# Predictive Model for Non-Sentinel Lymph Node Status in Thai Breast Cancer Patients with Positive Sentinel Lymph Node Biopsy

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***Background:*** *Sentinel lymph node (SLN) biopsy is a standard procedure for axillary staging in breast cancer patients with clinically negative axillary nodes. Several models were developed to predict the probability of non-sentinel lymph node (NSLN) metastases. However, differences in technique and setting may impact the accuracy of the models.*
***Objective:*** *To create novel models for predicting the probability of NSLN metastases and to validate the existing models in Thai breast cancer patients.*
***Material and Method:*** *Breast cancer patients who underwent SLN biopsy at the Division of Head Neck and Breast Surgery, Department of Surgery, Siriraj Hospital from January 2009 to October 2013 were recruited. All SLN biopsies were identified by blue dye and immediately examined by frozen section. All frozen SLNs were defrosted and confirmed by permanent section. The patients with positive SLN (either from frozen or permanent section) underwent axillary dissection. Associations between clinico-pathological parameters and NSLN status were determined by Chi-square statistics. Logistic regression was performed to create the predictive models.*
***Results:*** *Four hundred and thirty breast cancer patients who had positive SLN and underwent axillary lymph node dissection were recruited. NSLN metastasis accounted for 48.37% of the patients with positive SLN. In frozen section model, tumor type, tumor size, lymphovascular invasion, and ratio of positive SLN were associated with NSLN status. Tumor type, tumor size, ratio of positive SLN, and presence of extranodal extension of SLN were associated with NSLN status in permanent section model. The area under the receiver operating characteristic (ROC) curve (AUC) = 0.754 for frozen section model and 0.781 for permanent section model. Validation of the models in 56 patients revealed AUC of 0.788 and 0.831 for frozen and permanent section, respectively. The novel models better predict NSLN metastasis, when compared to the previously published models.*
***Conclusion:*** *The authors created two models using frozen and permanent section status of SLN which were practical and accurately predict NSLN status for Thai breast cancer patients.*

***Keywords:*** *Breast cancer, Sentinel lymph node biopsy, Axillary lymph node dissection, Predictive model*

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Sentinel lymph node (SLN) biopsy is a standard procedure for axillary staging in breast cancer patients with clinically negative axillary node. Then, axillary lymph node dissection (ALND) would be performed in the patients with positive SLN(1). However, 40 to 60% of positive SLN patients did not have non-sentinel lymph node (NSLN) metastasis(2).

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ALND might not be mandatory inthe patients with limited tumor burden in SLN(3). Advances in multimodality approach (adjuvant systemic treatment and radiotherapy) might replace ALND in term of regional control. Axillary radiotherapy and ALND provide excellent and comparable axillary control for patients with T1-T2 tumor and positive SLN(4). In the patients with T1-T2 and positive SLN not more than 2 nodes who received breast conserving surgery with postoperative systemic therapy and radiotherapy, ALND could be omitted with no inferior outcome(5). A randomized, non-inferiority trial compared ALND versus no ALND in the patients with micrometastasis in SLN showed that no further axillary treatment for the patients with micrometastasis in SLN resulted in no adverse effect on survival[6].

Identification of the patients who have gross residual disease in axilla that needs surgical removal after SLN biopsy is crucial for favorable outcome. Several models, such as those from the Memorial Sloan-Kettering cancer center (MSKCC) and Cambridge, were developed to predict the probability of NSLN metastases[7-14]. Differences in breast cancer population, technique and setting may impact the accuracy of the models. The authors created novel models to predict NSLN metastases for Thai breast cancer patients and compare the new models to MSKCC and Cambridge models.

## Material and Method

Breast cancer patients were recruited from Division of Head Neck and Breast Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University from January 2009 to October 2013. The patients with histopathologically diagnosed invasive breast cancer, clinically negative axillary lymph node, positive SLN biopsy and underwent ALND were included in the study. The patients who had history of neoadjuvant chemotherapy or hormonal therapy, incomplete pathological report and total lymph node dissection less than 10 nodes were excluded. Clinico pathological data was retrospectively reviewed. The patients' data was divided into two groups: a retrospective group, including the patients who had undergone SLN biopsy from January 2009 to April 2013, which was analyzed to develop the new models (n = 430) and a validation group, including the patients who had undergone SLN biopsy from May 2013 to October 2013, which was used to validate the models, (n= 65). The authors created two new models using SLN status examined by frozen section and permanent section.

