Gastric cancer : staging, treatment, and surgical quality assurance

Dikken, J.L.

PART I

Staging and prognostication

CHAPTER 4

Conditional probability of survival nomogram for one, two, and three year survivors after an R0 resection for gastric cancer

Johan L. Dikken[a,b], Raymond E. Baser[c], Mithat Gönen[c], Michael W. Kattan[d], Manish A. Shah[e], Marcel Verheij[f], Cornelis J.H. van de Velde[b], Murray F. Brennan[a], Daniel G. Coit[a]

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Departments of Surgery[a], Epidemiology and Biostatistics[b], and Medical Oncology[e], Memorial Sloan-Kettering Cancer Center, New York, USA
Department of Surgery[b], Leiden University Medical Center, Leiden, the Netherlands
Department of Quantative Health Sciences[d], Cleveland Clinic, Cleveland, USA
Department of Radiotherapy[f], the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

ABSTRACT

BACKGROUND

Survival estimates after curative surgery for gastric cancer are based on AJCC staging, or on more accurate multivariable nomograms. However, the risk of dying of gastric cancer is not constant over time, with most deaths occurring in the first two years after resection. Therefore, the prognosis for a patient who survives this critical period, improves. This improvement over time is termed Conditional Probability of Survival (CPS). Objectives of this study were to develop a CPS nomogram predicting 5-year disease-specific survival (DSS) from the day of surgery for patients surviving a specified period of time after a curative gastrectomy, and to explore whether variables available with follow-up improve the nomogram in the follow-up setting.

PATIENTS AND METHODS

A CPS nomogram was developed from a combined US-Dutch dataset, containing 1642 patients who underwent an R0 resection with or without chemotherapy/radiotherapy for gastric cancer. Weight loss, performance status, hemoglobin, and albumin one year after resection were added to the baseline variables of this nomogram.

RESULTS

The CPS nomogram was highly discriminating (concordance index: 0.772). Surviving one, two, or three years gives a median improvement of 5-year DSS from surgery of 7.2%, 19.1%, and 31.6%, as compared to the baseline prediction directly after surgery. Introduction of variables available at one year follow-up did not improve the nomogram.

CONCLUSIONS

A robust gastric cancer nomogram was developed, to predict survival for patients alive at time points after surgery. Introduction of additional variables available after one year of follow-up did not further improve this nomogram.

INTRODUCTION

Survival estimates for individual gastric cancer patients are usually based on AJCC staging,[1] or on more accurate multivariable nomograms.[2] A 5-year survival estimate based on either AJCC staging or a nomogram, represents the probability for a patient to be alive 5 years after surgery.

However, the risk of dying of gastric cancer is not constant over time, with most deaths occurring in the first two years after a curative resection (Figure 1). Therefore, the prognosis (and the 5-year survival probability from the day of surgery) of a patient who survives this critical period improves conditionally on having survived this period after surgery. This improvement of prognosis over time is termed Conditional Probability of Survival (CPS).

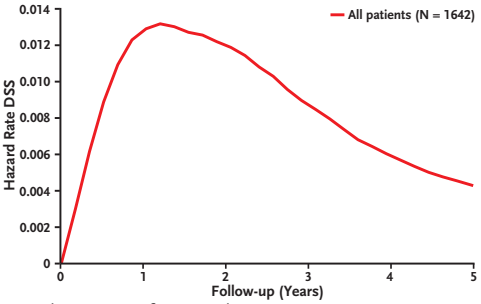
CPS is higher as compared to the survival probability at the time of surgery for a variety of cancers, including melanoma,[3] cancer of the CNS,[4] head and neck,[5] breast,[6] lung,[7] colon,[8,9] ovaries,[10] and stomach.[11] For gastric cancer, the difference between initial and conditional survival probability is greatest in patients with high stages who have a corresponding poor initial prognosis.[11]

Nomograms represent multivariable models predicting survival of individual patients based on several patient-specific parameters.[12] A US-derived nomogram predicting disease-specific survival (DSS) after an R0 resection for gastric cancer showed a high predictive accuracy with internal validation,[2] as well as external validation in Dutch[13], German[14], and Turkish[15] patients. This nomogram is based on patient and tumor characteristics of patients who underwent curative surgical resection alone, without adjuvant therapy. With the increasing clinical practice of preoperative and postoperative therapy for advanced gastric cancer, we felt that these patients should be included in an updated nomogram.

