Prognostication and treatment decision-making in early breast cancer

Fiets, Willem Edward

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Summary and general discussion

In this chapter the results and conclusions from the studies presented in the former chapters of this thesis are summarized and discussed in a broader perspective.

Advances in adjuvant therapy

Chapter 1 showed that in the past decade the breast cancer related mortality in The Netherlands decreased despite an increasing incidence. The decrease in mortality has been partly attributed to the enhanced use as well as the increased efficacy of adjuvant systemic therapy. Starting the 1980s, an increasing number of patients were treated with adjuvant systemic therapy. It is expected that the decrease in mortality will continue in the forthcoming years.[1]

Since the 1980s, new and more effective adjuvant therapy options and strategies have emerged, and are emerging. Cyclophosphamide, methotrexate, fluorouracil (CMF) has been replaced by anthracyclin containing regimens which are about 20% more effective.[2] Two years of tamoxifen has been replaced by 5 years of tamoxifen, and adjuvant chemotherapy and endocrine therapy are often combined, with an additive efficacy.[2] A recent trial shows that in patients with axillary node positive (ANP) breast cancer treatment with docetaxel, doxorubicin, cyclophosphamide (TAC), as compared to fluorouracil, doxorubicin, cyclophosphamide (FAC), results in a 28% reduction in the risk of disease recurrence, being the primary endpoint of this study.[3] The ATAC-trial shows that in postmenopausal patients with hormone receptor positive tumours adjuvant treatment with anastrozole, as compared to tamoxifen, reduces the incidence of the primary endpoint, disease recurrence rate, by about 13%.[4] Trastuzumab is a monoclonal antibody directed against the HER2/neu receptor. Recent trials with this new adjuvant therapy option, presented at the 2005 meeting of the American Society of Clinical Oncology (ASCO), show that the adjuvant administration of

trastuzumab reduces the disease recurrence rate in patients over expressing the HER2/neu receptor by about 50%.[5]

It is striking that almost all recent trials on adjuvant therapy in early breast cancer use disease recurrence, instead of "the gold standard" overall survival, as their primary study endpoint. It has been argued that the absence of recurrent disease is the best indicator of the efficacy of the anti-tumour strategy.[6] However, what is the primary goal of adjuvant systemic therapy: a reduction in disease recurrence, or a reduction in mortality? As shown in **Chapter 3**, a decrease of breast cancer recurrences is not automatically followed by a better overall survival. Besides, the definition of breast cancer recurrence varies between trials, and usually contains events that are not directly related to mortality, such as locoregional relapse and contralateral breast cancer. Non-disease related mortality is also often included in the definition of disease recurrence, but is not influenced by the adjuvant regimens regularly used.[2] **Chapter 3** shows that the inclusion of contralateral breast cancer and/or non-disease related death in the definition of outcome substantially influences estimates of breast cancer recurrence rate and survival, specifically in elder patients and patients with a good prognosis. Clear definitions of endpoints and competing events are therefore crucial for the interpretation and comparison of outcome studies, and should be provided in all clinical trials. It is my opinion that overall survival should be the primary study endpoint in trials that study the efficacy of adjuvant treatment options in elderly (e.g. postmenopausal) patients and in patients with a relative good prognosis (e.g. axillary node negative breast cancer).

Chapter 3 also studied the measure of bias generated by the Kaplan-Meier approach due to informative censoring of contralateral breast cancer or non-disease related death. The Kaplan-Meier method requires non-informative censoring, which means that those individuals who are censored should be as likely to have the subsequent event of interest as those who remain in the study.

In particular competing events might cause informative censoring. For this reason others have propagated an approach that accounts for informative censoring in survival analyses in the presence of competing events. In **Chapter 3** minor differences were observed between estimated outcome determined by the Kaplan-Meier method and a competing risk method. However, differences became more substantial when relative more patients were censored due to competing events. Nevertheless, in most follow-up studies on patients with early breast cancer informative censoring can be expected to cause only minor bias.

Prognostic factors

The evolvements in the adjuvant systemic therapy of early breast cancer have complicated decisions on whom to treat, and with what type of adjuvant systemic therapy. Information on baseline prognosis, i.e. without adjuvant systemic therapy, and on the efficacy of adjuvant systemic therapy regimens, as provided by randomised clinical trials and meta-analyses, has become indispensable for these decisions.

