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Prognostication and treatment decision-making in early breast cancer

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Edward Fiets

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Prognostication and treatment decision-making in early breast cancer

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Voor mijn ouders

CONTENTS

1

General introduction: Advances in prognosis and management of early breast cancer and outline of this thesis

ADVANCES IN PROGNOSIS AND MANAGEMENT OF EARLY BREAST CANCER

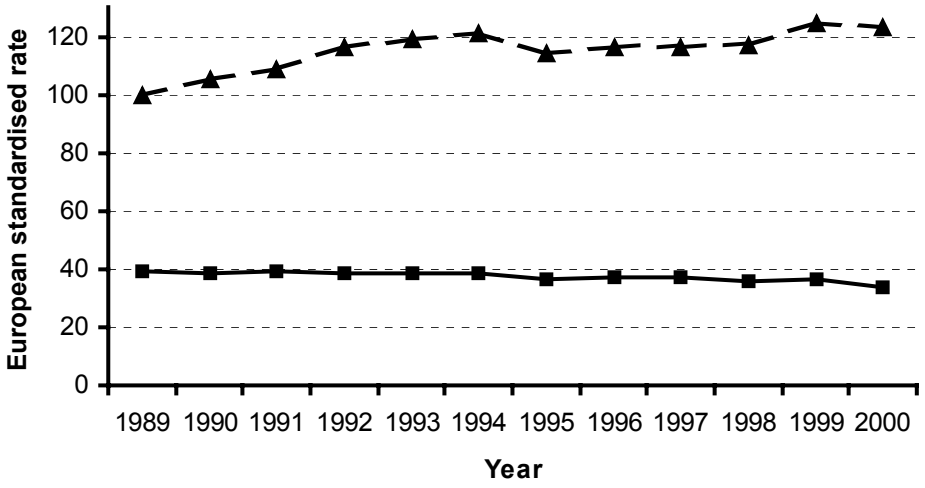
Breast cancer incidence and mortality

The incidence of breast cancer in The Netherlands is among the highest in the world. Breast cancer accounts for 33.6% of all cancers in Dutch women.[1] The absolute number of breast cancer cases increased from 7,900 in 1989 to 11,200 in 2000. In the same period the age standardised breast cancer incidence increased from 99.9 to 123.1 per 100,000 women (Figure 1). Based on present incidence rates, about 1 in every 8-9 women in The Netherlands will develop breast cancer.[1] Despite this increasing incidence, mortality due to breast cancer has slowly, but steadily, decreased from 39.0 per 100,000 women in 1989 to 33.5 in 2000 (Figure 1.1).[1] Between the 1970s and the early 2000s, the 5-year overall survival gradually increased from approximately 60% to approximately 80%.[2] The decrease in mortality has been attributed to the nationwide screening programme, which was gradually implemented in The Netherlands between 1989 and 1997.[3,4] However, evolvements in the management of early breast cancer, in particular the enhanced use of adjuvant systemic treatment, probably did have a greater impact on mortality.[5]

Primary treatment

Till 1980 primary surgical treatment of patients with early breast cancer consisted of modified radical mastectomy (MRM). In 1981 breast conserving therapy (BCT) was introduced in The Netherlands for patients with tumours ≤ 2 cm in diameter. In 1984 the indication for BCT was extended to tumours ≤ 3 cm. The proportion of patients receiving BCT gradually increased from 26% in 1984 to 53% in 1991.[6,7] Radiotherapy directed towards the whole breast, with an additional boost dose to

Figure 1.1. Annual, age-adjusted breast cancer incidence and mortality per 100.000 women between 1989 and 2000 *(Source: Netherlands Cancer Registry)*.



the original tumour site, was administered as part of BCT. Radiotherapy directed towards the thoracic wall and regional lymph nodes was given to almost all patients until the mid 1980s, but from that time the administration of locoregional radiotherapy was restricted to patients with a high risk for locoregional recurrence.[8] In the IKMN-region indications for locoregional radiotherapy were: tumour diameter more than 5 cm, irradical resection (axilla or thoracic wall), fixed axillary lymph nodes, more than 3 positive axillary lymph nodes, or a positive axillary top node.[9] The administration of locoregional radiotherapy in high-risk patients has a positive influence on survival. In the 1990s and early 2000s the primary management of early breast cancer remained largely unchanged, besides the introduction of the sentinel node biopsy procedure for staging the axilla in the late 1990s.

Adjuvant systemic therapy

In the 1980s and 1990s adjuvant systemic therapy was advised according to regional treatment guidelines. These guidelines recommended adjuvant systemic therapy for axillary node-positive (ANP) patients only. Chemotherapy was assigned to premenopausal ANP patients, and endocrine therapy to postmenopausal ANP patients (Table 1.1).[6,9] In premenopausal patients with ANP, oestrogen receptor (ER) positive tumours ovariectomy was considered equally effective as adjuvant chemotherapy,[10] but was generally not recommended. In the 1980s the proportion of ANP patients receiving any form of adjuvant systemic therapy increased from 49% in 1984 to 82% in 1991. The proportion of axillary node-negative (ANN) patients receiving adjuvant systemic therapy did not change and was less than 3%.[6] Between 1991 and 2000 the use of adjuvant systemic therapy remained stable,[4,5] but within The Netherlands differences in the management of ANN breast cancer grew.[11] Therefore, the Dutch Society for Medical Oncology organised in 1998 a consensus meeting on the adjuvant treatment of ANN breast cancer. Conclusions of this meeting were that adjuvant systemic treatment was indicated for all ANP patients, and for ANN

Table 1.1. 1996 IKMN-guideline for adjuvant systemic therapy.[9]

Number of positive nodes	Tumour size (cm)	Histological grade	HR	Age				
				<36	36-49	50-59	60-69	>=70
0	any	any	any					
>0	any	any	any					

□ no adjuvant systemic therapy

■ adjuvant chemotherapy (4 cycles AC)

■ adjuvant endocrine therapy (tamoxifen for at least 2 years)

HR: hormone receptor; AC: doxorubicin / cyclophosphamide.

Table 1.2. 2002 Dutch guideline for adjuvant systemic therapy.[13]

Number of positive nodes	Tumour size (cm)	Histological grade	HR	Age				
				<36	36-49	50-59	60-69	>=70
0	0.1-1.0	any	pos	■	□	□	□	□
			neg	▪	□	□	□	□
	1.1-3.0	I-II	pos	■	□	□	□	□
			neg	▪	□	□	□	□
		III	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	□
	>3.0	any	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	□
>0	any	any	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	□

□ no adjuvant systemic therapy

▪ adjuvant chemotherapy (4 cycles AC or 6 cycles CMF)

▪ adjuvant endocrine therapy (5 years tamoxifen)

■ adjuvant combination therapy (both modalities)

HR: hormone receptor; AC: doxorubicin / cyclophosphamide; CMF: cyclophosphamide / methotrexate / fluorouracil.

patients with a tumour diameter more than 3 cm, or with a tumour diameter between 1 and 3 cm and a poor histological grade or high mitotic counts.[11] The consensus was implemented in the multidisciplinary, evidence-based Dutch guideline for the treatment of breast cancer published in 2002 (Table 1.2),[12,13] and produced a 50% increase in the number of patients assigned to adjuvant systemic treatment.[14] In 2004 the 2002 guideline was revised. Indications for adjuvant systemic therapy were further extended (Table 1.3).[15]

Adjuvant endocrine therapy

In the 1980s adjuvant endocrine therapy with tamoxifen was recommended for patients with ER positive tumours only. But, between 1986 and 1991 the proportion of postmenopausal patients with ANP, ER negative tumours that received adjuvant tamoxifen increased from less than 10% to more than 40%,[6] a trend probably attributable to the results of some trials and meta-analyses reported in this period.[10,16,17] In line with this trend, the regional guideline from the Comprehensive Cancer Centre Middle Netherlands (IKMN), published in 1996, recommended tamoxifen for all ANP patients aged 50 years or more.[9] However, in 1998 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) concluded, based on their meta-analyses performed in1995, that in ER negative disease tamoxifen has little effect on recurrence or breast cancer related mortality.[18] On the other hand, in ER positive disease 5 years of treatment with tamoxifen reduces the breast cancer mortality rate by about 31%.[19] As a result, the 2002 Dutch guideline recommended that adjuvant tamoxifen should be given to patients with hormone receptor positive (oestrogen or progesterone) tumours only.[11-13] In recent years adjuvant treatment with aromatase inhibitors has emerged as a new, and probably more effective, option for postmenopausal patients with hormone receptor positive tumours.[20] In the ATAC trial, a trial comparing adjuvant treatment with anastrozole with adjuvant treatment with tamoxifen, anastrozole reduced the disease recurrence rate, by about 13%.[21] The 2004 Dutch guideline recommends an aromatase inhibitor after initial therapy with tamoxifen for all postmenopausal patients assigned to adjuvant endocrine therapy.[15]

Adjuvant chemotherapy

In the 1980s and early 1990s the preferred regimen of adjuvant chemotherapy comprised 6 cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF).

Table 1.3. 2004 Dutch guideline for adjuvant systemic therapy.[15]

Number of positive nodes	Tumour size (cm)	Histological grade	HR	Age				
				<36	36-49	50-59	60-69	>=70
0	0.0-1.0	I	any					
		II-III	pos					
			neg					
	1.1-2.0	I-II	pos					
			neg					
		III	pos					
			neg					
	2.1-3.0	I	pos					
			neg					
		II-III	pos					
			neg					
	>3.0	any	pos					
			neg					
1-3	any	any	pos					
			neg					
>3	any	any	pos					
			neg					

□ no adjuvant systemic therapy

■ adjuvant chemotherapy (5 cycles FEC or FAC, in specific patients 6 cycles TAC)

■ adjuvant endocrine therapy (premenopausal: 5 years tamoxifen; postmenopausal: tamoxifen for 2-3 years followed by an aromatase inhibitor for 3-2 years)

■ adjuvant combination therapy (both modalities)

HR: hormone receptor; FEC: fluorouracil / epirubicin / cyclophosphamide; FAC: fluorouracil / doxorubicin / cyclophosphamide; TAC: docetaxel / doxorubicin / cyclophosphamide.

In the 1990s this regimen was gradually replaced by a regimen comprising 4 cycles of doxorubicin and cyclophosphamide (AC). Although both regimens were considered equally effective[22] -both regimens reduce the annual breast cancer

mortality rate by about 27% among women aged under 50, and 11% among those aged 50-69[23]- AC was recommended instead of CMF, under the impression that AC was a lesser burden to the patient.[9] In 1998 the EBCTCG reported the suggestion that, compared to CMF, anthracycline-containing regimens produced somewhat greater effects on recurrence and mortality.[23] This suggestion was confirmed by their meta-analyses performed in 2000 (reported in 2005).[19] However, the anthracyclin-containing regimens tested were usually given for about 6 months, instead of 3 months with regular AC, and in combination with other cytotoxic drugs. Fluorouracil, doxorubicin, cyclophosphamide (FAC), and fluorouracil, epirubicin, cyclophosphamide (FEC) were the combinations most widely studied. Adjuvant treatment with FAC or FEC reduces the breast cancer mortality rate by about 38% among women aged under 50, and 20% among those aged 50-69.[19] The 2004 Dutch guideline for the treatment of breast cancer recommends adjuvant chemotherapy with a regimen comprising 5 cycles of FEC or FAC, instead of CMF or AC.[15] New, even more effective regimens are emerging. A recently published trial compared 6 cycles of treatment with either docetaxel, doxorubicin, cyclophosphamide (TAC) or FAC in women with axillary node positive breast cancer. In this trial treatment with TAC, as compared with FAC, resulted in a 28% reduction in the risk of disease recurrence.[24] Based on this trial, the 2004 Dutch guideline recommends TAC for premenopausal patients with ANP breast cancer overexpressing the HER2/neu receptor.[15]

OUTLINE OF THIS THESIS

As shown, in the past decades the management of early breast cancer has considerably changed. Adjuvant treatment decision-making has become much more complex, and prognostication has gained in importance. All studies in this thesis are dealing either with prognostication or with the consequences of a change in the management of early breast cancer.

Prognostic factors in early breast cancer are defined as measurements available at time of surgery that are associated with outcome. Prognostic factors are clinically relevant when they are used for treatment decision-making. In the 1980s involvement of the axillary lymph nodes was the only prognostic factor considered clinically relevant. The National Institutes of Health Consensus Panel on the Adjuvant Therapy and Endocrine therapy for Breast Cancer concluded in 1985 that routine administration of adjuvant systemic therapy in women with histological negative axillary lymph nodes could not be recommended.[25] But, in the late 1980s and early 1990s the administration of adjuvant systemic therapy to ANN patients became a mater of debate.[26,27] a major conclusion at the St. Gallen Conference held in 1988 was that most ANN patients should also be treated with some form of adjuvant therapy.[28] As a consequence, additional prognostic factors were needed to define high-risk ANN patients. For this matter, in 1989 a study was started in 5 hospitals located in the Middle-Netherlands. Consecutive patients with operable breast cancer were asked to participate in a prospective observational study on prognostic factors. The primary goal of this study was to evaluate the clinical relevance of a large number of potential prognostic factors. A secondary goal was to construct a prognostic index by which adjuvant therapy can be either omitted or adjusted to prognosis. This study is presented in **Chapter 2** of this thesis.

In studies on early breast cancer, outcome is usually defined as the time from diagnosis or surgery until a particular endpoint. The endpoint can vary, and may include death, disease related death, or recurrent disease. However, an explicit definition of the endpoint used is provided in less than half of published studies.[29] In **Chapter 3** data from the cohort of patients presented in Chapter 1 are used to evaluate the effects of various definitions of outcome on estimated outcome probability. The presented study specifically focuses on the influences of non-disease related death and contralateral breast cancer.

Hormone receptors are considered weak prognostic factors.[30] Three techniques for ER and progesterone receptor (PR) determination are commonly used: ligand binding assay (LBA), immunocytochemical assay (ICA), and enzyme immuno assay (EIA). At least until 1992, LBA has been the preferred and most commonly used method.[31] But nowadays, most, if not all, hospitals in the Netherlands use ICA. The prognostic value of EIA and ICA appear of the same magnitude compared with that of LBA.[32,33] But, the prognostic value of ICA and EIA has not been compared with each other before. In **Chapter 4** the prognostic value of ER and PR detected both by ICA and EIA is prospectively compared in a subgroup of patients from the cohort presented in Chapter 1.

The broad use of adjuvant systemic therapy in ANN breast cancer was introduced in the Netherlands after the 1998 consensus meeting. The Dutch guideline for the treatment of breast cancer, published in 2002, used tumour size, and histological grade or mitotic counts to select ANN patients for adjuvant systemic therapy.[12,13] In **Chapter 5** the reproducibility and prognostic value of histological grade and mitotic counts is studied specifically in patients with ANN breast cancer. Selected is a subgroup of patients from the cohort presented in Chapter 1, that is ANN and that did not receive adjuvant systemic therapy.

The major question, however, is not simply how to select patient categories that are at high risk for recurrence, but how to select patient categories for which the usefulness of adjuvant systemic therapy is high enough to justify its side effects and inconvenience. It is complex to predict the benefit of adjuvant systemic for an individual woman with early breast cancer. It involves integration of information about baseline prognosis, efficacy of various treatment options, and estimates of competing risk. In 2001 two computer programs, Adjuvant! and Numeracy, were introduced that provide an estimate of the absolute benefit associated with various commonly used regimens of adjuvant systemic therapy for the individual

woman with early breast cancer.[34,35] In **Chapter 6** the prognostic and predictive estimates made by Adjuvant! and Numeracy are mutually compared using the cohort of breast cancer patients presented in Chapter 1. In this chapter Adjuvant! is also validated for use in the Dutch setting. Prognosis determined with Adjuvant! is compared with the observed 10-year overall and relapse-free survival. In addition, the absolute benefit in overall survival from adjuvant systemic therapy as predicted by Adjuvant! is compared with the presence or absence of an indication for adjuvant systemic therapy according to the Dutch guideline from 2002 and the revised guideline from 2004.

For breast cancer patients, the optimal sequence of adjuvant chemotherapy and radiotherapy is not clearly defined. In the 1980s and 1990s both modalities were given concurrently in the IKMN-region. Theoretically, one can expect the largest treatment benefit with this policy.[36] However, it has been reported that the concurrent administration of the two modalities leads to an increased incidence of side effects.[37] In the 1990s adjuvant CMF chemotherapy was gradually replaced by adjuvant AC chemotherapy. In **Chapter 7** of this thesis the acute toxicity of radiotherapy alone, radiotherapy concurrent with AC, and radiotherapy concurrent with CMF is prospectively compared.

In **Chapter 8** the results and conclusions from the studies presented in this thesis are summarized and discussed in a broader perspective. **Chapter 9** is a translation in Dutch this chapter.

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2

Prognostic factors in breast cancer. Results of a prospective, multicentre, observational study on 463 patients with long-term follow-up.

W.E. Fiets, H. Struikmans, M.A. Blankenstein, J.W.R. Nortier

ABSTRACT

Background: The proper use of prognostic factors in primary breast cancer might enable individual tailoring of adjuvant treatment. The primary goal of this study was to evaluate the clinical relevance of a large number of prognostic markers. The secondary goal was to construct a prognostic index by which adjuvant therapy can be either omitted or adjusted to prognosis.

Methods: Between 1989 and 1993, 463 patients with operable, stage I to III breast cancer were included in this multicentre, prospective, observational study on 22 potential prognostic factors. End-points for outcome analysis were: locoregional relapse, disease free interval, disease free survival, overall survival, and disease specific survival. The median follow-up period was 124 months.

Results: Tumour size, number of involved axillary lymph nodes, and the urokinase plasminogen activator system were the strongest predictors of outcome. A prognostic index comprising these variables was able to select a large group of patients (30%) with a good prognosis.

Conclusion: The importance of the classical prognostic variables, lymph node status and tumour size, was confirmed. The data presented in our study suggest that the addition of the urokinase plasminogen activator or its inhibitor type 1 to this prognostic panel could be of value.

INTRODUCTION

The incidence of breast cancer in women in the Netherlands is among the highest in the world and rising. In the period 1989-1998, the number of newly diagnosed breast cancers in the Netherlands was approximately 95.000. In the same period almost 35.000 patients died from breast cancer, i.e. about 30-40% of patients initially diagnosed with breast cancer.[1] Adjuvant chemotherapy and endocrine therapy have shown to improve survival in patients with breast cancer, but also have potentially serious side effects, and are costly. In the late eighties and early nineties of the 20th century the presence of axillary lymph node metastases was the only prognostic indicator routinely used in the Netherlands to decide whether or not adjuvant systemic therapy had to be provided.[2] It was thought that in patients with axillary node negative (ANN) breast cancer the level of efficacy of the available adjuvant therapies was not high enough to outweigh the disadvantages. However, since approximately 30% of ANN patients will ultimately develop distant metastasis, it was also thought that additional prognostic factors could be helpful to identify those ANN patients in whom the benefits of adjuvant systemic therapy would outweigh the disadvantages. Prognostic factors could also be helpful to identify patients whose prognosis is so poor with conventional treatment that more aggressive therapy might be warranted. Combinations of prognostic factors might enable an improved prediction of the probability of recurrences, hence might be helpful tools to decrease the number of over- and under-treated patients.[3]

The primary goal of the present prospective observational study was to evaluate the clinical relevance of a large number of potential prognostic factors in early breast cancer. A secondary goal was to select a number of appropriate prognostic factors by which primary breast cancer patients can be optimally indexed according to prognosis and by which, as a result, the administration of adjuvant therapy could eventually be either omitted or adjusted to prognosis.

METHODS

Patient characteristics

Between October 1989 and March 1993, consecutive female patients diagnosed with operable breast cancer, were asked to participate in an observational study on prognostic factors. Patients were recruited in 5 hospitals affiliated with the Comprehensive Cancer Centre Middle Netherlands (IKMN). A total of 474 women gave their written informed consent, of these 463 (98%) were diagnosed with stage I-III disease. The IKMN has a cancer-registry that contains data from all newly diagnosed cancer patients treated in one of 11 hospitals located in the Middle Netherlands, a region with 1.3 million inhabitants. In the inclusion-period of this observational study in total 2243 female patients with stage I to III breast cancer were registered in the IKMN-registry. Of these, 2165 (97%) patients were actually operated. Patient- and tumour characteristics of the 2165 patients included in the IKMN-registry and the subset of those included in this registration study on prognostic factors were compared using the Chi-square test.

Prognostic variables

The clinical relevance as prognostic variable of the following patient-, tumour-, and treatment characteristics was evaluated: age (≤50, 51-60, 61-70, >70 year), menopausal status (pre-, postmenopausal), tumour lateralisation (left, right), tumour location in the breast (central, medial, lateral, overlapping), histological type (ductal, lobular, other or not otherwise specified), tumour size (0.1-1.0, 1.1-2.0, 2.1-3.0, >3.0 cm), tumour free margins (present, absent), in-situ component (none, marginal, extensive), in-situ component free margins (present, absent), number of axillary lymph nodes resected (0-6, 7-12, >12), number (0, 1-3, >3 positive nodes) and level (negative, positive top-node) of axillary lymph node metastases.

Moreover, the prognostic value of the following variables was studied: oestrogen- and progesterone receptor value using either enzyme immuno assay (≤15, >15 fmol/mg protein) or immunohistochemistry (≤10%, >10% positive staining), histological grade according to the revised Bloom-Richardson scoring system, mitotic counts (≤12, >12 mitoses/2mm^2), DNA-index (diploid, aneuploid), S-phase fraction (≤ median, > median value), and cathepsin-D, pS2, urokinase plasminogen activator (UPA) and its inhibitor type 1 (PAI-1) (all ≤ median, > median value). Pathological data were obtained from local pathology reports. DNA-index and S-phase fraction were determined with dual parameter flow cytometry at the University Medical Centre Utrecht. Biochemical tests (hormone receptors, Cathepsin D, pS2, UPA, and PAI-1) were performed at the department of endocrinology of the University Medical Centre Utrecht. Of some prognostic markers - histological grade (62%), mitotic counts (87%), S-phase fraction (86%), Cathepsin D (58%), pS2 (52%), UPA (46%), and PAI-1 (46%) - data were available for less then 90% patients.

Survival end-points

End-points for outcome analysis were time from primary surgery until death (overall survival, OS), time from primary surgery until death related to breast cancer (disease specific survival, DSS), time from primary surgery until recurrence (disease free interval, DFI), time from primary surgery until death or recurrence whichever came first (disease free survival, DFS), and time from primary surgery until locoregional recurrence (locoregional recurrence rate, LRRR). We defined locoregional recurrence as either recurrent disease in the skin or soft tissue of the chest wall, the ipsilateral breast and lymph nodes in the ipsilateral axilla, the infraclavicular fossa or the internal mammary chain. Death was classified as related to breast cancer when death was probably caused by breast cancer in the presence of distant metastases. Recurrence was defined as either locoregional recurrence or distant metastasis whichever came first.

Table 2.1. Patient and tumour characteristics. Comparison between study-population and patients with stage I to III breast cancer in the IKMN-registry.

	IKMN-registry (n=2165) %	Study population (n=463) %	
Age (years)			
≤ 50	31	35	*
51 – 70	43	44	
> 70	26	21	
Histology			
Ductal	74	68	*
Lobular	10	11	
Other	13	18	
Adenocarcinoma n.o.s.	3	3	
Pathological T-stage			
T1	57	61	*
T2	32	33	
T3 or T4	8	6	
Unknown	4	0	
Pathological N-stage			
N0	61	59	
N1, N2 or N3	36	39	
Unknown	2	2	
Postoperative treatment			
Radiation therapy	62	65	
Chemotherapy	13	16	
Hormonal therapy	26	31	*

** P<0.05. Abbreviations: n.o.s.: not otherwise specified.*

Statistical analysis

Median follow-up was determined with the inverse Kaplan-Meier method.[4] 10-year survival and event rates were determined using timetables. For all evaluated prognostic factors differences in LRRR, DFI, DFS, OS, and DSS were compared

using univariate Cox proportional hazard regression analyses. Selected prognostic factors were further analysed using multivariate Cox proportional hazard regression analyses.

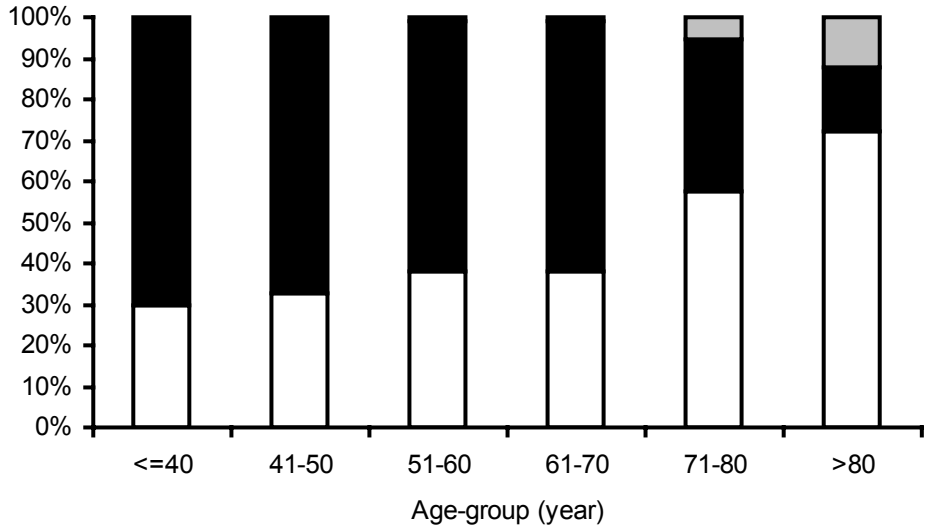
RESULTS

Patient-, tumour-, and treatment characteristics

Overall, the study-population was a representative sample of the IKMN-registry (Table 2.1). However, study-patients were slightly younger, with a median age of 58 years versus 60 years in the registry-population. The histological classification differed, with less infiltrating ductal carcinomas in the study-population. In the registry-population the T-stage was unknown in 4% op patients, compared with 0% in the study-population. And, more study-patients were treated with adjuvant tamoxifen. The studied population was not different from the IKMN-registered population considering axillary nodal status, and use of chemotherapy or radiotherapy.

