Prognostication and treatment decision-making in early breast cancer
Fiets, Willem Edward

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.
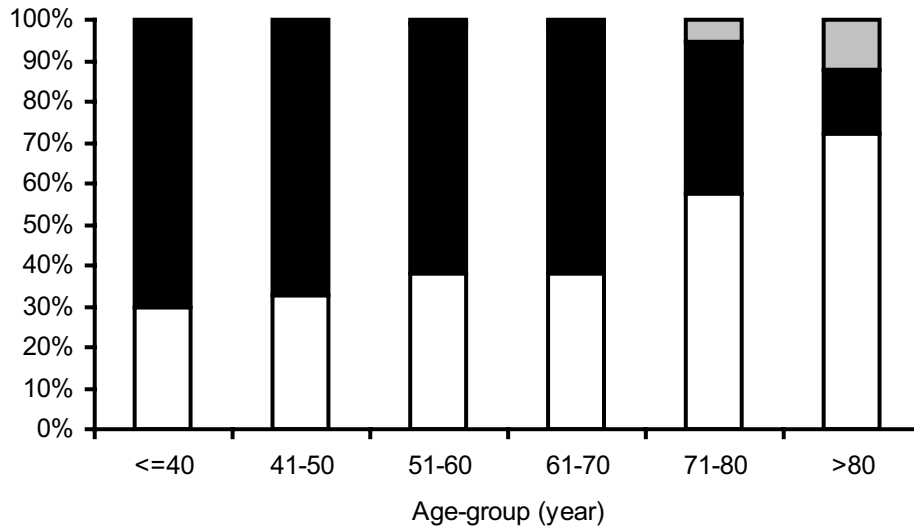
RESULTS

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.
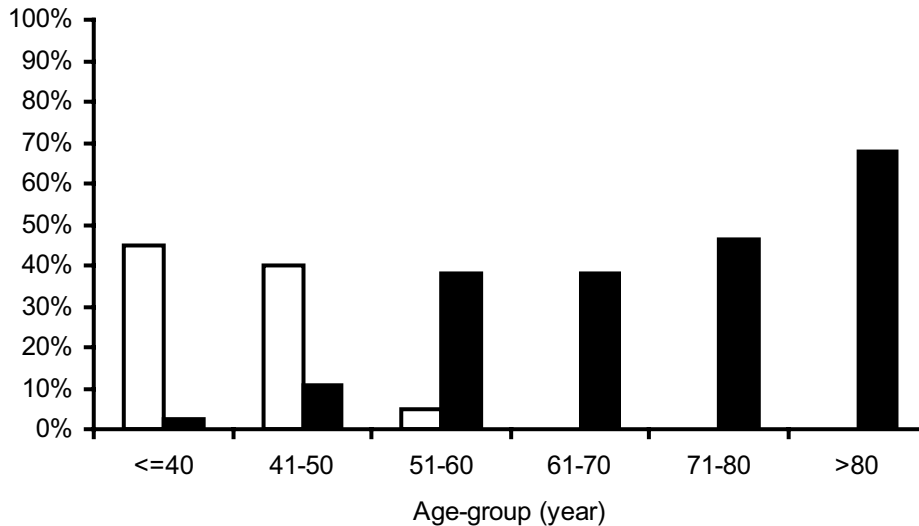
The 463 tumours included in this study were equally divided between the left and right breast, 41% of tumours were located in the lateral upper quadrant of the breast. In-situ carcinoma was found in 52% of patients, in 21% the in-situ component was extensive. The presence or absence of axillary lymph 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.
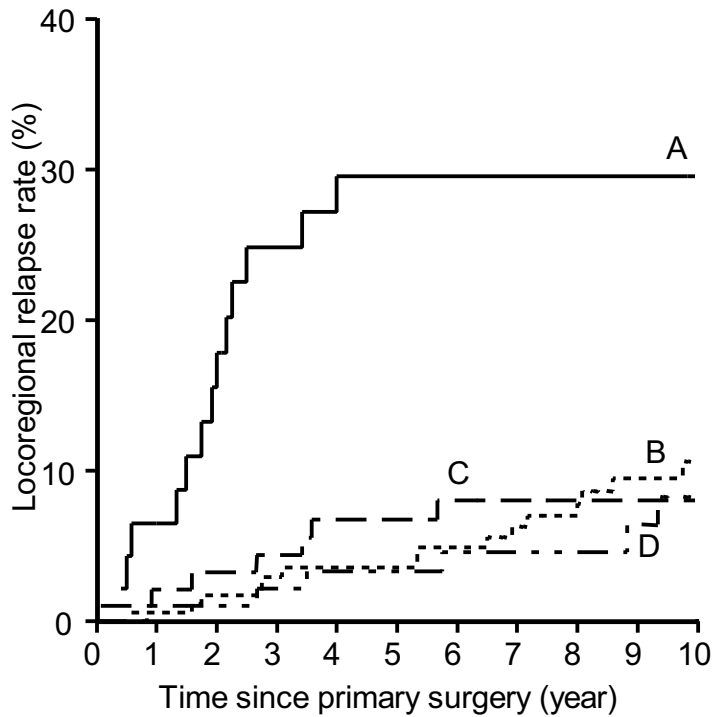
Survival end-points

