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Special Article

Breast Cancer and Breast Cancer Surgery in Thailand: A View from The Thai Journal of Surgery

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Abstract In the present article we review the recent history of breast surgery in Thailand, as exemplified by the articles published in the Thai Journal of Surgery within the past 40 years. We will focus exclusively on breast cancer, as most of the articles as well as abstracts published in the Journal were concerned with this topic. We will, more or less, be looking at these articles and papers chronologically rather than thematically, to show how ideas and practices change with time relative to one another. Contributions from outside of Thailand are included to help set the world stage at any particular period. Short summaries of certain key developments in the same period from the author's perspective are provided as an introduction to some articles. The overall presentation is unabashedly that of "whiggish" historiography, viewing everything from the high point of current knowledge. This approach is perhaps easier for clinicians to understand and tells a valid story of how we arrive at the present state of affairs, regardless of what the future may bring. We divide the review into sections named after the decade of publication and some dominant themes within that decade. At the end, we briefly list contributions on breast cancer in published abstracts of presentations given at the Annual Congress of the Royal College of Surgeons of Thailand within the past 40 years.

Keywords: Breast cancer, Breast cancer surgery, Thailand

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1970 - 1980: Setting the stage

First, let us quickly review the state of breast cancer surgery at the end of the 1970's. Breast cancer treatment for most of the 1970's was still dominated by radical surgery. After the establishment of basic surgical principles of breast cancer surgery in the early part of the 20th century (the "Halstedian paradigm"), surgical treatment remained, for the most part, essentially unchanged for 50 years. Although radiotherapy and various drugs for breast cancer was commonly used for more advanced stages, their use were limited in the earlier stages, as the evidence supporting their effectiveness was unclear, and their complications were considerable. Other surgical alternatives to mastectomy were not widely accepted, in particular breast conserving surgery was viewed as an inferior modality or valid only for very early stage breast cancers. However, breast reconstruction after mastectomy was becoming more popular and increasingly used. Axillary surgery as a separate consideration in breast cancer surgery for practical purposes did not exist. Less radical surgery, in the form of various modified radical mastectomies, won out at the end of the decade.

The very first issue of the Thai Journal of Surgery ("TJS") in 1980 contained an article by Professor Sompong Raksasook, from Ramathibodi Hospital Medical School, dealing with the then still controversial point of the relationship between fibrocystic condition (FCC) and breast cancer.[1] In a series of 256 patients diagnosed with FCC, of whom 103 were followed from 1 to 8 years, no breast cancer was detected. The study concluded that the evidence for an association between FCC and breast cancer was unclear. In the same volume, an observational study comparing Halsted radical mastectomy with or without radiation, simple mastectomy with or without radiation, and wide excision alone, in a randomly chosen group of 100 patients, the majority of whom had early stage cancers, was also reported by Professor Sompong.[2] This article clearly shows the ambivalence at that time towards the trend to less radical surgery, at least in Thailand. While not condemning simple mastectomy or wide excision, the author clearly favored radical mastectomy. It is notable also for an emphasis on arm lymphedema, of any degree, reporting an incidence of 35% for radical mastectomy. Irradiation was an important risk factor for lymphedema. As was common at the time, chemotherapy use was limited, and the analysis of cancer survival did not adjust for confounding factors (it was obvious that radical mastectomy was used for earlier stage cancers, and simple mastectomy mainly for more advanced cancers). With an average follow-up time of 39 to 46 months, the reported "within 5-year survival" was 69% and 82% for simple and radical mastectomy, respectively, an excellent result for the time.

1980 – 1990: Poor outcomes and systemic therapy

In volume 4 of the TJS in 1983, Professor Michael Baum, at that time of King's College Hospital Medical School, London, UK, in a review article attacked the Halstedian paradigm of breast cancer and presented the view favoring early breast cancer dissemination, by then the new predominant paradigm.[3] In operable breast cancer, prognosis was determined more by micrometastatic disease at the time of presentation than by local disease; micrometastasis can occur quite early on; axillary lymph node status reflected preexisting micrometastasis; and removing axillary nodes did not improve survival. Professor Baum discussed limited axillary dissection and suggestions for lymph node sampling, but then emphasized the need to await long-term results of large clinical trials comparing mastectomy to breast conserving surgery, still on going at that time, before embarking on conservative surgery in routine clinical practice.