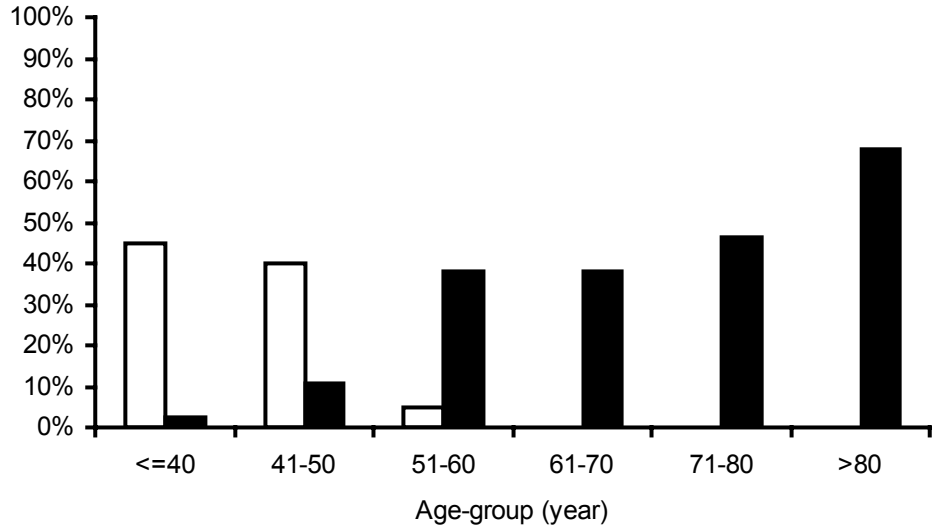
The 463 tumours included in this study were equally divided between the left and right breast, 41% of tumours were located in the lateral upper quadrant of the breast. In-situ carcinoma was found in 52% of patients, in 21% the in-situ component was extensive. The presence or absence of axillary lymph node metastases was investigated in 98% of patients. A median number of 13 nodes were investigated (range 0-31), in 69% of patients >10 axillary lymph nodes were investigated. 39% of tumours were axillary node positive (ANP), 59% were axillary node negative, and from 2% of tumours the axillary nodal status was unknown. In 39% of ANP patients 1 lymph node was involved; 2-3, 4-9, and >9 lymph nodes were involved in 29%, 15% and 17% of ANP patients, respectively. Positive axillary lymph nodes were found in 30%, 49%, and 73% of T1, T2 and

Figure 2.1. Relative proportion of patients treated with modified radical mastectomy [□], breast conserving therapy [■] and other surgical therapy [■] according to age at diagnosis.



T3-4 tumours respectively. Axillary top-nodes were involved in 31% of ANP patients. Primary surgical treatment consisted of breast conserving therapy (BCT) in 57% of patients, or modified radical mastectomy (MRM) in 41% of patients. Older patients were more often treated with MRM (Figure 2.1). Larger tumours, when compared with smaller ones, were also more often treated with MRM: 69%, 57% and 29% of T3, T2 and T1 tumours respectively. At initial surgery the infiltrative component was not radically resected in 10% of patients, the in-situ component was not radically resected in 6% of patients. Radiotherapy was administered to 65% of patients. After breast conserving surgery 99.6% of patients received radiotherapy. After MRM radiotherapy was administered to 19% of patients. Adjuvant systemic therapy was administered to 44% of patients; to 13% of axillary node negative patients and to 91% of axillary node positive patients. Adjuvant chemotherapy, either doxorubicin / cyclophosphamide (AC) or

Figure 2.2. Percentage of patients treated with chemotherapy [□] and hormonal therapy [■] according to age at diagnosis.



cyclophosphamide / methotrexate / fluorouracil (CMF), was administered exclusively to patients less than 60 years of age, adjuvant hormonal therapy predominantly to older patients (Figure 2.2). Hormone receptors were determined in 95% of patients. 76% of tumours were oestrogen receptor positive, 66% of tumours were progesterone receptor positive. 61% of tumours were both oestrogen- and progesterone receptor positive. Hormone receptor determination did not influence the number of patients treated with adjuvant hormonal therapy. Adjuvant hormonal therapy was administered to 28% of oestrogen-receptor negative patients and 31% of oestrogen-receptor positive patients. Although we have no data on duration of endocrine therapy, we expect most patients were treated with tamoxifen for 2 to 5 years.

Table 2.2. Association between evaluated prognostic variables and LRRR, DFI, DFS, OS, and DSS in univariate Cox-regression analyses.

	Number of patients	10-year rate (%)				
		LRRR	DFI	DFS	OS	DSS
All patients	463	12	69	59	67	78
Age						
≤ 50 year	163	14	62	60 †	70 ‡	73
51-60 year	100	10	72	69	75	79
61-70 year	102	8	74	62	72	87
> 70 year	98	13	73	39	44	79
Tumour size						
0.1 – 1.0 cm	79	8	85 ‡	70 ‡	76 ‡	92 ‡
1.1 – 2.0 cm	204	11	72	64	74	83
2.1 – 3.0 cm	104	10	67	55	57	68
> 3.0 cm	76	17	52	38	49	64
Axillary lymph nodes						
0 tumour positive	275	11	77 ‡	67 ‡	75 ‡	86 ‡
1 – 3 tumour positive	120	14	65	54	61	72
> 3 tumour positive	61	8	45	36	43	55
Unknown	7					
Axillary top-node						
Tumour negative	393	12	74 ‡	63 ‡	71 ‡	81 ‡
Tumour positive	57	9	44	34	43	58
Unknown	13					
Histological grade						
I	95	9	82 *	70 *	82 †	95 †
II	163	12	68	57	64	75
III	74	13	67	56	61	74
Unknown	131					
Mitotic counts						
≤ 12 mitoses / 2 mm^2	266	10 *	72 *	63 *	73 †	83 ‡
> 12 mitoses / 2 mm^2	139	15	63	54	60	69
Unknown	58					
Cathepsin D						
≤ median value	138	13	73	63 *	72 *	81
> median value	132	9	67	53	60	75
Unknown	193					
UPA						
≤ median value	108	12	75 *	69 †	78 †	84 *
> median value	107	15	60	47	56	70
Unknown	248					
PAI-1						
≤ median value	108	11	77 †	71 ‡	81 ‡	88 †
> median value	107	16	58	45	53	66
Unknown	248					

** P<0.05, † p<0.01, ‡ p<0.001. Abbreviations: LRRR: locoregional relapse rate; DFI: disease free interval; DFS: disease free survival; OS: overall survival; DSS: disease specific survival; UPA: urokinase plasminogen activator; PAI-1: plasminogen activator inhibitor type 1.*

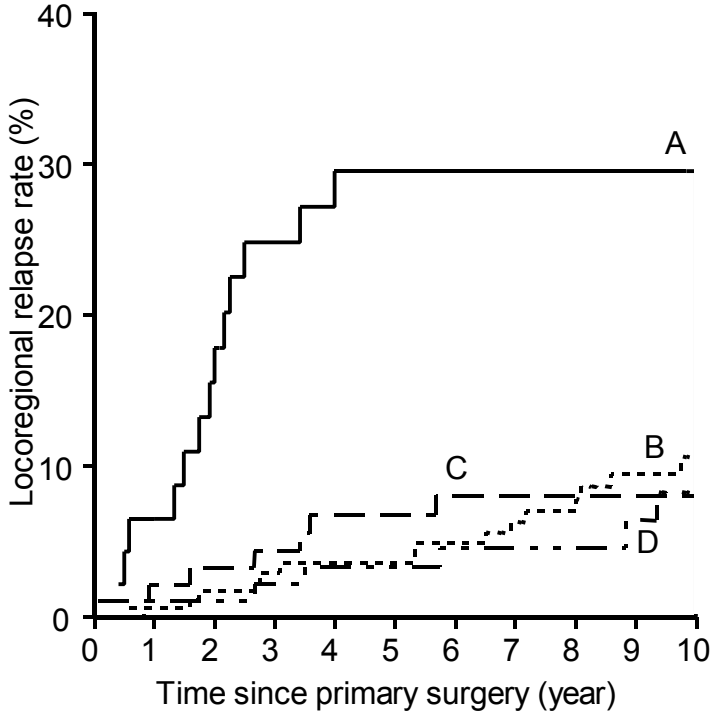
Survival end-points

Patients who survived were followed until December 2002. The median follow-up period was 10.3 years. During follow-up 151 patients died, 92 deaths were related to breast cancer, the other 59 patients died from causes unrelated to breast cancer. The 10-year OS was 67%, the 10-year DSS 78%. Distant metastases were diagnosed in 111 patients (10-year event rate 25%). In 49% of patients distant metastases were primarily diagnosed in the skeletal system. Loco-regional recurrence occurred 47 patients (10-year event rate 12%), and in 30 patients breast cancer was diagnosed in the contralateral breast. A second primary malignancy was diagnosed in 27 patients. The 10-year DFI was 69% (134 events), the 10-year DFS 59% (191 events).

Analysis of potential prognostic markers

In univariate analysis the following variables were not significantly associated with any of the survival end-points: menopausal status, tumour lateralisation, tumour location in the breast, histological type, tumour free margins, in-situ component, in-situ component free margins, number of axillary lymph nodes resected, oestrogen- and progesterone receptor value, DNA-index, S-phase fraction, and pS2. These markers were not further investigated. The univariate association between the other prognostic markers and the studied outcome end-points is provided in Table 2.2. A positive top-node was found in 13%, 61% and 84% of patients with 1-3, 4-9 and >9 positive axillary lymph nodes, respectively. After stratification for the number of axillary lymph node metastases no significant association between the presence of tumour cells in the highest axillary lymph node and DFI ($p=0.39$), DFS ($p=0.18$), OS ($p=0.35$) or DSS ($p=0.99$) remained. The prognostic value of the level of the lymph node metastasis was not further investigated. Age and Cathepsin D were associated with DFS and OS only. Age was primarily associated with non-breast cancer related mortality ($p<0.001$). The

Figure 2.3. Locoregional relapse rate according to mitotic counts and treatment with radiotherapy. A: high mitotic counts, no radiotherapy; B: low mitotic counts, radiotherapy; C: high mitotic counts, radiotherapy; D: low mitotic counts, no radiotherapy.



Number at

A	96	91	86	73	63	36
B	171	166	152	145	115	67
C	47	37	31	26	17	13
D	94	88	78	73	60	34

association between Cathepsin D and DFS (p=0.05) and OS (p=0.03) was not very strong. In univariate analysis BCT, compared with MRM, was associated with a significant better DFI (p=0.02), DFS (p=0.002), OS (p=0.001) and DSS (p=0.02). After stratification for tumour size no significant association with DFI (p=0.40), DFS (p=0.10), OS (p=0.06) or DSS (p=0.83) remained. The prognostic value of type of primary surgical therapy was not further investigated. The

administration of radiotherapy was associated with a significant better DFS and OS. After stratification for age no significant association with DFS (p=0.26) or OS (p=0.40) remained. In univariate analysis both the administration of radiotherapy and low mitotic counts were associated with a lower LRRR (p<0.05). In multivariate analysis, only patients with high mitotic counts, not treated with radiotherapy had an elevated risk of locoregional recurrence (Hazard ratio 5.0, 95% C.I. 2.0 – 12.6) (Figure 2.3). Adjuvant systemic therapy was primarily administered to ANP patients, and was associated with a significant (p<0.01) worse DFI, DFS, OS and DSS. After stratification for the number of axillary lymph node metastases no significant association with DFI (p=0.35), DFS (p=0.86), OS (p=0.29) or DSS (p=0.91) remained.

Construction of a prognostic index

In univariate analysis tumour size and the number of positive axillary lymph nodes were the strongest predictors of DFI, DFS, OS and DSS (p<0.001), and were determined in more than 98% of patients. Age over 70 years was strongly associated with a worse DFS and OS (p<0.001). Histological grade, mitotic counts, UPA, and PAI-1 were also significantly associated with DFI, DFS, OS, and DSS, but were hindered with higher numbers of missing data. The prognostic value of tumour size, number of positive axillary lymph nodes, and age combined with the administration of adjuvant therapy was investigated further in a multivariate Cox regression model (Table 2.3). They proved independent predictors of DFI, DFS, OS and DSS, and were subsequently used to construct 3 risk groups: low-risk (tumours ≤ 1.0 cm in diameter, and ANN), high-risk (tumours > 3.0 cm in diameter, or >3 axillary lymph nodes involved) and intermediate-risk (not low- or high-risk). 9% of patients in the low-risk group, compared with 69% of patients in the high-risk group were treated with adjuvant therapy. Patients in the low-risk group had a significant better prognosis compared with patients in the high-risk group (p<0.001) (Table 2.4). In the low-risk group prognosis was good

Table 2.3. Association between age, tumour size, number of axillary lymph nodes and adjuvant therapy and age, risk group and adjuvant therapy, and LRRR, DFI, DFS, OS, and DSS in multivariate Cox-regression analyses. Significant hazard ratios ($p<0.05$) are bold.

	Hazard ratio (95% confidence interval)			
	DFI	**DFS**	**OS**	**DSS**
Age				
≤ 70 year	1.0	1.0	1.0	1.0
> 70 year	0.71 (0.44-1.1)	**1.6 (1.2-2.3)**	**2.2 (1.5-3.1)**	0.92 (0.53-1.6)
Tumour size				
0.1-1.0 cm	1.0	1.0	1.0	1.0
1.1-2.0 cm	1.8 (0.93-3.5)	1.3 (0.80-2.1)	1.1 (0.63-1.9)	2.1 (0.83-5.5)
2.1-3.0 cm	**2.3 (1.2-4.6)**	1.6 (0.96-2.7)	**1.8 (1.0-3.2)**	**4.1 (1.6-10.9)**
> 3.0 cm	**3.2 (1.6-6.5)**	**2.0 (1.2-3.4)**	1.7 (0.96-3.2)	**4.0 (1.5-10.9)**
Axillary lymph nodes				
0 tumour positive	1.0	1.0	1.0	1.0
1-3 tumour positive	1.8 (0.99-3.3)	1.4 (0.85-2.3)	1.4 (0.78-2.4)	2.0 (0.97-4.2)
> 3 tumour positive	**3.1 (1.6-5.9)**	**2.2 (1.3-3.9)**	**2.2 (1.2-4.1)**	**3.5 (1.6-7.5)**
Adjuvant systemic therapy				
No	1.0	1.0	1.0	1.0
Yes	0.73 (0.41-1.3)	0.94(0.59-1.5)	1.1 (0.67-1.9)	0.88 (0.44-1.8)
Age				
≤ 70 year	1.0	1.0	1.0	1.0
> 70 year	0.66 (0.41-1.1)	**1.6 (1.2-2.2)**	**2.2 (1.5-3.0)**	0.83 (0.48-1.4)
Risk group				
Low or interm. / low PAI-1	1.0	1.0	1.0	1.0
Interm. / undetermined PAI-1	**1.8 (1.1-3.2)**	**1.7 (1.1-2.6)**	**2.0 (1.2-3.4)**	**3.6 (1.5-8.3)**
High or interm. / high PAI-1	**3.7 (2.2-6.2)**	**2.8 (1.8-4.2)**	**3.1 (1.8-5.2)**	**6.7 (3.0-15.1)**
Adjuvant systemic therapy				
No	1.0	1.0	1.0	1.0
Yes	1.1 (0.79-1.6)	1.2 (0.87-1.6)	1.4 (0.96-1.9)	1.4 (0.91-2.2)

Abbreviations: DFI: disease free interval; DFS: disease free survival; OS: overall survival; DSS: disease specific survival; interm.: intermediate; PAI-1: plasminogen activator inhibitor type 1.

enough to omit adjuvant systemic therapy, whereas patients in the high-risk group were clearly indicated to receive adjuvant systemic therapy. However, most

patients (60%) were classified intermediate-risk. Therefore, the prognostic significance of age, histological grade, mitotic counts, Cathepsin D, UPA and PAI-1 was further investigated in the 277 patients with an intermediate risk (Table 2.4). UPA and PAI-1 were the strongest predictors of DFI, DFS, OS, and DSS in the subgroup of patients with an intermediate risk based on tumour size and number of involved axillary lymph nodes ($p<0.01$). The DFI and DSS of intermediate-risk patients with a low UPA or PAI-1 were equal to the DFI and DSS of low-risk patients, whereas the DFI and DSS of intermediate-risk patients with a high UPA or PAI-1 were almost equal to the DFI and DSS of high-risk patients. UPA and PAI-1 were not determined in 145 (52%) intermediate-risk patients. The DFI and DSS of these patients were 74% and 80% respectively, comparable to the DFI (73%) and DSS (81%) of all 277 patients in the intermediate risk group. The intermediate-risk group was split up. Patients with an intermediate risk and a low PAI-1 value were added to the low-risk group. Patients with an intermediate risk and a high PAI-1 value were added to the high-risk group. Patients with an intermediate risk whose PAI-1 value was not determined remained in the intermediate-risk group. With these risk groups a large group of patients with low risk (10-year DSS 95%) could be distinguished from patients with high risk (10-year DSS 64%) (Figure 2.4). In multivariate analysis the prognostic value of these risk groups was independent of age and treatment with adjuvant therapy (Table 2.3). 20% of patients in the low-risk group were treated with adjuvant therapy.

DISCUSSION

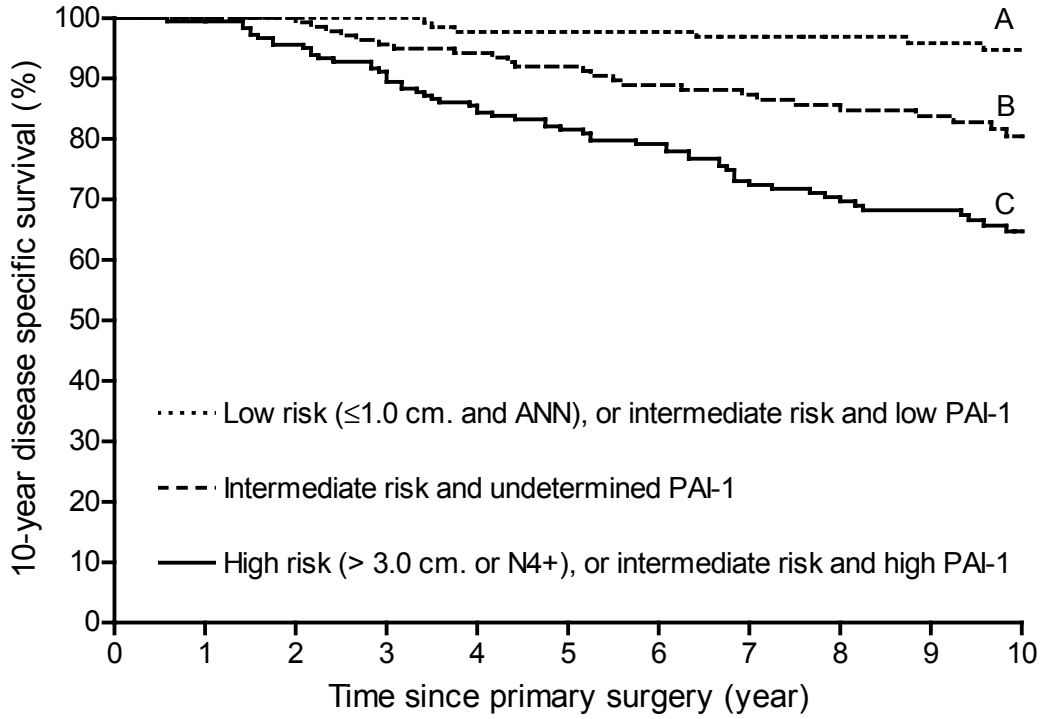
The 463 patients included in this study are a representative sample of patients diagnosed with stage I-III operable breast cancer in the Middle Netherlands. Patient- and tumour characteristics are in accordance with those reported in literature.[2,5,6] Treatment figures are also in accordance with the views in the inclusion period of this study. Surgical therapy was breast sparing in 57% of

Table 2.4. Association between risk group and LRRR, DFI, DFS, OS, and DSS, and between prognostic variables and LRRR, DFI, DFS, OS, and DSS for intermediate risk patients only.

	Number of patients	10-year rate (%) DFI	DFS	OS	DSS
Risk group					
Low *(≤1.0 cm and ANN)*	68	86 ‡	72 ‡	79 ‡	95 ‡
Intermediate (not low/high risk)	277	73	64	71	81
High *(>3.0 cm or N4+)*	118	51	38	49	63
Analyses of intermediate risk patients only (n=277)					
Age					
≤ 70 year	223	73	67 †	74 †	80
> 70 year	54	75	49	57	84
Histological grade					
I	59	83	73	84 *	94 *
II	104	71	64	69	76
III	46	70	57	65	77
Unknown	68				
Mitotic counts					
≤ 12 mitoses / 2 mm^2	167	74	66	75	82
> 12 mitoses / 2 mm^2	85	71	61	66	76
Unknown	25				
Cathepsin D					
≤ median value	86	77	69	79 *	87 *
> median value	78	71	62	67	76
Unknown	113				
UPA					
≤ median value	62	86 †	81 †	89 †	94 †
> median value	70	60	52	60	68
Unknown	145				
PAI-1					
≤ median value	68	85 †	81 ‡	90 ‡	95 †
> median value	64	59	49	57	67
Unknown	145				

** P<0.05, † p<0.01, ‡ p<0.001. Abbreviations: DFI: disease free interval; DFS: disease free survival; OS: overall survival; DSS: disease specific survival; ANN: axillary node negative; N4+: 4 or more axillary lymph nodes tumour positive; UPA: urokinase plasminogen activator; PAI-1: plasminogen activator inhibitor type 1.*

Figure 2.4. 10-year disease specific survival according to risk group.



number at risk

A	136	135	127	123	105	66
B	145	138	130	113	94	54
C	182	172	152	133	99	59

patients. Mastectomy was conducted particularly in older patients and in those with larger tumours. During the inclusion period of this study the benefit of adjuvant systemic therapy to ANN patients was a matter debate,[7,8] but in the Netherlands not routinely administered. A population-based study on the treatment of early breast cancer in the Southeast Netherlands between 1984 and 1991 reported that less than 3% of ANN patients received any form of adjuvant systemic therapy.[2] In the same study the proportion of ANP patients receiving any form of adjuvant systemic therapy increased between 1984 and 1991 from 49% to

82%.[2] In the present study adjuvant systemic therapy was administered to 13% of ANN patients, and 91% of ANP patients. Adjuvant hormonal therapy was administered equally to oestrogen-receptor negative and positive patients, probably because adjuvant tamoxifen was thought to have at least some effect in oestrogen-receptor negative patients.[9,10] Under the above outlined regimen 10-year survival data were comparable to, or even slightly better than, those reported in literature.[6] The 10-year overall survival rates for patients with 0, 1-3 and ≥3 positive axillary lymph nodes were 75% (expected 65-80%), 61% (expected 38-63%), and 43% (expected 13-27%) respectively.

The primary goal of this prospective study was to evaluate the clinical significance of a large number of potential prognostic markers in primary breast cancer. After median 10 years follow-up prognostic value for locoregional recurrence was found for mitotic counts and the administration of radiotherapy. Patients with high mitotic counts, not treated with radiotherapy had an elevated risk of locoregional recurrence. As a after breast conserving surgery 99.6% of patients were treated with radiotherapy, the patients at risk for locoregional recurrence were those with high mitotic counts, treated with MRM, and not treated with radiotherapy. Contemporary data on the post mastectomy LRRR and prognostic variables are sparse. Recently, Truong et al. reported that poor histological grade was associated with a high LRRR in patients with ANN breast cancer less than 5 cm in diameter, treated with mastectomy, but not with radiotherapy.[11] These results warrant further studies after the association between mitotic counts and locoregional recurrence after MRM.

After median 10 years follow-up prognostic value for disease recurrence or survival was found for age, number and level of positive axillary lymph nodes, tumour size, histological grade, mitotic counts, cathepsin D, UPA and PAI-1. In the last decades others have published data on the prognostic value of these, and many other markers. The results of these studies have been summarised in a

number of reviews and treatment guidelines.[12-16] But, the major prognostic markers that are used in clinical practice still are number of positive axillary lymph nodes and tumour size. Exactly these were the strongest prognosticators in the present study, and they were used to create 3 risk groups. Subsequently, UPA and PAI-1 were able to split-up the intermediate prognosis group in half. Patients with a low PAI-1 value had a prognosis equal to low-risk patients, whereas patients with a high PAI-1 value had a prognosis equal to high-risk patients. Unfortunately PAI-1 was determined in only 48% of patients. Despite this, we created, with the use of tumour size, axillary lymph node status and PAI-1, a subgroup of 136 (29%) patients with a 10-year DSS of 95% and a 10-year DFI of 85%. These results are promising, but need validation in an independent cohort of patients.

Consensus guidelines, such as the NIH-guideline, the St. Gallen guideline and the Dutch CBO-guideline, use sets of prognostic markers to select patients with good, intermediate and poor prognosis.[12,13,17] But, none of these guidelines uses UPA and/or PAI-1. The major drawback for broad use in clinical practise of UPA and PAI-1 is a lack in standardization with respect to immunoassays used, methods of tumour extraction and protein determination. However, the prognostic value of UPA and PAI-1 has already been shown both in a large prospective clinical trial,[18] and a pooled analysis of 18 datasets including 8377 patients.[19] In these studies, high levels of UPA and PAI-1 were the strongest predictors of pour disease-free and overall survival, apart from lymph node status. The data presented here confirm the prognostic impact of UPA and PAI-1, and suggest that the addition of UPA and/or PAI-1 to a prognostic panel is valuable.

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3

The effects of non-breast cancer related death and contralateral breast cancer on estimated outcome probability in patients with early breast cancer.

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ABSTRACT

Background: A wide variation of definitions of recurrent disease and survival are used in the analyses of outcome of patients with early breast cancer. Explicit definitions with details both on endpoints and censoring are provided in less than half of published studies.

Methods: We evaluated the effects of various definitions of survival and recurrent disease on estimated outcome in a cohort of 463 patients with primary breast cancer. Outcome estimates were determined both by the Kaplan-Meier method and by a competing risk method.

Results: The in- or exclusion of contralateral breast cancer or non-disease related death in the definition of recurrent disease or survival strongly affected estimated outcome probability. The magnitude was dependent on patient-, tumour-, and treatment characteristics. Minor differences were observed between estimated outcome determined by the Kaplan-Meier method and the competing risk method.

Conclusions: Insight in the contribution of non-disease related death or contralateral breast cancer to estimated recurrent disease rate or overall death rate is indispensable for a correct interpretation and comparison of outcome analyses.

INTRODUCTION

In studies on early breast cancer, outcome is usually defined as the time from diagnosis or surgery until a particular event of interest (endpoint). The event of interest can vary and may include death (overall survival), disease related death (disease specific survival), or recurrent disease (disease free survival).

Altman et al. systematically reviewed the appropriateness of the application and presentation of survival analysis in clinical oncology journals.[1] They found that among papers specifically dealing with death as an end-point, only 47% explicitly described this end-point as either any death or only cancer-related death. In as much as 61% of papers that studied time to progressive disease the handling of non-cancer related mortality was not clearly defined.

