ผลลบลวงของการผ่าตัดต่อมน้ำเหลืองเซนติเนลในผู้ป่วยมะเร็งเต้านมระยะเริ่มแรก ในโรงพยาบาลอุดรธานี

รุจิรา พนาวัฒนกุล กลุ่มงานศัลยกรรม โรงพยาบาลอุดรธานี

บทคัดย่อ

มะเร็งเต้านมเป็นมะเร็งที่พบบ่อยที่สุดในสตรีไทย มีวิธีการดูแลรักษาที่ก้าวหน้าทันสมัย และได้รับการพัฒนาต่อเนื่องมาโดยตลอด ทั้งการตรวจวินิจฉัย การผ่าตัด การให้ยา และรังสีรักษา ซึ่งในปัจจุบัน ผู้ป่วยมะเร็งเต้านมสามารถมีอัตราการอยู่รอดที่สูงขึ้น และมีคุณภาพชีวิตที่ดีขึ้น

การผ่าตัดต่อมน้ำเหลืองเซนติเนลถือเป็นการผ่าตัดมาตรฐานในการตรวจวินิจฉัยและกำหนดระยะของโรคสำหรับผู้ป่วยมะเร็งเต้านมระยะเริ่มแรก โดยเป็นการผ่าตัดเพื่อนำต่อมน้ำเหลืองที่รักแร้กลุ่มแรกที่รับการระบายน้ำเหลืองจากก้อนมะเร็งออกมาเพื่อส่งตรวจ โดยเทคนิคการผ่าตัด สามารถทำได้โดยการใช้สาร radioactive หรือ isosulfan blue หรือใช้ทั้งสองวิธีร่วมกัน ซึ่งมีอัตราการตรวจพบและผลลบลวงที่แตกต่างกันไปในแต่ละสถาบัน ผู้วิจัยจึงต้องการศึกษาถึงผลลบลวงของการผ่าตัดต่อมน้ำเหลืองเซนติเนลในผู้ป่วยมะเร็งเต้านมระยะเริ่มแรกในโรงพยาบาลอุดรธานี

ระเบียบวิธีวิจัย ทำการศึกษาและเก็บข้อมูลในผู้ป่วยมะเร็งเต้านมระยะเริ่มแรก ตั้งแต่ สิงหาคม 2558 ถึง กรกฎาคม 2560 โดยผู้ป่วยทุกรายจะได้รับการผ่าตัดต่อมน้ำเหลืองเซนติเนลโดยใช้สาร isosulfan blue และเจาะต่อมน้ำเหลืองรักแร้ระดับ 1 และ 2 เพื่อส่งตรวจทางพยาธิวิทยา ทำการวิเคราะห์ข้อมูลและแสดงผลออกมาเป็นผลลบลวง ค่าความไว ค่าความจำเพาะและค่าความแม่นยำ

ผลการศึกษาผู้ป่วยมะเร็งเต้านมระยะเริ่มแรกทั้งหมด 104 ราย ได้เข้ารับการผ่าตัดต่อมน้ำเหลืองเซนติเนล มีอายุเฉลี่ย 52 ปี ขนาดก้อนมะเร็งเฉลี่ย 2.7 เซนติเมตร และพบว่ามะเร็งชนิด invasive ductal carcinoma เป็นชนิดที่พบมากที่สุด สำหรับอัตราการตรวจพบต่อมน้ำเหลืองเซนติเนลในการศึกษานี้พบร้อยละ 100 โดยมีค่ามัธยฐานของต่อมน้ำเหลืองเซนติเนลคือ 2 ต่อม

