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위암 환자에서 각 구역별 림프절 전이율 예측 모델 구축

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Development of Lymph Node Metastasis Prediction Model on Each Station in Gastric Cancer Patient

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Abstract

Development of Lymph Node Metastasis Prediction Model on Each Station in Gastric Cancer Patient

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Background and Aim

The prediction of lymph node metastasis (LNM) on each lymph node (LN) station is important for tailored surgery. The aim of this study was to develop a prediction program which can calculate the probability of LNM according to LN stations in gastric cancer patients.

Methods

We retrospectively analyzed 4,660 patients who underwent gastrectomy for primary gastric cancer from 2003 to 2013 and the LN status was well examined in according to the LN stations, at Seoul National University Hospital. We reviewed preoperative endoscopic findings and/or gross pathologic findings, and reclassified

the tumor locations by the endoscopic terms. All of the involved locations were included into the analysis. The variables which can get preoperatively were evaluated. Multiple logistic regression analysis was used to develop a LNM prediction model using whole data for each LN station. The performance of the prediction model was validated in terms of discrimination and calibration using a total of 200 bootstrap samples.

Results

The multiple analysis identified depth of tumor, gross type, involved locations as covariates associated with LNM. But the significant factors were somewhat different according to the LN stations. In the validation, the prediction equation exhibited good discrimination. Calibration plot of the prediction equation predicted LNM rate corresponding closely with the actual rate.

Conclusions

We developed a LNM prediction program on each LN stations. Validation revealed good discrimination and calibration, suggesting good clinical utility. The LNM prediction program improved individualized predictions of LNM of each LN stations.

Key words: lymph node metastasis, prediction, gastric cancer, bootstrap
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Introduction

Gastric cancer is the 4th most common cancer in the world and the mortality is 3rd highest in the world. (1) Long term follow-up results of Dutch trial showed benefit of D2 lymph node(LN) dissection comparing D1 LN dissection in gastric cancer surgery.(2) After the results, debate about the extent of radical LN dissection has been disappeared, and it is accepted that the standard gastrectomy includes D2 LN dissection.(3)

However, the former report of Dutch trial denied the survival benefit of D2 LN dissection over D1 LN dissection.(4) It is the possible explanation that the high morbidity and mortality of D2 LN dissection can reduce the survival benefit of D2 LN dissection over D1 LN dissection.(5) There are some reports that the postoperative complication can be related with poor survival rate in gastric cancer.(6, 7) The impact of postoperative complication to poor oncologic outcome is more prominent in elderly patients.(7) Because we are rapidly moving into an aging society, we will be see and treat older patients more frequently. So, we need to balance surgical safety and radicality, especially in the elderly.

As the proportion of early gastric cancer increases, interest in quality of life after surgery is increasing.(8) The interest in modified gastrectomy including limited LN dissection is also increasing.

For balancing the surgical safety and radicality of gastrectomy and safe application of modified gastrectomy, we need to predict the possibility of LN metastasis on each lymph node station(LNS).

One promising method to evaluate the possibility of LN metastasis and modify the extent of dissection is sentinel node navigation surgery. But until now, we have many positive reports for the efficacy of sentinel node navigation surgery, and many negative results also. Sentinel node navigation surgery in gastric cancer has not been yet universal due to the complicated lymphatic flow from the stomach.(9)

The lack of biological methods to predict the occurrence of LN metastasis before surgery has led to the search for methods that combine existing demographic data with mathematical models. One famous method is Maruyama computer program (MCP), which calculates the probability of metastases in each LNS.(10) The application of this program to German patients has shown good predictability for the compartments, but it results in a large number of false positive predictions for the different LNSs.(11) MCP use one third location method for longitudinal location, only the center of tumor for the location information, and include sex and age as variable. One third location method for longitudinal location is not easy to classify preoperatively. And classification based only on the center of the tumor will increase the ambiguity of the location. And sex or age may not be related to LN metastasis.

Other group made an effort to develop a prediction system of LN metastasis with artificial neural networks. Sensitivity was higher than MCP (0.83 vs 0.74) but

specificity was lower than MCP (0.71 vs 0.75).(12) The system also used one third location method and only the center of tumor.

Seoul national university hospital (SNUH) gastric cancer data became to be larger than that of MCP. This study aimed to upbuild LN metastasis prediction program for each station by improving the weakness of MCP.

Patients and Method

Patients

SNUH database which was collected prospectively was reviewed. The patients who underwent gastrectomy for gastric adenocarcinoma from 2003 to 2013 were included. Who had insufficient data for LN metastasis of each stations were excluded. And multiple gastric cancer, gastrectomy after chemotherapy or endoscopic resection, no lesion on specimen, remnant stomach cancer, multiple primary cancer, or recurred after endoscopic resection were excluded. Finally, 4660 patients' data was enrolled.

Classification LN station and variables

LN station was classified according to Japanese classification of gastric carcinoma-2nd English Edition.(13) Just after gastrectomy, surgeon majoring in upper gastrointestinal surgery divided the LN stations in operating room. And the divided specimen was accepted for pathology department and examined by pathologist. The data for LN metastasis of each stations were collected on SNUH database with demographic, operative, histopathologic variables and etc.

To subdivide the location and classify more precisely with preoperative findings, endoscopic findings were used; Cardia, fundus, upper body, mid body, lower body, angle, antrum and pylorus. Instead of using the center of tumor for location, the all

locations which were involved by tumor were used for location classification. For this reclassification, report of endoscopy, endoscopic pictures, and/or specimen pictures were reviewed.

Because we aimed to predict the LN metastasis possibility preoperatively, the variables which are accessible preoperatively were included for analysis. Age, sex, depth of invasion, tumor size, gross type, histologic type, and longitudinal and circular location. The pathologic results were quoted for depth of invasion, tumor size, gross type and histologic type.

Although the total number of cases was large, the number of lymph node metastasis positive patients was too few in some LNSs. In such a case, there is a case where integrated reclassification of the variables is required to construct the model. In this case, the analysis was conducted by grouping variables that did not show a large difference in lymph node metastasis.

Statistical analysis

Method1: Dividing cases (Training set 70%: Validation set 30%)

For each station, the cases were randomly divided into two groups. 70% of data were allocated to the training set and 30% of data to the validation set. Correlation analysis between each parameters and LN metastasis were performed. T-test or Wilcoxon rank sum test for continuous variables, and Chi-square test of Fisher's exact test for categorical variables were performed. Logistic regression analysis for

correlation analysis and cubic spline analysis for assuming the correlation pattern between continuous variables and metastasis rate.

The prediction model was developed by stepwise variable selection method of multiple logistic regression using the training set. When using variable selection, the significance level was 0.05. And the model was validated by C-statistics and calibration plot using the validation set. C-statistics is the probability how exactly tell the LN metastasis presence or not. Calibration plot is the scatter plot of the actual metastasis probability and the mean of the predicted probability of each group, after classification into 10 groups in the order of predicted probability which is calculated by the prediction model. It can be interpreted that the closer to the diagonal line passing through the origin, the better the prediction probability reflects the actual probability.

The same method was applied for each LNS.

Method 2: Internal validation using bootstrap sample

The prediction model was developed using whole data without dividing. The candidate variables considered in the prediction model construction were significant at the significance level of 0.2. The multivariate model selected a variable that explains the LN metastasis significantly by using the stepwise method in the variable selection method, and the entry and elimination criteria of the

variable were set to the significance level of 0.05. The interaction of adjacent locations was considered.

To evaluate the performance of compensating overfitting of the prediction model, a total of 200 bootstrap samples were generated to estimate the optimism corrected c-statistic and calibration plot. Each bootstrap sample was generated on the same scale as the original data size, allowing repeated extraction from patient-wide data. The optimism corrected c-statistic (or bias corrected c-statistic), which corrected for the optimism of the prediction model, was calculated as "c-statistic - optimism". The process of optimism estimation is as follows.

- Construct the model in each bootstrap sample using the same method as the variable selection method applied to the prediction model construction in the previous data, and estimate the c-statistic in the bootstrap sample
- Estimate c-statistic when applying the model constructed from bootstrap sample to all data
- Calculate the difference between two c-statistic
- Mean of difference between two c-statistic estimated from 200 bootstrap samples = optimism

An optimism corrected calibration plot divided into five groups according to the probability of prediction was presented. The optimism of the prediction probability was estimated by a similar method to that of the optimism corrected c-statistic, and a plot was generated by correcting the optimism.

But, for LNS with less than 100 case of LN metastasis, the size of the lesion and the depth of invasion were considered in the model regardless of the statistical significance. In addition, the location of the tumor was included in the model with the significance level of 0.05 at the corrected level of tumor size and invasion depth.

Results

The characteristics of the patients were summarized in table 1. Because of the large number of variables, items that have similar effects on lymph node metastasis need to be grouped together to reduce the number of variables.

Thus, the gross type and histologic type were analyzed by grouping items that did not differ significantly in lymph node metastasis. (Table 1)

Table 2 summarizes the number of cases and the LN metastasis rate for each LNS. There was a difference in lymph node metastasis rate according to each LNS, with LNS 3 being the highest and LNS 4sb being the lowest. The case number of lymph node metastasis was distributed in as many as 922 cases and in as few as 27 cases.

1. Method 1 (Dividing cases)

For each LNS, a predictive model was developed by dividing cases into 70% training sets and 30% validation sets. The prediction formula were derived by stepwise variable selection method of multiple logistic regression using the training set.

There are so many LN stations that we cannot explain the process of every stations, so let me give you an example of number 3 LN station. A total of 4632 cases were examined in #3 station, divided into 3243 training set and 1389 validation set through random allocation. The parameters were shown in table 3.

Then, univariate analysis was performed by logistic regression method. (Table 4)

Multivariate logistic regression analysis was performed on the variables with a p-value less than 0.2 (age, tumor size, depth of tumor, gross type, histologic type, location) from the univariate analysis. Significant variables ($p < 0.05$) were selected using the stepwise variable selection method. (Table 5)

We can develop an equation for prediction of LN 3 station metastasis from the analysis. (Table 6) Then the equation was validated using validation set. C-statistics were calculated 89.7%. The calibration plots of the probabilities estimated by the prediction model and the actual metastasis probabilities are placed near the diagonal line with a slope of 1 across the origin. (Figure 2)

Analysis was done in all LNSs as in the above example. Table 6 summarizes the prediction formula for each LNS. It can be seen that age and gender did not enter into the predictive factor.

Tumor size was selected as a significant variable in most areas, and tumor depth and location were significant variables. Tumor location often has a negative effect on the equation. (For example, greater curvature in #3 LN station, lesser curvature in #4d station) This is probably due to the fact that each location is considered as a variable. Invasion farther from the LNS may be less likely to invade the side near the LNS. Therefore, the rate of lymph node metastasis to the LNS can be predicted to be low.

The prediction formulas were validated using the validation sets. The c-statistics were shown in table 8. The calibration plots were shown in figure 2.

In most LNSs, C-statistics is greater than 0.8, and it is close to the diagonal line passing the origin in the calibration plot. However, in the case of the LNS obtained only from the total gastrectomy, it is seen that the calibration plot deviates much from the diagonal line. In particular, c-statistics is also very low in the 11d area, suggesting that the prediction formula may not be appropriate.

2. Method 2 (Bootstrap sampling method)

To overcome the low number of cases in the LNSs which obtained only from the total gastrectomy, if the patient who has not undergone total gastrectomy is found to have no lymph node metastasis, we considered no lymph node metastasis in LNS 2, 4sa, 10, and 11d.

Because of the low power of prediction in some LNS, other method was applied. For each LNS, the prediction formula were derived using all data. The extraction of the equation is the same as described above except that the training set and the validation set are not divided and all the cases are used to perform the univariate analysis, the multivariate analysis and the variable selection method. Table 7 summarizes the prediction formula for each LNS from 2nd method. Gender is entered as variable only in LNS 5 and 7. We can see that the size of the tumor did not enter into the variables of the prediction equation in the LNS 1, 3, 5, 6 and 7.

The prediction formula were validated by bootstrap sample. The optimism corrected c-statistics were summarized in table 8, and the optimism corrected calibration plots were shown in figure 3.

The optimism corrected c-statistic was greater than 0.85 in all LNSs except the two LNSs 11p and 12a. In addition, the c-statistic of the method 2 was higher in all LNSs except the four LNSs of 1, 3, 4sb, and 11p. In particular, LNS 11d significantly get better in the method 2, thus the optimism corrected c-statistic was over 0.94. (Table 8)

In the calibration plot, the corrected average of the actual probabilities in most LNSs is located close to the diagonal line through the origin.

3. Comparison of the location classification

To compare the location classification of this study to that of Maruyama program, in the LNSs with more than 100 cases of lymph node metastasis, a prediction model based on the one third classification was derived by the same method as the method 2.

The prediction formula is shown in table 9. Tumor size is a significant factor in all LNS. Validation is also performed by bootstrap sampling method. And the results are summarized in table 10.

The optimism corrected c-statistics were quite high also. When comparing the two location classifications, the c-statistic of this study method (endoscopic location classification and consideration of all involved area) was higher in all LNS except LNS 1. However, the difference was significant only in two LNSs (LNS 3 and 6).

4. Effect of including LN negative cases among subtotal gastrectomy cases

As mentioned earlier in second section of results, to overcome the low number of cases in the LNSs which obtained only from the total gastrectomy, if the patient who has not undergone total gastrectomy is found to have no lymph node metastasis, we considered no lymph node metastasis in LNS 2, 4sa, 10, and 11d.

In order to investigate the effect of the increase in the number of cases except the difference of the statistical analysis method, the method 1 (training set 70% and validation set 30%) was analyzed with the increased cases in LNS 2, 4sa, 10 and 11d.

The prediction formula is summarized in Table 11.

