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Long-term outcome prediction by clinicopathological risk classification algorithms in node-negative breast cancer—comparison between Adjuvant!, St Gallen, and a novel risk algorithm used in the prospective randomized Node-Negative-Breast Cancer-3 (NNBC-3) trial

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Background: Defining risk categories in breast cancer is of considerable clinical significance. We have developed a novel risk classification algorithm and compared its prognostic utility to the Web-based tool Adjuvant! and to the St Gallen risk classification.

Patients and methods: After a median follow-up of 10 years, we retrospectively analyzed 410 consecutive node-negative breast cancer patients who had not received adjuvant systemic therapy. High risk was defined by any of the following criteria: (i) age <35 years, (ii) grade 3, (iii) human epithelial growth factor receptor-2 positivity, (iv) vascular invasion, (v) progesterone receptor negativity, (vi) grade 2 tumors >2 cm. All patients were also characterized using Adjuvant! and the St Gallen 2007 risk categories. We analyzed disease-free survival (DFS) and overall survival (OS).

Results: The Node-Negative-Breast Cancer-3 (NNBC-3) algorithm enlarged the low-risk group to 37% as compared with Adjuvant! (17%) and St Gallen (18%), respectively. In multivariate analysis, both Adjuvant! [$P = 0.027$, hazard ratio (HR) 3.81, 96% confidence interval (CI) 1.16–12.47] and the NNBC-3 risk classification ($P = 0.049$, HR 1.95, 95% CI 1.00–3.81) significantly predicted OS, but only the NNBC-3 algorithm retained its prognostic significance in multivariate analysis for DFS ($P < 0.0005$).

Conclusion: The novel NNBC-3 risk algorithm is the only clinicopathological risk classification algorithm significantly predicting DFS as well as OS.

Key words: Adjuvant!, breast cancer, node-negative, prognosis, St Gallen

introduction

Adjuvant systemic therapy has greatly improved survival in early breast cancer [1]. This has led to consensus recommendations proposing adjuvant systemic therapy for virtually all breast cancer patients [2]. Yet, potential adverse effects of adjuvant therapy negatively affect quality of life [3, 4]. In order to avoid over- as well as undertreatment, it is still advisable to select the appropriate treatment strategy on the basis of careful risk assessment for each individual patient. Beyond any doubt, the single most important histopathological factor for risk stratification in primary breast cancer is nodal status [5–7]. More than two-thirds of patients with node-negative breast cancer (NNBC) are alive at 10 years even without adjuvant systemic therapy [5, 6]. In order to further predict outcome in NNBC patients, age, tumor size, estrogen receptor (ER) status, and histological grade are considered useful in differentiating between patients with an only minimal risk of recurrence and those who might still profit from adjuvant chemotherapy [5]. These 'traditional' prognostic

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factors are needed for outcome prediction in the Web-based tool 'Adjuvant!' [8] which has gained widespread acceptance over time. Another well-accepted method for assigning patients to different risk categories is the St Gallen risk classification [2]. However, a major concern regarding the St Gallen risk categories is that this risk classification fails to identify a sufficiently large enough number of node-negative patients as low risk. To circumvent this shortcoming, we developed a novel, modified risk algorithm that is being evaluated prospectively in the NNBC-3 trial [9, 10].

The present retrospective study compares the prognostic utility of these three different risk classification algorithms in a cohort of 410 NNBC patients who had not received any adjuvant systemic treatment.

patients and methods

Five hundred and seven patients underwent primary surgery for NNBC at the Department of Obstetrics and Gynecology of the Johannes Gutenberg University, Mainz, between the years 1985 and 2000. According to local guidelines at the time, none of these patients received any adjuvant systemic therapy. Of the total cohort, 32 carcinomas were excluded because of microinvasive growth ($pT1_{mic}$) only. Sixty-five patients were excluded for logistical reasons (no paraffin material or follow-up available). The final study cohort thus consisted of 410 consecutive NNBC patients with appropriate follow-up and available paraffin blocks. The tumor size (in mm) and the presence of peritumoral vascular invasion (PVI) were collected from the original pathology reports of the Gynecological Pathology Division.

