

Identification Rate of Sentinel Lymph Node Biopsy using Single Technique (Isosulfan Blue Dye) in Early Breast Cancer in Lopburi Cancer Hospital

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บทคัดย่อ: อัตราความสำเร็จในการตรวจพบต่อมน้ำเหลืองเชนทิเนลโดยใช้วิธีจัดสี Isosulfan blue dye ในผู้ป่วยมะเร็งเต้านมระยะต้นของโรงพยาบาลมะเร็งลพบุรี

ภาณุจนา อารีรัตนเวช พ.บ.

โรงพยาบาลมะเร็งลพบุรี ตำบลกะเหลบุบศร อำเภอเมือง จังหวัดลพบุรี 15000

ภูมิหลัง: มะเร็งเต้านมเป็นมะเร็งที่พบอันดับ 1 ในสตรีไทย ในอดีตการตรวจหาการแพร่กระจายของมะเร็งเต้านมมาต่อมน้ำเหลืองที่รักแร้เป็นปัจจัยสำคัญที่สุดในการพยากรณ์โรค การผ่าตัดต่อมน้ำเหลืองที่รักแร้ในอดีตจำเป็นต้องเลาะต่อมน้ำเหลืองออกจำนวนมาก ในปัจจุบันมะเร็งเต้านมมีวิธีการดูแลรักษาที่ก้าวหน้าและได้รับการศึกษาพัฒนาต่อเนื่องมาโดยตลอด การผ่าตัดต่อมน้ำเหลืองที่รักแร้จึงมีทางเลือกในการเลือกวิธีการผ่าตัดเพิ่มขึ้น โดยการผ่าตัดต่อมน้ำเหลืองเชนทิเนล ถือเป็นการผ่าตัดมาตรฐานในการตรวจวินิจฉัยต่อมน้ำเหลืองที่รักแร้ สำหรับผู้ป่วยมะเร็งเต้านมระยะรีมแกรนท์ไม่มีลักษณะของการทางคลินิกที่ส่งสัญญาณการแพร่กระจายมาที่ต่อมน้ำเหลืองรักแร้ ซึ่งมีวิธีการทำ lymphatic mapping 2 วิธี คือ dye, radioisotope หรือใช้ห้อง 2 วิธีร่วมกัน ในที่นี้ ผู้วิจัยใช้ dye เป็น lymphatic mapping เทคนิคเดียว เนื่องจากเป็นวิธีที่สามารถจัดหาสารที่ใช้ฉีดได้ไม่ต้องใช้เครื่องมือตรวจพิเศษและค่าใช้จ่ายที่ต่ำกว่า **วัตถุประสงค์:** เพื่อประเมินอัตราความสำเร็จในการตรวจพบต่อมน้ำเหลือง เชนทิเนลของการทำการผ่าตัดต่อมน้ำเหลืองเชนทิเนลในผู้ป่วยมะเร็งเต้านม โดยการใช้สี Isosulfan blue dye ในโรงพยาบาลมะเร็งลพบุรี และศึกษาปัจจัยที่มีความสัมพันธ์กับอัตราความสำเร็จในการตรวจพบต่อมน้ำเหลือง เชนทิเนล **วิธีการ:** เป็นการศึกษาข้อมูลผู้ป่วยมะเร็งเต้านมที่ได้รับการผ่าตัดต่อมน้ำเหลืองเชนทิเนลในผู้ป่วยมะเร็งเต้านม โดยการใช้เทคนิคการฉีดสี Isosulfan blue dye ของโรงพยาบาลมะเร็งลพบุรี ตั้งแต่วันที่ 1 สิงหาคม พ.ศ. 2560 – 30 เมษายน พ.ศ. 2563 จำนวน 75 ราย โดยเบรียบข้อมูล 2 กลุ่มคือกลุ่มที่ตรวจพบต่อมน้ำเหลืองเชนทิเนลและกลุ่มที่ตรวจไม่พบต่อมน้ำเหลืองเชนทิเนล **ผล:** ผู้ป่วยมะเร็งเต้านมจำนวนทั้งหมด 74 ราย เข้ารับการผ่าตัดต่อมน้ำเหลืองเชนทิเนลทั้งหมด 75 ราย (1รายเป็นมะเร็งเต้านม 2 ข้าง) โดยใช้ Isosulfan blue dye เพียงอย่างเดียวในการทำ lymphatic mapping พบว่าอัตราการตรวจพบต่อมน้ำเหลืองเชนทิเนลเป็นร้อยละ 94.67 (71/75) **สรุป:** การผ่าตัดต่อมน้ำเหลืองเชนทิเนลในผู้ป่วยมะเร็งเต้านมระยะต้น โดยใช้เทคนิคการฉีดสี Isosulfan blue dye เพียงอย่างเดียวในการทำ lymphatic mapping ของโรงพยาบาลมะเร็งลพบุรีพบอัตราความสำเร็จในการตรวจพบต่อมน้ำเหลือง เชนทิเนลที่ยอมรับได้ตามมาตรฐานสมาคมศัลยแพทย์เต้านมของอเมริกาและสามารถทำได้

