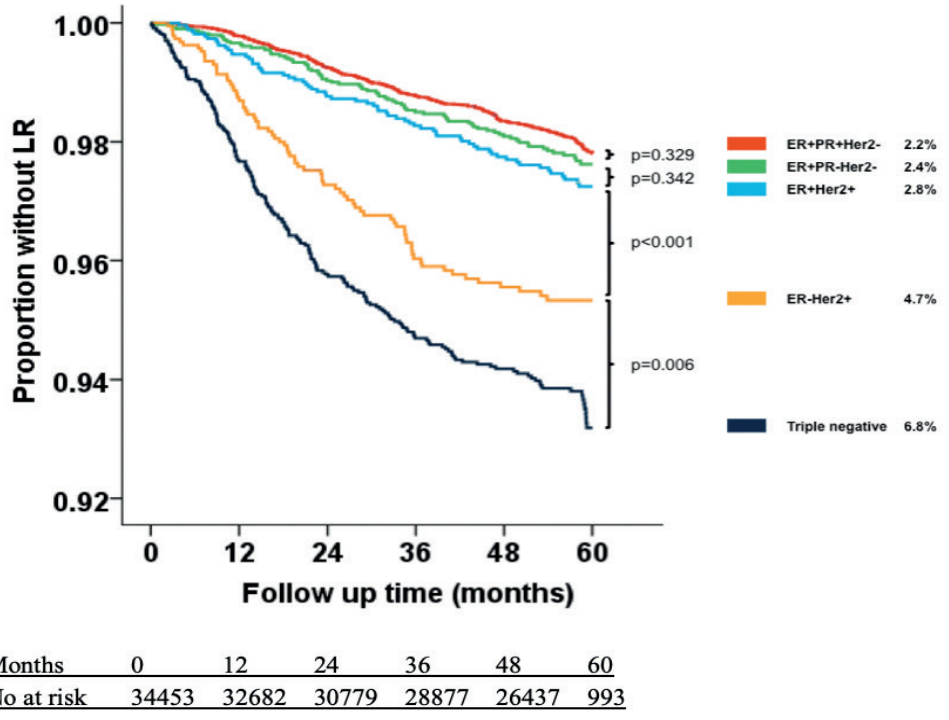

Figure 1. Kaplan-Meier estimator plot of risk of local recurrence as first event within five years after diagnosis in different subtypes of breast cancer

The effect of event-free years on the risk of local recurrence within five years

For each subtype, the risk of conditional five-year LR was calculated by selecting patients who were event free (i.e. no local, regional, or distant recurrence, no contralateral breast cancer, and no death) at 12, 24, 36, and 48 months. For each time point and each subtype, the risk of LR within five years of diagnosis (the end of regular follow-up) was calculated (Table 3). For the overall group, the risk of developing LR before the end of regular follow-up (five years) was 2.5%. This risk decreased with event-free years, to 2.0%, 1.4%, 0.9%, and 0.4% after one, two, three and four event-free years (Table 4). This decrease in risk was seen in all subtypes, and was proportionally largest in the subtypes with the highest baseline risk (triple negative and ER-Her2+ tumors). After three event-free years, the risk of developing LR before the end of regular follow-up (five years) was 1% or less in all subtypes but triple negative tumors (Table 4).

Table 3. Multivariable Cox regression to assess the impact of breast cancer subtype on five-year local recurrence as a first event, corrected for confounding factors

		HR	95% CI	p-value
Subtype vs	**ER+PR+Her2-**	*Ref*		
ER+PR-Her2-		1.134	0.876-1.467	0.341
ER+Her2+		1.535	1.120-2.105	0.008
ER-Her2+		1.525	1.044-2.228	0.029
Triple negative		2.102	1.613-2.740	<0.001
Age	Per year increase	0.992	0.984-0.999	0.019
N-stage	N+ vs N0	2.152	1.785-2.594	<0.001
T-stage	T3-4 vs T1-2	2.221	1.581-3.121	<0.001
Grade	3 vs 1-2	1.530	1.254-1.866	<0.001
Breast surgery	Mastectomy vs BCT	1.234	0.944-1.614	0.124
Radiation therapy	No vs yes	1.575	1.216-2.039	0.001
Chemotherapy	No vs yes	1.837	1.438-2.346	<0.001
Endocrine therapy No vs yes		2.428	1.934-3.049	<0.001
Trastuzumab No vs yes		1.656	1.104-2.485	0.015

Table 4. Impact of a number of event-free years on the risk of local recurrence as a first event within 5 years after diagnosis in subtypes of breast cancer

			Risk of LR within 5 years after diagnosis, assuming x event-free years - events/persons at risk (%)			
	N	**Risk of LR at diagnosis**	**After 1 event-free year**	**After 2 event-free years**	**After 3 event-free years**	**After 4 event-free years**
All patients	34453	3.0%	2.4%	1.6%	1.0%	0.6%
Approximate subtypes						
ER+PR+Her2-	17770	2.2%	2.0%	1.5%	1.0%	0.6%
ER+PR-Her2-	3930	2.4%	2.0%	1.4%	0.9%	0.5%
ER+Her2+	2689	2.8%	2.2%	1.5%	1.0%	0.4%
ER-Her2+	1897	4.7%	3.4%	2.0%	0.7%	0.2%
Triple negative	3619	6.8%	4.6%	2.7%	1.6%	1.1%

LR: local recurrence; ER: estrogen receptor, PR: progesteron receptor

Percentage of LRs occurring in each year of follow-up

On a group level (e.g. in clinical studies) it is of interest to know which proportion of LRs occurs in which years of follow-up. In ER-Her2+ and triple negative tumors, 62.4% and 69.5% of the total number of events occurred in the first two years, whereas 40% would be expected when LRs were distributed equally over five years of follow-up (100%/5 years = 20% per year). In the ER+ subtypes, the number of LRs was more equally distributed over the five years of follow-up (Table 5).

Table 5. Number of local recurrences as a first event within five years that occurred in each year of follow-up

		Number of LRs as a first event within 5 years after diagnosis that occurred in each year of follow-up				
	Total no. of LRs	**In 1st year***	**In 2nd year**	**In 3rd year**	**In 4th year**	**In 5th year**
All patients	874 (100%)	203 (23.2%)	238 (27.2%)	186 (21.3%)	127 (14.5%)	120 (13.7%)
Approximate subtypes						
ER+PR+Her2-	331 (100%)	39 (11.8%)	89 (26.9%)	77 (23.3%)	65 (19.6%)	61 (18.4%)
ER+PR-Her2-	79 (100%)	13 (16.5%)	23 (29.1%)	18 (22.8%)	13 (16.5%)	12 (15.2%)
ER+Her2+	66 (100%)	14 (21.2%)	18 (27.3%)	12 (18.2%)	12 (18.2%)	10 (15.1%)
ER-Her2+	77 (100%)	24 (31.2%)	24 (31.2%)	19 (24.7%)	7 (9.1%)	3 (3.9%)
Triple negative	203 (100%)	81 (39.9%)	60 (29.6%)	31 (15.3%)	14 (6.9%)	17 (8.4%)

** in 1st year: events within 3 months after initial diagnosis were counted as synchronous to the original tumor, thus, 1st year equals 3 months – 1 year after diagnosis.*
LR: local recurrence, ER: estrogen receptor, PR: progesterone receptor

Discussion

This population-based study of 34.453 breast cancer patients diagnosed between 2005 and 2008 showed that the risk of LR as a first event within five years after diagnosis was 3.0%. This risk differed significantly between subtypes, with triple negative tumors being at highest risk with 6.8% and ER+PR+Her2- at the lowest with 2.2%. The difference (ER+PR+Her2- compared to the other types) remained significant when corrected for age, T-status, N-status, grade, type of breast surgery, radiation therapy, chemotherapy, endocrine therapy, and trastuzumab (except ER+PR+Her2- compared to ER+PR-Her2-). With increasing number of event-free years, the risk of having a LR before the end of regular 5-year follow-up decreased. After three event-free years, the risk was 1.0% or less in all subtypes except triple negative breast cancer (1.6%). The decrease in the first four years after diagnosis was most pronounced in the higher risk subtypes, namely triple negative (6.8% to 1.1%) and ER-Her2+ (4.7% to 0.2%) tumors.

