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Nomograms to predict survival and the risk for developing local or distant recurrence in patients with rectal cancer treated with optional short-term radiotherapy

W. van Gijn[1,†*], R. G. P. M. van Stiphout[2,3,†], C. J. H. van de Velde[1], V. Valentini[4], G. Lammering[2], M. A. Gambacorta[4], L. Påhlman[5], K. Bujko[6] & P. Lambin[2]

[1]Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands; [2]Department of Radiation Oncology (MAASTRO), GROW, University Medical Centre Maastricht, Maastricht; [3]Department of Knowledge Engineering, Faculty of Humanities and Sciences, Maastricht University, Maastricht, The Netherlands; [4]Radiation Oncology Department, Università Cattolica del Sacro Cuore, Rome, Italy; [5]Department of Surgical Science, Uppsala University, Uppsala, Sweden; [6]Department of Radiotherapy, The Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland

Background: In many European countries, short-term 5×5 Gy radiotherapy has become the standard preoperative treatment of patients with resectable rectal cancer. Individualized risk assessment might allow a better selection of patients who will benefit from postoperative treatment and intensified follow-up.

Patients and methods: From patient's data from three European rectal cancer trials ($N = 2881$), we developed multivariate cox nomograms reflecting the risk for local recurrence (LR), distant metastases (DM) and overall survival (OS). Evaluated variables were age, gender, tumour distance from the anal verge, the use of radiotherapy, surgical technique (total mesorectal excision/conventional surgery), surgery type (low anterior resection/abdominoperineal resection), time from randomization to surgery, residual disease (R0 versus R1 + 2), pT-stage, pN-stage and surgical complications.

Results: Pathological T- and N-status are of vital importance for an accurate prediction of LR, DM and OS. Short-course radiotherapy reduces the rate of LR. The developed nomograms are capable of predicting events with a validation c-index of 0.79 (LR), 0.76 (DM) and 0.75 (OS). The proposed stratification in risk groups allowed significant distinction between Kaplan–Meier curves for outcome.

Conclusion: The developed nomograms can contribute to better individual risk prediction for LR, DM and OS for patients operated on rectal cancer. The practicality of the defined risk groups makes decision support in the consulting room feasible, assisting physicians to select patients for adjuvant therapy or intensified follow-up.

Key words: prediction, local recurrence, metastases, nomogram, short-term radiotherapy, rectal cancer

introduction

In the last two decades, treatment of rectal cancer has evolved from an exclusively surgical procedure to a multidisciplinary approach. While surgery is still the cornerstone for cure, (neo)adjuvant treatment modalities have become increasingly important. Several European trials investigated the effectiveness of short-term 5×5 Gy radiotherapy followed by immediate surgery. The 'Swedish Rectal Cancer Trial' showed a lower local recurrence (LR) rate and a higher survival with preoperative administration

of short-term radiotherapy [1]. Around the same time, Heald and Enker introduced the total mesorectal excision (TME). Instead of conventional blunt dissection, the complete mesorectum is sharply excised under a direct vision, resulting in spectacular improvements in tumour control, survival and nerve preservation [2]. To investigate the value of short-term radiotherapy in combination with TME, the Dutch Colorectal Cancer Group conducted the 'TME trial'. Among patients with clinically resectable rectal cancer who underwent TME surgery, preoperative short-term radiotherapy reduced the rate of LRs by half; there was no difference in survival [3].

In comparison of short-term radiotherapy and conventional chemoradiotherapy as preoperative therapy for patients with resectable rectal cancer, the 'Polish Rectal Cancer Trial' found no differences in sphincter preservation, local control, late toxicity

*Correspondence to: Dr Willem van Gijn, Department of Surgery, Leiden University Medical Center, K6-R, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel: +31-71-526-2309; Fax: +31-71-526-6750; E-mail: willem@vangijn.com

†The first two authors contributed equally to this work.

or survival, despite significant downsizing in the chemoradiation group [4].

Preoperative short-term radiotherapy seems to offer the same benefits as long-course chemoradiation if no tumour downsizing is required but with reduced costs and toxicity, better compliance and a reduced risk of pathological understaging [4–7]. Recently, similar results from an Australian trial were published, whereas results from a German trial are awaited [8, 9]. As a result, in many European countries, short-term radiotherapy has become the standard treatment of patients with resectable rectal cancer.