Although the current nomogram accurately estimates 5-year DSS directly after R0 surgery, it does not estimate the improved conditional survival of patients who remain alive at time points following resection, and is therefore not useful in the follow-up setting. Furthermore, we hypothesized that factors representing the patient's clinical status in the follow-up setting, such as weight loss and performance status, might contribute to and influence the estimate of patient prognosis in the follow-up setting in addition to variables available directly after surgery.

The first purpose of the current study is to develop a new, clinically useful nomogram predicting 5-year DSS after an R0 resection for gastric cancer, with or without chemotherapy and/or radiotherapy. The second purpose is to incorporate into this new nomogram the ability to predict conditional 5-year DSS from the day of surgery for patients surviving a specified period of time after an R0 resection for gastric cancer. The third purpose is to see if the introduction of variables available at one year of follow-up improves predictive accuracy of the new nomogram in the follow-up setting.

Figure 1. Hazard of death from gastric cancer for all patients (N = 1642)



DSS: disease-specific survival

PATIENTS AND METHODS

PATIENTS

The final dataset was derived from two prospective clinical databases.

The first database was from Memorial Sloan-Kettering Cancer Center (MSKCC), prospectively maintained since 1985, and the source of data for the initial gastric cancer nomogram.[2] This database contains information on 1473 patients who underwent curative resection for an adenocarcinoma of the stomach with or without (neo)adjuvant therapy, between January 1996 and December 2009. The study was approved by the MSKCC Institutional Review Board.

This dataset was combined with a Dutch dataset on which the original nomogram was validated,[13] containing information on 1078 patients who were randomized to undergo D1 or D2 lymph node dissection for adenocarcinoma of the stomach between 1989 and 1993, without receiving chemotherapy or radiation.[16,17] This study was approved by the principal investigator of the Dutch Gastric Cancer Trial.

From this combined dataset, patients with M1 disease (N = 441), patients with a positive resection margin (R1, R2, N = 216), and patients without all original nomogram variables available (N = 245) were excluded. Of the patients who died of unknown cause (N = 40), 7 were excluded and 33 were included as censored, leaving 1642 patients in the currently reported analyses. When the nomogram was regenerated excluding all 40 patients who died of unknown cause, no differences in CI were detected. The cause of death was based on available information on disease recurrence, which was generally confirmed with radiology, endoscopy, and/or histology.

SURVIVAL ANALYSES

Disease-specific survival (DSS) was calculated from the day of surgery until the day of death of gastric cancer (event), or death of other causes or the last day of follow-up (censored). The day of R0 surgery was chosen as the starting point for survival as this is the moment that all patients were considered 'disease-free'. The DSS hazard curve was plotted using kernel density smoothing.[18]

5-Year DSS in this study is defined as the probability of 5-year DSS *from the day of surgery*. Conditional Probability of Survival (CPS) was defined as the probability of DSS at five years from the day of surgery, given that the patient had not died of gastric cancer at a specified period of time (*x* years) after surgery. Calculations of CPS were performed using the standard definition of conditional probability:[19]

$$CPS\ (5|x) = S\ (5) / S\ (x)$$

in which

CPS (5/*x*) =	DSS probability 5 years after surgery, given the patient did not die of disease *x* years after surgery
S (5) =	DSS probability 5 years after surgery
S (*x*) =	DSS probability *x* years after surgery

For example, a patient's 1-year survival probability is 0.8, whereas his 5-year survival probability is 0.4. The probability of surviving the first 5 years after surgery, given that the patient already has survived the first year, is calculated as follows:

$$CPS\ (5|1) = S\ (5) / S\ (1) = 0.4 / 0.8 = 0.5$$

So, this patient's CS (5|1) is 0.5, which is higher than the originally 5-year survival probability (5|0), which is 0.4.