In clinical practice, this means that a breast cancer patient who has been event-free for three years, has a risk of 1% or less developing LR as a first event before the end of regular five year follow-up (unless triple negative, than 1.6%). In a research setting (for instance, in a study using LR as an endpoint) for every 100 event-free patients after three years of follow-up, one LR can be expected if follow-up is continued until five years. This suggests that although recurrences do occur later in follow-up, three-year results may produce similar results to five years, depending on the size of the study.

Our results are in line with publications on breast cancer survival and other cancers, suggesting that improvement with event-free years is greatest for tumors with the worst baseline prognosis.[8-11] The results reflect that ER- (particularly triple negative) tumors show relatively many early LRs (within two years), whereas ER+ tumors have a fairly constant rate of LRs throughout the five years of follow-up. A study investigating conditional disease-free survival in relation to subtype also showed that ER- tumors conditional DFS improved but suggested that conditional survival decreased for ER+ tumors. This study was limited by a very small number of patients at risk after more than three disease-free years (17).

The strength of this approach is the large, nationwide and comprehensive database, which includes substantial numbers of patients, even of the less common subtypes. Further, this study provides specific percentages of the chance of LR after a number of event-free years. Although the information on conditional LR can be partly deduced from the slope of the Kaplan-Meier curve, these exact percentages help using the information on the declining risk for determining the use of continued follow-up, both in clinical practice and breast cancer research. Limitations of this study are the lack of follow-up beyond five years, which would have been useful especially for ER+ tumors, in which late recurrences are known to occur (18). van Maaren et al. showed that the risk of ten-year LR was lowest for the luminal A subgroup (3.9%) and highest in triple negative disease (5.6%) and decreased with the number of event-free years. After nine event-free years, the risk ranged between 0.5 and 0.8% (21).

Further, in a population that was treated according to a guideline, confounding by severity will occur. This is partially overcome by multivariable analysis. Furthermore, confounding by severity is less important in this analysis compared to other studies, as determining exact estimates of the hazard ratios for treatment and tumor characteristics was not an objective of this study. Presented hazard ratios should be interpreted with caution. Furthermore, due to the inclusion period, tumors were classified according to the 6th edition of the AJCC TNM classification. This is, in terms of primary tumor and LR, the same as the current 7th edition (14). Finally, in this study, no distinction was made between "true recurrences" and ipsilateral second primary breast cancers, both were counted as local events (consistent

with an earlier consensus project (16)). This may lead to a higher estimate of LR when compared to studies that do make this distinction.

These results may be used as a starting point for tailoring follow-up to individual needs, both in clinical practice and for breast cancer research. First, a patient who has been event-free for three years may ask about the benefit of continued follow-up visits with physical examination and/or mammography to detect LR. Follow-up visits may have different goals beside detecting LR, including monitoring endocrine therapy and encouraging its use, monitoring and treating other side effects of breast cancer treatment, evaluation of psychosocial concerns, and patient reassurance. However, for some patients, a less than 1% chance of finding a LR may be a reason to discontinue follow-up or tailor it to individual needs. National guidelines may use this information to allow personalized decisions about the duration of follow-up. Different guidelines propose slightly different but similar recommendations for follow-up frequency in the first five years, and also differ in their recommendations after five years (return to screening program, continued annual mammograms, no recommendations) (4,5,7,19). Of these guidelines, only the ASCO guideline recommends to consider patient preferences and personal risk, based on age, specific diagnosis, and treatment protocol. None of these guidelines describe which specific patient and tumor characteristics should prompt higher or lower frequency or duration of follow-up. Data on conditional LR in relation to subtype may be used as a starting point for tailoring follow-up to individual patients. An even more personalized risk might be calculated with a nomogram, such as proposed by Witteveen et al. (20), partly on the same population. This model, however, does not incorporate the effect of trastuzumab. Additionally, for breast cancer research using LR as an endpoint, the information on the pattern of LR may be used to determine optimal follow-up time for clinical studies.

In conclusion, in this nationwide database including 34.453 breast cancer patients diagnosed between 2005-2008, the incidence of LR as a first event within five years was low overall with 3.0%. The incidence was different between subtypes of breast cancer, ER+PR+Her2- tumors posed the lowest risk and triple negative tumors the highest. The risk of developing a LR within five years of diagnosis decreased with event-free years. After three years, this risk was 1% or less in all subtypes except triple negative cancers. This improvement in prognosis is reassuring to patients during follow-up. It also suggests that follow-up beyond three years may have limited yield when it comes to finding additional LR, both for individual patients and clinical studies using LR as the primary outcome. Although there are many reasons to choose longer follow-up, this may be a starting point to tailor follow-up duration to individual needs and preferences.

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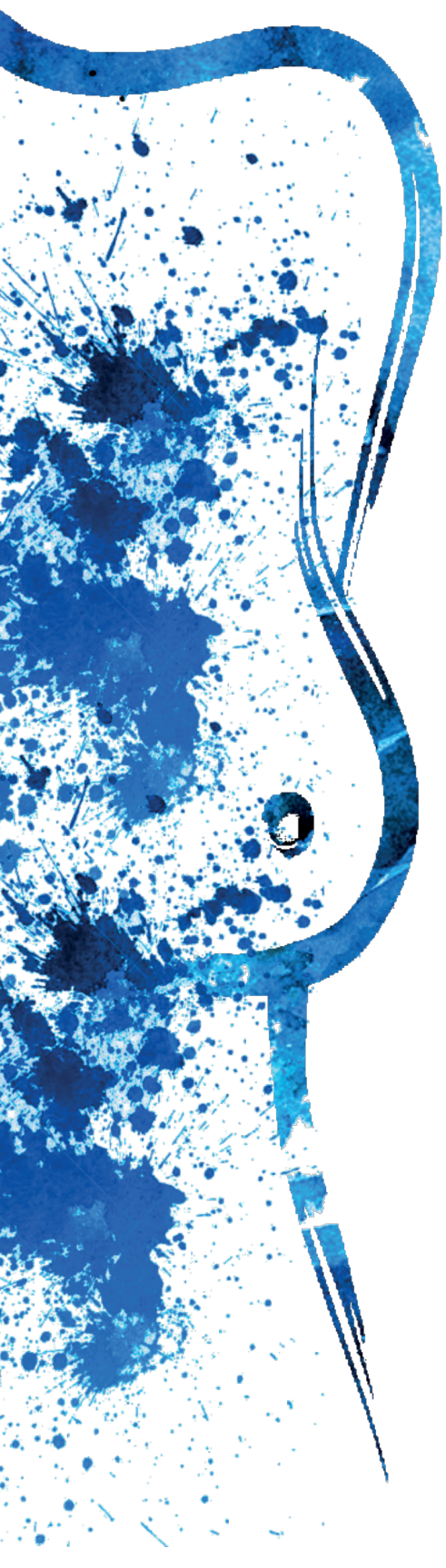

CHAPTER 8

NOVEL STAGING SYSTEMS INCORPORATING TUMOR BIOLOGY IN ESTROGEN RECEPTOR POSITIVE AND HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR NEFGATIVE BREAST TUMORS

EMBARGOED

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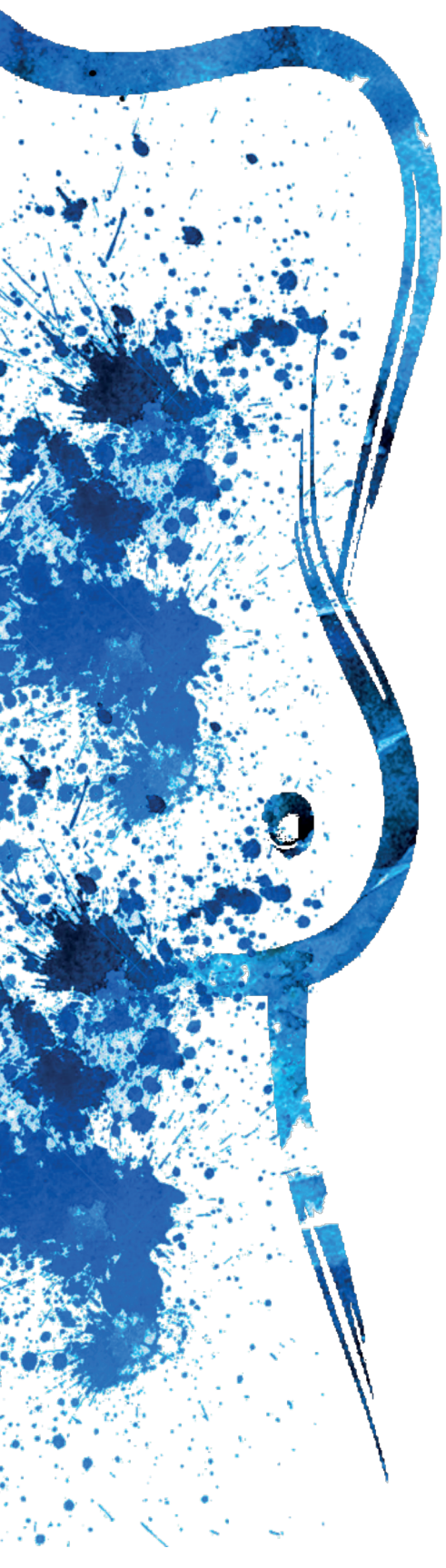

