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Blast from the past: Perioperative use of the Maruyama computer program for prediction of lymph node involvement in the surgical treatment of gastric cancer following neoadjuvant chemotherapy

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ABSTRACT

Background: Surgical quality assurance is a key element of gastric cancer treatment. The Maruyama Computer Program (MCP) allows to predict lymph node involvement in stations no. 1–16. The aim of the current study was to evaluate the accuracy of the MCP predictions in GC patients treated with neoadjuvant chemotherapy (nCTH) followed by gastrectomy with adequate lymphadenectomy.
Methods: 101 patients who underwent preoperative nCTH followed by D2 gastrectomy with curative intent were analysed. The response to nCTH was measured using the tumour regression grade system.
Results: Test sensitivity, specificity, PPV, NPV and accuracy of the MCP were 92%, 33%, 41%, 89%, and 53%, respectively. In patients with response to nCTH, number of false positive (FP) results was significantly higher than in patients who did not respond to nCTH both in the N1 (56.3% vs 28.9%, $p < 0.0001$) and in the N2 (59% vs 41%, $p < 0.0001$) trier. The risk for FP results was 6 times higher in N1 (OR = 6.50, 95%CI: 3.91–10.82,; $p < 0.0001$) and N2 (OR = 5.84, 95%CI: 2.85–11.96; $p < 0.0001$) triers. In patients with intestinal type GC, the risk for FP results was 4 times higher than in other histologic types of GC in both N1 (OR = 4.23, 95%CI: 2.58–6.95; $p < 0.0001$) and N2 (OR = 4.23, 95%CI: 2.02–9.62; $p = 0.0002$) triers.
Conclusions: MCP predictions in the GC patients treated with nCTH have low specificity due to significantly high number of FP results. Noticeably low accuracy level of predictions indicate a need for new prediction models, based on Laurén classification, since it may provide some information on expected regression grade.

Introduction

Despite the significant progress made recently in the treatment of gastric cancer (GC) reflected by decrease in surgical morbidity and mortality, GC is responsible for nearly 10% cancer-related death worldwide [1]. Surgery for GC, involving gastrectomy and dissection of the regional lymph nodes, is globally considered as the only curative treatment option. According to the 4th version of Japanese Gastric Cancer Association guidelines, D1 lymphadenectomy is defined as lymph node (LN) removal from the perigastric area (N1, stations 1–7), whereas D2 dissection extends along with the lymph nodes at the coeliac axis and its branches (D1 plus no. 8a, 9, 10, 11p, 11d, 12a) [2]. Eastern (Asian) and Western (Europe and the US) worlds show different therapeutic strategy for locally advanced GC. The preferred approach for stage II/III in the East is upfront

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gastrectomy followed by adjuvant chemotherapy, whereas in the West systemic (chemo-)therapy is recommended as perioperative (neoadjuvant) treatment combined with surgery [2–4] Furthermore, in Asian countries an extended lymph node dissection (D2) has been a standard procedure for many decades, while in Europe and North America consensus on D2 lymphadenectomy has been established recently [2,4,5]. Lymph node dissection is the only surgery-dependent prognostic factor in GC and most of local failures of the surgical treatment are believed to be sustained by insufficient nodal clearance [6]. Therefore, surgical quality assurance (SQA) is a key element of GC treatment, especially in the multimodal setting [7]. In recently published results of CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach), SQA has been evaluated through so called surgical compliance, surgicopathological compliance and surgical contamination [8]. Moreover, accurate evaluation of LN involvement may allow selection of patients who would benefit from an extended LN dissection [9]. Thirty years ago prof. Keichi Maruyama introduced a software – Maruyama Computer Program (MCP), developed on the basis of 4302 patients who underwent upfront surgery for primary GC in National Cancer Center Hospital in Tokyo. The MCP allows to assess expected (%) LN involvement in stations no. 1–16, as well as calculate so-called Maruyama Index of Unresected Disease (MI), quantitative expectation of residual LN involvement after GC surgery, based on 8 characteristics of the tumour. MCP was positively evaluated and validated in various studies from Far East [10,11] and Europe [12–14]. Moreover, as shown in the DGCT [15], the Intergroup 0116 [16], and recent CRITICS trial [8], the MI is the best quality indicator for adequate lymphadenectomy in GC. In the era of neoadjuvant chemotherapy in GC, a potential impact of systemic treatment into LN involvement should be investigated. Analysis of pathologic tumour response and nodal status in the MAGIC trial [17] revealed that LN metastases are the only independent predictor of survival after chemotherapy and surgery [18].

