Disqualification of Neoadjuvant Rectal Score Based on Data of 6596 Patients From the Netherlands Cancer Registry

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Abstract

We aimed to validate the neoadjuvant rectal score (NAR) using data of 6596 patients from the Netherlands Cancer Registry. We found that the prognostic value of the NAR score was inferior to a simple regression model with the factors clinical tumor stage, pathologic tumor, and nodal stage. Therefore, we advise against using the NAR score as a surrogate endpoint.

Background: The neoadjuvant rectal score (NAR) was developed as a surrogate endpoint for overall survival in patients with rectal cancer after neoadjuvant treatment. We aimed to validate the NAR score in patients from the Netherlands Cancer Registry database. **Patients and Methods:** We studied patients with rectal cancer treated with long-course neoadjuvant therapy followed by surgery in the Netherlands between 2007 and 2014. The probability of concordance with overall survival and the goodness of fit of several models were evaluated using Harrell's concordance index (*c* index) and the Akaike information criterion (AIC), which is used to compare the quality of statistical models. **Results:** The NAR score resulted in a *c* index of 0.665. We found that single pathologic parameters (pT or pN) have similar concordance as the NAR formula (*c* index of 0.663 and 0.655, respectively). A combination of pT and pN resulted in better concordance with the true endpoint, overall survival (*c* index 0.684), and a simple Cox regression model with the 3 parameters included in the NAR formula (cT, pT, and pN) improved the concordance even more (*c* index 0.689). When the AIC index was compared for all models, the NAR score model showed the worst fit to the true endpoint. **Conclusion:** We found no additional value for using the NAR formula as a surrogate endpoint for overall survival in rectal cancer patients treated with neoadjuvant therapy.

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Introduction

Rectal cancer treatment has evolved over the last decades. Total mesorectal excision surgery is still the standard of care for invasive rectal cancer, and the implementation of preoperative (chemo) radiotherapy has led to a significant improvement in local control.[1]

While adjuvant chemotherapy can be beneficial for colon cancer, there is no evidence of a survival benefit of adjuvant treatment for patients with rectal cancer. Moreover, the compliance of postoperative chemotherapy in patients recovering from major surgery is low. Therefore, neoadjuvant treatment has become the standard of care for locally advanced rectal cancer. Multiple ongoing clinical trials are now focusing on improving neoadjuvant treatment protocols; the Rapido trial[2] and the Prospect trial (ClinicalTrials.gov, NCT01515787) are examples.

Although the true clinical benefit of neoadjuvant treatment should be expressed in terms of improved survival, the use of overall survival or disease-free survival as primary endpoints in clinical trials can be challenging. For neoadjuvant treatment in patients treated with curative intent, a clinically relevant treatment effect will only be visible in 3- or 5-year survival rates. As multiple years of follow-up are required, financial and practical issues are not uncommon. More important, the use of 3- or 5-year overall survival as a primary

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endpoint is also undesirable for ethical reasons because it may delay implementation of new treatment protocols. For these reasons, there is a need for an outcome measurement that is readily available after neoadjuvant treatment and that can act as a surrogate for long-term prognosis in terms of survival.

The use of surrogate endpoints enables clinicians and researchers to use initial clinical and pathologic data to predict long-term outcome parameters such as overall survival and disease-free survival. A short-term clinical trial surrogate endpoint, the neoadjuvant rectal score (NAR), was developed by George et al.[3] This score is based on the Valentini nomogram to predict overall survival in rectal cancer patients after neoadjuvant treatment.[4] The score, a number ranging from 0 to 100, indicates poorer prognosis when closer to 100. The NAR formula includes the clinical tumor (cT) stage, pathologic tumor (pT), and node (pN) stage according to the tumor, node, metastasis classification system for colorectal cancers (Figure 1).

It was our primary objective to validate the NAR score using data of 6596 patients from the Netherlands Cancer Registry (NCR) database. Second, we aimed to investigate the prognostic value of the NAR score specifically in patients with a pathologic complete response after neoadjuvant therapy.

Patients and Methods

Data were acquired in an anonymized data set from the Netherlands Cancer Registry (NCR or IKNL), the Dutch quality institute for oncologic and palliative research and practice, which covers data collection of > 95% of all cancer patients within the Netherlands. For the present study, all patients diagnosed with rectal cancer and treated with neoadjuvant therapy between 2007 and 2014 were included. Patients treated with short-term radiotherapy followed by immediate surgery were excluded from this study, as no tumor downstaging is expected in these patients. Patients diagnosed with synchronous distant metastasis (stage IV) or in whom the tumor stage was unknown were excluded. The database included data on age, gender, type of neoadjuvant therapy, duration of neoadjuvant therapy, clinical and pathologic tumor stage, date of last follow-up, and survival status.