CHAPTER 9

DISCUSSION AND FUTURE PERSPECTIVES

Discussion

Axillary lymph node treatment for early breast cancer patients has changed dramatically in the past decades. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial started in 1970 by showing that a delayed axillary lymph node dissection (ALND) in clinically node negative breast cancer patients who developed clinically node positive disease during follow-up, did not affect recurrence and survival after 25-years follow up (1).

In 1994, the sentinel lymph node biopsy (SLNB) was introduced as a less invasive technique to assess the axillary lymph node status in clinically node negative patients (2,3). Subsequently, completion ALND was no longer performed in patients with a negative SLNB. More recently, the American College of Surgeons Oncology Group (ACOSOG) Z0011, the International Breast Cancer Study Group (IBCSG 23-01), and Agencia d' Avaluació de Tecnologia i Recerca Mediques (AATRM) 048/13/2000 trials showed that completion ALND could also be safely omitted in clinically node negative breast cancer patients treated with breast conserving therapy (BCT) and micro and/or limited macrometastases in the SLNB (4-8). Finally, the After Mapping of the Axilla, Radiotherapy or Surgery? (AMAROS) and Optimal Treatment Of the Axilla Surgery Or Radiotherapy (OTOASOR) trials introduced axillary radiotherapy (RT) as an alternative axillary treatment and showed no additional benefit of completion ALND compared with axillary RT in breast cancer patients with limited nodal tumor burden (9-12).

The aim of this thesis was to specify a subset of early breast patients in whom axillary treatment can be reduced, thereby lowering axillary morbidity rate and improving quality of life (QoL) while maintaining equal disease control and survival in early breast cancer. Part one of this thesis described the effect of omitting completion ALND in patients not meeting the inclusion criteria of previous mentioned randomized controlled trials (RCTs) (patients with extracapsular extension (ECE) in the sentinel lymph node (SLN) or treated with mastectomy). The second part described the next step in reducing axillary overtreatment by investigating whether the SLNB could be safely omitted in a subset of early breast cancer patients. In part three the follow-up period for current trials in reducing axillary overtreatment in early breast cancer patients was optimized and different staging systems based on tumor biology were investigated. Findings of this thesis are summarized and discussed in the following chapter.

Part I – Omission of the completion axillary treatment

Axillary treatment of early breast cancer patients changed by previous mentioned RCTs showing that completion ALND can be safely omitted in clinically node negative patients T1-2 (tumor size up to 3.5 cm in AATRM 048/13/2000) with limited SLN metastases (one to two macrometastases in ACOSOG Z0011, micrometastases in IBCSG 23-01 and AATRM 048/13/2000) treated with BCT (ACOSOG Z0011, IBCSG 23-01, and AATRM 048/13/2000) or mastectomy (IBCSG 23-01, AATRM 048/13/2000). Although results were implemented in clinical practice, the ACOSOG Z0011 trial was closed prior to the targeted accrual (n =1900), because the event rate was lower than anticipated at the time of study design (3). Despite prior closure, the ACOSOG Z0011 trial was able to demonstrate the non-inferiority of SLNB alone compared to completion ALND in clinically node negative breast cancer patients with up to two macrometastases in the SLN treated with BCT (4).

It was also discussed that the patient and tumor characteristics of the ACOSOG Z0011 and IBCSG 23-01 trials were not representative for all breast cancer patients: the number of estrogen receptor (ER) negative tumors were low (17% in the ACOSOG Z0011 versus 10% in the IBCSG 23-01), with high incidence of only micrometastases in the SLNB (37 - 44.8% in the ACOSOG Z0011), a median age of 55 years, and no patients with ECE in the SLN (13). Therefore, it was commented that these results might indicate selection bias and consequently only support safe omission of completion ALND in a specific subset of early breast cancer patients. However, breast cancer most commonly occurs in older women and about 80% of all breast cancer tumors are ER positive. The ACOSOG Z0011 showed no increased risk of locoregional recurrence (LRR) in ER positive compared to ER negative patients (4).

Mastectomy treated patients

Clinically node negative T1-2 breast cancer patients treated with mastectomy were not included in the ACOSOG Z0011 trial (4, 5), and underpowered in the IBCSG 23-01 (86/931) (6, 7), AATRM 048/13/2000 (28/233) (8), AMAROS (248/4.806) (9, 10) and OATASAR trials (44/2.106) (11, 12). Only the IBCSG 23-01 trial performed a subgroup analysis suggesting that omission of completion ALND might be acceptable for patients undergoing mastectomy as well [HR 0.52, 95%CI 0.09 – 3.10] (6, 7). In addition to the multicenter RCTs, three retrospective studies compared mastectomy and BCT treated patients in whom completion ALND was omitted after positive SLNB (14-16). There was no significant difference in regional recurrence (RR) in patients treated with mastectomy compared to BCT in whom completion ALND was omitted after positive SLNB (Milgrom et al. RR 1.2% vs. 1.0%, p = 0.5 and Fitz-Sullivan et al. RR 1.6% vs. 3.8%, p = 0.45) (14, 15).

Snow et al. and Fitz-Sullivan et al. showed no difference in survival rate for mastectomy patients treated with SLNB alone compared to SLNB followed by completion ALND (15, 16). Milgrom et al. showed a higher survival rate for mastectomy compared to BCT treated patients with a positive SLNB without completion ALND (disease-free survival (DFS) 94.8% vs. 90.1%, p = 0.02 and overall survival (OS) 92.6% vs. 97.8%, p = 0.002) (14). Due to this last and limited evidence, completion ALND remained standard of care for clinically node negative breast cancer patients with a positive SLN treated with mastectomy.

A Dutch population-based study showed that completion ALND was omitted more often in BCT (69%) compared to mastectomy (48%) in clinically node negative T1-2 SLNB positive breast cancer patients between 2011 to 2015 (p <0.001) (17). The number of patients receiving completion ALND declined for both BCT and mastectomy over the years. However, for mastectomy treated patients, omission of completion ALND was applied later compared to BCT (17), which can be explained by the limited evidence for mastectomy patients. Chapter 2 showed that clinically node negative T1-2 breast cancer patients with positive SLNB treated with mastectomy patients are more likely to receive completion ALND than BCT treated patients (71.0% versus 26.6%, p<0.001). Mastectomy and BCT are equivalent as surgical treatment for breast cancer patients. Majority of the included mastectomy patients (68.4%) could have avoided completion ALND if they had opted for BCT instead of mastectomy. During patients shared-decision making process, clinicians should be mentioning the consequence for axillary treatment when choosing mastectomy instead of BCT, with the potential risk of associated morbidity such as seroma, lymphedema, nerve injury, and limited shoulder function (18, 19).