The aim of the current study was to evaluate the possible influence of neoadjuvant chemotherapy (nCTH) on MCP predictions in GC patients and their potential efficacy in the multimodal setting.

Materials and METHODS

Inclusion criteria

After receiving institutional review board approval [KE-0254/297/2018] we collected data from a prospectively maintained database of all patients with primary gastric adenocarcinoma operated between August 2011 and September 2018 in the Department of Surgical Oncology and the 2nd Department and Clinic of General, Gastroenterological and Gastrointestinal Cancer Surgery, Medical University of Lublin, Poland. Patients who underwent preoperative nCTH followed by resection with curative intent were selected from the database. The exclusion criteria were: distant metastases (M1), surgicopathological noncompliance (removal of less than 10 lymph nodes), lack of tumour regression grading in the final pathological report. Data from 101 patients were eligible for the analysis. Clinicopathological features of selected patients are shown in Table 1.

Maruyama Computer Program

The MCP was used either preoperatively (assessment of sex, age, type of cancer, WHO histological type) or intraoperatively, yet before the decision on the extent of lymphadenectomy. Such timing of the MCP calculations has allowed precise intraoperative evaluation of all input variables (especially maximal diameter, location

Table 1
Clinicopathological features.

Variables	No. of patients n = 101 (%)
Sex:	
Male	58 (57.4)
Female	43 (42.6)
Age (years):	
Average	57.3
SD (±)	10.9
Median (min-max)	57 (31–77)
Bormann classification:	
B2	31 (30.7)
B3	64 (63.4)
B4	6 (5.9)
Depth of the tumour:	
Mucosa (MM)	2 (1.9)
Submucosa (SM)	7 (6.9)
Muscularis propria (PM)	36 (35.6)
Subserosa (SS)	19 (18.9)
Suspected serosal involvement (S1)	5 (4.9)
Definite serosal involvement (S2)	19 (18.9)
Neighbouring organ infiltration (S3)	13 (12.9)
Tumour maximal diameter (mm):	
Average	42.7
SD (±)	27
Median (min-max)	35.00 (10–150)
Tumour Location:	
Upper 1/3 Cardia	31 (30.7)
Middle 1/3 Middle	28 (27.7)
Distal 1/3, Antrum	42 (41.6)
Tumour position:	
Lesser curvature	44 (43.6)
Greater curvature	13 (12.8)
Anterior wall	9 (8.9)
Posterior wall	15 (14.9)
Circular	20 (19.8)
WHO type:	
Well differentiated	6 (5.9)
Moderately differentiated	32 (31.8)
Poorly differentiated	46 (45.6)
Signet ring carcinoma	2 (1.9)
Mucinous carcinoma	15 (14.8)
Lauren type:	
Intestinal	49 (48.5)
Diffuse	30 (29.7)
Mixed	22 (21.8)
Grading:	
G1	6 (5.9)
G2	30 (29.7)
G3	65 (64.4)
No of CTH cycles:	
1	2 (1.9)
2	8 (7.9)
3	64 (63.5)
4	20 (19.8)
6	7 (6.9)
CTH regimen	
EOX[a]	86 (85.1)
FLOT[b]	8 (7.9)
Other	7 (7)
Tumour Regression Grading, TRG (Classification of response)	
Grade 1 (Complete)	10 (9.9)
Grade 2 (Subtotal)	10 (9.9)
Grade 3 (Partial)	33 (32.7)
Grade 4 (Minimal/No regression)	48 (47.5)
ypT:	
T0	7 (6.9)
T1a	5 (4.9)
T1b	2 (1.9)
T2	20 (19.9)
T3	43 (42.8)
T4	18 (17.9)
T4a	5 (4.8)
T4b	1 (0.9)
ypN:	
N0	44 (43.7)

