Prognostication and treatment decision-making in early breast cancer

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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]

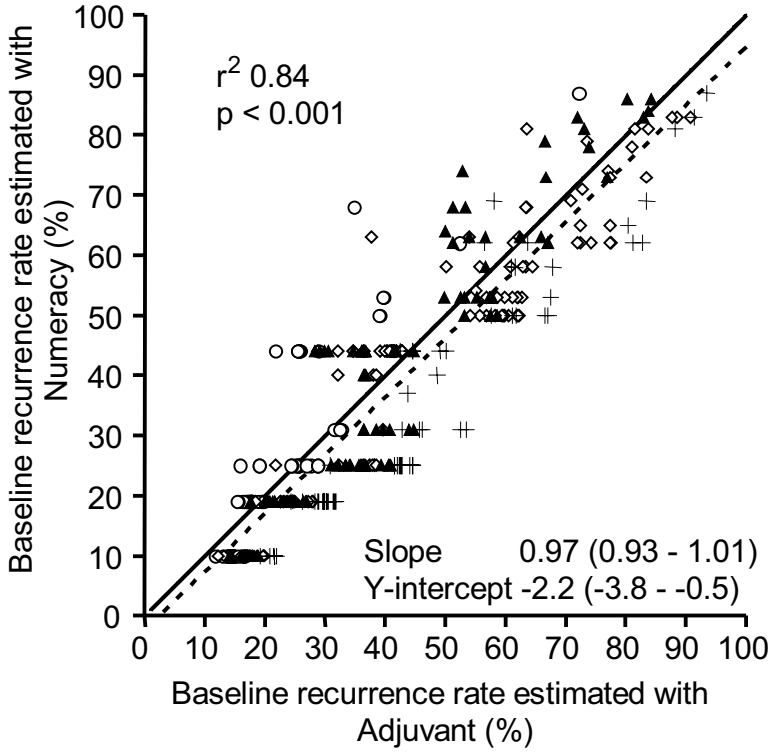
Subsequently, observed 10-year DFI was determined with the Kaplan-Meier method, for both all 434 patients and clinically relevant subgroups. In these analyses disease recurrence was defined as either locoregional recurrence, distant metastasis, or contralateral breast cancer. For the same groups, the 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.

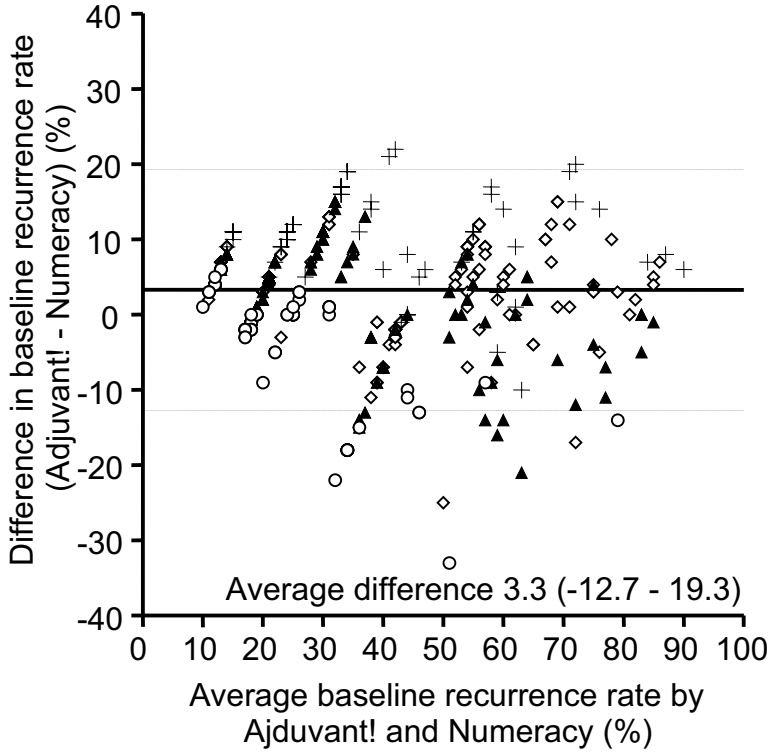
Figure 6.1. Correlation and linear regression analysis between baseline recurrence rates estimated by Adjuvant! and Numeracy, for tumours with histological grade I (o), grade II (▲), grade III (+) and with an unknown histological grade (◊).