คำสำคัญ: ต่อมน้ำเหลืองเชนทิเนล มะเร็งเต้านม โรงพยาบาลมะเร็งลพบุรี

Abstract

Background: Breast cancer is currently the most common cancer of woman in worldwide and also in Thailand. In the past, radical axillary surgery had been an integral part of breast cancer treatment to staging and provided locoregional control. During the past decade, surgical paradigm changed from standard axillary lymph node dissection for early breast cancer patients to

sentinel lymph node biopsy (SLNB) due to increasing evidence indicated that was safe and acceptably accurate method for determining axillary node staging in early-stage breast cancer patients without clinically axilla lymph node involvement. Sentinel lymph node was identified by lymphatic mapping. There were 3 techniques of lymphatic mapping; blue dye alone, radioisotope alone, or a combination of blue dye and radioisotope. In this

study, we used blue dye alone for lymphatic mapping due to simplicity and low cost. **Objective:** The purpose of this study to report an identification rate of sentinel lymph node using isosulfan blue dye alone in breast cancer patients at Lopburi Cancer Hospital and to find out factors that might affect the rate of sentinel lymph node identification. **Methods:** This study was retrospective observational study. Patients were enrolled between 1st August 2017 and 30th April 2020. Eligible criteria included T1 or T2 invasive breast cancer and all T size of ductal carcinoma in situ who underwent mastectomy, with all clinically negative axillary lymph nodes. All patients performed sentinel lymph node biopsy by using 1% isosulfan blue dye alone for lymphatic mapping at Lopburi Cancer Hospital. **Results:** A total of 74 female breast cancer patients representing 75 cases (1 bilateral breast cancer case) underwent SLNB using isosulfan blue dye alone. A sentinel node was identified in 71 of 75 cases (94.67%). **Conclusion:** The identification rate of sentinel lymph node biopsy using isosulfan blue dye alone in early breast cancer at Lopburi Cancer Hospital are acceptable and feasible.

Keywords: Lymphatic mapping, Sentinel lymph node, Breast cancer, Lopburi Cancer Hospital

Introduction

Breast cancer is currently the most common cancer of woman in worldwide and also in Thailand. In 2014, the Thai National Cancer Institute reported 14,804 new breast cancer patients and mean annual age-specific incidence rate of breast cancer was 31.4 per 100,000 persons (2013-2015)¹. Surgery of breast cancer had 2 parts, surgical management of primary breast and surgical management of axilla. In the past, radical axillary surgery had been an integral part of breast cancer treatment to staging and provided locoregional control. The disease status of axilla lymph nodes was the most significant prognostic factor of patients with early-stage breast cancer and determined adjuvant systemic therapy². During the past decade, surgical paradigm changed from standard axillary lymph node dissection for early breast cancer patients to sentinel lymph node biopsy (SLNB) due to increasing evidence indicated that sentinel lymph node biopsy was safe and acceptably accurate method for determining axillary node staging in early-stage breast cancer patients without clinically axilla lymph node involvement³. Moreover, SLNB also had less arm morbidity compared to ALND⁴, allowing axillary lymph node dissection (ALND) to be

limited to patients with nodal involvement. Thus, ALND may result in significant arm morbidity including seroma formation, chronic pain, and impair range of motion and lymphedema.

Sentinel lymph node was the first lymph node or a group of lymph nodes which encountered in the lymphatic drainage of the breast and was generally identified by lymphatic mapping³. There were 3 techniques of lymphatic mapping; blue dye alone, radioisotope alone, or a combination of blue dye and radioisotope. From metaanalysis of 69 trials between 1970-2003 reported identification rate of sentinel node in early-stage breast carcinoma using blue dye alone, radiocolloid alone, or both combined were 83.1%, 89.2% and 91.9%⁸. Subsequently, excellent results on sentinel node identification could achieve by whether using single or combined technique^{5,6,7}. Giuliano et al. reported sentinel node identification rate of 98% using isosulfan blue dye alone in SLNB, Krag⁶ reported sentinel node identification rate of 98% using radioisotope alone for mapping technique, and from NSABP-32 trial demonstrated the sentinel node identification 97.2% by using combined technique. As many studies suggested, the combined technique is much preferred by its higher success rate⁸. One of its explicit drawbacks are multidisciplinary team coordination (nuclear medicine, surgeon, nursing team) and high cost for radioisotope and required specific equipment (probe detector).