C-statistics was quite improved after including cases and became similar with those of the method 2. (Table 12)

However, it was found that calibration plot deviates much from the straight line passing the origin especially in LNSs 2 and 11d. (Figure 4)

Discussion

We developed a predictive formula that showed a c-statistic of 0.85 or higher in all LNSs and was located close to the diagonal in the calibration plot. Since there is no direct comparison with MCP, there is no way to determine how good the model developed with this study is. In order to differentiate from MCP, however, statistical methods were used and tumor location classification was different. MCP is simply a collection of similar patient populations expressed in the proportion of lymph node metastasis positive patients to each LNS. In this study, we have developed a predictive equation that reflects how much each variable contributes to the lymph node metastasis to each LNS. Therefore, we can observe that the gender and age used as the main variables in MCP are almost absent from the model of this study. Therefore, it is statistically incompatible to calculate the transfer rate by collectively applying gender and age.(10)

In this study, a new location classification method is applied. Because of the difficulty of location classification by the tertiary segment before surgery and the presence of a landmark that can distinguish the location from the endoscope, the use of endoscopic location classification is considered to be more appropriate to use the predictive model for preoperative planning. We tried to clarify the location of the tumor by using not only the center of the tumor but all the areas in which the tumor was involved. However, unlike our expectation, Table 10 shows no significant difference in the accuracy of the prediction equation. However, the predictive expression developed by our location classification method did not

include tumor size in many LNS. (Table 7) We should consider whether it is more accurate to measure the size of the tumor and to observe the invasion area through preoperative endoscopy. Most of the studies on the accuracy of endoscopy for the size of gastric cancer were performed in early gastric cancer, with an average of 2 to 5 mm smaller.(14, 15) However, in advanced gastric cancer which is larger than early gastric cancer, it is doubtful whether the size can be accurately judged because it is not caught in the endoscopic view. It is also necessary to analyze this part through future prospective data accumulation.

In some LNSs, the number of positive events is too small to implement a common method of program development and validation by dividing training and validation sets. So we changed the method and developed the program using all cases and performed the internal verification work using the bootstrap sampling method.(16) With this method, we could derive a better prediction equation.(Table 8)

And also, to overcome the low number of cases in the LNSs which obtained only from the total gastrectomy, if the patient who has not undergone total gastrectomy is found to have no lymph node metastasis, we considered no lymph node metastasis in LNS 2, 4sa, 10, and 11d. So in LNS 2, 4sa, 10 and 11d, the improvement of c-statistics was dramatic. If there is no lymph node metastasis in the patient who underwent partial resection, it can be predicted that there is no metastasis in the LNSs excised only when total gastrectomy is performed. However, there may be some controversy in the fact that lymph node studies have not been examined practically. However, if only the resected cases are included in the

analysis, there are problems that the number of cases is too small. And moreover only those cases who are highly likely to have lymph node metastasis are investigated and errors may occur that predict an abnormally high metastasis rate. The c-statistic of the predictive equation was significantly improved when the same statistical method was used. (Table 12) However, the validation result using the calibration plot was disappointing. (Figure 4) It can be thought that that is why the number of cases of the validation set was insufficient when analyzing by dividing method using small number of event cases. So the Bootstrap sampling validation method seems to be more useful.

In the second method, the predictive power of 11d is dramatically increased. (0.698→0.941081, Table 8) The calibration plot was also located close to the straight line passing the origin. (Figure 3) When comparing the two prediction formula, it was common that the lymph node metastasis rate was associated with the size or depth of the lesion. Concerning the location of the tumor, the second method seems to be more consistent with the clinical significance, as the presence of invasion in the upper part of the lesion was selected as a significant variable. (Table 6 and 7)

This study has some drawbacks.

First, this study was retrospective. The final pathology results were reviewed to determine tumor size, invasion depth, and histologic type. If the results of this study are used in the actual surgical planning stage of the future, the predictive

value may be lower than that of the present study because the preoperative information and the final histological examination result may be different. However, we thought that it is not correct to proceed this study by estimating the preoperative clinical stage that was not recorded in this retrospective study that already knew the correct answer. Since it is our direction to predict correct answers more accurately using multiple diagnostic methods, it has been deemed correct to construct a predictive model with the correct answer. However, in order to know the difference between the preoperative information and the final pathology results, it is necessary to accumulate prospective information.

Second, although the total number of cases was large, but there were several LNSs where the number of cases with lymph node metastasis was too small. In order to construct a robust model, there should be a certain number of positive cases, but the number of positive cases is too small to strengthen the predictive power of the predictive model. Recently, early detection of gastric cancer has been increasing, so it is not easy to collect enough data for this work. Collecting data jointly by the multi-institution may be the solution.

Third, this study has not been validated by external institute. In order to reclassify the tumor location, it is necessary to review the data of many patients again, and it is judged that it is difficult for the external institute to retrospectively perform. If we collect data prospectively, we would be able to make external institutes participate validation study without difficulty, and judged that verification work could be done with better quality data. Therefore, prospective and external

institutional validation work will be carried out at the same time through prospective validation work involving the multi-institutions.

Although primitive, a program has been developed that can predict lymph node metastasis by each LNS. Prospective and external institutional validation is needed and this prediction program will be further developed by accumulation of more data.

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Tables

Table 1 Characteristics of Patients (mean ±S.D., n(%))

	LN metastasis (-) (N=3201)	LN metastasis (+) (N=1459)	OR [95% CI]	p-value
Sex				0.9576
Male	2040	931 (31.3%)	1	
Female	1161	528 (31.3%)	1.00 [0.88, 1.13]	0.9576
Age (years)	58.7 ±11.84	60.1 ±12.52	1.10† [1.04, 1.16]	0.0004
Tumor size (cm)	3.0 ±1.91	5.6 ±3.13	1.57‡ [1.52, 1.63]	<0.0001
Depth of tumor				<0.0001
Mucosa	1380	32 (2.3%)	1	
Submucosa	1126	255 (18.5%)	9.63 [6.73, 14.25]	<0.0001
Proper muscle	354	221 (38.4%)	26.54 [18.30, 39.71]	<0.0001
Subserosa	236	451 (65.6%)	81.08 [56.20, 120.87]	<0.0001
Serosa	98	430 (81.4%)	185.62 [124.86, 284.58]	<0.0001
Adjacent organ	7	70 (90.9%)	399.23 [184.64, 988.04]	<0.0001
Gross type-Cat I				<0.0001
EGC (I, IIa)	392	75 (16.1%)	1	
EGC (IIb, IIc)	2147	228 (9.6%)	0.56 [0.42, 0.74]	<0.0001
EGC (III)	40	13 (24.5%)	1.70 [0.87, 3.33]	0.1227
Borrmann (1, 2, 3)	597	1005 (62.7%)	8.80 [6.74, 11.49]	<0.0001
Borrmann (4)	25	138 (84.7%)	28.85 [17.63, 47.21]	<0.0001
Gross type-Cat II				<0.0001
EGC (I, IIa, IIb, IIc)	2539	303 (10.7%)	1	
EGC (III)	40	13 (24.5%)	2.72 [1.44, 5.15]	0.0021
Borrmann (1, 2, 3)	597	1005 (62.7%)	14.11 [12.06, 16.49]	<0.0001
Borrmann (4)	25	138 (84.7%)	46.26 [29.72, 71.99]	<0.0001
Histologic type-Cat I				<0.0001
Pap, WD tub, MD tub	1631	523 (24.3%)	1	
PD tub, Muc, SRC	1570	936 (37.4%)	1.86 [1.64, 2.11]	<0.0001
Histologic type-Cat II				<0.0001
Pap, WD tub, SRC	1314	315 (19.3%)	1	
MD tub, PD tub	1858	1090 (37.0%)	2.45 [2.12, 2.83]	<0.0001
Muc	29	54 (65.1%)	7.77 [4.87, 12.40]	<0.0001

Table 1 (cont.)
Cat, Category; Pap, Papillary adenocarcinoma; WD tub, well differentiated tubular adenocarcinoma; MD tub, moderately differentiated tubular adenocarcinoma; PD tub, poorly differentiated tubular adenocarcinoma; Muc, muninous adenocarcinoma; SRC, signet ring cell carcinoma
† Mean odds ratio of lymph node metastasis by age 10 years increase
‡ Mean odds ratio of lymph node metastasis by size 1cm increase
All OR and p-value from Logistic regression

Table 2 Total case number and LN metastasis rate according to LNS

LNS	Total cases, N	LN metastasis(+), n(%)
1	4619	366 (7.9)
2	918	106 (11.6)
3	4632	922 (19.9)
4sa	968	61 (6.3)
4sb	4472	68 (1.5)
4d	4614	580 (12.6)
5	3896	216 (5.5)
6	4499	569 (12.7)
7	4618	460 (10.0)
8a	4506	274 (6.1)
9	4426	117 (2.6)
10	562	39 (6.9)
11p	4099	134 (3.3)
11d	588	27 (4.6)
12a	2901	74 (2.6)

Table 3 Characteristics of divided patients into training and validation set for LNS 3 (mean ±S.D., n(%))

	Total (N=4632)	Training set (N=3243)	Validation set (N=1389)
Sex			
Male, n(%)	2950 (63.7)	2057 (63.4)	893 (64.3)
Female, n(%)	1682 (36.3)	1186 (36.6)	496 (35.7)
Age (yrs)	59.1 ±12.08	58.9 ±12.12	59.7 ±11.95
Tumor size (cm)	3.8 ±2.63	3.8 ±2.61	3.8 ±2.67
Depth of tumor			
Mucosa	1409 (30.4)	979 (30.2)	430 (31.0)
Submucosa	1372 (29.6)	984 (30.3)	388 (27.9)
Proper muscle	569 (12.3)	393 (12.1)	176 (12.7)
Subserosa	684 (14.8)	471 (14.5)	213 (15.3)
Serosa	523 (11.3)	359 (11.1)	164 (11.8)
Adjacent organ	75 (1.6)	57 (1.8)	18 (1.3)
Gross type			
EGC (I, IIa, IIb, IIc, III)	2881 (62.2)	2033 (62.7)	848 (61.1)
B (I, II, III, IV),	1751 (37.8)	1210 (37.3)	541 (39.0)
Histologic type			
Pap, WD tub, SRC	1620 (35.0)	1132 (34.9)	488 (35.1)
MD tub, PD tub, Mucinous	3012 (65.0)	2111 (65.1)	901 (64.9)
Longitudinal location			
GEJ, cardia			
Not involved	4357 (94.1)	3052 (94.1)	1305 (94.0)
Involved	275 (5.9)	191 (5.9)	84 (6.1)
Fundus			
Not involved	4537 (98.0)	3173 (97.8)	1364 (98.2)
Involved	95 (2.1)	70 (2.2)	25 (1.8)
High body			
Not involved	3993 (86.2)	2790 (86.0)	1203 (86.6)
Involved	639 (13.8)	453 (14.0)	186 (13.4)
Midbody			
Not involved	3827 (82.6)	2689 (82.9)	1138 (81.9)
Involved	805 (17.4)	554 (17.1)	251 (18.1)
Lower body			
Not involved	3217 (69.5)	2242 (69.1)	975 (70.2)
Involved	1415 (30.6)	1001 (30.9)	414 (29.8)
Angle			
Not involved	3342 (72.2)	2346 (72.3)	996 (71.7)
Involved	1290 (27.9)	897 (27.7)	393 (28.3)
Antrum			
Not involved	2526 (54.5)	1771 (54.6)	755 (54.4)
Involved	2106 (45.5)	1472 (45.4)	634 (45.6)

	Total (N=4632)	Training set (N=3243)	Validation set (N=1389)
Pylorus			
Not involved	4350 (93.9)	3046 (93.9)	1304 (93.9)
Involved	282 (6.1)	197 (6.1)	85 (6.1)
Circular location			
Lesser curvature			
Not involved	2237 (48.3)	1571 (48.4)	666 (48.0)
Involved	2395 (51.7)	1672 (51.6)	723 (52.1)
Greater curvature			
Not involved	3354 (72.4)	2345 (72.3)	1009 (72.6)
Involved	1278 (27.6)	898 (27.7)	380 (27.4)
Anterior wall			
Not involved	3033 (65.5)	2151 (66.3)	882 (63.5)
Involved	1599 (34.5)	1092 (33.7)	507 (36.5)
Posterior wall			
Not involved	2819 (60.9)	1958 (60.4)	861 (62.0)
Involved	1813 (39.1)	1285 (39.6)	528 (38.0)

Pap, Papillary adenocarcinoma; WD tub, well differentiated tubular adenocarcinoma; MD tub, moderately differentiated tubular adenocarcinoma; PD tub, poorly differentiated tubular adenocarcinoma; Muc, muninous adenocarcinoma; SRC, signet ring cell carcinoma

Table 4 Univariate analysis in training set for LNS 3 (mean ±S.D., n(%))

	Training set			
	LN metastasis (-) (N=2596)	LN metastasis (+) (N=647)	OR [95% CI]	p-value
Sex				
Male	1645	412 (20.0)	1	
Female	951	235 (19.8)	0.99 [0.83, 1.18]	0.8830
Age (yrs)	58.8 ±11.94	59.5 ±12.80	1.01† [1.00, 1.01]	0.1754
Tumor size (cm)	3.3 ±2.06	6.1 ±3.33	1.48‡ [1.43, 1.54]	<0.0001
Depth of tumor				<0.0001
Mucosa	968	11 (1.1)	1	
Submucosa	905	79 (8.0)	7.68 [4.06, 14.53]	<0.0001
Proper muscle	325	68 (17.3)	18.4 [9.62, 35.24]	<0.0001
Subserosa	253	218 (46.3)	75.8 [40.7, 141.1]	<0.0001
Serosa	130	229 (63.8)	155.0 [82.4, 291.7]	<0.0001
Adjacent organ	15	42 (73.7)	246.4 [106.7, 569.1]	<0.0001
Gross type				
EGC (I, IIa, IIb, IIc, III)	1936	97 (4.8)	1	
B (I, II, III, IV),	660	550 (45.5)	16.6 [13.2, 21.0]	<0.0001
Histologic type				
Pap, WD tub, SRC	981	151 (13.3)	1	
MD tub, PD tub, Mucinous	1615	496 (23.5)	2.00 [1.64, 2.43]	<0.0001
Longitudinal location				
GEJ, cardia				
Not involved	2495	557 (18.3)	1	
Involved	101	90 (47.1)	3.99 [2.96, 5.38]	<0.0001
Fundus				
Not involved	2561	612 (19.3)	1	
Involved	35	35 (50.0)	4.19 [2.60, 6.74]	<0.0001
High body				
Not involved	2318	472 (16.9)	1	
Involved	278	175 (38.6)	3.09 [2.50, 3.83]	<0.0001
Midbody				
Not involved	2230	459 (17.1)	1	
Involved	366	188 (33.9)	2.50 [2.04, 3.06]	<0.0001
Lower body				
Not involved	1948	294 (13.1)	1	
Involved	648	353 (35.3)	3.61 [3.02, 4.32]	<0.0001
Angle				
Not involved	2002	344 (14.7)	1	
Involved	594	303 (33.8)	2.97 [2.48, 3.55]	<0.0001
Antrum				
Not involved	1454	317 (17.9)	1	