จากการตรวจทางพยาธิวิทยา พบการกระจายของมะเร็งในต่อมน้ำเหลืองเซนติเนล 38 ราย (ร้อยละ 36.5) ในขณะที่ผู้ป่วยอีก 66 ราย ไม่พบการกระจายของมะเร็งในต่อมน้ำเหลืองเซนติเนล แต่กลับพบว่ามีผู้ป่วย 3 รายที่พบการกระจายของมะเร็งในต่อมน้ำเหลืองรักแร้ ดังนั้น การผ่าตัดต่อมน้ำเหลืองเซนติเนลในงานวิจัยนี้พบว่า มีผลลบลวง ร้อยละ 4.5 มีความไวร้อยละ 90.9 ความจำเพาะร้อยละ 88.7 และความแม่นยำร้อยละ 89.4

สรุปผลการวิจัยการผ่าตัดต่อมน้ำเหลืองเซนติเนลในผู้ป่วยมะเร็งเต้านมระยะเริ่มแรกในโรงพยาบาลอุดรธานีมีความแม่นยำในการบ่งชี้การกระจายของมะเร็งไปยังต่อมน้ำเหลืองรักแร้โดยมีค่าผลลบลวงร้อยละ 4.5

คำสำคัญ: ต่อมน้ำเหลือเซนติเนล, มะเร็งเต้านม, การเจาะต่อมน้ำเหลืองรักแร้, ผลลบลวง

False negative rate of sentinel lymph node biopsy in patient with early breast cancer in Udonthani hospital

Rujira Panawattanakul, MD., Department of Surgery, Udonthani hospital.

Abstract

Background: In early stage breast cancer, sentinel lymph node biopsy is promising the standard method for the diagnosis of axillary lymph node status. That was determined by removal of the sentinel lymph nodes. Identification technique is performed by injection of radioactive tracer followed by lymphoscintigraphy, injection of blue dye or both. The detection rate and false negative rate were varies in multiple previous reviews. The purpose of this study was determining false negative rate of sentinel lymph node biopsy in patient with early breast cancer in Udonthani hospital.

Methods: Between August 2015 and July 2017, all patients with early stage breast cancer underwent sentinel lymph node biopsy with blue dye injection technique in Udonthani hospital. All sentinel lymph nodes were harvested and all patients were conducted to level I, II axillary lymph node dissection. Statistical analysis was performed and data expressed as false negative rate, sensitivity, specificity and overall accuracy.

Results: A total of 104 patients were enrolled in this study. The average age was 52 $\pm$ 11 years. Average tumor size was 2.7 $\pm$ 1.2 centimeter and invasive ductal carcinoma was common histological subtype. Sentinel lymph node biopsy was performed in all patients with 100% identification rate. Median of 2 (range 1-9) sentinel lymph nodes were found. The sentinel lymph node was positive in 38 patients (36.5%). However, 3 of 66 patients with negative sentinel lymph node had evidence of metastasis in axillary lymph node. False negative rate of sentinel lymph node biopsy was 4.5%. Sensitivity and specificity of sentinel lymph node biopsy in this study were 90.9% and 88.7%, respectively. The overall accuracy was 89.4%.

Conclusion:Sentinel lymph node biopsy in patient with early breast cancer in Udonthani hospital shows it to be reliable and accurate for prediction the axillary lymph node metastatic status with false negative rate of 4.5%.

Key words: Breast cancer, sentinel lymph node biopsy, axillary lymph node dissection, False negative rate

Background

Axillary lymph node surgery has been an integral component of the staging and treatment of invasive breast cancer. The status of axilla remains the most important prognostic indicator for overall survival and a major factor in determining adjuvant systemic therapy[1]. Surgical paradigm change since the concept of lymphatic mapping of the breast was introduced in the early 1990s.[2]

In early breast cancer, sentinel lymph node biopsy is promising the standard method for the diagnosis of axillary lymph node status, has replaced axillary lymph node dissection. It is associated with reduced morbidity such as seroma formation, arm weakness, restriction in shoulder mobility, lymphedema, axillary web syndrome and neurological complications.[2-8]

Sentinel lymph node is the first echelon node, draining by an afferent lymphatic channel from primary tumor. After drainage to this first node, metastatic spread to other nodes further up in the lymphatic basin occurs in orderly progression. The tumor status of sentinel lymph node reflects the tumor status of nodal basin. Only those sentinel lymph node positive for metastasis, patient were submitted to complete axillary clearance. In contrast of, negative sentinel lymph node that spare patient from having to undergo axillary lymph node dissection.