An interesting review paper on the epidemiology and risk factors of breast cancer was published also in 1983, from the Edinburgh Breast Screening Clinic at the University of Edinburgh, UK.[4] It is remarkable that new knowledge on risk factors gained since then is more of a refinement rather than anything groundbreaking. There was a discussion of possible environmental and endocrine factors in explaining age-related breast cancer incidence differences between Western and Eastern women. The then recently launched (1979) mammographic screening trial in the UK was described, with the hope of bringing down the 30% prevalence of stage III breast cancers in the UK at that time. A laboratory study funded by the Tenovus Institute for Cancer Research, Cardiff, UK, investigated the uses of salivary steroid hormone assays,[5] which in retrospect proved to be less useful than expected in breast cancer. Another laboratory study from Siriraj Hospital described dextran-coated charcoal versus polyethylene glycol methods of detecting estrogen receptor (ER) and progesterone receptor (PgR) in 381 breast cancer specimens, with clinical correlates.[6] We now, of course, routinely use immunohistochemical methods. A multicenter study of hormonal receptor expression as-

says as well as tamoxifen binding to cytosolic ER in 120 breast specimens, led by Chulalongkorn Hospital and the Thai National Cancer Institute, was also reported.[7] The latter 2 studies revealed interesting patterns of ER and PgR expressions in Thai breast cancer patients. These papers on epidemiology, risk factors, diagnosis and prognosis of breast cancer were of exceptional quality.

Possible mechanisms of action of tamoxifen on breast cancer were discussed in an article from the Tenovus Institute.[8] Tamoxifen had been under investigation, partly funded by the Tenovus Institute itself, and used for treating breast cancer for some time although its mechanism of action was not completely clear. The term Selective Estrogen Receptor Modulator (SERM) did not yet exist. Tamoxifen was on the market but expensive at the time (branded as Nolvadex, ICI, later AstraZeneca), and was not yet widely used in Thailand. Immediately following the tamoxifen article was an article on the prognosis of breast cancer by the Tenovus group in collaboration with the group from City Hospital, Nottingham, with special reference to the presence of ER and PgR in the tumor as prognosticators.[9] The latter group, of course, later developed the well-known Nottingham Prognostic Index for breast cancer.

There were a few papers on the hormonal treatment of breast cancer published in 1983. One excellent review article on tamoxifen, with an early form of meta-analysis, was from the Pharmaceuticals Division in the Medical Department of the Imperial Chemical Industries (ICI) UK,[10] prior to the Pharmaceutical Division's demerger to form the Zeneca Group in 1993. ICI, of course, developed tamoxifen. From its origins in the 1950's as a possible morning-after contraceptive pill to a treatment for infertility, then to an antitumoral agent in the 1970's, tamoxifen is one of the most important therapeutic agents developed for breast cancer in the past 50 years. In the early 1980's the use of tamoxifen in the adjuvant setting was just beginning, in contrast to its use in the metastatic setting, which was established. There were 6 recently conducted randomized controlled trials (RCT) collected in the review, with average follow-up duration ranging from 15 to 48 months. Stages I to III breast cancer patients either received tamoxifen, 20 to 40 mg per day in divided doses for 1 to 2 years, or none, but conventional radiotherapy and chemotherapy were given to some patients in both groups. The pooled analysis showed that there was an average reduction of 23.5% in breast cancer "failures" (mainly recurrences) in the tamoxifen group, which was a highly significant result.

Surgical manipulation of hormonal influences on breast cancer has always been a treatment of last resort, even today, sometimes used for metastatic or aggressive and hormonal responsive cancers in premenopausal women. These operations were of considerable morbidity, and in the past included oophorectomy, adrenalectomy and hypophysectomy. The hope of reducing the need for these operations came with the discovery that Gonadotropin-Releasing Hormone (GnRH) agonists at high dose could produce a "medical oophorectomy" (medical castration) as described in an article by researchers from the Tenovus Institute and the ICI.[11] ICI, of course, was developing a version of a GnRH agonist at the time. The article reported promising animal studies and a few cases of successful use in breast cancer patients. These drugs are now used in routine practice but are still expensive. It is noteworthy that drug companies and research institutes were collaborating very closely at that time, publishing articles together widely in all types of medical publications.

An epidemiological and demographical study of breast cancer in Thailand from the Thai National Cancer Institute (NCI) was published in 1984.[12] There were data on 331 patients seen during 1975 – 80, sent from 123 hospitals all over Thailand. Although the list of participating hospitals did not include those of some major medical schools, Siriraj Hospital was included. The very small number of breast cancer patients in the study raises the issue of completeness of data collection. Nonetheless, breast cancer was consistently the 2nd most common malignancy in Thai women at that time, with a peak frequency between 40 to 50 years of age, and 40% were seen in farmers and laborers. Metastatic disease was seen in 36% of patients. The annual incidence reported for the years between 1970 – 1980 showed an increasing trend, ranging from 1.5 to 2.6 per 100,000, but this was more than 10 time lower than those of Western countries at the time.[4]

A review of breast cancer cases and treatment at Chulalongkorn Hospital is an interesting snapshot of patient characteristics and clinical practice in Thailand in the late 1970's.[13] In a series of 322 female patients, treated during a 5 year period (1975 – 80), the peak frequency was between ages 41 to 50 years, and most were found to have advanced stage cancer (stages III and IV, 57%). Half of patients never returned for their follow-up after surgery, with only 25% remaining in follow-up after

