# Evaluation of the Benefit of Intraoperative Frozen Section Analysis of Sentinel Lymph Nodes in Clinically Negative Node Early Breast Cancer after ACOSOG Z0011 Era

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## Abstract

**Background:** Sentinel lymph node (SLN) biopsy (SLNB) is the standard practice for patients with clinically negative axillary lymph node. Frozen section was used to reduce the rate of re-operation in the case of sentinel lymph node (SLN) positive. From ACOSOG Z0011 and AMAROS trials, they supported that axillary lymph node dissection (ALND) can be omitted in selected patients. Globally, frozen section has been decreased significantly.

**Objective:** To determine the re-operative rate in the patient that limited SLN metastasis treated following ACOSOG Z0011 and determine factors that associated with metastatic involvement of axillary lymph nodes (ALN).

**Material and Method:** Patients who diagnosed early breast cancer with clinically node negative were retrospectively reviewed. All patients were initial treated with total mastectomy, lumpectomy, ALND and SLNB from 2014 to 2018 were collected. Demographic data was recorded, re-operative was calculated and the risk of metastasis to ALN were analyzed in relation to clinicopathological determinants.

**Result:** 190 patients were enrolled in this study. 19 patients (10%) required ALND. Factors associated with ALN metastasis in univariate analyses were age >50 year, HER-2 expression, lymphovascular invasion (LVI), and extra nodal extension. All factors identified with univariate analyses were entered into a multivariate logistic regression model and HER-2 expression (OR=2.42, p=0.006), LVI (OR=3.53, p<0.001) and extra nodal extension (OR=8.11, p= 0.008) remained as independent factors of ALN metastasis.

**Conclusion:** The chances of having to re-operation are relatively low following ACOSOG Z0011. HER-2 expression, LVI and extra nodal extension are factors that associated with ALN metastasis in patient with early breast cancer.

**Keyword:** early breast cancer, frozen section, sentinel lymph node

**Original Article**

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**Background**

Currently, breast cancer is the most common cancer in Thailand and the mortality rate is quite high.[1] Triple assessment includes three modalities, physical examination, imaging (mammography and/or ultrasound), and biopsy (fine needle aspiration and core biopsy) is standard practice and the robustness of assessment towards the diagnosis of breast cancer is crucial. Therefore, early detection of breast cancer and appropriate treatment are important. Mastectomy with axillary staging and breast conserving surgery (BCS) with axillary staging and radiation therapy are considered equivalent treatments for patients with early stage breast cancer.[2] Most patients with early breast cancer are candidates for BCS because of the cosmetic advantage, equivalent survival outcomes, positively impacts patient well-being and quality of life; however, there are contraindications in some situations.[3] The most important prognostic factors in early breast cancer is axillary lymph node involvement.[2-4] Axillary lymph node dissection(ALND) is still the standard procedure for axillary staging and therapeutic procedure for breast cancer. There are significant morbidities after ALND, including lymphedema of the ipsilateral arm, numbness, chronic pain, and reduced range of motion at the shoulder joint.[3-4] Recently, sentinel lymph node biopsy(SLNB) has been developed and become the standard of care for the patients with clinically lymph node negative breast cancer. SLNB is developed to reduce the morbidity associated with ALND while still providing accurate axillary staging.[2] However, if SLNB is positive, the standard treatment remains completion ALND.

The results of the ACOSOG Z0011 study have changed treatment practices. There is no overall survival difference for patients with 1 or 2 positive sentinel lymph nodes (SLNs) treats with breast conserving surgery who underwent completion ALND vs. those who have no further axillary surgery.[5-7] In addition, the American Society of Breast Surgeons issued a consensus statement supporting omission of ALND for patients who meet Z0011 criteria.[8] In the other hand, information from AMAROS trial suggests that patients who do not fit with the criteria of Z0011 trial, axillary radiotherapy is a valid treatment option with less morbidity than ALND.[9]

SLNB with intraoperative frozen section becomes common practice and review of the literature showed that the sensitivity varies between 52% and 89%.[10] Moreover, previous meta-analysis showed the test accuracy ranging from 88 to 96%.[10] ASCO guideline (2014) reviewed limitations of frozen section diagnosis but it does not encourage or discourage the use of frozen section diagnosis for SLNB.[11] Bishop (2016)[12] reported that following Z0011 trial, 97% of the patients are spared axillary lymph node dissection and intraoperative SLN evaluation has significantly decreased. Therefore, routine frozen section diagnosis for sentinel lymph node biopsies can be avoided in these patients. In addition, Caudle (2012)[13] and Wright (2015)[14] reported a decline in intraoperative evaluation of SLNB from 69% pre-Z0011 to 26% and from 92% to 45%, respectively.