Identification of sentinel lymph nodes is performed by injection of radioactive tracer followed by lymphoscintigraphy, injection of blue dye or both. With detection rate of 65.4-99.1% and false negative rate was 0-14.3% and overall accuracy was 90.9-97.1%.[6,9-21]

The pathologic status of the axillary lymph nodes was independently determined by removal of the first or first and second sentinel lymph nodes in 99%[10], removal of more than three sentinel lymph nodes did not increase accuracy of finding a positive node. Likewise, 40-70% of sentinel lymph node metastasis shown no additional non sentinel lymph node involvement. Thus, axillary lymph node dissection is unnecessary in all sentinel lymph node metastasis patients.[22]

The purpose of this study was determining false negative rate of sentinel lymph node biopsy with blue dye technique in patient with early breast cancer in Udonthani hospital.

Material and methods

Study design and patients

This study was conducted in all patients with early stage breast cancer in Udonthani hospital between August 2015 and July 2017. Patient who had clinical stage T1-2, N0 invasive breast cancer who underwent sentinel lymph node biopsy were eligible for enrollment. Exclusion criteria were patient who had history of blue dye allergy, histologically proven axillary lymph node metastasis, prior treatment with neoadjuvant chemotherapy or radiation, unable to identified sentinel lymph node during surgery, pregnant woman or patient still on lactation period.

Procedures

After informed consent was obtained, all patients underwent sentinel lymph node biopsy by single surgeon with using blue dye technique.

Sentinel lymph node biopsy was carried out at the operating theater. After induction of

general anesthesia, 1% Isosulfan blue dye 3 ml. was injected into intradermally at subareolar area 10 minutes prior to the surgical procedure.

Sentinel lymph node identified during these procedures were classified as

- Blue node: contained blue dye staining
- Suspicious node: palpated nodes but no contained blue dye staining

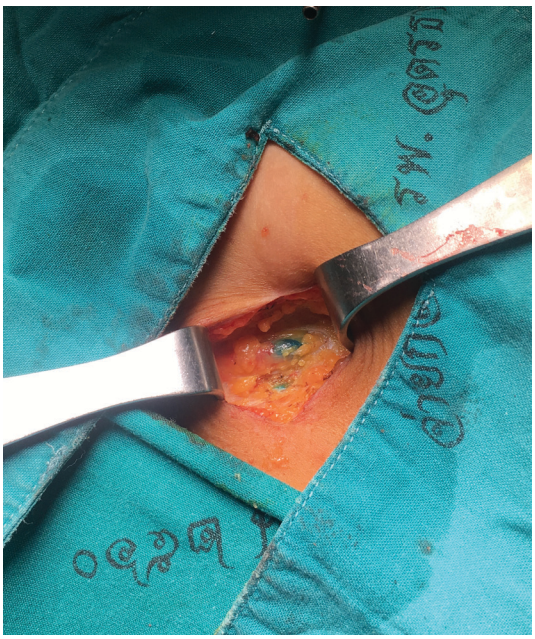

Figure 1 Sentinel lymph node contained blue dye (Blue node)

All identified sentinel lymph nodes were harvested and sent for permanent section with Haemotoxylin and Eosin (H&E) staining system and all patients were conduct to level I, II axillary lymph node dissection. Immunohistochemistry (IHC) staining was routinely used in the diagnosis of biological markers. Estrogen receptor (ER), Progesterone receptor (PR) and Human epidermal growth factor receptor 2 (Her-2) were documented by pathologist.

