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## A Cost-Utility Analysis Comparing Standard Axillary Lymph Node Dissection with Sentinel Lymph Node Biopsy in Patients with Early Stage Breast Cancer in Thailand

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### ABSTRACT

**Objectives:** In Thailand, axillary lymph node dissection (ALND) is the dominant form of treatment for breast cancer, even though the treatment often leaves patients with some degree of arm morbidity. Sentinel lymph node biopsy (SNB) is widely accepted globally as a preferable alternative procedure because of its lower rates of associated morbidity. This study compared the cost-utility of SNB and ALND in patients with early stage breast cancer in Thailand. **Methods:** A decision tree with a 5-year time horizon was developed. Outcomes that were relevant to SNB and ALND were included, along with locoregional recurrence of cancer and lymphedema scenarios. The model parameters were derived from a meta-analysis of international clinical trials and other relevant literature. The resources and cost data were derived from the medical records of tertiary hospitals. Health utilities were measured by using the standard gamble technique. A sensitivity analysis was performed using a set of plausible parameters. **Results:** The incremental cost-effectiveness ratio (ICER) in the base-case

analysis showed that SNB was more cost-effective than ALND. ICERs were –275,140 and –470,600 Thailand baht/quality-adjusted life-year gained from the provider perspective and the societal perspective, respectively. The most sensitive parameter was the utility score of patients with early stage breast cancer who had received breast-conserving therapy with lymphedema; the sensitivity and specificity of SNB had no impact on the ICER. **Conclusions:** The study confirmed that SNB was an economically viable alternative treatment to ALND. In developing countries, where resources are limited, nationwide implementation of SNB warrants widespread support from relevant stakeholders, including medical personnel and policymakers. **Keywords:** axillary lymph node dissection, breast cancer, cost-utility analysis, sentinel lymph node biopsy.

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### Introduction

Over the last 10 years, the incidence of breast cancer in Thailand has increased significantly. The age-standardized rate for breast cancer has risen from 20.4 per 100,000 in 2003 to 25.6 per 100,000 in 2006. Today, 29,167 cases are diagnosed each year [1], making it the leading cancer in women in Thailand. Advancements in cancer care that have occurred over the last 10 years, particularly the multidisciplinary approach that has resulted from collaboration between surgeons, oncologists, and radiologists, has resulted in a dramatic improvement in both the survival rate and the quality of life of patients with breast cancer. Although advanced adjuvant chemo-radiation plays an important role in cancer care, surgery is still the main treatment option for local control of disease. Because the breast lymphatic system is drained through axillary lymph nodes, axillary lymph node dissection (ALND) has become a standard treatment for both cancer staging and the

controlling of local recurrence (LR). Axillary recurrence decreases the 5-year survival rate of patients with breast cancer by approximately 28% to 40% [2,3]. However, ALND causes arm morbidity in around 20% of the patients, including symptoms such as frozen shoulder, armedema, and lymphagitis [4]. Following the introduction of screening mammograms, the number of stage breast cancer cases that exhibit axillary metastasis has decreased significantly because of earlier detection [5]. Many studies [6,7] report that as many as 70% to 80% of patients with early stage breast cancer show no axillary lymph nodes metastasis. For patients who show no palpable axillary lymph node, sentinel lymph node biopsy (SNB) is conducted to identify the first drainage lymph node, which can prevent the need for ALND. SNB has been widely accepted worldwide [8] as a comparative procedure to ALND that can identify early metastasis in patients with early stage breast cancer who have a tumor smaller than 5 cm and a clinically nonpalpable axillary lymph node. The procedure has

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been shown to reduce the risk of many short- and long-term complications associated with ALND, including long hospital stays, infection, lymphedema, and frozen shoulder. For instance, Kell et al. [9] reported a 70% reduction in the rate of lymphedema and a 75% reduction in the rate of arm numbness for patients who underwent SNB as opposed to ALND. Veronesi et al. [10] also found that SNB and ALND resulted in a similar 10-year survival, LR, and metastasis rates.

Although ALND causes higher levels of morbidity than does SNB, ALND is still the standard procedure for patients with breast cancer in Thailand, due to a lack of both trained personnel and facilities that are necessary to implement SNB nationwide. No economic evaluation has yet been undertaken in any developing country setting to compare the cost-effectiveness of ALND and SNB in terms of cost, treatment outcome, and complications. This study aimed to address this gap in the data by evaluating the cost-utility of SNB compared with ALND in patients with early stage breast cancer in Thailand. The results will help health care providers and policymakers decide whether to put SNB into clinical practice throughout the country.

## Methods

### Overview

In Thailand, all patients who are diagnosed with early stage breast cancer and who have no palpable axillary lymph nodes undergo either a mastectomy or breast-conserving therapy (BCT); these surgical treatment options are conducted with either SNB or ALND, depending on the surgeon's preference. ALND is far more common in standard treatment than is SNB, which is currently performed only in a few university and tertiary hospitals throughout Thailand. Following SNB or ALND, chemo-radiation is usually provided, followed by a 5-year hormonal treatment.