Several reports suggest that the effect of (neo)adjuvant therapy depends on factors such as TNM stage, tumour position, surgical technique, biological behaviour as well as on patient characteristics [10–14]. A more personalized approach, tailored to these factors, might improve the balance between beneficial and adverse effects of (neo)adjuvant treatment and allow better patient selection. We used the datasets of the three clinical trials mentioned above to develop nomograms for predicting LR, distant metastases (DM) and overall survival (OS) in patients with resectable rectal cancer optionally treated with short-term radiotherapy followed by immediate surgery.

methods

study population

The models were trained with a dataset from the three European trials mentioned above. The Swedish trial (1987–1990) randomly assigned 1179 patients to short-term radiotherapy with conventional surgery or conventional surgery alone. The Dutch TME trial (1996–1999) randomly assigned 1861 patients to 5×5 Gy radiotherapy followed by TME surgery or total TME surgery alone. The Polish rectal cancer trial (1999–2002) compared short-term radiotherapy and long-course chemoradiation followed by TME surgery; we included only patients from the short-term radiotherapy arm of this study ($N = 155$). In the pooled database, we excluded patients with DM (M1), unoperated patients and those with missing data; 2881 patients remained (Figure 1). The evaluated variables were age and gender, tumour distance from the anal verge, radiotherapy, surgery type (TME/conventional surgery), surgery group [low anterior resection/abdominoperineal resection (APR)], time from randomization to operation (days), presence of residual disease (R0 versus R1 + 2), pathological staging (pT-, pN- and UICC stage) and presence of post-surgical complications. Outcome events were the presence of LR, DM and OS. LR was defined as tumour presence in the pelvis or perineum or at the anastomosis as diagnosed by histology. Distant metastasis was defined as evidence of tumour in any other area. Any cause of death was included in the datasets. All outcomes were defined by occurrence or absence of an event (LR, DM or death) within the accrual time. For the development of the nomograms, we included only patients for whom at least 5-year follow-up was available.

statistical analysis

To compare the contributions of the evaluated factors, normalization of the variables was carried out by subtracting the mean and dividing by the standard deviation. Missing input values were substituted by the expectation–maximization algorithm. No variable in the pooled dataset exceeded 3% of missing values, except for pN-stage (11%). To test for dependencies between the input variables themselves and between the inputs and the outcomes, the Spearman's correlation coefficients were calculated and presented in a correlation matrix. The nomograms reflect 5-year event rates.

First, we carried out univariate analyses (Mann–Whitney U-test) to assess the variables separately for predictive power. Secondly, multivariate analyses
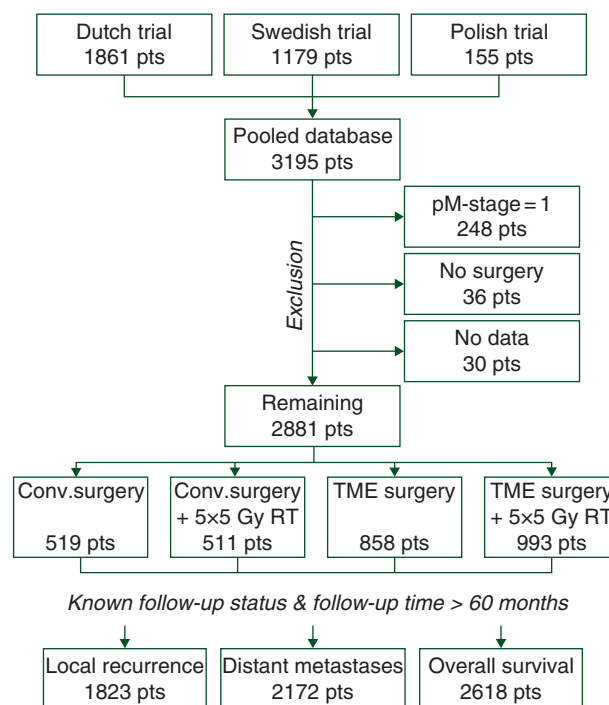

Figure 1. Schematic overview of the characteristics of the pooled patient database, including patient exclusion, treatment stratification and follow-up status.

were carried out with a method suitable for time-to-event data: Cox regression. The coefficients assigned to each variable were used to calculate hazard ratios. The performances for predicting the outcome were evaluated with the c-index, an equivalent of the area under the curve of the receiver operating characteristic curve for censored data [15]. The maximum value of the c-index is 1.0, indicating perfect prediction, whereas a value of 0.5 indicates a random chance of correct prediction. To ensure consistency in internal validation within the randomized datasets, a 10-fold cross-validation was carried out, resulting in mean c-indices with corresponding confident intervals (CIs). In this cross-validation, a model is trained on 90% of the data and validated on the remaining 10%. This is repeated 10 times; each time a completely new validation set is chosen, so that every patient is in a validation set only once. The final nomograms are based on all randomized patients. Nomograms can visualize the effect of each selected variable on the estimated probability [16]. Three risk groups were defined according to the probability for each event. The probability thresholds for the nomograms were calculated by maximizing the distance between the Kaplan–Meier curves of the three risk groups for that particular outcome with a minimal risk group size of 100 patients. Model calibration was carried out with Hosmer–Lemeshow statistic for five equal filled bins on the internal validation sets (10-fold). The algorithms for statistical analyses and nomograms were developed in Matlab (version 7.1, MathWorks, Inc., Natick, MA, USA).