1. NEW NOMOGRAM PREDICTING 5-YEAR DSS

The first purpose of the study was to develop a new, clinically relevant nomogram, predicting 5-year DSS after an R0 resection for gastric cancer based on patients who underwent curative resection, with or without (neo)adjuvant chemotherapy and/or radiotherapy. Age, sex, primary site (distal, middle, proximal, and gastroesophageal junction), Lauren classification (diffuse, intestinal, mixed), maximum tumor diameter (cm), number of positive lymph nodes resected, number of negative lymph nodes resected and depth of invasion were entered into the Cox proportional hazards model predicting DSS. The effects of age, number of positive and negative lymph nodes, and invasion depth were modeled using restricted cubic splines. Although this new nomogram was initially developed to predict 5-year DSS, it also has the ability to predict DSS for any point in time after surgery, which is necessary for the next step.

As AJCC stage-specific survival is the most common way a prognosis of a patient is assessed, all patients were staged according to the 7th edition of the AJCC staging system.[1] Then, the predictive accuracy of the new nomogram was compared to that of the staging system.

2. PREDICTING CPS WITH THE NEW NOMOGRAM

The second purpose was to use the newly developed nomogram to predict DSS 5-years from the day of surgery, given that the patient had not died of gastric cancer for a specified time (*x* years) after resection. The new nomogram can give a DSS probability for any point in time after surgery. To calculate a CPS prediction for an individual patient, both the 5-year and the *x*-year DSS probability are predicted by the nomogram, followed by dividing the 5-year DSS probability by the *x*-year DSS probability. For patients surviving one, two and three years after surgery, the probability of surviving the first five years after surgery is calculated as follows:

CPS (5|1) = 5-year DSS probability / 1-year DSS probability
CPS (5|2) = 5-year DSS probability / 2-year DSS probability
CPS (5|3) = 5-year DSS probability / 3-year DSS probability

3. INTRODUCTION OF FOLLOW-UP VARIABLES INTO THE NEW DSS-NOMOGRAM

The third purpose of this study was to evaluate if introduction of variables available at follow-up would improve predictive accuracy of the new nomogram. Variables used in this nomogram are all available directly after surgery and do not represent a patient's condition at the moment of follow-up. We hypothesized that weight loss, Eastern Cooperative Oncology Group (ECOG) performance status (PS), hemoglobin (HGB) and albumin (ALB) might have additional predictive value for DSS to the original variables alone, given that the patient had survived a certain period in time.

Weight, PS, HGB and ALB were retrospectively recorded for one year disease-free survivors treated at MSKCC (N = 769), within a time interval of three months before or after one year of follow-up. Although the original aim was to collect these data for one, two and three year survivors, data availability was limited because of retrospective collection and smaller number of patients surviving up to two years after surgery. To calculate weight loss, two independent weights had to be recorded. If a weight was available 1-4 months before the weight measured at follow up, weight loss was calculated. If a patient had remained stable or gained weight, a weight loss of 0 was recorded. ECOG PS was recorded as 0-1 versus 2-3.

First the predictive accuracy of the nomogram using only original variables was assessed in one year disease-free survivors. Secondly, the nomogram was extended with the collected follow-up variables. Different combinations of old and new variables were used to explore whether incorporation of any or all of these variables improved the concordance index.