Beside lymphatic mapping technique, factors that may affect the rate of sentinel lymph node identification revealed that surgeon experience (learning curve), older-age patient, tumor location, tumor size, prior excisional biopsy⁵.

In this study, we used blue dye alone for lymphatic mapping due to simplicity and low cost. The purpose of this study to reported identification rate of sentinel lymph node using isosulfan blue dye alone in breast cancer patients at Lopburi cancer hospital and to found out factors that might affect the rate of sentinel lymph node identification.

Materials and Methods

This study was retrospective observational study. Patients were enrolled 74 female breast cancer patients representing 75 cases (1 bilateral breast cancer case) between 1st August 2017 and 30th April 2020. Eligible criteria included T1 or T2 invasive breast cancer and all T size of ductal carcinoma in situ who underwent mastectomy,

with all clinically negative axillary lymph nodes. All patients performed sentinel lymph node biopsy by using 1% isosulfan blue dye alone for lymphatic mapping at Lopburi Cancer Hospital. Exclusion criteria were pregnancy, those who had neoadjuvant chemotherapy. The study was approved by the Ethics Committee for research involving human subjects of Lopburi Cancer Hospital administration for chart review.

Procedure: After induction of general anesthesia, 2.5 ml of 1% isosulfan blue dye was diluted with 3.5 ml of sterile water was injected into subareolar area. A 3-5 cm skin incision at axilla was made and blue-stained lymphatics was also sought. Sentinel nodes identified as blue staining nodes and palpable nodes also removal during operation. Frozen section examination was not performed. Permanent section was done for all sentinel lymph nodes for pathologic examination. If sentinel lymph node could not be identified, axillary lymph node dissection would be done in the same operation as standard treatment. If the result of sentinel lymph node indicated metastasis on pathologic report, completion axillary lymph node dissection was performed in 2nd operation. Factors that might affect the identification rate of sentinel lymph node; clinical and pathologic features (age, BMI, clinical detection, diagnostic methods, tumor location, tumor size, type of breast operation, diagnosis,

pathologic grading, LVI, PNI, ER, PR, HER2 status, Ki67) were recorded and analyzed. To determined the learning curve of surgical experience on sentinel node identification, data was divided into 2 groups; first 20 case performed compared to more than 20 case performed.

Statistical analysis

Demographic data were evaluated and reported using descriptive statistics (mean and percentage). Patient characteristics were compared using *t* tests for continuous variables and Fisher exact test for categorical variables. Univariate analysis and multivariate analysis of probability of sentinel node identification were done using multiple logistic regression. *p*<0.05 was considered statistically significant.

Result

A total of 74 female breast cancer patients representing 75 cases (1 bilateral breast cancer case) underwent SLNB using isosulfan blue dye alone. No patient had any side effects from isosulfan blue dye injection. 53 cases (70.67%) had mastectomy and 22 cases (29.33) had breast conserving surgery. The mean (standard deviation) patient age was 54.37(11) years and mean (standard deviation) patient body mass index was 26.38(4.57)(Table1).

Table 1 Characteristics of breast cancer patients

	SN not identified (n=4)		SN identified(n=71)		p value
	mean ± SD	Median (IQR)	mean ± SD	Median (IQR)	
Age (y)	58.50 ± 9.61	56.50 (18)	54.14 ± 11.10	54.00 (14)	0.540*
Weight(kg)	75.50 ± 9.15	75.00 (18)	63.20 ± 11.72	61.00 (17)	0.032*
Height(cm)	159.50 ± 8.06	160.00 (16)	155.31 ± 6.58	155.00 (9)	0.292*
BMI(kg/m ²)	29.78 ± 4.21	28.76 (7.48)	26.20 ± 4.55	26.22 (5.56)	0.101*

* Mann-Whitney U tests

Table 2 Comparison of patients without and with sentinel node (SN) identification