In studies on patients with early breast cancer a wide variation of definitions of disease free survival is used. These definitions always include local recurrence, regional recurrence, and distant metastasis, but sometimes also include non-disease related death, contralateral breast cancer and in some cases second primary cancer. For example, the 1998 overview of randomised trials on adjuvant therapy includes contralateral breast cancer in the analysis of disease recurrence, but does not include non-disease related death.[2] The Intergroup includes non-disease related death, but contralateral breast cancer only when it occurs concurrently with a locoregional or distant relapse.[3] In the original reports of the NSABP B14 and B20 trials both non-disease related death, contralateral breast cancer, and second primary cancer were included as events in the definition of disease free survival.[4,5] In a recent report with long-term findings from these trials the definition of recurrence free survival was restricted to local or regional recurrence, or distant metastasis.[6]

Despite these different definitions, many papers on breast cancer survival do not provide an explicit definition of recurrent disease. Mirza et al. wrote a review on prognostic factors in node-negative breast cancer.[7] In the methods section of their report they stated that only papers in which overall or disease free survival were specified were included in their review. Sixty-three papers from their reference list dealt with survival analysis in primary breast cancer. We reviewed the definitions of recurrent disease used in these 63 papers. In only 21 out of 47 papers that studied time to recurrent disease the definition of recurrent disease explicitly described the handling of non-cancer related mortality. Intercurrent deaths were censored in 14 papers and counted as events in 7 papers. Eight papers explicitly described the handling of contralateral breast cancer. Contralateral breast cancer was censored in 1 and considered as event in 7 papers. The handling of second primary cancer was described in 7 papers. Second primary cancer was censored in 2 and counted as event in 5 papers.

In most papers the survival probability is estimated with the Kaplan-Meier method from observed survival times, censored or uncensored.[8] Censoring may arise due to end of follow-up, loss to follow-up, but also due to a competing event that makes further follow-up impossible. 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.[9,10,11]

In the present study we used data from a cohort of 463 patients with primary breast cancer to evaluate the effects of various definitions of survival and relapse on estimated survival probability. We specifically focused on the influences of non-disease related death and contralateral breast cancer. A second goal was to

evaluate whether differences could be assessed in estimated outcome determined either by the Kaplan-Meier method or a competing risk method.

Table 3.1. Patient-, tumour-, and treatment characteristics

	Number of patients (%)
Age	
≤ 50 year	142 (31)
51-70 year	213 (46)
>70 year	108 (23)
Primary surgical therapy	
Breast conserving therapy	266 (57)
Modified radical mastectomy	190 (41)
Other	7 (2)
Adjuvant systemic therapy	
Hormonal therapy	142 (31)
Chemotherapy	72 (16)
Histology	
Ductal	290 (63)
Other	173 (37)
Tumour size	
≤ 20 mm	272 (59)
> 20 mm	191 (41)
Axillary lymph nodes	
Negative	278 (60)
Positive	185 (40)

MATERIAL AND METHODS

Between October 1989 and March 1993 463 patients diagnosed with operable, stage I to III breast cancer agreed to participate in a prospective registration study on prognostic factors. We obtained written informed consent from all patients. Treatment was given according to the guidelines of the Comprehensive Cancer Centre Middle Netherlands. Patient-, tumour- and treatment characteristics are shown in Table 3.1. We assessed follow-up data until December 2002.

The events that were used to determine the different definitions of outcome were local- and regional recurrent disease, contralateral breast cancer, distant metastasis, disease related death and non-disease related death. In the various analyses these events were either ignored, considered as event of interest or as competing event (censored), depending on the definition of outcome. Definitions of overall survival, diseases specific survival, disease free interval, and disease free survival are given in Table 3.2. We defined local recurrent disease as either recurrence in the skin or soft tissue of the chest wall or in the ipsilateral breast. Regional recurrent disease confined recurrence in the lymph nodes in the ipsilateral axilla, the infraclavicular fossa or the internal mammary chain. Contralateral breast cancer included invasive breast cancer lesions in the contralateral breast regardless of histological type, lymph node involvement, and time interval from initial therapy or from subsequent recurrent disease. Breast cancer lesions at any other site, including the ipsilateral supraclavicular lymph nodes, were classified as distant metastases. We classified death as disease related when death was probably caused by breast cancer in the presence of distant metastases. Otherwise we classified death as non-disease related.

Survival probabilities were determined both by Kaplan-Meier estimates,[8] and cumulative incidence competing risk analyses. As outlined by others, the competing risk analyses were determined in a two-step process.[9,10] First we

Table 3.2. Definitions of outcome.

Overall survival	Time from surgery until death from any cause
Disease specific survival	Time from surgery until death related to breast cancer. Death not related to breast cancer is censored (Kaplan-Meier analysis) or treated as competing event (competing risk analysis).
Disease free interval	Time from surgery until recurrent disease*. Death not related to breast cancer is censored (Kaplan-Meier analysis) or treated as competing event (competing risk analysis).
Disease free survival	Time from surgery until recurrent disease* or death from any cause.

** In the definition of recurrent disease local recurrence, regional recurrence, and distant metastasis are considered events; contralateral breast cancer is ignored, treated as event or censored (Kaplan-Meier analysis) / treated as competing event (competing risk analysis).*

determined outcome estimates with the Kaplan-Meier method considering both the events of interest and the competing risk events as 'events'. In the second step, we calculated the conditional probabilities of experiencing the event of interest. With these probabilities we estimated the cumulative incidences in the event of interest.

RESULTS

During median 10.0 years of follow-up 149 patients died. 91 deaths were related to breast cancer, and the other 58 patients died from causes unrelated to breast cancer. Local recurrences were diagnosed in 28 patients, regional recurrences in 24. Distant metastases occurred in 111 patients, and in 30 patients breast cancer was diagnosed in the contralateral breast.

Table 3.3. Estimated 10-year survival rate according to definition of survival determined both by Kaplan-Meier method and the competing risk analysis.

Survival definition	**10-year survival rate (%)**					
	all patients		**no adjuvant systemic therapy**		**adjuvant systemic therapy**	
	KM	**CR**	**KM**	**CR**	**KM**	**CR**
Overall survival	68.0	68.0	75.8	75.8	58.6	58.6
Disease specific survival	79.3	80.6	85.3	86.2	71.9	73.7
Disease free survival						
contralateral ignored	59.3	59.3	65.8	65.8	51.2	51.2
contralateral censored	58.6	59.4	64.9	66.0	51.1	51.6
contralateral event	55.5	55.5	59.9	59.9	50.2	50.2
Disease free interval						
contralateral ignored	69.4	70.9	74.6	75.8	63.0	64.9
contralateral censored	68.9	70.9	73.9	75.9	63.2	65.4
contralateral event	64.8	66.5	67.6	69.2	61.3	63.4

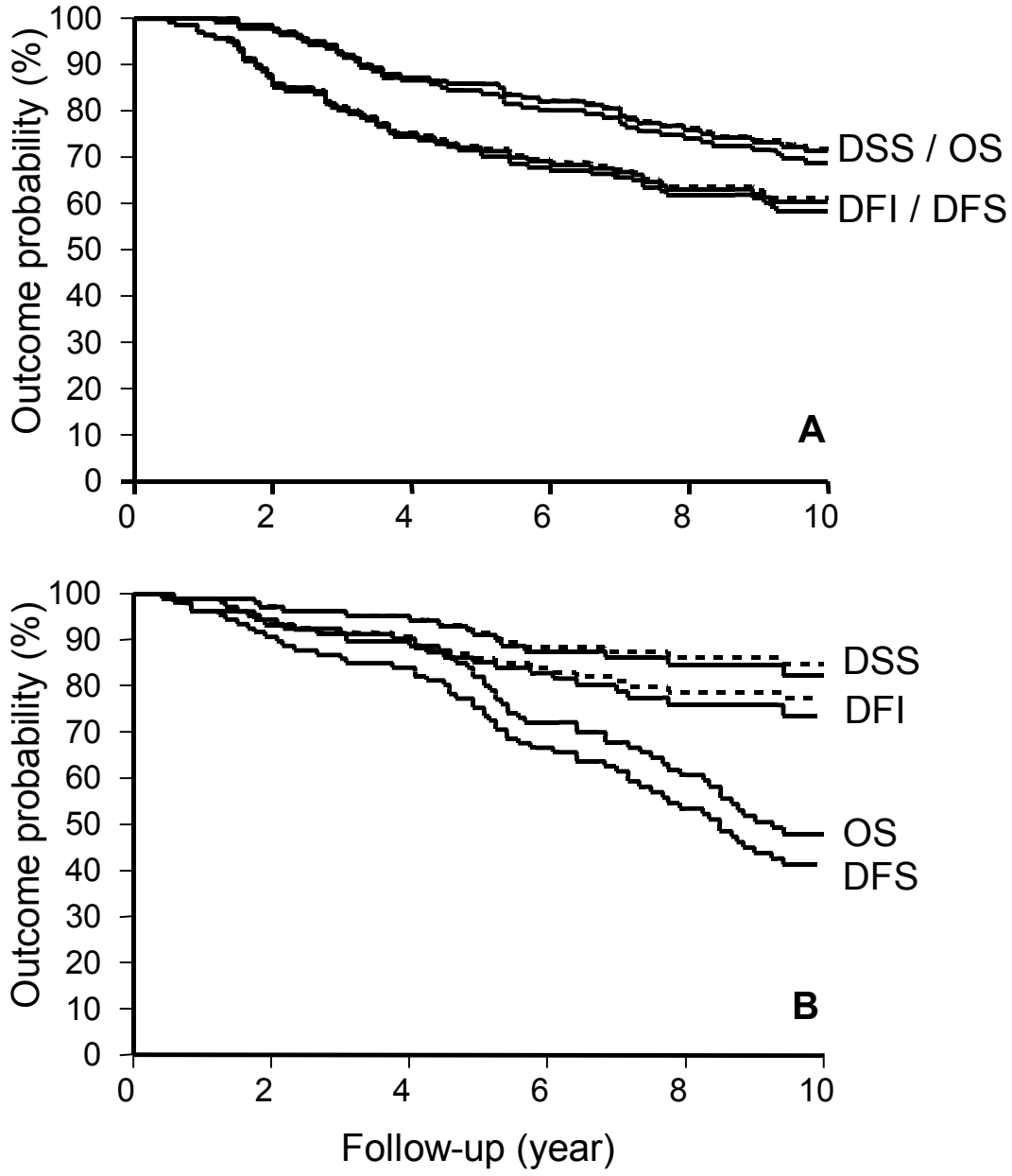
KM: Kaplan-Meier method; CR: competing risk analysis.

Estimated with the Kaplan-Meier method, after 10 years of follow-up 68% of patients were still alive (overall survival). If no one had died from causes other than breast cancer, 79% of patients would have been alive (disease-specific survival) (Table 3.3). The estimated 10-year risk of recurrent disease varied between 31% and 44% depending only on the definition of relapse. After 10 years of follow-up 56% to 59% of patients were still alive and free of recurrent disease (disease free survival), but if no one had died in the interim period 65% to 69% of patients would have been free of recurrent disease (disease free interval) (Table 3.3). Compared with the competing risk approach, the Kaplan-Meier method slightly underestimated 10-year survival rates when one or more competing events were censored instead of ignored. The largest difference (2.0 percent-point) was found when both non-disease related death and contralateral breast cancer were censored (Table 3.3).

Non-disease related death

The difference in estimated survival probability between overall survival and disease related survival, and between disease free survival and disease free interval is by definition caused by the handling of non-disease related death. As older age is associated with a higher probability of non-disease related death, we evaluated the effect of patient's age on estimated survival probability using the various definitions of survival. As shown in table 4, patients aged more than 70 years were at risk for dying from a cause unrelated to breast cancer, whereas patients aged 50 years or less seldom died from a cause unrelated to breast cancer. As a consequence, in the younger subgroup 10-year overall survival was almost equal to 10-year disease specific survival. Whereas in the elderly, estimated 10-year disease specific survival was more than 30 percent point better than estimated 10-year overall survival (Figure 3.1). In the younger subgroups differences between Kaplan-Meier and competing risk estimates were limited (≤ 1%). In the elderly estimations of 10-year disease specific survival were 82.2%

Figure 3.1. Influence of survival definitions on estimated outcome probability in breast cancer patients 50 years or less of age (A), and over 70 years of age (B). Both by Kaplan-Meier method (solid line) and competing risk analysis (dotted line).



DSS: disease specific survival; OS: overall survival; DFI: disease free interval; DFS: disease free survival. Contralateral breast cancer was ignored in the definition of relapse.

and 84.9% with Kaplan-Meier and competing risk analyses, respectively. Estimations of 10-year disease free interval were 73.6% and 77.6% respectively for two statistical methods.

Table 3.4. Estimated 10-year event rate according to age at diagnosis determined both by Kaplan-Meier method and competing risk analysis.

Event	10-year event rate (%)					
	≤ 50 yr		51-70 yr		> 70 yr	
	KM	CR	KM	CR	KM	CR
Overall death	31.1	31.1	23.5	23.5	52.0	52.0
Disease related death	28.6	28.1	16.4	15.7	17.7	15.1
Non-disease related death	3.6	3.0	8.5	7.8	41.7	36.9
Recurrent disease or death	41.5	41.5	32.2	32.2	58.7	58.7
Recurrent disease	39.5	38.8	26.8	25.8	26.3	22.4
Death without recurrent disease	3.2	2.7	7.5	6.5	43.8	36.2

KM: Kaplan-Meier method; CR: competing risk analysis. Recurrent disease was defined as either local recurrence, regional recurrence or distant metastasis whichever came first. Occurring contralateral breast cancer was ignored.

Contralateral breast cancer

We evaluated the effect of the inclusion of contralateral breast cancer as event in the analysis of disease recurrence on estimated disease free interval and disease free survival (Table 3.3). The administration of adjuvant systemic therapy is known to reduce the risk of contralateral breast cancer.[12,13] In the whole study

population the absolute reduction in disease free survival or disease free interval due to inclusion of contralateral breast cancer as event in the definition of relapse was approximately 4%; in patients not treated with adjuvant systemic therapy 6-7%, and in patients treated with adjuvant systemic therapy 1-2%. In the broadest definition of relapse 197 events were counted during 10-years follow-up, including 47 non-disease related deaths and 26 contralateral breast cancers. That is, in the analysis of disease free interval 17% of events were contralateral breast cancers, compared with 13% in the analysis of disease free survival. Consequently, the effect of the inclusion of contralateral breast cancer as event in the definition of relapse was greater when estimating disease free interval than when estimating disease free survival (Table 3.3).

Similarly, the greatest effect of the inclusion of contralateral breast cancer and non-disease related death as events on estimated disease recurrence rate was found in patients with low risk breast cancer. In a subgroup of 168 patients with T1N0 breast cancer, not treated with adjuvant systemic therapy, the 10-year relapse rate including local relapse, regional relapse, or distant metastasis was 23%. The estimated 10-year relapse rate rose to 31% both with the inclusion of either contralateral breast cancer or non-disease related death as event in the definition of relapse, and to 38% with the inclusion of both events in the definition of relapse.

DISCUSSION

In the present study we show in a cohort of patients with early breast cancer that the inclusion of contralateral breast cancer or non-disease related death as event in the definition of recurrent disease or survival strongly affects estimated outcome probability. The magnitude of the effect is dependent on patient-, tumour-, and treatment characteristics.

These findings, and the explicit definition of outcome seem of minor importance for the interpretation of a particular clinical trial as long as results are not compared with other trials. After all, all study arms use the same definition(s) of outcome. However, the effect of the intervention can be different for the various events that are counted, ignored or censored in the definition of outcome. As a consequence, the in- or exclusion of contralateral breast cancer or non-disease related death in the definition of outcome could influence the results of a trial. We can illustrate this with data from the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial.[14,15] 6241 patients are included in the 2 relevant arms of this trial. After a median follow-up of 68 months, 831 patients have died (411 patients treated with anastrozole and 420 patients treated with tamoxifen). More patients who were treated with tamoxifen died from breast cancer than patients who were treated with anastrozole (265 vs. 235), whereas fewer patients who received tamoxifen died from a cause not related to breast cancer (155 vs. 176). Treatment with anastrozole also led to a reduction in disease recurrences (402 vs. 498). A considerable part of this reduction was caused by the difference in occurrence of contralateral breast cancers (35 vs. 59). Consequently, anastrozole led to an improvement in disease free survival (Hazard Rate (HR) 0.87, p=0.01), and an even better improvement in disease free interval (HR 0.79, P=0.0005). Overall survival was similar for anastrozole and tamoxifen treated patients (HR 0.97), whereas disease specific survival was 12% better in the anastrozole group, although this was not significant (HR 0.88, p=0.20). These data from the ATAC trial illustrate that a clear definition of survival endpoints, including the contribution of non-disease related death and the contribution of contralateral breast cancer to the estimated disease recurrence rate are crucial for a correct interpretation of outcome analyses in clinical trials. These data also demonstrate that a significant difference in disease free survival is not automatically followed by a difference in overall survival.

The Kaplan-Meier method for estimating survival has repeatedly been criticised for possible biases in the estimation of event rates.[9,11,16] In the presence of competing events, cumulative incidence functions of the events of interest are probably evaluated more appropriately by taking into account other events within a competing risk framework. In general, event rates derived using the Kaplan-Meier approach are larger than estimates accounting for competing risks,[9,11] and differences between Kaplan-Meier and competing risk approaches can become substantial when the competing risk event is related to or is a result of the underlying disease. But, as presented by Satagopan et al., ignoring the informative censoring mechanism does not substantially influence the estimates of breast cancer-specific mortality.[9] We present similar results in our estimations of disease-specific survival and disease free survival. However, differences became more substantial when relative more patients were censored due to competing events.

In conclusion: Clear definitions of endpoints and competing events are crucial for the interpretation and comparison of outcome studies. In the present study on patients with early breast cancer, the inclusion of contralateral breast cancer and/or non-disease related death substantially influenced estimates of recurrent disease rate and survival, specifically in elder patients and patients with a good prognosis. Bias generated by the Kaplan-Meier approach due to informative censoring of contralateral breast cancer or non-disease related death was limited.

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4

The prognostic value of hormone receptor detection by enzyme immuno assay and immunohistochemistry; a prospective study in patients with early breast cancer.

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ABSTRACT

Background: The main reason to determine the oestrogen (ER) and progesterone receptor (PR) in breast cancer is their predictive value for response to endocrine therapy. In addition, ER and PR receptors are often used as prognostic indicators. Enzyme immuno assay (EIA) and immunohistochemistry (ICA) are two methods for determining ER and PR receptors. These two methods have not been compared to each other on clinical endpoints.

Methods: In the present study we prospectively evaluated the prognostic value of ER and of PR, as determined both by ICA and by EIA, in 223 and 207 patients, respectively with early breast cancer.

Results: ER was positive in approximately 77% of patients, PR was positive in approximately 65% of patients. The proportion of potential agreement beyond chance between EIA and ICA was 0,58 and 0,65 for ER and PR respectively. The median follow-up period was 86 months. Both ER and PR appeared to be weak prognostic factors. No differences in prognostic value according to time-point of analysis or cut-off value chosen were found. No differences in prognostic value of hormone receptors detected by ICA or EIA were found.

Conclusions: Both methods appear to be equivalent with respect to qualification and with respect to prognostic value.

INTRODUCTION

Oestrogen- (ER) and progesterone-receptors (PR) are routinely used in the clinical management of breast cancer. The main reason to determine ER and PR is their predictive value for response to hormonal therapy.[1,2] It has been noted that oestrogen- and progesterone-receptors are also weak prognostic factors. However, long-term disease free and overall survival are not significantly influenced by the hormone receptor status.[3]

There are three commonly used techniques for hormone receptor determination. Until recently the ligand binding assay (LBA) has been the most commonly used method. With this method the rates of binding affinity and capacity of a radioactively labelled steroid hormone with its receptors in cytosol are measured. Nowadays most hospitals in the Netherlands use immunocytochemical assays (ICA) for determination of the presence of hormone receptors in tumour cells. With this qualitative technique highly specific monoclonal antibodies directed against the partially purified receptor are used. ICA has advantages over LBA: it is more sensitive and specific in the identification of low concentrations of hormone receptor positive tumour cells or in identifying hormone receptors in benign epithelium under direct microscopic visualization.[4,5] Several efforts have been made to (semi-)quantify ICA results. Good intra- and inter-observer reproducibility have been reported.[6,7] McClelland et al., however, compared the quantitative analyses of eight experienced, independent pathologists in the interpretation of ER and PR immunocytochemically stained breast tumour sections and observed a high interobserver variability.[8] The method of enzyme immunoassay (EIA) also uses specific monoclonal antibodies for hormone receptor determination, but in a quantitative way. It therefore shares many of the advantages of LBA and ICA. However, it lacks the control of presence or absence of receptor proteins in tumour cells. Concordance rates of 75% - 85% and

correlation coefficients of 0.70 – 0.97 between EIA, ICA and LBA have been reported and are found to be acceptable.[5-7,9-17]

The predictive and prognostic values both of EIA and of ICA appear of the same magnitude compared with that of LBA.[11,18,19] The prognostic value of ICA and EIA have not been compared with each other. To our knowledge there has been only one study comparing the predictive value of EIA and ICA.[15] In the present study we prospectively evaluated the prognostic value detected both by ICA and by EIA of ER in 223 and of PR in 207 breast cancer patients after a median follow-up of 86 months.

PATIENTS AND METHODS

Patients and primary treatment

In 5 hospitals affiliated with the Comprehensive Cancer Centre Middle Netherlands (IKMN) patients with operable breast cancer, diagnosed between October 1989 and March 1993, were asked to participate in a registration study on prognostic factors. 463 patients with stage I-III breast cancer gave their written informed consent. Follow-up information from all patients was collected until August 1999. ER-ICA, ER-EIA, PR-ICA and PR-EIA were determined in this multicentre study in 328, 337, 318 and 321 patients respectively. ER-ICA as well as ER-EIA was determined in 223 patients. Both ER-ICA and ER-EIA were not determined in 21 patients. PR-ICA as well as PR-EIA was determined in 207 cases. Both PR-ICA and PR-EIA were not determined in 30 patients. Survival analyses for ER and PR were performed on these 223 and 207 patients, respectively. Analyses were also performed on those patients in whom hormone receptors were not measured in order to exclude significant selection bias.

Enzyme immunoassay

EIA for specimens from all institutions was performed at the department of Endocrinology of the University Medical Centre Utrecht. Cytosols were prepared according to the EORTC procedure.[20] EIA was performed according to the instructions of the manufacturer (Abbott Laboratories, Chicago, IL, USA). Briefly, cytosol was incubated with beads coated with an anti-receptor monoclonal antibody (H222 for ER and KD68 for PR). Unbound material present in the cytosol was removed by aspirating the fluid and washing the beads. A second monoclonal anti-receptor antibody conjugated with horseradish peroxidase detected the presence of immune reactions in standards, controls, and cytosol samples. The chromogenic substrate was represented by orthophenylendiamine, developing a colour that was analysed by a spectrophotometer at 492 nm. and allowed a measurement of bound receptor conjugate, expressed as fmol/mg protein. Specimens with receptor values > 15 fmol/mg protein were considered positive according to the instructions of the manufacturer.

Immunocytochemical assay

ER- and PR-determination by ICA were performed at the local pathology department on fresh frozen tumour-tissue. ER-ICA and PR-ICA were performed according to the instructions of the manufacturer (Abbott Laboratories, Chicago, IL, USA) using monoclonal rat antibodies to respectively human ER and PR. Tumours were considered hormone receptor positive if more than 10% of tumour cells showed positive staining.[11,12,16] In this study ICA data were obtained from routine pathology reports and are therefore reported as positive or negative.

Table 4.1. Treatment modalities and tumour characteristics.

	Oestrogen receptor			Progesterone receptor		
	Control Group	**Study group**		**Control group**	**Study group**	
Number of patients	240	223		256	207	
Primary surgical treatment						
Modified radical mastectomy	38%	43%		39%	43%	
Breast conserving therapy	60%	55%		59%	55%	
Local excision only	2%	2%		2%	2%	
Radiation therapy	67%	64%		67%	64%	
Adjuvant chemotherapy	15%	16%		15%	16%	
Adjuvant hormonal therapy	27%	35%	†	28%	35%	
Tumour diameter						
0 – 10 mm.	22%	11%	*ƒ*	22%	10%	*ƒ*
11 – 20 mm.	35%	48%		35%	49%	
> 20 mm.	38%	40%		38%	41%	
Unknown	5%	1%		5%	0%	
Axillary lymph node status						
Tumour negative	61%	55%		60%	56%	
Tumour positive	38%	43%		38%	43%	
Unknown	2%	2%		2%	2%	
Age						
0 – 45 years	18%	19%		18%	20%	
46 – 55 years	31%	26%		29%	27%	
56 – 70 years	33%	32%		33%	31%	
> 70 years	19%	23%		19%	22%	

ƒ p<0.001; † p<0.05.

Statistics

Statistical analysis was carried out using the statistical package SPSS for Windows, release 9.0 (SPSS Inc.). Kappa statistics were used to measure the degree of agreement as determined by the two methods. Univariate associations between hormone receptor-status by ICA or EIA and control groups, treatment modalities and other categorized prognostic variables were assessed by the Pearson chi-square test. Endpoints of the study were disease free survival (DFI) and overall survival (OS). For DFI time to failure was computed from the date of surgery until recurrence (loco regional recurrence or distant metastasis) or until the last date patient was known to be free of disease. Patients who developed contralateral breast cancer were censored at the date of diagnosis. Patients who died from a cause not related to breast cancer were censored at the date of decease. Overall survival was calculated from the date of surgery until death or until the date the patient was last known to be alive. Univariate analyses were performed with life tables and with the time-fixed Cox regression procedure. For survival analyses follow-up was truncated at 84 months. Events that took place after more than 84 months of follow-up were not included in the analyses.

RESULTS

In the present registration study 463 patients were suitable for survival analysis. Both ER-EIA and ER-ICA were determined in 223 patients. The remaining 240 patients were used as control group in order to exclude selection bias. Both PR-EIA and PR-ICA were determined in 207 patients; the other 256 patients were used as a control group. Treatment modalities and tumour characteristics in the study groups were compared with those of the control groups (Table 4.1). Breast conserving therapy was performed in 55% - 60%, mastectomy in 38% - 43% of patients. Local excision only was done in 2% of patients. Radiation therapy was

Table 4.2. Percentages hormone-receptor positive tumours according to tumour characteristics and adjuvant treatment modalities.

	Oestrogen receptor			Progesterone receptor		
	ER-ICA	**ER-EIA**		**PR-ICA**	**PR-EIA**	
Total	77%	78%		67%	63%	
Adjuvant chemotherapy						
Yes	75%	72%		71%	76%	
No	77%	79%		66%	60%	
Adjuvant hormonal therapy						
Yes	80%	85%		63%	57%	
No	75%	74%		70%	66%	
Tumour diameter						
0 – 10 mm.	58%	58%	†	38%	§ 38%	‡
11 – 20 mm.	81%	83%		75%	70%	
> 20 mm.	75%	79%		64%	60%	
Axillary lymph node status						
Tumour negative	72%	73%		63%	60%	
Tumour positive	81%	83%		72%	65%	
Age						
0 – 45 years	67%	67%		68%	68%	
46 – 55 years	74%	76%		73%	71%	
56 – 70 years	77%	77%		56%	55%	
> 70 years	86%	90%		74%	59%	

§ $p<0.01$; ‡ $p<0.025$; † $p<0.05$

administered in 64% - 67% of patients, and adjuvant chemotherapy in 15% - 16% of patients. The percentage of patients that received adjuvant hormonal therapy was higher in the groups in whom both ER-EIA and ER-ICA were determined

compared to the control group, 35% vs. 27%. Of 21 patients in whom ER was not determined by ICA or EIA, 7 (33%) received adjuvant hormonal therapy. In the study group hormonal therapy was not given significantly more in ER-positive tumours compared to ER-negative tumours (table 4.2). The control groups contained significantly more small tumours with a diameter < 11 mm compared to the study groups (22% vs. 11%). In all groups almost 60% of tumours were less than 2 cm in diameter, 55% - 61% of tumours were axillary lymph node negative.

