Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

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To cite this article: Marinde J. G. Bond, Patricia A. H. Hamers, Geraldine R. Vink, Wilhelmina M. U. van Grevenstein, Miangela M. Laclé, Maarten van Smeden, Miriam Koopman, Jeanine M. L. Roodhart, Cornelis J. A. Punt & Anne M. May (2022) External validation of the MSKCC nomogram to estimate five-year overall survival after surgery for stage I–III colon cancer in a Dutch population, Acta Oncologica, 61:5, 560-565, DOI: 10.1080/0284186X.2022.2044514

To link to this article: https://doi.org/10.1080/0284186X.2022.2044514

ACTA ONCOLOGICA
2022, VOL. 61, NO. 5, 560–565
https://doi.org/10.1080/0284186X.2022.2044514

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ORIGINAL ARTICLE

External validation of the MSKCC nomogram to estimate five-year overall survival after surgery for stage I–III colon cancer in a Dutch population

Marinde J. G. Bond[a]*, Patricia A. H. Hamers[b]*, Geraldine R. Vink[b,c], Wilhelmina M. U. van Grevenstein[d], Miangela M. Laclé[e], Maarten van Smeden[a], Miriam Koopman[b], Jeanine M. L. Roodhart[b], Cornelis J. A. Punt[a] and Anne M. May[a]

[a]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [b]Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [c]Department of Research and Development, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands; [d]Department of Surgical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [e]Department of Pathology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

ABSTRACT

Introduction: The Memorial Sloan Kettering Cancer Centre (MSKCC) nomogram has been developed to estimate five-year overall survival (OS) after curative-intent surgery of colon cancer based on age, sex, T stage, differentiation grade, number of positive and examined regional lymph nodes. This is the first evaluation of the performance of the MSKCC model in a European population regarding prediction of OS.

Material and methods: Population-based data from patients with stage I–III colon cancer diagnosed between 2010 and 2016 were obtained from the Netherlands Cancer Registry (NCR) for external validation of the MSKCC prediction model. Five-year survival probabilities were estimated for all patients in our dataset by using the MSKCC prediction equation. Histogram density plots were created to depict the distribution of the estimated probability and prognostic index. The performance of the model was evaluated in terms of its overall performance, discrimination, and calibration.

Results: A total of 39,805 patients were included. Five-year OS was 71.9% (95% CI 71.5; 72.3) (11,051 events) with a median follow up of 5.6 years (IQR 4.1; 7.7). The Brier score was 0.10 (95% CI 0.10; 0.10). The C-index was 0.75 (95% CI 0.75; 0.76). The calibration measures and plot indicated that the model slightly overestimated observed mortality (observed/expected ratio = 0.86 [95% CI 0.86; 0.87], calibration intercept = −0.14 [95% CI −0.16; −0.11], and slope 1.07 [95% CI 1.05; 1.09], ICI = 0.04, E50 = 0.04, and E90 = 0.05).

Conclusions: The external validation of the MSKCC prediction nomogram in a large Dutch cohort supports the use of this practical tool in the European patient population. These personalised estimated survival probabilities may support clinicians when informing patients about prognosis. Adding potential relevant prognostic factors to the model, such as primary tumour location, might further improve the model.

ARTICLE HISTORY
Received 2 February 2021
Accepted 14 February 2022

KEYWORDS
Colon cancer; survival; prognosis; nomogram; external validation

Introduction

In the Netherlands, approximately 80% of colon cancer patients present with stage I–III disease at diagnosis [1]. Twenty percent eventually develops metastatic disease [2], leading to an increased mortality risk in these patients. The current American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification system is widely used for staging and estimating survival in patients with colon cancer. It classifies cancers by the size and extent of the primary tumour (T), involvement of regional lymph nodes (N), and the presence of distant metastases (M). However, patients within the same TNM stage vary considerably in prognosis because other factors influence prognosis: five-year overall survival (OS) varies between 68 and 83% for stage II, and between 45 and 65% for stage III colon cancer [3]. Hence, in clinical practice there is a need for more accurate prediction of survival for the individual patient to aid in patient counselling, treatment decision making, patient selection for trials, and surveillance scheduling.