### *Evaluation of SLN*

Identification of SLN was performed using isosulfan blue dye. The nodal tissue was frozen in liquid nitrogen and examined by step sectioning with hematoxylin and eosin (H&E) staining and reported intraoperatively (frozen section). Permanent section was performed in all patients using defrosted nodal tissue and examined by H&E staining. The patients who had negative SLN frozen section but had positive SLN by permanent section underwent subsequent ALND. SLN status was reported as an isolated tumor cell ($\leq$0.2 mm), micrometastasis (>0.2 mm and $\leq$2 mm) or macrometastsis (>2 mm). The size of metastasis was reported on permanent section.

### *Statistical analysis*

Associations between NSLN status and clinicopathological parameters were analyzed by Chi-square tests and independent sample *t*-tests in univariate analysis. The *p*-values of <0.05 were considered to be statistically significant. Multivariate analysis was performed using logistic regression. Regression coefficients of significant variables were employed to create the equation. The models were created based on patients in the retrospective groups. Validation of the nomograms was performed by determination of area under the receiver operating characteristic (ROC) curve (AUC). All analysis was performed with SPSS version 21.

## Results

Four hundred and thirty breast cancer patients with positive SLN were enrolled. There were 9 patients that had negative frozen section result but had positive permanent section result. Seven patients had micrometastasis identified by permanent section while the other 2 patients had macrometastasis. Clinicopatholigical features of the studied population were summarized in Table 1. Table 2 and Table 4. summarized the parameters that had significant correlation with NSLN status in univariate and multivariate analysis according to frozen section and permanent section results, respectively. Table 3 and Table 5 showed regression coefficients for the equation using the results by frozen section and permanent section, respectively. Regression coefficients and variables were used in equation to create a predictive model by frozen section (Fig. 1) and permanent section (Fig. 2).

Validation of the model was performed using the data of validation group (n = 56). The area under the receiver operating characteristic (ROC) curve (AUC) was 0.788 (Fig. 3). Fig. 4 showed comparison of the new model (Siriraj frozen section) to previous models (MSKCC and Cambridge) using data from retrospective group (n = 421), the AUC of Siriraj frozen section was 0.754 compared to 0.692 (MSKCC) and 0.635 (Cambridge). Validation of the model using results of permanent section showed that the AUC was 0.831 (Fig. 5). Comparison of the model using permanent section result (n = 430) showed that AUC of the current model was slightly higher than MSKCC and Cambridge

