

# The paradigm shift in axillary management of invasive breast cancer

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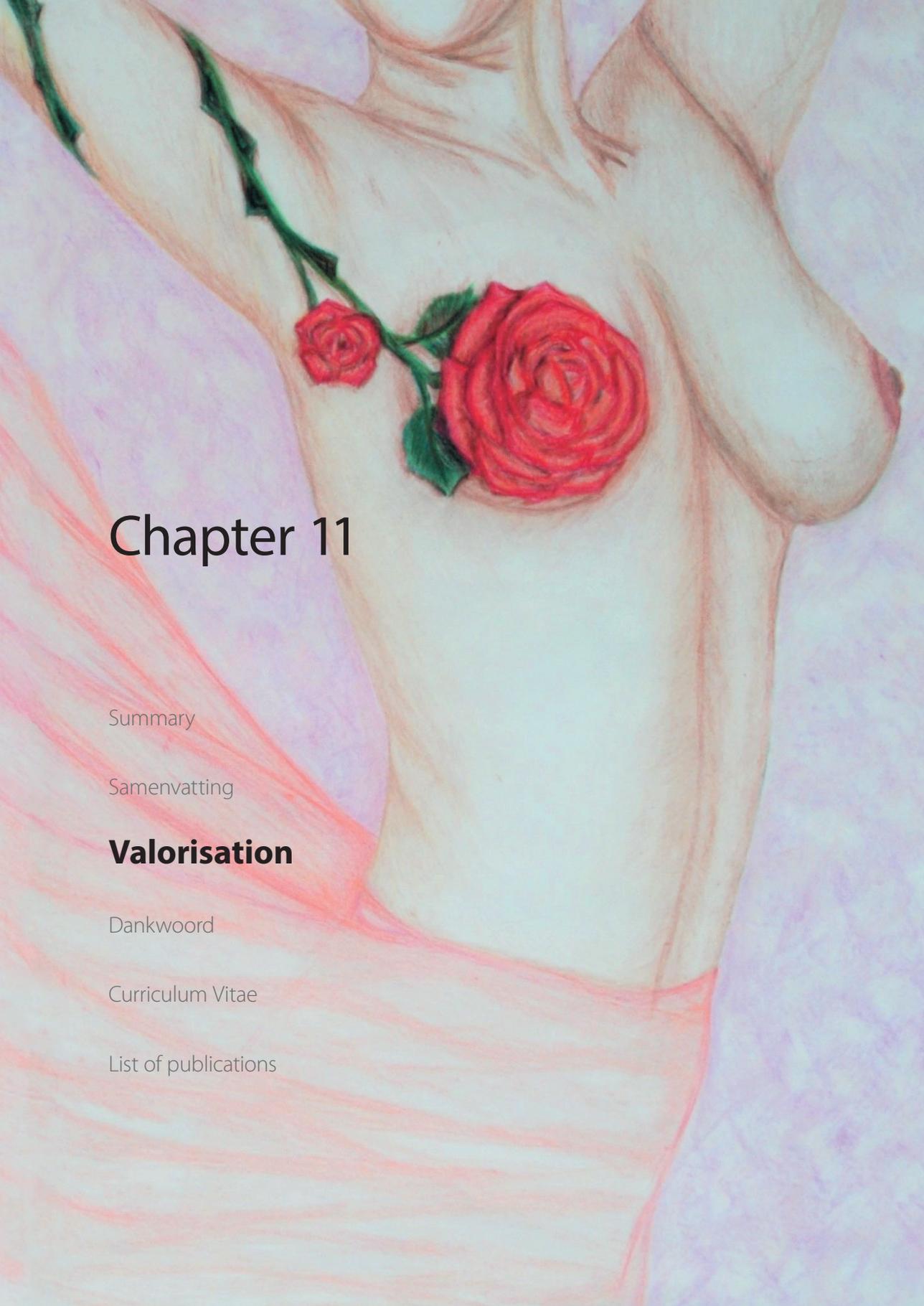
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# Chapter 11

