PART I

Staging and prognostication

CHAPTER 5

Performance of a nomogram predicting disease-specific survival after an Ro resection for gastric cancer in patients receiving postoperative chemoradiotherapy

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Submitted

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ABSTRACT

BACKGROUND

The internationally validated Memorial Sloan-Kettering Cancer Center (MSKCC) gastric cancer nomogram was based on patients who underwent curative (R0) gastrectomy, without any other therapy. The purpose of the current study was to assess the performance of this gastric cancer nomogram in patients who received chemoradiotherapy after an R0 resection for gastric cancer.

PATIENTS AND METHODS

In a combined dataset of 76 patients from the Netherlands Cancer Institute (NKI), and 63 patients from MSKCC, who received postoperative chemoradiotherapy (CRT) after an R0 gastrectomy, the nomogram was validated by means of concordance index and a calibration plot.

RESULTS

The concordance index for the nomogram was 0.64, which was lower than the CI of the nomogram for patients who received no adjuvant therapy (0.80). In the calibration plot, observed survival was about 20% higher than the nomogram predicted survival for patients receiving postoperative CRT.

CONCLUSIONS

The nomogram significantly underpredicted survival for patients in the current study, suggesting an impact of postoperative CRT on survival in patients who underwent an R0 resection for gastric cancer, which has been proved by randomized controlled trials. This analysis stresses the need for updating nomograms with the incorporation of (neo) adjuvant strategies.

INTRODUCTION

Until the late nineties, surgery was considered the only treatment option for resectable gastric cancer.[1] While complete resection remains the only potentially curative treatment, several recent studies have demonstrated that combining surgery with other modalities can improve outcome. The British MAGIC trial showed improved overall survival after perioperative chemotherapy for resectable, advanced gastric and distal esophageal cancer.[2] A Japanese randomized study found improved overall survival after postoperative administration of S-1 (an oral fluoropyrimidine).[3] The US Intergroup 0116 study demonstrated that postoperative chemoradiotherapy (CRT) improves overall survival among patients who have undergone an R0 resection for advanced gastric cancer.[4] As a result of the Intergroup 0116 trial, postoperative CRT is now considered a standard treatment option for patients receiving surgery without preoperative chemotherapy for locally advanced gastric cancer.[5,6]

The identification of patients who should undergo postoperative treatment can be done by postoperative AJCC tumor stage, but also with the use of nomograms. Nomograms are prediction tools that calculate survival probability for individual patients based on patient, tumor and treatment characteristics. These statistically based tools not only use the factors included in a clinical staging system but also incorporate additional factors suspected to have an effect on outcome. The internationally validated MSKCC gastric cancer nomogram predicts disease-specific survival (DSS) after an R0 resection for gastric cancer (Figure 1).[7] Patients included to develop the nomogram underwent surgery only, and did not receive any other therapy. Therefore, the nomogram can be used to identify high-risk patients who underwent surgery only and might be candidates for postoperative therapy. However, it is unknown how well the nomogram will predict survival for patients who underwent surgery followed by postoperative chemoradiotherapy. Based on the survival benefit for postoperative chemoradiotherapy that was shown in the Intergroup 0116 study, it is suspected that the nomogram will underpredict survival for patients receiving postoperative chemoradiotherapy. Therefore, the purpose of the current study was to assess the performance of the gastric cancer nomogram in patients who received postoperative chemoradiotherapy after an R0 resection for gastric cancer.