Histologic grade was assigned according to Elston and Ellis [11] by two of the authors (MS and HAL) routinely involved in the histological diagnosis of breast cases in the Breast Cancer Center and unaware of the clinical outcome.

immunohistochemistry

Immunohistochemical analyses were carried out on 4-μm thick sections according to standard procedures as previously described in detail [12]. Briefly, serial sections of formalin-fixed and paraffin-embedded tumor tissues were stained with monoclonal ER antibodies (clone 1D5, Dako, Glostrup, Denmark), monoclonal progesterone receptor (PR) antibodies (clone PgR 636, Dako) as well as polyclonal human epithelial growth factor receptor (HER)-2 antibodies (A0485, Dako). HER-2 was scored from 0 to 3+ according to the well-published manufacturer's instructions. HER-2 3+ tumors were considered HER-2 positive. ER and PR expressions were analyzed as percentage of all tumor cells and any nuclear expression >0 was considered positive.

FISH

All HER-2 2+ cases were confirmed by FISH using a dual-color probe (DakoCytomation) containing a spectrum orange-labeled HER-2 gene (17q11.2-q12) probe and a spectrum green-labeled centromere control for chromosome 17 (17p11.1-q11.1). HER-2 tumors with 2+ HER-2 amplification were finally considered HER-2 positive.

Patients had been treated either with modified radical mastectomy ($n = 186$; 45%) or breast-conserving surgery followed by irradiation ($n = 224$; 55%). Median age of patients at diagnosis was 59 years (range 33–91 years). The retrospective study was approved by the ethical review board of the medical association of Rhineland-Palatinate.

The median follow-up time was 10 years. Fifty-five patients (13%) are known to have died of breast cancer and 111 patients (27%) to have relapsed. Fifty patients (12%) died of nonbreast cancer-related reasons. Patients in whom breast cancer could not definitely be ruled out as cause of death ($n = 5$) were considered as having died from breast cancer. The patients dying of reasons other than breast cancer were censored for the survival analyses at their date of death.

risk classification algorithms

St Gallen. The node-negative patients were allocated according the latest St Gallen risk classification [2] as follows: low-risk group was applicable if all the following features [$T_{1a–c}$, G 1, ER and/or PR expressed (positive), HER-2 neither expressed nor amplified (negative), absence of PVI, age ≥35] were present. If one of the above criteria was not met, patients were considered intermediate risk.

Adjuvant!. Adjuvant! (Standard version 8.0) was used to determine the predicted 10-year overall survival (OS) for all patients by one of the authors (MS) blinded to the actual clinical outcome. Patient age, tumor size, nodal status (by definition 0), ER status, and tumor grade were entered into the model for each patients and 10-year OS was calculated. The comorbidity assumption 'average for age' was used for the entire cohort as a default setting. To dichotomize the patients, we then used the cut-off point currently evaluated in the Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) trial [13]. A 10-year breast cancer survival possibility of at least 88% for ER-positive (>10% of tumor cells stained) and of at least 92% for ER-negative (<10% of tumor cells stained) carcinomas was selected as cut-off point.

NNBC-3. The NNBC-3 algorithm classifies node-negative patients with G III, HER-2 positivity, PR negativity (<10% of tumor cells stained), age <35, or PVI as high risk, if at least one of the features is present. If none of these well-established high-risk features is present, all patients with G 1 and tumor size $pT_{1a–c}$ or pT_2 as well as those patients with G 2 and tumor size $T_{1a–c}$ are classified as low risk [9, 10].

statistical analysis

Survival rates were calculated using the Kaplan–Meier method. Disease-free survival (DFS) was computed from the date of diagnosis to the date of disease recurrence or death from cancer if there was no earlier recurrence. Breast cancer-specific OS was computed from the date of diagnosis to the date of death from breast cancer. Patients who died of an unrelated cause were censored at the date of death. Cox regression analyses for survival were carried out, both considering each prognostic factor in univariate (each factor dichotomized to render a low/high-risk assessment) as well as in a forward stepwise multivariate fashion. In the stepwise models, a likelihood ratio test P value ≤0.05 was used as inclusion boundary.

Additionally, sensitivity and specificity for metastasis or death within 5 and 10 years, respectively, were calculated.