results

data distribution

The 2881 patients in the three trials were all operated on (35.8% conventional surgery and 64.2% TME) and in total 52.2% received 5×5 Gy radiotherapy (Figure 1). The three cohorts show similar data distributions (Table 1). Treatment heterogeneity concerns conventional surgery versus TME surgery and

Table 1. Patients' characteristics compared for the three trials and the pooled database

	Dutch trial	Swedish trial	Polish trial	Total
	N = 1708	N = 1030	N = 143	N = 2881
Age (years)				
Median	66.0	68.5	62.7	66.6
Range	23.0–92.0	27.3–82.1	30.9–75.8	23.0–92.0
Gender				
Male	1078 (63.1)	610 (59.2)	92 (64.3)	1780 (61.8)
Female	630 (36.9)	420 (40.8)	51 (35.7)	1101 (38.2)
Tumour distance from anal verge (cm)				
Median	7.0	8.0	6.0	7.0
Range	0.0–25.0	0.0–20.0	2.0–10.0	0.0–25.0
Radiotherapy				
No	858 (50.2)	519 (50.4)	0 (0.0)	1377 (47.8)
Yes	850 (49.8)	511 (49.6)	143 (100.0)	1504 (52.2)
Surgery type				
Conventional surgery	0 (0.0)	1030 (100.0)	0 (0.0)	1030 (35.8)
Total mesorectal excision	1708 (100.0)	0 (0.0)	143 (100.0)	1851 (64.2)
Surgery group				
Low anterior resection	1155 (67.6)	430 (41.7)	85 (59.4)	1670 (58.0)
Abdominoperineal resection + Hartmann	553 (32.4)	595 (57.8)	56 (39.2)	1204 (41.8)
Unknown	0 (0.0)	5 (0.5)	2 (1.4)	7 (0.2)
Time from randomization to surgery (days)				
0–20	971 (56.9)	793 (77.0)	84 (58.7)	1848 (64.1)
20–40	685 (40.1)	219 (21.3)	53 (37.1)	957 (33.2)
>40	52 (3.0)	18 (1.7)	6 (4.2)	76 (2.6)
Residual (R1 + 2)				
No	1416 (82.9)	907 (88.1)	123 (86.0)	2446 (84.9)
Yes	283 (16.6)	120 (11.7)	19 (13.3)	422 (14.6)
Unknown	9 (0.5)	3 (0.3)	1 (0.7)	13 (0.5)
Pathological T-status				
0	26 (1.5)	0 (0.0)	1 (0.7)	27 (0.9)
1	90 (5.3)	79 (7.7)	3 (2.1)	172 (6.0)
2	545 (31.9)	319 (31.0)	54 (37.8)	918 (31.9)
3	974 (57.0)	629 (61.1)	81 (56.6)	1684 (58.5)
4	50 (2.9)	0 (0.0)	0 (0.0)	50 (1.7)
Unknown	23 (1.3)	3 (0.3)	4 (2.8)	30 (1.0)
Pathological N-status				
0	1020 (59.7)	430 (41.7)	70 (49.0)	1520 (52.8)
1	395 (23.1)	247 (24.0)	32 (22.4)	674 (23.4)
2	251 (14.7)	113 (11.0)	32 (22.4)	396 (13.7)
Unknown	42 (2.5)	240 (23.3)	9 (6.3)	291 (10.1)
Pathological UICC TNM stage				
0	30 (1.8)	0 (0.0)	1 (0.7)	31 (1.1)
1	519 (30.4)	336 (32.6)	42 (29.4)	897 (31.1)
2	508 (29.7)	331 (32.1)	33 (23.1)	872 (30.3)
3	638 (37.4)	360 (35.0)	64 (44.8)	1062 (36.9)
Unknown	13 (0.8)	3 (0.3)	3 (2.1)	19 (0.7)
Post-surgical complications				
No	809 (47.4)	638 (61.9)	96 (67.1)	1543 (53.6)
Yes	897 (52.5)	392 (38.1)	43 (30.1)	1332 (46.2)
Unknown	2 (0.1)	0 (0.0)	4 (2.8)	6 (0.2)
Local recurrences within 5 years				
No	962 (56.3)	539 (52.3)	12 (8.4)	1513 (52.5)
Yes	115 (6.7)	183 (17.8)	12 (8.4)	310 (10.8)
Unknown	7 (0.4)	57 (5.5)	4 (2.8)	68 (2.4)
Ineligible (follow-up <5 years)	624 (36.5)	251 (24.4)	115 (80.4)	990 (34.4)