3 years. Modified radical mastectomy was the main treatment modality for stages I and II breast cancers, while simple mastectomy was used for stage III cancers with clinically negative axillary nodes. (Note that staging systems used then were somewhat different from those of the present time, but most followed the AJCC TNM system). Radiation was mainly used for patients with recurrent disease, or those refusing surgery. Relatively few patients received radiation therapy in combination with surgery, and most of these patients had extensive regional nodal involvement. Similarly, chemotherapy and hormonal therapy were reserved for advanced cancers, mainly metastatic and recurrent disease. There were no data on cancer survival. Most of the discussion section was focused on socioeconomic limitations in Thailand at the time, explaining why radiotherapy and chemotherapy were used only sparingly and why radical surgery was still the best option.

A small clinical trial from Ramathibodi Hospital in 1980 led by Professor Sompong attempted to clarify the benefit of adding chemotherapy to locoregional treatment of early stage breast cancer.[14] While clinical trials conducted in other countries showing some benefit of adjuvant chemotherapy for early stage breast cancer existed at this time, in Thailand the use of adjuvant chemotherapy was limited, as mentioned before. Professor Sompong wanted to show similar benefits in Thai patients to encourage the use of adjuvant chemotherapy. But with a sample of 46 pseudo-randomized patients and a drop out of 12 leaving 34 in the analysis, no statistically significant differences between chemotherapy and no chemotherapy could be demonstrated after an average follow-up of only 22 months. Also, chemotherapeutic agents used in the study are no longer commonly in use for breast cancer today (thiotepa and nandrolone decanoate, the latter an androgenic steroid) and only 2 to 3 courses were given, each course lasting about 2 months.

Chemotherapy for operable breast cancer, often called adjuvant chemotherapy because it was seen as an "add-on" to surgical treatment when it was first introduced, was the subject of a 1983 review article by investigators from Manchester and Birmingham, UK.[15] The article is a masterpiece of clear and concise writing, worth reading as an introduction to the basic ideas of chemotherapy even today. After discussing the evidence behind the early dissemination theory of breast cancer, a brief overview of the rationale of adjuvant chemotherapy, as well as timing and duration of therapy, and evidence supporting early deposition theory of micrometastasis was given. Summaries of mostly small clinical trials of single chemotherapeutic agents were provided and contrasted with studies of combination chemotherapy. Even at this early date, the CMF (Cyclophosphamide, Methotrexate, 5-fluorouracil) RCT from Milan, Italy, which was the largest and had the longest follow-up up to that time, stood out as showing relatively clear evidence of efficacy of adjuvant chemotherapy and a significant overall survival benefit, but only for premenopausal patients. Other early and promising trials ongoing at that time, controlled or otherwise, with smaller number of patients, included those of chemotherapy in combination with tamoxifen, and chemotherapy regimens based on doxorubicin. Interestingly the usefulness of the concept of immunomodulators was tested using non-specific agents such as the BCG vaccine and levamisole but without success. Lingering questions remained at the end of the review, including the dosing of chemotherapeutic agents, timing of initiation, duration of treatment, effects with and of radiotherapy, effects on and of ovarian suppression, and selection of patients for chemotherapy and long-term toxicity and adverse events including secondary malignancies.

A study of the results of chemotherapy used in breast cancer from Siriraj Hospital by Professor Thira Limsila, published in 1984, was an interesting window into local practice and treatment results at another major medical institution.[16] For example, in the 1970's, among 152 stage II breast cancers who underwent surgery and radiotherapy, those who completed treatment (only 64% did so) had a recurrence rate of 63%, although the time frame was not reported. However, the study's main focus was on the 50 breast cancer patients who were treated with chemotherapy after failure of these "conventional" treatments in the period between 1969 – 1981 and all of whom died by the last follow-up in 1983. We assume, as was the case with Chulalongkorn Hospital, that chemotherapy was provided only for advanced, metastatic or recurrent disease, and thus these 50 patients represented almost all the experience with chemotherapy for breast cancer at Siriraj Hospital up to that time. There were multiple regimens of single or combination chemotherapy, in addition to radiotherapy and hormonal therapy, the latter including surgical and radiological castration. Of the 50 patients, 44 had prior surgery, and radical mastectomy was the most frequently used procedure.

Almost all patients had multiple organ metastasis, the most common site being the lungs. These drugs were given with doses dependent upon patient condition and tumor response, as well as the presence of bone marrow toxicity and drug resistance. Results included the finding that CMF regimen had the best tumor response and best patient survival, and could be improved if doxorubicin was added. With such a poor-risk sample, however, it was not surprising that 62% would die within the 1st year and only 4% survived past the 4th year. The article ended with an emphasis on a multidisciplinary approach to breast cancer management.