	Training set			
	LN metastasis (-) (N=2596)	LN metastasis (+) (N=647)	OR [95% CI]	p-value
Involved	1142	330 (22.4)	1.33 [1.12, 1.58]	0.0014
Pylorus				
Not involved	2464	582 (19.1)	1	
Involved	132	65 (33.0)	2.09 [1.53, 2.84]	<0.0001
Circular location				
Lesser curvature				
Not involved	1428	143 (9.1)	1	
Involved	1168	504 (30.1)	4.31 [3.52, 5.27]	<0.0001
Greater curvature				
Not involved	1914	431 (18.4)	1	
Involved	682	216 (24.1)	1.41 [1.17, 1.69]	0.0003
Anterior wall				
Not involved	1821	330 (15.3)	1	
Involved	775	317 (29.0)	2.26 [1.89, 2.69]	<0.0001
Posterior wall				
Not involved	1673	285 (14.6)	1	
Involved	923	362 (28.2)	2.30 [1.93, 2.74]	<0.0001

Pap, Papillary adenocarcinoma; WD tub, well differentiated tubular adenocarcinoma; MD tub, moderately differentiated tubular adenocarcinoma; PD tub, poorly differentiated tubular adenocarcinoma; Muc, muninous adenocarcinoma; SRC, signet ring cell carcinoma

† Mean odds ratio of lymph node metastasis by age 10 years increase

‡ Mean odds ratio of lymph node metastasis by size 1cm increase

All OR and p-value from Logistic regression

Table 5 Selection of significant variables for LNS 3 metastasis by variable selection method of multiple logistic regression using the training set

	OR [95% CI]	p-value
Depth of tumor		<0.0001
Mucosa	1	
Submucosa	7.28 [3.83, 13.85]	<.0001
Proper muscle	5.23 [2.03, 13.46]	0.0006
Subserosa	15.59 [5.87, 41.38]	<.0001
Serosa	25.51 [9.47, 68.75]	<.0001
Adjacent organ	36.82 [11.55, 117.37]	<.0001
Gross type		
EGC (I, IIa, IIb, IIc, III)	1	
B (I, II, III, IV)	3.50 [1.64, 7.44]	0.0012
Longitudinal location		
High body involved (ref: not involved)	2.09 [1.56, 2.82]	<.0001
Lower body involved (ref: not involved)	2.60 [2.05, 3.31]	<.0001
Angle involved (ref: not involved)	1.49 [1.14, 1.95]	0.004
Circular location		
Lesser curvature involved (ref: not involved)	2.06 [1.60, 2.66]	<.0001
Greater curvature involved (ref: not involved)	0.68 [0.52, 0.89]	0.0057
Anterior wall involved (ref: not involved)	1.34 [1.06, 1.71]	0.0162
Posterior wall involved (ref: not involved)	1.39 [1.10, 1.75]	0.0056
c-statistic	0.895	

Table 6 Prediction formula according to LNS, from method 1 (Dividing cases)

LNS	Prediction formula: $\log_e (p/(1-p))$
1	-4.8536+0.0578 Size+1.7079 (PM)+ 2.5515 (SS)+ 2.9757 (S, Adj)+ 0.7439 (GEJ, Cardia, Fundus, HB)+ 0.3812 (LC)
2	-6.7017+0.1816 Size+ 0.9379 (PM)+ 1.7868 (SS)+ 2.4245 (S, Adj)+ 1.5289 (GEJ ,Cardia, Fundus, HB)-0.9427 (Antrum, Pylorus)+ 0.8272 (LC)
3	-5.449+1.9852 (SM)+ 1.6536 (PM)+ 2.7465 (SS)+ 3.2391 (S)+ 3.6061 (Adj)+ 1.2513 (Borrmann(1, 2, 3, 4))+ 0.7388 (HB)+ 0.9559 (LB)+ 0.3960 (Angle)+ 0.7228 (LC)- 0.3846 (GC)+ 0.2949 (AW) + 0.3269 (PW)
4sa	-5.9182 +0.1124 Size+ 1.6002 (PM)+ 2.6556 (SS)+ 3.1429 (S, Adj)
4sb	-8.7801 +0.0608 Size+ 3.2471 (SS)+ 4.1272 (S, Adj)+ 1.8602 (GEJ, Cardia, Fundus, HB)+ 2.2017 (MB, LB, Angle)- 1.6629 (LC)+0.8051 (GC)
4d	-6.2076 + 0.0677 Size + 2.0328 (SM) + 2.7989 (PM) + 3.5291 (SS) + 4.2735 (S) + 3.9589 (Adj) -0.6742 (HB) + 0.4937 (MB) + 1.1499 (LB) + 1.0204 (Antrum)- 0.5691 (LC) + 1.1023 (GC)
5	-6.6606+ 1.8332 (PM)+ 2.3126 (SS)+ 2.6839 (S, Adj)-0.431 (MB, LB, Angle)+1.9662 (Antrum, Pylorus)+1.2811 (LC)
6	-7.0597 + 2.334 (SM) + 3.4549 (PM) + 3.98 (SS) + 4.6205 (S) + 4.7603 (Adj) - 0.7490 (HB) + 0.3514 (LB) + 2.2166 (Antrum) + 0.5062 (Pylorus) + 0.5817 (GC) + 0.3388 (PW)
7	-4.966+ 0.2886 (PM)+0.9952 (SS)+ 1.4973 (S, Adj)+1.3222 (Borrmann(1, 2, 3, 4))+0.6744 (GEJ, Cardia, Fundus, HB)+0.8427 (MB, LB, Angle)+0.9051 (LC)
8a	-6.043+ 0.0699 Size+1.7326 (PM)+2.2525 (SS)+ 2.8083 (S, Adj)+1.3647 (Antrum, Pylorus)+0.8255 (LC)
9	-7.111+ 0.1296 Size+0.7388 (PM)+2.1285 (SS)+3.1018 (S, Adj)+1.3155 (LC)
10	-7.0151 +0.00671 Size+ 2.2768 (SS)+ 3.7834 (S, Adj)+ 1.4025 (GEJ, Cardia, Fundus, HB)+ 0.5275 (MB, LB, Angle)+ 0.4222 (GC)
11p	-5.534+ 0.0903 Size+1.2423 (PM)+2.465 (SS)+ 2.9824 (S, Adj)
11d	-4.8041 +0.0201 Size+ 0.8627 (SS)+ 1.9113 (S, Adj)+ 0.7721 (MB, LB, Angle)+ 0.4579 (GC)
12a	-7.1541+1.9416 (PM)+2.3304 (SS)+ 3.3928 (LB, Adj) +1.8143 (Antrum, Pylorus)

LNS, lymph node station; PM, proper muscle; SS, subserosa; S, serosa; Adj, adjacent organ; GEJ, gastroesophageal junction; HB, high body; LC, lesser curvature; SM, submucosa; LB, lower body; GC, greater curvature; AW, anterior wall; PW, posterior wall

Table 7 Prediction formula according to LNS, from method 2 (All cases)

LNS	Prediction formula: $\log_e$ (p/(1-p))
1	-4.9038 + 1.9364 (PM)+2.624 (SS)+ 3.26 (S)+ 3.4302 (Adj)+ 0.9602 (GEJ, Cardia)+ 0.3743 (MB)+ 0.4856 (LB) - 0.4062 (Angle)+ 0.4953 (LC)
2	-7.5048+0.2432 Size+ 1.5636 (SS)+ 2.430 (S, Adj)+ 2.3487 (GEJ, Cardia, Fundus, HB)- 0.7692 (MB, LB, Angle)-1.1416 (Antrum, Pylorus)+ 0.9345 (LC)
3	-4.5715 + 0.6787 (PM)+1.6109 (SS)+ 2.2097 (S)+ 2.5645 (Adj)+ 0.8312 (Borrmann(1, 2, 3, 4))+ 0.481 (MD tub, PD tub, Muc)+ 0.7124 (HB)+ 0.7979 (MB)+ 0.9727 (LB)-0.838 (MB & LB)+ 0.1136 (Angle)+ 0.1924 (Antrum) + 0.5673 (Angle & Antrum) + 0.7039 (LC)-0.4657 (GC)+ 0.321 (AW)+ 0.3965 (PW)
4sa	-7.4376+ 0.1070 Size+ 2.9150 (SS)+ 3.5160 (S, Adj)+ 1.6817 (GEJ, Cardia, Fundus, HB)-0.7273 (LC)+ 0.7448 (GC)
4sb	-8.7469+0.0722 Size+ 3.1887 (SS)+ 4.004 (S, Adj)+ 1.9302 (GEJ, Cardia, Fundus, HB)+ 1.8705 (MB, LB, Angle)-1.5808 (LC)+ 0.7039 (GC)
4d	-5.0365 +0.0988 Size+ 1.1946 (PM)+2.0444 (SS)+2.6725 (S)+ 2.8338 (Adj)+ 0.3738 (MD tub, PD tub, Muc)-0.9799 (GEJ, Cardia)+ 0.3862 (MB)+ 1.0053 (LB) + 0.9489 (Antrum)-0.6071 (LC)+ 1.0623 (GC)
5	-7.5048-0.41 (Female)+ 1.6752 (PM)+ 2.1139 (SS)+2.5217 (S)+3.0007 (Adj)+1.8121 (Antrum, Pylorus)+ 0.974 (LC)
6	-5.3664+ 1.6902 (PM)+2.0776 (SS)+2.7212 (S)+ 2.88648 (Adj)-0.5731 (HB)+ 0.3139 (LB) + 2.2515 (Antrum)+ 0.5124 (Pylorus)+ 0.4828 (GC)+ 0.2556 (AW)+ 0.3169 (PW)
7	-4.8529 + 0.3785 (Female)+ 0.5117 (PM)+1.345 (SS)+ 1.6074 (S)+ 2.053 (Adj) + 0.8734 (Borrmann(1, 2, 3, 4))+ 0.503 (GEJ, Cardia)-0.8552 (Fundus)+ 0.6109 (HB)+ 0.7201 (LB) + 0.3814 (Angle) + 0.6377 (LC)+0.3172 (PW)
8a	-6.0397+0.0718 Size+ 1.7387 (PM)+2.3013 (SS)+2.6748 (S)+3.0216 (Adj)+1.3077 (Antrum, Pylorus)+ 0.7975 (LC)
9	-6.5151+0.1206 Size+2.1191 (SS)+2.954 (S, Adj)+0.9146 (LC)
10	-9.2506+0.0898 Size+ 3.9814 (SS)+ 5.3432 (S, Adj)+1.7365 (GEJ, Cardia, Fundus, HB)
11p	-5.4234+1.2458 (SS)+1.9746 (S, Adj)+ 1.1131 (Borrmann(1, 2, 3, 4))+0.7828 (GEJ, Cardia, Fundus, HB)+0.455 (Antrum, Pylorus)
11d	-7.8918+0.00963 Size+ 2.9491 (SS)+3.7111 (S, Adj)+ 1.276 (GEJ, Cardia, Fundus, HB)+ 1.0978 (MB, LB, Angle)
12a	-6.7602+0.0499 Size+ 0.984 (SS)+1.9189 (S, Adj)+ 1.3511 (Antrum, Pylorus)+ 1.349 (LC)

Table 7 (cont.)
LNS, lymph node station; PM, proper muscle; SS, subserosa; S, serosa; Adj, adjacent organ; GEJ, gastroesophageal junction; MB, mid body; LB, lower body; LC, lesser curvature; HB, high body; MD tub, moderately differentiated tubular adenocarcinoma; PD tub, poorly differentiated tubular adenocarcinoma; Muc, mucinous adenocarcinoma; GC, greater curvature; AW, anterior wall; PW, posterior wall

Table 8 C-statistics and Optimism corrected c-statistics of prediction formula according to LNS from Method 1 and Method 2 respectively

LNS	Method 1	Method 2	
	c-statistic	optimism corrected c-statistic	optimism in c-statistic
1	0.867	0.856785	0.006851
2	0.873	0.962281	0.003051
3	0.897	0.889254	0.003893
4sa	0.838	0.946019	0.001844
4sb	0.9977	0.946753	0.00389
4d	0.887	0.890142	0.003794
5	0.83	0.851163	0.005393
6	0.891	0.892745	0.003975
7	0.833	0.850165	0.00648
8a	0.857	0.866446	0.003803
9	0.87	0.880013	0.005935
10	0.866	0.971699	0.000395
11p	0.853	0.829014	0.009037
11d	0.698	0.941081	0.009402
12a	0.822	0.83172	0.008637

Table 9 Prediction formula according to LNS, from method 2 (one third location classification)