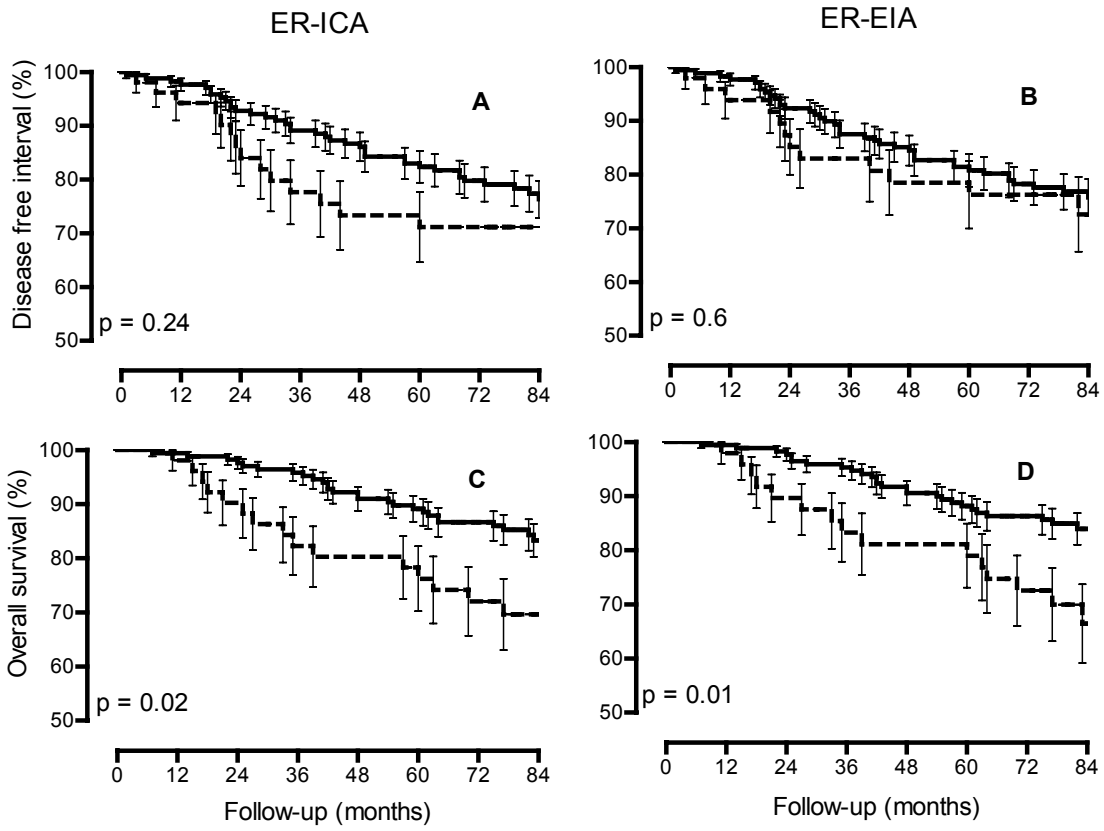
Table 4.3. 2 x 2 tables ICA and EIA.

		ER-ICA		
		Negative	**Positive**	**Total**
ER-EIA	**Negative**	34	15	49
	Positive	18	156	174
	Total	52	171	223

		PR-ICA		
		Negative	**Positive**	**Total**
PR-EIA	**Negative**	56	21	77
	Positive	12	118	130
	Total	68	139	207

Median ER-EIA value was 101 fmol/mg protein (range 0 – 1975); median PR-EIA value was 44 fmol/mg protein (range 0 – 1985). ER-EIA and ER-ICA were positive in 174 (78%) and 171 (77%) cases, respectively. PR-EIA and PR-ICA were positive in 130 (63%) and 139 (67%) cases, respectively. Small tumours (< 11 mm.) were significantly less often ER- or PR-positive compared to larger tumours (Table 4.2). The proportion of potential agreement beyond chance (Kappa) between EIA and ICA was moderate to substantial. Results from ER-EIA

Figure 4.1. Oestrogen receptor and disease free interval (A and B) and overall survival (C and D). Solid line: receptor positive tumours; dotted line: receptor negative tumours. ER-ICA: A and C; ER-EIA: B and D.

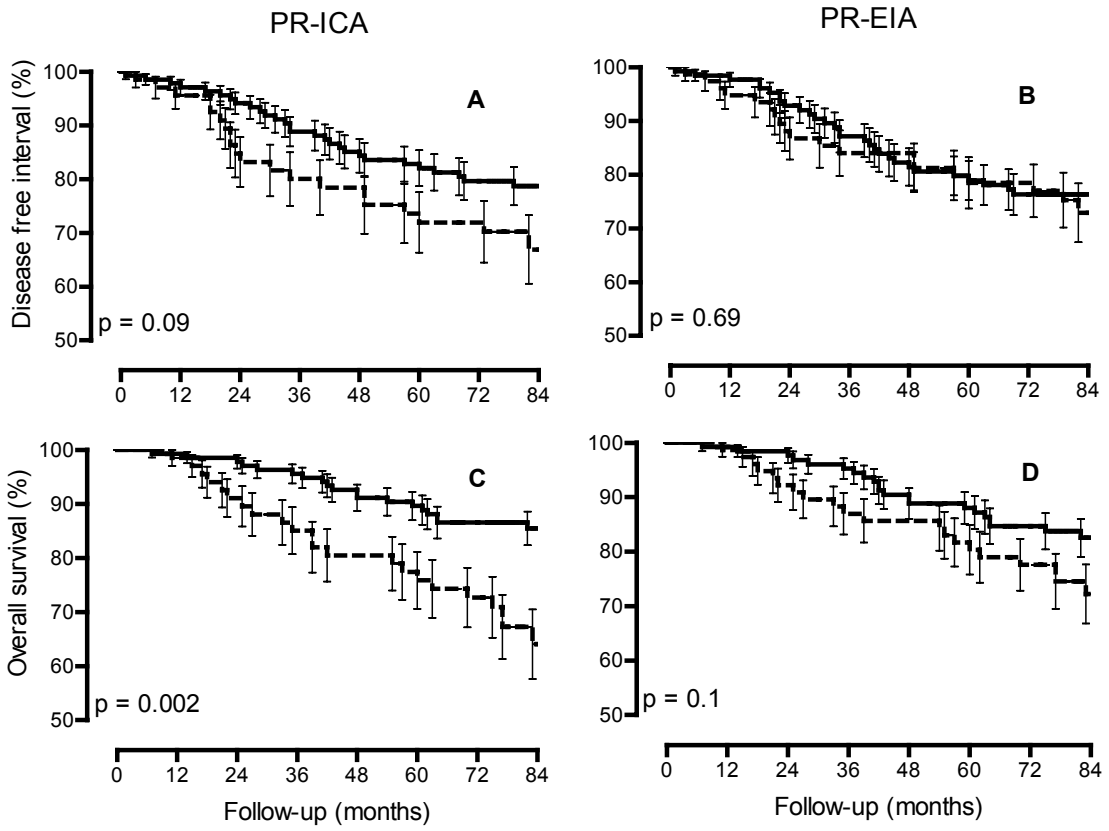


and ER-ICA agreed in 85% of cases (Kappa 0.58). Results from PR-EIA and PR-ICA agreed in 84% of cases (Kappa 0.65). Two by two tables are depicted in table 4.3. Immunohistochemistry of discordant specimens from one of the three pathology departments was re-examined. None of 7 ER-ICA negative and 6 PR-ICA negative marked specimens were converted to positive, 1 of 4 ER-ICA positive and 1 of 4 PR-ICA positive marked specimens were converted to negative (the cells that were stained positive were interpretated as carcinoma in situ). Unfortunately we were not able to re-evaluate EIA measurements.

The median follow-up was 86 months (range 44 – 110). For survival analyses follow-up was truncated at 84 months. During 84 months of follow-up 17% - 20% of patients died, 12% - 14% died related to breast cancer. Contra-lateral breast cancer was diagnosed in 3% - 5% of patients. In 23% of patients breast cancer relapsed. Distant metastases were diagnosed in 19% - 20% of patients, loco-regional relapses in 7% - 10% of patients. The rate of events did not differ significantly between study- and control-groups. DFI and OS did not differ significantly between study- and control-populations. After 84 months of follow-up ER-ICA, ER-EIA and PR-ICA were significant prognosticators of OS. Significance remained after stratification for adjuvant hormonal therapy. No significance was found for DFI after 7 years (Figure 4.1 and 4.2). EIA measurements were quantitative. The prognostic significance of ER-EIA and PR-EIA as continuous variables was determined. No significance was found for DFI or OS. Three, 5 and 7 year DFI- and OS-rates were determined and compared (Table 4.4). No differences were found between study- and control groups. Three, 5 and 7 year DFI was 86%, 81% and 75% respectively. DFI-rates in hormone receptor positive patients were slightly higher compared to hormone receptor negative patients. These differences were not statistically significant. Three, 5 and 7 year OS was 93%, 87% and 80% respectively. Differences between OS-rates in hormone receptor positive and negative patients were greater and frequently statistical significant (Table 4.4).

In continuous variables the cut-off level used for survival analysis can be chosen at an arbitrary level. The cut-off level for EIA of 15 fmol/mg protein used in the present study was advised by the manufacturer of the antibodies. Other cut-off values were studied (Figure 4.3). The relative risk of disease free survival of patients with EIA negative- compared to EIA positive tumours varied between 0.4 and 1.1 for ER, and between 0.5 and 1.0 for PR. The relative risk of overall survival of patients with EIA negative- compared to EIA positive tumours varied

Figure 4.2. Progesterone receptor and disease free interval (A and B) and overall survival (C and D). Solid line: receptor positive tumours; dotted line: receptor negative tumours. PR-ICA: A and C; PR-EIA: B and D.



between 0.5 and 0.6 for ER, and between 0.3 and 0.7 for PR. The differences in hazard ratios for the different cut-off levels were not significant.

DISCUSSION

Both EIA and ICA are commonly used methods for determining hormone receptors in breast cancer. The main purpose to determine hormone receptors is

their ability to predict efficacy of endocrine therapy. But hormone receptors are also used as a prognostic indicator. We have prospectively compared the prognostic value of the oestrogen- and progesterone receptor values as determined by ICA and EIA in a routine clinical setting.

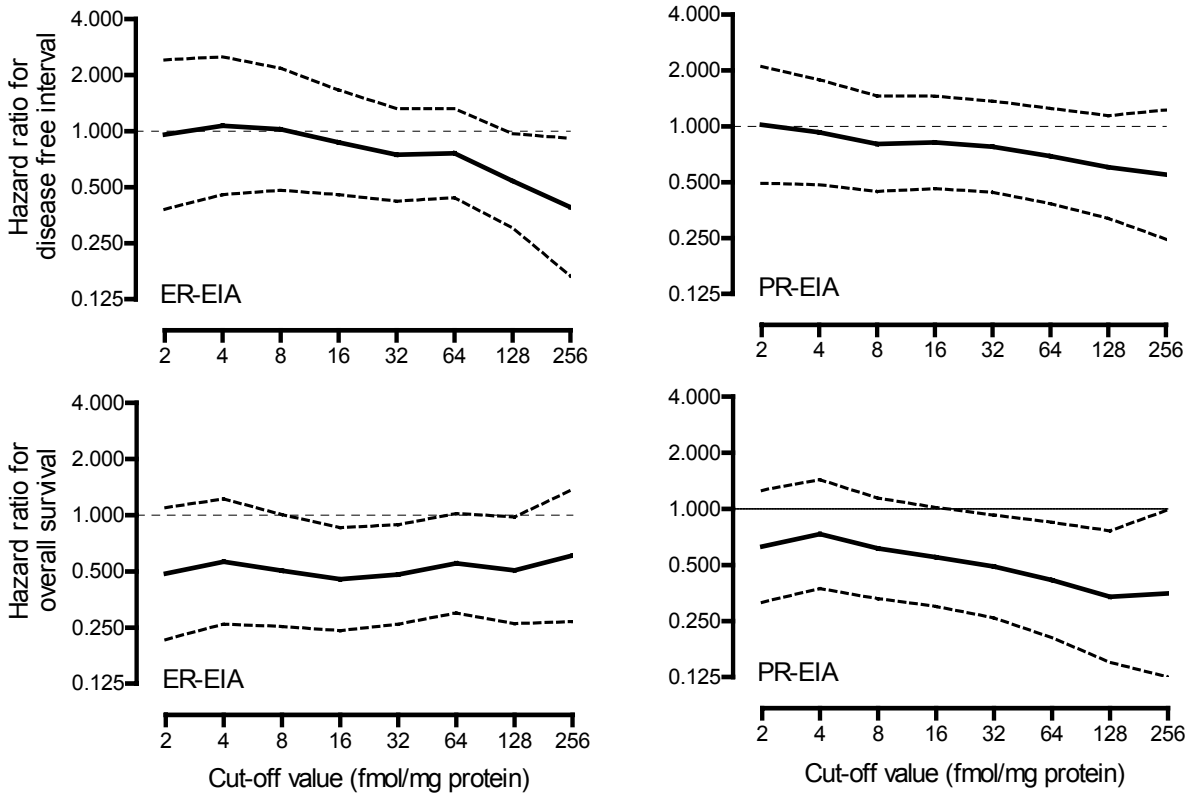
Between 1989 and 1993 in total 463 early breast cancer patients were included in a multicentre, prospective registration study on prognostic factors. ER and PR could be determined both by EIA and by ICA in less than 50% of patients (48% and 45% respectively). In order to evaluate a potential bias, the remaining patients in whom ICA and/or EIA were not determined were used as a control group. Most tumour characteristics and primary treatment modalities differed not significantly between the study and the control groups. However, the percentage of patients that received adjuvant hormonal therapy was higher in the ER-study group compared with that of the ER-control group. We could not find a suitable explanation for this phenomenon. Treatment selection based on hormone receptor values is not likely since hormonal therapy was not given significantly more in ER-positive tumours compared with that of ER-negative tumours. In tumours in which the ER was not determined at all, hormonal therapy was provided to 33% of patients. At the time of patient inclusion hormone receptors were not used as predictive factor. The rate of small tumours (< 11 mm.) was significantly higher in the control groups compared to the study groups. This was at least partly due to selection, since it is not possible to perform an adequate and reliable EIA in micro-invasive cancer. However, the consequences of this bias appear to be low. During follow-up the rate of events did not differ significantly between study- and control groups. No differences in Cox-regression analyses and in 3, 5 and 7 year survival rates were found between study- and control groups either. Therefore, we conclude that the groups of patients in whom ER and PR were determined were representative for the whole population of breast cancer patients.

Table 4.4. Three, 5 and 7 year disease free interval and overall survival.

	Cumulative disease free interval			Cumulative overall survival					
	3 year rate (SE)	5 year rate (SE)	7 year rate (SE)	3 year rate (SE)		5 year rate (SE)		7 year rate (SE)	
Oestrogen receptor									
Study	0.86 (0.02)	0.80 (0.03)	0.75 (0.03)	0.94 (0.02)		0.86 (0.02)		0.80 (0.03)	
Control	0.87 (0.02)	0.81 (0.03)	0.75 (0.03)	0.93 (0.02)		0.87 (0.02)		0.80 (0.03)	
ER-ICA									
Negative	0.78 (0.06)	0.73 (0.06)	0.71 (0.07)	0.82 (0.05)	‡	0.78 (0.06)		0.69 (0.07)	†
Positive	0.89 (0.02)	0.83 (0.03)	0.76 (0.03)	0.96 (0.02)		0.89 (0.02)		0.83 (0.03)	
ER-EIA									
Negative	0.83 (0.06)	0.78 (0.06)	0.73 (0.07)	0.83 (0.05)	†	0.81 (0.06)	†	0.67 (0.07)	†
Positive	0.88 (0.03)	0.81 (0.03)	0.76 (0.03)	0.95 (0.02)		0.88 (0.02)		0.84 (0.03)	
Progesterone receptor									
Study	0.86 (0.02)	0.81 (0.03)	0.75 (0.03)	0.94 (0.01)		0.87 (0.02)		0.82 (0.03)	
Control	0.86 (0.02)	0.80 (0.03)	0.75 (0.03)	0.92 (0.02)		0.86 (0.02)		0.79 (0.03)	
PR-ICA									
Negative	0.80 (0.05)	0.74 (0.06)	0.67 (0.06)	0.85 (0.04)	‡	0.77 (0.05)	†	0.64 (0.06)	§
Positive	0.89 (0.03)	0.83 (0.03)	0.79 (0.04)	0.96 (0.02)		0.90 (0.03)		0.86 (0.03)	
PR-EIA									
Negative	0.84 (0.04)	0.80 (0.05)	0.73 (0.05)	0.87 (0.04)	†	0.82 (0.04)		0.72 (0.05)	
Positive	0.87 (0.03)	0.80 (0.04)	0.76 (0.04)	0.95 (0.02)		0.88 (0.03)		0.82 (0.04)	

§ p<0.01; ‡ p<0.025; † p<0.05

Figure 4.3. Relative risk of disease free- and overall survival (solid line) with 95% confidence interval (dotted lines) at progressively higher cut-off values for ER-EIA and PR-EIA.



The oestrogen receptor was positive in approximately 77% of patients, the progesterone receptor was positive in approximately 65% of patients. The proportion of potential agreement beyond chance between EIA and ICA was moderate to substantial (Kappa 0,58 and 0,65 respectively for ER and PR). These results are in line with that of the literature.[7,10,11,13,15-17,21-23] Concordance between EIA and ICA found in the present study was substantial (85%), but there also were a substantial number of tumours with a discordant result. Re-evaluation of 22 ICA samples, with discordant EIA/ICA results, led to only 2 conversions. Unfortunately it was not possible to re-evaluate EIA samples. Explanations for discordant EIA/ICA results are: effect of fixation and processing on the

preservation of hormone receptors,[24] intratumoural heterogeneity,[12,13] improper handling of the specimens or unsuitable samples of the tumour sent for EIA,[12] hormone receptor positive benign- or intraductal components in the EIA sample,[12] borderline EIA and ICA results.[13] The major theoretical advantage of ICA over EIA is microscopic verification of the presence of the receptor proteins in tumour cells. It has been suggested that ICA is a more specific and more sensitive test for the measurement of receptor content in breast cancer.[12] It is, however, impossible to draw conclusions concerning specificity and sensitivity and the discordant results in the present study.

After 7 years of follow-up ER-ICA, ER-EIA and PR-ICA were significant prognosticators of OS. Significance remained after stratification for adjuvant hormonal therapy. No significance was found for DFI though. The absence of prognostic significance in the present study for DFI was not unexpected. The number of patients studied was relatively small. ER and PR are considered to be weak prognostic factors.[2] The observed prognostic significance of the hormone receptors for OS was probably caused by a better response in relapsed disease to hormonal treatment of patients with initial hormone receptor positive tumours.

Although long-term DFI and OS are thought not to be significantly influenced by the hormone receptor content, hormone receptor positive tumours are thought to have a somewhat more indolent course during the first few years after primary treatment.[2] This could not be supported by the differences in DFI-rate and OS-rate between hormone receptor negative and positive tumours at 3, 5 and 7 year, as they appeared to be constant over time and independent upon time-point of analysis.

The major theoretical advantage of EIA over ICA is its objective quantification. Several efforts have been made to (semi-)quantify ICA results and good intra- and inter-observer reproducibility has been reported by several authors.[6,7] Others,

however, observed a high interobserver variability.[8] In the present study ICA-results were binominal, no efforts were made to (semi)quantify ICA using a scoring system in order to reflect the routine clinical practice. The cut-off value was arbitrarily chosen at 10% staining. Results from EIA were quantitative. The cut-off value chosen to separate receptor-negative from receptor-positive tumours was 15 fmol/mg protein, according to the instructions of the manufacturer of the antibodies. But, the prognostic value of continuous variables, such as ER and PR, may be influenced by the cut-off level chosen.[25] Therefore, other cut-off values were studied. No significant differences in prognostic value of different cut-off values were found.

To our knowledge there has been only one study comparing the predictive value of EIA and ICA .[15] No former studies have been conducted comparing the prognostic value ER and PR as determined by either EIA or ICA. In the present study we prospectively evaluated the prognostic value detected both by ICA and by EIA of ER in 223 and of PR in 207 breast cancer patients after a median follow-up of 86 months. Both ER and PR appeared to be weak prognostic factors. No differences in prognostic value according to time-point of analysis or cut-off value chosen were found. No differences in prognostic value of hormone receptors detected by ICA or EIA were found. Both methods appear to be equivalent with respect to qualification and with respect to prognostic value.

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5

Prognostic value of mitotic counts in axillary node negative breast cancer patients with predominantly well-differentiated tumours.

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ABSTRACT

Background: In axillary node negative (ANN) breast cancer patients additional prognostic markers are needed to decide whether adjuvant systemic treatment might be useful.

Methods: In the present study the prognostic relevance of mitotic counts and Bloom-Richardson grade (BR-grade) was evaluated in 164 ANN breast cancer patients. No adjuvant systemic treatment was given to any of these patients. Mitotic counts were determined twice, in routine practice and in revision.

Results: A substantial reproducibility of mitotic counts was found, provided that the cut-off value chosen was high enough. After a median follow-up of 10 years, mitotic counts had no prognostic significance for survival at any cut-off value. A trend towards a significant worse survival was found for patients with Bloom-Richardson grade II or III in comparison with grade I.

Conclusions: Based on data in the literature a positive association between both mitotic counts and Bloom-Richardson grade and survival in axillary node negative breast cancer may exist, but the extent of this putative association and its clinical relevance can be argued, particularly in a group of patients with predominantly well-differentiated tumours.

INTRODUCTION

A number of guidelines for the adjuvant systemic treatment of axillary node negative (ANN) breast cancer have been published.[1-3] In these guidelines tumour size is used to decide whether adjuvant systemic treatment is indicated. However, in patients with tumours of intermediate size other prognostic factors are needed to define low or average/high risk subgroups. A number of markers have been suggested for this purpose. However, with the exception of histological grade, the clinical relevance of these markers specifically in ANN breast cancer is not established.

Proliferative capacity is important in the progression of cancer and mitotic counts (MC) represent tumour cell proliferation. MC are also an important component of all histological grading systems. In the present study we evaluated the reproducibility and prognostic relevance of MC and Bloom-Richardson grade (BR-grade) in 164 ANN breast cancer patients. No adjuvant systemic treatment has been administered to these patients. The objective was to determine whether either MC or BR-grade could be used to determine a subgroup of ANN breast cancer patients in whom adjuvant systemic treatment might result in a clinically relevant increase of survival.

PATIENTS AND METHODS

Patients

In 5 hospitals affiliated with the Comprehensive Cancer Centre Middle Netherlands (IKMN) consecutive patients with operable, stage I to III breast cancer, diagnosed between October 1989 and March 1993, were asked to

Table 5.1. Patient and treatment characteristics of eligible and non-eligible patients with negative axillary lymph nodes.

	Number of patients	
	Eligible (n=164)	**Non-eligible** (n=111)
Age median (range)	58	61
< 50 years	48	26
50 – 59 years	45	27
60 – 69 years	37	33
≥ 70 years	34	25
Primary treatment		
Modified radical mastectomy	55	37
Breast conserving therapy	108	68
Other	1	6
Histological type		
Ductal carcinoma	126	83
Lobular carcinoma	17	9
Mixed type	8	6
Other	13	13
Tumour size		
< 11 mm	31	36
11 – 30 mm	117	67
> 30 mm	15	8
Unknown	1	0

participate in our study. From 463 patients we obtained written informed consent. In the present study we specifically focused on ANN breast cancer patients (n=275). Not included were 38 (14%) patients who received adjuvant systemic therapy. Another 58 tumours were non-eligible because we were unable to acquire the exact routine MC from the pathology reports. Finally, specimens from 14 tumours could not be retrieved for revision and of 1 specimen fixation quality

was found not good enough to revise MC. So, eligible were 164 ANN breast cancer patients who received no adjuvant systemic therapy and in whom MC were performed both in routine practice and in revision. Patient- and treatment characteristics of the eligible patients and non-eligible ANN breast cancer patients were comparable and are shown in Table 5.1. The study was performed in a period when mammographic screening was systematically practiced in the IKMN district for patients between 50 and 70 years of age. Follow-up was assessed until December 2002. The median follow-up period was 10.2 years.

Mitotic counts

MC were determined routinely in three pathology departments. Data were obtained from the pathology reports. Routine MC were determined using microscopes with a 400x magnification, a 40x objective and a field area of 159 μm^2. Mitoses were counted in 10 consecutive high power fields. The MC were revised according to the criteria proposed by Baak and Clayton.[4-8] In most cases it was clear which slide was initially used for mitosis counting. In some cases we had to re-select a slide from the provided material. The quality of the provided sections varied, but was interpreted as good in the majority (91%) of cases. MC were revised using a microscope with a 400x magnification, a 40x objective and a field area of 310 μm^2. Mitoses were counted in 20 consecutive fields. Two observers (EF, FB) evaluated the sections simultaneously. In this study the MC were defined as the number of mitoses per 2 mm^2, instead of the number of mitoses per 10 high power fields. This was done in order to overcome the variety in field sizes of the various microscopes used.

Modified Bloom-Richardson grade

In all revised cases histological grade was evaluated using the modified Bloom Richardson grading system as proposed by Elston and Ellis.[9] In this grading

system three parameters: tubule formation, nuclear pleomorphism, and MC are determined. To each parameter a score of 1 to 3 is assigned. The final BR-grade is based on the summed score of these three parameters. For the MC Elston and Ellis used a field area of 274 μm^2. Up to 9 mitoses per 10 fields scored 1 point, 10-19 scored 2 points and more than 20 scored 3 points. This point system was recalculated from mitoses per 2.74 mm^2 (10 x 274 μm^2) to mitoses per 2 mm^2: Up to 7 mitoses per 2 mm^2 scored 1 point, 8 - 14 scored 2 points and more than 14 scored 3 points.

Statistics

Statistical analysis was carried out using the statistical package SPSS for Windows, release 10.0 (SPSS Inc.). Correlations between routine and revised MC were assessed using the nonparametric Spearman test. The agreement and the proportion of potential agreement beyond chance that was actually achieved (Kappa) between routine and revised MC were determined using cut-off values ranging from 4 to 18 mitoses / 2 mm^2. Association between MC and BR-grade was assessed using the Kruskal-Wallis test. Univariate and multivariate survival analyses were performed with the time-fixed Cox regression procedure. Survival endpoints of the study were disease free survival (DFS), distant metastasis free survival (DMFS) and overall survival (OS). For DFS time to failure was computed from the date of surgery until relapse or until the last day patient was known to be disease free. For DMFS time to failure was computed from the date of surgery until distant metastasis or until the last day patient was known to be free of distant metastasis. Patients who died during follow-up were censored at the date of death. Patients who developed contra-lateral breast cancer were censored at the date of diagnosis. OS was calculated from the date of surgery until death or until the date patient was last known to be alive.