Reconstruction after mastectomy was the subject of an article, in 1985, from a private plastic surgery clinic in Belleville, Illinois, USA.[17] It is interesting to see the latissimus dorsi myocutaneous flap combined with silicone prothesis being used to reconstruct the breast at this time. This is at present at least as common as pure autologous reconstruction. CO2 laser was used for dissection and hemostasis at the clinic, and this in fact was the main selling point of the paper. The attitude towards reconstruction at this date can be seen by the authors' reassurances that plastic surgeons will not interfere with cancer surgery, that "early" reconstruction at 6 months after cancer surgery was safe, and the silicone prosthesis itself was safe. The result of reconstruction was not particularly nice, as the authors mentioned tempering patient expectations with "the result is no cosmetic triumph", "her breasts will not be equal", and "the aim is to look well in clothes … and not in the nude".

1990 - 2000: Conservative surgery and achieving world-class standards

We now jump to 1990 with an article on breast lumps from Siriraj Hospital.[18] The study comprised of 1,060 cases operated on during 1973 – 1984. There was mention of the increasing use of radiologic methods of diagnosis, but more emphasis was on clinical methods. If the lump was of high suspicion for cancer on clinical and radiologic grounds, an excisional or incisional biopsy would be performed under general anesthesia, so that breast cancer surgery could be done in a single setting if the result of the frozen section examination was positive for cancer. This was called the "double set-up" procedure, and is rarely performed today (see below). Although the highest frequency of breast cancer was still in the age group 41 to 50 years, as a proportion of all breast lesions the percentage of breast cancer was highest (81%) in patients older than 60 years. The overall proportion of breast cancer was 19% (199/1,060). In an earlier study from Chulalongkorn Hospital examining breast specimens obtained between 1977 – 1981,[19] the annual proportion of cancer varied from 13% to 16%, which was somewhat lower. Interestingly, both the latter and current study found that 7% of breast cancers occurred in patients younger than 30 years. This was 2 to 3 time higher than those seen in Western countries, and was confirmed in later studies from other institutions in Thailand and East Asia. A recommendation for surgical treatment of breast cancer in the Siriraj article now included breast conserving surgery ("segmental mastectomy") with breast irradiation, and axillary lymph node dissection for stages I and II disease, as well as adjuvant chemotherapy for stage II disease. It seems that by the late 1980's mature results from clinical trials comparing breast conserving therapy and mastectomy as well as adjuvant chemotherapy trials were making an impact on clinical practice in Thailand. But by no means was breast conserving surgery widely practiced in the country at this time.

The impact of mammography on the diagnosis and management of breast cancer was the subject of a retrospective study from Samitivej Hospital published in 1991.[20] Mammography was increasing used in Thailand since the mid 1980's, as exemplified by Samitivej Hospital's program beginning in 1988. Included in the study were 838 mammograms performed during the period 1988 – 1990, with 47% for screening and 53% for diagnostic purposes. Biopsies were done in 134 patients, of whom 38 (28%) had cancer. Overall sensitivity and specificity of the mammogram for detecting cancer were 42% and 85%, respectively. This value for sensitivity would be considered rather low by current standards. Other uses of mammography, specifically for localization of non-palpable lesions and confirmation of complete removal during surgery, were described. Early diagnosis of non-palpable cancers was enthusiastically emphasized. In view of later screening mammography controversy, it was remarkable that cost-effectiveness, radiation safety, accuracy, and proper selection of patients were also mentioned in the article.

By the year 1998 we enter a more familiar territory. Within a period of less than 20 years adjuvant and neoadjuvant chemotherapy was clearly established for breast cancer in Thailand. Standard chemotherapy regimens were being used all over the country and CMF

and anthracycline-based chemotherapy were the norm. Tamoxifen was also widely used. Indications for radiotherapy became clearer. A major reason for this change was the accumulating high-quality research work and a framework for thinking about and synthesizing evidence. Statisticians and clinical epidemiologists began systematically collecting such evidence for synthesis, forming various research groups with specific clinical disciplines. The most prominent, in breast cancer, was perhaps the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), a global research collaboration based in Oxford, UK, established in 1985. Their earliest publication was a systematic review of tamoxifen and chemotherapy for early breast cancer, in 1988.

As breast cancer survival improved dramatically, women became more aware of the disease and its consequences. Breast cancer screening became more common, and breast cancer incidence began to rise, slowly edging out cancer of the uterine cervix to become the number one cancer in Thai women by the beginning of the new millennium. Refinement of indications and new predictors for various surgical and adjuvant therapy for breast cancer emerged. Dramatic innovations in the surgery for breast cancer were just behind the corner and the era of targeted therapy for cancer was dawning.