**Table 1.** Clinicopathological parameters of the patients in retrospective group

| Characteristics | Frozen section, n (%) | | Permanent section, n (%) | |
|---|---|---|---|---|
| | Tumor-free NSLN (n = 215) | Tumor-involved NSLN (n = 206) | Tumor-free NSLN (n = 222) | Tumor-involved NSLN (n = 208) |
| Patient age (years), mean (SD) | 50.55 (9.35) | 51.37 (9.45) | 50.51 (9.28) | 51.38 (9.50) |
| Multifocality | | | | |
| Absent | 145 (67.4) | 137 (66.5) | 152 (68.5) | 138 (66.3) |
| Present | 70 (32.6) | 69 (33.5) | 70 (31.5) | 70 (33.7) |
| Tumor type | | | | |
| Invasive ductal carcinoma | 210 (97.7) | 188 (91.3) | 217 (97.7) | 190 (91.3) |
| Non-invasive ductal carcinoma | 5 (2.3) | 18 (8.7) | 5 (2.3) | 18 (8.7) |
| Tumor size (cm), mean (SD) | 2.37(1.01) | 2.95 (1.56) | 2.40 (01.04) | 2.94 (1.56) |
| Tumor grade | | | | |
| NA | 1 (0.5) | 5 (2.5) | 3 (1.4) | 9 (4.3) |
| Well differentiated | 20 (9.4) | 16 (7.9) | 20 (9.0) | 16 (7.7) |
| Moderately differentiated | 129 (60.6) | 122 (60.1) | 135 (60.8) | 122 (58.7) |
| Poor differentiated | 63 (29.6) | 60 (29.6) | 64 (28.8) | 61 (29.3) |
| ER status | | | | |
| Negative | 42 (19.5) | 41 (19.9) | 43 (19.4) | 41 (19.7) |
| Positive | 173 (80.5) | 165 (80.1) | 179 (80.6) | 167 (80.3) |
| PR status | | | | |
| Negative | 56 (26.0) | 55 (26.7) | 58 (26.1) | 55 (26.4) |
| Positive | 159 (74.0) | 151 (73.6) | 164 (73.9) | 153 (73.6) |
| HER2 status | | | | |
| Negative | 130 (60.5) | 112 (54.4) | 135 (60.8) | 113 (54.3) |
| Equivocal | 40 (18.6) | 50 (24.3) | 42 (18.9) | 51 (24.5) |
| Positive | 45 (20.9) | 44 (21.4) | 45 (20.3) | 44 (21.2) |
| Angiolymphatic invasion | | | | |
| Absence | 143 (66.5) | 106 (51.5) | 148 (66.7) | 108 (51.9) |
| Presence | 72 (33.5) | 100 (48.5) | 74 (33.3) | 100 (48.1) |
| Number of positive SLN | | | | |
| Mean (SD) | 1.11 (0.32) | 1.46 (0.8) | 1.33 (0.73) | 2.16 (1.56) |
| Median (range) | 1 (1-3) | 1 (1-5) | 1 (1-5) | 2 (1-10) |
| Number of negative SLN | | | | |
| Mean (SD) | 2.30 (2.02) | 1.46 (1.52) | 3.68 (3.08) | 2.06 (2.23) |
| Median (range) | 2 (0-11) | 1 (0-8) | 3 (0-15) | 1 (0-16) |
| Isolated tumor cell, n (%) | 0 (0) | 0 (0) | 1 (0.5) | 0 (0) |
| Micrometastases, n (%) | 3 (1.4) | 4 (1.9) | 15 (6.8) | 7 (3.4) |
| Macrometastases, n (%) | 212 (98.6) | 202 (98.1) | 206 (92.8) | 201 (96.6) |
| Extranodal extension | | | | |
| Absence | NA | NA | 167 (75.2) | 101 (48.6) |
| Presence | NA | NA | 55 (24.8) | 107 (51.4) |

model (0.781 compared to 0.738 and 0.634, respectively) (Fig. 6).

## Discussion

In the current study, the authors created two models that based on the results of frozen section and permanent section of SLN to predict NSLN status. In frozen section model, the factors that predict NSLN metastasis were tumor type other than invasive ductal carcinoma, size of primary tumor, number of positive SLN, and number of negative SLN. In permanent section model, presence of extranodal extension was also the predictor of NSLN metastasis.

When compare to the previous models, the current models predicted NSLN involvement slightly better than the MSKCC and Cambridge models[11,14].

**Table 2.** Univariate and multivariate analysis of clinicopathological parameters using results from frozen section of 421 patients

| Parameters | *p*-value | |
|---|---|---|
| | Univariate | Multivariate |
| Tumor type(Invasive ductal carcinoma/ non-invasive ductal carcinoma) | 0.004 | 0.045 |
| Tumor size | <0.001 | 0.001 |
| Angiolymphatic invasion | 0.002 | 0.053 |
| Number of positive SLN | <0.001 | <0.001 |
| Number of negative SLN | 0.002 | <0.001 |

**Table 3.** Logistic regression coefficients for the frozen section model

| Variables | Regression coefficient | *p*-value |
|---|---|---|
| Constant | -1.6 | <0.001 |
| Tumor type(Invasive ductal carcinoma/ non-invasive ductal carcinoma) | 1.132 | 0.045 |
| Tumor size | 0.295 | 0.001 |
| Number of positive SLN | 0.812 | <0.001 |
| Number of negative SLN | -0.316 | <0.001 |