All P values are two sided. As no correction for multiple testing was carried out, these are descriptive measures.

results

distribution of prognostic factors

In this group of 410 node-negative primary breast cancer patients without adjuvant systemic treatment, established pathological and clinical parameters were assessed such as age, tumor size, histological grade, PVI, ER, PR, and HER-2 (Table 1).

Seventy-four (18%) of the patients were categorized as low-risk according to the St Gallen risk classification and 71 (17%) according to Adjuvant! online. The algorithm of the NNBC-3 study put 153 (37%) of the patients in the low-risk group. The remaining cases were categorized as intermediate or high risk.

Table 1. Clinicopathological characteristics of all patients ($n = 410$)

Characteristics	*n*	%
Age at diagnosis		
<50	114	28
>50	296	72
pT stage		
pT_1	268	65
pT_2 or pT_3	142	35
Histological grade		
G 1	105	26
G 2	223	54
G 3	82	20
ER		
Positive	314	77
Negative	96	23
PR		
Positive	282	69
Negative	128	31
HER-2		
Positive	59	14
Negative	351	86
PVI		
Yes	74	18
No	336	82
St Gallen 2007		
Low risk	74	18
Intermediate risk	336	82
Adjuvant! online		
Low risk	71	17
High risk	339	83
NNBC-3		
Low risk	153	37
High risk	257	63

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epithelial growth factor receptor-2; PVI, peritumoral vascular invasion; NNBC-3; node-negative breast cancer-3 algorithm.

breast cancer-specific DFS

prognostic factors. univariate analysis. Among the traditional prognostic factors, histological grade, PVI, HER-2 positivity as well as ER negativity had a significant influence on DFS. All results are listed in Table 2.

multivariate analysis. In a multivariate Cox regression analysis entering the traditional prognostic factors mentioned above in a forward fashion, only histological grade 3 versus <3 [$P < 0.0005$, hazard ratio (HR) 2.98, 95% confidence interval (CI) 2.02–4.40], PVI ($P = 0.019$, HR 1.68, 95% CI 1.09–2.58), and HER-2 positivity ($P = 0.016$, HR 1.75, 95% CI 1.11–2.77) showed significant impact on DFS.

risk classification algorithms. univariate analysis. The St Gallen 2007 risk classification was associated with DFS ($P = 0.002$, HR 3.27, 95% CI 1.52–7.03). Kaplan–Meier estimates showed that after 10 years 90% of the patients in the low-risk group were free of disease compared with only 68% in the intermediate-risk group (Figure 1A). Risk classification according to Adjuvant! did not predict DFS in our cohort of

Table 2. Univariate analysis for disease-free survival in all patients ($n = 410$)

Prognostic factors	*P*	Hazard ratio	95% confidence interval
Age (>50 versus ≤50)	0.373	1.20	0.81–1.78
T (>1 versus 1)	0.407	1.18	0.80–1.73
Histological grade			
>1 versus 1	0.001	2.74	1.54–4.89
3 versus <3	<0.0005	3.31	2.26–4.85
ER			
Negativity versus positivity	0.049	1.50	1.00–2.25
PR			
Negativity versus positivity	0.154	1.32	0.90–1.94
HER-2			
Positivity versus negativity	<0.005	2.26	1.46–3.49
PVI			
Positivity versus negativity	0.001	2.07	1.37–3.13
St Gallen 2007			
High- versus low risk	0.002	3.27	1.52–7.03
Adjuvant!			
High- versus low risk	0.103	1.60	0.91–2.80
NNBC			
High- versus low-risk	<0.005	2.47	1.55–3.95

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epithelial growth factor receptor-2; PVI, peritumoral vascular invasion; NNBC; node-negative breast cancer algorithm.

patients well ($P = 0.103$, HR 1.60, 95% CI 0.91–2.80). Eighty-two per cent of the low-risk group were free of disease after 10 years, compared with 70% of the high-risk group (Figure 1B). Conversely, the algorithm used for clinical risk assessment in the NNBC-3 trial significantly predicted DFS ($P < 0.0005$, HR 2.47, 95% CI 1.55–3.95). Eighty-six per cent of the low-risk patients were free of disease after 10 years, versus only 64% of the patients of the high-risk group (Figure 1C).