	SN not identified (n=4)	SN identified (n=71)	p value
Weight			
<70 kg	1	51	0.083*
≥70 kg	3	20	
Clinical detection			
Palpable lesion	3	60	0.510*
Imaging detect	1	11	

Table 2 Comparison of patients without and with sentinel node (SN) identification (Continue)

	SN not identified (n=4)	SN identified (n=71)	p value
Tumor location			
Upper outer quadrant	1	28	0.043*
Upper inner quadrant	0	22	
Lower outer quadrant	1	11	
Lower inner quadrant	0	6	
Central	2	4	
Diagnosis methods			
CNB/FNA	2	66	0.041*
Excision biopsy	2	5	
Diagnosis			
DCIS	0	7	1.000*
DCIS with microinvasion	0	7	
LCIS	0	0	
Invasive lobular carcinoma	0	0	
Invasive ductal carcinoma	4	57	
Operation performed			
BCS	0	22	0.314*
Mastectomy	4	49	
Pathologic tumor size			
Tumor <2 cm	1	36	0.238*
Tumor >2-3 cm	1	22	
Tumor >3-5 cm	1	9	
Tumor >5 cm	1	4	
Pathologic grading			
Grade 1	0	5	1.000*
Grade 2	2	33	
Grade 3	2	30	
LVI			
Yes	2	37	1.000*
No	2	34	
PNI			
Yes	0	8	1.000*
No	4	63	

*Fisher exact test

Table 3 Immunohistochemistry of breast cancer patients

Immunohistochemistry	SN not identified (n=4)	SN identified (n=71)	p - value
ER			
Yes	4	48	0.306*
No	0	23	
PR			
Yes	4	32	0.048*
No	0	39	
HER2			
1+	2	26	0.839*
2+	2	29	
3+	0	15	
Kl67 ($\geq 20\%$)			
Yes	1	37	0.430*
No	3	26	
Confirm DISH test			
Positive	0	3	0.334*
Negative	1	3	

*Fisher exact test

63 cases (84%) were presenting with palpable lesion and 12 cases(16%) were mammographically detected. Of these, 68 cases were diagnosed by core needle biopsy technique and 7 cases were diagnosed by previous excisional biopsy. All of 75 cases were diagnosed as following; 61 cases (81.33%) as invasive ductal carcinoma, 7 cases(9.33%) as DCIS and 7 cases (9.33%) as DCIS with microinvasion. Greater than 1/3 of patients (29 cases, 38.67%) tumor location were in upper

outer quadrant, and the second most (22 cases, 29.33%) were in upper inner quadrant. The amount patients with T1, T2, T3 were 37 cases (49.33%), 33 cases (44%) and 5 cases (6.67%), respectively. And 97.33% of patients in this study were stage 0-II. The 75 cases were divided into 2 groups based on whether sentinel lymph node could be identified. The factors significantly difference between 2 groups were body weight, tumor location, diagnostic methods, and PR status (Table1,2,3).

Table 4 Result of sentinel lymph node (n=75)

	n (%)
SLN identified	71 (94.67%)
SLN not detected go on ALND (n=4)	
Positive ALND	1/4 (25%)
Negative ALND	3 / 4 (75%)
SLN positive (n=12)	12/71 (16.90%)
Micrometastasis	3/12 (25%)
Macrometastasis	9/12 (75%)

Table 4 Result of sentinel lymph node (n=75) (Continue)

	n (%)
SLN positive go on ALND (n=9)	
Positive ALND	1/9 (11.10%)
Negative ALND	8/9 (88.90%)
Number of sentinel node (mean ± SD)	6.40 ± 3.26

A sentinel node was identified in 71 of 75 cases (94.67%) and contained metastasis in 12 cases (16.90%). In case whom sentinel node can not identified (4 cases) go on axillary lymph node dissection intraoperative had node metastasis in 1 case. In the sentinel node positive 12 case, 3 of 12 cases (25%) had micrometastasis and 9 of 12 cases (75%) had macrometastasis. 9 of 12 cases go on axillary lymph node dissection. Of these, 1 case had

metastasis in non- sentinel node (1/9, 11.1%) and the sentinel node was the only node containing metastasis in 8 cases (8/9, 88.9%). The mean (standard deviation) number of sentinel nodes identified was 6.40 (3.26) (Table 4). The effect of surgeon experience on sentinel node identification was examined for first 20 cases performed compared to after 20 cases performed, the result was not significant difference.