To compare the economic value of SNB with ALND, we conducted an evaluation using a hypothetical cohort of women aged 50 years who were diagnosed with early stage breast cancer and had clinically nonpalpable axillary lymph nodes. We chose to focus on postmenopausal women aged 50 years because this is the age at which breast cancer incidence peaks in Thai women [1]. All costs and outcomes after the first year were discounted at a rate of 3% per annum, as recommended by Thailand's health technology assessment guidelines [11].

### Design of analysis model

The study was based on a decision analytic model that compared the cost and utility of ALND with those of SNB in patients with early stage breast cancer in Thailand from societal and provider perspectives. We generated a decision tree with a 5-year time horizon (Fig. 1) that covered all relevant outcomes, including lymphedema and locoregional recurrence rates. All patients were postmenopausal and underwent BCT and either axillary dissection or SNB. For each procedure, the pathology results may be positive (true positive, false negative) or negative (true negative, false positive). Some patients who undergo SNB may later undergo ALND as well, in cases in which the axillary lymph nodes were found to have metastasized. There are two main techniques used to identify the sentinel lymph node in SNB—either a blue dye or a radioactive substance is injected near to the tumor site. In this study, only the blue dye technique was included in the analysis because this is the procedure that is commonly used in the Thai setting. Given the lack of frozen section data in Thailand, we assumed the frozen section data from the diagnosis stage of SNB, which is conducted intra-operationally, to be 100% accurate. Although sensitivity and specificity of SNB were reported from the final histopathology examination, we conducted sensitivity analysis on these two

parameters to minimize these parameters and frozen section uncertainty. Another model assumption was that all SNBs were performed by experienced surgeons who had passed the "learning curve" period. After both SNB and ALND, there is a risk that patients may experience lymphedema in the second and third years after treatment. In the fourth and fifth years, patients experience one of three possible outcomes—LR, regional recurrence (RR), or no locoregional recurrence. For those who experience LR, a mastectomy is usually conducted, either with or without axillary dissection; for those who experience RR, axillary clearance is usually conducted. In both recurrence groups, there is a risk that patients might experience lymphedema after the second surgery. All patients received chemotherapy and radiation after treatment, as per standard guidelines.

Final health states represent the outcomes measurement in most clinical trials, which use the presence of lymphedema, LR, and RR in the arm (or absence thereof). The distance metastasis rate in patients with early stage breast cancer is predominantly dependent on initial staging, which is usually similar in both arms; therefore, we did not assess this in the analysis.

### Model parameters

Clinical parameters were decided on the basis of an extensive search of the published data. They are summarized in Table 1. The prevalence of axillary lymph node metastasis in 2-cm tumors was 31.5%, which increased in-line with tumor size. The sensitivity and specificity of SNB were derived from a meta-analysis of six randomized controlled trials (RCTs) [15–20], which compared SNB and ALND in patients with early stage breast cancer. The locoregional recurrences of SNB were derived from a meta-analysis of five RCTs [10,15,22,23], while the recurrence rate for ALND was derived from a single RCT [24] because no other published data were available. Because many of the clinical trials that examine lymphedema measurements use many different methods, we used data only from one RCT (NSABP B-32) to avoid confusion. The NSABP B-32 trial measured the lymphedema rates for both SNB and ALND patients using the water displacement method, which is recognized as the most reliable method for assessing lymphedema rates [26]. We analyzed the lymphedema rate as part of our sensitivity analysis.

### Utility

Quality-adjusted life-years (QALYs) were derived from the patients' life-years and utility scores. Utility was measured using the standard gamble technique in 110 healthy Thai women aged 26 to 60 years because women in these ages can develop breast cancer. All hypothetical health states were developed on the basis of evidence from the literature review and expert opinions. Patient-reported outcomes [28,29] related to health quality of life in patients with breast cancer were reviewed and modified so that they were appropriate for the Thai context. Although the cognitive interview included questions related to sexual well-being, these responses were excluded from health state description because they were deemed irrelevant. Content validation was conducted by three medical professionals who specialized in caring for patients with breast cancer and five patients with breast cancer. The construct validity was proven by the statistical difference between better health states and worse health states (such as early stage breast cancer and recurrence of breast cancer). The six health states were as follows: 1) early stage breast cancer treated with BCT, with no recurrence, but with lymphedema; 2) early stage breast cancer treated with BCT, with no recurrence and without lymphedema; 3) LR of breast cancer, with lymphedema; 4) LR of breast cancer without lymphedema; 5) RR of breast cancer, with lymphedema; and 6) RR of breast cancer without lymphedema. Patients who experienced LR were treated with a mastectomy with axillary dissection, whereas those experiencing RR were treated with only additional axillary dissection. We assumed that the outcomes of

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