RESULTS

Reproducibility

The mean and median MC measured routinely and after revision are listed per pathology department in table 5.2. Mean and median values were comparable between the 3 pathology departments and between routine and revised evaluation. In the revised evaluation significantly higher maximum MC were scored than in routine evaluation. In the revised specimens the BR-grade was determined as well (Table 5.2). Seventy-four tumours (45%) were histological well differentiated, 59 (36%) were of intermediate grade and 31 (19%) were poorly differentiated.

Table 5.2. Routine and revised mitotic counts and Bloom-Richardson grade according to pathology department.

	Pathology department		
	A	**B**	**C**
Number of patients	62	50	52
Routine mitotic counts			
Median (range)	7 (1-47)	6 (0-44)	8 (0-54)
Mean	11	10	12
Revised mitotic counts			
Median (range)	7 (0-92)	6 (0-85)	5 (0-91)
Mean	11	12	12
Bloom-Richardson grade			
I	45%	40%	50%
II	44%	34%	29%
III	11%	26%	21%

Routine and revised MC correlated well ($r = 0.76$, $p < 0.001$). The observed agreement between routine and revised MC varied between 0.76 and 0.90, kappa varied between 0.37 and 0.66, depending on the cut-off value used. Kappa was lower specifically when lower cut-off values were used. BR-grade and MC were strongly associated ($p<0.0001$). Median revised MC was 3 per 2 mm^2 in grade I tumours, 9 per 2 mm^2 in grade II tumours, and 22 per 2 mm^2 in grade III tumours.

Prognostic value

During follow-up 36 patients had recurrent disease (28 patients with distant metastases) and 37 patients died (23 deaths were caused by breast cancer). After 5 year DFS was 83% (DMFS 86%), OS was 90% (disease specific survival 94%). After 10 year DFS was 76% (DMFS 81%), OS was 77% (disease specific survival 85%).

The prognostic value of revised MC for DFS, DMFS and OS was analysed. Hazard ratios were determined using progressively higher cut-off values. Significance was not found for DFS, DMFS or for OS at any cut-off value. Comparable results were found when the analyses were performed on routine MC or were restricted to patients younger than 70 years of age, tumours 11 to 30 mm in diameter, or ductal carcinomas only (data not shown). As an example Figure 5.1 shows the overall survival curves according to revised MC using 13 mitoses / 2 mm^2 as cut-off value (Figure 5.1).

The risk for relapse (including loco-regional relapses) did not differ significantly between well, moderately and poorly differentiated tumours. The risk for distant metastasis was highest in patients with poorly differentiated tumours, but not significantly different from that of patients with well-differentiated tumours ($p=0.12$). Patients with moderately differentiated tumours had a significant higher

risk (p=0.04, RR 2.2) for death than patients with well-differentiated tumours (Figure 5.2).

In multivariate analysis including age, tumour size, BR-grade and MC, age was associated with OS (p=0.03) and BR-grade was associated with DSS (p=0.04)

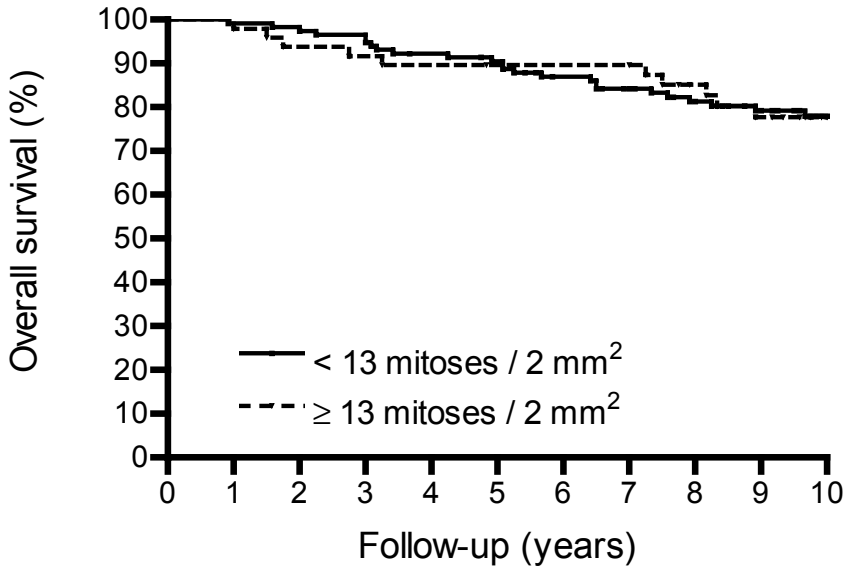
DISCUSSION

In published studies on MC in breast cancer the MC are usually expressed as number of mitoses per 10 high-power fields. But, these high-power fields are not uniformly defined. The area of the high-power fields used, if mentioned at all, varies from 0.102 mm^2 to 0.216 mm^2.[10,11] Consequently interpretation of results is difficult. To overcome this problem we have defined MC as the number of mitotic figures per 2 mm^2.

In the present study the median MC was 6 mitoses per 2 mm^2. In other reports the median MC (recalculated into mitoses per 2 mm^2) varied from 2.7 to 13.9 mitoses per 2 mm^2.[4,8,10-12] This variation can probably be explained by differences in patient characteristics: Tumours detected by screening have lower MC and MC in ANN patients are lower than those in node positive patients.[11,13] But, the observed wide variation in median values of MC also may suggest a low interobserver (or intergroup) reproducibility.

To assess the reproducibility of MC we have revised tumour samples from 164 patients. The MC were initially determined in routine practice at 3 separate pathology departments. The correlation coefficient found between routine and revised MC was 0.76. Bergers et al. found slightly better correlations.[14] The correlation coefficients found by van Diest et al. were much better with an overall r of 0.91.[7] But, in that study the counting areas were marked, which might explain

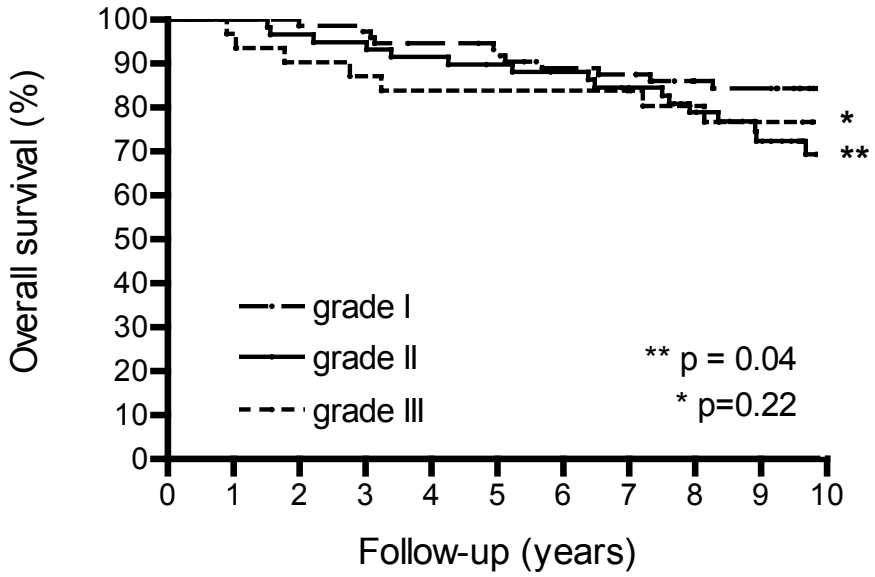
Figure 5.1. Overall survival according to mitotic counts using 13 mitoses / 2 mm^2 as cut-off value.



the higher correlation coefficients.[15] The reproducibility of MC is said to depend on the quality of the slides and on the pathologist's interpretation.[5] In our opinion the correlation coefficient of 0.76 is a good reflection of the reproducibility of MC obtainable in routine practice. The wide variation in median MC found among the investigational groups can probably be explained by a poor agreement between them in the recognition and/or interpretation of (abnormal) mitoses.[16]

For survival analyses the MC are often dichotomised, but the cut-off value used and proposed for this purpose varies. In dichotomised variables kappa is a measure of reproducibility. The reproducibility of the MC is smaller when the number of mitotic figures counted is smaller.[17] In the present study a substantial kappa (> 0.60) was reached when the cut-off value used was at least 6 mitoses per 2 mm^2. Reproducibility of MC and, as a consequence, its prognostic value

Figure 5.2. Overall survival according to Bloom-Richardson histological grade.



declined when lower cut-off values were used. Therefore, the cut-off value used must be sufficiently high to obtain reproducible and reliable analyses of the prognostic value of MC.

Mirza et al. have recently reviewed the published literature on prognostic factors in patients with ANN breast cancer, focusing principally on recent studies with large sample sizes and extended follow-up periods.[18] Four studies were identified that assessed the prognostic value of MC for decreased survival.[8,19-21] We have found three more studies.[22-24] In the present study no significant association between MC and survival was found, but the number of events (relapse and death) was relatively low. The strongest association between MC and DFS or OS in ANN breast cancer was reported by van Diest and Baak.[24] But the number of patients and events in that study was low. Clayton showed a positive association between MC and DSS in a study with sufficient events.[8] But, in that study the

median value for the MC was low, which might have had a negative influence on reproducibility.[17] In the largest study, performed on 1028 patients with T1N0 breast cancer, no significant association between MC and survival was found.[23] Page showed a significant association between MC and OS only when the analysis was restricted to the first 5 years of follow-up.[22] The association disappeared with longer follow-up time. In the study performed by Aaltomaa DFS and DSS were positively associated with MC, but DFS could not be predicted by MC in patients with tumours ≤2 cm in diameter.[19] Based on these studies we submit that a positive association between MC and survival in ANN breast cancer may exist, but that the extent of this putative association is a matter of debate. The extent probably depends on other tumour characteristics such as tumour size and histological grade.

In the present study a trend towards a significantly worse survival was found in patients with poorly or moderately differentiated tumours compared with patients with well-differentiated tumours. The number of well-differentiated tumours was relatively large (45%). In the study performed by van Diest only 12% of ANN tumours were well differentiated. In that study no significant association between BR-grade and OS was found, in contrast to a strong association between MC and OS.[24] In the studies performed by Aaltomaa, Clahsen, Clayton and Page the BR-grade was positively associated with DSS and OS respectively.[8,19,21,22] In the studies performed by Aaltomaa and Clayton the MC were slightly better in predicting DSS. In the studies performed by Clahsen and Page the BR-grade was slightly better.

In conclusion the determination of MC is an inexpensive, fast and reproducible way of assessing proliferation in routine practice. But, apparently, there is a poor agreement between the different investigational groups in the recognition and/or interpretation of (abnormal) mitoses. When cut-off values are used for survival analyses, they must be sufficiently high to obtain reproducible and reliable

analyses. Based on data in the literature it is likely that in patients with ANN breast cancer the MC are positively associated with survival, but the extent of this association can be a matter of debate. In the present study no significant association between MC and a number of relevant survival end-points was found. The favourable tumour characteristics and the associated low number of events can probably explain this. The prognostic value of the BR-grade is likely to be comparable to that of the MC. In the present study a trend towards a significant worse survival was found in patients with grade II or III tumours compared with patients with grade I tumours. In ANN breast cancer patients the prognostic value of the BR-grade may be superior to MC if the tumours are predominantly well differentiated, whereas MC may be superior to BR-grade if the tumours are predominantly poorly differentiated.

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6

A comparison and validation in the Dutch setting of Adjuvant! and Numeracy; two web-based models predicting outcome for early breast cancer.

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Submitted

ABSTRACT

Introduction: Adjuvant! and Numeracy, are programs predicting the 10-year outcome for patients with early breast cancer treated without adjuvant systemic therapy or with various commonly used schemes of adjuvant systemic therapy.

Methods: We have compared the prognostic and predictive estimates made by Adjuvant! and Numeracy using the characteristics of a population-based cohort of breast cancer patients. Subsequently, we have compared estimated outcomes with observed outcome. Finally we have compared the survival benefit from adjuvant systemic therapy as predicted by Adjuvant! with the presence or absence of an indication according to the 2002 and 2004 Dutch guidelines on treatment of primary operable breast cancer.

Results: Baseline 10-year recurrence rates estimated with Adjuvant! and Numeracy correlated well, but individual estimates differed up to 20%. Average baseline recurrence rate estimates and average estimates of the benefit of adjuvant systemic therapy were lower when determined with Numeracy than with Adjuvant!. Averages of Adjuvant! outcome estimates significantly associated with observed outcome percentages, whereas Numeracy averages did not. The predicted benefit from adjuvant chemotherapy was less than 5% for 50% and 16% of patients with a chemotherapy-indication according to the guidelines from 2002 and 2004, respectively. The predicted benefit from endocrine therapy was less than 5% for 37% and 43% of patients with an indication according to the guidelines from 2002 and 2004, respectively.

Conclusion: In our opinion Adjuvant! is the preferred model. Adjuvant! is a useful and accurate aid for predicting outcome, and can be used in combination with the current Dutch treatment guidelines.

INTRODUCTION

Adjuvant systemic therapy improves disease free and overall survival in women with early breast cancer, with larger absolute gains for those at greater risk.[1-3] However, adjuvant systemic therapy has side effects and is inconvenient; it is not useful for many patients. The question is therefore not whether adjuvant systemic therapy is effective, but for which patient categories its usefulness is high enough to justify its side effects and inconvenience. It is complex to predict the benefit of adjuvant systemic for an individual woman with early breast cancer. It involves integration of information about baseline prognosis, efficacy of various treatment options, and estimates of competing risk. Estimates of the benefit of chemotherapy and hormonal therapy influence a women's willingness to accept these therapies, and minimise opportunities for arbitrary decisions.[4-7] Estimates of the benefit of adjuvant systemic therapy are understood best when presented with data in the absolute survival benefit format.[8]

Several tools have been developed to make individualised estimates of baseline prognosis and absolute survival benefit of adjuvant systemic therapy.[5,9-11] Two of these tools, Adjuvant! and Numeracy, are freely available, web-based programs.[9,10] 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. But, as shown in Table 6.1, the programs do differ.

Since 2002, breast cancer patients in The Netherlands are treated according to the guideline "Behandeling van het mammacarcinoom", initiated by The Dutch Institute for Healthcare Improvement (CBO).[12,13] This guideline was revised in 2004, and is available through oncoline [www.oncoline.nl], or the CBO-website [www.cbo.nl].[14] One of the major starting points of the CBO-guidelines is that adjuvant systemic therapy for early breast cancer can be considered standard

Table 6.1. Summary of characteristics of the programs Adjuvant! and Numeracy.

	Adjuvant!	Numeracy
Internet address	www.adjuvantonline.com	www.mayoclinic.com/calcs
Eligible breast cancer patients	Unilateral, unicentric, invasive adenocarcinoma, adequate local treatment, and no evidence of distant metastasis, T4 features, inflammatory breast cancer, or of mated or fixed axillary nodes	Adequate local treatment, tumours graded II or III
Estimation of baseline prognosis	Surveillance, Epidemiology, and End-Results data	Oncology experts' predictions
Estimation of risk reduction by adjuvant therapy	EBCTCG data, and data from individual randomised trials	EBCTCG data, and data from individual randomised trials
Baseline factors requested	Age, tumour size, axillary lymph node status, co morbidity, tumour grade, oestrogen receptor status	Age, tumour size, axillary lymph node status, hormone receptor status
End-points of the program	10-year disease free survival, overall survival, breast cancer related mortality, non-breast cancer related mortality, recurrence rate	10-year disease free interval.
Adjuvant therapies which effectiveness is estimated	Tamoxifen, anastrozole, or ovarian ablation and/or a number of chemotherapy regimens which are considered equally effective as CMF, or 10%, 20% or 35% more effective than CMF	Tamoxifen alone, tamoxifen and AC, tamoxifen and AC and paclitaxel (every 3 weeks), tamoxifen and AC and paclitaxel (dose dense)

EBCTCG: Early Breast Cancer Trialists' Collaborative Group; AC: doxorubicin, cyclophosphamide; CMF: cyclophosphamide, methotrexate, fluorouracil.

therapy under the condition that it increases the absolute 10-year survival with 5% or more. This 5% benefit is assumed for each treatment modality.

In the present study we have compared the prognostic and predictive estimates made by Adjuvant! and Numeracy. Subsequently, we have compared estimated outcomes with observed outcome. Finally we have validated Adjuvant! for use in combination with the Dutch guidelines.

METHODS

Patients

Between October 1989 and March 1993, consecutive female patients diagnosed with operable breast cancer, were asked to participate in an observational study on prognostic factors. Patients were recruited in 5 hospitals affiliated with the Comprehensive Cancer Centre Middle Netherlands (IKMN). A total of 463 patients with stage I to III breast cancer gave their written informed consent. Of these 456 were treated with either modified radical mastectomy or breast conserving therapy, including axillary lymph node dissection. In the inclusion-period of this study in the entire IKMN-region in total 2165 women had surgery for stage I to III breast cancer. The T-stage and N-stage of the 456 study patients when compared to the other IKMN-registered patients did not differ significantly. The study patients were slightly younger: median age 58 vs. 60 years.

Within the scope of this observational study the prognostic factors required for the programs Adjuvant! and Numeracy were prospectively registered. In all study patients we also prospectively registered whether adjuvant chemotherapy and/or tamoxifen was administered. Adjuvant chemotherapy consisted of 6 cycles of cyclophosphamide, methotrexate and fluorouracil (CMF), or 4 cycles of

doxorubicin, cyclophosphamide (AC). CMF and AC were considered equally effective. Tamoxifen was prescribed once daily, 20 to 40 mg for 2 to 5 years. Patients were followed until December 2002, with a median follow-up period of 10.3 years.

Numeracy requires the hormone-receptor status for the estimation of the benefit of adjuvant systemic therapy. The oestrogen-receptor status was determined in 434 of the 456 patients (95%). Therefore, the comparisons between Adjuvant! and Numeracy were performed on these 434 patients. The subsequent analyses validating Adjuvant! for use in the Dutch setting used the characteristics from all 456 patients.

Comparisons between Adjuvant! and Numeracy

Of each patient the prognostic and predictive characteristics required were entered in both Adjuvant! (Version 6.0) and Numeracy. Adjuvant! requires information on the general health status of the patient. Since we did not register comorbidity data, we used the default comorbidity assumption of the program: “Minor health problems”. Adjuvant! provides a number of survival end-points (Table 6.1). Numeracy provides only one survival end-point, which is called "chance of being alive without recurrent cancer", i.e. disease free survival (DFS). However, in the estimation of baseline prognosis the program does not account for age or comorbidity, and in the estimation of 10-year event-free survival with adjuvant therapy Numeracy treats non-breast cancer related mortality as a competing cause of death.[10] Non-breast cancer related mortality is low in young patients, but in the studied cohort only 31% of patients were aged 50 years or less. Therefore, we have interpreted the survival end-point estimated by Numeracy as the chance of being without recurrent cancer, i.e. disease free interval (DFI). Numeracy was updated in September 2003. In this update histological grade was added to the baseline factors. Patients with grade I

infiltrative ductal cancer were excluded from the Numeracy model as they were expected to have a better prognosis than the majority of patients with grade II and III cancers. In the cohort of 434 patients grade was determined in 314 (72%) patients, 225 patients had a grade II or III tumour. We have compared Adjuvant! and Numeracy both using characteristics of these 225 patients and of all 434 patients. The correlation between the recurrence rates estimated by Adjuvant! and Numeracy was determined with Pearson correlation coefficient and linear regression analyses. The agreement was determined with Bland-Altman plots.[15]

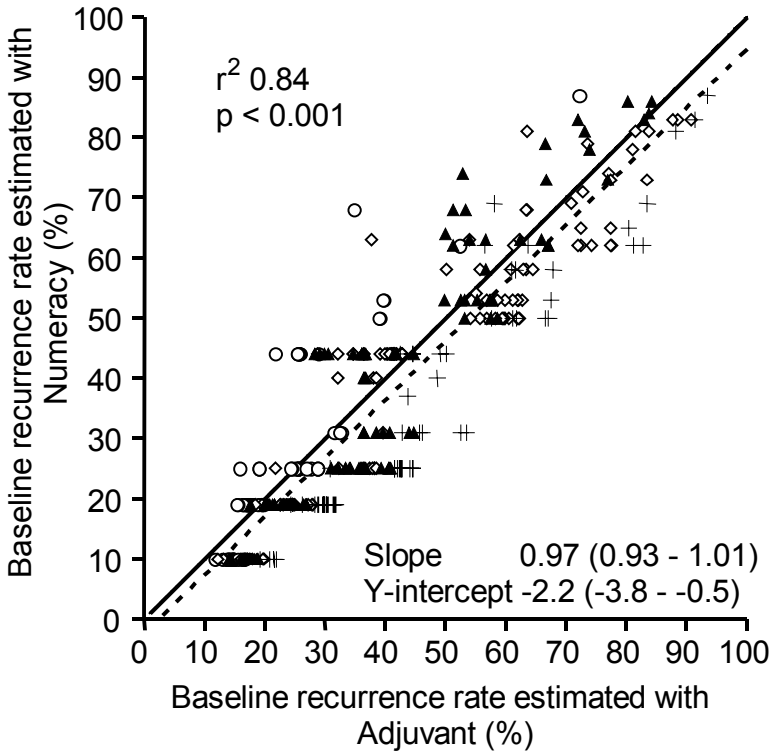
Subsequently, observed 10-year DFI was determined with the Kaplan-Meier method, for both all 434 patients and clinically relevant subgroups. In these analyses disease recurrence was defined as either locoregional recurrence, distant metastasis, or contralateral breast cancer. For the same groups, the average Adjuvant! and Numeracy estimated values were calculated. Numeracy DFI estimates of patients treated with adjuvant chemotherapy only were made by using data from the original report by Loprinzi et al.[10] In the comparisons between observed percentage and average estimated value we assumed the latter constant. Therefore, the difference between observed percentage and average estimated value was considered significant when it exceeded 1.96 times the standard error of the observed percentage. Average Adjuvant! and Numeracy estimated DFI values of the entire cohort and the subgroups were mutually compared with the two-sided paired-samples t-test.

Validation of Adjuvant! for use in the Dutch setting

The two major outcome figures estimated by Adjuvant! are 10-year DFS and overall survival (OS). Average Adjuvant! estimated values of 10-year DFS and OS were calculated for all 456 patients and for clinically relevant subgroups. For the same groups observed 10-year DFS and OS were determined with the Kaplan-Meier method. In these analyses DFS was defined as the time between primary

surgery and death, locoregional recurrence, distant metastasis, or contralateral breast cancer whichever came first. OS was defined as the time between primary surgery and death. The difference between observed percentage and average estimated value was considered significant when it exceeded 1.96 times the standard error of the observed percentage.

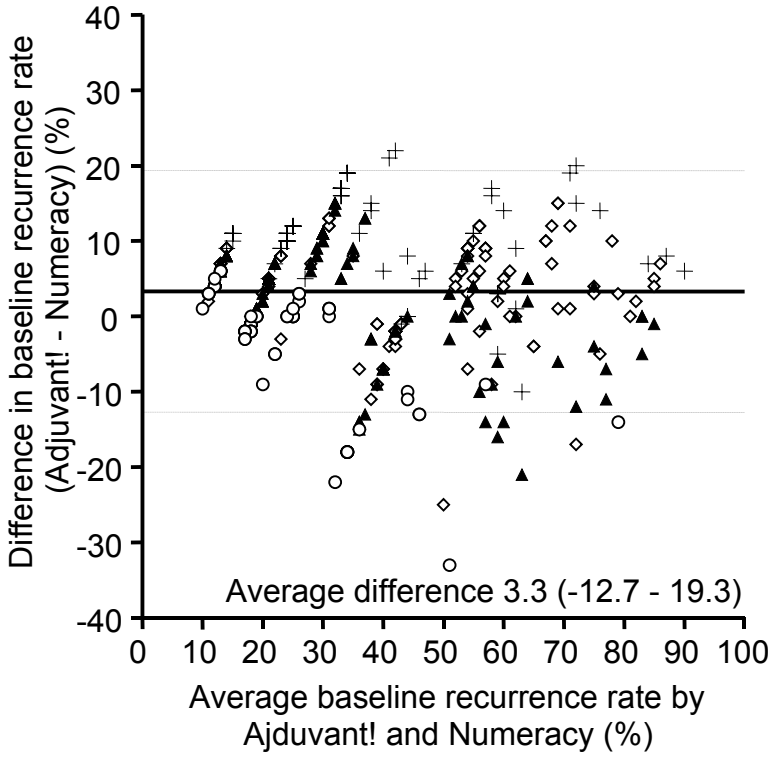
Figure 6.1. Correlation and linear regression analysis between baseline recurrence rates estimated by Adjuvant! and Numeracy, for tumours with histological grade I (o), grade II (▲), grade III (+) and with an unknown histological grade (◊).



Besides, 9 equally sized subgroups with a rising 10-year OS were formed. The first subgroup contained the 50 patients with the worst prognosis, the ninth subgroup the 56 patients with the best prognosis. The association between

observed and average Adjuvant! calculated 10-year OS of these 9 groups was compared with the perfect association (observed and calculated 10-year OS are equal) using linear regression analysis. In the same way 9 subgroups with a rising 10-year DFS were formed and analysed.

Figure 6.2. Agreement, average difference with 95% confidence interval, between baseline recurrence rates estimated by Adjuvant! and Numeracy, for tumours with histological grade I (o), grade II (▲), grade III (+) and with an unknown histological grade (◊).



Finally, using the characteristics of each patient, a comparison was made between the presence or absence of an indication for adjuvant chemo- or endocrine therapy according to the 2002 and 2004 CBO-guidelines and the by Adjuvant! estimated absolute benefit in survival with the adjuvant chemo- or

endocrine therapy regimens advised in these guidelines. Both guidelines give no standard advice concerning adjuvant chemotherapy for patients aged 70 years or more with an ER negative tumour. In the present study, in accordance with common practice, all patients aged 70 years or more were classified with a negative advice for adjuvant chemotherapy.