Definitions

For each subject, the NAR score was calculated as suggested by George et al[3] (Figure 1). In this formula, pN can range from 0 to 2; cT from 0 to 4; and pT from 0 to 4. As previously suggested, the data were categorized in 3 risk groups on the basis of the NAR score as low (NAR < 8), intermediate (NAR 8-16), or high risk (NAR > 16).[3] A subgroup analysis was performed in patients with pathologic complete response (ypT0N0). Categorical variables were presented as frequencies and percentages, and numerical variables as mean and standard deviation or median and interquartile range based on distribution.

Statistical Analysis

Statistical analysis was performed by SPSS 23 software (IBM, Armonk, NY) and the software package R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). Differences in baseline characteristics between patients were tested by the Pearson chi-square test for categorical data and the Kruskal-Wallis test for continuous data. Median follow-up was calculated using the reverse Kaplan-Meier method. Survival analysis was performed using Kaplan-Meier methods, and a log-rank test was used to test the differences between NAR categories.

Figure 1 NAR Score Formula

$$\mathrm{NAR} = \frac{[5pN - 3(cT - pT) + 12]^2}{9.61}$$

Abbreviations: cT = clinical tumor stage; NAR = neoadjuvant rectal score; pN = pathologic lymph node stage; pT = pathologic tumor stage.

Cox proportional hazard models were used to calculate hazard ratios for the single elements of the NAR formula (cT, pT, and pN). Subsequently, combinations of these factors were tested. Harrell's concordance index (*c* index) was calculated to assess the probability of concordance between the observed and the predicted outcome. A higher *c* index corresponds to better discrimination. The Akaike information criterion (AIC) was used to assess the goodness of fit of the model on the database, where lower values indicate better fit. The bootstrap method was used to obtain 95% confidence intervals of the differences between *c* indices of different models, using 999 resamples. $P < .05$ was considered statistically significant.

An exploratory subgroup analysis was performed comparing the outcomes in 2 historical subgroups (2007-2010 and 2011-2014, respectively) to investigate whether our results were influenced by changes in patient selection for chemoradiotherapy over the years.

Results

Patients

Data from 18,275 patients were retrieved from the NCR, 6596 of which met the inclusion criteria. The final database included 178 patients (2.7%) with stage I disease, 1393 patients (21.1%) with stage II disease, and 5025 patients (76.2%) with stage III disease (Table 1). NAR scores were calculated, and on the basis of the NAR formula, patients were categorized into low-, intermediate-, and high-risk categories. Overall, the mean ± standard deviation age was 64 ± 10.2 years. The median follow-up period was 5.33 (interquartile range, 3.69-7.27) years. The duration of follow-up was longer in the intermediate and high NAR category (median 5.17 years in the low NAR category, 5.35 years in intermediate, and 5.43 years in high).

Survival Predictions

The observed 5-year overall survival in this patient cohort was 75%. The intermediate and high NAR score categories were associated with worse overall survival compared to the low NAR score category ($P < .001$). Five-year overall survival was 86%, 76%, and 60.1% for the low, intermediate, and high NAR categories respectively. Multivariate analysis showed similar results (Table 2). cT, pT, and pN were tested as continuous and categorical variables. As these showed similar results, only the results of Cox regression analysis with continuous variables are shown.

Table 1 Patient Characteristics

Characteristic	Variable	Value
Age	Mean (SD)	64 (10.2)
Gender	Male	4186 (63.5%)
	Female	2410 (36.5%)
Follow-up (years)	Median (interquartile range)	5.33 (3.69-7.27)
cT	0-1	43 (0.7%)
	2	655 (9.9%)
	3	4651 (70.5%)
	4	1247 (18.9%)
cN	0	1243 (18.8%)
	1	2404 (36.5%)
	2	2290 (34.7%)
	Missing	659 (10.0%)
pT	0	1175 (17.8%)
	1	409 (6.2%)
	2	1742 (26.4%)
	3	2915 (44.2%)
	4	355 (5.4%)
pN	0	4594 (69.6%)
	1	1858 (28.2%)
	2	144 (2.2%)

Abbreviations: cN = clinical lymph node stage; cT = clinical tumor stage; pN = pathologic lymph node stage; pT = pathologic tumor stage.