multivariate analysis. In forward multivariate analysis of these three risk classification models, only the NNBC-3 algorithm was entered into the model. Since the NNBC-3 algorithm was the only factor in the model, HR and *P* values remained the same as in univariate analysis.

breast cancer-specific OS

prognostic factors. univariate analysis. Among the prognostic factors, histological grade, PVI, and HER-2 were related to OS in univariate analysis. Neither age at diagnosis nor ER or PR expression had an important impact on OS (Table 3).

multivariate analysis. After the forward selection, only histological grade = 3 versus <3 ($P < 0.0005$, HR 4.17, 95% CI 2.50–6.97) and PVI ($P = 0.025$, HR 1.87, 95% CI 1.08–3.24) remained in the model as predictors of breast cancer-specific OS.

risk classification algorithms. univariate analysis. The St Gallen risk classification 2007 failed to predict OS in our cohort of

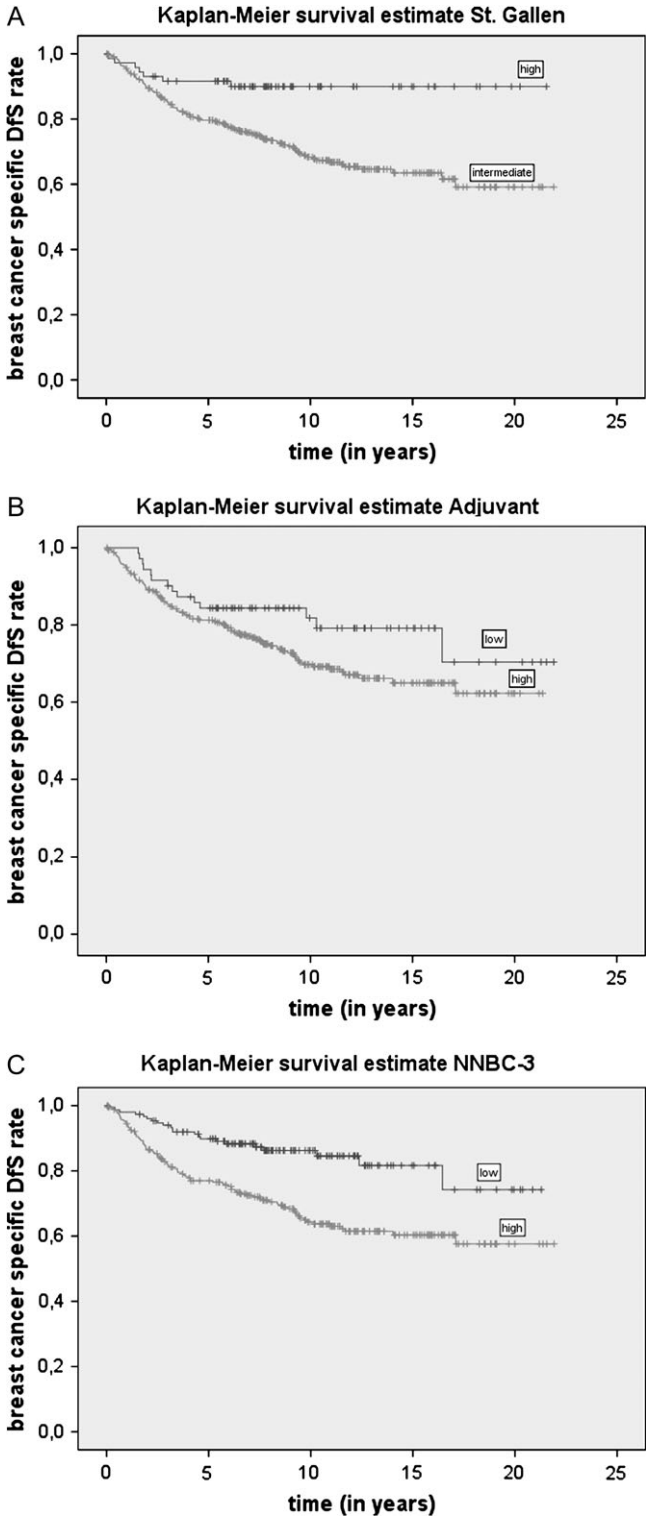

Figure 1. Prediction of disease-free survival in node-negative breast cancer patients ($n = 410$) using two established and a novel risk algorithm: (A) St Gallen 2007 risk classification, (B) Adjuvant! risk classification (C), and the novel node-negative-breast cancer-3 algorithm.

patients ($P = 0.156$, HR 1.84, 95% CI 0.79–4.29). According to Kaplan–Meier estimates, 92% of patients in the low-risk group versus 87% in the intermediate-risk group survived their breast cancer for 10 years (Figure 2A). In contrast, Adjuvant!