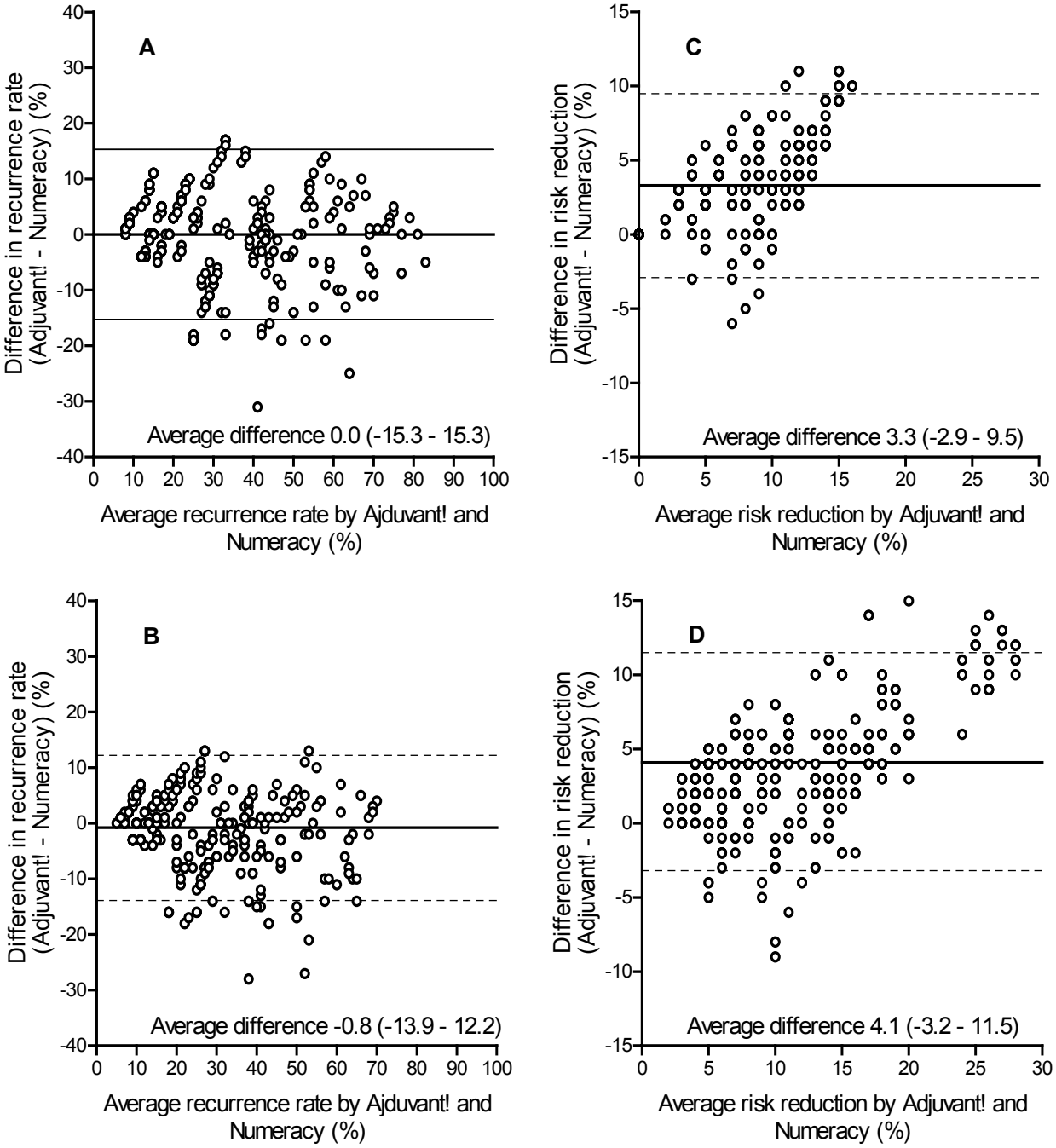
A major revision in the 2004 guideline is the advise to use, instead of AC or CMF, a more effective chemotherapy regimen comprising 5 cycles of fluorouracil, epirubicin, cyclophosphamide (FEC), or in certain cases 6 cycles of docetaxel, doxorubicin, cyclophosphamide (TAC). Treatment with TAC is advised for premenopausal women with a HER2/neu receptor over expressing tumour and positive axillary lymph nodes. The HER2/neu receptor was not determined in the patients included in the present study. As a consequence it is not known which patients would have been considered for treatment with TAC. Adjuvant! values FEC to be 20% more effective than CMF. In the comparison between the presence or absence of an indication for adjuvant chemotherapy according to the 2004 guideline and the calculated benefit of chemotherapy according to Adjuvant! for each patient the absolute benefit in 10-year OS was calculated with the adjustment “20% lower RR than CMF”.

RESULTS

Comparison between Adjuvant! and Numeracy

Baseline 10-year recurrence rates estimated by Adjuvant! and Numeracy correlated well (Figure 6.1). The Pearson correlation coefficient r^2 was 0.84 analysing the entire cohort, and 0.85 analysing grade II or III tumours only. But individual recurrence rate estimates could differ up to 20%, the average baseline recurrence rate was 3.3% (95% C.I. –12.7 - 19.3%) higher estimated with

Figure 6.3. Agreement, average difference with 95% confidence interval, between recurrence rates estimated with Adjuvant! and Numeracy using the prognostic and predictive characteristics of 434 patients, for treatment with adjuvant tamoxifen (A), or adjuvant tamoxifen and doxorubicin / cyclophosphamide (B). And agreement between reductions in recurrence rate estimated with Adjuvant! and Numeracy for treatment with adjuvant tamoxifen (C), or adjuvant tamoxifen and doxorubicin / cyclophosphamide (D).



Adjuvant! than with Numeracy (Figure 6.2). Divided into subgroups according to histological grade, average Adjuvant! estimated baseline recurrence rates were 2.3% (95% C.I. -12.6 - 17.2%) lower for grade I tumours, and 3.4% (95% C.I. -10.7 – 17.5%), 11.1% (95% C.I. –1.2 – 23.4%), 2.9 (95% C.I. –11.3 – 17.1%) higher for grade II, grade III, and unknown grade tumours, respectively.

With adjuvant systemic therapy average Numeracy recurrence rate estimates were slightly higher than average Adjuvant! recurrence rate estimates (Figure 6.3): 0.0% (95% C.I.: -15.3 – 15.3%) with adjuvant tamoxifen, 0.8% (95% C.I.: -12.2 – 13.9%) with adjuvant tamoxifen combined with AC, and 2.9% (95% C.I.: -10.4 – 16.1%) with adjuvant tamoxifen combined with AC and paclitaxel. Estimates of the benefit of adjuvant systemic therapy were lower with Numeracy than with Adjuvant! (Figure 6.2). Estimated with Numeracy, the average absolute benefit of adjuvant tamoxifen was 3.3% (95% C.I.: -2.9 – 9.5%) lower, the average absolute benefit of tamoxifen combined with AC was 4.1% (95% C.I.: -3.2 – 11.5%) lower, and the average absolute benefit of tamoxifen combined with AC and paclitaxel was 6.2% (95% C.I.: -4.6 – 16.9%) lower. Similar results were found when the analyses were restricted to the 225 patients with a grade II or III tumour: Correlated with Adjuvant!, the average absolute benefit of adjuvant tamoxifen, tamoxifen combined with AC, and tamoxifen combined with AC and paclitaxel estimated with Numeracy was 3.6% (95% C.I.: -2.7 – 9.9%), 4.9% (95% C.I.: -2.2 – 12.0%), and 7.1% (95% C.I.: -3.3 – 17.5%) lower, respectively.

Comparison with observed outcomes

In Table 6.2 average estimated DFI values determined with Adjuvant! and Numeracy are compared with observed outcome percentages. The average Numeracy outcome estimates were 3.6% higher than the average Adjuvant! DFI estimates. In subgroup analyses average Numeracy survival estimates were also

Table 6.2. Patient-, tumour-, and treatment characteristics with observed and estimated 10-year disease free interval.

	Number of patients	Disease free Interval (%)		
		Obs (SE)	Adj!	Num
Total	434	65 (2.5)	68	71 *†
Age (year)				
≤ 50	134	56 (4.5)	65 †	73 *†
51 – 60	199	67 (3.5)	68	73 *
> 70	101	72 (5.2)	70	69
ER-status				
Negative	104	66 (4.9)	63	72 *
Positive	330	64 (2.8)	69	71 *†
Histological grade				
I	89	76 (4.9)	80	80
II / III	225	63 (3.4)	66	72 *†
Unknown	120	60 (4.8)	62	64 *
Tumour size (cm)				
≤ 2.0	267	69 (3.0)	75 †	78 *†
> 2.0	167	58 (4.1)	56	61 *
Axillary lymph nodes				
Negative	261	70 (3.0)	76	84 *†
Positive	173	62 (4.2)	56	53 *†
Adjuvant systemic therapy				
No	244	67 (3.2)	74	82 *†
Yes	190	61 (3.8)	60	58 *

*Obs: Observed 10-year event rate, Adj!: 10-year event rate estimated by Adjuvant!, Num: 10-year event rate estimated by Numeracy, SE: standard error, ER: oestrogen receptor. * significant difference between average disease free interval (p<0.05) estimated by Adjuvant! and by Numeracy; † significant difference with observed disease free interval (p<0.05).*

higher, except for the subgroups of patients aged more than 70 years, and patients with grade I tumours (not significant), and for patients treated with adjuvant systemic therapy (significantly lower). Average Numeracy DFI estimates

Table 6.3. Patient-, tumour-, and treatment characteristics with observed and estimated 10-year disease free survival and overall survival.

		Overall survival (%)		Disease free survival (%)	
	Number of patients	Obs. (SE)	Absolute difference Adj! - Obs.	Obs. (SE)	Absolute difference Adj! - Obs.
Total	456	68.0 (2.3)	+1.9	55.5 (2.4)	+1.9
Age (year)					
≤ 50	163	70.5 (3.7)	+6.4	57.6 (4.0)	+5.8
51 – 60	97	78.8 (4.2)	-1.4	66.1 (4.9)	-1.9
61 – 70	102	69.4 (4.8)	+1.6	53.5 (5.1)	+4.5
> 70	94	48.1 (5.8)	+0.7	41.8 (5.6)	-2.4
ER-status					
Negative	104	64.8 (4.9)	+1.2	55.9 (5.0)	+0.4
Positive	330	68.5 (2.7)	+2.2	55.3 (2.8)	+2.1
Unknown	22	78.9 (9.6)	-2.1	61.0 (10.8)	+2.3
Histological grade					
I	93	84.2 (3.9)	-1.5	66.3 (5.1)	+3.3
II	162	64.1 (4.0)	+7.4	52.9 (4.1)	+5.4
III	73	62.6 (5.9)	+0.1	50.7 (6.0)	-0.7
Unknown	128	64.1 (4.4)	-1.5	53.8 (4.6)	-2.3
Tumour size (cm)					
0,1 – 1,0	80	74.8 (5.0)	+6.8	66.3 (5.4)	+3.1
1,1 – 2,0	204	76.1 (3.1)	-0.3	58.0 (3.6)	+5.1
2,1 – 3,0	103	57.0 (5.3)	+2.7	51.8 (5.2)	-4.5
> 3,0	69	51.8 (6.2)	+2.4	41.7 (6.1)	+0.2
Positive lymph nodes					
0	275	75.6 (2.7)	+2.2	61.2 (3.1)	+2.2
1 – 3	120	63.5 (4.5)	+2.0	53.3 (4.7)	+1.1
> 3	61	43.4 (6.6)	-0.7	34.6 (6.2)	-2.8
Tamoxifen					
No	319	74.0 (2.6)	+1.7	59.1 (2.9)	+2.8
Yes	137	54.0 (4.5)	+2.4	47.2 (4.4)	-0.2
Chemotherapy					
No	384	68.3 (2.5)	+2.0	55.3 (2.6)	+2.3
Yes	72	66.1 (5.7)	+1.5	56.4 (5.9)	+0.3

Obs: Observed 10-year event rate, Adj!: 10-year event rate estimated by Adjuvant!, SE: standard error, ER: oestrogen receptor.

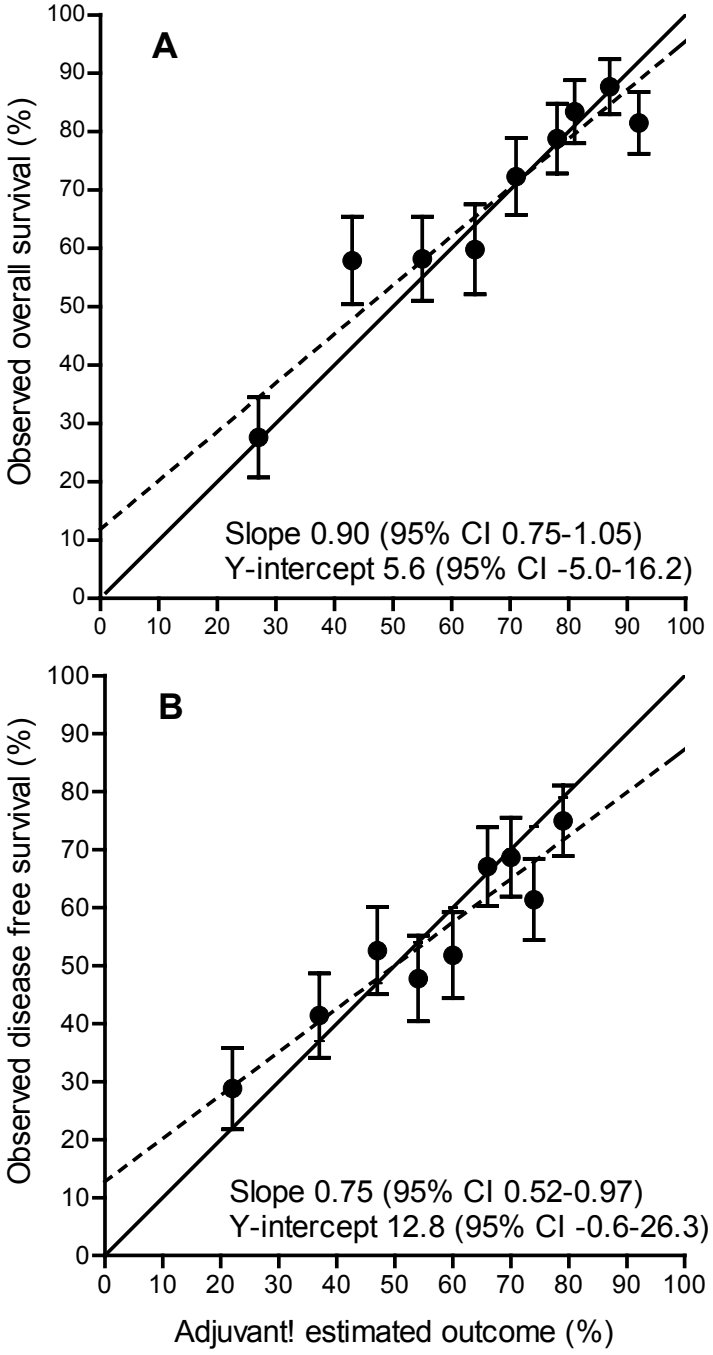
were significantly higher than observed DFI percentages for the entire cohort ($p<0.01$), for patients aged 50 years of less ($p<0.001$), with an oestrogen-receptor positive tumour ($p=0.01$), with a grade II or III tumour ($p<0.01$), with a tumour 2.0 cm or less in diameter ($p<0.01$), without positive axillary lymph nodes ($p<0.001$), and not treated with adjuvant systemic therapy ($p<0.001$). Numeracy underestimated DFI for patients with positive axillary lymph nodes ($p=0.04$). Average Adjuvant! DFI estimates corresponded well with observed DFI percentages, but were significantly higher for patients aged 50 years or less ($p=0.04$), and for patients with a tumour 2.0 cm or less in diameter ($p=0.04$). Average Adjuvant! estimated values of 10-year DFS and OS, calculated for all 456 patients and for clinically relevant subgroups, were not significantly different from observed 10-year DFS and OS (Table 6.3). Adjuvant! predicted 10-year OS well, but 10-year DFS was underestimated by Adjuvant! when the DFS was low and overestimated when the DFS was high ($p<0.05$ for slope) (Figure 6.4).

Validation of Adjuvant! for use in the Dutch setting

75 of 149 (50%) patients with tumour characteristics adjudging them an indication for adjuvant chemotherapy according to the 2002 CBO-guideline, had less than 5% benefit in 10-year OS from this therapy according to Adjuvant! (Table 6.4). For 62 of 89 (70%) patients with an ER-positive tumour and an indication for adjuvant chemotherapy Adjuvant! estimated less than 5% benefit in 10-year OS, as compared with 10 of 53 (19%) patients with an ER-negative tumour and an indication for adjuvant chemotherapy. According to Adjuvant! all 35 patients aged 50 years or more with an ER-positive tumour, and an indication for adjuvant chemotherapy according to the 2002 CBO-guideline had less than 5% benefit in 10-year OS from this therapy.

23 of 173 (16%) patients with tumour characteristics adjudging them an indication for adjuvant chemotherapy according to the 2004 CBO-guideline, had less than

Figure 6.4. Observed overall survival (A) and disease free survival (B) with standard error of 9 subgroups with an according to Adjuvant! increasing prognosis. Determined (dotted line) and perfect (solid line) linear associations are not significantly different for overall survival, but are significantly different for disease free survival.



5% benefit in 10-year OS from this therapy according to Adjuvant! (Table 6.5). For 24 of 110 (22%) patients with an ER-positive tumour and an indication for adjuvant chemotherapy Adjuvant! estimated less than 5% benefit in 10-year OS, as compared with 1 of 56 (2%) patients with an ER-negative tumour and an indication for adjuvant chemotherapy. For 11 patients with positive axillary lymph nodes, and an indication for adjuvant chemotherapy Adjuvant! estimated less than 5% benefit in 10-year OS from this therapy. The remaining prognostic features in these patients were favourable (≤ 2 cm, histological grade I-II, ER-positive, ≤ 3 positive lymph nodes). For 31 patients with positive axillary lymph nodes and a negative indication for adjuvant chemotherapy Adjuvant! estimated 5% or more benefit in 10-year OS. 23 of these 31 patients were aged 70 years or more.

17 patients – with a grade II tumour, 2.1 to 3.0 cm in diameter, and without positive axillary lymph nodes – had a negative indication for adjuvant endocrine therapy according to the 2002 CBO-guideline, but a positive indication according to the 2004 CBO-guideline (Table 6.4 and 6.5). For none of these patients Adjuvant! estimated 5% or more benefit in 10-year OS from endocrine therapy (average 4.2%). 59 patients without positive axillary lymph nodes were aged 70 years or more. Of these 11 had a positive indication for adjuvant endocrine therapy. For none of these 11 patients Adjuvant! estimated 5% or more benefit in 10-year OS from endocrine therapy (average 3.6%).

DISCUSSION

In this study we have compared two computer-based programs that predict 10-year breast cancer outcomes with and without adjuvant systemic therapy: Adjuvant! and Numeracy. Adjuvant! determines its estimates of baseline prognosis based on data from the Surveillance, Epidemiology, and End Results

Table 6.4. 10-year overall survival benefit with adjuvant systemic therapy estimated with Adjuvant! subdivided after indication for this treatment according to the 2002 CBO-guideline.

Indication adjuvant systemic therapy according to the 2002 CBO-guideline		Estimated benefit in 10-year overall survival					
		6xCMF / 4xAC			Tamoxifen		
		n < 5%	n ≥ 5%	avg.	n < 5%	n ≥ 5%	avg.
N0	No	224	4	1.0%	222	0	1.0%
	Yes	24	13	4.3%	25	8	4.0%
	Insuff. data	10	0	2.2%	20	0	2.6%
N+	No	68	0	1.7%	40	0	0.0%
	Yes	51	61	5.4%	36	97	5.7%
	Insuff. data	1	0	1.9%	4	4	4.3%

CMF: cyclophosphamide, methotrexate, fluorouracil; AC: doxorubicin, cyclophosphamide; n < 5%: number of patients with less than 5% benefit in overall survival; n ≥ 5%: number of patients with 5% or more benefit in overall survival; N0: no regional lymph node metastases; N+: regional lymph node metastases; avg.: average; insuff. data: insufficient data available to indicate.

(SEER) registry,[9] whereas Numeracy's baseline prognostic estimates are based on oncology experts' predictions.[10] Baseline disease recurrence risk estimates made by the two programs correlated well, but individual estimates of baseline disease recurrence risk differed up to 20%. Baseline outcome estimates determined by Numeracy were, on average, higher. Although baseline outcome estimates provided by Numeracy were interpreted as DFI estimates, instead of DFS estimates as named by the program, Numeracy's outcome estimates were still significantly higher than both Adjuvant!'s DFI estimates, and most observed

Table 6.5. 10-year overall survival benefit with adjuvant systemic therapy estimated with Adjuvant! subdivided after indication for this treatment according to the 2004 CBO-guideline.

Indication adjuvant systemic therapy according to the 2004 CBO-guideline		Estimated benefit in 10-year overall survival					
		5xFEC / 6xTAC			Tamoxifen / AI		
		n < 5%	n ≥ 5%	avg.	n < 5%	n ≥ 5%	avg.
N0	No	204	8	1.9%	204	0	0.8%
	Yes	16	35	7.1%	42	8	4.0%
	Insuff. data	9	3	4.0%	21	0	2.6%
N+	No	27	31	5.2%	40	0	0.0%
	Yes	11	111	9.5%	36	97	5.7%
	Insuff. data	0	1	5.1%	4	4	4.3%

FEC: fluorouracil, epirubicin, cyclophosphamide; TAC: docetaxel, doxorubicin, cyclophosphamide; AI: aromatase inhibitor; n < 5%: number of patients with less than 5% benefit in overall survival; n ≥ 5%: number of patients with 5% or more benefit in overall survival; N0: no regional lymph node metastases; N+: regional lymph node metastases; avg.: average; insuff. data: insufficient data available to indicate.

10-year DFI percentages. The average outcome estimates determined by Adjuvant! were close to most observed outcome percentages. The Adjuvant!-program has recently been validated in a large, prospective, population-based study.[16] According to that study Adjuvant!'s estimates of prognosis are reliable, but overestimate both OS and DFS in women younger than age 35 years, and DFS in premenopausal women. Our finding that Adjuvant! overestimated prognosis for the subgroup of patients aged 50 years or less is in line with this observation.

Information regarding the benefit of adjuvant systemic therapy is most easily understood when presented as absolute survival benefit.[8] Both Adjuvant! and Numeracy use the relative risk reduction data from the 1998 EBCTCG overviews to predict the absolute risk reductions of adjuvant systemic therapy,[1,2] but results are different. Compared with Numeracy, Adjuvant! predicted an average absolute 3.3 – 6.2% larger risk reduction of adjuvant systemic therapy. DFI, DFS and OS predicted with Adjuvant! closely matched the respective observed outcomes for patients treated with and without adjuvant systemic therapy. These results are in accordance with data from the validation study.[16] The average Numeracy predicted DFI was significantly higher than the average Adjuvant! predicted DFI and the observed DFI for patients treated without adjuvant systemic therapy, but were significantly lower than the average Adjuvant! predicted DFI and matched with the observed DFI for patients treated with adjuvant systemic therapy. These findings suggest that Numeracy underscores the benefit of adjuvant systemic therapy.

However, it is not possible to make a judgement on the reliability of the measure of benefit from adjuvant systemic therapy as estimated by Adjuvant!. For this the efficacy of the adjuvant systemic therapies is too limited in proportion to size of the confidence interval of the observed OS, DFI and DFS in the subgroups treated with adjuvant tamoxifen and chemotherapy. A study with much more patients is needed. But, such a large study keeps the limitation that it can only validate the efficacy of the adjuvant systemic therapy regimens as given 10-years before.

In order to make a judgement on estimations made by Adjuvant! of the efficacy of adjuvant systemic therapy, the characteristic of the patients in our cohort were used to determine the measure of benefit Adjuvant! would have estimated if these patients were treated with the therapies recommended in the 2002 and 2004 CBO-guidelines. ER-positive patients, and in particular ER-positive patients aged

50 years or more, had, if treated with chemotherapy according to the 2002 guideline and to a lesser extent if treated with chemotherapy according to the 2004 guideline, according to Adjuvant! a relatively low estimated benefit from this therapy. Adjuvant! values the efficacy of adjuvant chemotherapy relatively lower in older, and in ER-positive patients. The CBO-guidelines also discern a lower efficacy of chemotherapy for women aged 50 years or more, and in particular women with an ER-positive tumour, but take no account of this when indicating women 50 to 60 years of age.[12-14] The guidelines start from an average 25% relative reduction in mortality with adjuvant chemotherapy. However, the relative reduction in mortality with adjuvant AC or CMF for patients aged 50-69 years with an ER-positive tumour is only 10%.[2] Both Adjuvant! and the CBO-guidelines base their estimations of the absolute survival benefit with adjuvant tamoxifen on the 1998 EBCTCG meta-analyses.[1] The CBO-guidelines start for ER-positive patients from a 6% absolute benefit in 10-year OS with tamoxifen for patients without, and 11% for patients with positive axillary lymph nodes. But, in the cohort studied the average 10-year absolute OS benefit with adjuvant tamoxifen was only 4% for ER-positive patients without, and 5.7% for ER-positive patients with positive axillary lymph nodes. Apparently the prognosis of the patients in the cohort studied was better than the prognosis the guidelines used to base their indications for adjuvant endocrine therapy on.

In summary, 10-year DFI estimates determined by Adjuvant! and Numeracy correlate well, both for patients who are, and who are not treated with adjuvant systemic therapy. However, there is no good agreement between the two methods. 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. Adjuvant! estimates of outcome correspond closely to observed outcome. In our opinion Adjuvant! is the preferred prognostic model. Adjuvant! appears an accurate aid for

predicting the risk of mortality and disease recurrence in patients with early breast cancer, and can be used in combination with the Dutch treatment guidelines.

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7

Acute toxicity of concurrent adjuvant radiotherapy and chemotherapy (CMF or AC) in breast cancer: a prospective, comparative, non randomised study.

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ABSTRACT

Background: The concurrent administration of adjuvant chemotherapy and radiotherapy in breast cancer treatment might lead to an increased incidence of side effects.

Methods: In this prospective, non-randomised, comparative study the acute toxicity of radiotherapy alone (RT) and radiotherapy concurrent with doxorubicin-cyclophosphamide (AC/RT) and radiotherapy concurrent with cyclophosphamide-methotrexate-5-fluorouracil (CMF/RT) was compared. We used the Common Toxicity Criteria (CTC) to score the level of acute toxicity before, during and 6 months after the completion of the period of irradiation. The number of hospital admissions as well as the compliance of chemotherapy, were noted.

Results: We observed that patients treated with AC/RT and CMF/RT had significant higher incidences of (high-grade) skin-toxicity, oesophagitis, dyspnoea, malaise, anorexia, nausea and hospital admission compared with those treated with RT only. The target-volume of radiotherapy was the main predictor of (high-grade) acute skin toxicity and oesophagitis. AC/RT was associated with significant more (high-grade) skin toxicity than CMF/RT. The dose of chemotherapy was reduced to less than 85% of the planned dose in 11% of patients, 17% of patients treated with concurrent chemotherapy and radiotherapy needed admission to hospital .

Conclusions: From the results of our study, we conclude that the concurrent administration of adjuvant chemotherapy and radiotherapy leads to an unacceptably high level of acute toxicity.

INTRODUCTION

The optimal sequence of radiotherapy and adjuvant chemotherapy in breast cancer patients is not clearly defined. The delivery of both regimens can be planned sequentially (chemotherapy administered before or after radiotherapy), concurrently (chemotherapy and radiotherapy given simultaneously), or alternating (radiotherapy administered in the midst of the chemotherapy courses, commonly referred to as “sandwich” therapy).