The Memorial Sloan Kettering Cancer Centre (MSKCC) prediction model for OS [4] has shown superior prognostic accuracy to the TNM staging system by incorporating several

CONTACT Marinde J. G. Bond M.J.G.Bond-2@umcutrecht.nl Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, Utrecht 3584, CX, The Netherlands
*These authors contributed equally to this work.

Supplemental data for this article can be accessed here.

clinical and pathological variables readily available in daily practice (https://www.mskcc.org/nomograms/colorectal/overall_survival_probability). It uses both number of examined lymph nodes and number of positive lymph nodes instead of N stage, and adds the following variables: patient's age and sex, and differentiation grade of the tumour. The model was developed in patients who were diagnosed in the United States (US) between 1994 and 2005. The authors report a C-index of 0.68 (95% CI 0.67; 0.68) and recommend to use the model in clinical practice.

Since the MSKCC prediction model for OS was published in 2011, it has only been externally validated once, in a small Chinese population of 985 patients treated between 1996 and 2008 (C-index 0.71) [5]. Diagnostics, treatment, and thereby prognosis have evolved considerably since 2005 [6], arguing for external validation [7] in a new population and a new epoch. Here, we assessed the performance of the MSKCC prediction model in a large cohort of Dutch patients diagnosed between 2010 and 2016.

Material and methods

Study population

Population-based data from adult patients with stage I-III colon cancer, diagnosed and surgically treated in the Netherlands between January 2010 and December 2016, were requested from the Netherlands Cancer Registry (NCR). ICD-O-3 topography codes C18.0 (caecum) until C18.7 (sigmoid) were included.

The NCR registers all newly diagnosed malignancies in the Netherlands and covers the total Dutch population of over 17 million people. The NCR is linked to the automated pathology archive comprising all histologically confirmed cancer diagnoses, and to the National Registry of Hospital Discharge Diagnoses. Trained data managers collect patient, tumour, and treatment characteristics from medical records. Follow-up on vital status occurs through annual linkage between the NCR and National Municipal Personal Records Database, which contains information on vital status of all Dutch inhabitants. The most recent linkage occurred on 1 February 2021. Surviving patients were censored at this date.

In accordance with the patient selection process of Weiser et al. [4], patients were included with adenocarcinoma histology, T1–T4 tumours and regional lymph nodes examined. TNM classification was based on the 7th edition [8]. Patients were excluded in case of perioperative mortality (survival $<$ 0 days), if they underwent local excision or polypectomy only, or if they presented with more than one primary tumour. Patients with unknown differentiation grade, treated with neoadjuvant chemotherapy, or missing number of examined or positive lymph nodes were also excluded. Consistent with Weiser et al. [4], age $>$ 99 years was converted to 99, examined lymph nodes $>$ 45 were winsorised (recoded to 45) and positive lymph nodes $>$ 16 were winsorised (recoded to 16).

Adjuvant chemotherapy

During the study period, the Dutch Colorectal Cancer Guidelines [9] recommended oxaliplatin-based adjuvant chemotherapy for 6 months for patients with stage III colon cancer. For patients with high-risk stage II colon cancer (only in case of proficient mismatch repair tumours as of 2013), adjuvant chemotherapy could be considered. High-risk stage II was defined as either pT4 tumours, insufficient lymph node sampling ($<$10), clinical presentation with obstruction or perforation, poor/undifferentiated grade, and/or vascular invasion.