Continued

Table 1. *Continued*

|	Dutch trial	Swedish trial	Polish trial	Total
	N = 1708	N = 1030	N = 143	N = 2881
Distant metastases within 5 years				
No	908 (53.2)	534 (51.8)	11 (7.7)	1453 (50.4)
Yes	421 (24.6)	262 (25.4)	36 (25.2)	719 (25.0)
Unknown	1 (0.1)	57 (5.5)	2 (1.4)	60 (2.1)
Ineligible (follow-up <5 years)	378 (22.1)	177 (17.2)	94 (65.7)	649 (22.5)
Death within 5 years				
No	965 (56.5)	563 (54.7)	13 (9.1)	1541 (53.5)
Yes	595 (34.8)	442 (42.9)	40 (28.0)	1077 (37.4)
Unknown	0 (0.0)	23 (2.2)	0 (0.0)	23 (0.8)
Ineligible (follow-up <5 years)	148 (8.7)	2 (0.2)	90 (62.9)	240 (8.3)
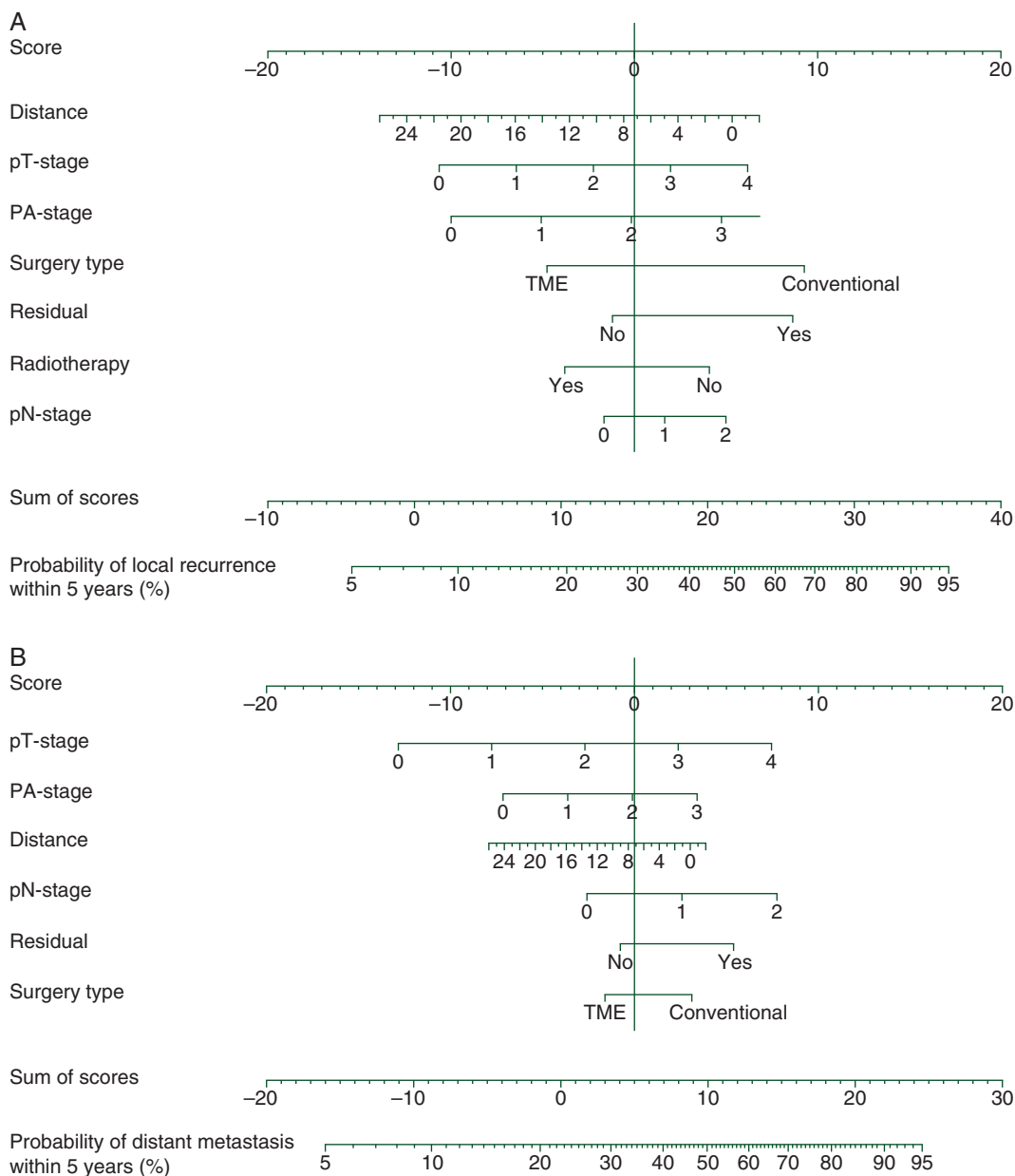
Figure 2. Nomograms for prediction of (A) local recurrence, (B) distant metastases and (C) overall survival. Each value of a predictor is assigned to a score (upper scale). The sum of these scores corresponds to a probability for the event (lower scale).
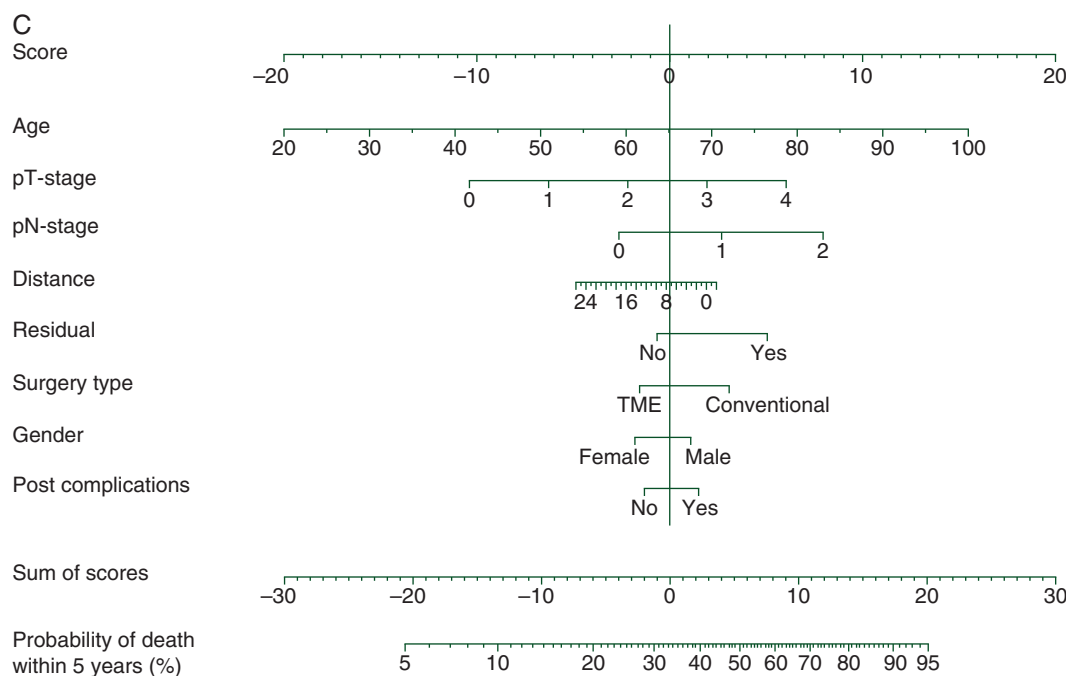
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Fig. 2 *Continued*