A review of breast cancer survival and prognosis from the Thai NCI was published in 1998.[21] There were 873 patients in the study treated between 1992 – 1996. The average age was 48 years, with a standard deviation (SD) of 12 years. By this time, using the TNM staging system, almost 60% had early stage breast cancer, and 12% had metastatic disease. Invasive ductal carcinoma constituted 81% of all cancers. Chemotherapy was now used in stages I to III breast cancer in over 70% of patients. Hormonal therapy was used in 30% of patients. Stage I breast cancer had an expected survival of over 80% at 5 years, but stages II and III had significantly lower survival, at slightly over 60% and 30% respectively. Stage IV cancer had slightly above 10% 5-year survival. Prognostic factors considered included TNM stage, histology, tumor grade, ER and PgR status, which could now be obtained almost routinely, menopausal status, socioeconomic status and various types of cancer treatment. HER2/neu (currently, ERBB2) expression was being increasingly used as another important prognosticator.

Breast conserving therapy (BCT) was, by the end of 1990's, an established alternative to mastectomy, widely believed to have equivalent survival whenever BCT was feasible. Long-term evidence from well-conducted, large clinical trials was available. In fact, a high rate of BCT became, for a time, a measure of quality of a specialist Breast Cancer Center. But a key requirement was radiation therapy to the remaining breast tissue. Recurrence after BCT was still somewhat unpredictable, but might there be markers or predictors of recurrence after breast irradiation? A study published in 1999, from the University of Florida Health Science Center, Jacksonville, USA, attempted to find such markers.[22] There were 112 breast cancer patients in the study who were treated with BCT between 1983 – 1994 at the Center. First of all, these were rather good risk patients with a median age of 59 years, with 91% of patients having tumors less than 2 cm in size and 65% were node negative, and adjuvant chemotherapy (all either CMF or doxorubicin + cyclophosphamide) and hormonal therapy were given as indicated. Whole breast irradiation with total doses of 5000 to 5040 cGy was given in 25 to 28 fractions in addition to 5 fractions of 1000 cGy boost to the tumor bed, as well as supplemental supraclavicular and axillary irradiation for patients with large tumors or axillary lymph node involvement. After a median follow up of approximately 7 years, 5-year disease-free survival probabilities were 92%, 85% and 83% for stages I, II and III cancer, respectively. This was an outstanding result, even for today, though limited by the sample size. The survival gaps of different-stage cancers were closing partly because of more effective and tailored treatment.

Second, the paper focused on immunohistochemical markers, recently introduced into routine practice, so methods used could differ between institutions and standardization was an issue. These markers included ER, PgR, HER2/neu (oncogene), p53 (tumor suppressor gene) and MDR1, the latter being a marker for multidrug resistance. The principal finding was that both p53 and MDR1 were frequently (50% to 80%) positive in local or distant recurrences (these were few, however). These latter markers may, as the authors hypothesized, represent predictors of resistance to radiation or chemotherapy. We have now entered the molecular / genetic era of cancer therapy, and as the human genome project was in its final phase the dream and realization of personalized medicine based on knowledge of the genome seemed almost inevitable.

With increasing use of BCT in Thailand, it was natural to ask the patient what her preference would be if given a choice between BCT and mastectomy, and why.

A study from Ramathibodi Hospital was published in 1999, in which patients were asked precisely these questions.[23] A questionnaire was administered to 263 patients seen at the breast clinic of the hospital. Of these, 60 had already been treated for breast cancer by mastectomy, and 203, some of whom did not have cancer, had yet to be surgically treated. Of those who were treated and followed for less than 3 months, 68% preferred mastectomy and 32% preferred BCT. Of those treated and followed for more than 1 year, 75% preferred mastectomy and 25% preferred BCT. However, when asked whether breast reconstruction or the use of breast prosthesis was desirable, 32% to 56% of the treated patients (by mastectomy) answered in the affirmative. In the untreated group, 46% of those who had cancer preferred mastectomy and 54% preferred BCT, while those who did not have cancer preferred mastectomy in only 28% and BCT in 72%. When the two groups were combined, factors significantly related to the preference for BCT included: younger age (less than 40 years); being single; fear of, or perceived, image problems; being a student or an office worker or working for the government; and not yet surgically treated for cancer. It seems, for Thai patients at that time, that once mastectomy had been performed or decided on, there was not much regret, but prior to surgery there was slight preference for mastectomy over BCT. Times have changed, however, and as the younger generation ages and a few have become breast cancer patients themselves, BCT is now a dominant preference, at least in certain regions of the country.