Currently, several RCTs are investigating whether completion ALND could be omitted in mastectomy patients as well (POSNOC, SINODAR ONE and SENOMAC trial) (20-22). The POsitive Sentinel NOde: Clearance or axillary radiotherapy (POSNOC) from the United Kingdom is currently including 1.900 early stage breast cancer patients with unifocal or multifocal cT1-2N0 treated with BCT or mastectomy with one or two macrometastases in the SLNB. Patients are randomized to adjuvant systemic therapy alone or adjuvant systemic therapy with axillary treatment, consisting of completion ALND or axillary RT (20). July 2021, inclusion of 1.900 patients was completed. The Italian multicenter SINODAR ONE trial currently includes 2.000 patients aged ³40 and £75 years with unifocal cT1-2N0 breast cancer treated with BCT or mastectomy with one or two macrometastases in the SLNB (21). Patients are randomized to completion ALND with adjuvant systemic therapy or adjuvant systemic therapy only. In total, 900 patients were included, recruitment was closed in April 2020. The SENOMAC trial includes 3.500 cT1-3N0 breast cancer patients treated with BCT or mastectomy with up to two macrometastases in the SLNB to completion ALND or watchful waiting (22). Until October 2022, 2.750 patients were included. The

Dutch BOOG 2013-07 trial was the only RCT designed to randomize cT1-2N0 breast cancer patients treated with mastectomy and with up to three macrometastases in the SLN to axillary treatment (completion ALND or axillary RT) or SLNB only (watchful waiting) (23). Unfortunately, this RCT was closed prematurely due to slow accrual rates. Most important reason was the randomized controlled design of the study and current trend of omitting completion ALND. Clinicians and patients were not eager to randomize between completion axillary treatment or watchful waiting, but patients opted for watchful waiting in the context of shared decision making, and did not want the 50% risk of randomizing to completion axillary treatment. A patient preference trial would probably have been more successful. Furthermore, clinical practice caught up science: majority of the study population are nowadays treated with neoadjuvant systemic therapy, thereby allowing lymph node metastases to convert to axillary pathologic complete response and are therefore in need of modified axillary treatment strategies. First results of current POSNOC, SENOMAC and SINODAR ONE are not expected before 2025.

Extracapsular extension

Patients with ECE in the SLN were excluded in the ACOSOG Z0011 and IBCSG 23-01 trial and ECE was not mentioned in the AATRM 048/13/2000 trial (4-8). ECE is defined as extension of neoplastic cells through the nodal capsule into perinodal adipose tissue in case of positive SLN (24). Earlier, presence of ECE had no consequence for nodal treatment. However, ECE is associated with presence of additional non-SLN metastases and other prognostic factors, such as lymph vascular invasion and macrometastases (25-32). Since patients with ECE in SLN were excluded, it remained unclear whether completion ALND could also be safely omitted in clinically node negative breast cancer patients with ECE in the SLNB. In response to the publication of the ACOSOG Z0011, Gooch et al. was the first to investigate whether patients with ECE in the SLN needed to be treated with completion ALND. Of the patients with ECE >2 mm, 33% had ≥4 lymph node metastases at completion ALND, compared to 9% in patients with ECE <2 mm ($p < 0.0001$). ECE appeared to be the strongest predictor of involvement of ≥4 lymph node metastases (33).

Chapter 3 was the first study to evaluate the effect of ECE in the SLNB on the involvement of ≥4 lymph node metastases at completion ALND in combination with five-year DFS and 10-year OS. Results showed that despite increased nodal tumor burden (involvement of ≥4 lymph node metastases at completion ALND) in patients with ECE in the SLN (15.7% vs. 5.8%, $p <0.001$), patients did not have inferior five-year DFS (86.4% versus 88.8%, $p=0.085$). Ten-year OS rate was 78.6% compared to 83.0%, respectively ($p=0.018$). However, cox regression analysis showed that ECE was not an independent prognostic factor for both DFS and OS. (34).

In addition, Barrio examined the effect of microscopic ECE in the SLN on LRR in 811 patients with clinically node negative T1-2 breast cancer. No RR was observed at a median follow-up of 41 months. In total, 11 nodal recurrences (two supraclavicular and axillary, four ipsilateral breast tumors, and five distant recurrence) were observed. The five-year LRR rate was 1.6% and did not differ in case of microscopic ECE (2.3% vs. 1.3%; $p = 0.84$). This study concluded that presence of microscopic ECE in the SLN should not be an indication for completion ALND, but could be one of many factors that should be considered in determining the optimal locoregional treatment (35).

Currently, patients with ECE in the SLN are still treated with completion ALND (or axillary RT). Therefore, it is important that current ongoing trials include patients with ECE in order to demonstrate if omission of completion axillary treatment is safe in this subgroup of patients as well. Clinically node negative T1-2 breast cancer patients with ECE in the SLN are included in the POSNOC trial (18). The study protocol of the SINODAR ONE and SENOMAC trials do not mention ECE as in- or exclusion criterium (21, 22).

Part II – Omission of the sentinel lymph node biopsy

Studies showed that completion ALND can be safely omitted in a subset of early breast cancer patients, the value of pathological lymph node status and therefore SLNB is also being questioned. Three ongoing (i.e. BOOG 2013-08, SOUND and INSEMA) trials are currently investigating whether the SLNB can be safely omitted in clinically node negative T1-2 breast cancer patients treated with BCT (1-3). Chapter 4 presented the study design of the Dutch BOOG 2013-08 multicenter RCT. Clinically node negative T1-2 breast cancer patients treated with BCT are randomized to SLNB or watchful waiting (no SLNB). Although morbidity rates of SLNB are lower compared to ALND, it still is an invasive staging method leading to (mostly transient) symptoms like numbness, paresthesia or impairment of arm mobility, but could even result to (chronic) lymphedema and decreased QoL (36, 37).

Earlier, the SLNB was performed to obtain prognostic information, maintaining RR and improve survival. The identification rate of the SLNB is 95%, false-negative rate (FNR) of 4% and negative predictive (NPV) of 96% (38-43). Less than 20% of the clinically node negative breast cancer patients have a positive SLNB. Patients treated with BCT are more likely to have micrometastases or negative SLNB compared to patients treated with mastectomy. Furthermore, studies showed that the 10-year RR rates are very low for

clinically node negative patients treated with BCT (44). WBRT following breast conserving surgery contributes to the elimination of possible lymph node metastases left in situ. Wely et al. showed that WBRT is associated with a significantly lower RR rate after a negative SLN procedure (45). The study of Van Roozendaal et al. showed that 55% of axilla level I and II receive 95% of the prescribed dose by whole breast irradiation (46). Adjuvant systemic therapy is also known to decrease local recurrence (LR) and RR rates (41). Pathologic complete response rates of 20-40% for axillary lymph node metastases following neoadjuvant systemic therapy demonstrate that systemic therapy eradicates lymph node metastases left in situ (47-51). Previous mentioned RCT (ACOSOG Z001, IBCSG 23-01 and AATRM 048/13/2000 trials) showed that by omission of completion ALND, RR rates were low and survival rates were not affected.

Other reasons to perform an SLNB are to obtain prognostic and treatment information. The outcome of the SLNB is generally used for adjuvant chemo- hormone-, targeted and radiation therapy recommendations and to predict response to therapy. A consequence of omitting SLNB is the absence of pathological lymph node status information. Medical oncologists expressed their concerns that patients with known tumor characteristics but unknown pathological lymph node status could be at risk for chemotherapy undertreatment, potentially resulting in an increased risk of distant metastasis and decreased DFS and OS. Yet, the study of Van Roozendaal et al. showed that pathological lymph node status changed the decision to recommend adjuvant systemic treatment in only 1.0% of the patients when using Adjuvant! Online and in 3.6% using Dutch breast cancer guideline (52). Furthermore, the diagnostic tool of the SLNB could be replaced by gene expression profiles using the primary tumor.

Inclusion of the BOOG 2013-08 started medio 2015 at the Maastricht University Medical Center. Currently, all patients were included, first follow-up results are expected in 2026 (53). Two other European RCTs are currently investigating whether the SLNB can be safely omitted in early breast cancer patients treated with BCT (INSEMA and SOUND trial) (54,55). The German Intergroup-Sentinel-Mamma (INSEMA) Trial included clinically node negative T1-2 breast cancer patients. Patients were randomized to SLNB or no SLNB. Secondly, patients randomized to SLNB with 1-3 macrometastases in the SLN were randomized to SLNB alone or completion ALND (54). Until October 2022, 5.154 patients were included.