short-term radiotherapy versus no radiotherapy. Median follow-up times for the Dutch, Swedish and Polish trials are 69.2, 75.3 and 31.9 months, respectively.

The Spearman matrix in supplementary Figure S1, available at *Annals of Oncology* online shows the correlations between all input variables. APR, usual in low situated tumours, was carried out more often in the conventional surgery group. Pathological stage is very predictive for all outcomes, whereas surgery type and group are only predictive for LR and OS. Administration of radiotherapy has only effect on a lowering LR rate. Postoperative complications were only predictive for OS.

nomograms

Exclusion of patients with <5 years of follow-up reduced patient numbers to 1823 for LR, 2172 for DM and 2618 for OS (supplementary Table S1, available at *Annals of Oncology* online). On univariate analysis, all variables with the exception of gender and postoperative complications were predictive for LR. Age, radiotherapy and surgery type did not affect the rate of DM. For OS, radiotherapy and time to surgery were not predictive.

The validation c-index of LR prediction was 0.787 with a 95% CI of 0.761–0.814. For DM, the accuracy was 0.761 (95% CI 0.740–0.784). OS gave a c-index of 0.752, with a narrower confidence interval for internal validation because of the larger number of patients (95% CI 0.733–0.769). The resulting nomograms (Figure 2) predict the probability for an outcome event through a score (upper scale) for each predictor value. The lower two scales are then used to convert the sum of these scores to a probability. In all nomograms, pathological stage and radicality of the operation are most important, as reflected by the size of the scales of pT-stage, pN-stage and the presence of residual disease. Each probability is assigned to a risk group

(low, medium and high) for that particular outcome. Each risk group was evaluated for the real outcome fraction after 5 years of follow-up (Figure 3). This resulted in KM curves that were all statistically different. Model calibration with the Hosmer–Lemeshow test with five equal filled bins resulted in good calibration for the internal validation datasets. For LR, the average validation *P*-value was 0.68 (range: 0.13–0.99), for DM: 0.82 (range: 0.61–0.99) and for OS: 0.77 (range: 0.39–0.96). In this test, small *P*-values represent the lack of fit of the validation data; therefore, the reported *P*-values show a good validation fit.

discussion

Combination of three major European rectal cancer trials shows that pathological T-status, N-status and residual status (R0 versus R1 + 2) are the most important predictors for LR, DM and OS, respectively. The identified predictors correspond with those found earlier [17]. The developed nomograms can facilitate clinicians to predict individual patient risk for developing LR, DM and OS.

With the widespread use of preoperative radiotherapy and TME surgery, LR rates have dropped dramatically. Good quality surgery seems the most important factor for reducing LR [18]. Preoperative radiotherapy, though indisputably reducing LR, has considerable side-effects: impaired wound healing, urinary and faecal incontinence as well as sexual dysfunction. Because of further refinements in TME surgery and clinical staging with MRI, a patient group with 'good prognosis' can be selected that has such a small chance of developing LR that the morbidity of preoperative radiotherapy probably outweighs a (further) reduction in LR [19]. The estimated risk for LR defines the benefit of preoperative radiotherapy. MRI allows adequate clinical staging
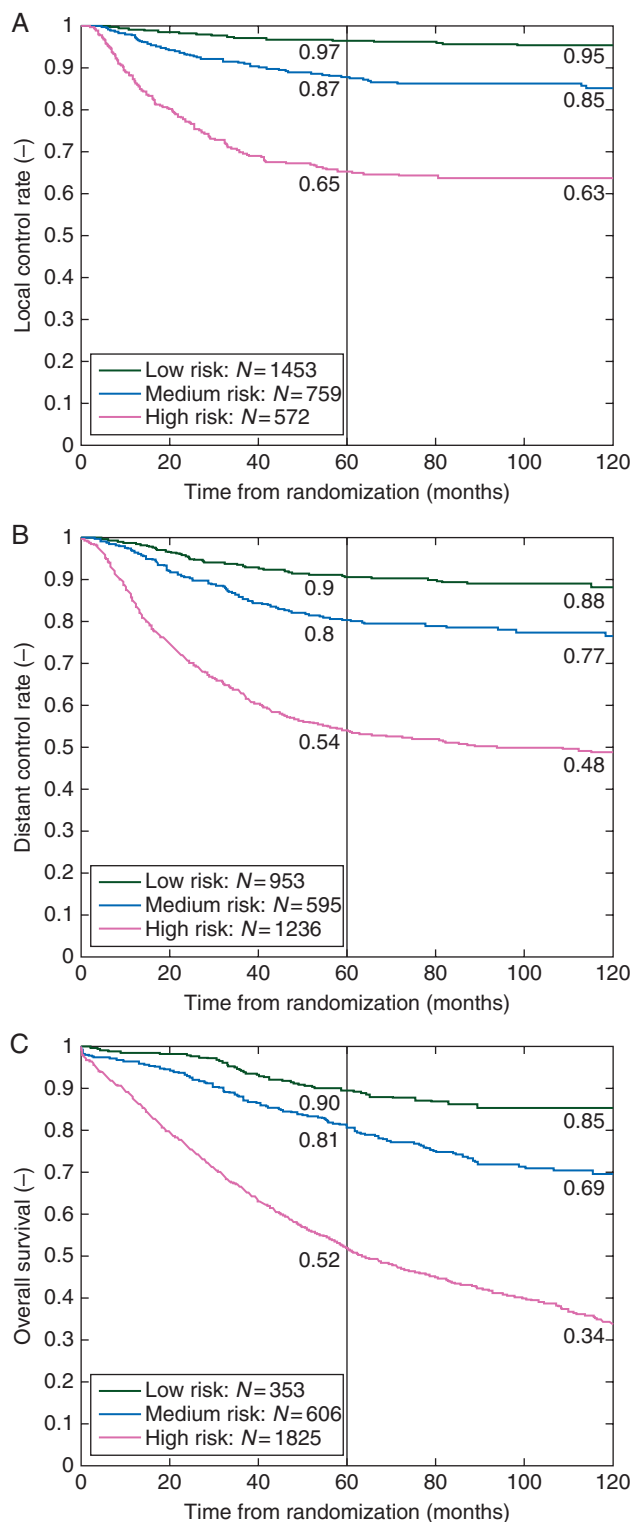
Figure 3. Kaplan–Meier curves stratified by low-, medium- or high-risk groups for (A) local recurrences, (B) distant metastases and (C) overall survival. Five- and 10-year control rates are reported in the plots.