Table 3. Univariate analysis for breast cancer-specific overall survival in all patients ($n = 410$)

Prognostic factors	*P*	Hazard ratio	95% confidence interval
Age (>50 versus ≤50)	0.302	0.74	0.42–1.31
T (>1 versus 1)	0.509	1.19	0.71–2.00
Histological grade			
>1 versus 1	0.017	2.62	1.19–5.76
3 versus <3	<0.0005	4.37	2.62–7.30
ER			
Negativity versus positivity	0.095	1.57	0.93–2.67
PR			
Negativity versus positivity	0.341	1.29	0.77–2.16
HER-2			
Positivity versus negativity	0.043	1.85	1.02–3.37
PVI			
Positivity versus negativity	0.008	2.11	1.22–3.64
St Gallen 2007			
High versus low risk	0.156	1.84	0.79–4.29
Adjuvant!			
High versus low risk	0.008	4.84	1.51–15.52
NNBC			
High versus low risk	0.007	2.48	1.29–4.78

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epithelial growth factor receptor-2; PVI, peritumoral vascular invasion; NNBC; node-negative breast cancer algorithm.

predicted breast cancer-specific OS more accurately ($P = 0.008$, HR 4.84, 95% CI 1.51–15.52). Ninety-seven per cent of the patients in the low-risk group survived their breast cancer for 10 years compared with only 86% in the high-risk group (Figure 2B). Similarly, the NNBC-3 algorithm predicted OS well ($P = 0.007$, HR 2.48, 95% CI 1.29–4.78): 94% of the low-risk patients as compared with only 84% of the patients allocated to the high-risk group survived at 10 years (Figure 2C).

multivariate analysis. Only the two risk classification algorithms according to Adjuvant! utilizing the cut-off point used in the MINDACT trial ($P = 0.027$, HR 3.81, 95% CI 1.16–12.47) and the one used in the NNBC-3 trial ($P = 0.049$, HR 1.95, 95% CI 1.00–3.81) were selected in a forward multivariate model. Thus, both add relevant information regarding OS. However, the risk classification according to St Gallen 2007 did not seem to have a strong predictive effect regarding OS.

sensitivity and specificity for the metastasis occurrence or death within 5 and 10 years, respectively

As shown in Table 4, the NNBC-3 risk classification showed lower sensitivity compared with St Gallen and Adjuvant!; however, it has greater specificity than the other two algorithms when predicting either metastasis or tumor-related death within the first 5 or 10 years after diagnosis.