MSKCC model

The MSKCC model has been described in detail previously [4]. In short, the MSKCC model was developed in 128,853 patients with colon cancer from the Surveillance, Epidemiology, and End Results (SEER) registry from 1994 to 2005. The model was built to estimate five-year OS defined as the proportion of patients surviving for five years after diagnosis. Cox proportional hazards regression was used to estimate survival probabilities. Predictor variables include age (continuous, maximum 99 years), sex (male or female), T stage (1, 2, 3, 4a, or 4b), differentiation grade (poor or moderate/well), total number of regional lymph nodes examined (continuous, 1–45+), and number of positive regional lymph nodes (continuous, 0–16+). The formula of the model can be found in Box 1.

Box 1. Prediction equation.

$$\text{Estimated probability} = 0.678^{\exp(\text{prognostic index})}$$

$$\begin{aligned}\text{Prognostic index} = {} & -1.841896 + 0.01846885\ \text{Age} + 2.605625 \times 10^{-5}(\text{Age} - 50)^3{}_+ \\ & -6.327947 \times 10^{-5}(\text{Age} - 70)^3{}_+ + 3.722322 \times 10^{-5}(\text{Age} - 84)^3{}_+ \\ & -0.1932243\ \{\text{Sex} = \text{F}\} \\ & + 0.1577426\ \{\text{T stage} = 2\} + 0.4591902\ \{\text{T stage} = 3\} + 0.7196826 \\ & \{\text{T stage} = 4\text{a}\} + 1.0965831\ \{\text{T stage} = 4\text{b}\} \\ & + 0.1492084\ \{\text{Grade} = \text{Poor}\} \\ & -0.03441869\ \text{Total} + 5.401583 \times 10^{-5}\ (\text{Total} - 4)^3{}_+ - 8.310127 \\ & \times 10^{-5}\ (\text{Total} - 11)^3{}_+ + 2.908545 \times 10^{-5}\ (\text{Total} - 24)^3{}_+ \\ & + 0.2889049\ \text{Positive} - 0.01505269\ (\text{Positive})^3{}_+ + 0.02007025 \\ & (\text{Positive} - 1)^3{}_+ - 0.005017563\ (\text{Positive} - 4)^3{}_+\end{aligned}$$

External validation

Five-year survival probabilities were estimated for all patients in our dataset by using the MSKCC prediction equation. Histogram density plots were created to depict the distribution of the estimated survival probability and prognostic index and the mean, variance, skewness, and kurtosis were calculated. The performance of the MSKCC nomogram in our dataset was assessed in three steps. First, overall performance was evaluated by the Brier score. The Brier score is the squared difference between observed and estimated values at a fixed time point and can range from 0 for a perfect

model to 0.25 for a non-informative model. Second, discrimination at a fixed time point was assessed by the C-index, which was calculated by Uno's time-dependent area under the curve (AUC) [10,11]. Discrimination of a model refers to the capacity of a model to discriminate between individuals who develop the event (death) and those who do not. We used five years for the fixed time point since we were interested in the ability of the model estimating five-year OS. Values close to one indicate perfect discrimination ability, while values close to 0.5 indicate poor discrimination ability. Third, calibration was estimated at three levels [12]. The observed/expected ratio (calibration-in-the-large) was determined to evaluate the agreement between predicted and observed mortality. An observed/expected ratio < 1 indicates overestimation and > 1 underestimation of observed mortality. The calibration intercept, which is also an assessment of calibration-in-the-large, has a perfect value of zero whereas a negative value indicates overestimation and a positive underestimation of observed mortality. The calibration slope evaluates the spread of the predicted risks and should be close to 1. Calibration was graphically represented by a flexible calibration curve, complemented with the Integrated Calibration Index (ICI), E50 and E90 [13]. If points are below the 45-degree line in the calibration plot, the model overestimates the observed mortality and points above indicate underestimation. The ICI can be interpreted as the weighted difference between smoothed observed outcomes and predicted risks in which observations are weighted by the empirical density function of the predicted risks. E50 and E90, represent the median and 90th percentile of the absolute difference between observed outcomes and predicted mortality risks. Bootstrap percentiles using 100 bootstrap samples were used to calculate 95% confidence intervals (CIs). Due to the small amount of missing data (0.07%) in the predictors number of regional lymph nodes examined and number of positive lymph nodes, missing data was handled by complete-case analysis. In practice, we find it likely that the model would not be used on patients with missing data. With over 10,000 events observed, our sample size far exceeds the generally recommended minimum of 200 events which is recommended for external validation of prediction models with a survival outcome [14].

