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

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%).