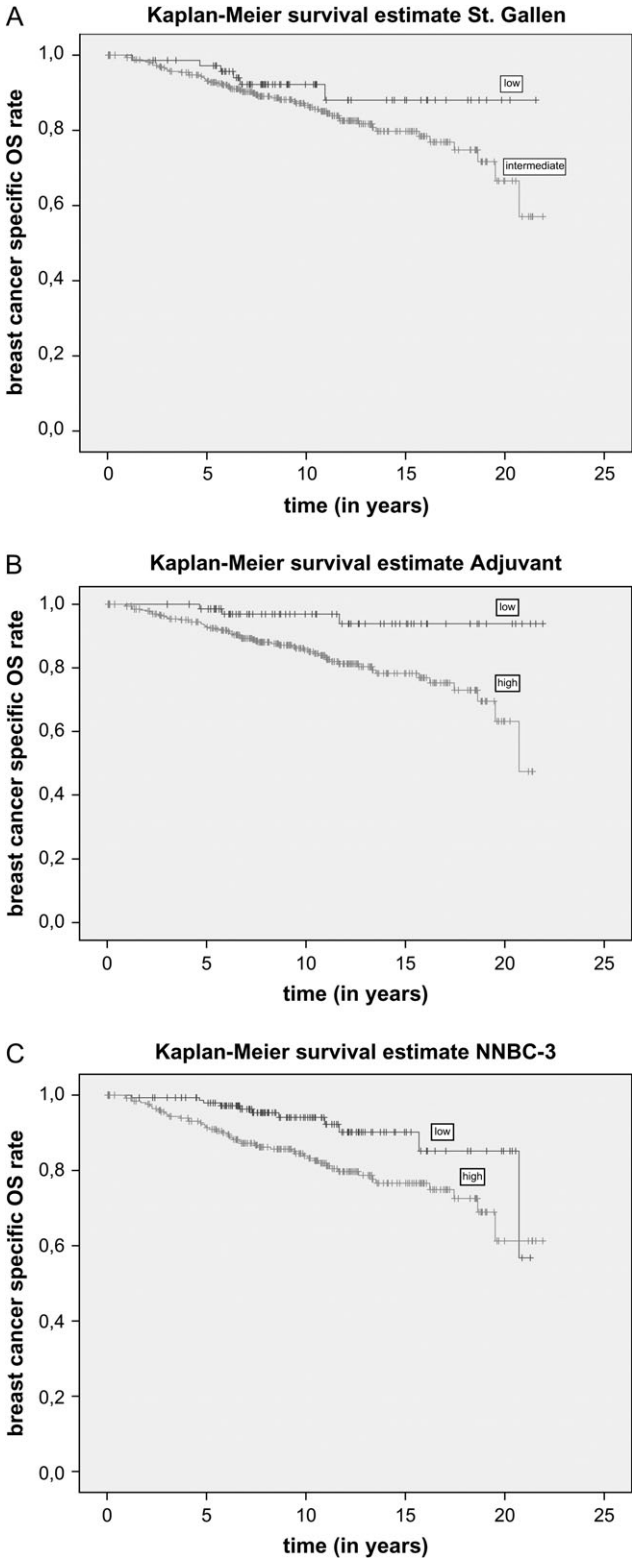

Figure 2. Prediction of breast cancer-specific overall survival in node-negative breast cancer patients ($n = 410$) using two established and a novel risk algorithm: (A) St Gallen 2007 risk classification, (B) Adjuvant! risk classification, and (C) the novel node-negative-breast cancer-3 algorithm.

discussion

The premise 'first—select the target' [14] is the current paradigm for selecting adjuvant therapy in breast cancer. However, assessment of individual risk is also of crucial importance when advising patients to undergo adjuvant therapy. Since single prognostic factors alone are not sufficient for proper risk assessment, combinations of several clinicopathological prognostic factors are currently used for clinical decision making.

In Europe, the most commonly used risk classification algorithm is the St Gallen risk stratification which is updated regularly after each biannual St Gallen consensus meeting.

In recent years, several studies have validated the St Gallen risk categories. Applying the 1998 risk classification to Japanese patients with NNBC allocated only 3% to the minimal/low-risk group [15] as compared with 10% of the Australian patients [16]. Even though the Australian patients had a 10-year distant relapse-free survival of 100%, the authors argued that an algorithm is useless if it spares chemotherapy only for a small fraction of NNBC patients. A subsequent analysis of the 2001 St Gallen classification by the same group of authors classified more patients as low risk with a 10-year distant DFS of 97%. In addition, they were able to increase the percentage of low-risk patients substantially to 41%, with a comparably excellent clinical outcome, when also classifying G 2 tumors with a maximum diameter of 15 mm as low risk [17].

Another validation of the 2001 risk classification in a cohort of Spanish patients showed a significant separation between high- and low risk, but again classified only 14% as low risk [18]. Similarly, Otsuki et al. [19] investigated the 2003 modification of the St Gallen risk classification and found a statistically significant separation of node-negative cases between minimal and average risk regarding DFS. However, they also noticed that only 17% of patients were classified as minimal risk and were therefore candidates for being spared chemotherapy.