Table 5 Stepwise logistic regression of probability of sentinel node identification

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p - value	Odds ratio (95% CI)	p - value
Weight group	7.65 (0.75-77.96)	0.086	1.29 (0.04-38.71)	0.883
Tumor location				
Upper outer quadrant	0.51 (0.05-5.17)	0.570	0.20 (0.01-6.24)	0.361
Upper inner quadrant	0.00 (0.00-N/A)	0.998	0.00 (0.00-N/A)	0.995
Lower outer quadrant	1.82 (0.17-19.12)	0.618	5.92×10^{14} (0.00-N/A)	0.996
Lower inner quadrant	0.00 (0.00-N/A)	0.999	0.07 (0.00-N/A)	1.000
Central	16.75 (1.85-151.83)	0.012	2.89×10^8 (0.00-N/A)	0.999
Diagnosis method	13.20 (1.52-114.52)	0.019	5.71×10^{14} (0.00-N/A)	0.995
PR status	0.00 (0.00-N/A)	0.998	0.00 (0.00-N/A)	0.994

A stepwise logistic regression analysis of variables was used to find significantly factors influenced the success of sentinel node identification using both univariate and multivariable models and shown in Table 5. Patients with tumor location at center and previous excisional biopsy were factors that found to effect on the success of sentinel node identification in univariate, then were subjected to further multivariable analysis shown not effect on the success of sentinel node identification (Table 5).

Discussion

The benefit of sentinel lymph node biopsy in breast cancer patients with clinically negative axilla node, is to reducing the number of negative axilla lymph node dissection, thereby reducing the complication rate. The rationale of knowing axillary node status is the single most important predictor of survival, is for accurate staging and for consider adjuvant treatment. But does not appear to be therapeutic benefit to treating the axilla. In the NSABP B-32 trial, demonstrated no statistically significant difference in the survival or nodal recurrence between sentinel node negative patients who had a completion axillary lymph node dissection or sentinel lymph node

biopsy alone(8 years follow up)⁹. Identification rate of sentinel lymph node in breast cancer patients may affected by many factors such as lymphatic mapping technique, experience of surgeon, BMI, tumor location, previous excisional biopsy at breast^{7,10,11}. Finding from many clinical trials and metaanalyses about lymphatic mapping, shows that most successful technique for identifying SLN is albumin colloid or combination of blue dye and radiocolloid range of identification rate of SLN were 82-98%^{12,13,14}. However, in a later studied of lymphatic mapping using blue dye alone, Giuliano et al reported a 94% success rate of sentinel node identification¹⁵. Morrow et al demonstrated no advantage of using combined blue dye and radioactivity compared with blue dye alone on identification rate of SLN⁷. American society of breast surgeons developed the guideline for performance of sentinel lymphadenectomy in breast cancer. In 2003, recommended a rate of SLN identification of 85%, with false-negative rate of 5% or less³. And update guideline on 2014, recommend that SLN should be identified in >95% of eligible patients¹⁶. Case volume and experience of surgeon are important affect the success of sentinel lymph node biopsy. Surgeons should perform at least 20 SLNB cases with acceptable result before abandoning routine axillary lymph node dissection or under direct supervision^{17,18}. Previous excision biopsy was factor that affect the success of sentinel node identification in some early studies based on concern that breast lymphatics were disrupted¹⁹. This concern was not supported by later studies; Haigh et al. reported that success rate of SLNB did not affected by biopsy method (stereotactic,

core needle biopsy, fine needle aspiration, or excision biopsy)²⁰, Wong et al. also demonstrated excision biopsy did not significant affected in SLN identification rate or false negative rate²¹.

In Thailand, there are reports from many studies of sentinel lymph node biopsy in breast cancer using blue dye alone technique for lymphatic mapping found that identification rate were range in 80-100%¹⁹⁻²². In this study, the identification rate of sentinel lymph node using isosulfan blue dye alone was 94.67%. In multivariate analysis of clinicopathologic features found that no factor affect on identification rate of SLN. Tumor location at center and previous excision biopsy were factors that found to effect the success of sentinel node identification in univariate analysis, but not statistical significant in multivariable analysis, may be due to our limitation in small number of unsuccess sentinel node identification cases (4 cases).

And about surgeon experience on SLN identified on this study was not difference between first 20 cases and after 20 cases had been performed. And only 16.9% of successful SLN identified patients in this study had positive sentinel nodes, that reduced the number of negative ALND over 80%.

Conclusions

The identification rate of sentinel lymph node biopsy using isosulfan blue dye alone in early breast cancer at Lopburi cancer hospital are acceptable and feasible. This method are simplicity and low cost.

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