LNS	Prediction formula: $\log_e$ (p/(1-p))
1	-3.6624+0.0556 Size+1.8751 (PM)+2.5053 (SS)+3.2064 (S)+3.3737 (Adj)-0.3408 (M)-1.0812 (L)-0.3827 (E)-0.2698 (GC)-0.8546 (AW)-0.7511 (PW)-0.0381 (Circular)
3	-3.5441+0.1508 Size+0.5968 (PM)+1.6085 (SS)+2.2514 (S)+2.5256 (Adj) +0.9133 (Borrmann(1,2,3,4,))+ 0.4473 (MD tub, PD tub, Muc)+ 0.4613 (M)-0.0567 (L)-0.1447 (E)-1.1711 (GC)-0.7799 (AW)-0.8448 (PW)-0.402 (Circular)
4d	-7.3297+0.2012 Size+ 1.2284 (PM)+ 2.1386 (SS)+2.881 (S)+2.9069 (Adj)+ 0.3863 (MD tub, PD tub, Muc) + 2.3192 (M)+2.5363 (L)+ 1.942 (E)+ 1.6351 (GC)+ 0.1065 (AW)+ 0.174 (PW)+ 0.4924 (Circular)
5	-6.744-0.442 (Female)+0.0812 Size+1.6489 (PM)+2.1200 (SS)+ 2.5485 (S)+3.125 (Adj)+ 1.5554 (M)+ 2.8679 (L)+1.7074 (E)-0.7156 (GC)-1.2301 (AW)-1.2174 (PW)-0.00443 (Circular)
6	-7.5565+0.1277 Size+0.8163 (PM)+1.2146 (SS)+1.9171 (S)+ 2.0783 (Adj)+ 0.8768 (Borrmann(1,2,3,4))+0.3404 (MD tub, PD tub, Muc)+2.1303 (M)+ 3.9416 (L)+ 2.5603 (E)+ 0.169 (GC)-0.4432 (AW)-0.1959 (PW)+0.555 (Circular)
7	-3.8667+0.3475 (Female)+0.1047 Size+0.4859 (PM)+1.3695 (SS)+1.7061 (S)+ 2.0602 (Adj) + 0.9362 (Borrmann(1,2,3,4))+0.1947 (M)-0.2303 (L)+0.0932 (E)-0.8246 (GC)-0.7158 (AW)-0.8451 (PW)-0.2809 (Circular)
8a	-6.2335+0.1197 Size+1.7732 (PM)+2.3818 (SS)+ 2.7452 (S)+3.164 (Adj)+1.0796 (M)+ 1.8633 (L)+0.8129 (E)-0.7938 (GC)-0.5461 (AW)-0.8037 (PW)+0.1778 (Circular)

LNS, lymph node station; PM, proper muscle; SS, subserosa; S, serosa; Adj, adjacent organ; M, middle third; L, lower third; E, entire longitudinal; GC, greater curvature; AW, anterior wall; PW, posterior wall; MD tub, moderately differentiated tubular adenocarcinoma; PD tub, poorly differentiated tubular adenocarcinoma; Muc, mucinous adenocarcinoma

Table 10 Optimism corrected c-statistic of the predict formula by one third location classification and comparison between two location classifications

LNS	Optimism corrected c-statistic	Difference of c-statistic[$]
1	0.85957	-0.00061 (95% CI: -0.00704, 0.0343)
3	0.880984	0.00994 (95% CI: 0.00579, 0.0141)
4d	0.888481	0.00219 (95% CI: -0.00253, 0.00691)
5	0.842078	0.00465 (95% CI: -0.00718, 0.0165)
6	0.880229	0.0131 (95% CI: 0.00491, 0.0214)
7	0.84364	0.00566 (95% CI: -0.00082, 0.0121)
8a	0.858993	0.00512 (95% CI: -0.00142, 0.0117)

[$]Difference of c-statistic=c-statistic of this study (endoscopic location classification and consideration of all involved area)-c-statistic of one third location classification (tumor center only)

Table 11 Prediction formula according to LNS, from method 1 (including LN negative cases among subtotal gastrectomy cases)

LNS	Prediction formula: $\log_e (p/(1-p))$
2	-8.5596+0.1469size+ 2.3282 (PM)+ 2.7261(SS)+ 3.7770 (Adj) + 3.1261(GEJ, Cardia, Fundus or HB)
4sa	-7.0951+0.1349size+2.7127 (SS)+3.6023(Adj)+1.6341(GEJ, Cardia, Fundus, or HB)- 0.8546(LC)
10	-8.9739 +0.0090size+ 3.8455(SS)+ 4.8545(Adj)+ 2.0506(GEJ, Cardia, Fundus, or HB)+ 0.9815(GC)
11d	-7.1640 +0.0969size + 2.9826(SS) + 4.1344(Adj)

LNS, lymph node station; PM, proper muscle; SS, subserosa; Adj, adjacent organ; LC, lesser curvature; C, greater curvature; HB, high body

Table 12 C-statistics and Optimism corrected c-statistics of prediction formula according to LNS from Method 1(original), method 1 (including LN negative cases among subtotal gastrectomy cases) and Method 2 respectively

LNS	Method 1	Method 1 (including LN negative cases among subtotal gastrectomy cases)	Method 2	
	c-statistic	c-statistic	optimism corrected c-statistic	optimism in c-statistic
2	0.873	0.9433	0.962281	0.003051
4sa	0.838	0.9530	0.946019	0.001844
10	0.866	0.9770	0.971699	0.000395
11d	0.698	0.8691	0.941081	0.009402

Figures

Figure 1 Causes of exclusion

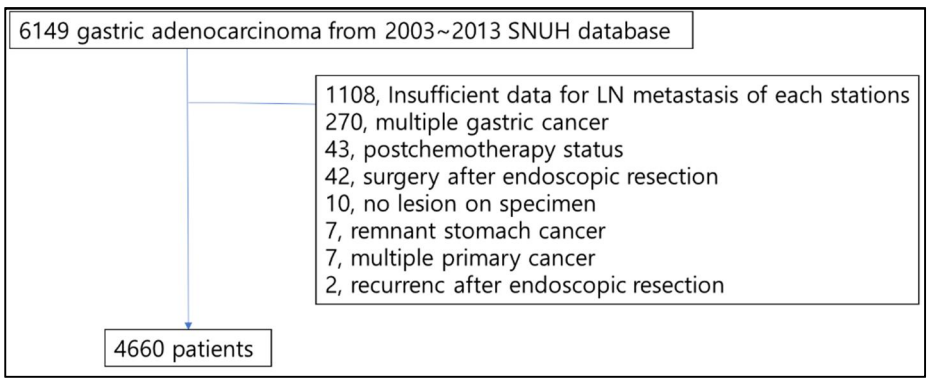


Figure 2 Calibration plot according to LNS, from method 1 (dividing cases)
Error bar represents 95% confidence interval.

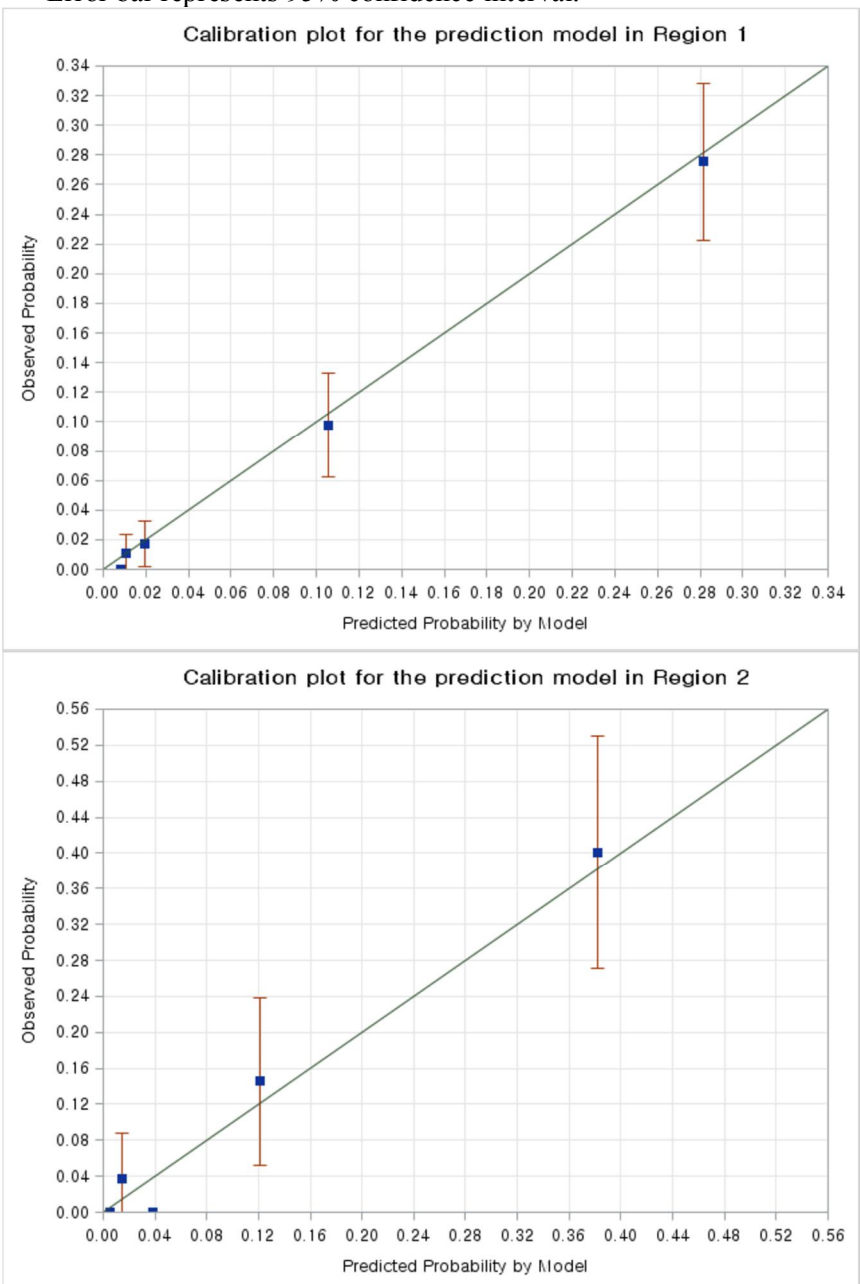
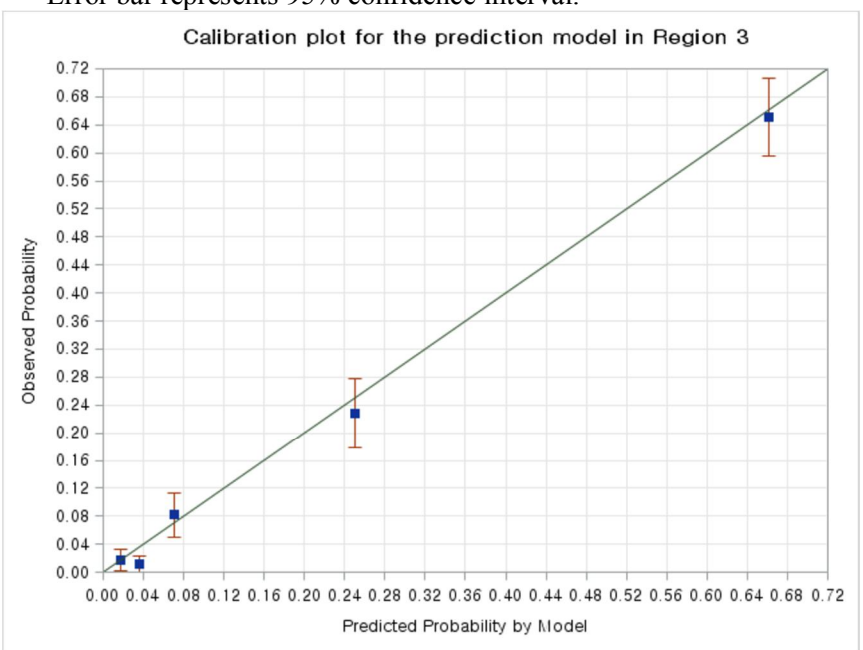


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.



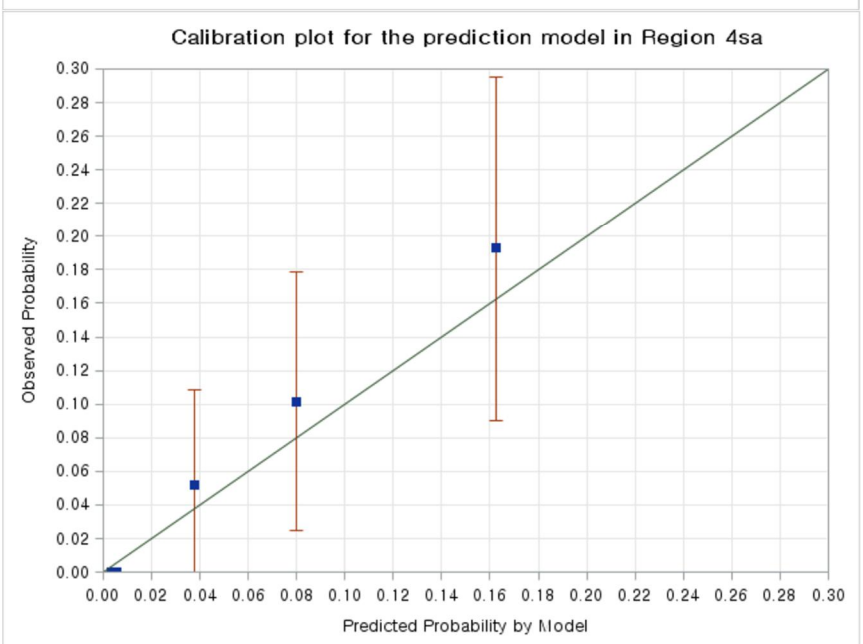
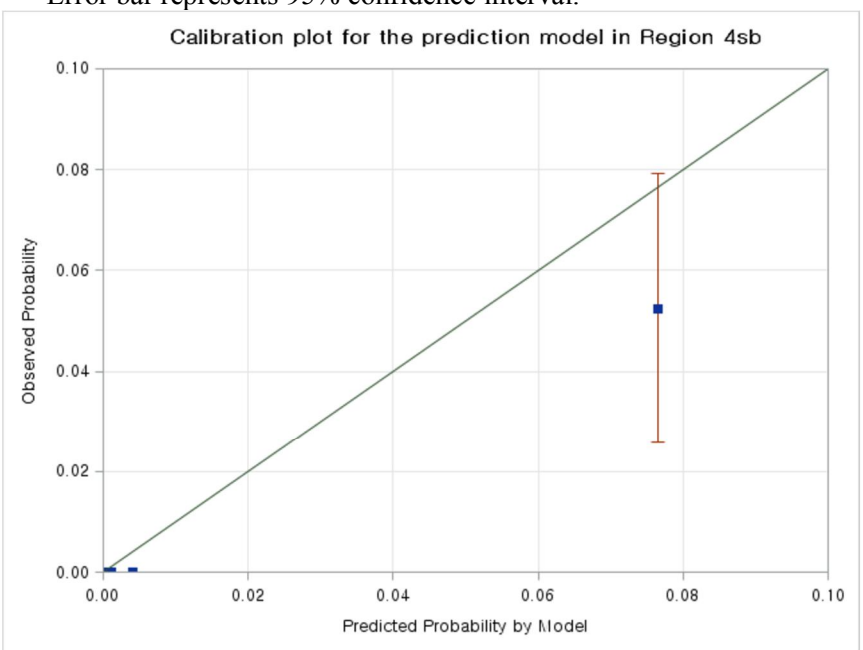


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.