Research Ethics

The project has been reviewed and approved by the ethics committee, Udonthani hospital

Statistical analysis

Data management and statistical analysis was performed. Quantitative data were expressed as median, mean, range and standard deviation. Furthermore, qualitative data were summarized as percentage. Statistical analyses based on 2x2 contingency table. False negative rate, sensitivity, specificity and accuracy of sentinel lymph node biopsy were compared to axillary lymph node dissection.

Result

From August 2015 to July 2017, a total of 104 patients with early stage of invasive breast cancer were enrolled. All patients underwent sentinel lymph node biopsy by single surgeon under general anesthesia with isosulfan blue dye technique alone.

103 patients were women and only 1 patient was man, the average age of patient was 52 $\pm$ 11 years (range 30-82 year). 44.2% were premenopausal and 54.8% were postmenopausal women.

Among the 104 patients with early breast cancer, 53 patients (51.0%) had lesion on right side and 50.9% of all tumors were located in upper outer quadrant. For the 76.9% of breast operations were mastectomy and others 23.1% were conservative breast surgery. Immediate breast reconstruction include latissimus dorsi myocutaneous flap and/or prosthesis performed in 3 patients (2.9%) as shown in Table 1.

Table 1 Patient characteristics (N=104)

Patient characteristics	n (%)
Age Mean (S.D.) 52 (11)	Range 30-82
< 50	45 (43.2)
50-70	53 (51.0)
> 70	6 (5.8)
Sex	
Man	1 (1.0)
Woman	103 (99.0)
Status	
Premenopausal	46 (44.2)
Postmenopausal	57 (54.8)
Side	
Left	51 (49.0)
Right	53 (51.0)
Location	
Upper outer	53 (50.9)
Upper inner	21 (20.2)
Lower outer	8 (7.7)
Lower inner	6 (5.8)
Central	16 (15.4)
Breast operation	
Mastectomy	80 (76.9)
Breast conserving surgery	24 (23.1)

Most common histological subtype was invasive ductal carcinoma, 100 patients (96.1%) and moderately differentiation was identified in 60.6%. Besides 39.4% were demonstrated lymphovascular invasion. Average tumor size was 2.7 $\pm$ 1.2 centimeters (range 0.1-5.0 cm.). Estrogen and progesterone receptor expressed in 43 patients (41.3%), in contrast of 40 patients (38.5%) had both hormonal receptors negative. Moreover, Her-2 overexpression was recorded in 23 patients (22.1%). Tumor characteristics are shown in Table 2.

Table 2 Tumor characteristics of 104 breasts

Tumor characteristics	n(%)
Histology	
Ductal	100 (96.2)
Mucinous	2 (1.9)
Papillary	2 (1.9)
Tumor stage/size(cm) Mean(S.D.)	2.7 (1.2)
T1mi (< 1 cm)	2 (1.9)
T1 (1-2 cm)	34 (32.7)
T2 (>2 cm)	68 (65.4)
Grade	
Well differentiated	9 (8.6)
Moderately differentiated	63 (60.6)
Poorly differentiated	32 (30.8)
Lymphovascular invasion	
Present	41 (60.6)
Absent	63 (39.4)
Hormonal receptor	
ER+ PR+	43 (41.3)
ER+ PR-	18 (17.3)
ER- PR+	3 (2.9)
ER- PR-	40 (38.5)
Estrogen receptor	
ER+	61 (58.7)
ER-	43 (41.3)
Progesterone receptor	
PR+	46 (44.2)
PR-	58 (55.8)
Her-2 status by IHC	
Negative	70 (67.3)
Equivocal	11 (10.6)
Overexpression	23 (22.1)

Sentinel lymph nodes were identified in all 104 operations, detection rate was 100%. Median of sentinel lymph node detected was 2 (range 1-9 nodes). Thirty eight of 104 patients (36.5%) documented of positive cancer cell in sentinel nodes. Furthermore, axillary lymph node dissection was performed in all patients. Median of axillary lymph node harvested was 10.5 (range 2-26 nodes). 33 of 104 patients

