Towards patient-tailored surgical treatment in breast cancer
Straver, M.E.

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Introduction and outline of the thesis
Breast cancer is the most common type of cancer in women in the Netherlands. The incidence of breast cancer is increasing. In 1996, 115 new cases were diagnosed per 100.000 women while in 2006 the incidence increased to 127 new cases per 100.000 women.\textsuperscript{1} The life time risk of women to get breast cancer is 12-13\%. A hopeful actuality is that the mortality rate of breast cancer is decreasing in the last decennia.\textsuperscript{2} In the period from 1979 to 1994 the number of deaths as a result of breast cancer was stable. In the early nineties the number of deaths through breast cancer started to decrease, largely a result of effective adjuvant systemic therapy and screening introduced in 1988.\textsuperscript{3-6} A rising problem created by the increased administration of adjuvant therapy and early detection of breast cancer is overtreatment. Overtreatment can be defined as excessive treatment that does not benefit the patient while it causes serious side effects. Overtreatment is observed in both the surgical and adjuvant treatment of breast cancer patients. The major cause of overtreatment is improper patient selection. Overtreatment can be decreased by patient-tailored treatment; treating only those patients that will have benefit from adjuvant treatment and omit adjuvant therapies in those having a good prognosis with optimal locoregional therapy, where possible with less invasive procedures. The aim of this thesis was to improve the selection of patients who can be treated more conservatively. We focused on (1) the treatment of the axilla in patients with early breast cancer, and (2) the surgical treatment of the breast and axilla after neoadjuvant chemotherapy.
TOWARDS PATIENT-TAILORED AXILLARY TREATMENT IN EARLY BREAST CANCER

The main route of lymphatic drainage of the breast is to the axillary region. Consequently, the axillary lymph nodes are often the first site of regional metastatic disease in breast cancer. Axillary clearance provides knowledge on the presence or absence of dissemination to the axillary lymph nodes and thus important information for prognosis and staging. It also assures regional tumour control and may in some cases improve survival. Therefore, prophylactic axillary lymph node dissection of the axilla used to be the standard treatment of patients with breast cancer. In many patients with early breast cancer, however, no axillary metastases were found while an axillary lymph node dissection can have severe side effects. Morbidity including lymph oedema and decreased arm and shoulder function is seen in 5-39% of the patients. In patients with clinically negative lymph nodes, staging of the axilla by an axillary lymph node dissection is nowadays largely replaced by the sentinel node biopsy procedure, a less extensive surgical procedure than axillary clearance. The sentinel node biopsy procedure is based on Virchow’s theory of stepwise dissemination. A node that receives lymph fluid directly from a tumour is most likely also the first node to contain metastatic disease if lymphatic spread occurs. Sentinel node biopsy in breast cancer was first reported by Giuliano et al. in 1994. The first draining node, the sentinel node, is removed to obtain information about the lymphatic spread. Metastatic cancer is found in sentinel nodes in only 26-34% of the patients, in whom additional axillary clearance is performed. The axillary recurrences rate after omitting an axillary lymph node dissection in patients with a negative sentinel node is low; 0.3% after a median follow of 34 months. Although randomized trials, like the NASBP B-32, have to provide definitive proof regarding the survival and local control, it has already become the standard of care to omit an axillary lymph node dissection in patients with a negative sentinel node. With the widespread introduction of the sentinel node biopsy procedure the question was raised how to deal with potential additional lymph node metastases in case of a positive sentinel node. The standard treatment of patients with a positive sentinel node is an axillary lymph node dissection. However, more than 50% of the patients have no additional metastases. In these patients an axillary lymph node dissection provides no additional prognostic information and will neither have a therapeutic effect. A less invasive alternative for an axillary lymph node dissection in case of a positive sentinel node might be axillary radiation therapy. To investigate differences in regional control, survival and long term morbidity between an axillary lymph node dissection and axillary radiotherapy, an international multicenter phase III trial was initiated in 2001 by the European...
Towards Patient-Tailored Treatment in Neoadjuvant Chemotherapy

The Latin “adjuvans” means to help, particularly to reach a goal. Adjuvant treatment is an addition designed in helping to reach the ultimate goal. Adjuvant treatments are used to help eliminate tumour cells that may still be present after a breast tumour has been surgically removed. Adjuvant therapy includes systemic therapy like chemotherapy and targeted therapy and locoregional radiotherapy.