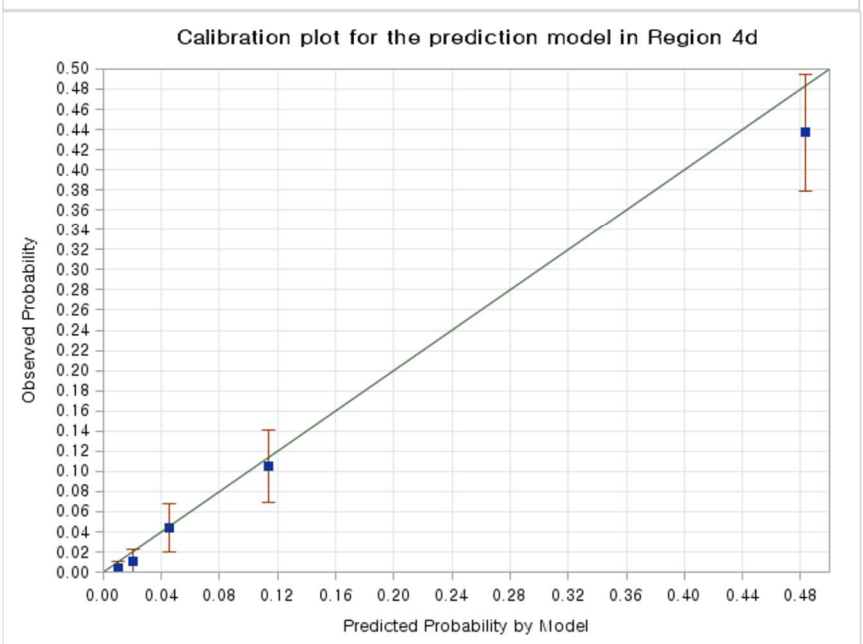
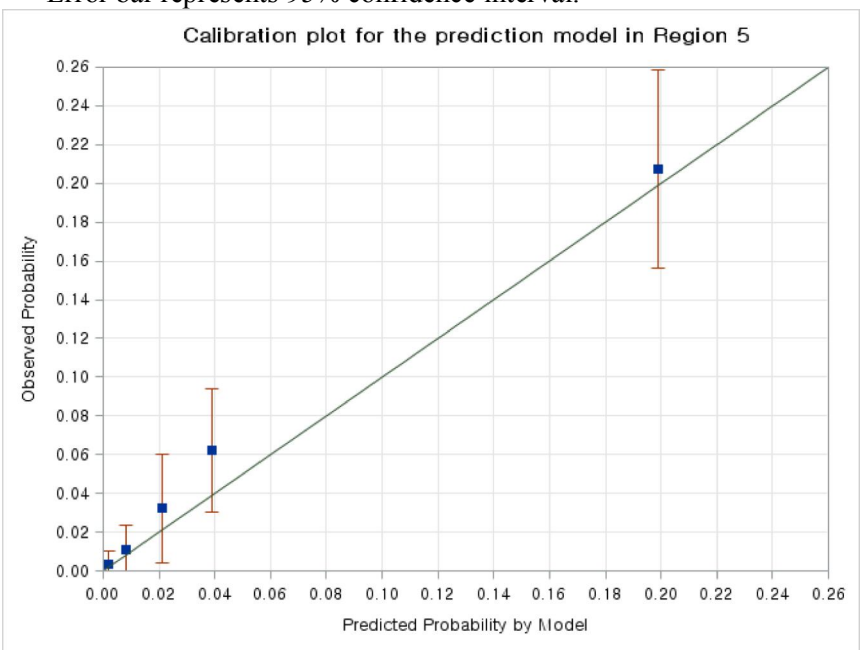


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.



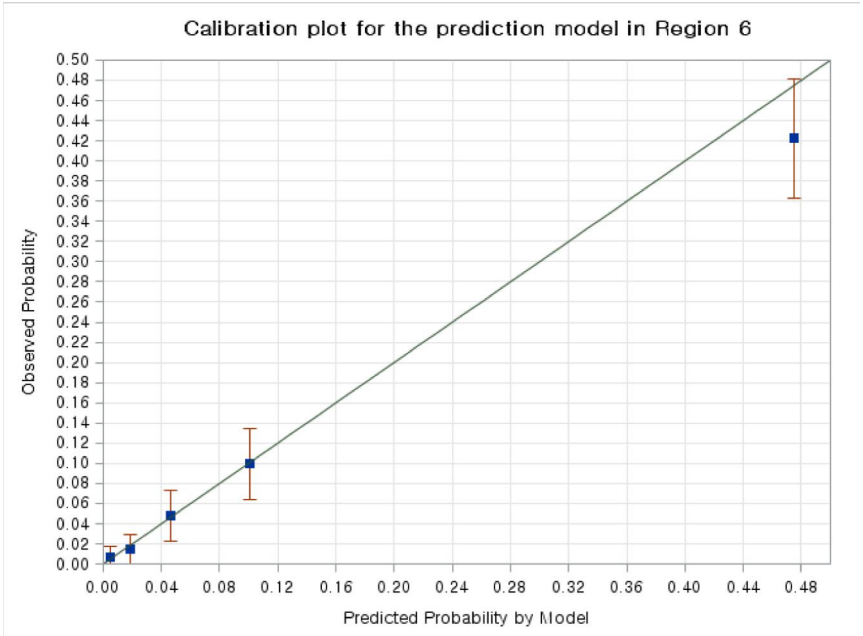
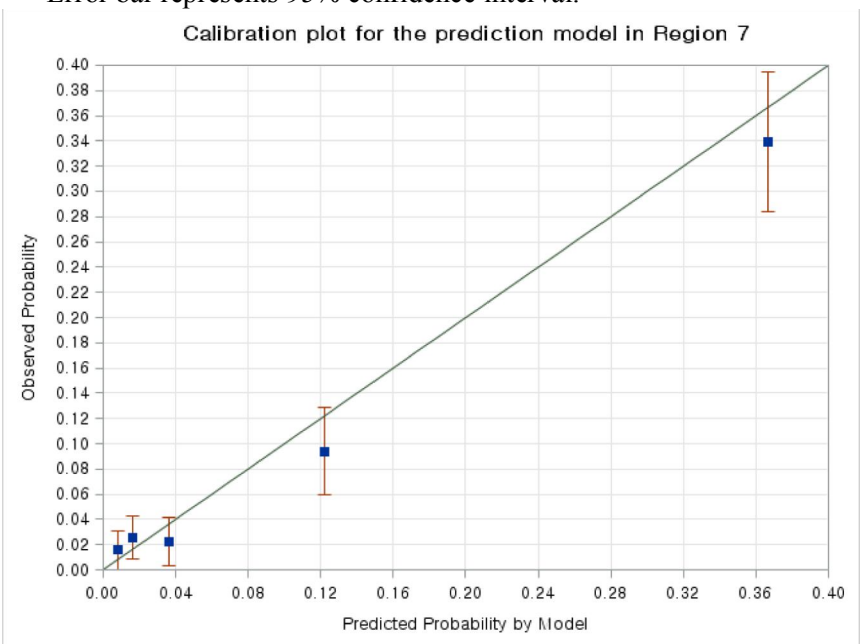


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.



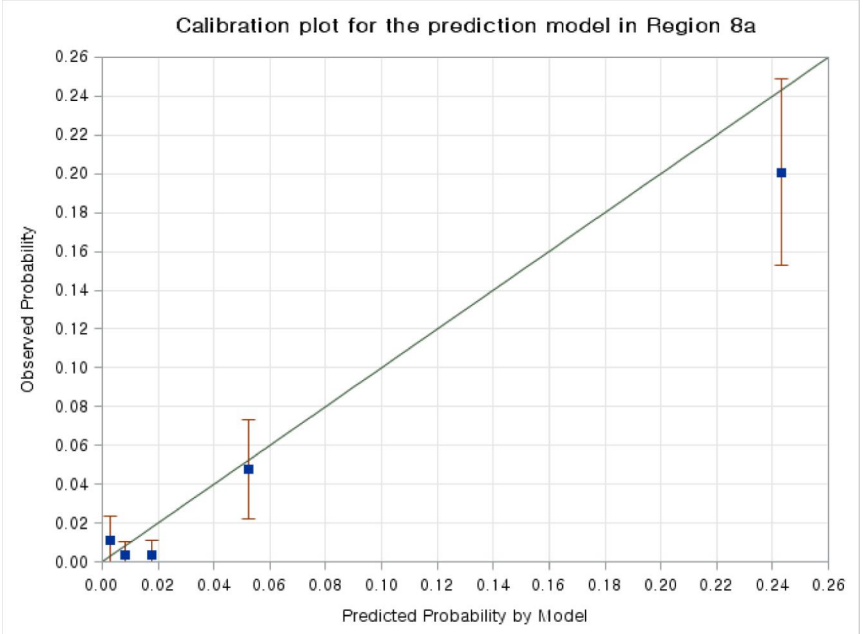
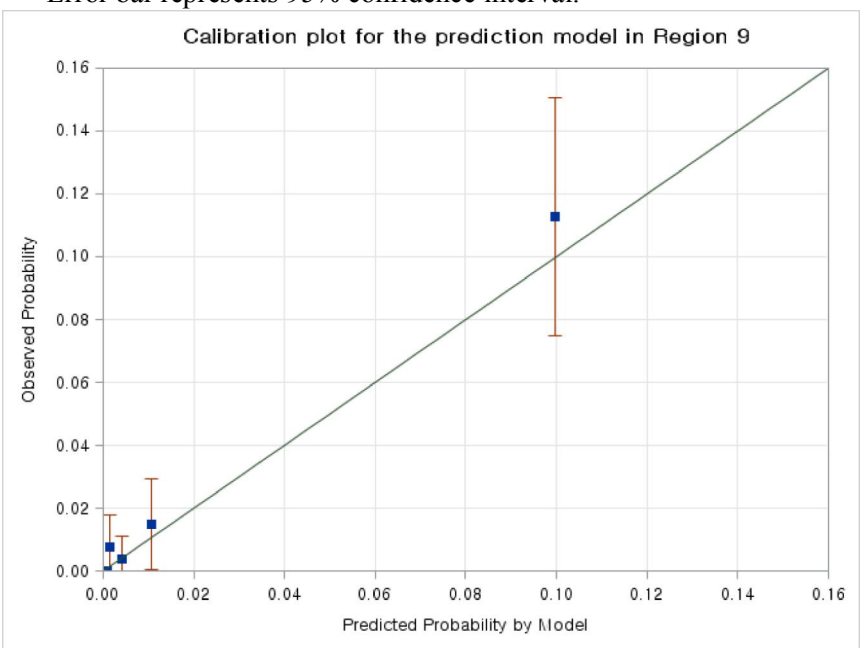


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.



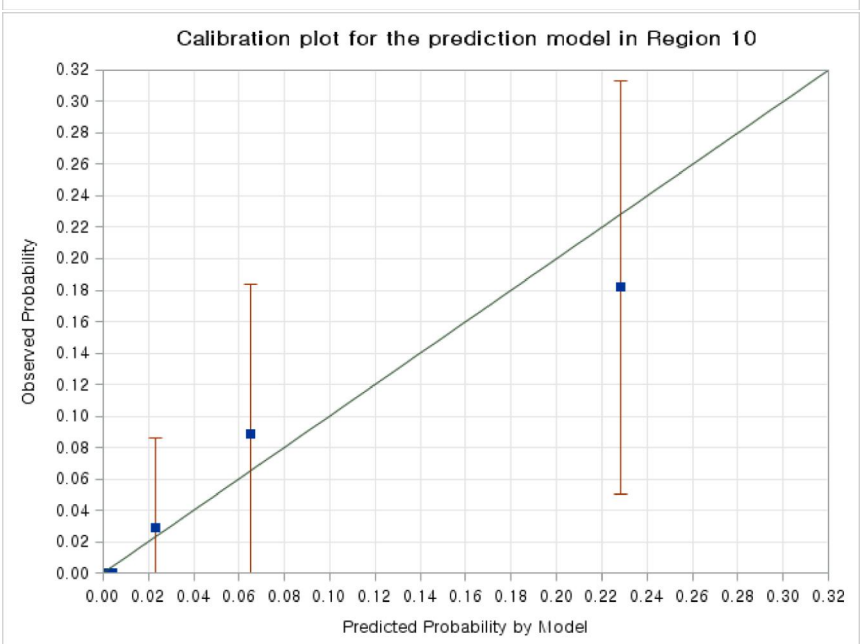


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.