CALCULATING PREDICTIVE ACCURACY OF THE NOMOGRAMS

The nomogram was validated using two methods. First, discrimination was quantified with the concordance index (CI).[20] CI is a measure of how well the predictions match the

observed outcomes. In particular, CI is the probability that, in a randomly selected pair of patients, the patient with the better prediction also has the longer observed survival. CI of a nomogram is calculated by comparing all possible pairs of patients in the dataset, and adding scores of all individual pairs. The current dataset contains censored patients, who did not die of gastric cancer at the last follow-up. If such a patient has the shorter follow-up in a certain pair, it is impossible to determine which of the two patients had the best outcome. These pairs are called non-informative, and were excluded from the CI calculation. All CIs were corrected for overfit by bootstrapping. A bootstrapped significance test was used to assess differences between CIs.
Secondly, calibration was assessed by grouping patients with respect to their nomogram-predicted probabilities and then comparing the mean of the group with the observed DSS Kaplan-Meier estimate, correcting by bootstrap for overfit. All analyses were performed using R (version 2.11.0).

RESULTS

Patient characteristics are presented in Table 1. Median follow-up of all patients was 66 months, and 565 (34%) events (death of disease) occurred in this population.

1. NEW NOMOGRAM PREDICTING 5-YEAR DSS

A nomogram predicting 5-year DSS after an R0 resection for gastric cancer directly after surgery (0-year survivors) was developed based on the current dataset of 1642 patients (Figure 2). Variables that were used in the original nomogram,[2] are highly predictive in the current dataset. The CI of the new nomogram is 0.772. A calibration plot for this nomogram shows a high correspondence between the predicted and actual survival (Figure 3a).
Chemotherapy with or without radiation was administered to 29.5% of the patients. However, the addition of a variable in the nomogram indicating the use of chemotherapy or radiation did not improve the CI of the new nomogram. When using the current dataset to compare the new nomogram with the previously published nomogram,[2] there was no difference in CI (0.772 versus 0.771, $P = 0.18$).
When comparing this nomogram with the AJCC staging system 7th edition, the nomogram outperformed the staging system in discriminative ability (CI = 0.772 versus 0.766, $P = 0.03$).

2. PREDICTING CPS WITH THE NEW NOMOGRAM

The new nomogram can predict 5-year DSS from the day of surgery for patients alive at time points up to 5 years after an R0 resection for gastric cancer. The probability of 5-year DSS from the day of surgery shows a median increase of 7.2%, 19.1% and 31.6%, respectively for one, two and three-year survivors, as compared to patients for who 5-year DSS was predicted directly after surgery (Table 2).

Table 1. Patient characteristics (N = 1642)

	N	%
Sex		
male	1016	*61.9*
female	626	*38.1*
Age		
mean ± SD	64.9 ± 11.9	
median (IQR)	67 (57-74)	
Primary site		
GEJ	359	*21.9*
proximal	283	*17.2*
middle	415	*25.3*
distal	585	*35.6*
Lauren histotype		
intestinal	1050	*63.9*
diffuse	434	*26.4*
mixed	158	*9.6*
Invasion depth		
mucosa	170	*10.4*
submucosa	325	*19.8*
muscularis propria	243	*14.8*
subserosa	340	*20.7*
serosa	479	*29.2*
adjacent organs	85	*5.2*
Tumor size (cm)		
mean ± SD	4.1 ± 2.9	
No. of nodes evaluated		
mean ± SD	23.6 ± 12.6	
median (IQR)	21 (15-31)	
No. of positive nodes		
mean ± SD	3.0 ± 5.5	
median (IQR)	1 (0-4)	
Preoperative/postoperative chemotherapy/radiotherapy	484	*29.5*