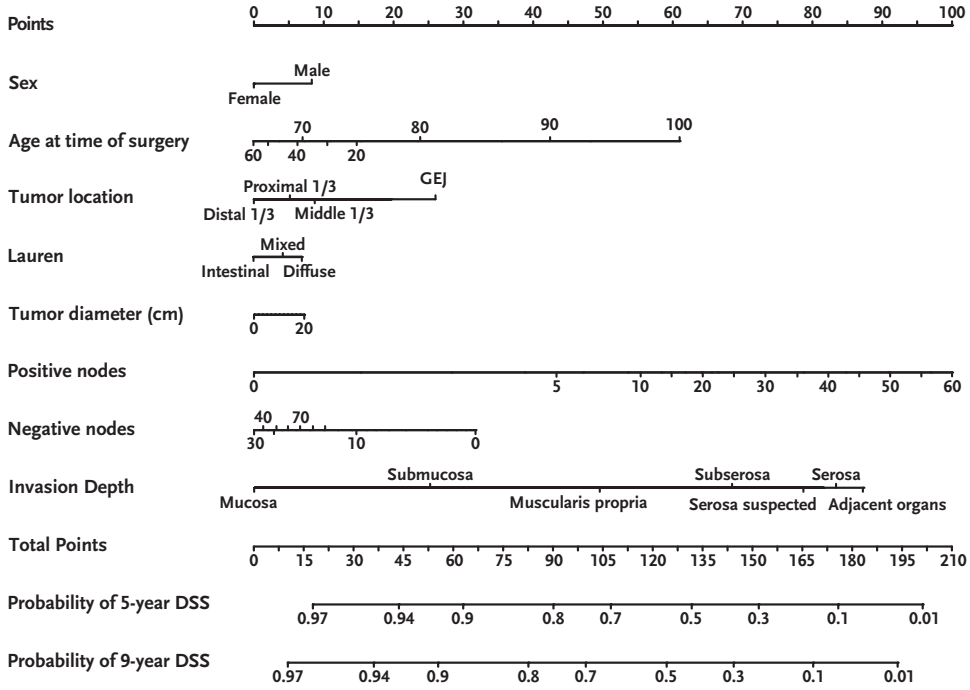
PATIENTS AND METHODS

A combined dataset with patients treated at the Netherlands Cancer Institute and patients treated at Memorial Sloan-Kettering Cancer Center was used for this analysis.

NETHERLANDS CANCER INSTITUTE PHASE I/II STUDIES

From 2000 to 2008, 113 patients with locally advanced adenocarcinoma of the stomach or gastroesophageal junction, stage Ib-IV according to the 6th edition of the American Joint Committee on Cancer (AJCC),[8] underwent gastric resection followed by CRT at the Netherlands Cancer Institute. No patients received preoperative therapy. Patients who

Figure 1. Previously published nomogram predicting disease-specific survival (DSS) after an R0 resection for gastric cancer



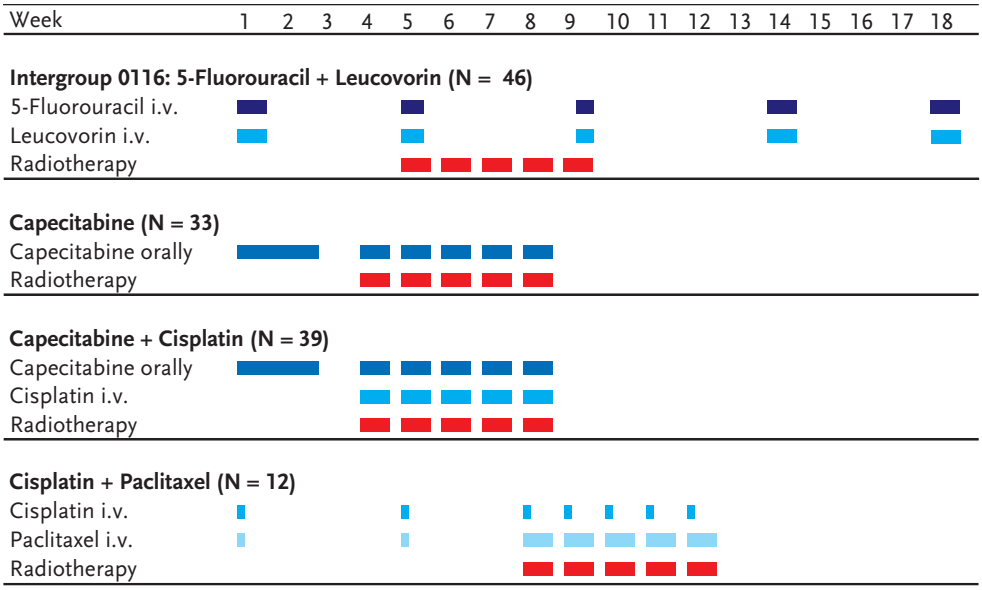
Instructions
Locate the patient's sex on the **Sex** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards gastric cancer-specific death the patient receives for his or her sex. Repeat this process for the other axes, each time drawing straight upward to the **Points** 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 surviving gastric cancer assuming he or she does not die of another cause first.

did not undergo an R0 resection (N = 29), and patients for whom not all the nomogram variables were available (N = 8) were excluded, leaving 76 patients for analysis.

All patients underwent R0 gastrectomy with at least a D1 lymph node dissection, without routine splenectomy or pancreatic tail resection. After satisfactory recovery from surgery, patients were offered participation in one of the phase I-II trials of postoperative chemoradiotherapy.