Table 1 (*continued*)

Variables	No. of patients n = 101 (%)
N1	9 (8.9)
N2	15 (14.9)
N3	2 (1.9)
N3a	15 (14.8)
N3b	16 (15.8)
No of examined LN stations:	
Stations no. 1–6 (D1)	402 (52.3)
Stations no. 7–12 (D2)	304 (39.7)
Stations no. 13–16 (D3)	62 (8)
Lymphadenectomy:	
D2	93 (91.9)
D2+/D3	8 (8.1)
No. of retrieved LN per patient	
Median (Range)	28 (12–78)
Mean	31,5
Surgicopathological compliance	
Compliance	96 (95.5)
Minor noncompliance	5 (4.5)

[a] EOX (Epirubicin, Oxaliplatin, Capecitabine).
[b] FLOT (Docetaxel, Oxapliplatin, Fluorouracil & Folinic Acid).

and position of the tumour and final verification of serosal involvement), as well as increasing extent of lymphadenectomy if necessary. The lymphadenectomy was extended if the MCP indicated high risk (more than 5%) of any lymph node station involvement from the N3 trier (13–16). For program analysis, we used its most updated version, Win.Estimate 2.5 [14], with kind permission of prof. K Maruyama. At least D2 lymphadenectomy was performed in every patient, regardless of Win Estimate 2.5 predictions. Diagnostic efficacy of MCP in neoadjuvant chemotherapy response in N1-N2 trier and D2 lymphadenectomy were assessed for three cohorts based on Lauren classification: intestinal type, diffuse type and mixed type.

Neoadjuvant chemotherapy tumour regression grading

Pathological tumour regression grading (TRG) was based on modified Becker's system [19,20] - Grade 1: no residual tumour (complete response); Grade 2: <10% residual tumour (subtotal regression); Grade 3: 10–50% residual tumour (partial regression); Grade 4: >50% residual tumour (minimal/no regression). Evaluation of TRG with this system has been recently advocated by a panel of gastrointestinal pathology experts [20]. TRG allowed to define two cohorts in the statistical analysis: patients with response to nCTH (TRG = 1,2,3) and patients who did not respond to nCTH (TRG = 4).

Lymph node involvement assessment

The surgicopathological compliance (sampling of a minimum of 15 lymph nodes), minor noncompliance (removal of a minimum of 10 LN) and noncompliance (removal of less than 10 lymph nodes) was defined as proposed by Claassen et al. [8,21]. MCP results were verified with the final pathological report of the resection specimen with all consecutive lymph node station samples marked separately and retrieved *ex-vivo* by surgeon's assistant during or immediately after the operation. This meticulous technique allowed to create false positive (FP), false negative (FN), true positive (TP) and true negative (TN) predictions for every LN station trier (N1-N2). Due to relatively small number of LN retrieved in stations 13–16 (8% of all retrieved LN), the results in N3 trier were not considered. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were also assessed. (Definitions of FP,FN,TP,TN, sensitivity, specificity, PPV, NPV and accuracy are given in the Supplementary material.)

Statistical analysis

All analyses were performed using MedCalc 15.8 (MedCalc Software, Belgium). All variables with p-values below 0.05 were considered significant. Chi-squared test was used to compare MCP predictions with histopathological assessment of lymph node involvement in N1-N2 trier based on selected variables. Odds Ratios (OR) were calculated for FP results in N1-N2 trier. Receiver operating characteristic (ROC) curves were used to verify the efficacy of MCP in nCTH response prediction in intestinal, diffuse and mixed type cohorts. For maximizing the validity of predictions, different cut-off points values of MCP outcomes were established. The performance of ROC curves was evaluated using the areas under the curve (AUC).