Prior to the published ACOSOG Z0011 trial results, ALND is performed to almost breast cancer patients in our institution. We analyzed the data of axillary lymph node (ALN) study in early breast cancer patients with clinically negative node which SLNB is the standard in the axillary management. However, false negative rate for SLNB less than 5%.[3] The aim of this study is to determine re-operative rate in patients with limited SLN metastasis treats following ACOSOG Z0011 trial. In addition, we also determine the factors that associated with metastatic involvement of the axillary lymph nodes (ALN) and promote SLNB in the rural area of Thailand that frozen section is unavailable.

**Material and Method**

This hospital-based descriptive study was performed at Suratthani Hospital, Suratthani, Thailand, from January 2014 to December 2018. It includes all patients with T1-2 primary and clinically negative. 190 from 202 patients were eligible for this study. We excluded 12 patients due to incomplete clinicopathological data. They have initial treats with total mastectomy, lumpectomy, ALND and SLNB. Demographic data, clinical and pathological characteristics are retrospectively collected. Following ACOSOG Z0011 trial, the patient required ALND if the SLN is positive more than 2 nodes. We analyzed the patient who have 3 or more positive of SLN in percentage. The risks of metastasis to ALN are analyzed in relation to clinicopathological determinants.

Approval from our institutional ethics committee is obtained for this study. Continuous variables are reported using mean values. Categorical variables are reported as counts and proportions, and compared using the Chi square test or the Fisher exact test as appropriate. Multiple logistic regression is performed to identify independent predictors of renal exploration. The significance of the difference is estimated using Chi square for qualitative variables. Variables attaining $p < 0.05$ on univariate analysis or considered clinically relevant are included in the multivariate analysis. Statistical analysis is performed with STATA®. A probability value of $p < 0.05$ is considered statistically significant.

**Result**

During the study period, 190 patients with T1-2 primary and clinically negative are included in our study. All patients are women with 53-year mean age while 100 patients (56.2%) are over 50 years. 91 patients (47.9%) are obese (BMI ≥ 25) and 69 patients (36.3%) have co-morbidity. Only 5 patients (2.6%) have family history of breast cancer. More than half of patients have tumor located lateral on left side. 181 patients (95.2%) are underwent total mastectomy while 185 patients (97.3%) are underwent ALND.

Average tumor size is 24 mm. and 62.6% of patients are staged $T_2$. Invasive ductal carcinoma is the most common type of breast cancer and the lesser types are metaplastic carcinoma, squamous cell carcinoma, invasive lobular carcinoma, invasive papillary carcinoma and mucinous carcinoma. The histologic Bloom-Richardson grade I, II and III are 12 (6.3%), 84 (44.2%) and 89 (46.8%), respectively. Most of patients have ER-positive (72.6%), PR-positive (65.2%) and HER-2 negative (65.8%) meanwhile the

luminal A is the most of luminal subtype (48.9%) and triple negative subtype (16.8%). More than half of patients have LVI; however, only 10 patients (5.2%) have extra nodal extension. Epidemiologic characteristics, clinical and histopathologic data of the study patients are given in the Table 1.

**Table 1** Patient and Tumor Characteristics (n=190)

| *Characteristic* | | Spare ALND | | ALND | *P value* |
|---|---|---|---|---|---|
| | | **LN 0-mi (n=125)** | **LN 1-2 (n=46)** | **LN ≥ 3 (n=19)** | |
| ***Age*** | Mean (years) | 54 | 51 | 48 | *<0.001* |
| | > 50 | 73 | 22 | 5 | *0.025* |
| | ≤ 50 | 52 | 24 | 14 | |
| ***BMI*** | ≥ 25 | 62 | 20 | 9 | *0.776* |
| | <25 | 63 | 26 | 10 | |
| ***Underlying disease*** | Yes | 49 | 16 | 4 | *0.300* |
| | No | 76 | 30 | 15 | |
| ***Family Hx*** | Yes | 2 | 3 | 0 | *0.153* |
| | No | 123 | 43 | 19 | |
| ***Location*** | lateral | 76 | 28 | 15 | *0.301* |
| | medial | 49 | 18 | 4 | |
| ***Side*** | Rt. | 51 | 28 | 8 | *0.062* |
| | Lt. | 74 | 18 | 11 | |
| ***Breast surgery*** | mastectomy | 118 | 45 | 18 | *0.642* |
| | **lumpectomy** | **7** | **1** | **1** | |