Patients were treated with 25 fractions of 1.8 Gy of radiotherapy to a total dose of 45 Gy (5 fractions/week). The clinical target volume consisted of the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes. Radiotherapy was combined with escalating doses of capecitabine and cisplatin (N = 39),[9] capecitabine (N = 33),[10] or with fluorouracil (5-FU) and leucovorin, according to the Intergroup 0116 scheme (N = 4) (Figure 2). The design of these studies is described in more detail in the original publications.[9,10]

Figure 2. Chemoradiotherapy regimens



Radiotherapy was administered in 5 fractions/week
i.v.: intravenous

MEMORIAL SLOAN-KETTERING CANCER CENTER

Patients treated at Memorial Sloan-Kettering Cancer Center (MSKCC) were selected from a prospectively maintained database containing information on 2590 patients who underwent a resection for an adenocarcinoma of the stomach between 1985 and 2009. Of these 2590 patients, 72 patients received postoperative chemoradiotherapy between 2000 and 2009. Patients who received preoperative chemotherapy (N = 8) and patients who did not undergo an R0 resection (N = 2) were excluded, leaving 63 patients for analysis.

All patients underwent a gastrectomy, usually with D2 lymphadenectomy, without routine splenectomy or pancreatic tail resection. Postoperatively, all patients received 45 Gy of radiotherapy on the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes in 25 fractions of 1.8 Gy.

Radiotherapy was combined with one of several chemotherapy regimens. The majority of patients (N = 43) received 5-FU with leucovorin according to the Intergroup 0116 protocol (Figure 2). The other patients received cisplatin combined with paclitaxel (N = 10), cisplatin, paclitaxel and 5-FU (N = 2), epirubicin, cisplatin and 5-FU (N = 4) single-agent 5-FU (N = 2), or single-agent capecitabine (N = 2). This study was approved by the Institutional Review Board of MSKCC.

Table 1. Patient characteristics (N = 139)

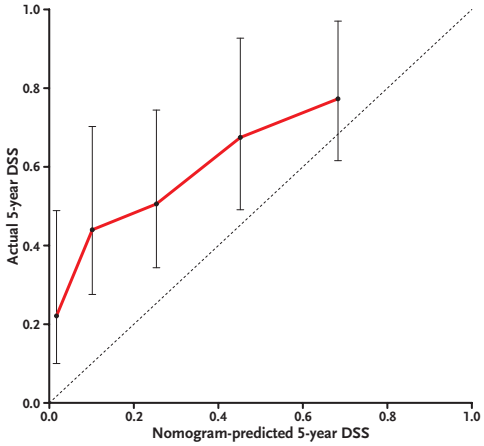
	Total (N = 139)		NKI (N = 76)		MSKCC (N = 63)	
	N	%	N	%	N	%
Sex						
male	96	*69.1*	56	*73.7*	40	*63.5*
female	43	*30.9*	20	*26.3*	23	*36.5*
Age						
median (IQR)	61	(51-68)	57	(49-65)	65	(52-72)
Primary site						
GEJ	16	*11.5*	9	*11.8*	7	*11.1*
proximal	17	*12.2*	9	*11.8*	8	*12.7*
middle	47	*33.8*	26	*34.2*	21	*33.3*
distal	59	*42.5*	32	*42.1*	27	*42.9*
Lauren classification						
intestinal	56	*40.3*	28	*36.8*	28	*44.4*
diffuse	54	*38.9*	31	*40.8*	23	*36.5*
mixed	29	*20.9*	17	*22.4*	12	*19.0*
Invasion depth						
mucosa	1	*0.7*	1	*1.3*	0	*0*
submucosa	7	*5.0*	0	*0*	7	*11.1*
muscularis propria	13	*9.4*	6	*7.9*	7	*11.1*
subserosa	34	*24.5*	24	*31.6*	10	*15.9*
serosa suspected	21	*15.1*	21	*27.6*	0	*0*
serosa	58	*41.7*	21	*27.6*	37	*58.7*
adjacent organs	5	*3.6*	3	*3.9*	2	*3.2*
Tumor size						
median (IQR)	5	(2.9-6.5)	5.0	(3.5-6.8)	4.5	(2.8-6.5)
Positive lymph nodes						
median (IQR)	4	(2-10)	4	(3-11)	5	(2-9)
Negative lymph nodes						
median (IQR)	11	(4-20)	4	(2-11)	17	(13-26)
AJCC 7th edition stage group						
IA	0	*0*	0	*0*	0	*0*
IB	3	*2.2*	1	*1.3*	2	*3.2*
IIA	7	*5.0*	1	*1.3*	6	*9.5*
IIB	20	*14.4*	10	*13.2*	10	*15.9*
IIIA	39	*28.1*	25	*32.9*	14	*22.2*
IIIB	33	*23.7*	20	*26.3*	13	*20.6*
IIIC	37	*26.6*	19	*25.0*	18	*28.6*