The Italian Sentinel Vs. Observation After Axillary Ultra-souND (SOUND) trial randomized clinically T1 (<2cm) node negative tumors treated with BCT to SLNB or watchful waiting (55). This RCT was closed prematurely (n=1.463 in June 2017) due to

stagnation of the inclusion rate, because the study design forced patients with positive SLN to be treated with completion ALND. Results are expected to be published late 2021. The SOUND trial published the physical function of the ipsilateral upper limb of the first included 176 patients (94 in SLNB arm and 82 in watchful waiting arm). Preliminary results showed that patients who underwent SLNB had a significantly higher rate of disability (increase to 24%) in the early post-operative period (after six and twelve months) compared to patients who were randomized for watchful waiting (increase 10.6%) (56).

Axillary ultrasound

European guidelines advise physical examination followed by axillary ultrasound (US) to assess the preoperative axillary lymph node status in newly diagnosed breast cancer patients (57). American guideline describes its use in case of palpable lymph nodes only (58). In contrast to previous Z0011 and IBCS 23-01 trials, current BOOG 2013-08, SOUND and INSEMA trials adopted standard axillary US in their study protocol.

The influence of breast cancer subtypes on the diagnostic performance of axillary US was unknown. Breast cancer subtypes have become important, since they have different patterns of disease presentation, metastatic spread and response to treatment (59-64). Chapter 5 evaluated whether the diagnostic performance, in particular negative predictive value (NPV), of axillary US differs per subtype of breast cancer (ER+ progesterone receptor (PR)+ human epidermal growth factor receptor 2 (HER2)-, HER2+ and ER-PR-HER2-). A total of 1.129 breast cancer cases were included. Sensitivity, specificity and accuracy of axillary US did not significantly differ between these three breast cancer subtypes. But there was in fact a significant difference for NPV between ER-PR-HER2- tumors and HER2+ tumors (90.3% vs. 80.2%, p=0.05) and between HER2+ and ER+PR+HER2- tumors (80.2% vs. 87.2%, p = 0.04). This difference can be explained by the different prevalence of axillary lymph node metastases among the breast cancer subtypes (highest in HER2+ tumors with 32.7% and lowest in ER-PR-HER2- tumors with 15.8% (65). Helfgott et al. also investigated the influence of breast cancer subtypes on axillary ultrasound accuracy and showed that sensitivity was significantly lower in luminal A and B tumors (25.0% and 39.8%) compared to triple negative (68.8%) and HER2+ tumors (71.4%, p = 0.0032). There were no significant differences between the breast cancer subtypes with respect to specificity, PPV and NPV (66). Recruitment of patients of all different breast cancer subtypes remains important for current RCTs that investigate the role of SLNB.

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

RR is the most common used endpoint in several recent and ongoing trials investigating the reduction of axillary treatment in clinically node negative T1-2 breast cancer patients. Most studies report their first results after only five or 10-years of follow-up. It has been suggested that most RRs, an often chosen study endpoint, occur in the first few years after diagnosis. Chapter 7 and 8 showed that the risk in the first five years after diagnosis was low with LR of 3.0% and RR of 1.3% in clinically node negative T1-2 breast cancer patients (67, 68). The risk of and LR decreased from 3.0% to 1.0% after three-event-free years and RR decreased from 1.3% at baseline to 0.8% after two event-free years. The low absolute yield suggests that longer follow-up is of limited value for RR and allows first disclosure of results after three years instead of five or 10-years, and may speed up implementation of RCT outcome.

Breast cancer subtypes have become more important for patient tailored treatment. Tailoring follow-up to breast cancer subtypes is first step towards reacting to the biologic behavior of the tumor. Chapter 7 and 8 investigated the risk of LR and RR in different subtypes of breast cancer (ER+PR+HER2-, ER+PR-HER2-, ER+HER2+, ER-HER2+, and ER-PR-HER2-). Majority of tumors were ER+PR+HER2- (51.6 – 55.1%), followed by ER+PR-HER2- (11.3 – 11.4%), triple negative (9.5 - 10.5%), ER+HER2+ (6.8 - 7.8%), and ER-HER2+ (3.7 - 5.5%). The risk of LR varied for different subtypes with the highest incidence in triple negative tumors (6.8%) and lowest in ER+PR+HER2- tumors (2.2%). The fastest decrease was seen in subtypes with the highest baseline risk (ER-HER2+ from 4.7% at baseline to 0.2% after five years of follow-up and triple negative tumors from 6.8% to 1.1%, respectively). The risk of RR was also highest for triple negative (3.7%) and lowest for ER+PR+HER2- tumors (0.8%). The fastest decrease was seen in triple negative tumors, the subtype with the highest baseline at risk (3.7% at baseline to 0.4% after five years of follow-up). The slowest decrease was seen in subtypes with the best prognosis at baseline (ER+PR+HER2- from 0.8% at diagnosis to 0.2% after five-years of follow-up and ER+HER2+ tumors from 0.4% to 0.4%, respectively). Van Maaren et al. showed luminal B and HER2 positive tumors treated with adjuvant trastuzumab had better outcomes compared to patients not treated with adjuvant trastuzumab (69).

Longer follow-up might be necessary for ER+ patients, since the effect of endocrine therapy on conditional recurrence in ER+ breast cancer patients after five years of diagnosis is unknown.

Breast cancer is usually staged according to the TNM system based on tumor size, lymph node status, and presence or absence of distant metastasis. Despite that subtypes of breast cancer have become more important for patient tailored treatment; tumor biology is not yet included in the TNM staging system. The 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system recognized the lack of tumor biology and introduced a prognostic stage group that is based on combination of the anatomic stage group with tumor grade, ER, PR, and HER2 receptor status (70). Bioscore, another novel staging system, includes pathologic tumor size, lymph node status, and tumor biology in terms of tumor grade, ER and HER2 receptor status (71). In Chapter 8 the five- and 10-year recurrence-free survival (RFS) for the anatomic and prognostic stage group of the 8th AJCC TNM system and the Bioscore staging system were compared for ER+HER2- breast cancer patients. Ten-year RFS using the anatomic stage group of the 8th AJCC TNM system ranged from 52.9 - 83.4% (stage IIIC and IIA) and from 31.8 - 84.6% using the prognostic stage group (stage IIIC and IA+B). Weiss et al. showed that the prognostic stage group provided a more accurate five-year DSS stratification compared to anatomic stage group (C-statistic 0.84 versus 0.81) (72).

Ten-year RFS using the Bioscore staging system ranged from 47.1-85.1% (Bioscore 6 and 1). Mittendorf et al. reported a five-year DSS ranged from 33.3% to 100% for different tumor stages using Bioscore, compared to 79.5% to 99.1% using the anatomic stage group of the 7th AJCC TNM staging system (71, 72). Both systems similarly discriminated groups according to the risk of recurrence, with comparable c-statistic score (anatomic stage group 0.58, prognostic stage group 0.60, and Bioscore staging system 0.60). However, the prognostic stage group (IIIC) identified a group with a very poor prognosis (31.8%) which could not be identified using the other staging systems (stage IIIC, 52.8% or Bioscore 6, 47.1%). Based on these results we would like to suggest that hospitals, who have access to analysis of biological factors, use the prognostic stage group (or Bioscore) in addition to the anatomic stage group of the 8th AJCC TNM staging system to determine a more patient-tailored prognosis.

Conclusions and recommendations

The aim of this thesis was to specify a subset of early breast cancer patients in whom axillary treatment can be reduced, thereby reducing axillary morbidity and improve QoL of these patients. Though, the road towards less axillary treatment is not finished yet. Ongoing POSNOC, SENOMAC and SINODAR ONE trials will answer the question whether completion axillary treatment can be safely omitted in clinically node negative breast cancer patients with positive SLN treated with mastectomy as well. Meanwhile,

if patients have the ability to choose between mastectomy and BCT, it should be noted that extensive axillary treatment might be avoided in case of BCT. This thesis appoints the importance of including patients with ECE in the trials to demonstrate the safety of reducing axillary treatment in this subgroup of patients. Ongoing BOOG 2013-08, SOUND and INSEMA trials will answer the question whether SLNB can be safely omitted in clinically node negative breast cancer patients treated with BCT. Axillary ultrasound should be performed in clinically node negative breast cancer patients despite of the breast cancer subtypes. Studies showed that the risk of LR and RR are low and different patterns of LR and RR were seen in different breast cancer subtypes. 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 in both clinical and research setting. The prognostic stage group and Bioscore are novel staging systems for breast cancer patients, combining the traditional AJCC with tumor biology. Hospitals who have access to analysis of biological factors should use the prognostic stage group (or Bioscore) in addition to the anatomic stage group of the 8th edition of AJCC TNM staging system to determine a more patient-tailored prognosis.