The major prognostic variables that are used in clinical practice still are the number of (tumour) positive axillary lymph nodes and tumour size. But, as shown in **Chapter 2**, a number of other variables, such as in this study histological grade, mitotic counts (MC), cathepsin D, urokinase plasminogen activator (UPA) and it's inhibitor type 1 (PAI-1), are associated with disease recurrence and survival as well. In particular UPA and PAI-1 appeared to be strong prognostic variables. The prognostic value of UPA and PAI-1 has also been shown in a large prospective clinical trial,[7] and a pooled meta-analysis.[8] In my opinion the clinical value of UPA and PAI-1 is undervalued. As it appears that the major drawback for broad use in clinical practise of UPA and PAI-1 is a lack in standardisation with respect to immunoassays used, methods of tumour extraction and protein

determination, a large prospective multicentre study on the reproducibility, attainability and clinical relevance of UPA and PAI-1 is warranted.

In **Chapter 4** the prognostic value of oestrogen receptor (ER) and progesterone receptor (PR), as determined both by immunocytochemical assay (ICA) and by enzyme immuno assay (EIA) was prospectively evaluated. The agreement between EIA and ICA was moderate to substantial (Kappa 0,58 and 0,65 respectively for ER and PR). No differences in prognostic value of hormone receptors detected by ICA or EIA were found. Both ER and PR proved to be weak prognostic factors. But, of course, the main purpose to determine hormone receptors is their ability to predict the efficacy of endocrine therapy. Although ER was identified more than 30 years ago, still much needs to be learned. There is convincing evidence that ER operates in a complex interacting network that ensures the viability of the cancer cells.[9] Resistance to tamoxifen is linked to overexpression of HER2/neu, and aromatase inhibitors show particular benefit in ER postive, PR negative patients.[9,10] It has been shown that ER positive tumours are genetically distinct from ER negative tumours.[11] ER negative and ER positive breast cancer should be considered different diseases, requiring not only different treatment strategies, but probably also different panels of variables for determination of prognosis. It has to be studied which way of assessing the ER status of a breast tumour (ICA, EIA, or on gene level) is best when ER is used in this light.

The prognostic value of MC in axillary node negative breast cancer is still a matter of debate. As shown in **Chapter 5**, the determination of MC is an inexpensive, fast and reproducible way of assessing proliferation in routine practice. But, in the study presented in **Chapter 5** no significant association between MC and disease recurrence and survival was found, which eventually could be explained by the favourable tumour characteristics of this group of patients and the associated low number of events. Based on data in the literature a positive association between

MC and survival in axillary node negative breast cancer may exist, but in **Chapter 5** the extent of this putative association and its clinical relevance is argued. Others, however, are certain that the prognostic value of MC holds for premenopausal patients with axillary lymph node negative disease, and state that MC should be used in clinical practice.[12] Just recently the results from the multicentre morphometric mammary carcinoma project (MMMCP) were published. In this study the absolute difference in 10 year disease specific survival between ANN breast cancer patients with low and high MC was 22% (92% vs. 70%) (HR 4.42, 95% C.I. 2.79 – 7.01).[13] These results are far better than those reported in the past by other investigational groups.

New techniques for the study of potential prognostic variables are rapidly developing at both the gene and protein level.[14] Two of these techniques, reverse transcriptase polymerase chain reaction (RT-PCR) and DNA sequencing (microarray techniques) allow the simultaneous analysis of the expression of a large number of genes in a single experiment. Paik et al. identified 21 genes that can be detected by RT-PCR analysis and used them to group breast cancer patients into risk categories with distant recurrence rates at 10 years of 6.8% and 30.5%.[15] Van 't Veer et al. and van de Vijver et al. used microarray analysis and grouped patients according to a 70-gene expression profile into categories with 94.5% and 54.6% survival rates at 10 years.[16,17] These results are promising, but not substantially better than those achievable with classical variables.[18] In **Chapter 2** of this thesis a prognostic index was created using tumour size, number of postive axillary lymph nodes and PAI-1. 29% of patients were in the good prognosis group with a 10-year disease specific survival of 95% and a 10-year disease free interval of 85%. The clinical relevance of both the 21-gene RT-PCR and the 70-gene expression profile will soon be tested and compared with the classical methods of prognostication in large multicentre clinical trials. The 21-gene RT-PCR will be tested in the PACCT (Program for the Assessment of Clinical Cancer Tests) trial, the 70-gene expression profile in the MINDACT

(Microarray for Node Negative Disease may Avoid Chemotherapy) trial. These trials are indispensable to establish the clinical value of the genomic techniques. The prognostic value of genomic tests will probably increase when they are combined with classical prognosticators, such as tumour size or axillary lymph node status. At this moment the 70-gene expression profile and the 21-gene RT-PCR, though commercially available, should not be used outside the setting of a clinical trial, yet.