All analyses were done in R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). The study is reported following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidance [15] (Supplement 1).

Results

Study population

A total of 39,805 patients were included in the external validation cohort as shown in Figure 1. Twenty-seven patients (0.07%) with missing data were excluded. Table 1 shows patient characteristics of our NCR validation cohort and the MSKCC development cohort. Compared to patients from the MSKCC cohort, patients from the NCR cohort had more

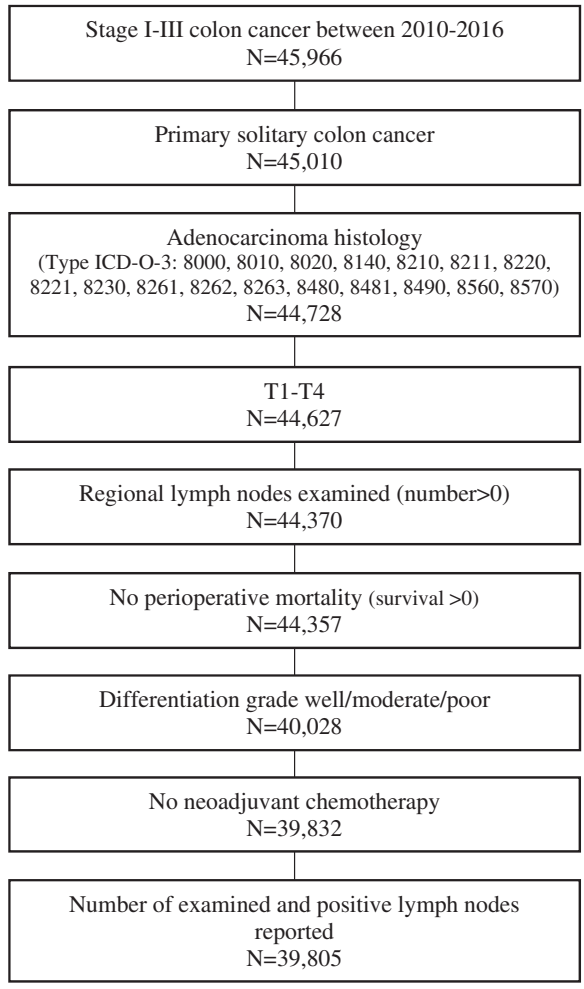

Figure 1. Flow chart for patient selection.

examined and less positive lymph nodes, more often tumours with a higher differentiation grade and stage II tumours, and less often stage III tumours. In the NCR cohort, five-year OS was 71.9% (95% CI 71.5; 72.3) with a median follow up of 5.6 (IQR 4.1; 7.7) years. The number of events was 11,051 at five years. Two patients (0.005%) were older than 99 years, in 673 patients (1.7%) > 45 lymph nodes were examined and in 179 patients (0.4%) > 16 lymph nodes were positive.

Assessment of model performance

Among the patients in our study, the estimated five-year survival probability varied from zero to almost one, with a relatively high proportion of patients estimated to have a five-year survival probability around 70% (Figure 2). This reflects the observed five-year OS of 71.9%. The distribution of the prognostic index is depicted in Supplementary Figure 1. The Brier score was 0.10 (95% CI 0.10; 0.10), which is closer to 0 (perfect model) than to 0.25 (non-informative model). The C-index, which assesses discriminative ability, was 0.75 (95% CI 0.75; 0.76). The calibration estimates and plot (Figure 3) indicated that the model slightly overestimated observed mortality. The observed/expected ratio was 0.86 (95% CI 0.86; 0.87).