In order to limit the side-effects experienced, most centres deliver radiotherapy and adjuvant chemotherapy sequentially. However, a delay in the delivery of radiotherapy[1-5] or systemic therapy[6] might have a negative effect on treatment outcome. In an evaluation of data from a number of trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP), in which concurrent treatment was compared with sequential treatment, concurrent treatment was associated with a decreased incidence of ipsilateral breast recurrences after breast conserving therapy (BCT).[7] However, it is known that the concurrent administration of radiotherapy and chemotherapy leads to an increased incidence of side effects,[8-15] that the chemotherapy regimens used in these NSABP trials are considered substandard today and that the degree of toxicity of combined chemotherapy and radiotherapy also depends on the type of cytotoxic drugs used.[16,17] The increased level of toxicity, caused by the concurrent administration of chemo- and radiotherapy, might compromise optimal dose delivery, with respect to both radiotherapy and chemotherapy treatments.[15,18] This might have negative influence on treatment outcome. Hence, the balance between gain in disease control versus the side-effects might be different with the current chemotherapy and radiotherapy regimens.

In this prospective, comparative, non-randomised study, the acute toxicity of radiotherapy concurrent with cyclophosphamide-methotrexate-fluorouracil (CMF/RT) was compared with that of radiotherapy concurrent with (epi-)doxorubicin-cyclophosphamide (AC/RT). A third group treated with radiotherapy only (RT) was added.

Table 7.1. Patient-, tumour- and treatment-characteristics.

	AC/RT	CMF/RT	RT
Number of patients	61	51	42
Median age in years (range)	47 (27-64)	43 (28-56)	53 (37-74)
Interval between date of surgery and start of radiotherapy in days (range)	57 (35-119)	58 (31-103)	53 (31-98)
Interval between date of surgery and start of chemotherapy in days (range)	35 (15-91)	29 (9-92)	
Primary surgical treatment			
Breast conserving therapy	34 (56%)	37 (73%)	36 (86%)
Modified radical mastectomy	27 (44%)	14 (27%)	6 (14%)
Tumour size			
≤ 20 mm	18 (30%)	25 (49%)	28 (67%)
21 – 50 mm	36 (59%)	24 (47%)	13 (31%)
> 50 mm	7 (11%)	2 (4%)	1 (2%)
Axillary lymph node status			
Tumour negative	4 (7%)	3 (6%)	27 (64%)
Tumour positive	57 (93%)	48 (94%)	15 (36%)
Target-volume radiation therapy			
Local	25 (41%)	28 (55%)	30 (71%)
Loco-regional	36 (59%)	23 (45%)	12 (29%)

AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil; RT, radiotherapy.

MATERIAL AND METHODS

Patients

Between January 1996 and August 1999, all eligible patients referred to the department of radiotherapy at the University Medical Centre Utrecht (UMC Utrecht) were asked to participate in this prospective, comparative study. Informed consent was obtained from 154 patients. Patients were eligible if they were referred for RT or chemotherapy (CT)/RT, both after BCT and modified radical mastectomy (MRM). 112 patients received CT/RT; 61 patients were treated with AC/RT and 51 with CMF/RT. 42 patients treated with RT only were studied as controls. The choice between AC and CMF was made by the treating medical oncologist and was based on personal preference. Table 8.1 depicts the patient and treatment characteristics for the 3 patient groups. The AC/RT and CMF/RT groups were not fully balanced, specifically with respect to tumour and treatment characteristics . However, these differences were not statistically significant ($P>0.05$). The differences in patient-, tumour- and treatment characteristics between the CT/RT and RT groups can be explained by the treatment protocols used. In premenopausal patients, chemotherapy was given in the presence of axillary lymph node metastases. Since patients in the CT/RT groups were mostly premenopausal, we preferably included patients less than 50 years of age in the RT group. As a consequence, most patients included in the RT only group were axillary lymph node-negative. The higher rate of patients treated with BCT and local radiotherapy in the RT group can be explained by the fact that local radiotherapy is part of BCT. Radiation therapy of the breast (including a boost dose) was an integral part of the BCT. Patients treated with MRM were referred for radiotherapy based on characteristics of either the primary tumour and/or the axillary lymph node status. In these patients, adjuvant systemic therapy was indicated in most cases.

Radiotherapy

Radiation therapy was administered at the Department of Radiotherapy at the UMC Utrecht. After lumpectomy and axillary dissection, radiotherapy (whole breast irradiation (WBI) and a boost dose) was indicated. Thoracic wall irradiation (TWI) after MRM was administered when resection margins were found to be tumour-positive or when skin involvement was assessed by the pathologist. Regional radiotherapy encompassing the axillary, infraclavicular, supraclavicular and parasternal lymph node areas, was added in the presence of 4 or more positive axillary lymph node metastases; tumour involvement of the apical axillary lymph node; extranodal tumour growth; or when skin involvement was assessed by the pathologist. WBI, as well as TWI, were administered using opposed tangential photon fields on a 6 or 10 MV linear accelerator to a dose of 50 Gy at 2 Gy per fraction. In case of WBI, a boost dose of 14-16 Gy (tumour free resection margins) or 20 Gy (focally tumour positive resection margins) was given using either photon wedge fields or electrons. The dose was specified at the isocentre, according to the guidelines of the International Commision on Radiation Units and Measurements (ICRU) report 50.[19] In all cases of TWI, tissue equivalent material was applied on the skin to ensure a 100% skin dose. The thoracic wall, as well as the axillary, infraclavicular, supraclavicular and parasternal lymph node areas were treated using a technique described earlier.[20] A dose of 50 Gy was given. With regard to the parasternal field, an anterior-posterior field was given. Thirteen fractions were administered with photons (encompassing the oesophagus) and 12 fractions with electrons. In 2 patients, who required regional radiotherapy, it was possible to include the parasternal lymph node chain within the breast tangential fields. 7 patients who were referred for local radiotherapy after breast-conserving tumorectomy participated in the European Organization for Research and Treatment of Cancer (EORTC) 10925/22922 trial (parasternal/medial supraclavicular radiotherapy versus none) and were treated with a parasternal field and a medial supraclavicular field in addition to their breast tangential fields.

The median interval between the date of surgery and the start of radiotherapy was 56 days (range 31-119 days). No difference in duration of the duration of interval period was noted between chemotherapy-patients and controls.

Chemotherapy

During the accrual period of this study (1996-1999), the medical oncologists had their own preference with regard to prescribing either AC or CMF as adjuvant systemic treatment. However, a change was observed over the years. In 1996, two thirds of the patients who required chemotherapy received CMF, whilst in 1998 two thirds received AC. The drugs were administered according to the following doses and schedules: AC: doxorubicin - 60 mg per square meter of body-surface area intravenously (i.v.) on day 1; cyclophosphamide - 600 mg per square meter i.v. on day 1; cycles were repeated every 21 days for a total of four cycles. CMF: cyclophosphamide - 100 mg per square meter orally for 14 days, starting on day 1; methotrexate – 40 mg per square meter i.v. on days 1 and 8; 5-fluorouracil – 600 mg per square meter i.v. on days 1 and 8; cycles were repeated every 28 days for a total of six cycles. Depending on the level of haematological toxicity (leucocytes $<3.0x10^9$, granulocytes $<1.5x10^9$ or thrombocytes $<50x10^9$), the medical oncologist decided to reduce chemotherapy doses or expel deliverance. The median interval between the date of surgery and start of chemotherapy was 35 days (range 15-91 days) for AC/RT patients and 29 days (range 9-92 days) for CMF/RT patients. Five percent of AC/RT patients received the first cycle of chemotherapy during radiotherapy, 49% received one cycle before start of radiotherapy, 39% two cycles and 7% three cycles. Eight percent of CMF/RT patients received their first cycle of chemotherapy during radiotherapy, 47% received one cycle before start of radiotherapy, 41% two cycles and 4% three cycles. Planned and delivered chemotherapy doses were calculated in mg per meter squared per week. Dose reduction was calculated by subtracting the delivered dose divided by the planned dose from one.

Table 7.2. Common Toxicity Criteria.

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	None or no change	Scattered macular or popular eruption or erythema that is asymptomatic	Scattered macular or popular eruption or erythema with pruritis or other associated symptoms	Generalized symptomatic macular, popular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Oesophagitis / dysphagia	None	Painless ulcers, erythema, or mild soreness or dysphagia	Painful erythema, oedema, or ulcers, or moderate dysphagia but can eat without narcotics	Cannot eat solids, or requires narcotics to eat	Requires parenteral or enteral support or complete obstruction or perforation
Cough	No change	Mild, relieved by NPM meds	Requires narcotic antitussive	Uncontrolled cough	
Dyspnea	None or no change	Asymptomatic with abnormality in pulmonary function tests	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest
Radiation pneumonitis	None	Radiographic changes, no steroids needed	Steroids required	Oxygen required	Assisted ventilation required
Malaise	None	Mild, able to continue normal activities	Impaired normal daily activity or bedrest <50% of waking h	In bed or chair 50% of waking h	Bedridden or unable to care for self
Anorexia	None	Mild	Moderate	Severe	Life-threatening
Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	
Vomiting	None	Once in 24 h	2–5 x in 24 h	6–10 x in 24 h	>10 episodes in 24 h, or requiring i.v. support
Fever (in absence of infection)	None	37,1–38,0 ºC	38,1–40,0 ºC	>40,0 ºC <24 h	>40,0 ºC >24 h or fever with hypotension

meds, medicines; h, hours; i.v., intravenous; NPM, non prescription medication.

Side effects

Toxicity parameters were scored using the Common Toxicity Criteria (CTC) as developed by the National Cancer Institute (NCI).[21] In the present study toxicity parameters were prospectively scored by the treating radiation oncologist before the start of radiotherapy, every two weeks during radiotherapy, and 3 weeks, 6 weeks, 3 months and 6 months after the completion of radiotherapy. Items scored were the level of skin-toxicity, the severity of symptoms like oesophagitis/ dysphagia, cough, dyspnoea, malaise, anorexia, nausea, vomiting, and fever (Table 8.2). When cough was scored as grade 2 or 3, or when dyspnoea was scored as grade 3 or 4, or in case of other pulmonary complaints, a chest X-ray was taken in order to evaluate the presence or absence of radiation pneumonitis. When skin toxicity grade 4 was scored, the desquamated skin surface area was measured in square centimetres. The maximum surface area of skin desquamation was noted. For all of the toxicity parameters, the maximum toxicity grade was taken. For all of the toxicity parameters, except for skin, toxicity grade 2 or higher was considered clinically relevant and therefore high-grade. For skin toxicity grade 3 or higher was considered clinically relevant and therefore defined as high-grade. The number of hospital admissions that took place during the follow-up period was registered. Dose reductions of chemotherapy to less than 85% of planned dose (in mg/m^2/week) were considered to be of clinical relevance.

Statistical analyses

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) for Windows, release 9.0 (SPSS Inc.). Incidences of high-grade maximum toxicity were compared in univariate analyses using the Pearson Chi-square test. Incidences of high-grade toxicity (significant in univariate analysis), hospital admissions and clinically relevant dose reductions of chemotherapy were compared in logistic regression analysis. Independent variables included in the

Table 7.3. Incidences of maximum common toxicity criteria grade 2, 3 and 4 during follow-up.

Toxicity	AC/RT	CMF/RT		CT/RT	RT	
Number of patients	61	51		112	42	
Skin			§			‡
Grade 2	15 (25%)	20 (39%)		35 (31%)	22 (52%)	
Grade 3	0 (0%)	3 (6%)		3 (3%)	2 (5%)	
Grade 4	43 (70%)	21 (41%)		64 (57%)	9 (21%)	
Esophagitis / dysphagia			§			†
Grade 2	14 (23%)	7 (14%)		21 (19%)	2 (5%)	
Grade 3	8 (13%)	0 (0%)		8 (7%)	0 (0%)	
Grade 4	0 (0%)	2 (4%)		2 (2%)	0 (0%)	
Cough						
Grade 2	7 (11%)	4 (8%)		11 (10%)	2 (5%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Dyspnea						†
Grade 2	23 (38%)	18 (35%)		41 (37%)	5 (12%)	
Grade 3	3 (5%)	3 (6%)		6 (5%)	2 (5%)	
Grade 4	0 (0%)	1 (2%)		1 (1%)	0 (0%)	
Radiation pneumonitis						
Grade 2	3 (5%)	2 (4%)		5 (4%)	1 (2%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Malaise						‡
Grade 2	38 (62%)	31 (61%)		69 (62%)	17 (40%)	
Grade 3	15 (25%)	6 (12%)		21 (19%)	2 (5%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Anorexia			§			‡
Grade 2	25 (41%)	10 (20%)		35 (31%)	1 (2%)	
Grade 3	6 (10%)	5 (10%)		11 (10%)	1 (2%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Nausea			§			†
Grade 2	15 (25%)	6 (12%)		21 (19%)	1 (2%)	
Grade 3	3 (5%)	1 (2%)		4 (4%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Vomiting						§
Grade 2	8 (13%)	4 (8%)		12 (11%)	0 (0%)	
Grade 3	1 (2%)	0 (0%)		1 (1%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Fever						§
Grade 2	7 (11%)	5 (10%)		12 (11%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	

AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil; CT, chemotherapy; RT, radiotherapy. Incidences of maximum high-grade toxicities compared in bivariate analyses. § P<0.05; † P<0.01; ‡ P<0.001.

analysis were age, primary surgical therapy (MRM vs. BCT), target-volume of radiotherapy (local radiotherapy vs. loco-regional radiotherapy) and chemotherapy regimen (CT/RT vs. RT and CMF/RT vs. AC/RT). Since WBI was delivered after BCT only and TWI after MRM only, MRM vs. BCT could - in cases of acute skin toxicity - also be interpreted as TWI vs. WBI. T-stage or N-stage were not considered to be confounding factors, and we therefore decided not to include these variables in the multivariate analyses. The influence of the independent variables mentioned above on the duration of skin toxicity, oesophagitis/dysphagia and malaise was determined using Cox regression analysis. Their effect on the natural logarithm of the maximum area of skin desquamation was determined using linear regression analysis.

RESULTS

Incidences of maximum toxicity grades 2, 3 and 4 are presented in Table 8.3. Significantly more patients receiving CT/RT than patients receiving RT only experienced severe skin toxicity (60% vs. 26%), and moderate or severe esophagitis / dysphagia (28% vs. 5%), dyspnoea (43% vs. 17%), malaise (81% vs. 45%) anorexia (41% vs. 4%), nausea (22% vs. 2%), vomiting (12% vs. 0%) and fever (11% vs. 0%). When patients receiving AC/RT were compared with those receiving CMF/RT more high-grade skin-toxicity (70% vs. 47%) and moderate to high-grade toxicity of the oesophagus (36% vs. 18%) was observed for the AC/RT group. The intake of food was also significantly decreased (30% vs. 14%), and more patients experienced moderate to high (Grades 2 and 3) anorexia (51% vs. 29%).

The three study groups (AC/RT, CMF/RT and RT) were not fully balanced with respect to other potential risk factors for acute toxicity such as primary surgical treatment, radiotherapy regimen and age (Table 1). Hence, a logistic regression

Table 7.4. Multiple logistic regression analysis on incidences of high-grade toxicities.

	CT/RT vs. RT	AC vs. CMF	Loco–regional vs. local radiotherapy
	p-value O.R. (95% C.I.)	p-value O.R. (95% C.I.)	p-value O.R. (95% C.I.)
Skin	0.02 3.4 (1.2-9.5)	0.05 2.4 (1.0-5.8)	0.001 5.7 (2.1-15.5)
Oesophagitis / dysphagia	0.03 7.2 (1.2-43)	0.08 2.4 (0.90-6.1)	0.001 7.6 (2.2-26)
Dyspnoea	0.003 5.1 (1.7-15)	0.68 0.85 (0.39-1.9)	n.s.
Malaise	<0.001 7.1 (2.6-20)	0.11 2.3 (0.84-6.1	n.s.
Anorexia	0.001 13 (2.8-67)	0.06 2.1 (0.96-4.8)	n.s.
Nausea	0.03 12 (1.4-100)	0.06 2.6 (0.96-6.9)	n.s.

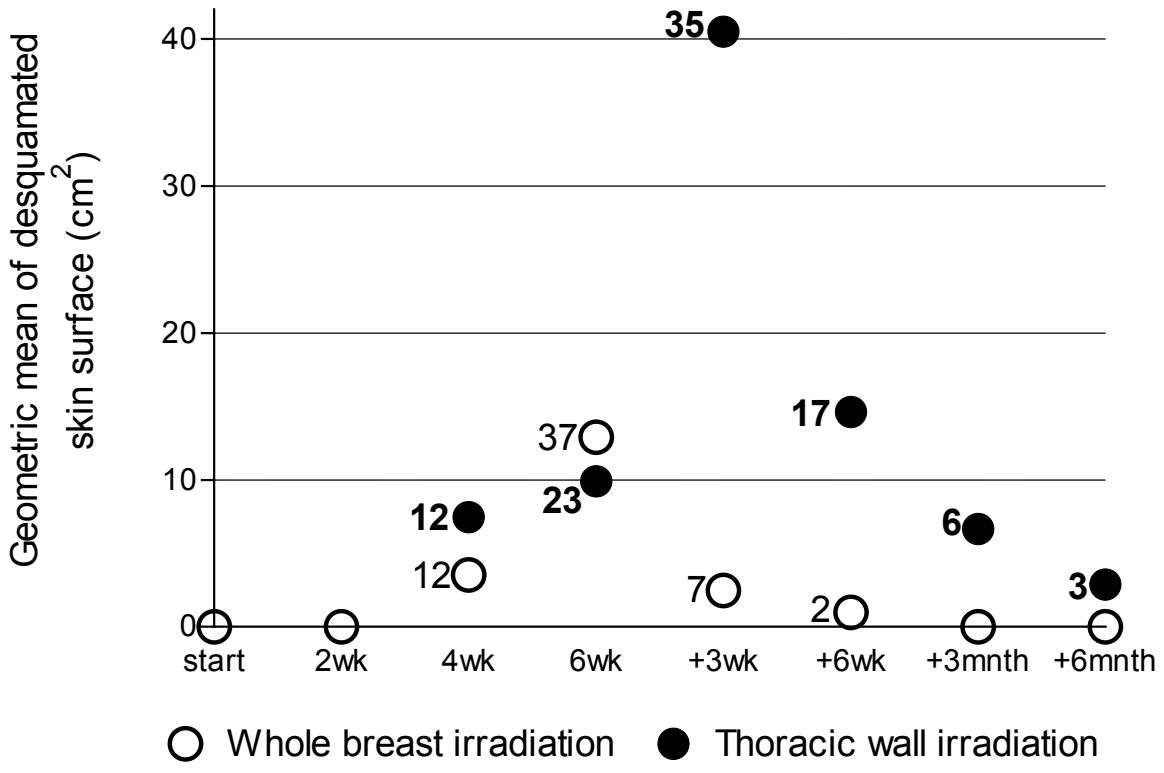
Age and type of primary surgical treatment were not significantly associated with the end-points and are therefore not shown.

n.s, not significant; O.R., odds ratio; 95% C.I., 95% confidence interval; CT, chemotherapy, RT, radiotherapy; AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil; MRM, modified radical mastectomy; BCT, breast conserving therapy.

analysis was performed. The results are given in Table 8.4. The administration of CT/RT, compared with RT, was associated with significantly more high-grade skin toxicity, oesophagitis/dysphagia, dyspnoea, malaise, anorexia and nausea. After adjustment for the other potential risk factors, when the AC/RT group was compared with the CMF/RT group, a borderline significance was noted

specifically with respect to more high-grade skin toxicity (P=0.05, odds ratio (OR) 2.4). There was also a trend towards more high-grade oesophagitis/dysphagia, anorexia and nausea in patients receiving AC/RT compared with patients receiving CMF/RT (p=0.06-0.08, OR 2.1-2.6) (Table 8.4). The inclusion of regional lymph node areas in the radiotherapy regimen was associated with significantly more high-grade skin-toxicity and oesophagitis/dysphagia. The type of primary surgical treatment was not significantly associated with any of these endpoints.

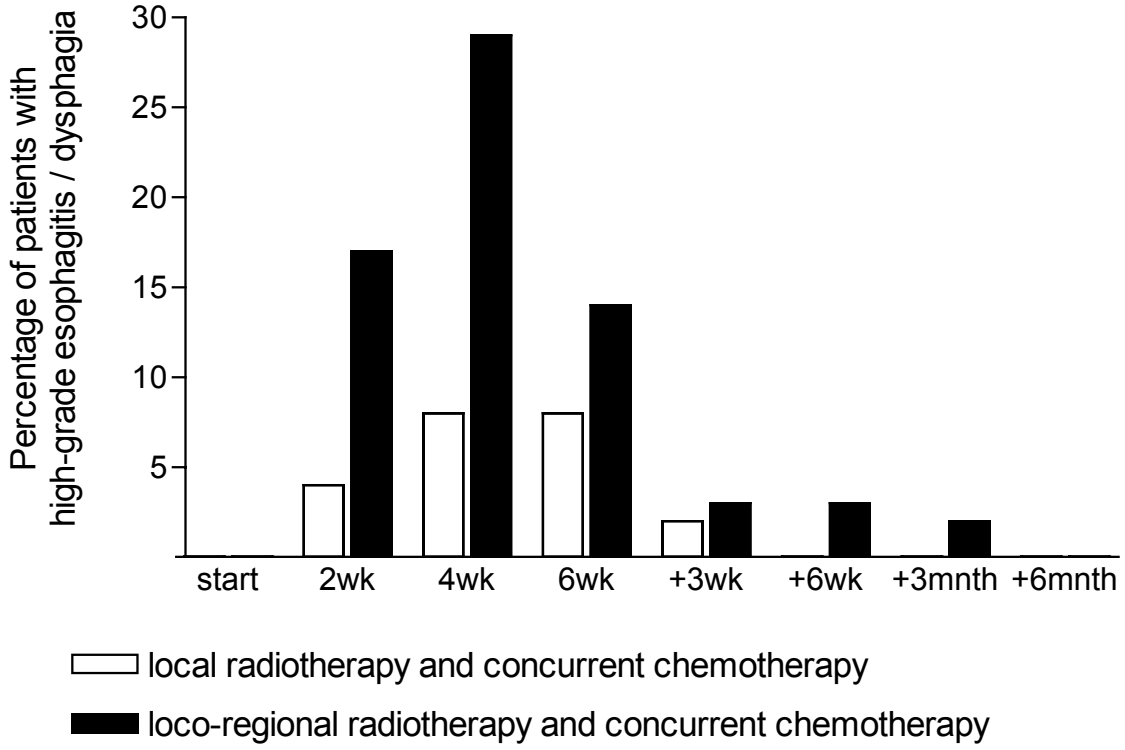
Figure 7.1. The effect of radiotherapy on the geometric mean of desquamated skin surface area in patients treated with concurrent radio- and adjuvant chemotherapy, 2 weeks, 4 weeks and 6 weeks after start of radiotherapy, and 3 weeks, 6 weeks, 3 months and 6 months after completion of radiotherapy. Geometric means of areas of desquamated surface are presented together with number of patients involved.



The administration of CT/RT was, after adjustment for the other potential risk factors, associated with significantly more hospital admissions. During the follow-up, 19 of 112 patients (17%) treated with CT/RT were (in total 30 times) admitted to hospital with acute complications of treatment. Only 1 patient (2%) treated with RT only was admitted to hospital. The median duration of hospital admissions was 11 days (range 2-64 days). More than half of the hospital admissions was related to local toxicity in the irradiated area. A dose reduction of chemotherapy to less than 85% of the planned dose was necessary in 12 patients (11%) and was independent of treatment regimen, tumour and patient characteristics.

The duration of high-grade skin toxicity was significantly longer after TWI (median 34 days) than after WBI (median 22 days) (p=0.02). The geometric mean value of surface areas of skin desquamation was higher after TWI than that after WBI (Figure 8.1). After WBI 41 patients (38%) developed high-grade skin toxicity for a median period of 22 days (range 14 – 92 days). After TWI 37 patients (79%) developed high-grade skin toxicity for a median of 34 days (range 14 –221 days). Six weeks after the completion of radiotherapy, 19 patients had not recovered from high-grade skin toxicity. All 19 patients had received concurrent chemotherapy and radiotherapy on the regional lymph nodes (including WBI or TWI). Six months after completion of radiotherapy 3 patients still had high-grade skin toxicity. The incidence of high-grade toxicity of the oesophagus was significantly higher in patients treated with loco-regional radiotherapy compared with that in patients treated with local radiotherapy (Figure 8.2), but the duration of complaints did not differ significantly. 33 patients developed high-grade oesophagitis/dysphagia for a median duration of 16 days (range 9 – 217 days). 109 patients developed high-grade malaise for a median duration of 64 days (range 13 – 224 days). The duration of high-grade skin toxicity, oesophagitis/dysphagia and malaise, and the maximum surface area of skin desquamation, was not associated with the type of chemotherapy.

Figure 7.2. The effect of concurrent chemotherapy and local and loco-regional radiotherapy on the prevalence of high-grade oesophagitis/dysphagia 2 weeks, 4 weeks and 6 weeks after start of radiotherapy, and 3 weeks, 6 weeks, 3 months and 6 months after completion of radiotherapy.



DISCUSSION

For breast cancer patients, 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.[7] However, it has been reported that the concurrent administration of the two modalities leads to an increased incidence of side effects.[8] In retrospective studies on the combination of chemotherapy and radiotherapy the following results were reported: a worsened cosmetic outcome after breast conserving therapy;[9,10] an increased

level of haematological toxicity;[11] an increased incidence of severe skin toxicity;[12,15] a higher incidence of radiation pneumonitis[11,14] and arm oedema.[13] Moreover it has been reported that an increased level of toxicity compromises an optimal dose delivery, with respect to both radiotherapy and chemotherapy.[15,18] In some retrospective studies, however, no or only a minor increase in toxicity has been found when chemotherapy and radiotherapy were given concurrently.[13,18,22]

The enhancement of side effects of radiation by chemotherapy does not only depend on the sequencing of radiotherapy and chemotherapy, but also on the type of cytotoxic drugs used. Skin effects are more frequently reported with the use of doxorubicin and 5-Fluorouracil.[17] Others found that doxorubicin in particular potentiated the effect of radiotherapy on the skin and the normal mucosa of the oesophagus.[16] In the present study, we prospectively compared the acute toxicity of two commonly used adjuvant chemotherapy regimens (CMF and AC) administered concurrently with radiotherapy. A third group treated with radiotherapy only was added.