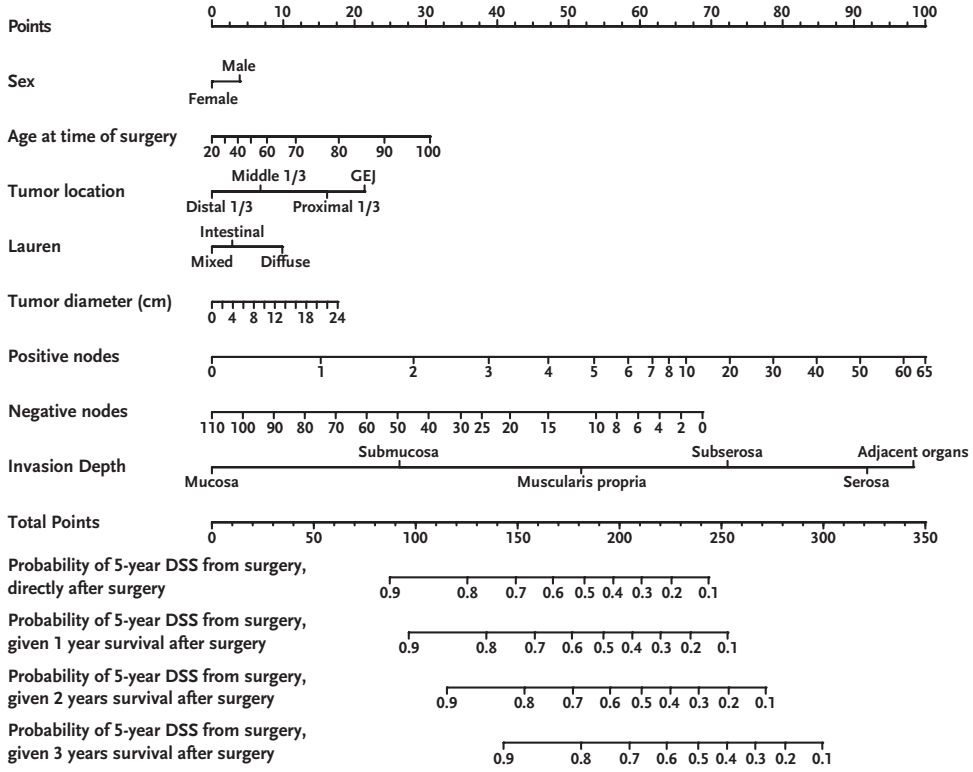
SD: standard deviation, IQR: inter quartile range, GEJ: gastro esophageal junction

This is illustrated in Figure 3b, in which the three curves show the improvement in 5-year DSS probability from the day of surgery for one, two and three year survivors as compared to 0-year survivors.

3. Introduction of follow-up variables into the original DSS-nomogram

Weight loss, performance status, HGB and ALB were retrospectively recorded for patients that were alive and had not recurred one year after surgery. Table 3 compares the CI of the nomogram based on original variables only, with the CI of nomograms with follow-up variables. Addition of weight loss, hemoglobin, albumin, and performance status or a combination of those did not improve the CI of the nomogram that was based on original variables only.

Figure 2. Nomogram predicting 5-year disease-specific survival from the day of surgery based on 1642 patients who underwent an R0 resection for gastric cancer



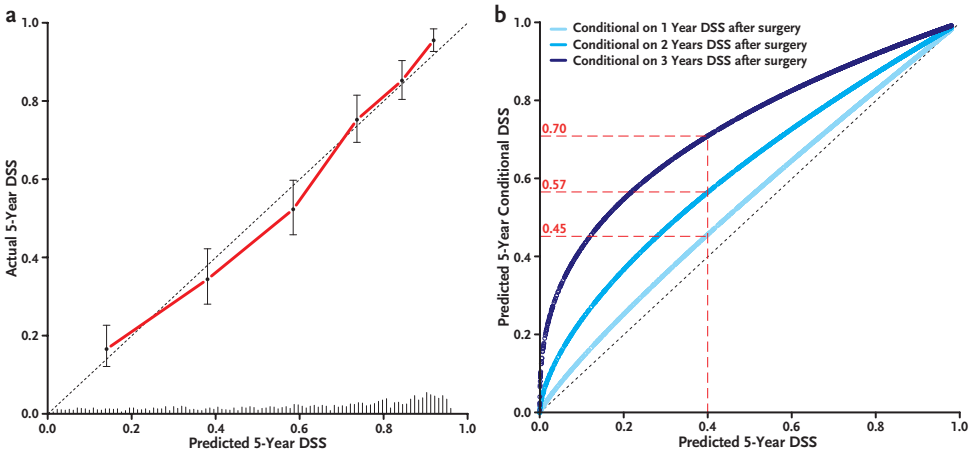
Instructions
Locate the patient's sex on the **Sex** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards gastric cancer-specific death the patient receives for his or her sex. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total points** axis. Draw a line straight down to the **disease-specific survival** axes to find the patient's probability of 5-year DSS from the day of surgery, directly after surgery, or one, two or three years after surgery.