Table 1. Baseline characteristics.

	Validation NCR ($N = 39,805$)	Development MSKCC ($N = 128,853$)
Age		
Mean (SD)	70.4 (10.5)	69.2 (13.1)
Median [interquartile range]	71.0 [64–78]	71 [61–79)
Sex		
Male	20,850 (52.4%)	62,293 (48.3%)
Female	18,955 (47.6%)	66,560 (51.7%)
Pathological T stage		
T1	3813 (9.6%)	–
T2	7239 (18.2%)	–
T3	23,521 (59.1%)	–
T4a	3511 (8.8%)	–
T4b	1721 (4.3%)	–
Stage		
I	9225 (23.2%)	31,128 (24.2%)
II	19,149 (48.1%)	51,900 (40.3%)
III	11,310 (28.4%)	45,825 (35.6%)
Missing (NX or N1m)	121 (0.3%)	–
Number of examined regional lymph nodes		
Mean (SD)	18.3 (9.50)	12.9 (9.2)
Median [Min, Max]	16.0 [1, 143]	11 [1, 90]
Number of positive regional lymph nodes		
Mean (SD)	1.26 (2.82)	3.5 (3.6)
Median [Min, Max]	0 [0, 61]	2 [0, 96]
Differentiation grade		
Well/moderate differentiation	34,408 (86.4%)	99,635 (77.3%)
Poor differentiation	5397 (13.6%)	24,192 (18.8%)
Unknown differentiation	4329[a]	5026 (3.9%)
Primary tumour location		
Caecum	7807 (19.6%)	–
Ascending colon	6630 (16.7%)	–
Hepatic flexure	2327 (5.8%)	–
Transverse colon	3068 (7.7%)	–
Descending colon	1957 (4.9%)	–
Splenic flexure	1596 (4.0%)	–
Sigmoid	15,638 (39.3%)	–
Overlapping	479 (1.2%)	–
Unspecified	303 (0.8%)	–
Adjuvant chemotherapy	10,489 (26.4%)	–
Stage I	38 [0.4%][b]	–
Stage II	3259 [17.0%][b]	–
Stage III	7164 [63.3%][b]	–

[a]Patients with unknown differentiation were already excluded in the patient selection process.
[b]The percentage refers to the proportion of patients treated with adjuvant chemotherapy within each stage.

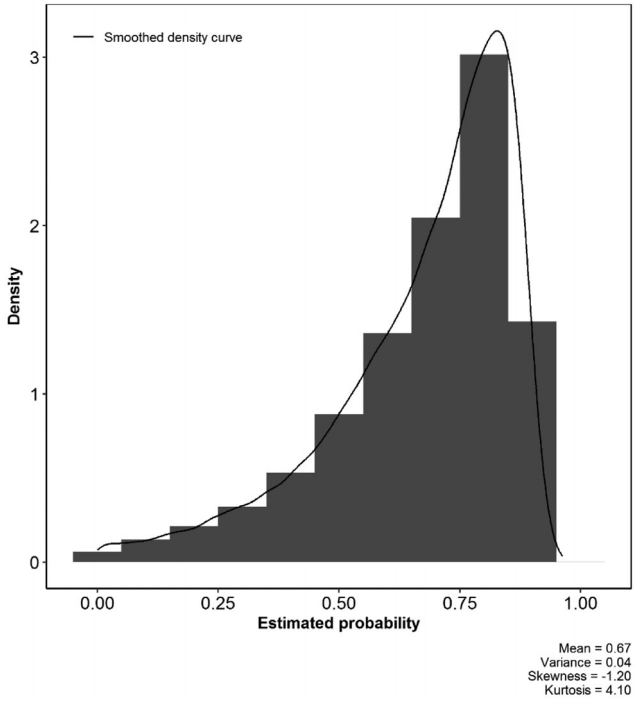

Figure 2. Histogram density plot estimated probability.