Others have already stated that although conservative surgery combined with breast irradiation is associated with low incidences of significant (late) complications, both cosmetic result en the risk of complications can be unfavourably influenced by the addition of nodal irradiation and/or chemotherapy.[8] In the present study, the addition of adjuvant chemotherapy, concurrent with radiotherapy, did increase the risk of acute toxicity. CT/RT, AC/RT more than CMF/RT, caused a higher incidence of high-grade skin toxicity than RT alone. However, the inclusion of regional nodal areas in the irradiation field was of greater importance. As shown in Table 8.5, almost 90% of patients treated with concurrent AC and loco-regional radiotherapy developed high-grade skin toxicity compared with 44% of patients treated with concurrent AC and local radiotherapy. TWI was the main predictor of duration of high-grade skin toxicity and of the extent of desquamated skin surface. This could be explained by the fact that, in

cases of TWI, tissue equivalent material was applied on the skin to ensure a 100% skin dose. In contrast, during WBI (as part of radiotherapy during BCT), no tissue equivalent material was used, resulting in a lower skin dose of approximately 75%. In our multivariate analysis, TWI was not significantly related to the incidence of high-grade skin toxicity.

Loco-regional radiotherapy (encompassing the oesophagus) and the addition of concurrent chemotherapy to radiotherapy were the most important risk factors for developing high-grade oesophagitis/dysphagia. There was a trend towards more high-grade oesophagitis/dysphagia when AC/RT was administered instead of CMF/RT. As shown in Table 8.5, more than half of all patients treated with loco-regional radiotherapy concurrent with AC developed high-grade oesophagitis/dysphagia, compared with only 12% of patients treated with local radiotherapy (and hence no irradiation of the oesophagus) concurrent with AC.

In the present study, symptomatic radiation pneumonitis was observed in only a small proportion of patients. Grade 2 pneumonitis (requiring steroid treatment) was seen in 2% of patients treated with RT and in 4% of patients treated with CT/RT. Because of these low incidences of pneumonitis, it was not possible to draw any further conclusions. Lingos and colleagues retrospectively reviewed 1624 breast cancer patients for the risk of developing radiation pneumonitis.[14] They concluded, in line with our observations, that radiation pneumonitis following conservative surgery and radiation therapy for breast cancer is a rare complication, but that it was more likely to occur in patients treated with both loco-regional radiotherapy and chemotherapy (particularly when given concurrently with radiation therapy). Others found similar results.[13] In the present study, the administration of chemotherapy concurrently with radiotherapy did cause significant more dyspnoea on exertion. But only 5% of patients (in all three groups) experienced dyspnoea at normal levels of activity, and only one patient

experienced dyspnoea at rest. We found no difference in incidence of lung toxicity between CMF/RT and AC/RT.

Table 7.5. Acute toxicity, hospital admissions and chemotherapy dose reduction according to radiotherapy- and chemotherapy regimen.

	Local radiotherapy			Loco-regional Radiotherapy		
	RT	**CMF/RT**	**AC/RT**	**RT**	**CMF/RT**	**AC/RT**
High-grade skin toxicity	20%	25%	44%	42%	74%	89%
High-grade skin toxicity six weeks after completion of radiotherapy	0%	0%	0%	0%	30%	36%
High-grade oesophagitis/dysphagia	3%	7%	12%	8%	30%	53%
Hospital admissions	3%	11%	8%	0%	22%	25%
Chemotherapy dose reduction (< 85%)		7%	4%		17%	14%

RT, radiotherapy; AC, doxorubicin-cyclophosphamide; CMF, cyclophosphamide-methotrexate-fluorouracil

The administration of chemotherapy was the sole risk factor for developing high-grade malaise, anorexia, nausea, vomiting and fever. There was a trend towards more high-grade anorexia and nausea in the group of patients receiving AC/RT compared with the group of patients receiving CMF/RT. In the RT group high-grade malaise, anorexia, nausea, vomiting and fever hardly developed. In the chemotherapy groups, nausea, vomiting and fever were mainly limited to grade 2 (moderate) toxicity level.

As shown in table 8.5, the risk of acquiring a complication necessitating hospital admittance was higher during or after a concurrent chemotherapy and loco-regional radiotherapy regimen than after than after local RT. More than 20% of patients treated with concurrent loco-regional radiotherapy and chemotherapy compared with approximately 10% of patients treated with concurrent local radiotherapy and chemotherapy and 3% of patients treated with radiotherapy alone were admitted to hospital. In addition, more patients received an inadequate dose of chemotherapy when chemotherapy was combined with concurrent loco-regional radiotherapy. When chemotherapy was combined with local radiotherapy approximately 5% of patients received an inadequate dose, compared with approximately 15% of patients when chemotherapy was combined with loco-regional radiotherapy (Table 8.5). Denham and colleagues also found a trend towards a lower mean delivered fraction of planned dose of chemotherapy while extending the radiation field.[18] Dubey and colleagues studied the delivery of CMF concurrent with a reduced, local radiotherapy regimen. Seven percent of patients received inadequate drug doses.[15]

We conclude that in the treatment of patients with early breast cancer, the administration of adjuvant chemotherapy concurrently with loco-regional radiotherapy is too toxic. In particular, 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. However, the administration of local radiotherapy concurrent with AC still leads to high-grade skin toxicity in 44% of patients. As anthracyclin-containing regimens, in particular 4 courses of AC, are considered standard for adjuvant chemotherapy in early breast cancer in many countries, the concurrent administration of adjuvant chemotherapy and radiotherapy is not recommended.

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8

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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9

Samenvatting en algemene discussie

In dit hoofdstuk worden de resultaten en conclusies van de studies gepresenteerd in de voorgaande hoofdstukken van dit proefschrift samengevat en besproken in een breder perspectief.

Ontwikkelingen in de aanvullende behandeling van het mammacarcinoom

Hoofdstuk 1 liet zien dat in de afgelopen tien jaar de aan mammacarcinoom gerelateerde sterfte in Nederland is afgenomen ondanks een toegenomen incidentie. De afname in sterfte is ten dele toe te schrijven aan een toename van gebruik en effectiviteit van aanvullende systemische therapie. Vanaf de jaren 80 zijn steeds meer patiënten behandeld met aanvullende systemische therapie. De verwachting is dat de daling in sterfte in de komende jaren zal doorzetten.[1]

Nieuwe, effectievere aanvullende behandelopties en -strategieën zijn sinds de jaren ‘80 ontwikkeld, en ontwikkelen zich. Cyclofosfamide, methotrexaat, fluorouracil (CMF) is vervangen door anthracycline-bevattende schema's, welke zo'n 20% effectiever zijn.[2] Twee jaar behandeling met tamoxifen is vervangen door 5 jaar en aanvullende chemotherapie en endocriene therapie worden veelal gecombineerd met een additief effect.[2] Een recente studie bij patiënten met okselklier positief mammacarcinoom laat zien dat behandeling met docetaxel, doxorubicine, cyclofosfamide (TAC), vergeleken met fluorouracil, doxorubicine, cyclofosfamide (FAC), resulteert in een 28% afname van het risico van recidief ziekte, het primaire eindpunt van deze studie.[3] De ATAC-studie laat bij postmenopausale vrouwen met hormoon receptor positief mammacarcinoom zien dat aanvullende behandeling met anastrozole, in vergelijking met tamoxifen, de kans op het primaire eindpunt van de studie, recidief ziekte, vermindert met ongeveer 13%.[4] Trastuzumab is een monoklonaal antilichaam gericht tegen de HER2/neu receptor. Recente studies met deze nieuwe behandeloptie,

gepresenteerd in 2005 op het congres van “the American Society of Clinical Oncology” (ASCO), laten zien dat aanvullende behandeling met trastuzumab bij patiënten met een tumor met overexpressie van de Her2-receptor de kans op recidief ziekte vermindert met zo’n 50%.[5]

Het is opvallend dat vrijwel alle recente studies naar aanvullende behandeling bij het mammacarcinoom recidief ziekte, in plaats van de “gouden standaard” overleving, als primair eindpunt gebruiken. Het is beargumenteerd dat het ontbreken van recidief ziekte de beste indicator is voor de effectiviteit van een antitumor strategie.[6] Maar wat is het primaire doel van aanvullende systemische behandeling: een vermindering van recidief ziekte of een vermindering van sterfte? **Hoofdstuk 3** laat zien dat een verschil in mammacarcinoom recidief niet automatisch gevolgd wordt door een verschil in overleving. Daarnaast verschilt de definitie van mammacarcinoom recidief tussen de studies en bevat deze meestal gebeurtenissen die niet direct gerelateerd zijn aan sterfte, zoals locoregionaal recidief en contralateraal mammacarcinoom. Niet mammacarcinoom gerelateerde sterfte wordt ook vaak opgenomen in de definitie van mammacarcinoom recidief, maar wordt niet beïnvloed door de gewoonlijk gebruikte aanvullende behandelingen.[2] **Hoofdstuk 3** laat zien dat het wel of niet opnemen van contralateraal mammacarcinoom en/of niet-ziekte gerelateerde sterfte in de definitie van uitkomst een substantiële invloed heeft op de schattingen van het mammacarcinoom recidiefcijfer en sterftecijfer, met name bij oudere patiënten en patiënten met een goede prognose. Heldere definities van eindpunten en concurrerende gebeurtenissen zijn daarom cruciaal voor de interpretatie en vergelijking van uitkomst studies en zouden gegeven moeten worden in alle klinische studies. Naar mijn mening moet overleving het primaire eindpunt zijn in studies die aanvullende systemische behandelopties bestuderen in oudere (bijv. postmenopausale) patiënten en patiënten met een relatief gunstige prognose (bijv. met een okselklier negatief mammacarcinoom).

Hoofdstuk 3 bestudeert ook de mate van bias gegenereerd door de Kaplan-Meier methode ten gevolge van informatieve censurering van contralateraal mammacarcinoom en niet-ziekte gerelateerd overlijden. De Kaplan-Meier methode vereist niet-informatieve censurering, wat betekent dat de individuen die gecensureerd worden een even grote kans hebben op een nog te volgen gebeurtenis van interesse als de individuen die in de studie blijven. Met name concurrerende gebeurtenissen kunnen informatieve censurering veroorzaken. Om deze reden hebben anderen een benadering gepropageerd die in de overlevingsanalyses rekening houdt met informatieve censurering in de aanwezigheid van concurrerende gebeurtenissen. In de studie beschreven in **Hoofdstuk 3** werden slechts kleine verschillen geobserveerd tussen uitkomst-schattingen bepaald met de Kaplan-Meier methode en een methode die rekening houdt met concurrerende gebeurtenissen. Wel werden de verschillen groter wanneer relatief meer patiënten gecensureerd werden vanwege een concurrerende gebeurtenis. Desalniettemin mag verwacht worden dat informatieve censurering in de meeste follow-up studies bij patiënten met vroeg mammacarcinoom slechts een geringe bias veroorzaakt.

Prognostische factoren

De ontwikkelingen in de aanvullende systemische behandeling van het mammacarcinoom hebben beslissingen omtrent wie te behandelen en met welk type aanvullende systemische therapie gecompliceerd. Informatie over basale prognose (d.w.z. zonder aanvullende systemische therapie) en effectiviteit van aanvullende systemische behandelingen, verkregen uit gerandomiseerde klinische studies en meta-analyses, is onmisbaar geworden voor het nemen van deze beslissingen.

De belangrijkste prognostische factoren gebruikt in de klinische praktijk zijn nog steeds het aantal aangedane okselklieren en de grootte van de tumor. Maar zoals aangetoond in **Hoofdstuk 2** zijn vele andere variabelen, zoals in deze studie histologische graad, mitose index (MI), cathepsine D, urokinase plasminogeen activator (UPA) en zijn remmer type 1 (PAI-1), geassocieerd met recidief ziekte en overleving. Met name UPA en PAI-1 blijken sterke prognostische variabelen. De prognostische waarde van UPA en PAI-1 is ook aangetoond in een grote prospectieve klinische studie[7] en in een meta-analyse.[8] Naar mijn mening wordt de prognostische waarde van UPA en PAI-1 op dit moment onvoldoende gewaardeerd. De belangrijkste redenen om UPA en PAI-1 niet in de klinische praktijk te gebruiken lijken te zijn een gebrek aan standaardisatie van de gebruikte immunoassays en van de methode van tumor extractie en eiwit bepaling. Een grote prospectieve studie in meerdere centra naar de reproduceerbaarheid, haalbaarheid en klinische relevantie van UPA en PAI-1 is daarom gerechtvaardigd.

In **Hoofdstuk 4** wordt de prognostische waarde van zowel de oestrogeen receptor (ER) als de progesteron receptor (PR), bepaald met een immunocytochemische assay (ICA) en een enzym immuno assay (EIA) prospectief geëvalueerd. De overeenstemming tussen EIA en ICA was redelijk tot substantieel (Kappa respectievelijk 0,58 en 0,65 voor ER en PR). Het maakte geen verschil voor de prognostische waarde van de hormoonreceptoren of deze bepaald werden met ICA of EIA. Zowel ER als PR bleken zwakke prognostische factoren. Maar de belangrijkste reden om de hormoonreceptoren te bepalen is uiteraard hun vermogen om de effectiviteit van endocriene therapie te voorspellen. De ER is reeds meer dan 30 jaar geleden geïdentificeerd, maar er valt nog steeds veel te bestuderen. Inmiddels is er overtuigend bewijs dat de ER opereert in een complex interactief netwerk wat de levensvatbaarheid van kankercellen moet waarborgen.[9] Resistentie tegen tamoxifen is gerelateerd aan overexpressie van HER2/neu en aromatase remmers hebben met name een

voordeel ten opzichte van tamoxifen bij patiënten met een ER positieve, PR negatieve tumor.[9,10] Het is aangetoond dat ER positieve tumoren genetisch sterk verschillen van ER negatieve tumoren.[11] ER negatief en ER positief mammacarcinoom moeten als verschillende ziekten beschouwd worden en vereisen niet alleen een verschillende behandelstrategie, maar waarschijnlijk ook verschillende sets van variabelen om de prognose te bepalen. Het moet nog uitgezocht worden welke methode om de ER te bepalen (ICA, EIA, of op gen niveau) het beste is, wanneer de ER in dit kader wordt gebruikt.

De prognostische waarde van de MI in okselklier negatief mammacarcinoom is nog altijd onderwerp van discussie. Zoals aangetoond in **Hoofdstuk 5** is het bepalen van de MI een goedkope, snelle en reproduceerbare methode om in de dagelijkse praktijk de mate van proliferatie vast te stellen. Maar de studie gepresenteerd in **Hoofdstuk 5** toont geen significante associatie tussen MI en recidief ziekte en overleving aan, wat verklaard wordt door de prognostisch gunstige tumorkarakteristieken en het hiermee samenhangende lage aantal als eindpunt gedefinieerde gebeurtenissen. Gebaseerd op data uit de literatuur lijkt een positieve associatie tussen MI en overleving in okselklier negatief mammacarcinoom waarschijnlijk, maar de mate van deze veronderstelde associatie en de bijkomende klinische relevantie wordt in **Hoofdstuk 5** betwist. Anderen zijn er echter van overtuigd dat de MI relevante prognostische waarde heeft voor premenopausale patiënten met een okselklier negatief mammacarcinoom en stellen dat de MI gebruikt moet worden in de klinische praktijk.[12] Zeer recent zijn de resultaten van het “multicentre morphometric mammary carcinoma project (MMMCP)” gepubliceerd. In deze studie bedroeg het absolute verschil in 10 jaars overleving tussen patiënten met een okselklier negatief mammacarcinoom met lage en hoge MI 22% (92% vs. 70%) (HR 4.42, 95% C.I. 2.79 – 7.01).[13] Deze resultaten zijn veel beter dan in het verleden gerapporteerde resultaten van andere onderzoeksgroepen.

In hoog tempo ontwikkelen zich nieuwe technieken voor het bestuderen van potentiële prognostische factoren, zowel op gen niveau als op eiwit niveau.[14] Twee van deze technieken, te weten reverse transcriptase polymerase chain reaction (RT-PCR) en DNA-sequencing met microarray technologie, maken het mogelijk een groot aantal genen gelijktijdig te analyseren in één enkel experiment. Paik en anderen identificeerden met behulp van RT-PCR een panel van 21 genen, waarmee ze patiënten met mammacarcinoom konden groeperen naar de kans op het hebben van een metastase op afstand na 10 jaar van 6,8% en 30,5%.[15] Van 't Veer e.a. en van de Vijver e.a. gebruikten microarray technologie en groepeerden patiënten met behulp van een 70-genen expressie profiel in categorieën met een 94,5% and 54,6% overlevingskans na 10 jaar.[16,17] Deze resultaten zijn veelbelovend, maar niet substantieel beter dan de resultaten die te bereiken zijn met klassieke, klinische variabelen.[18] In **Hoofdstuk 2** van dit proefschrift is een prognostische index gecreëerd met gebruikmaking van de tumorgrootte, het aantal aangedane okselklieren en de PAI-1 bepaling. 29% van de patiënten werden ingedeeld in de groep met een gunstige prognose en hadden na 10 jaar een kans op overlijden aan mammacarcinoom van 5%, en op recidief ziekte van 15%. De klinische relevantie van zowel het 21-genen RT-PCR panel, als het 70-genen expressie profiel zal binnenkort getest en vergeleken worden met de klassieke methoden van prognosestelling in grote gerandomiseerde klinische studies. Het 21-genen RT-PCR panel zal getest worden in de PACCT (Program for Assessment of Clinical Cancer Tests) studie, het 70-genen expressie profiel in de MINDACT (Microarray for Node Negative Disease may Avoid Chemotherapy) studie. Deze studies zijn essentieel om de klinische waarde van de genomische technieken vast te stellen. Waarschijnlijk zal de prognostische waarde van genomische testen toenemen wanneer deze gecombineerd worden met klassieke prognostische factoren zoals tumor grootte en okselklierstatus. Op dit moment zouden het 70-genen expressie profiel en het 21-genen RT-PCR panel, hoewel commercieel beschikbaar, nog niet gebruikt moeten worden buiten studieverband.

Computer programma's te gebruiken bij het maken van behandel beslissingen

Er zijn de afgelopen jaren diverse hulpmiddelen ontwikkeld om een geïndividualiseerde schatting te maken van basale prognose en absolute winst van aanvullende systemische therapie. Twee van deze hulpmiddelen, Adjuvant! en Numeracy, zijn gratis programma's, via internet te gebruiken.[19,20] Beide programma's bepalen voor een patiënt haar risico op recidief ziekte en/of overlijden na 10 jaar zonder aanvullende therapie en geven een schatting van het absolute voordeel geassocieerd met diverse veel gebruikte aanvullende systemische therapie schema's. In **Hoofdstuk 6** wordt getoond dat schattingen van het 10-jaars recidief ziekte vrije interval gemaakt door Adjuvant! en Numeracy een goede correlatie vertonen. Er is echter geen goede overeenstemming tussen de schattingen gemaakt door beide programma's. In vergelijking met zowel schattingen gemaakt door Adjuvant! als geobserveerde uitkomsten zijn de door Numeracy gemaakte schattingen van de basis-prognose te hoog en die van de absolute risico reductie door aanvullende systemische therapie te laag. De door Adjuvant! gemaakte schattingen van ziektevrije overleving en overleving zijn accuraat wanneer deze vergeleken worden met daadwerkelijk geobserveerde uitkomsten. Adjuvant! is daarom het prognostische model van voorkeur. De data gepresenteerd in **Hoofdstuk 6** betreffende de betrouwbaarheid van Adjuvant! komen overeen met de resultaten van een recent gepubliceerde, grote, prospectieve, validatie studie.[21] De website van Adjuvant! wordt regelmatig geactualiseerd. Momenteel (juli 2005) zijn er 4 verschillende versies van Adjuvant! for Breast Cancer beschikbaar op de Adjuvant! website (www.adjuvantonline.com): Een standaard versie 6.0 (gebruikt in Hoofdstuk 6), een standaard versie 7.0 (de meest actuele versie, met kleine veranderingen met betrekking tot behandel opties en effectiviteit en prognostische schattingen bij zeer jonge vrouwen), een genomics versie 7.0 (voor patiënten waarvan prognostische informatie van het 21-genen RT-PCR panel beschikbaar is) en een

versie ontworpen voor behandel-beslissingen voor hormoon receptor positieve postmenopausale patiënten op het moment dat ze 5 jaar aanvullend met tamoxifen behandeld zijn (gebruikmakend van de resultaten van de studie van Goss en anderen).[22] Het is waarschijnlijk dat Adjuvant! in de nabije toekomst een steeds belangrijkere plaats in de klinische praktijk zal innemen. Naar mijn mening zou Adjuvant! standaard gebruikt moeten worden wanneer patiënten geïnformeerd worden over de voor- en nadelen van aanvullende systemische therapie. Adjuvant! zou door de behandelend specialist gebruikt moeten worden om de winst in (ziektevrije) overleving door zowel de voorgestelde behandeling als door alternatieve behandelopties te demonstreren. Het moet echter benadrukt worden dat de betrouwbaarheid en accuraatheid van het computer programma met regelmaat gevalideerd zullen moeten worden.

De volgorde van aanvullende chemotherapie en post-operatieve radiotherapie

De optimale volgorde van radiotherapie en aanvullende chemotherapie is onduidelijk. Theoretisch kan het grootste behandeleffect verwacht worden wanneer beide modaliteiten gelijktijdig gegeven worden.[23] Maar het is gerapporteerd dat de gelijktijdige toediening van beide modaliteiten kan leiden tot een verhoogde incidentie van bijwerkingen.[24] **Hoofdstuk 7** laat zien dat het toedienen van aanvullende chemotherapie gelijktijdig met, met name locoregionale radiotherapie, te toxisch is. Meer ontvelling van de huid en gemiddeld tot ernstige oesofagitis / dysfagie werden gezien. Bovendien werden meer dan 20% van de patiënten opgenomen in het ziekenhuis met acute complicaties van de behandeling en ongeveer 15% van de patiënten ontvingen minder dan 85% van de geplande dosis chemotherapie. De gelijktijdige toediening van lokale radiotherapie op de mamma en chemotherapie is minder toxisch. Maar de gelijktijdige toediening van lokale radiotherapie en AC

veroorzaakt nog altijd hooggradige huidtoxiciteit bij 44% van de patiënten. Aangezien anthracycline bevattende schema's –te weten FAC, FEC of TAC welke als meer toxisch beschouwd worden dan de behandelschema's gebruikt in **Hoofdstuk 7**- de standaard aanvullende chemotherapeutische behandeling zijn geworden, wordt de gelijktijdige toediening van aanvullende chemotherapie en radiotherapie afgeraden.

Als postoperatieve radiotherapie en aanvullende chemotherapie niet gelijktijdig gegeven kunnen worden, zullen ze na elkaar gegeven moeten worden. De vraag is vervolgens welke modaliteit eerst gegeven moet worden, radiotherapie of chemotherapie. Als de radiotherapie gegeven wordt na het afronden van de aanvullende chemotherapie leidt dit tot een verhoogde incidentie van locoregionale recidieven.[25] Aan de andere kant draagt uitstel van chemotherapie het risico van een verhoogde incidentie van metastasen op afstand.[26] Er is één kleine (n=244) gerandomiseerde studie gepubliceerd die radiotherapie gevolgd door chemotherapie vergelijkt met chemotherapie gevolgd door radiotherapie.[27] Deze studie liet geen verschil in overleving zien tussen de twee armen. Maar het chemotherapieschema in deze studie wordt tegenwoordig als suboptimaal beschouwd. Binnenkort wordt in Nederland een grote gerandomiseerde studie opgestart met als doel de vraag te beantwoorden welke modaliteit eerst gegeven moet worden. Eindpunten van deze studie zullen zijn: lange termijn locoregionale controle, metastase op afstand vrije overleving en overleving.

REFERENTIES

De referenties waarnaar verwezen wordt in hoofdstuk 9 zijn te vinden aan het einde van hoofdstuk 8.

LIST OF ABBREVIATIONS

AC	doxorubicin, cyclophosphamide
ANN	axillary node negative
ANP	axillary node positive
BCT	breast conserving therapy
BR-grade	Bloom-Richardson grade
CBO	Kwaliteitsinstituut voor de gezondheidszorg
CI	confidence interval
CMF	cyclophosphamide, methotrexate, fluorouracil
CTC	Common Toxicity Criteria
DFI	disease free interval
DFS	disease free survival
DMFS	distant metastasis free survival
DSS	disease specific survival
EBCTCG	early breast cancer trialists' collaborative group
EIA	enzyme immuno assay
ER	oestrogen receptor
FAC	fluorouracil, doxorubicin, cyclophosphamide
FEC	fluorouracil, epirubicin, cyclophosphamide
HR	hazard rate
ICA	immunocytochemical assay
IKMN	Comprehensive Cancer Centre Middle Netherlands
LBA	ligand binding assay
LRRR	locoregional recurrence rate
MC	mitotic counts
MRM	modified radical mastectomy
OS	overall survival
PAI-1	plasminogen activator inhibitor type 1
PR	progesterone receptor
RT	radiotherapy
RT-PCR	reverse transciptase polymerase chain reaction
TAC	docetaxel, doxorubicin, cyclophosphamide
TWI	thoracic wall irradiation
UPA	urokinase plasminogen activator
WBI	whole breast irradiation

Nawoord

Het is zover, mijn boek is af. Maar een proefschrift schrijf je niet alleen. Dit proefschrift is dan ook niet compleet zonder een aantal mensen te bedanken.

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CURRICULUM VITAE

De auteur van dit proefschrift wordt op 8 januari 1969 geboren te Apeldoorn. In 1987 behaalt hij cum laude het atheneum B diploma aan het Christelijk Lyceum te Apeldoorn. Na een jaar werktuigbouwkunde gestudeerd te hebben aan de Universiteit Twente, wordt in 1988 begonnen aan de studie geneeskunde aan de Universiteit van Utrecht. In 1993 haalt hij zijn doctoraal examen, gevolgd door het artsexamen in januari 1996. Nog diezelfde maand start hij zijn loopbaan als arts-assistent, in het Bosch Medicentrum, locatie Willem-Alexander Ziekenhuis, te ’s Hertogenbosch. Een jaar later wordt de overstap gemaakt naar het Diakonessenhuis te Utrecht. Alhier begint hij rond mei 1997 op uitnodiging van dr. J.W.R. Nortier, destijds als internist werkzaam in het Diakonessenhuis, aan het controleren, aanvullen, corrigeren, en analyseren van de database die de basis zou gaan vormen van de meeste hoofdstukken van dit proefschrift. In september 1999 mag hij aan de opleiding tot internist beginnen. Eerst perifeer in het Diakonessenhuis Utrecht (opleider: dr. J.B.L. Hoekstra), vervolgens academisch in het Universitair Medisch Centrum Utrecht (opleider: prof. dr. D.W. Erkelens). In januari 2004 stapt hij over naar het Leids Universitair Medisch Centrum om opgeleid te worden in het aandachtsgebied Medische Oncologie (opleider: prof. dr. J.W.R. Nortier). Deze opleiding vindt deels plaats tijdens de opleiding tot internist, welke in Leiden wordt afgerond op 31 augustus 2004 (opleider: prof. dr. A.E. Meinders). Sinds september 2005 is hij werkzaam als internist-oncoloog in het Medisch Centrum Leeuwarden te Leeuwarden. De auteur is in 2003 getrouwd met Charlotte van der Weerd. Samen hebben ze één dochter, Merel.

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