DISCUSSION

The original gastric cancer nomogram that was published in 2003 predicts five and nine-year DSS after an R0 resection of gastric cancer, based on patients who only received an R0 resection without chemotherapy or radiation.[2] Although this nomogram is highly precise, and has been validated in databases from three different countries in Europe,[13-15] the predictive accuracy in patients who received chemotherapy or radiation has not been investigated.

In the present study, a new nomogram was developed, predicting 5-year DSS for patients who received an R0 resection for gastric cancer, with or without chemotherapy and/or radiation. To increase nomogram accuracy, MSKCC data were combined with data in which the original nomogram has been previously validated[13]. Incidence rates for

Figure 3. Calibration plots for the 5-year disease-specific survival nomogram (N = 1642)
(a) predicting 5-year DSS directly after surgery (0-year survivors)
(b) predicting 5-year DSS conditional on surviving of gastric cancer for 1, 2 or 3 years



Instructions Figure 3b
In the example the nomogram predicts a 5-year DSS of 40%.
- step 1: draw a line from the original (0-year survival prediction) axis.
- step 2: the probability for this patient to survive the first 5 years after surgery, without dying of gastric cancer is:
  - 40% directly after surgery (0 years survival)
  - 45% after surviving 1 year without dying of gastric cancer
  - 57% after surviving 2 years without dying of gastric cancer
  - 70% after surviving 3 years without dying of gastric cancer

gastric cancer are generally comparable between the USA and the Netherlands[21]. When comparing the new with the previously published nomogram, no differences in CI were detected. This attests to the strength of the initial predictive model and indicates robustness of the new nomogram. Overall, the discriminative ability (CI) of the new nomogram is relatively high by standards of cancer prognosis. The calibration plot (Figure 3a), which shows how well the nomogram predictions (x-axis) correspond with the actual unconditional 5-year DSS of the patients in this study (y-axis), reveals a high predictive accuracy. Furthermore, the CI of the new nomogram is higher than the CI of the AJCC staging system, indicating more accurate predictions are provided by the nomogram as compared to the AJCC staging system.

With the original gastric cancer nomogram, there was no accurate way to predict the outcome for patients who had survived over a certain period in time after their surgery for gastric cancer, as the original nomogram prediction is only useful directly after surgery and not after a certain period of follow-up. Using the new nomogram, it is now possible to estimate the (improved) probability of 5-year DSS from the day of surgery for patients alive at time points after an R0 resection for gastric cancer. The improvement in prognosis ranges from a median of 7.2% for 1-year survivors to a median of 31.6% for

Table 2. Increase of 5-year DSS from the day of surgery, when compared with the baseline prediction directly after surgery (0-year survival), using the new nomogram

	Median increase (%)	IQR (%)
1 year after surgery	7.2	2.9-17.6
2 years after surgery	19.1	7.4-50.7
3 years after surgery	31.6	11.9-90.6

IQR: inter quartile range

Table 3. Introduction of follow-up variables into the nomogram. All patients are one-year disease-free survivors from the MSKCC group