**Table 4.** Univariate and Multivariate analysis of clinicopathological parameters using results from permanent section of 430 patients

| Parameters | *p*-value | |
|---|---|---|
| | Univariate | Multivariate |
| Tumor type (IDC/ Non IDC) | 0.003 | 0.017 |
| Tumor size (cm) | <0.001 | 0.004 |
| Angiolymphatic invasion | 0.002 | 0.351 |
| No. of positive SLN | <0.001 | <0.001 |
| No. of negative SLN | <0.001 | <0.001 |
| Extranodal extension | <0.001 | <0.001 |

**Table 5.** Logistic regression coefficients for the permanent section model

| Variables | Regression coefficient | *p*-value |
|---|---|---|
| Constant | -1.565 | <0.001 |
| Tumor type (IDC/non IDC) | 1.441 | 0.017 |
| Tumor size | 0.261 | 0.003 |
| No. of positive SLN | 0.645 | <0.001 |
| No. of negative SLN | -0.231 | <0.001 |
| Extranodal extension | 0.934 | <0.001 |

$$P = \frac{e^z}{1 + e^z}$$

$$Z = -1.6 + (1.132 * Tumor\ type) + (0.295 * Size) + (0.812 * Number\ of\ positive\ SLN) + (-0.316 * Number\ of\ negative\ SLN)$$

**Fig. 1** Predictive model of NSLN involvement using frozen section results. P = probability of NSLN involvement; Tumor type = invasive ductal carcinoma = 0; Other type = 1; Size = the size of primary tumor in centimeter.

Absence of size determination of nodal metastasis was the frequently cited limitation of MSKCC model. However, in the current breast cancer population, including the size of nodal metastasis in Cambridge model did not result in better AUC when compare to MSKCC model. This might be due to the difference in characteristics of SLN between the populations. There was no difference in size of SLN metastasis between negative and positive NSLN patients in the current study.

A small proportion of the patients in the current study had isolated tumor cell or micrometastasis in SLN. This was in contrast to the previous studies by Alran et al and Kohrt et al, which showed significant higher proportion of the patients with micrometastasis in SLN[10,15]. The difference in setting and technique in

$$P = \frac{e^z}{1 + e^z}$$

$$Z = -1.565 + (-1.441 * Tumor\ type) + (0.261 * Size) + (0.645 * Number\ of\ positive\ SLN) + (-0.231 * Number\ of\ negative\ SLN) + (0.934 * extranodal\ extension)$$

**Fig. 2** Predictive model of NSLN involvement using permanent section results. P = probability of NSLN involvement; Tumor type = invasive ductal carcinoma = 0; Other type = 1; Size = the size of primary tumor in centimeter; Extranodal extension = absence = 0; presence = 1.

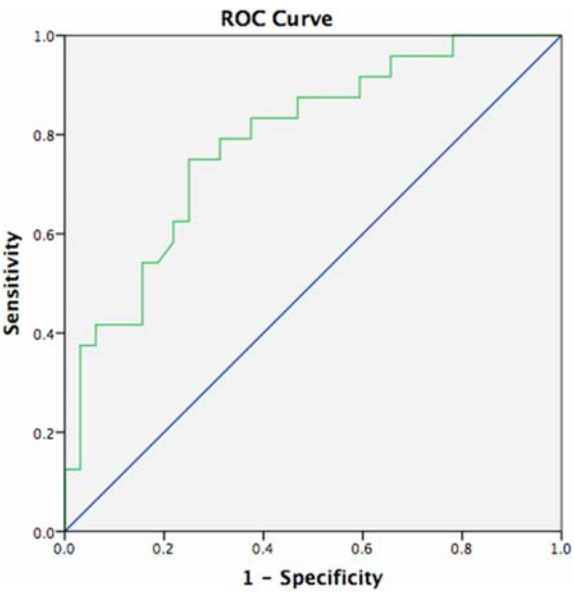
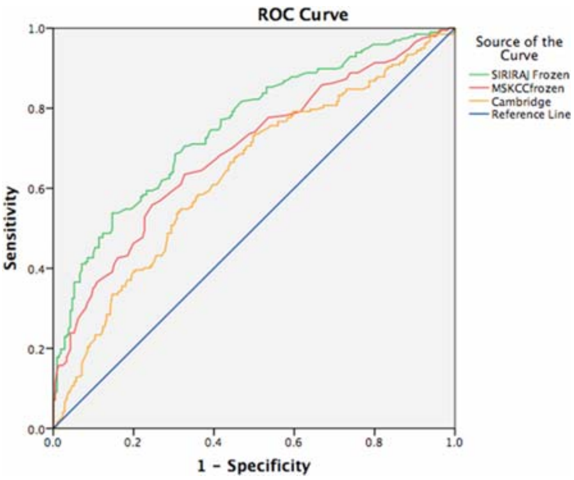