of T-stage and distance from anatomical margins. Because the pathological T-stage used in the nomograms corresponds well with current MRI staging, the nomograms could be used as an extra tool to identify patients for which preoperative radiotherapy can be safely omitted.

In contrast to colon cancer, for which adjuvant chemotherapy improves survival according to many trials, evidence is less convincing for rectal cancer.

A 2012 Cochrane review pooled 21 randomized, controlled trials in which curatively operated rectal cancer patients were randomized between adjuvant chemotherapy and observation. The results show a significant increase in (disease-free) survival in the chemotherapy group [20]. However, the results are not specified for individual TNM stages, while in colon cancer the effect of chemotherapy significantly varies between different stages. Furthermore, a minority of the included studies used preoperative (chemo)radiation or TME surgery.

The recently published ADORE trial showed a survival benefit for stage II and III rectal cancer patients who were treated with FOLFOX chemotherapy after preoperative chemoradiation and TME surgery compared with fluorouracil and leucovorin alone [21].

Another recently published study is the CHRONICLE trial comparing adjuvant XELOX chemotherapy with observation for locally advanced rectal cancer patients who received preoperative chemoradiation. No statistically significant differences were found in disease-free survival or OS. However, the study has little power because it closed prematurely [22].

Despite the incomplete evidence for adjuvant chemotherapy for patients treated with preoperative radiotherapy and TME surgery, many oncologists believe that adjuvant chemotherapy might be beneficial for selected rectal cancer patients. Our nomograms can assist in the decision when to treat a rectal cancer patient with adjuvant chemotherapy, based on the individual risk for LR and death.

Another application of the nomograms could be the opportunity to tailor follow-up schedules. Apart from early management of complications, documentation of outcome and maintaining the patient–doctor relationship, the main aim of clinical follow-up is improvement of survival. While it seems obvious that intensive follow-up improves patient outcome, there is debate about the intensity. The recently published FACS trial showed that intensive follow-up provided an increased rate of surgical treatment of recurrence with curative intent compared with minimal follow-up without a difference in survival [23]. A 2014 review concludes that follow-up strategies should include risk stratification, suggesting that it is more useful to screen patients with a high risk of developing local or distant recurrence than those with a low risk [24]. The nomograms could assist in creating an individual follow-up schedule.

Inevitably, there are also downsides to this study. Since closure of the Swedish rectal cancer trial and the Dutch TME trial in the 1990s, many aspects have changed in the treatment of rectal cancer. First, the conventional surgery used in the Swedish trial has been abandoned in favour of TME surgery and it is likely that current quality of TME surgery is higher than the TME surgery carried out in the Dutch and Polish trial. Secondly, in the Dutch and the Swedish trial, resectability was in most cases assessed only by digital rectal examination. Since adequate preoperative imaging together with multidisciplinary team meetings have been shown to improve outcome, routine MRI scanning followed by a multidisciplinary team discussion are standard of care for rectal cancer in northern Europe [25]. In our study, tumour distance from the anal junction is the most

significant predictor of LR. The risk of an involved circumferential margin is especially high in low tumours because of distal coning of the mesorectum. However, with preoperative imaging and multidisciplinary assessment of resectability, tumour distance may have become a less important predictor of LR.

Another disadvantage of our study is that we could include only variables that were documented in all three clinical trials. Recently, several publications have reported on the predictive value of pathological and biological markers [26, 27]. A final issue is that we could not perform an external validation of the nomograms, but in that circumstance the 10-fold cross-validation was the most valid method with the lowest uncertainties.

In the future, we plan to refine our models with data from improved imaging modalities, and new morphological and biological markers to improve the predictive value of the nomograms and, most important, the selection of patients who will benefit most from (neo)adjuvant therapy and as well as those in whom side-effects probably outweigh the benefits.