The early dissemination theory of breast cancer posited that axillary surgery did not improve survival, but information on regional disease in the axilla was important for prognosis and prediction of appropriate treatment. It seems logical that if minimal axillary surgery can be performed to obtain sufficient information on nodal metastasis, the morbidity associated with axillary dissection might be reduced. At the very least, if nodal metastasis cannot be detected or predicted to be minimal, then full axillary dissection can be omitted. This would be feasible if there were an identifiable small group of regional nodes that first drains cancerous cells, and these nodes could be removed for preliminary examination. Such elegant ideas began to take shape in the early 1990's alongside the successful implementation of a similar idea in the treatment of cutaneous melanoma and squamous cell carcinoma. This was the beginning of sentinel lymph node biopsy in breast cancer, now a standard practice globally. The rapidity of its acceptance is in contrast to the much more gradual acceptance of BCT.

Two studies on sentinel lymph node biopsy (SLNB) was published back to back in 1999. One study was from the Orebro Medical Center in Sweden.[24] This was a pilot study to evaluate the accuracy of SLNB in 61 clinical node-negative stages I to III breast cancer patients, treated between March 1998 – April 1999, using a combination of radiotracer (Tc99 nanocolloid) and a blue dye (Patent Blue V) to identify SLNs. Preoperative scintigraphy as well as intraoperative gamma radiation probe were used to localize the radiotracer. All patients underwent standard axillary lymph node dissection after SLNB. The axillae contained metastasis in 34% of patients. An average of 2 SLN's were removed. The combined identification rate was 92% and the false negative rate was 14%, slightly higher than that acceptable today. The study concluded, "before being use [sic] in routine clinical practice, results from randomized clinical trials are needed".

Another SLNB study was from Siriraj Hospital,[25] led by Professor Adune Ratanawichitrasin, probably the first such study in Thailand, conducted between December 1998 – May 1999. This was also a pilot study, but using only isosulfan blue dye (ISB) to identify the SLNs. There were 15 early stage breast cancer patients. ISB dye, made in-hospital as a 1% solution, was injected at multiple sites around the tumor or tumor cavity, totaling 3 to 5 mL. After SLNB, axillary dissection was done on all patients. On average 2.5 nodes were removed. The identification rate was 87% (13/15). The false negative rate was 17% (1/6). The authors concluded that "further studies should be carried out…".

A brief review article on SLNB was published in 2000, from Samitivej Hospital.[26] It concisely summarized the importance of axillary staging in breast cancer, and the origins and rationale of SLNB. Several agents for lymphatic mapping or tracers were discussed along with their benefits and drawbacks. The article mentioned the controversy surrounding the routine use of SLNB at the time, and the remaining technical issues needing clarification or further study before such routine use. Some of these included the choice and timing of tracer injection, the appropriate selection of patients, methods of staining sections, the role of internal mammary nodes, and the accuracy of SLNB itself. Most of these issues have now been resolved, but the tone of the article was

cautiously optimistic, a very reasonable stance when new medical innovations are evaluated.

2000 – 2010: SLNB, HER2 and breast reconstruction

Accurate prediction of axillary lymph node metastasis in all cases of breast cancer prior to surgery is almost like the Holy Grail in the sense that it has never been found, and may perhaps never be found. Nevertheless, in extreme cases the prediction of no metastasis or definite metastasis might be accurately and reliably made. Those in between can undergo SLNB. With such predictions, unnecessary axillary surgery could be reduced even further. Some predictive or scoring systems are in current use for these purposes, such as the Memorial Sloan Kettering Cancer Center (MSKCC) Nomograms (e.g., for SLNs), an online tool, but their accuracy and reliability might not be as good as we would like. This is in the nature of the methodology used for their development and implementation. The use of Artificial Intelligence in this area could perhaps improve the usefulness of predictive systems.

A study from Vajira Hospital in 2002 was similar in spirit,[27] attempting to determine predictors of metastasis to axillary lymph nodes prior to surgery. This was a retrospective study of 203 stages I to III breast cancer patients, treated between 1994 - 2001. Of these 42% (85/203) had axillary node metastasis. Factors predictive of axillary lymph node metastasis on multivariable analysis included presence of palpable mass, tumor size greater than 1.5 cm, and presence of lymphovascular invasion (LVI). The absence of all 3 risks was associated with only 3.7% axillary node metastasis. Note, however, that LVI might be difficult to determine preoperatively if inadequate biopsy methods were used.

Breast reconstruction and breast conserving surgery (BCS) were now being used extensively for breast cancer. In Thailand, the trend was similar. In particular, breast reconstruction immediately after mastectomy was now on the rise, mainly using autologous tissue such as the Transverse Abdominis Myocutaneous (TRAM) flap. Breast reconstruction overshadowed BCS in many institutions possibly due to patient preference, since there is no remaining breast to worry about, and surgeon preference, perhaps because of the enticing technical challenge and perceived cosmetic advantages. The dominant technique was the pedicled TRAM flap, with the occasional "free" flap (myocutaneous flaps, mainly from the abdominal area, with attached vascular supply to be anastomosed to local recipient vasculature) being employed.