**Fig. 3** Validation of the model using results from frozen section (n = 56) AUC=0.788, standard error 0.061, 95% CI: 0.67 to 0.91.

SLN examination might contribute to the discrepancy. Examination of SLN by immunohistochemistry can detect micrometastasis but has limitation in detection of metastasis in poorly differentiated cancer[16]. Combination of H&E and immunohistochemistry improved the detection of micrometastasis and 21.6% of the patients with micrometastasis in SLN had positive NSLN[17]. In the current study, examination of SLN was performed by frozen section and the result was reported to the surgeon intraoperatively. Then the frozen tissue was defrosted and examined by H&E staining to confirm the result. If the permanent section revealed negative for malignancy, no further immunohistochemistry staining was performed.

In Thailand, breast ultrasonography is usually performed along with mammography due to high breast density that obscure the lesion detected by mammography. Any suspicious axillary node identified




| | AUC | Standard error | 95% CI |
|---|---|---|---|
| SIRIRAJ frozen | 0.754 | 0.024 | 0.71 to 0.80 |
| MSKCC frozen | 0.692 | 0.026 | 0.64 to 0.74 |
| Cambridge | 0.635 | 0.028 | 0.58 to 0.69 |

**Fig. 4** Comparison of Siriraj frozen section model with MSKCC and Cambridge models. The AUC of Siriraj frozen section model was slightly higher than that of MSKCC and Cambridge models.

by ultrasonography (cortical thickness >3 mm, loss ofthe fat hilum, or round shape) will be investigated by ultrasound-guided fine needle aspiration (FNA). Axillary ultrasonography with FNA can identify the patients with heavy axillary nodal disease burden[18,19]. The patients with positive FNA result will be proceed to ALND while the patients with negative result will be proceed to SLN biopsy. In the majority of rural hospital in Thailand, feasibility of frozen section is still limited due to lack of experienced pathologists and instruments. In this situation, determination of SLN status by permanent section and subsequent ALND after positive SLN is generally performed to achieve the benefit of regional control.

Several lines of evidence emphasize the role of radiotherapy in loco-regional control of breast cancer. According to the study by Giuliano et al[5], the patients with no more than 2 positive SLNs, receiving lumpectomy and tangential whole-breast irradiation, omit ALND did not resulted in inferior survival. Similar study by Donker et al included the patients with positive SLN underwent ALND or irradiation to axillary node level I to III and the medial part of supraclavicular

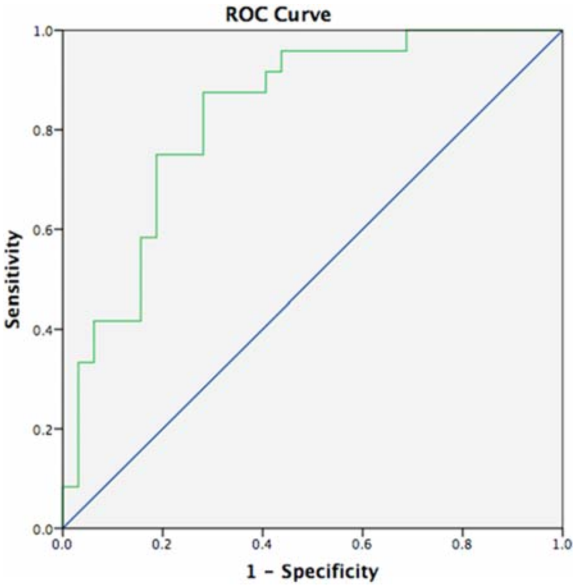
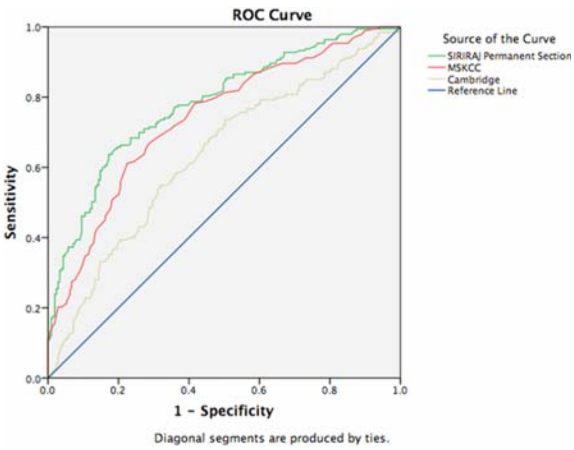