Results

The impact of clinicopathological features on the risk of FP and TP results in N1-N2 triers is shown in Table 2.

Comparison of false positive (FP) results in N1 trier

In the N1 trier there were 177 (44.0%) FP results, 11 (2.7%) FN results, 126 (31.6%) TP results, and 88 (21.7%) TN results. The sensitivity, specificity, PPV, NPV, and test accuracy were 92%, 33%, 41%, 89%, and 53%, respectively.

Table 2
Impact of clinicopathological features on false positive (FP) and true positive (TP) results ratio for N1–N3 triers.

Variables	N1			N2		
	FP (%)	TP (%)	OR (95%CI), p	FP (%)	TP (%)	OR (95%CI), p
Intestinal type	108 (76.1%)	34 (23.9%)	4.23(2.57–6.95) p < 0.0001	70 (88.6%)	9 (11.4%)	4.40 (2.01–9.61) p = 0.0002
Non-intestinal type (Diffuse and Mixed)	69 (42.9%)	92 (57.1%)		83 (63.8%)	47 (36.2%)	
Response to nCTH[a] ([b]TRG 1–3)	125 (78.6%)	34 (21.4%)	6.50 (3.91–10.82) p < 0.0001	94 (88.6%)	12 (11.4%)	5.84 (2.85–11.96) p < 0.0001
No response to nCTH (TRG - 4)	52 (36.1%)	92 (63.9%)		59 (57.3%)	44 (42.7%)	
Grading 1 and 2	69 (70.4%)	29 (29.6%)	1.72 (0.83–3.56) p = 0.1383	49 (80.3%)	12 (19.7%)	1.72 (0.83–3.56) p = 0.1383
Grading 3	108 (52.7%)	97 (47.3%)		104 (70.8%)	44 (29.2%)	
Intestinal type and response to nCTH (TRG 1–3)	80 (88.9%)	10 (11.1%)	6.85 (2.91–16.11) p < 0.0001	48 (96%)	2 (4%)	7.63 (1.46–39.78) p = 0.0158
Intestinal type and no response to nCTH (TRG - 4)	28 (53.8%)	24 (46.2%)		22 (75.8%)	7 (24.2%)	
Diffuse type and response to nCTH (TRG 1–3)	29 (76.3%)	9 (23.7%)	9.47 (3.74–23.98) p < 0.0001	29 (87.9%)	4 (12.1%)	6. 47(1.99–20.98) p = 0.0019
Diffuse type and no response to nCTH(TRG 4)	17 (25.3%)	50 (74.7%)		28 (52.8%)	25 (47.2%)	
Mixed type and response to nCTH(TRG 1–3)	16 (51.6%)	15 (48.4%)	2.74 (0.89–8.42) p = 0.0779	17 (73.9%)	6 (26.1%)	3.77(1.06–13.45) p = 0.0403
Mixed type and no response to nCTH (TRG 4)	7 (28%)	18 (72%)		9 (42.8%)	12 (57.2%)	

[a] nCTH (neoadjuvant chemotherapy).
[b] TRG – Tumour Regression Grade.

Lauren classification

In patients with intestinal type GC, number of FP results was significantly higher than in diffuse type GC and mixed type GC, respectively (61% vs 26% vs 13%,; x^2 49.36; $p < 0.0001$).

Grading

In patients with grade G1/2 tumours, number of FP results was significantly higher than in patients with G3 tumours (50.4% vs 40.7%, x^2 12.74; $p = 0.0052$).

nCTH response

In patients with response to nCTH, number of FP results was significantly higher than in patients who did not respond to nCTH (70.6% vs 29.4%; x^2 70.78; $p < 0.0001$). In detail, in patients with complete response to nCTH (TRG = 1), number of FP results was significantly higher than in patients with subtotal regression (TRG = 2), partial regression (TRG = 3) and minimal/no regression (TRG = 4), respectively (62,5% vs 55% vs 54,9% vs 28,9%,; x^2 78.36; $p < 0.0001$).