A study published in 2004 from Siriraj Hospital addressed a problem with breast reconstruction and BCS when the nipple is left in situ or used as a graft.[28] This was the nipple areolar complex (NAC) involvement in breast cancer. The study was performed on 46 mastectomy specimens obtained from stages I to III breast cancer patients treated during the period July 2003 – May 2004, who had no clinical NAC lesions. The aim was to test the accuracy of frozen section examination of the subnipple area compared to permanent section, and to identify risk factors for positive NAC involvement. The proportion of NAC involvement was 37% (17/46). The sensitivity of the frozen section examination was 88% and the specificity was 97% compared to permanent section. Only two factors were related positive NAC involvement: larger tumors and larger tumor size to tumor-to-NAC distance ratio (as measured on mammography). Thus, after selecting appropriate patients based on these risk factors, intraoperative frozen section examination may help further decide whether to preserve the NAC or not.

By this time the first successful targeted therapy for breast cancer had been developed and was on the market, but was still very expensive and not in wide spread use in Thailand. This was trastuzumab, an "anti-HER2" monoclonal antibody, US FDA approved in 1998 via expedited process. It is difficult to overstate its importance. Targeted therapy refers to treatment focused on the tumor and sparing normal cells, via some molecular mechanism specific to a tumor's growth and viability, such as the HER2 receptor proteins over-expressed under genetic mutations specific to the tumor. In contrast, chemotherapy is non-specific and will affect any fast-dividing cell. This was an almost revolutionary approach to treating cancer, brought about by the exponential growth in the knowledge of tumor molecular biology. The rapid development in the biotechnology industry, including gene and protein sequencing technology, of the 1970's through to the 1990's laid the groundwork. We are still in the midst of this development.

Testing for HER2 protein overexpression via immunohistochemical (IHC) staining methods in the early days were riddled with inaccuracy, poor reproducibility and lack of standardization. It was only after the year 2006 that guidelines and recommendations for standardization of laboratory practices became widely accepted, which helped reduce variation in test results. Similar

standardization occurred in Thailand some time later. This was extremely important for the effective use of trastuzumab, and a big step towards the drug becoming more widely available.

A study from Rajavithi Hospital in 2005 attempted to determine the relationship between HER2 overexpression and other predictive and prognostic IHC markers in breast cancer.[29] There were concerns with the accuracy of the IHC test for HER2 in the study, as an unapproved antibody staining technique was used, but the test was validated by the fluorescence in-situ hybridization (FISH) technique. FISH is a test for gene amplification and may complement IHC methods especially if the IHC staining test result is equivocal. The study was performed on 251 specimens from 251 breast cancer patients treated between January 2003 – February 2005. Axillary lymph nodes were positive for cancer in 41% of patients, ER was positive in 39%, PR was positive in 28% and HER2 was positive in 25%. The proportion of positive HER2 was in accord with results from other and later studies, both in and outside of Thailand. There was a negative correlation between ER, PR positivity and HER2 positivity and a positive correlation between axillary lymph node positivity and HER2 positivity. These findings are commonly accepted today.

Refinements in the use and technique of SLNB continued throughout the decade. An important clinical trial on the use of SLNB as the sole staging procedure in certain patients with minimal positive SLNs was published at the end of the decade (the ACOSOG Z0011 trial from the American College of Surgeons Oncology Group), which also established its safety as the sole therapeutic axillary procedure for those patients. Micrometastasis seen on SLNB was no longer an indication for further axillary clearance, according to another trial published in the early 2010's (IBCSG 23-01). Detected macrometastasis in the axilla, however, continued to be treated mainly by surgery.

A study from Phramongkutklao Hospital and College of Medicine in 2005 examined the accuracy of bisectioning versus serial sectioning of the SLNs in detecting macrometastasis.[30] At the institute, SLNs were often bisected for pathological examination, and this had led to the concern that the bivalve method might not be sufficiently accurate, hence the present study was conceived. There were 45 early stage breast cancer patients in the study, who were treated between January 2000 – June 2004. The blue dye method was used for detecting SLN's, with an identification rate of 93% (42/45). The average number of nodes removed was 1.8 nodes, and 76 nodes were available for study. The bivalve method was compared to the conventional serial sectioning at 2 mm intervals, using routine hematoxylin and eosin (H&E) staining as well as cytokeratin IHC. There were 28 positive nodes and 48 negative nodes on bisection examination. Since the only possible difference in the detection of macrometastasis would be for nodes found negative on bisection, the focus was on the serial sectioning for the 48 negative nodes. Due to certain management and other errors, only 42 negative nodes were available. All 42 nodes were also negative on serial sectioning. Thus, bisectioning seemed to be similar to serial sectioning in the detection of macrometastasis. If true, this might help expedite the pathological analysis of SLNs. Of course, with only 76 nodes and incomplete information, further study is necessary.