Added variables	No. of patients with available data	No. of events in group	Step 1 Nomogram with original variables (CCI)	Step 2 Nomogram with new variables (CCI)[a]
only original variables	769	170	0.721	
PS	485	103	0.731	0.728
WL	377	93	0.712	0.729
HGB	319	83	0.736	0.732
ALB	311	81	0.725	0.734
WL+ALB	249	69	0.702	0.739
HGB+ALB	298	78	0.731	0.734
PA+HGB+ALB	275	71	0.720	0.729
PA+WL+ALB	245	68	0.696	0.729
WL+HGB+ALB	238	66	0.706	0.727
PS+WL+HGB+ALB	235	66	0.705	0.723

[a]None of the differences in CI between step 1 and step 2 were significant
WL: weight loss, PS: performance status, HGB: hemoglobin, ALB: albumin, CCI: corrected concordance index, event: death of disease

3-year survivors (Table 2). The added feature of the nomogram will be useful for patient counseling, as it is now possible to give a patient an accurate estimation of the improved survival probability as time after surgery goes by, and for the timing of surveillance, clinical assessments, and diagnostic tests. For example, patients for whom the CPS after a certain period is nearly a 100% might consider to reduce the follow-up frequency, while patients with a relatively low CPS might have more frequent follow-up visits.

The CPS for an individual patient can be calculated manually with Figure 2, simply by entering the values and reading from the correct DSS axis in the bottom of the figure. CPS can also be calculated with Figure 3b, using the 0-year survival prediction from Figure 2. For example, a patient's 5-year DSS probability derived from the 0-year survival axis in Figure 2 is 0.4. By entering the 5-year DSS probability of 0.4 on the x-axis of Figure 3b, the probability of 5-year DSS conditional on the fact that the patient survives one, two or three years after surgery can be derived from the y-axis and is 0.47, 0.58 and 0.73 respectively. The new nomogram can also be accessed on the internet,[22] and can calculate CPS by entering patient variables and the time of follow-up.

Extending static nomograms to provide conditional survival estimates has been previously illustrated for both prostate cancer and renal cell carcinoma.[23,24] Both studies use variables available directly after surgery. Unique to the approach of the current study

is the use of variables available with follow-up, as it can be assumed that there are clinical markers representing the current status of the patient that ultimately become more important than baseline characteristics and surgical variables.
The third aim of the present study was to explore whether the introduction of clinical variables available at follow-up could improve the accuracy of the 5-year DSS nomogram. This objective was based on the assumption that as time goes by after diagnosis, clinical factors other than surgical and pathological variables available only at the time of surgery may become important in predicting survival in gastric cancer. This approach is entirely novel in the development of nomograms. Introduction of new variables for the nomogram, however, did not improve the CI, as can be seen in Table 3: for most 'cohorts' with a certain newly added variable available, the CI for the nomogram with original variables was essentially equal to the CI of the nomogram with follow-up variables. This might be explained by the limited availability of follow-up variables (weight loss, PS, HGB, ALB), which has led to a relatively low number of one-year survivors that could be included in these analyses. Clinical data on two- and three-year disease-free survivors was even more limited and no analyses on these patients could be performed. Secondly, with the very high CI of the nomogram based on baseline variables, newly added follow-up variables would need to be very strongly predictive in order to improve the CI, which might not be the case with the currently used new variables. In order to reassess this question in a more thorough way, follow-up data should be prospectively collected at fixed time points. The absence of an improvement in CI with the introduction of multimodality therapy use in the nomogram does not necessarily indicate that chemotherapy and/or radiotherapy did not affect survival in the current population. Rather, the predictive accuracy of the current nomogram can be considered very high by means of concordance, and despite a proven effect on survival, multimodality therapy use was simply unable to further improve this concordance.

In conclusion, decisions about postoperative adjuvant therapy, and intensity of follow-up are based on our best risk assessments at the time of surgery. However, follow-up is a dynamic process, with the risk of cancer-related death decreasing over time. The current nomogram has the ability to estimate risk of cancer-related death at time points after initial treatment, and offers useful insight to the patient and clinician about what to expect in the years ahead.

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