The calibration intercept was −0.14 (95% CI −0.16; −0.11, SE −0.42) and slope 1.07 (95% CI 1.05; 1.09, SE 0.01). The ICI was 0.04, E50 was 0.04 and E90 was 0.05.

Discussion

Our study is the first European external validation of the US-based MSKCC model regarding prediction of OS in a large dataset of stage I–III colon cancer patients. The C-index we found is slightly higher than the C-indexes that were reported in the development data [4] and in the external validation in a Chinese population [5]. The calibration measures indicated that the model slightly overestimated the observed mortality, which was not seen in the Chinese population [5]. An explanation might be that, in general, OS is better in this new epoch as a result of improved diagnostics and treatment, the most important improvement being the increased use of adjuvant chemotherapy for patients with stage III (and high-risk stage II) colon cancer [6].

We preferred to externally validate an existing model rather than develop yet another prediction model for

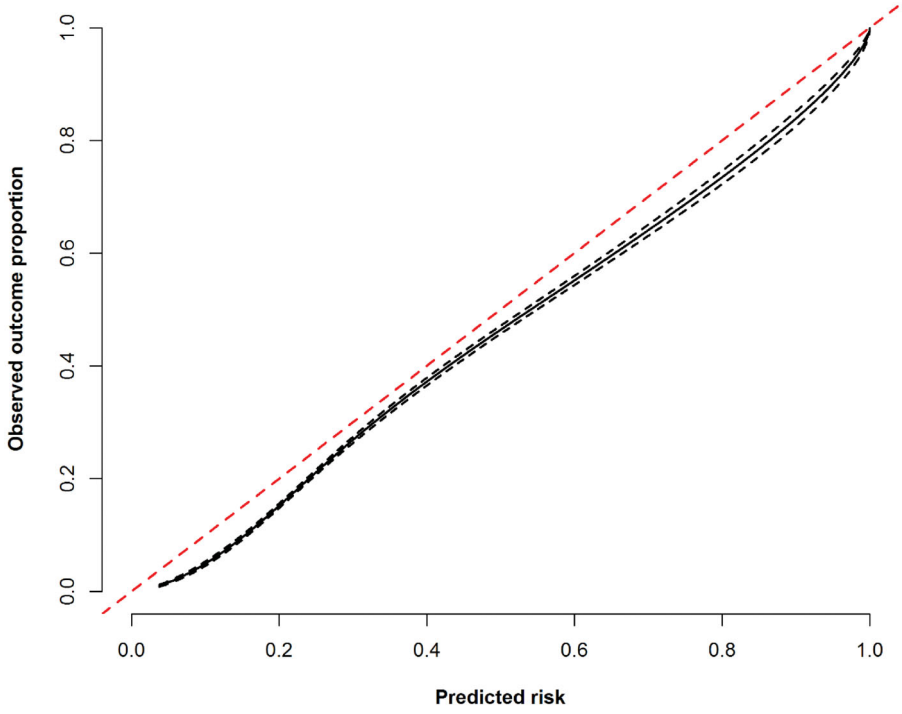

Figure 3. Calibration curve.

estimating survival after curative surgery for stage I–III colon cancer patients. Numerous newly developed prognostic models are published to meet the need for better prognostication. However, few of these are used in daily practice. One of the reasons for this is that because many prognostic models have not been validated in other populations, clinicians may (and perhaps should) distrust probabilities provided by these models [16]. Many experts in the field support the view that no prediction model should be implemented in practice until, at a minimum, its performance has been validated in new individuals [16]. We decided to validate the MSKCC model as this is the only one using variables that are readily available in daily practice and it has the advantage of a web-based interface [17] that provides easy access to its use. Besides, the web-based tool provides a 'likely range' around the survival probability that informs on the uncertainty of the estimates.