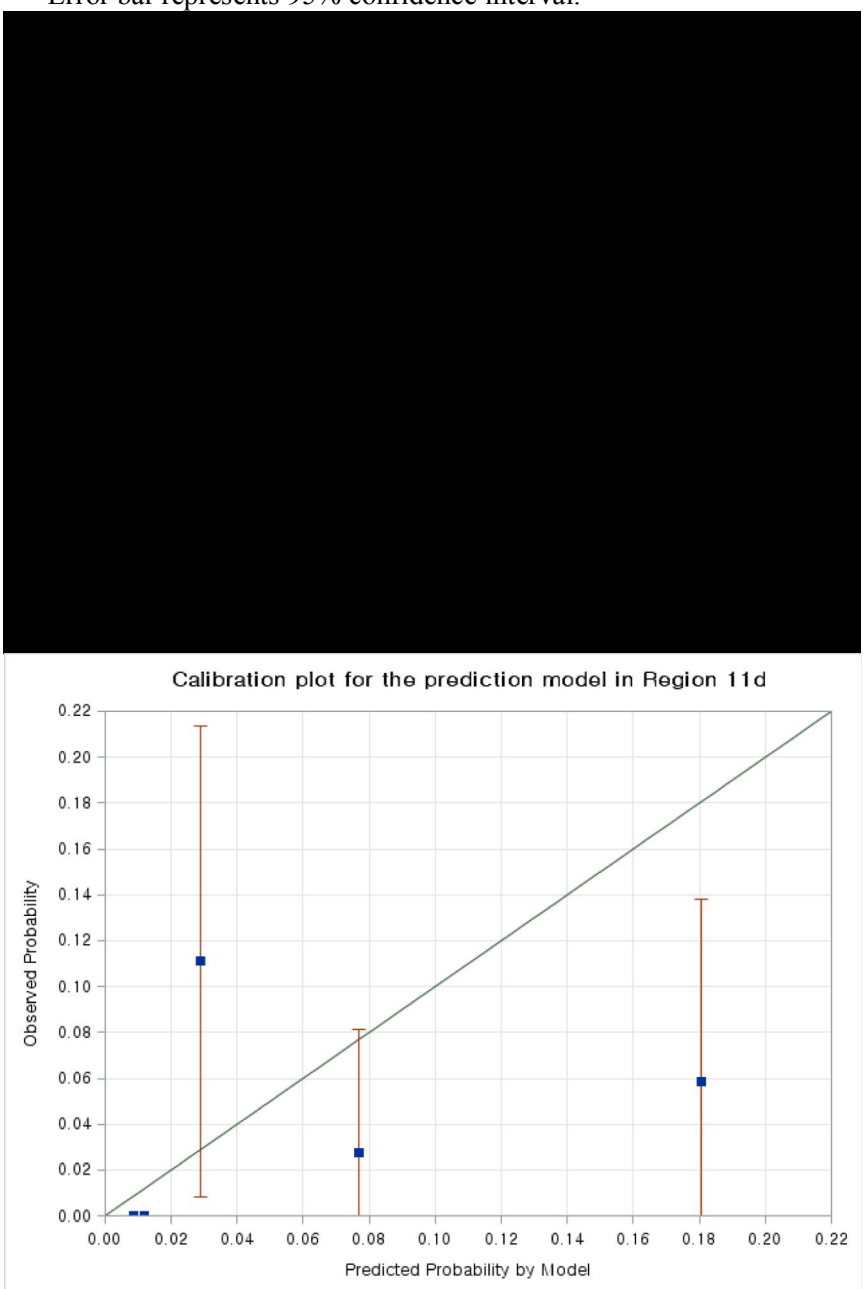


Figure 2-continue Calibration plot according to LNS, from method 1 (dividing cases)

Error bar represents 95% confidence interval.

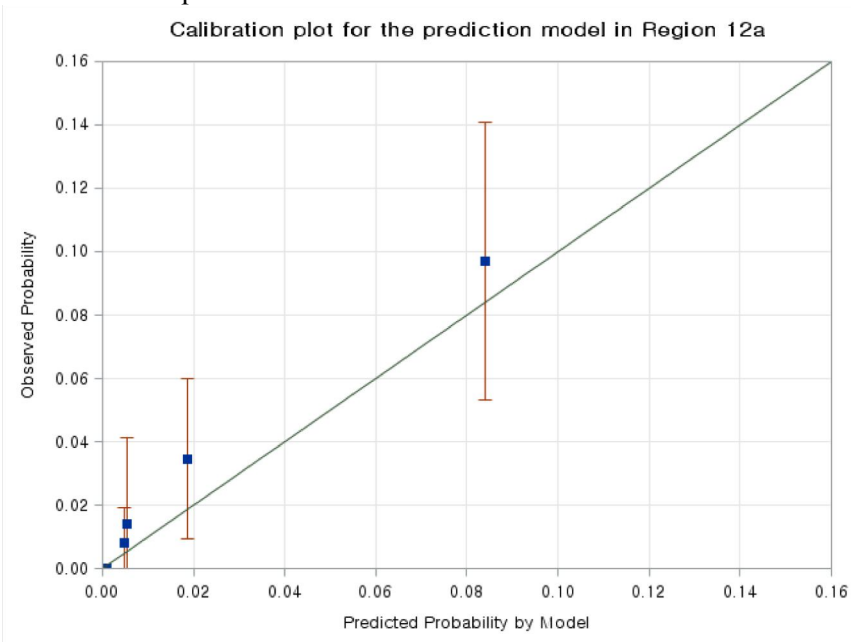
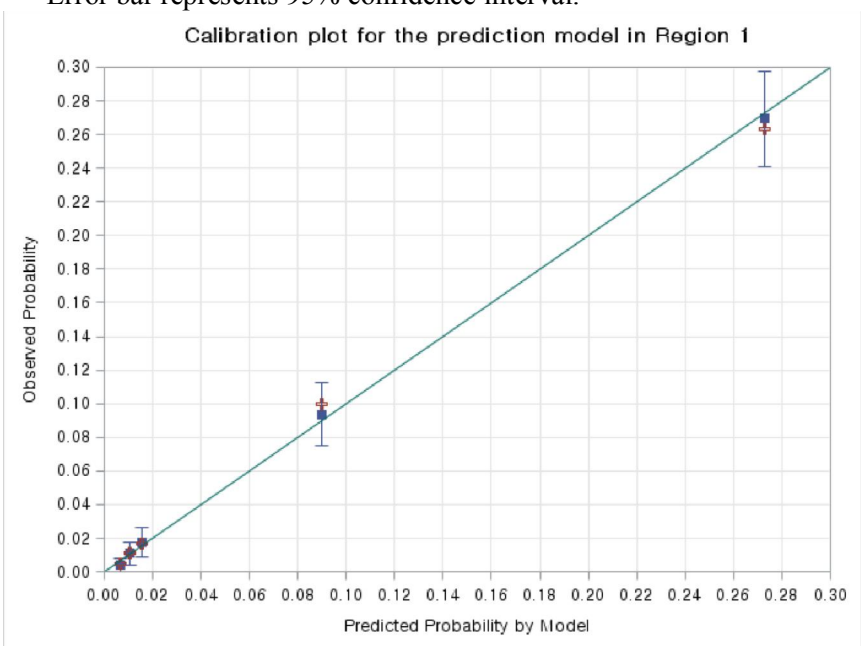


Figure 3 Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.



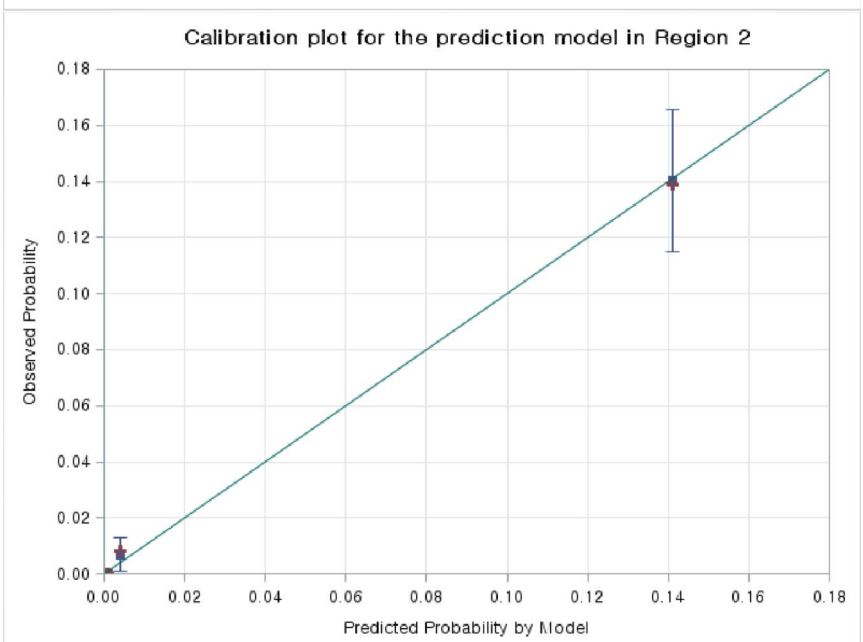


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.

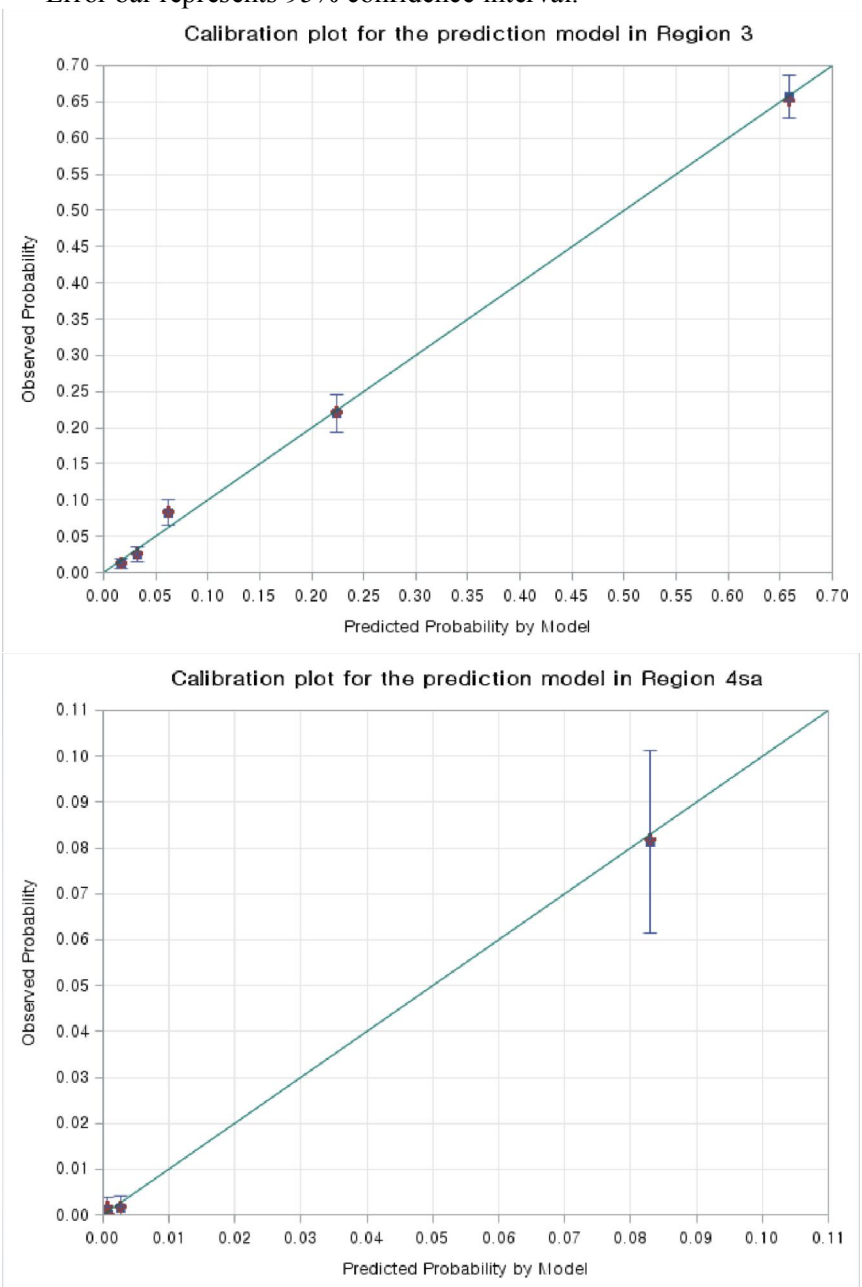
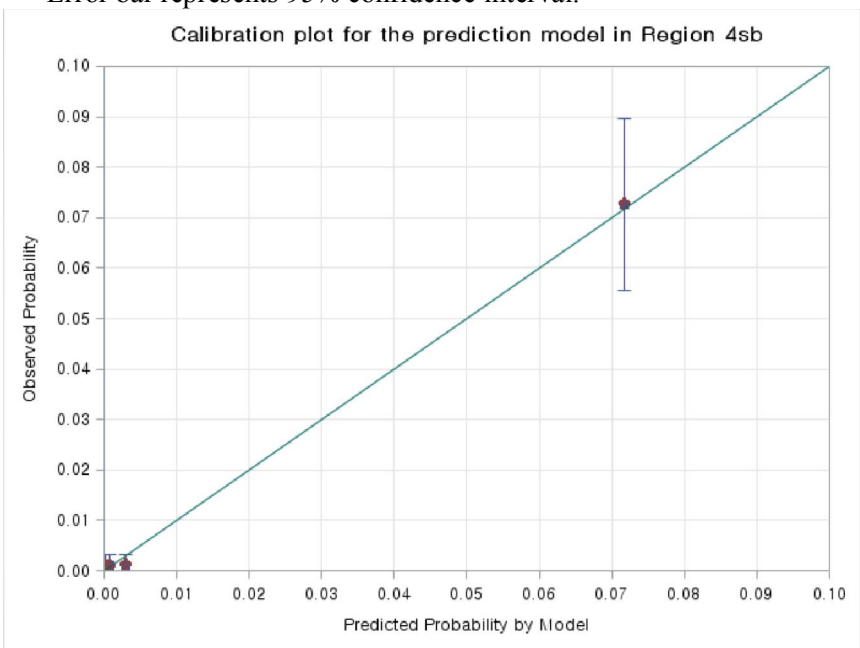


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.