(31.7%) shown cancer metastasis in the axilla. Interestingly, 3 of 66 patients had no malignant cell in sentinel lymph node shown metastasis in further complete level I, II axillary lymph node clearance. Overall false negative rate of sentinel lymph node biopsy in this study was 4.5%. In our study sensitivity and specificity of sentinel lymph node biopsy were 90.9% and 88.7%, respectively. Totally, in comparison to axillary clearance, the accuracy of sentinel lymph node biopsy was 89.4% as shown in Table 3

Table 3 Sentinel lymph node biopsy followed by axillary lymph node dissection of 104 breast operations

		Axillary lymph node dissection		subtotal
		Positive	Negative	
Sentinel lymph node biopsy	Positive	30	8	38
	Negative	3	63	66
subtotal		**33**	**71**	

Discussion

Axillary lymph node status is one of the important prognostic and predictive factors for breast cancer. Nowadays, sentinel lymph node biopsy has become a standard diagnostic tool for axillary staging of early breast cancer and has many advantages in comparison with axillary dissection.[7]

This study shows median number of sentinel node removed was 2, varies from 1-9 nodes. However, previous report with only 1-5 nodes identified.[7,19] This higher number may be explained by different of timing from injection to operation and definition of sentinel lymph node in each study.

Sentinel lymph node biopsy in early breast cancer in Udonthani hospital had successfully 100% detection rate and overall false negative rate was 4.5% with single blue dye mapping technique. Thus, negative sentinel lymph node biopsy could be protected most of all patients (95.5%) from unnecessary axillary lymph node surgery. However, in case of positive sentinel lymph node biopsy, a complete axillary lymph node dissection is still standard therapy since rate of additional non sentinel lymph node involvement in our setting was 78.9%.

The ability to identified sentinel lymph node in our report was 100%, higher than previous study with 91% identification rate with use of isosulfan blue dye alone.[14] Surgeon experience, definition of sentinel lymph node and amount of blue dye might be explained this higher identification rate.

Like a previous review, a combination of isotope and dye to map the sentinel lymph node is superior to either method used alone, in order to highest identification rates and lowest false negative rates.[11,20] Besides, recent meta-analysis of 9,306 patients, the use of blue dye alone was associated with higher false negative rate, should be accompanied by a radioactive tracer to achieve a significantly lower false negative rate.[23]

The accuracy of combine technique sentinel lymph node biopsy reported in previous articles. Sensitivity and specificity were 88-92%[2,7,15] and 87.5-100%[2,7,15] respectively. False negative rate was 4.3-8%[2,7,15] and the overall accuracy was also 90.9%.[2,7,15] These results was similar rate when compare with blue dye technique alone in our data.

Thus, in our setting, combine technique sentinel lymph node biopsy in Udonthani hospital could not be performed since limitation of radioactive tracer and nuclear medicine technician. Sentinel lymph node biopsy with isosulfan blue dye technique alone shows reliability for axillary staging with high detection rate and low false negative rate.

Conclusion

Sentinel lymph node biopsy in patient with early breast cancer in Udonthani hospital shows it to be reliable and accurate for prediction the axillary metastatic lymph node status with false negative rate of 4.5%.

References

1. Fisher ER, Anderson S, Redmond C, Fisher B. Pathologic findings from the national Surgical Adjuvant Breast Project Protocol B-06: 10 year pathological and clinical prognostic discriminants. Cancer. 1993;71:2507-2514.

2. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection VS no axillary dissection in women with invasive breast cancer and sentinel node metastasis:a randomized clinical trial. JAMA. 2011;305:569-575.

3. Bergmann A, Mendes VV, de Almeida Dias R, do Amaral ESB, da Costa Leite Ferreira MG, Fabro EA. Incidence and risk factors for axillary web syndrome after breast cancer surgery. Breast cancer research and treatment. 2012;131(3):987-92.