Summary

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## Introduction

Breast cancer is a worldwide health problem, with a yearly incidence of 89.7 new patients per 100,000 women in Western Europe.<sup>1</sup> In the Netherlands, one in every seven women is diagnosed with breast cancer during her lifetime, which accounts for 28.6% of all invasive cancers among women in the Netherlands.<sup>2</sup> Although the incidence of invasive breast cancer has increased in the last years to 14,551 patients in 2015, at the same time the prognosis of breast cancer has improved, with an average relative survival rate of 87% after 5 years and 77% 10 years after diagnosis.<sup>3</sup> This improved survival rate is the result of not only the introduction of the national screening program, introduced between 1990 and 1996, but also of improved treatment modalities, such as (neo-)adjuvant systemic treatment and radiotherapy.<sup>3,4</sup> Historically, all patients with invasive breast cancer underwent ablation of the breast, combined with a complete axillary lymph node dissection (ALND) for diagnostic purposes and for regional tumor control of the disease.<sup>5</sup> Although the axillary lymph node status is still an important parameter, especially when making decisions about the use of adjuvant treatment, it can also cause significant morbidity.<sup>6</sup> Therefore, less invasive axillary staging methods were developed to identify patients with axillary metastases, such as the ultrasound-guided lymph node biopsy (UGLNB) and the sentinel lymph node biopsy (SLNB). These methods have gradually replaced the ALND as a diagnostic modality. Initially, the ALND was omitted in patients with a negative SLNB, and in later years, studies showed that the ALND could also be omitted in patients with micrometastases in the sentinel lymph node (SLN) without negatively affecting disease-free and overall survival, since 40-70% of the patients with a positive SLNB do not have metastases in additional non-sentinel axillary lymph nodes.<sup>6-9</sup> This paradigm shift from “treat all, except...” to “treat none, unless...” has initiated a surge in scientific research to identify patients in whom the ALND can safely be omitted.

## Clinical relevance of this thesis

This thesis concentrated on the axillary work-up of patients with invasive breast cancer. The implementation of these minimally invasive diagnostic procedures, such as the SLNB and the UGLNB, has dramatically changed the indication to perform an ALND. An important study which has contributed to this paradigm shift in axillary treatment is the American ACOSOG Z0011 trial.<sup>10</sup> This trial has shown that in patients with a small tumor and with a maximum of two positive sentinel nodes with macrometastases, the ALND could be omitted without negatively affecting (disease-free) survival, even after a 10-year follow-up period, provided they were treated with breast conserving therapy including radiotherapy and with adjuvant systemic therapy.<sup>10,11</sup> To select such patients, the Z0011-criteria were formulated. In addition, multiple predictive tools, such as nomograms and scoring systems, were developed to identify patients with a minimal tumor burden in whom the ALND could be omitted.<sup>6,12-18</sup> Although these predictive systems may be promising, their applicability to Dutch patients with breast cancer has been proven to be of moderate value.<sup>19</sup> Conversely, it may be increasingly important to identify patients with extensive nodal involvement, in whom the ALND may still be necessary for regional disease control. Therefore, in Chapter 3 of this thesis we have developed a new scoring system identifying patients with extensive nodal involvement, which can easily be used in the clinical setting.

The second part of this thesis addresses the various patient categories with invasive breast cancer for whom there remains uncertainty on whether the ALND may be omitted without negatively affecting survival. In Chapters 4, 5 and 6 we examined potential differences between UGLNB and SLNB positive patients and concluded that UGLNB positive patients have less favorable disease characteristics and a worse (disease-free) survival compared to SLNB positive patients. However, since the ACOSOG Z0011 trial showed promising results in identifying patients in whom the ALND could be omitted, in Chapter 7 we also examined the potential impact of implementing the inclusion criteria derived from the ACOSOG Z0011 trial in a Dutch population, thereby also including UGLNB positive patients. This study shows that when retrospectively applying the Z0011 derived criteria to Dutch patients with breast cancer, the number of ALNDs could be decreased by 61% in node-positive patients. Implementation of these criteria in clinical practice may therefore result in fewer unnecessary ALNDs and their associated morbidities.