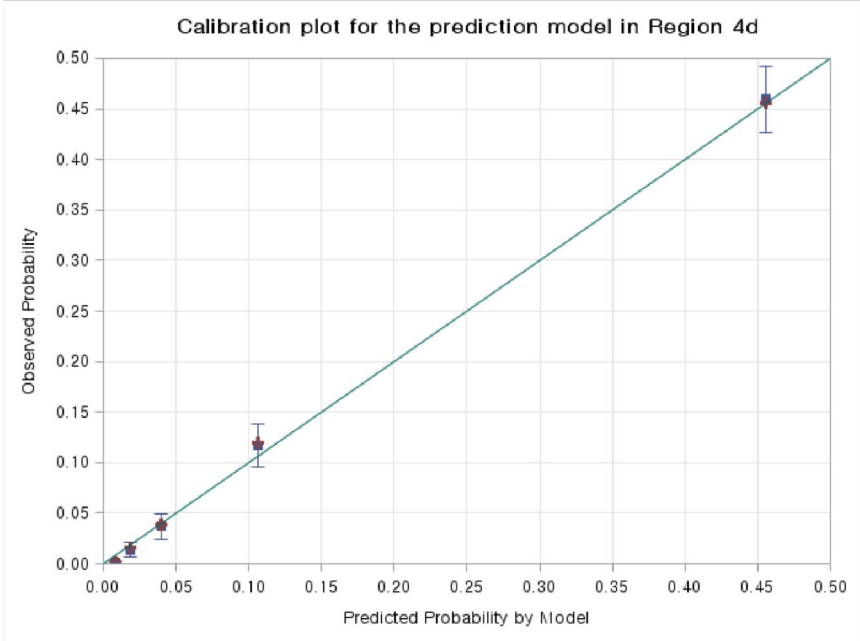
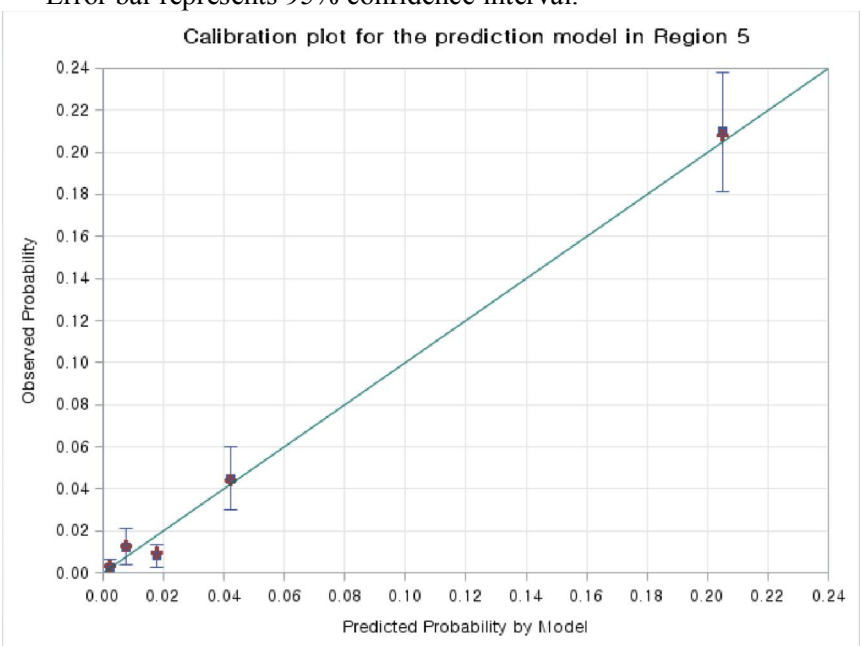


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.



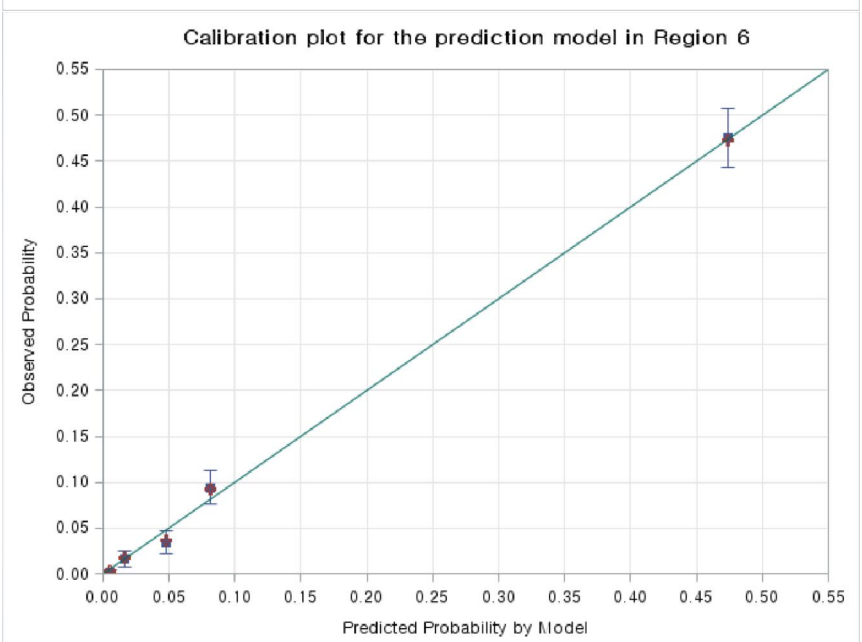
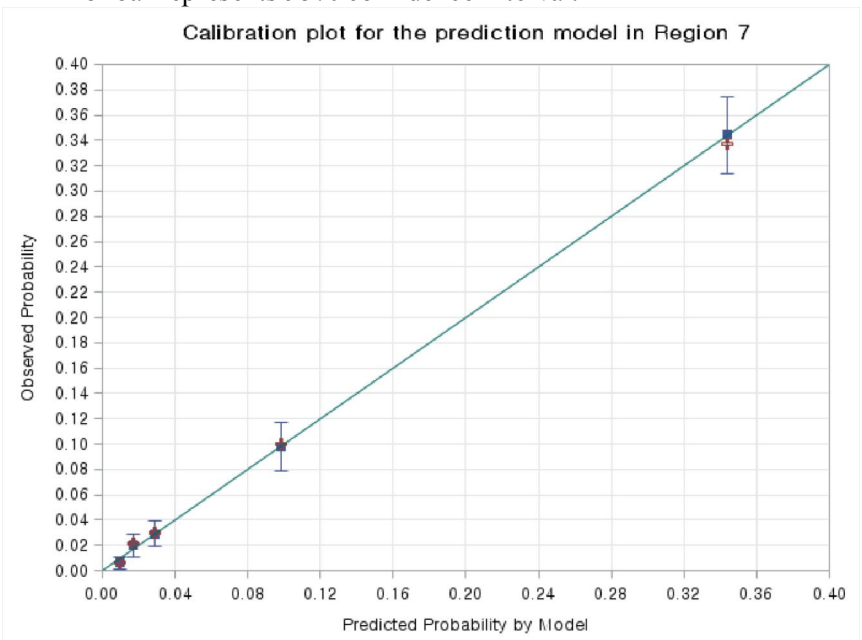


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.



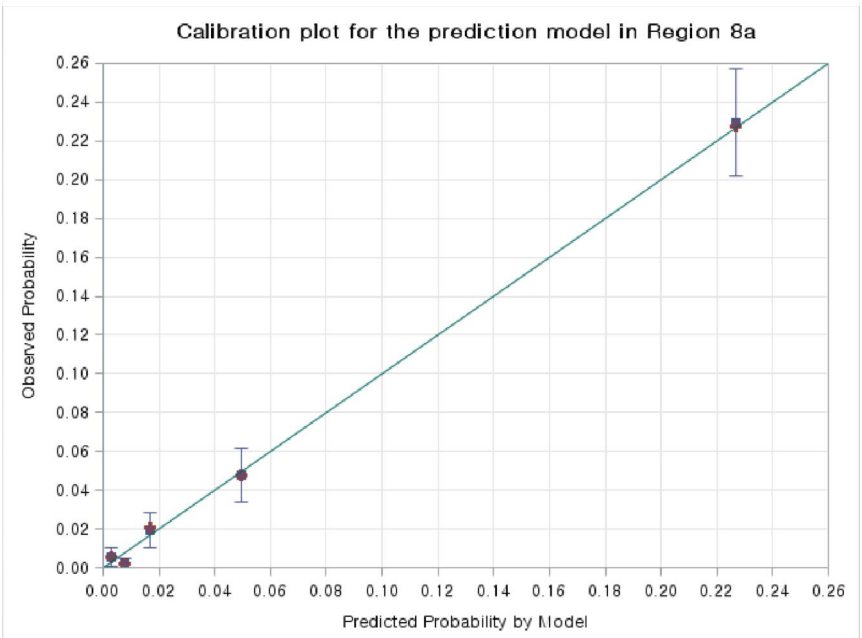
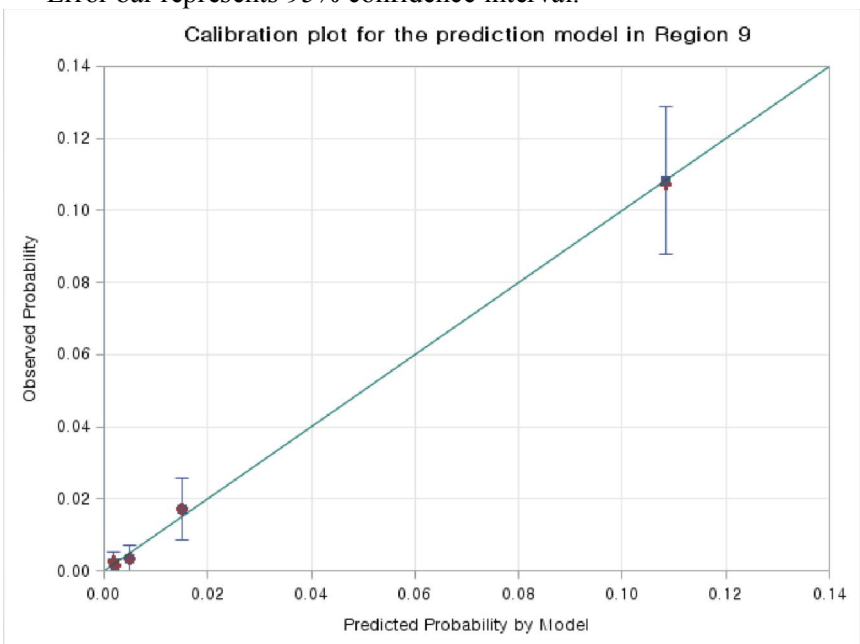


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.



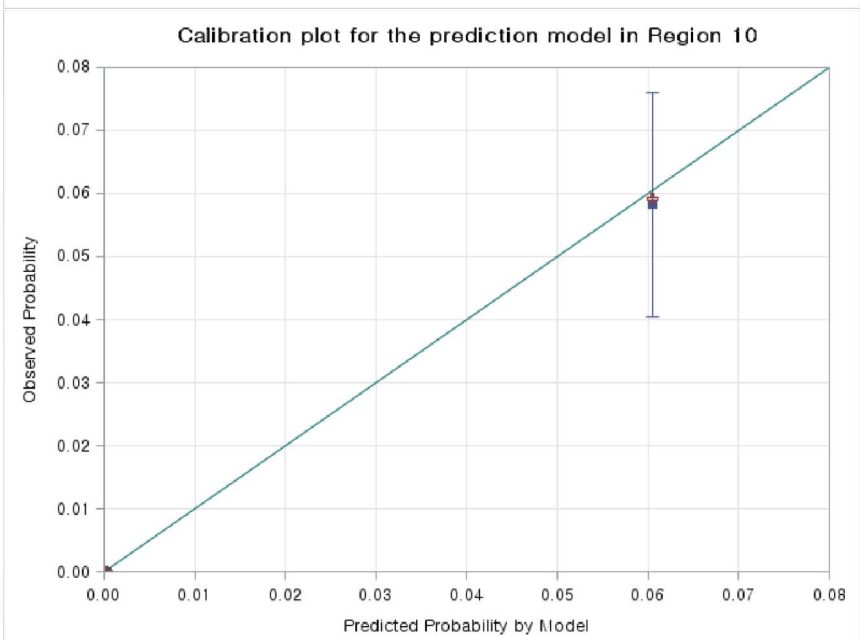
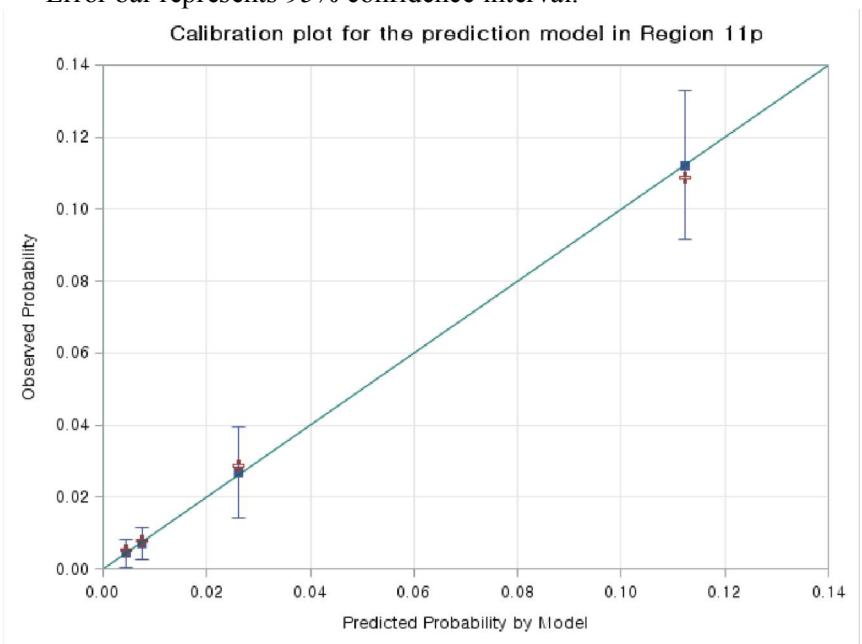


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.