Multifactorial comparisons

In patients with intestinal type GC and response to nCTH (TRG = 1,2,3), the number of FP results was significantly higher than in intestinal type GC patients without nCTH response (TRG = 4) (59,7% vs 42.4%; x^2 26.86, $p < 0.0001$). In patients with diffuse type GC and response to nCTH, the number of FP results was significantly higher than in patients with diffuse type GC without nCTH response (64.4% vs 21%, x^2 26.79; $p < 0.001$). In patients with mixed type GC and response to nCTH, the number of FP results was significantly higher than in patients with mixed type GC without nCTH response (37.2% vs 21.2%, x^2 8.51; $p = 0.0366$).

Comparison of false positive (FP) results in N2 trier

In the N2 trier there was 153 (50.3%) FP results, 18 (5.9%) FN results, 56 (18.42%) TP results, and 77 (25.3%) TN results. The sensitivity, specificity, PPV, NPV and test accuracy were 75%, 33%, 26%, 81%, and 43%, respectively.

Lauren classification

In patients with intestinal type GC, number of FP results was significantly higher than in diffuse type GC and mixed type GC, respectively (45.75% vs 37.25% vs 17%; x^2 37.11; $p < 0.0001$).

Grading

In patients with grade G1/2 tumours, number of FP results was significantly higher than in patients with G3 tumours (52% vs 47.1%, x^2 9.94; $p = 0.0190$).

Neoadjuvant chemotherapy response

In patients with response to nCTH, number of FP results was significantly higher than in patients who did not respond to nCTH (58,7% vs 41%; x^2 46.05; $p < 0.0001$). In detail, in patients with complete response to nCTH (TRG = 1), number of FP results was significantly higher than in patients with subtotal regression (TRG = 2), partial regression (TRG = 3) and minimal/no regression (TRG = 4), respectively (64.5% vs 50% vs 59.6% vs 41%; x^2 34.83; $p < 0.0001$).

Multifactorial comparisons

In patients with intestinal type GC and response to nCTH, the number of FP results was significantly lower than in intestinal type GC patients without nCTH response (52.7% vs 55%; x^2 13.35, $p = 0.0039$). In patients with diffuse type GC and response to nCTH, the number of FP results was significantly higher than in patients with diffuse type GC without nCTH response (76.3% vs 41%, x^2 16.38; $p = 0.0009$). In patients with mixed type GC and response to nCTH, the number of FP results was non-significantly higher than in patients with mixed type GC without nCTH response (54.8% vs 25%, x^2 7.01; $p = 0.0716$).

Comparison of false positive (FP) results in N3 trier

In the N3 trier there was 15 (24.2%) FP results, 8 (12.9%) FN results, 4 (6.4%) TP results, and 35 (56.5%) TN results. Sensitivity, specificity PPV, NPV and test accuracy were 17%,70%,21%,81%, and 63%, respectively.

Lauren classification

In patients with intestinal type GC, number of FP results was non-significantly lower than in diffuse type GC and mixed type GC, respectively (15% vs 18.7% vs 34.6%; x^2 6.47; $p = 0.3727$).

Grading

In patients with grade G1/2 tumours, number of FP results was non-significantly lower than in patients with G3 tumours (11.1% vs 29.5%, x^2 3.63; $p = 0.3042$).

Neoadjuvant chemotherapy response

In patients with response to nCTH, number of FP results was significantly higher than in patients who did not respond to nCTH (28.13% vs 20%; x^2 11.36; $p = 0.0099$). In detail, in patients with complete response to nCTH (TRG = 1), number of FP results was non-significantly higher than in patients with minimal/no regression (TRG = 4) and lower than in patients with partial regression (TRG = 3), respectively (30% vs 20% vs 35.2%; x^2 14.75; $p = 0.0980$).