Other patients who are underrepresented in the literature are those in whom the sentinel node cannot be visualized (non-vSLN). Due to scarce scientific research on patient and disease characteristics and prognosis of patients with a non-vSLN, international guidelines differ in their axillary treatment recommendations. The Dutch, Australian and ESMO guidelines recommend immediately performing an ALND, whereas the NCCN guideline states that in case of treatment with mastectomy and radiation therapy, an extended radiation field to the axilla may also be sufficient.<sup>20-23</sup> To gain more insight into these patients, we have examined the prevalence, various patient and disease characteristics and survival of patients with non-vSLN in Chapter 8. This study showed that patients with a non-vSLN have less favorable disease characteristics and a worse survival, compared to patients in whom the SLN could be visualized. Subsequently, Chapter 9 describes a survey on the currently applied axillary treatment strategies of Dutch surgical oncologists in patients with non-vSLN, which illustrates that there has been a shift in axillary treatment in recent years in the Netherlands, especially after publication of the Z0011 trial.

## Societal relevance of this thesis

The introduction of the national screening program has improved the survival of patients with breast cancer due to the detection of the disease at an earlier stage.<sup>3</sup> However, earlier detection has also caused an increasing incidence of patients with breast cancer who require treatment, thereby increasing the disease burden in the general population. The total cost of breast cancer is more than 696 million Euros each year, of which 65 million Euros are spent on the national screening program. This accounts for 0.8% of the total health care costs in the Netherlands.<sup>3,24</sup> Although finances should never be the main driving force behind health care decisions, these costs illustrate the importance of critically evaluating the current management of breast cancer in an effort to optimize the cost-effectiveness of care. Therefore, it is imperative to find a balance between optimal individual health care and minimal disease burden for the general population by minimizing unnecessary treatments with their related morbidities. Since the ALND can cause significant long-term morbidity, without significantly improving survival in patients with a minimal tumor burden, recent studies have focused on identifying patients in whom the ALND can be omitted. The numerous prediction tools that are currently available and the criteria formulated in the Z0011 trial may assist in identifying these patients in clinical practice. However, it is important to realize that, in some patients with a high tumor load and/or extensive nodal involvement, axillary treatment, by either ALND or radiotherapy, may still be

mandatory for disease control. Therefore, a clear distinction has to be made between patients in whom the ALND may be omitted because of eligibility for application of the currently available predictive tools and the Z0011 criteria versus those who may still benefit from a complete or a modified ALND, such as the ARM (Axillary Reversed Mapping) technique.<sup>25,26</sup> This is crucial to prevent undertreatment of patients with a high tumor burden. Therefore, this thesis addressed various categories of breast cancer patients for whom axillary treatment recommendations are ambiguous, since these patient categories were not included in the various models.

## **What will the future bring?**

The treatment of breast cancer will become more personalized and will increasingly be based on tumor and patient specific characteristics, due to increasing knowledge in the field of molecular (tumor) biology and genetics. Simultaneously, the trend towards a minimally invasive treatment of breast cancer will continue and may result in either omitting axillary treatment entirely in patients with limited disease burden or replacing the complete ALND with other axillary treatment strategies, such as axillary radiotherapy. Also, improvements in (neo-)adjuvant systemic therapy regimens will coincide with a gradual reduction of surgical interventions. Since neo-adjuvant therapy may also cause a complete pathological response in initially positive axillary lymph nodes, studies are now focusing on whether a complete or partial ALND is still necessary in patients with a good pathological response to neo-adjuvant treatment. Predictive tools on the axillary management of breast cancer will become increasingly important in the current era of personalized medicine; however, as illustrated in the present thesis, more research is necessary on the various patient categories for whom existing prediction models may not be applicable. Moreover, strategies have to be developed for implementing these prediction models adequately into clinical practice.

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