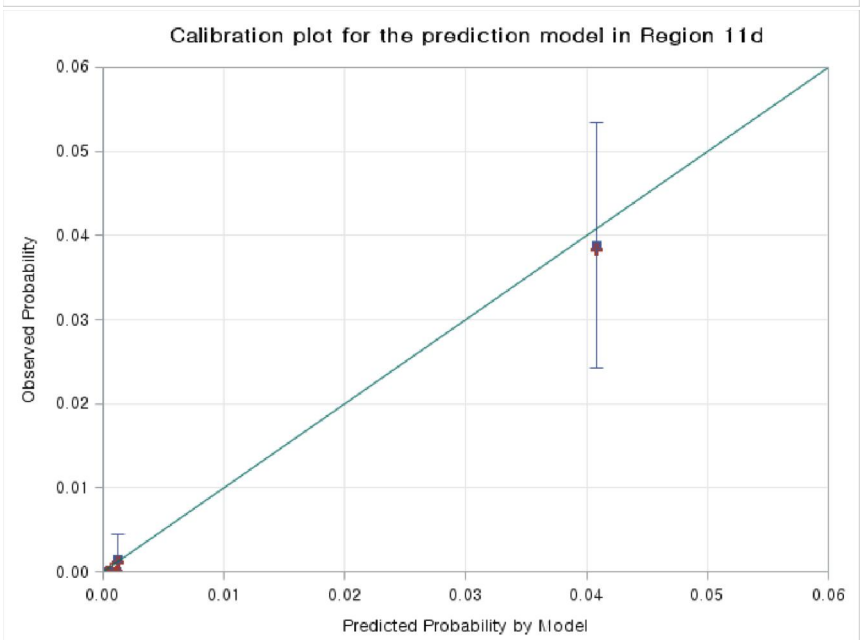


Figure 3-continue Optimism corrected calibration plot according to LNS, from method 2 (Bootstrap sampling)

Error bar represents 95% confidence interval.

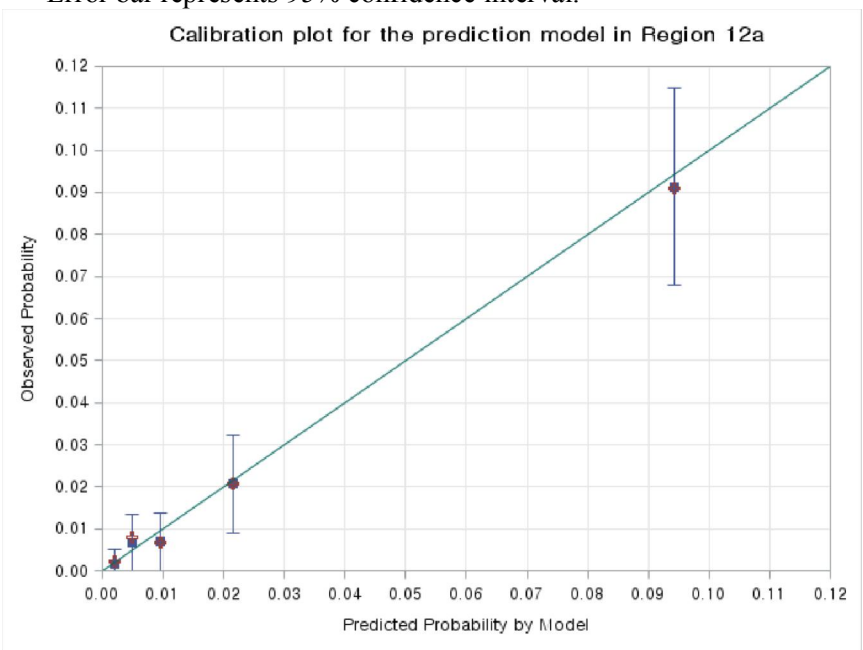


Figure 4 Calibration plot according to LNS, from method 1 (including LN negative cases among subtotal gastrectomy cases)

Error bar represents 95% confidence interval.

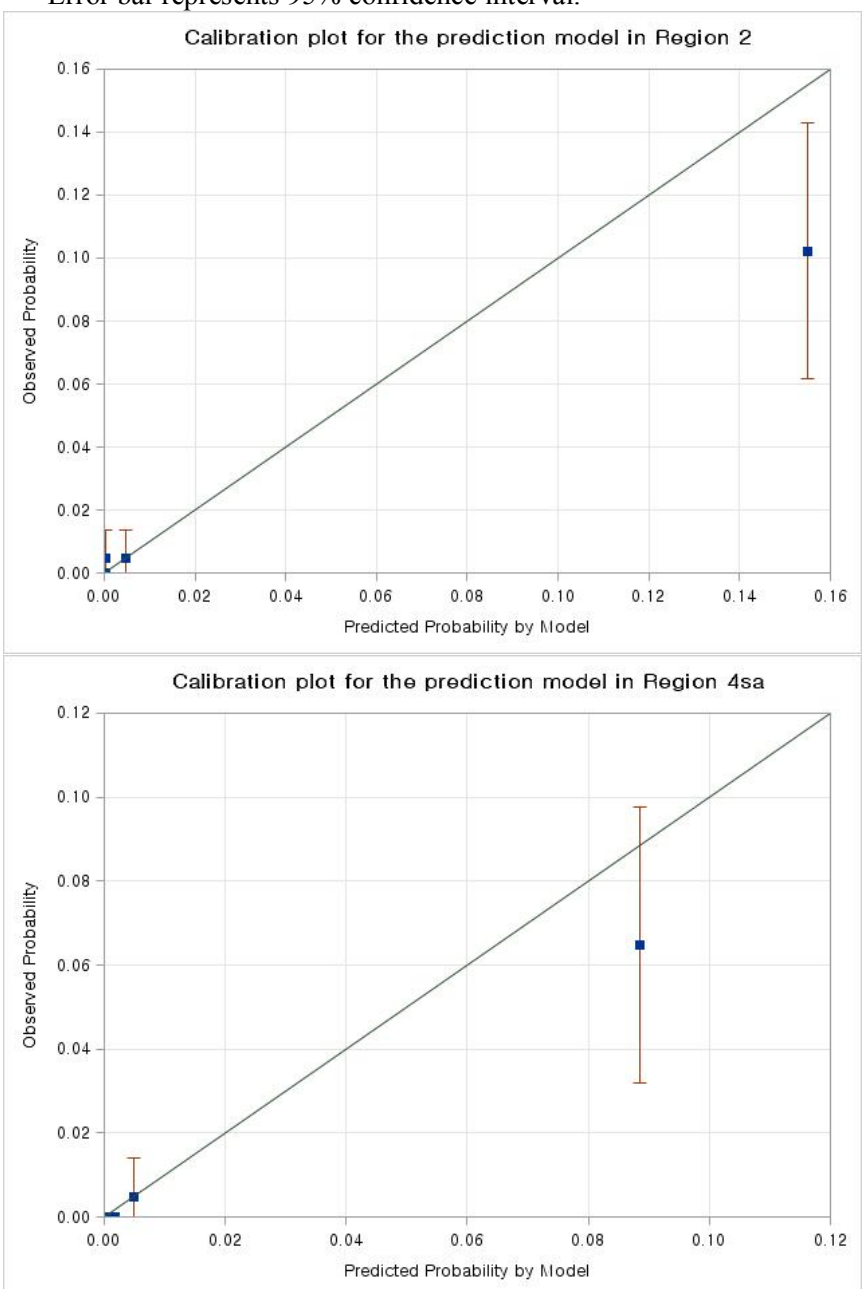
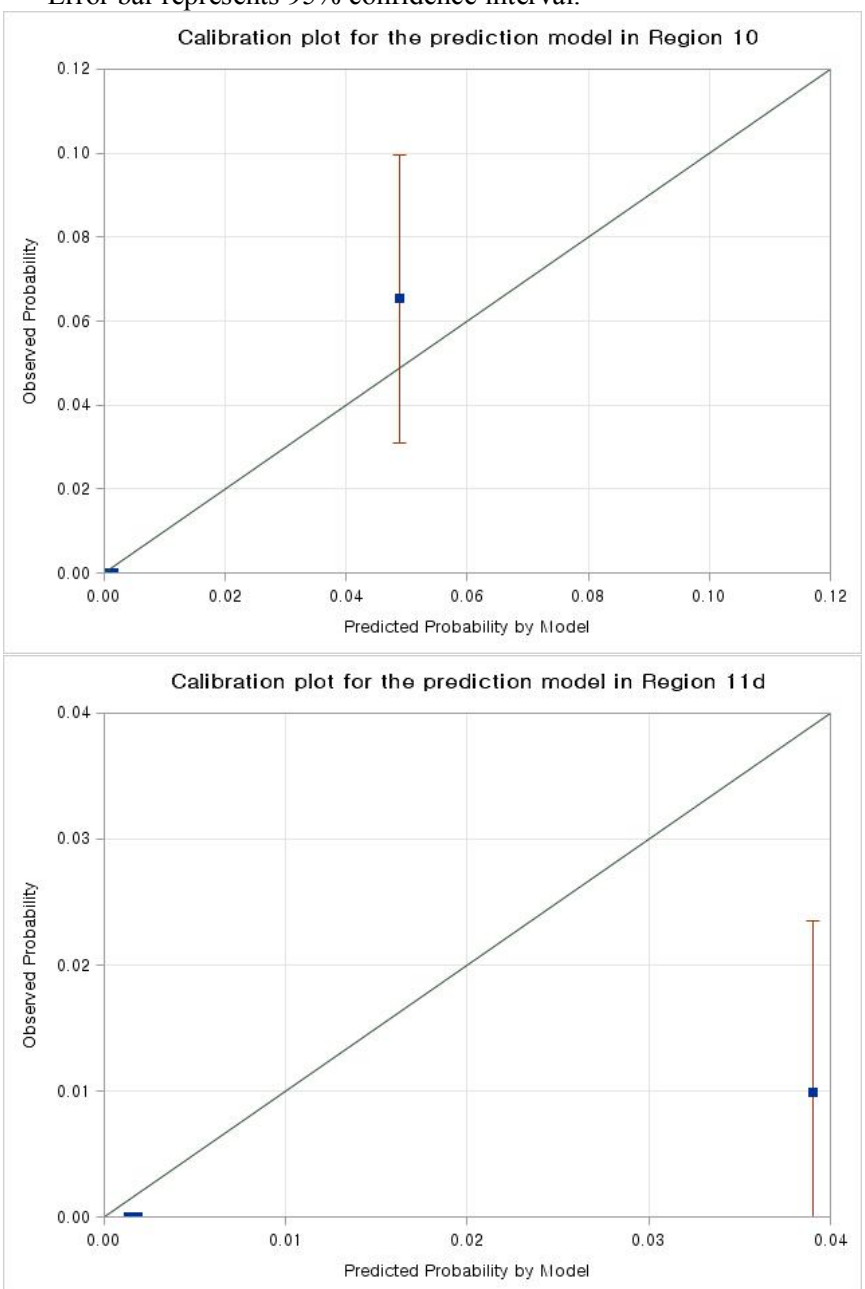


Figure 4 Calibration plot according to LNS, from method 1 (including LN negative cases among subtotal gastrectomy cases)

Error bar represents 95% confidence interval.



국문 초록

위암 환자에서 각 구역별 림프절 전이율 예측 모델 구축

서울대학교 대학원

의학과 외과학전공

김 종 원

<배경 및 목적>

각 림프절 구역으로 림프절 전이 여부를 예측하는 것은 위암의 맞춤형 수술에 매우 중요한다. 본 연구의 목적은 위암 환자의 각 림프절 구역에 따라 림프절 전이 확률을 계산할 수 있는 예측 프로그램을 개발하는 것이다.

<대상 및 방법>

서울대학교 병원에서 2003 년부터 2013 년까지 원발성 위암으로 위절제술을 시행 한 환자 중에 각 구역별로 림프절 전이 여부에 대한 검사가 잘 시행된 4,660 명의 환자를 후향적으로 분석하였다. 저자들은

수술 전 내시경 소견 및 전체 병리 소견을 다시 검토하여 종양 위치를 내시경적 용어를 사용하여 재분류 하였다. 종양이 침범한 모든 구역을 분석에 포함하였다. 수술 전에 평가하여 이용할 수 있는 변수들을 수집하였다. 각 림프절 구역별로 다중 로지스틱 회귀 분석을 사용하여 림프절 전이 예측 모델을 개발하였다. 모델 개발을 위해서 모든 환자 데이터를 이용하였고, 예측 모델의 성능은 총 200 개의 부트 스트랩 샘플을 사용하여 식별력 (discrimination) 및 캘리브레이션 (calibration) 측면에서 검증되었다.

<결과>

다중 분석은 종양의 심도, 육안형, 침범 위치 등이 림프절 전이와 관련된 변수로 확인되었다. 그러나 유의 한 인자들은 각 림프절 구역에 따라 다소 차이가 있었다. 확인 과정에서 예측 식은 훌륭한 식별력을 나타냈으며, 예측 방정식의 캘리브레이션 플롯은 실제 전이율과 밀접하게 일치하는 림프절 전이율을 예측하였다.

<결론>

각 림프절 구역에 대하여 림프절 전이율을 예측하는 프로그램을 개발하였다. 검증을 통해 탁원한 식별력과 캘리브레이션을 보이는

것으로 입증되어 임상적 유용성이 있음을 시사한다. 림프절 전이 예측 프로그램은 각 림프절 구역의 림프절 전이에 대한 개별화된 예측을 향상시켰다.

주요어: 림프절 전이, 예측, 위암, 부트스트랩
학 번: 2010-30508