4. De Gournay E, Guyomard A, Coutant C, Boulet S, Arveux P, Causeret S, et al. Impact of sentinel node biopsy on long-term quality of life in breast cancer patients. British journal of cancer. 2013;109(11):2783-91

5. Disipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. The Lancet Oncology. 2013;14 (6):500-15.

6. Krag DN, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel node in breast cancer-a multicenter validation study. N Engl J Med 1998;339:941-6.

7. Moghimi M, Ghoddosi I, Rahimabadi AE, Sheikhvatan M. Accuracy of sentinel node biopsy in breast cancer patients with a high prevalence of axillary metastases. Scandinavian Journal of Surgery. 2009;98(1):30-33.

8. Monleon S, Murta-Nascimento C, Bascuas I, Macia F, Duarte E, Belmonte R. Lymphedema Predictor Factors after Breast Cancer Surgery : A Survival Analysis. Lymphatic research and biology.2015;13(4):260-7.

9. Acuna SA, Angarita FA, Escallon J. Assessing patterns of practice of sentinel lymph node biopsy for breast cancer in Latin America. World journal of surgery. 2014;38(5): 1077-83.

10. Canavese G, Gipponi M, Catturich A, Di Somma C, Vecchio C, Rosato F, et al. Sentinel lymph node mapping in early-stage breast cancer: technical issues and results with vital blue dye mapping and radioguided surgery. Journal of surgical oncology. 2000;74(1): 61-8.

11. Cody HS III. Clinical aspects of sentinel node biopsy. Breast cancer research : BCR. 2001;3(2):104-8.

12. Gipponi M, Bassetti C, Canavese G, Catturich A, Di Somma C, Vecchio C, et

al. Sentinel lymph node as a new marker for therapeutic planning in breast cancer patients. Journal of surgical oncology. 2004;85(3):102-11.

13. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Annals of Surgery. 1994;220:391-398.

14. Kantaraksa N, Kongdan Y, Suvika pakornkul R, Wasutit Y, Chirappapha P, Lert-sithichai P. The relative false negative rate of isosulfan blue in detecting sentinel lymph nodes in early breast cancer. Journal of the Medical Association of Thailand. 2012;95(2):181-5.

15. Kern KA. Concordance and validation study of sentinel lymph node biopsy for breast cancer using subareolar injection of blue dye and technetium 99m sulfur colloid. Journal of the American College of Surgeons. 2002;195(4):467-75.

16. Khalifa K, Pereira B, Thomas VA, Mokbel K. The accuracy of intraoperative frozen section analysis of the sentinel lymph nodes during breast cancer surgery. International journal of fertility and women's medicine. 2004;49(5):208-11.

17. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. The Lancet Oncology. 2007;8(10):881-8.

18. Krag DN, Ashikaga T, Harlow SP, Skelly JM, Julian TB, Brown AM, et al. Surgeon training, protocol compliance, and technical outcomes from breast cancer sentinel lymph node randomized trial. Journal of the National Cancer Institute. 2009;101(19):1356-62

19. Schrenk P, Rehberger W, Shamiyeh A, Wayand W. Sentinel node biopsy for breast cancer: does the number of sentinel nodes removed have an impact on the accuracy of finding a positive node? Journal of surgical oncology. 2002;80(3):130-6

20. Somasundaram SK, Chicken DW, Keshtgar MR. Detection of the sentinel lymph node in breast cancer. British medical bulletin. 2007;84:117-31.

21. Wong SL, Edwards MJ, Chao C, Tuttle TM, Noyes RD, Carlson DJ, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. Journal of the American College of Surgeons. 2001;192(6):684-9; discussion 9-91

22. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma:a mta-analysis. Cancer.2006;106:4-16.

23. Pesek S, Ashikaga T, Krag LE, Krag D. The false-negative rate of sentinel node biopsy in patients with breast cancer: a meta-analysis. World journal of surgery. 2012;36(9):2239-51.