STATISTICAL ANALYSIS

Disease-specific survival (DSS) was calculated from the day of surgery until death of gastric cancer (event) or death of other causes, or alive at last follow-up (censored). The Cox proportional hazards model was used to compare DSS between NKI and MSKCC patients adjusted for factors present in the nomogram.

In agreement with our previous report, the following prognostic variables were used for the nomogram: age, gender, primary site (distal one-third, middle one-third, proximal one-third, and gastroesophageal junction), Lauren histologic type (diffuse, intestinal, mixed), number of positive lymph nodes resected, number of negative lymph nodes resected, and invasion depth. For each of the patients, the nomogram 5-year DSS probability was computed.

Figure 3. Calibration plot of the nomogram validated in patients who received postoperative chemoradiotherapy (N = 139)



Nomogram validation comprised two activities. First, discrimination was quantified with the concordance index (CI).[11] The concordance index is similar to the area under the receiver operating characteristic curve, but appropriate for censored data, and ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). Given a randomly selected pair of patients, the concordance index is the probability that the patient who dies first had the worst predicted outcome by the nomogram. Secondly, calibration was assessed. This was done by grouping patients with respect to their nomogram predicted probabilities and then comparing the mean of the group with the observed Kaplan-Meier estimate of DSS. All analyses were performed using R statistical software package (version 2.11.0).

RESULTS

Table 1 depicts patient characteristics of the 139 patients that were included in the current study. Most patients (69.1%) were male. The median age in the NKI group (57 years) was lower as compared to the median age in MSKCC patients (65 years). In both groups, the majority of patients had a tumor in the middle (33.8%) or distal stomach (42.5%). As suspected, most patients (78.4%) had pathology stage III gastric cancer; this proportion being slightly higher for the NKI group (84.2%) than for the MSKCC group (71.4%).
With a median follow-up of 51 months, 62 patients (44.6%) had died of disease. Median survival was almost 6 years (71 months). On multivariate Cox regression, adjusting for the prediction based on all variables present in the nomogram, no significant difference in DSS was detected between NKI and MSKCC patients (HR 0.996, $P = 0.989$), indicating the feasibility of combining both datasets to assess the performance of the nomogram.
The nomogram performance in the current patient cohort was tested in two ways. First, discrimination between individual patients was assessed with the concordance index (CI). The CI for the nomogram was 0.64, which can be considered moderately predictive.

However, this is lower than the CI for patients who received no adjuvant therapy, which was 0.80.[7] Secondly, the observed and the predicted survival were compared with a calibration plot (Figure 3), which showed that the nomogram significantly underpredicted the 5-year DSS probability in the current patient cohort with about 20%.

DISCUSSION

In the current study, the performance of the existing gastric cancer nomogram was evaluated for patients who received postoperative chemoradiotherapy after an R0 resection for gastric cancer. In the current patient cohort, discriminative ability, which was tested by means of the CI, was lower than the CI for patients who received no adjuvant therapy.[7] As expected based on results from the Intergroup 0116 study, the nomogram significantly underpredicted 5-year DSS in the current patient cohort, indicating the need for updating nomograms with the incorporation of (neo)adjuvant strategies.

Postoperative CRT has proven to improve outcomes for patients with resectable gastric cancer in several early randomized trials in the eighties and nineties.[12-15] However, patient numbers in these studies were small (below 200), limiting the value of this observation. The key trial supporting the use of postoperative CRT in advanced, resectable gastric cancer is the Intergroup 0116 trial.[4] In this study, 556 patients were randomized after surgery for postoperative CRT with 5-FU and leucovorin, or no further treatment. The 5-year overall survival rate was significantly higher in patients receiving chemoradiotherapy (40% vs 28%), which was confirmed in a recent update with follow-up of over 10 years.[16] This trial was criticized because of the low number of D2 dissections (10%), the fact that patients were highly selected (only R0 resections with adequate postoperative recovery), the treatment compliance of 64%, and the complexity of the chemoradiotherapy protocol. Despite this critique, since publication of the Intergroup 0116 results in 2001, postoperative CRT has become a standard treatment option in both Europe and the United States for patients undergoing curative resection of stage Ib-IV gastric cancer who did not receive neoadjuvant therapy.[5,6] This might also be caused by the high number of patients who first receive surgery, after which their postoperative treatment plan is discussed in a multidisciplinary team. A SEER database analysis showed that postoperative radiotherapy use in the United States increased from 6.5% to 13.3% before and after 2000, likely reflecting an increased use of postoperative CRT.[17]