Multifactorial comparisons

In patients with intestinal type GC and response to nCTH, the number of FP results was non-significantly lower than in intestinal type GC patients without nCTH response (12.5% vs 25%; x^2 6.91, $p = 0.0750$). In patients with diffuse type GC and response to nCTH, the number of FP results was non-significantly higher than in patients with diffuse type GC without nCTH response (71.4% vs 21%, x^2 6.39; $p = 0.0942$). In patients with mixed type GC and response to nCTH, the number of FP results was non-significantly higher than in patients with mixed type GC without nCTH response (22.2% vs 14.3%, x^2 4.76; $p = 0.1904$).

ROC curve analysis

In the ROC curve analysis, sensitivity and specificity of MCP predictions in nCTH response in patients undergoing D2 lymphadenectomy were 55% and 73%, respectively (AUC 0.67, cut-off point $\leq$124, $p = 0.0012$). In patients with intestinal type GC, sensitivity and specificity in N1 trier were 60% and 76%, respectively (AUC 0.7; cut-off point $\leq$79, $p = 0.0115$), whereas sensitivity and specificity in N2 trier were 78% and 59%, respectively (AUC = 0.73, cut-off point $\leq$45, $p = 0036$). In patients with diffuse type GC, sensitivity and

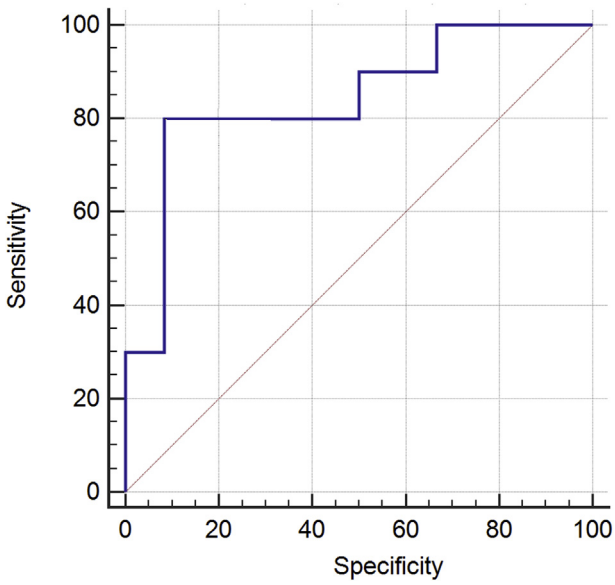

Fig. 1. ROC curve analysis for MCP predications in mixed type DC patitents (N1 trier).

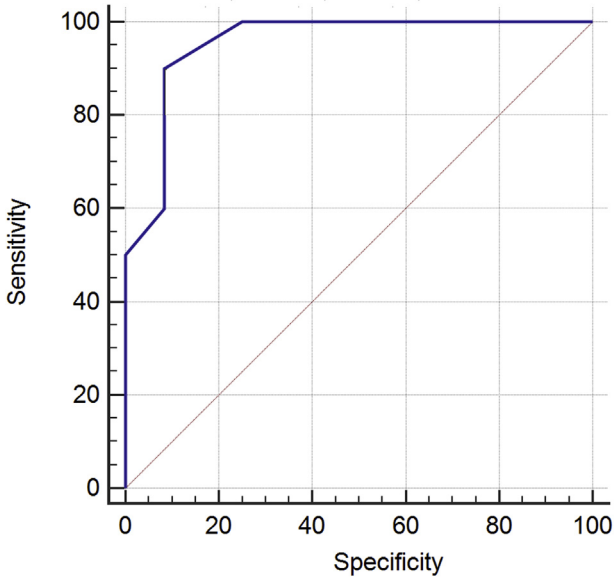

Fig. 2. ROC curve analysis for MCP predications in mixed type GC patitents (N2 trier).

specificity in N1 trier were 100% and 21%, respectively (AUC 0.51, cut-off point >72, p = 0.8765), whereas sensitivity and specificity in N2 trier were 72% and 47%, respectively (AUC 0.54, cut-off point ≤57; p = 0.660). The highest validity of MCP predictions was found in patients with mixed type GC, where sensitivity and specificity in N1 trier were 80% and 92%, respectively (AUC 0.84, cut-off point ≤54, p = 0.0002) (Fig. 1), whereas sensitivity and specificity in N2 trier were 90% and 92%, respectively (AUC 0.95, cut-off point ≤ 11, p < 0.0001) (Fig. 2).