Despite our preference to externally validate the existing MSKCC model, we do believe this model has potential limitations. First, not all relevant prognostic factors were considered in the development process (i.e., primary tumour location, mismatch repair status, consensus molecular subtype, comorbidity, and performance status). Adding primary tumour location to the model might further improve its performance since it is a known and readily available prognostic factor, i.e., left-sided tumours are associated with a significantly better OS compared to right-sided tumours [18,19]. To ensure clinical applicability of the model, other potential predictors should preferably only be included in a prognostic model if they are widely implemented in clinical practice, which is for example not true for consensus molecular subtype and (at the time) for mismatch repair status. Second, the MSKCC model cannot be applied to patients with an unknown tumour differentiation grade. Differentiation grade cannot be determined in all histologic tumour types in all cases, such as in mucinous or signet ring cell carcinoma. Therefore, including a category unknown in the model would result in a wider applicability. Third, the model was based on the 7th edition [8] of the TNM classification, while the 8th edition [20] was implemented globally in 2018. However, classification of stage I–III was identical in both versions.

The strength of this study is that the MSKCC prediction model was externally validated in a recent time period and a different geographic region by independent investigators not involved in the development of the model. The large sample size and large number of events ensuring sufficient statistical precision further strengthen the external validation. Furthermore, we followed the TRIPOD guideline for the external validation. We applied the model to a population-based dataset including all patients diagnosed within the specified time period with almost no missing values, ensuring a low risk of bias.

Conclusions

This external validation showed good performance of the web-based easy to use MSKCC prediction model and we recommend its use in clinical practice to estimate five-year OS in patients with stage I–III colon cancer after surgery. These personalised estimated survival probabilities may aid patient counselling, treatment decision making, patient selection for trials, and surveillance scheduling. When using the model for

any of these purposes, the slight overestimation of mortality risk should be considered.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the NCR. The authors thank Dr. Martin Weiser, Dr. Mithat Gönen and their colleagues for providing the prediction equation of the MSKCC model.

Ethics approval and consent to participate

According to the Central Committee on Research involving Human Subjects, this type of registry-based study does not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board and the scientific council of the Netherlands Comprehensive Cancer Organisation (IKNL) which collects and guards the data for the NCR. All data were pseudonymised prior to the transfer from IKNL to the researchers. The NCR uses an opt-out approach to consent.

Disclosure statement

G. R. V. reports research grants/funding paid to her institution by Servier, BMS, Bayer, Merck, PGDx, and Sirtex. M.K. reports having an advisory role for Nordic Farma, Merck-Serono, Pierre Fabre, Servier, and institutional scientific grants from Bayer, Bristol Myers Squibb, Merck, Roche, and Servier. J.M.L.R. reports research grants/funding or honoraria paid to her institution by Bayer, BMS, Merck, Pierre Fabre, and Servier. C. J. A. P. reports an advisory role for Nordic Pharma. A. M. M. reports advisory fees from Novartis paid to her institution. All remaining authors have declared no conflicts of interest.

Funding

The authors received no specific funding for this work.

ORCID

Marinde J. G. Bond http://orcid.org/0000-0003-0225-5456
Patricia A. H. Hamers http://orcid.org/0000-0002-1703-0121
Geraldine R. Vink http://orcid.org/0000-0002-6731-9660
Wilhelmina M. U. van Grevenstein http://orcid.org/0000-0002-3466-1777
Miangela M. Laclé http://orcid.org/0000-0003-3466-3569
Maarten van Smeden http://orcid.org/0000-0002-5529-1541
Miriam Koopman http://orcid.org/0000-0003-1550-1978
Jeanine M. L. Roodhart http://orcid.org/0000-0003-1398-8970
Cornelis J. A. Punt http://orcid.org/0000-0003-0846-1445
Anne M. May http://orcid.org/0000-0003-4857-8189

Data availability statement

The data that support the findings of this study are available from the NCR but restrictions apply to the availability of these data, which were used under licence for this study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the NCR.

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