Model Comparison

The concordance (*c* index) of the original NAR score model and overall survival (adjusted for age and gender) was 0.665 (Table 2). First, we compared this to the separate elements used in the NAR score, pathologic T and N stage (*c* indices 0.663 and 0.655, respectively), and clinical T stage (*c* index 0.615). Second, the NAR model was compared to a simple Cox proportional hazards regression model including only pathologic parameters (pT and pN, hereafter referred to as the pathologic model), which resulted in a *c* index of 0.684. Finally, the NAR score model was compared to a combined Cox proportional hazards regression model including cT, pT, and pN stage as continuous variables, without any mathematical terms (hereafter referred to as the combined model). This resulted in the highest *c* index (0.689). The superior correlation to overall survival of this model compared to the NAR model is visualized in Figure 2. In the Kaplan-Meier curves, overall survival is plotted for tertiles representing the highest, intermediate, and lowest score as proposed by George et al[3] (Figure 2A). Figure 2B shows overall survival in tertiles with highest, intermediate, and lowest score according to the combined model.

For the NAR formula, the pathologic model, and the combined model, the AIC index was calculated (Table 2). Because lower values indicate better fit of the model to the true endpoint (overall survival), the NAR score showed the worst fit to the true endpoint.

Bootstrapping of 999 resamples indicated that the combined and the pathologic model were, both without exception, superior to the NAR score model in predicting overall survival, with a mean difference in *c* index of 0.020 (95% confidence interval, 0.014-0.024) for the pathologic model and 0.025 (95% confidence interval, 0.017-0.032) for the combined model. Because all 999 resamples found both models to be superior than the NAR formula, this can be interpreted as a statistically significant difference of $P < .001$.

An exploratory subgroup analysis was performed comparing patients included in the 2007-2010 cohort with patients in the 2011-2014 cohort. The second group included relatively more patients with cT3 tumors (74% vs. 66%) and more patients with cN2 disease at baseline (21% vs. 45%, respectively). In both subgroups, the NAR formula showed the lowest *c* index and the highest AIC compared to the pathologic model and the combined model, indicating the worst fit to the endpoint of overall survival.

Pathologic Complete Response

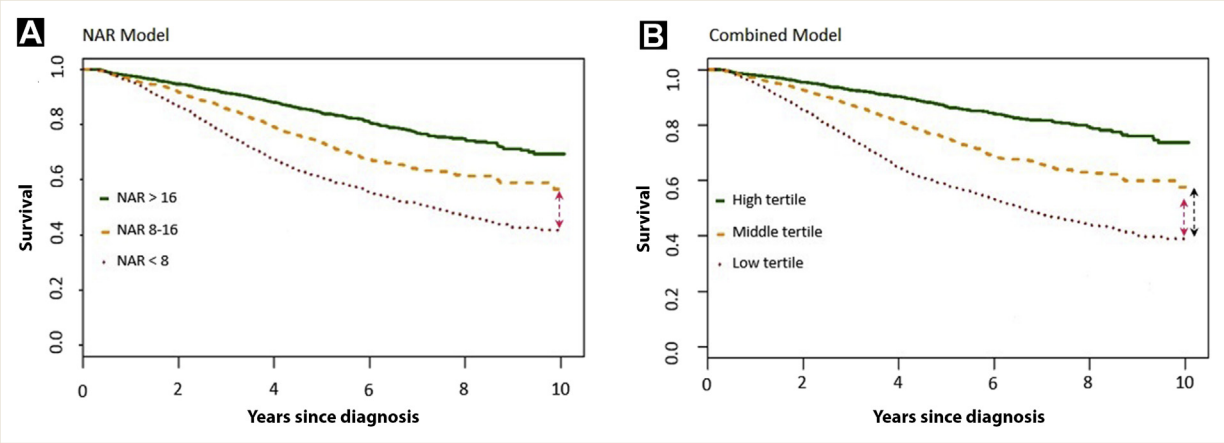
A pathologic complete response (pCR) of the tumor (ypT0N0) was seen in 1071 patients in the database (16%). Of these, 12.1% were diagnosed with a cT4 tumor, 74.3% with cT3 tumor, and 13.5% with cT2 or smaller tumors. All except 9 patients had a NAR score of < 8 (low risk). These 9 patients were categorized as intermediate risk (0.8%, NAR 8-16) and were all diagnosed with cT1 or cT0 tumors. In pCR patients, no difference in survival was detected between the low and intermediate NAR categories