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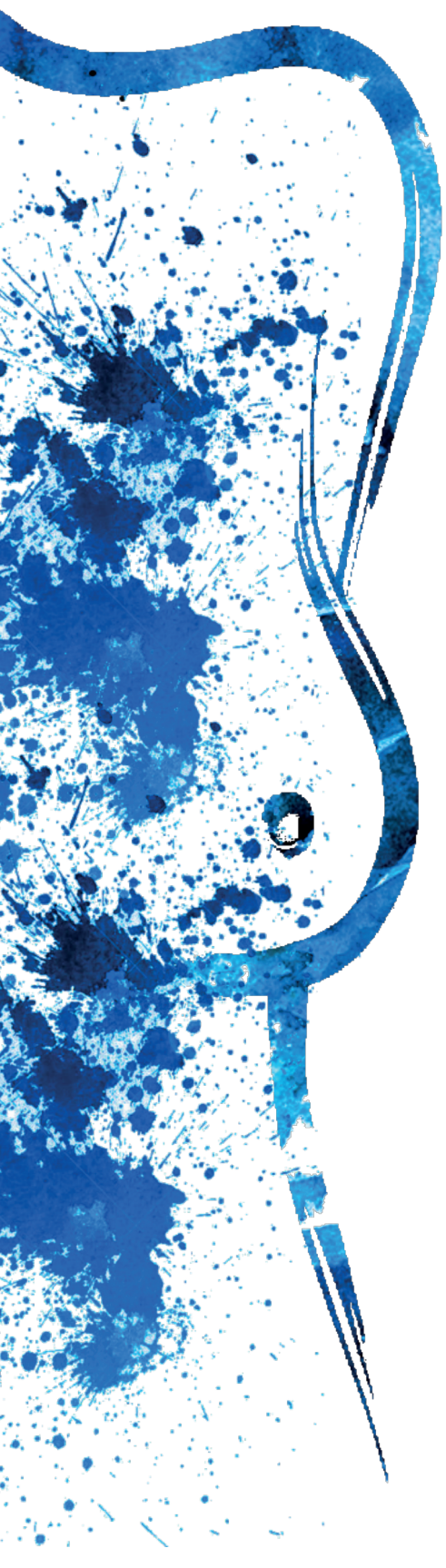


Chapter 10

SUMMARY

Summary

This thesis aimed to specify a subset of early breast cancer patients in whom axillary treatment can be reduced while remaining disease control and survival, thereby reducing axillary overtreatment and morbidity, and improving quality of life (QoL) in early breast cancer survivors. The second aim of this thesis was to optimize the follow-up period for trials in early breast cancer patients and to investigate different staging systems based on tumor biology.

Part I – Omission of completion axillary treatment

Based on previous randomized controlled trials (RCTs), completion axillary lymph node dissection (ALND) is often omitted in patients with a positive SLN treated with breast conserving therapy (BCT), but still standard of care in case of mastectomy. **In Chapter 2** of this thesis we investigated in whom completion ALND could be avoided by choosing BCT instead of mastectomy. In the study cohort, completion ALND was performed in 71.0% of SLN positive mastectomy patients and in 26.6% in case of BCT ($p < 0.001$). Of the included patients, 68.4% could avoid completion axillary treatment if they had opted for BCT instead of mastectomy. Clinicians should appoint this during shared-decision making process.

Currently, patients with extracapsular extension (ECE) in the sentinel node (SLN) are standardly treated with completion axillary treatment (ALND or axillary radiotherapy (RT)). In **Chapter 3** we investigated whether ECE in the SLN is associated with involvement of more than three lymph node metastases at completion ALND and the effect on five-year disease-free survival (DFS) and 10-year overall survival (OS). This chapter showed that clinically node negative T1-2 breast cancer patients with ECE in the SLN was associated with involvement of more than three lymph node metastases (15.7% vs. 5.8%, $p < 0.001$). However, patients with ECE in the SLN did not have an inferior five-year DFS (86.4% vs. 88.8%, $p = 0.085$) and 10-year OS (78.6% vs. 83.0%, $p = 0.018$). Currently, patients with ECE in the SLN are still treated with completion ALND or axillary RT. Therefore, it is important that current ongoing trials include patients with ECE in order to 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

Chapter 4 described the rationale and study design of a Dutch prospective multicenter RCT: the BOOG 2013-08. Clinically node negative T1-2 breast cancer patients treated with BCT are randomized to sentinel lymph node biopsy (SLNB) or watchful waiting (no SLNB). This RCT is currently including patients in 26 hospitals in the Netherlands.

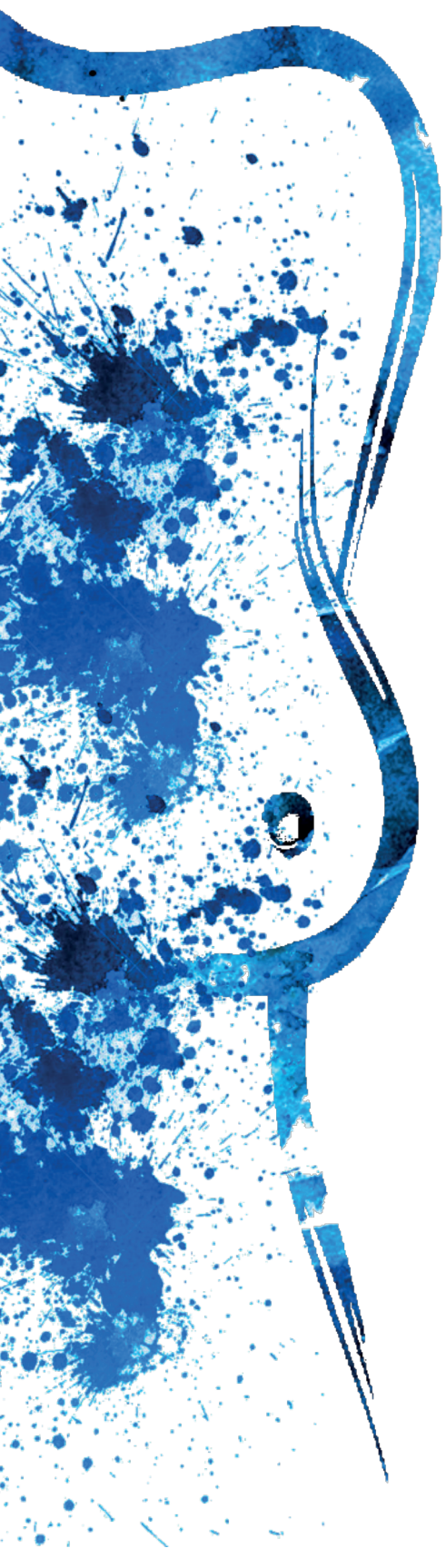
Chapter 5 evaluated whether the diagnostic performance, in particular negative predictive value (NPV), of axillary ultrasound (US) differs per breast cancer subtype, comparing ER+PR+HER2- to HER2+ and ER-PR-HER2- tumors. Sensitivity, specificity and accuracy of axillary US did not significantly differ between these breast cancer subtypes. Though there was a significant difference for NPV between ER-PR-HER2- tumors and HER2+ tumors (90.3% versus 80.2%, p = 0.05), and between HER2+ and ER+PR+HER2- tumors (80.2% versus 87.2%, p = 0.04), 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 (32.7%) and lowest in ER-PR-HER2- tumors (15.8%). Recruitment of patients of all different breast cancer subtypes remains important for the current RCTs that investigate whether the SLNB can be safely omitted in early breast cancer patients.

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

Chapter 6 and 7 investigated the occurrence of local recurrence (LR) and regional recurrence (RR), and the influence of event-free years in different subtypes of breast cancer (ER+PR+HER2-, ER+PR-HER2-, ER+HER2+, ER-HER2+, and ER-PR-HER2-). The overall risk of recurrence in the first five years after diagnosis was low with LR of 3.0% and RR of 1.3% in clinically node negative T1-2 breast cancer patients. The risk of LR and RR varied for different subtypes with the highest risk in triple negative (LR 6.8% and RR 3.7%) and lowest in ER+PR-HER2- tumors (LR 2.2% and RR 0.8%). Patients with highest risk at baseline showed proportionally the highest peak (i.e. triple negative, RR from 3.7% at diagnosis to 0.4% after five years of follow-up). **Chapter 6** showed that the risk of RR in the three years after two event-free years was negligible (0.8%), meaning that for every 125 event free patients after two years, only one RR can be expected in the upcoming three years. Similar results are presented for the risk of LR in **Chapter 7:** after three years of follow-up the risk of LR was only 1.0%. This suggests that longer follow-up is of limited value for LR and RR and could lead to earlier publication and implementation of results of current RCTs.