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.

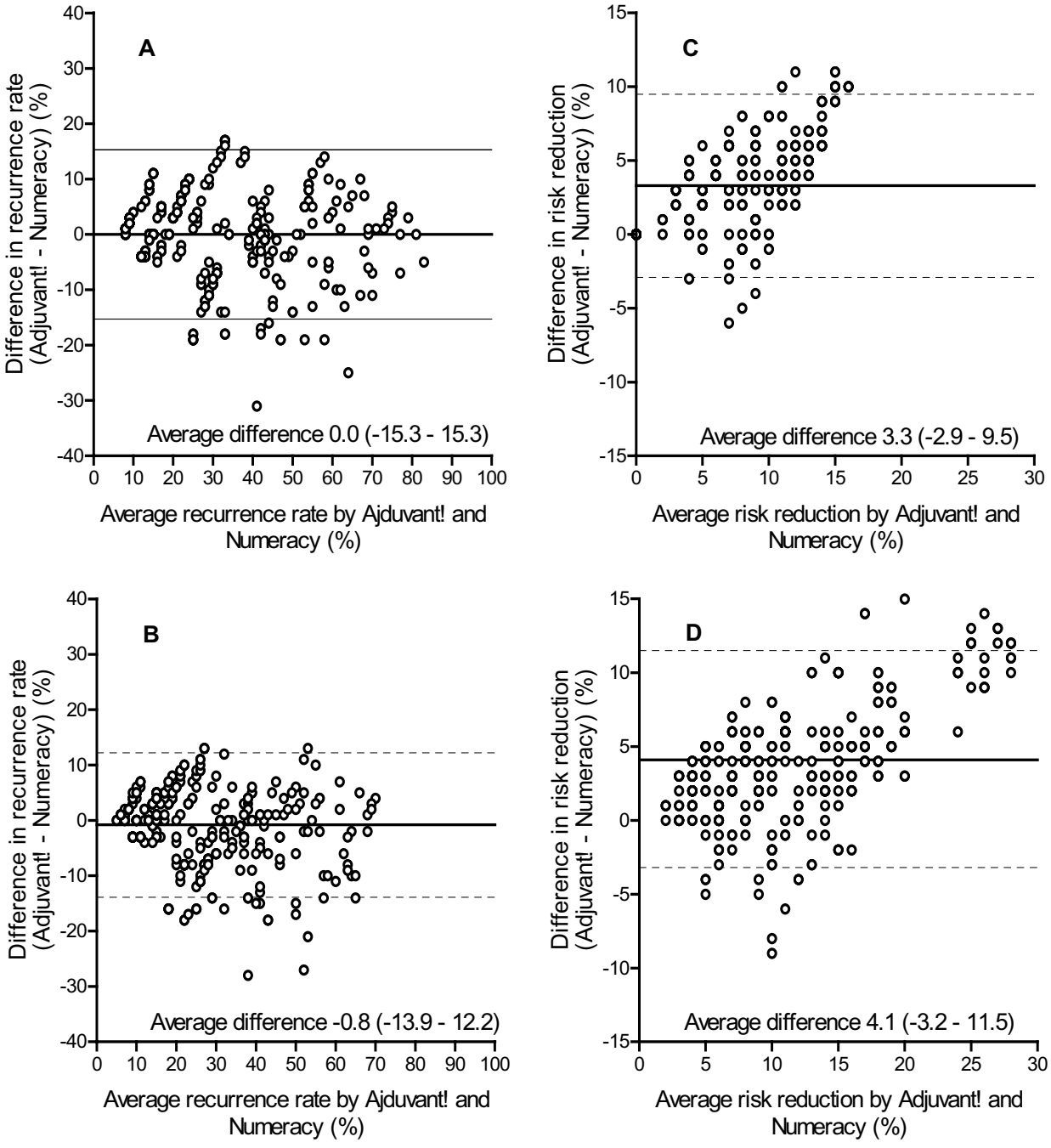
A major revision in the 2004 guideline is the advise to use, instead of AC or CMF, a more effective chemotherapy regimen comprising 5 cycles of fluorouracil, epirubicin, cyclophosphamide (FEC), or in certain cases 6 cycles of docetaxel, doxorubicin, cyclophosphamide (TAC). Treatment with TAC is advised 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 (C). And agreement between reductions in recurrence rate estimated with Adjuvant! and Numeracy for treatment with adjuvant tamoxifen (B), 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.