In Korean patients with NNBC, only 4% were assigned to the minimal risk group when applying the strict St Gallen criteria of the 2003 consensus [20]. However, when the authors assigned patients with G 2 tumors who had no additional risk factors (for instance a tumor size >20 mm) to the minimal risk group instead of the average risk group, they could substantially increase the number of patients in the minimal risk group with still excellent long-term outcome. This approach prompted us to develop our more elaborated risk algorithm which is also used in the prospectively randomized NNBC-3 trial. Here, G 2 carcinomas without any other risk factors (like LVI or HER-2 positivity) are considered high risk only if tumors measure >20 mm in diameter. It is hence comprehensible that this novel algorithm categorizes substantially more patients in the low-risk category. This resolves a major concern of the St Gallen risk category that this risk classification fails to identify a sufficiently important number of node-negative patients as low risk, which is ever so ironic as the majority of NNBC patients are cured by locoregional therapy alone.

The clinical need for more accurate risk classification in NNBC has led to the investigation of a plethora of novel

Table 4. Sensitivity and specificity for metastasis or death within 5 and 10 years

Prognostic factors	Metastasis or death within 5 years (49 of 377)		Metastasis or death within 10 years (71 of 251)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
St Gallen 2007	94	20	93	15
Adjuvant!	92	20	92	19
NNBC	84	41	85	33

NNBC; node-negative breast cancer algorithm.

prognostic markers. Among those, only urokinase-type plasminogen activator (u-PA) and plasminogen activator inhibitor type-1 (PAI-1) have been validated prospectively in a randomized clinical trial [21]. In recent years, the prognostic impact of microarray-based gene expression analysis received great attention in NNBC [22–24], but their relevance for routine patient management remains to be confirmed.

Microarray-based gene expression analysis as well as u-PA/PAI-1 have recently been put forward for clinical routine use in the American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer [25]. They are currently prospectively investigated in randomized trials in NNBC, the NNBC-3 trial [10], the TailorX [26], as well as the MINDACT trial [13]. Since two of these trials, MINDACT and NNBC-3, also use clinical risk classification in addition to the tumor biological assessment, we realized the need to compare the prognostic impact of three widely used clinical risk classification algorithms.

We found that the NNBC-3 algorithm more than doubled the number of patients classified low risk (37%) as compared with the St Gallen risk classification (18%) or Adjuvant! (17%) with slightly lower sensitivity but considerably higher specificity. The percentage of low-risk patients according to the current 2007 St Gallen classification is within the expected range. DFS was predicted only in univariate analysis by the St Gallen risk categorization. However, in a multivariate model, the NNBC-3 risk algorithm predicted DFS more accurately. Furthermore, breast cancer-specific OS was not predicted by the St Gallen risk classification.

In spite of the widespread acceptance of Adjuvant! it is surprising that only very few studies have as yet tried to validate this Web-based prognostic tool. Olivotto et al. [27] stated that Adjuvant! carried out reliably in a cohort of 4083 breast cancer patients from British Columbia when adjusting for certain risk factors. Euler et al. [28] showed that Adjuvant! rather accurately predicted 10-year DFS and OS for NNBC patients from a randomized prospective trail run mostly in Germany. However, when risk group assessment was based on uPA and PAI-1, Adjuvant! overestimated risk in the low-risk group and underestimated risk in the high-risk group which would have again led to overtreatment of actually low-risk node-negative patients. Conversely, Buyse et al. [24] failed to show a significant association with DFS or OS, when applying the same strict survival probability cut-off point to the Adjuvant! estimates that will be used in the MINDACT trial. In our present study, this very same cut-off point led to an excellent breast cancer-specific OS of 97% for the low-risk group, but failed to render a significant prediction of DFS. One has to keep in mind, however, that this survival probability cut-off used in the MINDACT trial is based on OS prediction. Adjuvant! also delivers prognostic probabilities for DFS. Using these estimates, the predictive accuracy of Adjuvant! might have been more accurate for DFS.

In summary, the NNBC-3 algorithm turned out to be the only risk classification in our cohort of >400 NNBC patients that independently predicted DFS as well as OS, with a breast cancer-specific 10-year OS of 94%. If our results will be confirmed prospectively in the current NNBC-3 trial, this algorithm might prove to be a valuable tool for clinical risk classification of NNBC patients superior to previously established clinical risk classification algorithms. In addition, NNBC-3 will reveal prospectively how an optimal clinical risk classification algorithm rates compared with tumor biological risk group classification, in this case using uPA/PAI-1.

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