**Table 1** Patient and Tumor Characteristics (n=190) (cont.)

| *Characteristic* | | Spare ALND | | ALND | *P value* |
|---|---|---|---|---|---|
| | | LN 0-mi (n=125) | LN 1-2 (n=46) | LN ≥ 3 (n=19) | |
| *Axilla surgery* | ALND | 120 | 46 | 19 | *0.263* |
| | SLNB | 5 | 0 | 0 | |
| *Size* | mean (mm) | 23 | 25 | 24 | *0.330* |
| *T staging* | T1 | 51 | 15 | 5 | *0.356* |
| | T2 | 74 | 31 | 14 | |
| *Histologic type* | Invasive ductal CA | 118 | 44 | 19 | *0.537* |
| | Other | 7 | 2 | 0 | |
| *Histologic grading* | 1 | 11 | 1 | 0 | *0.461* |
| | 2 | 53 | 20 | 11 | |
| | 3 | 57 | 24 | 8 | |
| | unknown | 4 | 1 | 0 | |
| *ER* | positive | 92 | 33 | 13 | 0.884 |
| | negative | 33 | 13 | 6 | |
| *PR* | positive | 83 | 27 | 14 | 0.463 |
| | negative | 42 | 19 | 5 | |
| *HER-2* | positive | 34 | 20 | 11 | 0.010 |
| | negative | 91 | 26 | 8 | |
| *Luminal* | A | 66 | 20 | 7 | 0.072 |
| | B | 27 | 15 | 7 | |
| | HER-2 enrich | 7 | 5 | 4 | |
| | triple neg | 25 | 6 | 1 | |
| *LVI* | positive | 56 | 35 | 12 | 0.001 |
| | negative | 69 | 11 | 7 | |
| *Extra nodal extension* | yes | 0 | 7 | 3 | <0.001 |
| | no | 125 | 39 | 16 | |

We compare all clinical data, histopathologic data and immunohistochemistry data of the patients who candidate to omitted ALND following ACOSOG Z0011 trial (spare ALND group; N = 171) with patients required ALND (ALND group; n = 19), so the re-operation rate in our study is 10%. We found that there are no significant differences between both groups in terms of BMI, underlying disease, family history of breast cancer, location of tumor, operation, characteristics of tumor and hormonal receptor status. However, significant differences between both groups are found regarding to age, HER-2 expression, presence of LVI and extra nodal extension (Table 1).

We found that 65 patients (34.2%) who had positive ALN. So, to define those independently-associated factors with ALN metastasis, we show logistic regression analysis. In univariate analysis, patients age over 50 years, HER-2 expression, presence of LVI and extra nodal extension are significantly correlated with ALN metastasis (table 2).

**Table 2** Univariate analysis (n=190)

| *Characteristic* | *Univariate Analysis* | | | |
|---|---|---|---|---|
| | 95% CI | | P value | OR |
| | lower | upper | | |
| *Age > 50* | 0.275 | 0.930 | 0.028 | 0.51 |
| *Family Hx of breast CA* | 0.484 | 18.276 | 0.239 | 2.97 |
| *Lateral side* | 0.633 | 2.159 | 0.618 | 1.17 |
| *T2* | 0.821 | 2.929 | 0.176 | 1.55 |
| *Histologic type (non IDCA)* | 0.455 | 2.634 | 0.840 | 1.09 |
| *Histologic gr. III* | 0.634 | 2.108 | 0.634 | 1.16 |
| *ER-negative* | 0.446 | 1.691 | 0.678 | 0.87 |
| *PR-negative* | 0.462 | 1.616 | 0.648 | 0.86 |
| *HER-2 expression* | 1.356 | 4.766 | 0.004 | 2.54 |
| *Triple negative* | 0.197 | 1.185 | 0.112 | 0.48 |
| *Present of LVI* | 1.851 | 6.758 | <0.001 | 3.53 |
| *Extra nodal extension* | 1.933 | 42.69 | 0.005 | 9.08 |

However, all statistically-significant factors in univariate analysis are included in the multivariable analysis. The results show that HER-2 expression (OR= 2.42, CI 1.28-4.57, P=0.006), presence of LVI (OR=3.53, CI 1.81-6.88, P <0.001), and extra nodal extension (OR= 8.11, CI 1.74-37.83, P=0.008) remains as independent factors of ALN metastasis (table 3).