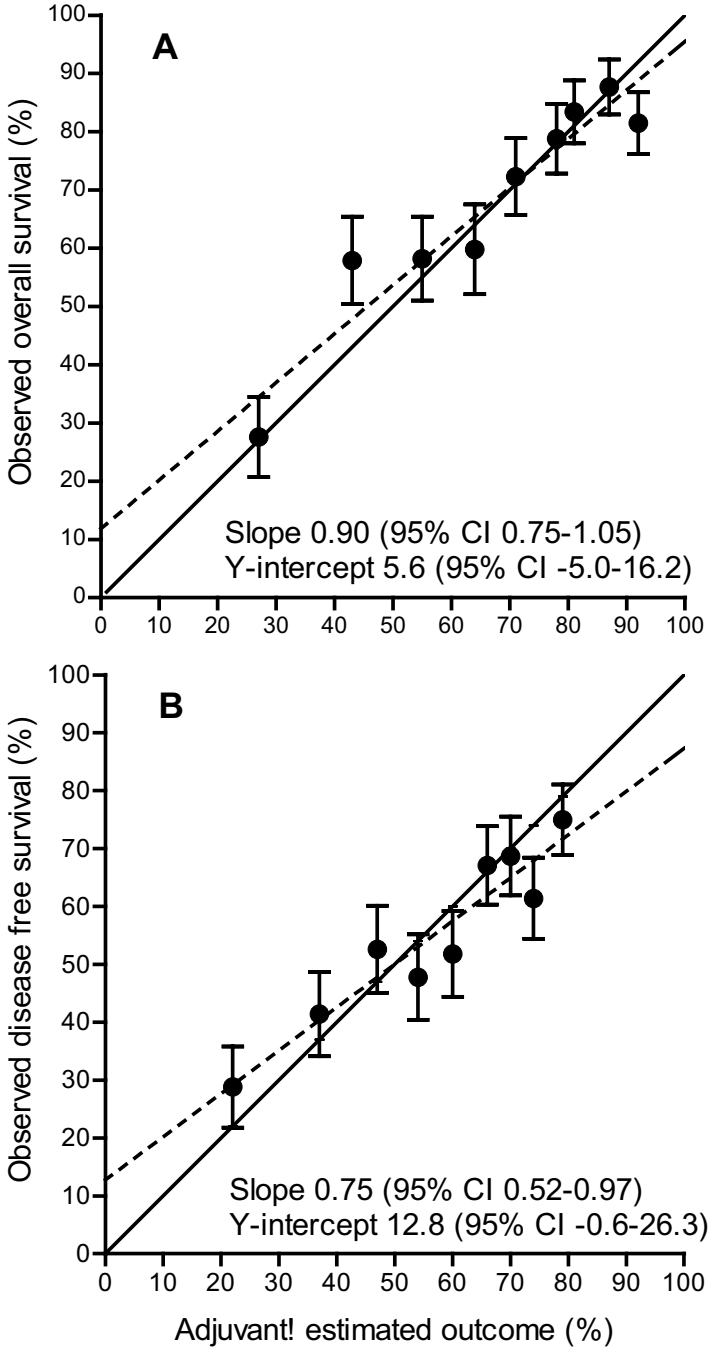
were significantly higher than observed DFI percentages for the entire cohort ($p<0.01$), for patients aged 50 years of less ($p<0.001$), with an oestrogen-receptor positive tumour ($p=0.01$), with a grade II or III tumour ($p<0.01$), with a tumour 2.0 cm or less in diameter ($p<0.01$), without positive 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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