Discussion

Preoperative diagnostic modalities (CT, MRI, PET-CT, EUS, staging laparoscopy) have limited sensitivity and specificity, which results in suboptimal accuracy of GC clinical staging [22,23]. More importantly, cN staging remains challenging and seems to be even less accurate [24,25]. Since the survival rate of the GC patients is significantly increased by the response to preoperative therapy [17,26], it is difficult to effectively predict the response to therapy at the time of diagnosis [27,28]. Thus, comprehensive lymph node assessment, especially after preoperative therapy remains crucial for the accurate survival prediction. Patients with clinically positive LNs (cN+) who underwent preoperative therapy and achieved good pathological response (ypN0) have good prognosis with similar overall survival (OS) as patients without LN metastases (cN0/ypN0) [29].

On the other hand, nCTH followed by radical surgery in patients with clinical T3/T4 GC is associated with the risk of preoperative overdiagnosis by which more than 10% of patients with pathological (early) stage I disease may receive unnecessary intensive chemotherapy [30]. Predictive tools could optimise adjuvant chemotherapy delivery in patients with resectable gastric cancer and avoid overtreatment [31].

GC has a tendency to histological heterogeneity. Predicting the tumours' behavior as well as LN metastases based on Lauren classification is important for selection of the optimal treatment. Recent study by Pyo et al. has shown that mixed type GC is associated with aggressive clinical features and higher risk of LN metastases compared with the intestinal or diffuse type GC [32]. Interestingly, our study showed high utility of MCP for predicting the outcome of nCTH in mixed type GC.

The MCP provides pre- or intraoperative nodal assessment, which allows to tailor the extent of lymph node dissection in every case. The MI is a quantitative measure for the lymphadenectomy adequacy evaluation in GC. Based on analysis of surgery alone prospective randomized trial, strong suggestion in favour of low-MI surgery was proposed [33]. Next evidence level I trial with neoadjuvant therapy for GC validated the concept of low-MI surgery [34]. Additionally, clinical use of the MCP creates a possibility for surgical quality control and optimal adherence to surgical protocol [9]. Accuracy of the MCP in predicting LN metastases in various studies ranged from 56% to 96% [10–14,35–38]. Hungarian study showed lower clinical impact of the MCP compared with that of sentinel node biopsy (SNB). However, combining these two methods allows to determine the appropriate extent of lymphadenectomy and tailored surgery in GC [36]. Similarly, Bollschweiler et al. found 15% lower accuracy of the MCP as compared to artificial neural networks in the prediction of LN metastases [37]. Gretschel et al. questioned the clinical impact of the MCP due to low specificity and a low positive predictive value [38]. Nevertheless, the authors of the program pointed out that the crucial measure of the MCP is the negative predictive value (NPV), which indicates the number of patients with unpredicted LN metastases, who would undergo inadequate lymphadenectomy if the extent of their surgery was based on computer prediction alone [14]. In the original study it occurred in only 1.8%. In our study, the false negative ratio was 2.7%. Moreover, MI (based on MCP) allows to consequently improve the quality of lymphadenectomy in GC, especially in the multimodal setting [7].

Our study showed that response to nCTH and Lauren classification are important predictors of LN metastases, as assessed by means of MCP. Responders to nCTH had significantly higher number of FP results in comparison to non-responders in both N1 and N2 triers. Although MCP predictions are based on WHO, not Lauren classification, significantly worse prognosis can be expected in diffuse and mixed type tumours, with lesser number of FP results and higher number of TP results respectively, in comparison to intestinal type (Table 2).