Neoadjuvant chemotherapy refers to systemic treatment given prior to surgery; a novel strategy to administer adjuvant systemic therapy. Synonymous terms include ‘primary systemic therapy’ or ‘induction chemotherapy’. Neoadjuvant chemotherapy was applied first in 1973 in patients with inoperable, locally advanced breast cancer to afford tumour shrinkage and to render these tumours manageable by radical mastectomy or radiotherapy. In 1989 the interest in neoadjuvant chemotherapy arose after Fisher and colleagues reported that breast surgery could release tumour cells and resulted in an increase in circulating growth-stimulating factors in animal models. Systemic therapy given prior to surgery might prevent the production of circulating factors and sterilize areas of micrometastases and prevent further cancer growth after resection of the primary tumour. However, a survival benefit for neoadjuvant chemotherapy compared to adjuvant chemotherapy is not observed in the largest randomized trials. Other advantages have resulted in an increased use of neoadjuvant chemotherapy in large operable breast tumours. On average in 20% of the patients downstaging of the tumour occurs so that breast-conserving surgery could become a viable alternative to radical mastectomy.

Another major advantage of neoadjuvant chemotherapy is the opportunity to evaluate the response of the primary tumour to chemotherapy. Patients with a pathological complete remission after neoadjuvant chemotherapy do have a better disease-free survival than patients with incomplete remission. Alternatively, by surgically removing the primary tumour and subsequently giving adjuvant therapy, the tumour response remains unknown until the appearance of distant metastases or the lack thereof. As the
CHAPTER 1
Introduction and outline

Pathological tumour response can be easily assessed, neoadjuvant chemotherapy also provides a very attractive setting for translational research which gives us more insight in the behaviour of different tumour subtypes and predictive factors for chemotherapy response. 

Early response monitoring, so during the course of chemotherapy, provides the opportunity to adjust the therapy to the response of the primary tumour; patient-tailored treatment. In patients with non-responding tumours, the chemotherapy regimen could be switched to a potential non-cross resistant chemotherapy. Early identification of favourable responders could permit administration of shorter courses of neoadjuvant chemotherapy, minimizing toxicity. Unfortunately, the only trials assessing the influence of a regimen switch in non-responders did not show a survival benefit. In these trials conventional methods to assess the tumour response were used. FDG-PET/CT and contrast enhanced MRI are promising imaging modalities to more accurately monitor the early tumour response and are addressed in this thesis.

The locoregional treatment after neoadjuvant chemotherapy consists of surgical treatment of the breast, the axilla and adjuvant radiotherapy. One of the variables that determines the type of surgery to the breast after neoadjuvant chemotherapy, i.e. breast conserving surgery or mastectomy, is the response of the tumour. With the help of imaging studies, the size and pattern of decline (concentric or diffuse) of the primary tumour can be measured. Therefore, imaging techniques that accurately visualize the extent of residual tumour and the pattern of decline are crucial to select patients for the appropriate surgical treatment. Several studies have shown that contrast-enhanced magnetic resonance imaging (MRI) is superior to conventional methods to assess the extent of residual disease. Other variables that influence the surgical decision are the presence of ductal carcinoma in situ (DCIS), the breast-tumour index, age and patients preference. The aim is to accurately select those patients that can be safely treated with breast conserving surgery, however omitting surgery is currently inappropriate. In a recent meta-analysis, neoadjuvant chemotherapy was associated with a higher locoregional recurrence compared to adjuvant therapy (risk ratio 1.22 p=0.015). This increased risk was largely attributed to those trials in which radiotherapy alone without surgery was used in patients who achieved clinically a complete remission. This suggest that no subgroup can be identified, including patients with a clinically complete remission, for whom surgery may be omitted.

The rationale of axillary surgical treatment in the setting of neoadjuvant chemotherapy is twofold. First, the actual nodal stage prior to neoadjuvant chemotherapy can be only be determined by means of a surgical procedure in patients with a clinically negative axilla by ultrasound examination. Secondly, the response of axillary lymph node metastases to neoadjuvant chemotherapy can be assessed. Both the nodal status before neoadjuvant chemotherapy as well the axillary response after neoadjuvant chemotherapy yields prognostic information. The optimal timing to perform nodal staging by the sentinel node biopsy
procedure, prior to or after neoadjuvant therapy, is therefore a matter of debate. By performing a sentinel node biopsy procedure before neoadjuvant chemotherapy, an accurate initial nodal stage can be obtained and patients with negative sentinel nodes can be spared an axillary lymph node dissection after neoadjuvant chemotherapy.42 By performing a sentinel node procedure after neoadjuvant chemotherapy, axillary clearance can be avoided in patients with initially negative sentinel nodes and patients with an axillary complete response to neoadjuvant chemotherapy.43 However, the initial nodal staging remains unknown. Furthermore, patients with an axillary response in the sentinel node may not be adequately treated without any regional treatment, i.e. radiotherapy, of the other lymph nodes in the axilla.