**Fig. 5** Validation of the model using results from permanent section (n = 56) AUC = 0. 831, standard error 0.054, 95% CI: 0.72 to 0.94.




| | AUC | Standard error | 95 % CI |
|---|---|---|---|
| SIRIRAJ final | 0.781 | 0.023 | 0.74 to 0.82 |
| MSKCC | 0.738 | 0.025 | 0.69 to 0.79 |
| Cambridge | 0.634 | 0.028 | 0.58 to 0.69 |

**Fig. 6** Comparison of Siriraj permanent section model with MSKCC and Cambridge models. The AUC of Siriraj permanent section model was slightly higher than that of MSKCC and Cambridge models.

fossa. The outcome of regional irradiation was not inferior to ALND[4]. Regional nodal irradiation in early-stage breast cancer patients has been reported to reduce the rate of breast cancer recurrence irrespective of number of positive node[20,21].

In some patients, underlying medical conditions might hinder subsequent ALND. In addition, concerning of arm morbidity after ALND should be addressed. The decision to omit or perform subsequent ALND should be based on risk and benefit assessment for individual patients. The model to predict NSLN status might be used to assess the risk and could be used as prognostic information for radiation oncologist to determine the field of radiation.

The current study recruited data from single institution and the number of patients in validation group was small. Validation of the models by other institution should be carried out before put into practice.

## Conclusion

The authors created two models which were practical and could accurately predict NSLN status for Thai breast cancer patients. The model using permanent section results might be used as a guide for management of positive SLN patients diagnosed by permanent section both surgical and radiological treatment.

## What is already known on this topic?

ALND might be omitted in selected patients. Several models had been created to predict NSLN status and validated in different population.

## What this study adds?

The novel models based on Thai breast cancer patients were practical and better predicted NSLN status when compared to the existing models.

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## Potential conflict of interest

None.

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***สมการทำนายการกระจายของมะเร็งเต้านมไปยังต่อมน้ำเหลืองรักแร้ในผู้ป่วยที่มีการกระจายของมะเร็งไปยังต่อมน้ำเหลืองเซนติเนล***

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***ภูมิหลัง:*** *การผ่าตัดตรวจต่อมน้ำเหลืองเซนติเนล (ต่อมน้ำเหลืองรักแร้กลุ่มแรกที่รับน้ำเหลืองจากเต้านม) เป็นการผ่าตัดเพื่อประเมินระยะของมะเร็งเต้านมในระยะเริ่มต้น เมื่อพบว่ามีการกระจายของมะเร็งไปยังต่อมน้ำเหลืองเซนติเนล ผู้ป่วยจะได้รับการผ่าตัดเลาะต่อมน้ำเหลืองรักแร้ อย่างไรก็ตาม ผู้ป่วยส่วนหนึ่งไม่มีมะเร็งกระจายไปยังต่อมน้ำเหลืองรักแร้ที่ทำการผ่าตัดเพิ่มเติม ที่ผ่านมามีการสร้างสมการเพื่อคำนวนโอกาสการกระจายของมะเร็งไปยังต่อมน้ำเหลืองรักแร้ แต่ความเหมาะสมถูกต้องอาจแตกต่างกันไปเมื่อนำไปใช้ในแต่ละสถาบัน*