The prognostic stage group of the 8th edition of the American Joint Committee on Cancer (AJCC) TNM system and Bioscore are novel staging systems for breast cancer patients, combining the traditional anatomic stage group of the 8th edition of the AJCC TNM staging system with tumor biology. **In Chapter 8** the five- and 10-year recurrence-free survival (RFS) for the anatomic and prognostic stage group of the 8th edition of the AJCC TNM system and the Bioscore staging system were compared for ER+HER2- breast cancer patients. Ten-year RFS using the anatomic stage group ranged from 52.9 - 83.4% (stage IIIC and IIA) and from 31.8 - 84.6% using the prognostic stage group (stage IIIC and IA+B). For the Bioscore staging system this ranged from 47.1 - 85.1% (Bioscore 6 and

1). All systems similarly discriminated groups according to the risk of recurrence, with comparable c-statistic score (anatomic stage group 0.58, prognostic stage group 0.60 and Bioscore staging system 0.60, respectively). The prognostic stage group (IIIC) identified a group with a very poor prognosis (31.8%) which could not be identified using the other staging systems (stage IIIC, 52.8% or Bioscore 6, 47.1%).



Chapter 10

NEDERLANDSE SAMENVATTING

Samenvatting

Dit proefschrift had tot doel patiënten met een vroeg stadium van borstkanker te selecteren bij wie okselbehandeling of stadiëring veilig achterwege gelaten kan worden, met behoudt van risico op een recidief en overleving om overbehandeling en morbiditeit te verminderen, waardoor de kwaliteit van leven van borstkanker patiënten verbeterd. Het tweede doel van dit proefschrift was het optimaliseren van de follow-up periode voor klinische studies en het onderzoeken van verschillende stadiëringssystemen op basis van tumor biologie in patiënten met een vroeg stadium van borstkanker.

Deel I – Achterwege laten van aanvullende okselbehandeling

Op basis van eerdere gerandomiseerde onderzoeken wordt een aanvullend okselkliertoilet achterwege gelaten bij borstkanker patiënten met een positieve schildwachtklier die behandeld worden met een borstsparende behandeling, dit is nog wel de standaardbehandeling voor patiënten die behandeld worden met een borstamputatie. In **Hoofdstuk 2** van dit proefschrift hebben we onderzocht bij wie een aanvullend okselkliertoilet achterwege gelaten kan worden door voor een borstsparende behandeling te kiezen in plaats van een borstamputatie. In het studiecohort werd een aanvullend okselkliertoilet uitgevoerd in 71.0% van de patiënten met een positieve schildwachtklier die behandeld werden met een borstamputatie in vergelijking met 26.6% in patiënten die borstsparend werden behandeld ($p < 0.001$). In 68.4% van de geïncludeerde patiënten kon een aanvullend okselkliertoilet achterwege gelaten worden indien patiënten gekozen zouden hebben voor een borstsparende operatie in plaats van een borstamputatie. Artsen dienen dit tijdens shared-decision making te bespreken met de patiënten.

Op dit moment ondergaan patiënten met extranodale groei in de schildwachtklier nog standaard aanvullende okselbehandeling (okselkliertoilet of radiotherapie van de oksel). In **Hoofdstuk 3** onderzochten we of extranodale groei in de schildwachtklier voorspellend is voor meer dan drie lymfekliermetastasen en het effect van extranodale groei op de vijfjaars-ziektevrije overleving en 10-jaars algehele overleving. Dit hoofdstuk toonde dat klinisch klier negatieve T1-2 borstkanker patiënten met extranodale groei in de schildwachtklier vaker een hogere tumorload in de oksel hadden bij meer dan drie lymfekliermetastasen (15.7% vs. 5.8%, $p < 0.001$). Deze patiënten hebben echter géén slechtere vijfjaars-ziektevrije overleving (86.4% vs. 88.8%, $p = 0.085$) of 10-jaars algehele overleving (78.6% versus 83.0%, $p = 0.018$) ten opzichte van patiënten zonder extranodale groei in de schildwachtklier. Het is daarom van belang dat patiënten met extranodale groei in de schildwachtklier geïncludeerd worden in de huidige gerandomiseerde studies om aan te tonen of het ook

veilig is om in deze patiëntengroep okselbehandeling achterwege te laten.

Deel II – achterwege laten van schildwachtklierprocedure

Hoofdstuk 4 beschrijft de rationale en studie design van een Nederlandse prospectieve multicenter randomisatie studie: de BOOG 2013-08. Klinisch klier negatieve T1-2 borstkanker patiënten die een borstsparende behandeling ondergaan worden gerandomiseerd voor de schildwachtklierprocedure of geen schildwachtklierprocedure. Deze studie includeert momenteel patiënten in 26 ziekenhuizen in Nederland.

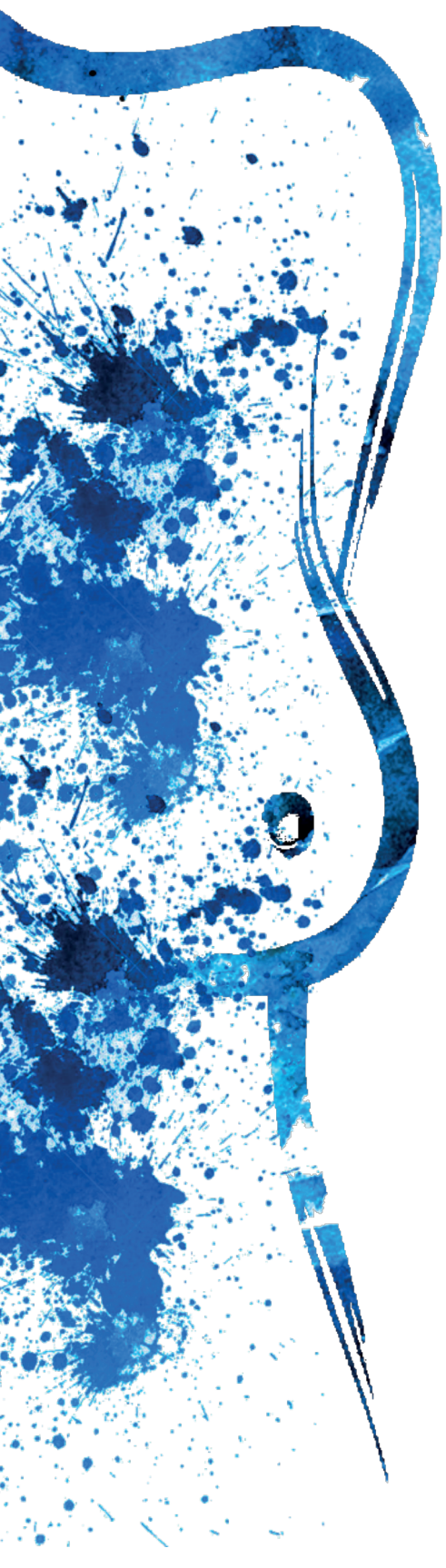
In Hoofdstuk 5 werd onderzocht of de diagnostische waarde van de echo van de oksel, in het bijzonder de negatief voorspellende waarde voor lymfekliermetastasen, verschilt tussen de verschillende subtypen van borstkanker (ER+PR+HER2-, ER+PR+HER2+, ER-PR-HER2-). De sensitiviteit, specificiteit en nauwkeurigheid van de echo van de oksel waren niet significant verschillend voor de verschillende subtypen. Wel werd er een significant verschil gevonden in de negatief voorspellende waarde tussen ER-PR-HER2- tumoren en HER2+ tumoren (90.3% versus 80.2%, p = 0.05) en tussen HER2+ en ER+PR+HER2- tumoren (80.2% vs. 87.2%, p = 0.04). Dit verschil kan worden verklaard door het verschil in prevalentie van lymfekliermetastasen, met de hoogste prevalentie in HER2+ tumoren (32.7%) en de laagste prevalentie in ER-PR-HER2- tumoren (15.8%). Het is belangrijk dat alle subtypen van borstkanker worden geïncludeerd in de huidige gerandomiseerde studies die onderzoeken of de schildwachtklier veilig achterwege gelaten kan worden in klinisch klier negatieve T1-2 borstkanker patiënten.