During the past years, the concept of concurrent postoperative CRT has further evolved, with newer, potentially less toxic CRT schedules that have been tested in several studies. A study from Germany in which patients were treated with 45 Gy of radiotherapy plus folinic acid, 5-FU, paclitaxel and cisplatin, showed that this four-drug regimen has an acceptable toxicity profile.[18] In a US Phase II study, a combination of cisplatin, paclitaxel, and radiotherapy showed an acceptable toxicity profile, but failed show a favourable disease-free survival rate.[19] Several phase I/II studies from the Netherlands combining capecitabine with or without cisplatin with radiotherapy revealed feasibility of these

regimens.[9,10,20] A regimen with daily capecitabine and weekly cisplatin that emerged from these studies is currently tested in a phase III randomized trial (CRITICS, clinicaltrials.gov NCT00407186).

Other new regimens that have been tested include irinotecan,[21] docetaxel,[22] and liposomal cisplatin.[23] A US Intergroup trial comparing the Intergroup 0116 regimen with postoperative CRT with epiribicin, cisplatin, and 5-FU (ECF) showed that the ECF regimen has an acceptable toxicity profile, without an improvement in survival compared to 5-FU and leucovorin.[24] In the Korean ARTIST trial, 458 patients were randomized after gastrectomy with a D2 lymphadenectomy for postoperative chemotherapy with cisplatin and capecitabine with or without 45 Gy radiotherapy. Compliance for the postoperative schedule in both arms was high (75% and 82%), but no difference in disease free survival was shown.[25]

The currently available gastric cancer nomogram can be used to estimate 5-year and 9-year DSS after an R0 resection for gastric cancer.[7] The nomogram shows a high predictive accuracy with internal validation, and with external validation in several European datasets.[26-28] This nomogram has two distinct purposes: risk stratification and informing patients. With risk stratification, the survival probability of an individual patient that is predicted by the nomogram can be used to determine if a patient is at high risk of recurrence, and should consider postoperative therapy. Secondly, patients can be informed on their risk of DSS. Because none of the patients from the datasets in which the nomogram was developed received any form of preoperative or postoperative chemotherapy or radiation, the nomogram can very well be used to stratify patients who underwent surgery into a high-risk and a low-risk category. This risk stratification gives a recommendation about postoperative therapy use. As it is expected that postoperative chemoradiotherapy will improve survival, it can be hypothesized that the nomogram will underpredict survival in patients receiving postoperative chemoradiotherapy.

In the current study, the performance of the gastric cancer nomogram was assessed in a cohort of 139 patients who received postoperative CRT after an R0 resection for gastric cancer, without receiving preoperative therapy. Different CRT schedules were used reflecting the ongoing search for better and less toxic CRT regimens over the years. Most patients in the current study had stage III disease based on postoperative pathology, which is expected since these patients are candidates for adjuvant therapy. Neither of the populations (NKI or MSKCC) was significantly associated with better survival after correcting for variables present in the nomogram.

The number of events in this dataset was too small to create a new nomogram specifically for patients who received postoperative CRT. However, the number of events was sufficient to assess the performance of the existing nomogram in this dataset. The concordance index, which indicates discriminative ability, was moderately high in this population. The calibration plot at 5-years, however, showed significant underprediction of the nomogram in this patient cohort of about 20%. Since postoperative CRT has

shown to improve survival compared to surgery alone in a randomized setting, and the nomogram is based on surgery only patients, this was an expected finding. Therefore, the nomogram provided DSS probability should not directly be used in patients who received postoperative CRT. Since it is unlikely that a large group of patients who received chemoradiation and who are sufficiently followed can be assembled to construct a separate nomogram, we recommend that, as a rule of thumb, approximately 20% should be added to the nomogram-predicted 5-year DSS probability.

In conclusion, while the gastric cancer nomogram accurately risk-stratifies patients who received an R0 resection alone for gastric cancer, it significantly underpredicts 5-year DSS for patients who receive postoperative CRT after an R0 resection for gastric cancer.

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