Table 2 Overview of HR (Univariate and Multivariate Cox Regression) and Quantitative Measurements of Models for Their Concordance With Overall Survival

	Univariate Analysis			Cox Regression Analysis				
Factor	HR	95% CI	*P*	HR	95% CI	*P*	AIC[a]	*C* Index[a]
Age	1.034	1.029-1.039	<.001	1.035	1.030-1.041	<.001		
Gender	1.112	1.017-1.238	.021	1.277	1.157-1.411	<.001		
cT	1.511	1.388-1.644	<.001	1.488	1.270-1.743	<.001		0.615
pN	1.996	1.846-2.158	<.001	1.398	1.048-1.866	.023		0.655
pT	1.574	1.498-1.654	<.001	1.273	1.130-1.433	<.001		0.663
NAR score	1.035	1.032-1.039	<.001	1.016	0.998-1.035	.081	28571.48	0.665
pT and pN (pathologic model)							28386.63	0.684
cT, pT, and pN (combined model)							28349.32	0.689

Abbreviations: AIC = Akaike information criterion; CI = confidence interval; *c* index = Harrell concordance index; cT = clinical tumor stage; HR = hazard ratio; NAR = neoadjuvant rectal score; pN = pathologic lymph node stage; pT = pathologic tumor stage.
[a]All models included age and gender as variables.

Figure 2 Overall Survival According to 3 Categories of the NAR Formula (A), and Combined Model (B). (A) Green, Orange, and Red Lines Represent Low (NAR < 8), Intermediate (NAR 8-16), and High (> 16) Risk Categories, Respectively. (B) Data are Divided Into Tertiles Based on Outcome of the Combined Model



Abbreviation: NAR = neoadjuvant rectal score.

($P = .874$). No patients were categorized as having a high NAR score because this is not possible when pT and pN equal zero in the formula.

Discussion

In this study, we intended to validate the NAR score as a surrogate endpoint for overall survival using data from the NCR.[3] We confirmed that the 3 proposed NAR score categories correlate to overall survival. However, when using only pT or pN, we found similar *c* indices as for the NAR formula. Moreover, using a simple Cox regression model including only pathologic data (pT and pN), we found a better correlation with overall survival (*c* index 0.684 vs. 0.665 for the NAR formula). Finally, when using cT, pT, and pN together in a Cox regression model as continuous variables, we found a much better correlation (*c* index 0.689 vs. 0.665) and a lower AIC (28,349.32 vs. 28,571.48). On the basis of these results, we concluded that the combined model provides superior prognostic information compared to the NAR formula. It seems that the mathematical terms and relative weights not only unnecessarily complicate the NAR formula for use in clinical practice, but also degrade the correlation to the true endpoint overall survival.

For implementation of a meaningful surrogate endpoint, there are 2 criteria to which the surrogate endpoint must comply.[5] First, the surrogate endpoint must correlate to the true endpoint. Second, a correlation between treatment effect on the surrogate endpoint and treatment effect on the true endpoint should be confirmed. George et al[3] described the found correlation between the surrogate endpoint and the true endpoint, but omitted evaluating the correlation between the treatment effect on the surrogate endpoint (NAR) and the treatment effect on the true endpoint (overall survival). In other words, overall survival in patients with tumor downstaging should have been compared to overall survival in patients without tumor downstaging (eg, in whom no neoadjuvant treatment was applied).

Considering the NAR score formula, a few aspects remain unclear. First, the reasoning behind the stratification into specifically 3 risk categories is not defined. Second, the given relative weights used for the elements in the NAR score lack specific reasoning. Finally, the NAR formula follows the assumption that the prognosis gets better with more tumor regression independent of the clinical tumor stage at diagnosis (cT).

This last assumption was not tested by the developers of the formula, and its ambivalence becomes clearer in the subgroup analysis of the validity of the NAR formula in pCR patients. Because pT and pN equal 0 in pCR patients, the score is purely based on the clinical T stage, and the NAR formula results in higher scores with lower cT stages (Figure 1). This would indicate that pCRs of smaller tumors have worse prognosis than pCRs from larger tumors. For example, patients with initial cT2 tumors that show complete tumor regression have a worse prognosis, according to the NAR score, than initial cT3-4 tumors with complete tumor regression. However, the contrary is generally accepted in patients with a clinical complete response who were treated with a watch and wait approach: smaller tumors are associated with lower rates of tumor regrowth and better overall survival.[6] Our data included 9 patients with a pCR who were diagnosed with early tumors at diagnosis (cT0-1); these were all categorized as having an intermediate NAR score but showed excellent 5-year overall survival (88%).