Computer programs used for treatment decision-making

Several tools have been developed to make individualised estimates of baseline prognosis and absolute survival benefit of adjuvant systemic therapy. Two of these tools, Adjuvant! and Numeracy, are freely available, web-based programs.[19,20] Both programs determine a patient's baseline risk of recurrence and/or death at 10 years without adjuvant therapy, and provide an estimate of the absolute benefit associated with various commonly used schemes of adjuvant systemic treatment. As shown in **Chapter 6**, 10-year disease free interval estimates determined by Adjuvant! and Numeracy correlate well. However, there is no good agreement between the estimates made by the two programs. Compared with both Adjuvant! estimates and observed outcome, Numeracy estimates of baseline prognosis are too high, and Numeracy estimates of absolute risk reduction of adjuvant systemic therapy are too low. Estimates of recurrence free survival and overall survival made by Adjuvant! are accurate, when compared with observed outcome. Therefore, Adjuvant! is the preferred prognostic model. The data presented in **Chapter 6** concerning the reliability of Adjuvant! are in line with the results from a recently published, large, prospective, population-based, validation study.[21] The Adjuvant! website is regularly updated. Currently (July 2005), there are 4 different versions of Adjuvant! for breast cancer available on the Adjuvant! website (www.adjuvantonline.com): a standard version

6.0 (used in Chapter 6), a standard version 7.0 (the most current version, with modest changes about treatment options and efficacy, and prognostic estimates for very young patients), a genomic version 7.0 (for patients for whom prognostic information from the 21-gene RT-PCR is available), and a version designed for decision making for hormone receptor positive postmenopausal patients at the time of completing 5 years of adjuvant tamoxifen (using data from the study published by Goss et al.).[22] It is likely that Adjuvant! will gain in importance in clinical practice in the nearby future. In my opinion Adjuvant! should be routinely used when informing patients on the pros and cons of adjuvant systemic therapy. Adjuvant! should be used by the treating physician to demonstrate the expected benefit of both the proposed and alternative adjuvant treatment strategy options. However, it should be stressed that the reliability and accuracy of the computer program should be validated on a regular basis.

Sequence of adjuvant chemotherapy and post-operative radiotherapy

The optimal sequence of radiotherapy and adjuvant chemotherapy is not clearly defined. Theoretically, one can expect the largest treatment benefit when both modalities are given concurrently.[23] However, it has been reported that the concurrent administration of the two modalities can lead to an increased incidence of side effects.[24] **Chapter 7** showed that the administration of adjuvant chemotherapy concurrently with, in particular loco-regional radiotherapy is too toxic. More skin desquamation and moderate to severe oesophagitis/dysphagia can be anticipated. In addition, more than 20% of patients need to be admitted to hospital with acute complications of therapy, and approximately 15% of patients receive less than 85% of the planned dose of chemotherapy. The concurrent administration of local radiotherapy to the breast and chemotherapy is less toxic. But, the administration of local radiotherapy concurrent with AC still leads to high-

grade skin toxicity in 44% of patients. As anthracyclin-containing regimens have become standard for adjuvant chemotherapy in early breast cancer -i.e. FAC, FEC, or TAC which are considered more toxic than the regimens studied in **Chapter 7**- the concurrent administration of adjuvant chemotherapy and radiotherapy is dissuaded.

If post-operative radiotherapy and adjuvant chemotherapy are not to be given concurrently, they have to be administered sequentially. The question that arises is which modality should be given first, radiotherapy or chemotherapy. Radiotherapy given after completion of adjuvant chemotherapy leads to an increased incidence of locoregional recurrences.[25] On the other hand, postponement of chemotherapy carries the risk of an increased incidence of distant metastasis.[26] One, small sized (n=244), randomised trial with long-term follow-up has been published that compared radiotherapy followed by chemotherapy to chemotherapy followed by radiotherapy.[27] This trial did not show any survival benefit for either sequence. However, the chemotherapy regimen provided in this trial is nowadays considered sub optimal. Soon, a large multicentre randomised trial will be started in The Netherlands to answer the question which modality should be given first. Endpoints of this study will be long-term locoregional tumour control, distant metastasis free survival, and overall survival.

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