**Table 3:** Multivariate analysis

| *Characteristic* | *Multivariate Analysis* | | | |
|---|---|---|---|---|
| | 95% CI | | P value | OR |
| | lower | upper | | |
| *Age > 50* | 0.289 | 1.004 | 0.052 | 0.539 |
| *HER-2 expression* | 1.281 | 4.573 | 0.006 | 2.42 |
| *Present of LVI* | 1.809 | 6.885 | <0.001 | 3.53 |
| *Extra nodal extension* | 1.737 | 37.835 | 0.008 | 8.11 |

## Discussion

After the results of ACOSOG Z0011 trial published in 2010-2011, it has made dramatically changes in surgical practice for treatment of early breast cancer. Patients with criteria of ACOSOG Z0011 trial, T1 to T2 tumor and 1-2 positive lymph nodes are treated with BCS and whole-breast irradiation, they can omit ALND. In this study, 90% of patients with ACOSOG Z0011 criteria would be spared by ALND. Similarly, other studies reported the same rate of patients who could be spared ALND.[9, 12, 13, 15] Of course, the complications from ALND will be reduced as well. Moreover, the AMAROS trial which was studied in the same population as ACOSOG Z0011 trial, demonstrates that the axillary recurrence-free rate of patients with SLNB-proven metastasis treated with radiotherapy is non-inferior to those treated with ALND.[9]

Post ACOSOG Z0011 trial, frozen section of SLN has been decreased significantly.[12, 13, 15] It corresponds to the rural area of Thailand that frozen section is unavailable. Therefore, if we can select patients who have low risk to non-SLN metastasis, it will promote more SLN and reduce complications from unnecessary ALND. In this study, only 10% of patients who could be proceeded to ALND. If these patients can undergo by SLNB without frozen section, the re-operation rate is about 10%. However, even if the ACOSOG Z0011 trial was followed, there were still 3 factors that maybe correlated to re-operation, from Table 1. It is just a minor difference from the several demonstrated studies.[12, 15] It may be because of the fewer of sample size.

Patient selection is important. Therefore, we have studied the risk factors for ALN metastasis and found that age (>50 years), HER-2 expression, presence of LVI and extra nodal extension are significant factor in univariate analysis. Several studies[16, 18, 19] showed that there are the same factors to this study, while another studies[17, 20] that demonstrated different results. For examples, young women (<40 years), tumor size (>2 cm.), multifocality, lateral TQLs (tumor quadrant locations), invasive ductal carcinoma, histological grade and hormonal receptor status. However, in multivariable analysis, HER-2 expression (OR=2.42 [95% CI,1.28-4.57]; p=0.006), presence of LVI (OR=3.53 [95% CI, 1.81-6.88]; p<0.001) and extra nodal extension (OR=8.11 [95% CI,1.74-37.83]; p= 0.008) are the strong factors associated with ALN metastasis. So, our study

recommend that patient who clinical T1-2 primary with clinically negative node and no factor that associated with ALN metastasis would be appropriated to performed SLNB without intraoperative frozen section analysis.

However, there are several limitations of this study. First, it is a retrospective nature review that only enrolled patients from a single center. Second, the sample size included in this study is relatively small. It causes other variables to have less significant difference even those factors have significant difference in univariate analysis. Based on the result, clinicians may refer the strong factors and make better clinical decisions.

## Conclusion

Base on the data of ACOSOG Z0011 trial, we found that lower rate of ALND in early breast cancer patients in the meantime of lower rate of re-operation in case of limited frozen section. HER-2 expression, LVI and extra nodal extension are significant factors associated with ALN metastasis in patients with early breast cancer. In this study, we recommended that SLNB without frozen by selecting low risk patients is proper for the rural area with frozen section limitation and it also decreases the unnecessary complication from ALND.

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