Furthermore, as organ-preserving strategies such as watch and wait in patients with clinical complete response are gaining interest, development of a surrogate endpoint for overall survival that does not include pathologic tumor stage is highly desirable.

Following the original publication by George et al,[3] several studies have been published on validation of the score, which are summarized in Table 3. All studies agree on the NAR score's being significantly correlated with overall survival or disease-free survival. As expected, the Valentini nomogram remains preferred over the NAR score because it incorporates more clinical variables and thus results in

Table 3 Overview of Literature

Study	No. of Patients	Findings
Yothers (2014),[7] George (2015)[3]	1479	NAR categories were significantly correlated with 5-year OS.
		Continuous NAR score showed better correlation with OS than pCR.
		Continuous NAR score showed lower AIC than pCR.
Raissouni (2014)[8]	1172	NAR categories significantly correlated with 5-year OS.
		NAR score showed lower AIC index than pCR for OS.
Hong (2014)[9]	111	Higher NAR score was associated with worse DFS.
Weiner (2014)[10]	80	Mean NAR score was significantly higher in patients who developed recurrent rectal cancer compared to recurrence-free patients.
Roy (2016)[11]	706	Mean NAR score was significantly higher in patients who developed recurrent rectal cancer compared to recurrence-free patients.
		NAR formula showed stronger correlation with DFS and OS than pCR.
Yothers (2016)[12]	4705	NAR score showed better prognostic value for OS than pCR.
Sun (2017)[13]	522	NAR score categories significantly correlated with DFS.
		Higher NAR scores were associated with fewer pCR, lower TRG, and higher ypTNM stage.
		Novel nomogram showed a *c* index of 0.701.
Rosello (2017)[14]	158	NAR score and VPN correlated with OS.
This study	6596	Comparison of 3 models indicated that NAR formula had worse correlation to OS than simpler regression models (*c* index 0.665 vs. 0.689; AIC 28,571 vs. 28,349).

All patients included in studies received neoadjuvant treatment followed by total mesorectal excision.
Abbreviations: AIC = Akaike information criterion; *c* index = Harrell concordance index; DFS = disease-free survival; NAR = neoadjuvant rectal score; OS = overall survival; pCR = pathologic complete response; TRG = tumor regression grade; VPN = Valentini prediction nomogram; ypTNM = pathologic tumor, node, metastasis status.

better prognostic information. Interestingly, none of these studies has evaluated the correlation between the treatment effect on the surrogate endpoint and the treatment effect on the true endpoint. It is commonly accepted that the threshold for a strong model is a *c* index of > 0.8. None of the studies on the NAR score, including the present study, has found a *c* index exceeding this threshold.

Limitations

Data for this study were assembled by a national data institution. Although regular quality checks are performed, entry errors might have occurred. The database did not contain detailed information on patient factors such as comorbidity or medical history, and details of neoadjuvant therapy schedules were not specified. This could potentially have biased our results. Furthermore, this study only included patients treated with long-course chemoradiotherapy, possibly leading to heterogeneity in the study population over the years and treatment allocation bias. Last, we had no data on disease-related events such as local recurrence and distant metastasis. Because treatment for recurrent disease has improved over the last years, it is possible that this influenced our results. An exploratory subgroup analysis confirmed that despite variety in the historical data and expected improvements in the selection of high-risk patients and the treatment of recurrent disease, the NAR score remained invalid as a surrogate endpoint in this population.

Conclusion

There is a need for a surrogate endpoint for patients with rectal cancer treated with neoadjuvant therapy. However, the NAR score is insufficient as a surrogate endpoint; simpler Cox regression models using the same variables provide a more precise correlation to overall survival. We therefore advise against using the NAR score as a clinical surrogate endpoint in clinical trials.

Clinical Practice Points

- There is an urgent need for surrogate endpoints for survival in rectal cancer trials, as the use of 3- or 5-year survival is undesirable for ethical, practical, and financial reasons.
- The NAR score was developed as a surrogate endpoint for overall survival in patients with rectal cancer treated with neoadjuvant treatment followed by surgery using cT, pT, and pN tumor stage.
- Although several validation studies have been performed, none has formally evaluated the correlation between the treatment effect on the surrogate endpoint and the treatment effect on the true endpoint.
- In this study, we found that the prognostic value of the NAR score was inferior to simple regression models.
- Considering these results, we advise against using the NAR score as a surrogate endpoint in clinical trials.

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Disclosure

The authors have stated that they have no conflict of interest.

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