Deel III – adequate follow-up tijd in studies naar oksel behandeling

Hoofdstuk 6 en 7 onderzochten het lokaal en regionaal recidief risico en de invloed van event-vrije jaren in de verschillende subtypen van borstkanker (ER+PR+HER2-, ER+PR-HER2-, ER+HER2+, ER-HER2+ en ER-PR-HER2-). Het risico op een lokaal of regionaal recidief in de eerste vijf jaar na de diagnose was laag met 3.0% lokale recidieven en 1.3% regionale recidieven in klinisch klier negatieve T1-2 borstkanker patiënten. Het risico op lokale en regionale recidieven varieerde per subtype met het hoogste risico voor triple negatieve tumoren (lokaal recidief 6.8% en regionaal recidief 3.7%) en het laagste risico voor ER+PR-HER2- tumoren (lokaal recidief 2.2% en regionaal recidief 0.8%). Patiënten met het hoogste risico op het moment van diagnose lieten proportioneel de hoogste daling zien (het regionaal recidief risico voor triple negatieve tumoren daalde van 3.7% op het moment van diagnose naar 0.4% na vijf jaar follow-up). **Hoofdstuk 6** toonde aan dat het risico op een regionaal recidief in de drie jaar na twee event-vrije jaren te verwaarlozen is (0.8%). Dit wil zeggen dat voor 125 event-vrije patiënten na twee jaar, er slechts één regionaal recidief kan worden verwacht in de drie jaar nadien. Vergelijkbare resultaten werden gepresenteerd voor het risico op een lokaal recidief: na drie jaar follow-up was het

risico op lokaal recidief slechts 1.0% (**Hoofdstuk 7)**. Dit suggereert een beperkte waarde van een langere follow-up periode voor het lokaal en regionaal recidief en kan gebruikt worden voor het eerder publiceren en implementeren van studieresultaten.

De prognostische groep van de 8e editie van American Joint Committee (AJCC) TNM systeem en de Bioscore zijn nieuwe stadiëringssystemen voor borstkanker patiënten, die de traditionele anatomische groep van de 8e editie van AJCC TNM combineren met tumorbiologie. In **Hoofdstuk 8** werden de vijf- en 10-jaars recidiefvrije overleving voor het anatomische en prognostische stadium van de 8e editie van AJCC TNM en het Bioscore stadiëringssysteem met elkaar vergeleken voor ER+HER2-borstkanker patiënten.
De 10-jaar recidiefvrije overleving voor de anatomische groep van het 8e AJCC TNM systeem varieerde van 52.9 - 83.4% (stadium IIIC en IIA) en van 31.8 - 84.6% voor de prognostische groep (stadium IIIC en IA + B). Voor de Bioscore stadiëringssysteem varieerde dit van 47.1 - 85.1% (Bioscore 6 en 1). Alle 3 de stadiëringssystemen onderscheidden de groepen op vergelijkbare wijze op basis van het recidief risico met een vergelijkbare c- score (anatomische groep 0.58, prognostische groep 0.60, Bioscore 0.60). De prognostische groep (IIIC) identificeerde een groep met een zeer slechte prognose (31.8%) die niet kon worden geïdentificeerd met de andere stadiëringssystemen (stadium IIIC van anatomische groep (52.8%) of Bioscore 6 (47.1%)).



Appendices

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 (POSNOC, 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.

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Mijn terugkomgroep in Eindhoven, we kennen elkaar pas twee maanden, maar nu al hebben met veel met elkaar gedeeld. Ik hoop op een leuk en leerzaam jaar met z'n allen. Hierna snel een donderdagmiddag borrel plannen ergens in de buurt van Strijp!

Liefste leukste vriendinnetjes. Van pubers op 't Niftarlake College, nachten in 't Schippertje en de Jam, tot weekendjes in Someren. Het is jullie eindelijk gelukt om me uit het Limburgse te ontvoeren;) Suusje, mijn oudste vriendinnetje, al bijna 30 jaar aan herinneringen samen, van Spice Girls, groep 8 kamp, examenreis, en eindeloze uren samen op het hockeyveld, wat is het bijzonder om nog steeds herinneringen samen te maken! Lieve As, tijdens onze eerste reis samen naar Cuba kwamen we erachter dat we de beste travellers in crime zijn. Van dolle taxiritten in Panama, geweigerd worden in Nicaragua, tot de beste en slechtste ceviche in Bacalar, stroomstoring in Curacao. Liefste Lies, vriendinnen vanaf klas 4 tijdens biologie en natuurkunde lessen. "Vanessaaaa opletten", met als hoogtepunten onze nominatie, uitwisseling met Tsjechië, werkweek naar Londen. Later werden dat tripjes naar Albufeira, Barcelona en later heerlijke weekenden in de beste huisjes in de middle of nowhere.
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Lieve Yvonne, mijn roomie en promotiepartner in crime. Wat ik mis ik onze tijd samen op UNS-40 en later 50. Van deadlines, onze koffie momentjes, wall of shame, kots avonturen in Phantasialand, vrijgezellenfeeset, tot jouw bezoek aan Los Angeles. Wat een lol hebben we die paar dagen gehad (wie vliegt er nu voor 4-5 dagen even op en neer?) Ik ben ongelofelijk trots en weet zeker dat je de beste traumachirurg van het Zuiden gaat worden!! En ik had me echt geen betere promotiepartner in crime kunnen wensen, op nog veel avonturen samen.

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List of publications

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Curriculum Vitae

Marissa Laurine Ghislaine was born on September 11th 1989 in Utrecht, and grew up in Maarssen, the Netherlands. In 2011 she obtained her bachelor's degree in Biomedical Sciences at the Vrije University in Amsterdam. Thereafter she started her Master Arts-Klinisch Onderzoeker (Msc/MD) at Maastricht University. During her senior elective, she combined her clinical and scientific internship at the Department of Surgery in Maastricht University Medical Center. As a student, she participated in the European oncology course for Medical Students from the European Society for Oncology in Valencia, Spain. She was nominated for the Pélerin Science student award ("Quality assurance postoperative chest wall irradiation in the BOOG 2013-07 population").

Directly, after obtaining her medical degree in 2015, she continued her research and started as a PhD candidate under supervision of Marjolein L. Smidt and dr. Lori M. van Roozendaal. Her research focused on safely omitting axillary treatment in early breast cancer patients and faster implementation of these study results. During her PhD she coordinated two nationwide multicenter breast cancer trials regarding the value of axillary treatment in early breast cancer patients (BOOG 2013-07 and BOOG 2013-08 trial). In 2016 she won the first prize in category "Improvement of Care at the Science Day" of Maastricht UMC+ ("Sentinel lymph node biopsy can be omitted in DCIS patients treated with breast conserving therapy"). During the 4th Dutch Breast Surgeon Cours in 2017, she was awarded for the best oral presentation ("Extracapsular extension in sentinel lymph node metastasis: a marker of poor prognosis in *c*T1-2N0 breast cancer patients?"). She was nominated for the Pélerin Science award in 2017 ("The accuracy of axillary ultrasound for different molecular subtypes in breast cancer patients").

In 2018, she received several travel grants (GROW – School for Oncology & Developmental Biology, Stichting de Drie Lichten, Prof. Michaël- van Vloten Fonds) which made it possible to work as a research assistant at the department of surgery at Cedars-Sinai Hospital in Los Angeles, under supervision of dr. Armando E. Giuliano. After her PhD, she worked as a surgical resident not in training (ANIOS) at the Zuyderland Medical Center and VieCuri Medical Center. She helped out during the COVID pandemic at the VieCuri Medical Center and worked as a general practioner resident not in training (supervision of drs. P. Luijten, Maasbracht). As of September 2022, she started as a general practioner in training (HAIO) in Eindhoven (supervision of drs. R. Mertens, Valkenswaard). In her spare time, she loves to cook, playing sports, and spending time with family and friends