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.
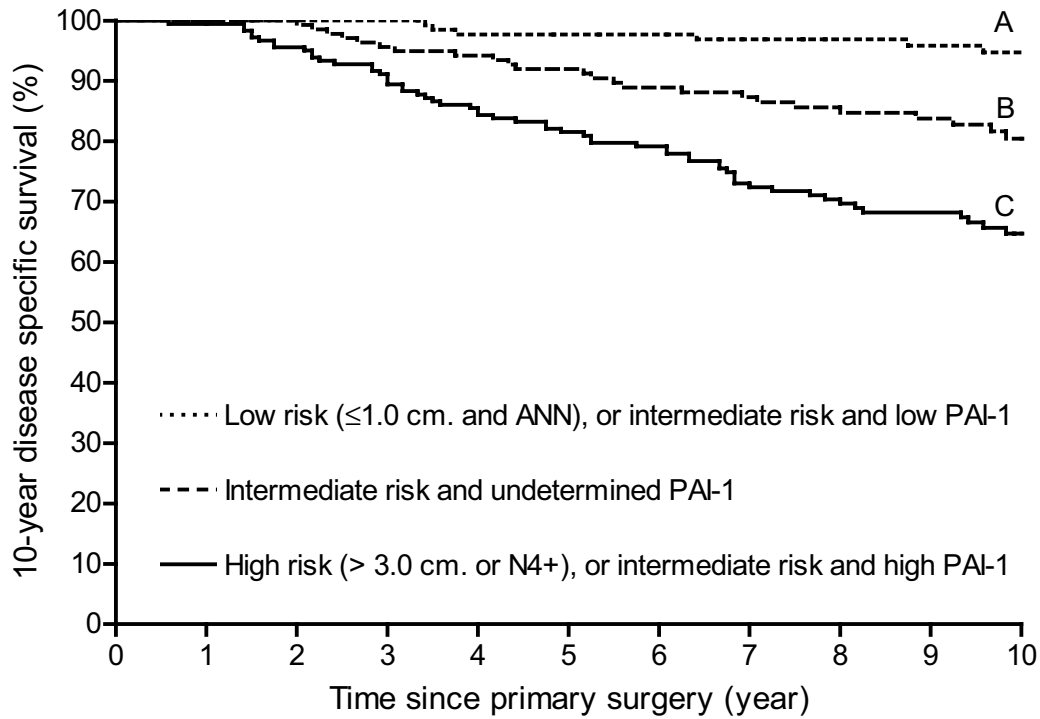
DISCUSSION

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.

REFERENCES

1. Visser O, Siesling J, van Dijck AAM, Editors. Incidence of cancer in the Netherlands 1999/2000. Eleventh report of the Netherlands Cancer Registry. 2003. www.ikcnet.nl/bibliotheek.

2. Voogd AC, van Beek MWPM, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JWW. Management of early breast cancer in southeast Netherlands since 1984. A population based study. Acta Oncologica 1994; 33: 753-757.

3. McGuire WL, Tandon AK, Allred C, Chamness GC, Clark GM. How to use prognostic factors in axillary node-negative breast cancer patients. J Natl Cancer Inst 1990; 82: 1006-1015.

4. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996; 4: 343-346.

5. Bernoux A, de Cremoux P, Lainé-Bidron C, Martin EC, Asselain B, Magdelénat H. Estrogen receptor negative and progesterone receptor postive primary breast cancer: Pathological characteristics and clinical outcome. Breast Cancer Res Treatm 1998; 49: 219-225.

6. Harris JR, Hellman S. Natural history of breast cancer. In Diseases of the breast. Harris JR, Lippman ME, Morrow M. Hellman S editors. Lippincott-Raven Publishers, Philadelphia 1996.

7. McGuire WL. Adjuvant therapy of node-negative breast cancer. N Eng J Med 1989; 320: 525-527.

8. DeVita Jr VT. Breast cancer therapy: exercising all our options. N Engl J Med 1989; 320: 527-529.

9. Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. Adjuvant tamoxifen in the management of operable breast cancer. Lancet 1987; 2: 171-175.

10. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339: 1-15.

11. Truong PT, Lesperance M, Culhaci A, Kader HA, Speers CH, Olivotto IA. Patient subsets with T1-T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy. Int J Radiat Oncol Biol Phys 2005; 62: 175-82.

12. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B. Meeting highlights: updated international consensus on the treatment of early breast cancer. J Clin Oncol 2003; 21: 3357-3365.

13. National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: Adjuvant therapy for breast cancer, November 1-3, 2000. J Natl Cancer Inst Monogr 2001; 30: 5-14.

14. Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, Ruby SG, et al. Prognostic factors in breast cancer. College of American Pathologists consensus statement 1999. Arch Pathol Lab Med 2000; 124: 966-978.

15. Isaacs C, Stearns V, Hayes DF. New prognostic factors for breast cancer recurrence. Semin Oncol 2001; 28: 53-67.

16. Mirza AN, Mirza NG, Vlastos G, Singletary SE. Prognostic factors in node-negative breast cancer: a review of studies with sample size more than 200 and follow-up more than 5 years. Ann Surg 2002; 235: 10-26.

17. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Richtlijn 'Behandeling van het mammacarcinoom'. Utrecht: CBO; 2002.

18. Janicke F, Prechtl A, Thomssen C, Harbeck N, Meisner C, Untch M, et al. Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type 1. J Natl Cancer Inst 2001; 93: 913-920.

19. Look, MP, van Putten WLJ, Duffy MJ, Harbeck N, Christensen IJ, Thomssen C, Kates R, et al. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. J Natl Cancer Inst 2002; 94: 116-128.