***วัตถุประสงค์:*** *เพื่อสร้างสมการทำนายสภาวะของต่อมน้ำเหลืองรักแร้ในผู้ป่วยมะเร็งเต้านมชาวไทยและทดสอบความแม่นยำของสมการที่มีอยู่*

***วัสดุและวิธีการ:*** *ข้อมูลของผู้ป่วยมะเร็งเต้านมที่ได้รับการผ่าตัดต่อมน้ำเหลืองเซนติเนลที่สาขาศัลยศาสตร์ศีรษะ คอ และเต้านม ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล ตั้งแต่ เดือนมกราคม พ.ศ. 2552 ถึง ตุลาคม พ.ศ. 2553 และตรวจพบการกระจายของมะเร็งไปยังต่อมน้ำเหลืองเซนติเนลได้รับการรวบรวมและทบทวน ต่อมน้ำเหลืองเซนติเนลได้รับการค้นหาโดยใช้สีบอกตำแหน่งและตรวจในระหว่างการผ่าตัดโดยพยาธิแพทย์ด้วยวิธี frozen section หลังจากนั้นทำการตรวจยืนยันทางพยาธิวิทยาตามปกติ ผู้ป่วยที่มีการกระจายของมะเร็งมายังต่อมน้ำเหลืองเซนติเนลจะได้รับการผ่าตัดเลาะต่อมน้ำเหลืองรักแร้ ความสัมพันธ์ระหว่างปัจจัยทางพยาธิวิทยาคลินิกต่าง ๆ ได้รับการวิเคราะห์โดย Chi-square statistics สมการทำนายสภาวะของต่อมน้ำเหลืองรักแร้ใช้ค่าสัมประสิทธิ์ตัวแปรที่ได้จาก Logistic regression และทำการเปรียบเทียบกับสมการทำนายที่มีก่อนหน้า*

***ผลการศึกษา:*** *มีผู้ป่วยที่มีมะเร็งกระจายไปยังต่อมน้ำเหลืองรักแร้ทั้งหมด 430 ราย ที่ได้รับการผ่าตัดเลาะ ต่อมน้ำเหลืองรักแร้ ในจำนวนนี้มี 48.37% ที่มีมะเร็งกระจายไปยังต่อมน้ำเหลืองรักแร้ ชนิดของมะเร็งเต้านม การลุกลามเข้าในหลอดเลือดท่อน้ำเหลือง จำนวนต่อมน้ำเหลืองเซนติเนลที่มีมะเร็งกระจายไปและไม่มีมะเร็งกระจายไปมีความสัมพันธ์กับภาวะของต่อมน้ำเหลืองรักแร้เมื่อใช้การตรวจโดย frozen section นอกจากนี้การลุกลามออกนอกต่อมน้ำเหลืองก็มีความเกี่ยวข้องเช่นกันเมื่อทำการตรวจทางพยาธิวิทยาตามปกติ สมการใหม่นี้มีพื้นที่ใต้กราฟ (area under the receiver operating characteristic curve) 0.754 สำหรับสมการ frozen section และ 0.781 สำหรับสมการที่ใช้การตรวจทางพยาธิวิทยาตามปกติ เมื่อทำการทดสอบสมการนี้ในผู้ป่วย 56 ราย พบว่าพื้นที่ใต้กราฟเป็น 0.788 และ 0.831 ตามลำดับ และเมื่อเปรียบเทียบสมการใหม่นี้กับสมการที่มีอยู่เดิมพบว่าสามารถทำนายภาวะของต่อมน้ำเหลืองรักแร้ได้ดีกว่า*

***สรุป:*** *จากการศึกษานี้ได้สมการสำหรับทำนายภาวะของต่อมน้ำเหลืองรักแร้สองแบบ โดยใช้ตัวแปรที่ได้จากการตรวจ frozen section และการตรวจทางพยาธิวิทยาตามปกติ ซึ่งเหมาะสมกับบริบทในประเทศไทยและสามารถทำนายได้แม่นยำกว่าสมการที่มีการรายงานก่อนหน้านี้*