We have demonstrated, that the MCP, even though originally based on patients undergoing upfront surgery, can be used with acceptable sensitivity and NPV in multimodal setting. In selected

Table 3
Comparison of selected variables in MCP studies.

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	ROC (0–1)
Omejc et al. [12]	93	89	87	94	91	–
Guadagni et al. [13]	–	–	–	–	81.6	0.74–0.94
Bollschweiler et al. [14]	97	43	80	94	82	–
Toth et al. [35]	91.3	64	72.4	81.8	75	0.72–0.78
Present study	86	34	36	85	53	0.65–0.95

variables, our results are comparable with other, non-neoadjuvant studies, as shown in Table 3. However, MCP predictions in the GC patients undergoing nCTH have low specificity due to significantly high number of FP results. Therefore, achieving ypN0 status is an important hallmark demonstrating the effectiveness of preoperative therapy for GC [39].

The MI was not designed to predict LN involvement after nCTH, since the data that was used to establish the MI came from patients who underwent upfront surgery, and thus it could be expected that the MI would not show sufficient accuracy among nCTH patients. When we try to establish a LN status predictive model, all items integrated in the model should be available before or during surgery. Since Laurén classification influenced predictions in our study, its possible incorporation in new predictive models could be taken into consideration. Importantly, histological typing according to the Laurén classification of GC can be reliably determined in the initial diagnostic endoscopy biopsy sampling [40]. The postoperative negative LN status correlates with good outcome, whereas diffuse-type histology correlates with poor outcome [41]. Results of large multicentre study (AGAMENON registry) indicate that Laurén classification histotypes may predict survival with different response to chemotherapy [42].

Currently, GC surgery is generally considered to be standardized rather than personalized. Presumably, advances in technology and better understanding of GC biology will successively favour tailored surgery [43]. In recent years, the use of indocyanine green (ICG)-based fluorescence navigated lymphadenectomy gained great interest [44]. Studies predicting the positivity of perigastric, regional and extra-regional nodes based on intraoperatively measured ICG load are awaited.

In the near future, the extent of lymphadenectomy may be also based on molecular classification. The Cancer Genome Atlas (TCGA) project divided GC into four subtypes: Epstein-Barr virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN) and genomically stable (GS) [45], while the Asian Cancer Research Group (ACRG) molecularly classifies GC into: Mesenchymal subgroup (MSS/EMT), Microsatellite Instability subgroup (MSI), Microsatellite Stable TP53 positive (MSS/TP53+) and Microsatellite Stable TP53- tumours (MSS/TP53-) [46]. These classifications are expected to be included in multidisciplinary treatment of GC: in the MSI type, a less extended lymphadenectomy probably is sufficient, while the MSS/EMT type shows very high propensity to both, lymph node and peritoneal dissemination, and may benefit from extended lymphadenectomy and prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) when confirmed in prospective trials [47]. Similarly, human epidermal growth factor receptor 2 (HER2) is likely overexpressed and/or amplified in locally advanced gastric cancer with extensive (bulky N2 or paraaortic) lymph node metastasis, and therefore this group of patients may benefit from neoadjuvant chemotherapy with anti-HER2 antibodies [48]. Whether lymphadenectomy in these patients should be extended is unknown. A possible role of the HER2 overexpression for tailored surgical approach should be investigated in prospective studies.

The major limitation of this study is its retrospective nature. Additionally, The sample size of the present study was not large enough for subgroup stratification analysis.

Conclusions

Maruyama Computer Program predictions in the GC patients treated with neoadjuvant chemotherapy have low specificity due to significantly high number of FP results. Noticeably low accuracy level of predictions indicate a need for new prediction models, based on Laurén classification, since it may provide some information on expected regression grade.

Conflict of interest

Declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.001.

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