At this moment, a European multidisciplinary, outcome-based quality improvement programme is underway: the European Registration of Cancer Care (EURECCA) [28]. This audit registration can accomplish transparency, benchmarking and feedback across national borders, and can decrease variation and improve overall outcomes around the continent. Furthermore, EURECCA can provide updated and detailed data that enhance the quality of the nomograms, resulting in even more refined prediction of adverse outcomes.

Until then, the current nomograms provide an easy-to-use prediction model to define risk groups, feasible for the consulting room, supporting physicians while informing patients and in the difficult selection of patients for postoperative adjuvant therapy or intensified follow-up. To disseminate this knowledge, we have made the models available online at http://www.predictcancer.org.

funding

disclosure

All authors declare that this submission is own work and has not been published before. All authors agree with the submission and the authors have declared no conflicts of interest.

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The *AURKA/TPX2* axis drives colon tumorigenesis cooperatively with *MYC*

Y. Takahashi[1,2,†], P. Sheridan[3,†], A. Niida[3,†], G. Sawada[1,2], R. Uchi[1], H. Mizuno[4], J. Kurashige[1], K. Sugimachi[1], S. Sasaki[5], Y. Shimada[6], K. Hase[7], M. Kusunoki[8], S. Kudo[9], M. Watanabe[10], K. Yamada[11], K. Sugihara[12], H. Yamamoto[2], A. Suzuki[13], Y. Doki[2], S. Miyano[3], M. Mori[2] & K. Mimori[1]*

[1]Department of Surgery, Kyushu University Beppu Hospital, Beppu; [2]Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita; [3]Laboratory of DNA Information Analysis, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo; [4]Department of Discovery Research, Kamakura Research Laboratories, Chugai Pharmaceutical Co., Ltd, Kamakura; [5]Department of Surgery, Omori Red Cross Hospital, Tokyo; [6]Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo; [7]Department of Surgery, National Defense Medical College, Tokorozawa; [8]Department of Surgery, Mie University, Tsu; [9]Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama; [10]Department of Surgery, Kitasato University, Sagamihara; [11]Department of Surgery, Takano Hospital, Kumamoto; [12]Department of Surgery, Tokyo Medical and Dental University, Tokyo; [13]Division of Cancer Genetics, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan

Background: The *MYC* oncogene has long been established as a central driver in many types of human cancers including colorectal cancer. However, the realization of *MYC*-targeting therapies remains elusive; as a result, synthetic lethal therapeutic approaches are alternatively being explored. A synthetic lethal therapeutic approach aims to kill *MYC*-driven tumors by targeting a certain co-regulator on the *MYC* pathway.

Patients and methods: We analyzed copy number and expression profiles from 130 colorectal cancer tumors together with publicly available datasets to identify co-regulators on the *MYC* pathway. Candidates were functionally tested by *in vitro* assays using colorectal cancer and normal fibroblast cell lines. Additionally, survival analyses were carried out on another 159 colorectal cancer patients and public datasets.

Results: Our *in silico* screening identified two *MYC* co-regulator candidates, *AURKA* and *TPX2*, which are interacting mitotic regulators located on chromosome 20q. We found the two candidates showed frequent co-amplification with the *MYC* locus while expression levels of *MYC* and the two genes were positively correlated with those of *MYC* downstream target genes across multiple cancer types. *In vitro*, the aberrant expression of *MYC*, *AURKA* and *TPX2* resulted in more aggressive anchorage-independent growth in normal fibroblast cells. Furthermore, knockdown of *AURKA* or *TPX2*, or treatment with an *AURKA*-specific inhibitor effectively suppressed the proliferation of *MYC*-expressing colorectal cancer cells. Additionally, combined high expression of *MYC*, *AURKA* and *TPX2* proved to be a poor prognostic indicator of colorectal cancer patient survival.

Conclusions: Through bioinformatic analyses and experiments, we proposed *TPX2* and *AURKA* as novel co-regulators on the *MYC* pathway. Inhibiting the *AURKA/TPX2* axis would be a novel synthetic lethal therapeutic approach for *MYC*-driven cancers.

Key words: MYC, AURKA, TPX2, synthetic lethality, co-amplification

Correspondence to: Prof. Koshi Mimori, Department of Surgery, Beppu Hospital, Kyushu University, 4546, Tsurumihara, Beppu 874-0838, Japan. Tel: +81-977-27-1650; Fax: +81-977-27-1651; E-mail: kmimori@beppu.kyushu-u.ac.jp

†These authors contributed equally to this work.