In patients with clinically positive axillary lymph nodes and cytological proven node-positive disease at presentation the standard of care would require an axillary lymph node dissection after neoadjuvant chemotherapy. However, neoadjuvant chemotherapy eradicates axillary lymph node metastases in 22%-38% of the patients, and this can result in unnecessary axillary lymph node dissections.44-46 The challenge is therefore to tailor axillary surgery to the response of the axillary lymph node metastases. The accuracy of the sentinel node biopsy after neoadjuvant chemotherapy in patients with clinically positive lymph nodes at presentation is questionable.47-50 In this thesis novel methods to monitor the response of axillary lymph node metastases in order to select patients for axilla-conserving therapies are presented.

Outline of the thesis

Part I focuses on the axillary treatment of patients with early breast cancer and a clinically negative axilla treated in the EORTC 10981 AMAROS trial. Chapter 2 describes several aspects of the sentinel node biopsy procedure; the identification rate, the ratio of tumour-positive and negative sentinel nodes, the incidence of additional lymph node metastasis and the detection of extra-axillary sentinel nodes. Patients with a tumour-positive sentinel node are randomized between an axillary lymph node dissection and axillary radiation therapy. Chapter 3 describes the influence of axillary radiation therapy, and consequently an unknown extent of nodal involvement, on decisions concerning adjuvant systemic treatment.

Part II describes challenges to better adjust the treatment of breast cancer patient according to the response to neoadjuvant chemotherapy. Chapter 4 provides several insights to improve the patient selection for neoadjuvant chemotherapy. In chapter 4.1 the outcome of neoadjuvant chemotherapy, i.e. the increase in breast conserving surgery and the complete remission of the tumor, is described for histological and receptor-based subtypes of breast cancer. Chapter 4.2 describes the response of lobular invasive
cancer to neoadjuvant chemotherapy. It focuses on the differences in response between the histological classical and pleiomorphic subtype and assesses the importance of HER2-status in lobular carcinomas.

In chapter 4.3 the predictive value of the 70-gene profile is presented which may help to select patients for neoadjuvant chemotherapy.

After neoadjuvant chemotherapy patients are selected to undergo breast-conserving surgery or a mastectomy. The assessment of the extent of residual disease by MRI plays an important role in the decision to undertake breast-conserving surgery. Chapter 5 describes the potential of MRI to guide selection of surgery after neoadjuvant chemotherapy. MRI features that improve the patient selection for breast-conserving surgery are explored.

In chapter 6 the treatment of the axilla after neoadjuvant chemotherapy is described. In chapter 6.1 the axillary staging before neoadjuvant chemotherapy and the response of axillary lymph node metastases to neoadjuvant chemotherapy is discussed. Furthermore it describes the value of the sentinel node biopsy procedure in the neoadjuvant setting. Chapter 6.2 presents the feasibility to remove sufficient lymph nodes during an axillary lymph node dissection after neoadjuvant chemotherapy.

At present, axilla-conserving surgery is not yet a benefit of neoadjuvant chemotherapy in patients with a favourable response of their axillary lymph node metastases. In chapter 7 novel methods are presented in order to allow for more safe axilla-sparing treatments. Chapter 7.1 describes the feasibility to monitor the axillary response with FDG-PET/CT. Chapter 7.2 presents a novel method to mark lymph nodes with radioactive Iodine-125 seeds and selectively remove them after neoadjuvant chemotherapy with the objective to determine the response of axillary lymph node metastases, and consequently adjust the axillary treatment. The appendix is an article in Dutch describing neoadjuvant chemotherapy in primarily operable breast cancer, published in Het Nederlands Tijdschrift Van de Geneeskunde.

The thesis ends with concluding remarks and future prospects (Chapter 8) and a general summary in English and Dutch (Chapter 9).