Another study of SLNs compared scrape imprint cytology to serial sectioning.[31] This study was from Prince of Songkhla University, and included 72 lymph nodes harvested from 33 breast cancer patients treated between April 2005 – March 2006. Combined ISB dye and isotope tracer were used to identify SLNs, with an identification rate of 97%. Scrape imprint of the SLNs was stained with cytokeratin ICC (immunocytochemical) methods which yielded results in 30 minutes. Thus, imprint cytology might be useful for intraoperative detection of cancer in the SLNs. If this was negative, the nodes would then be sent for routine serial sectioning with H&E, and if H&E was negative, further 20-micron section of the nodes with cytokeratin IHC staining was done. The sensitivity of scrape imprint ICC was 33% (5/15), the sensitivity was 94% (17/18) compared to serial sectioning and H&E + IHC. It was concluded that imprint ICC was not sufficiently accurate but further study might be needed. Note that the use of cytokeratin IHC in permanent sections is generally not recommended today by many international cancer societies following several recent studies, since further detection of micrometastasis might not be clinically meaningful.

Methods of tissue biopsy have made a huge impact on clinical practice. We will discuss this topic after the presentation of a study from Suratthani Hospital.[32] This was published in 2008, but was a prospective study of 92 patients with breast tumors treated between October 2004 – September 2005. The average tumor size was 3.1 cm with a range between 1.8 cm to 8.2 cm. Core needle

biopsy (CNB) was performed using a manual small-bore biopsy needle (probably 14-gauge) under local anesthesia, with palpation as the localization method, obtaining 3 to 5 core specimens for examination. All lesions were subsequently excised or incised for definite diagnosis. There were 86 cancers. The sensitivity of the CNB was 92% (79/86) and the sensitivity was 100% (6/6). The false negative rate was 8%. These measures of accuracy were comparable to those published elsewhere for small-bore CNB. Complications were minor, consisting of pain and bruising at the biopsy site.

Core needle biopsy is now standard for breast cancer. With over 90% sensitivity (close to 100% with large-bore, 11-gauge, CNB) and almost 100% specificity for the diagnosis of cancer, and the possibility of obtaining prognostic and predictive markers at the same time, it is the initial biopsy method of choice. If the breast lesion is suspected of being cancerous, CNB is performed first, by an experienced radiologist or surgeon under imaging guidance, and the results are discussed with the patient. Locally advanced lesions or subcutaneous nodules can be biopsied using core needles as well. Subsequent surgical treatment planning is minimally affected by CNB, unlike excisional or incisional biopsy. Excision may still be required if the result of CNB is equivocal or in conflict with other evidence, or if CNB is not feasible. "Double set-up" procedures for simultaneous diagnosis and treatment of breast cancer are no longer routine. With CNB, the patient has more control over her treatment decisions.

We end this decade with a small study on the impact of waiting times on cancer survival, from Ramathibodi Hospital, published in 2009.[33] The study is used as a summary of the practice and what was achieved in Thailand by the year 2000. The study was based on 359 breast cancer patients treated between January 2000 to December 2001 with available information. Of note, at this date only 1% of patients had BCT, the rest had modified radical mastectomy. All had axillary node dissection. Open biopsy was done in 77% of patients (278/359), including double set up in 35% (125/359). CNB was done, mainly by surgeons, in only 16% (56/359). Fine needle aspiration cytology (FNAC) was used for diagnosis in the remaining. The only IHC marker available was the ER, obtained in 80% of patients. Despite an average tumor size of 3.2 cm (SD, 1.6 cm), most patients had TNM stages I and II (80%) disease. The median follow-up time was 66 months and the 5-year overall survival of the whole cohort was 90% (95% confidence interval [CI]: 86% - 93%) and the 5-year disease free survival was 79% (95% CI: 74% - 83%). The overall survival was certainly world-class, even for today. The lower disease-free survival probably reflected considerable recurrence, but with longer survival, possible with powerful therapeutic agents and treatment guidelines available before the new millennium. Adjuvant chemotherapy and hormonal therapy were used in 74% and 52% of patients, respectively, with chest wall irradiation used in 30%. These percentages are similar to what are seen today, except for the current increased use of radiation therapy.

Waiting time, here defined as the time from diagnosis to surgery (patients who had neoadjuvant chemotherapy were excluded), did not have a significant effect on breast cancer survival. Perhaps this was because the median waiting time was only 1.9 weeks (range, 1 day to 32 weeks). At present, the waiting time in many major breast cancer centers could be much longer. One interesting finding was that open biopsy was associated with poorer survival, as compared to needle biopsy, despite adjusting for many confounding factors in the analysis. The most rational explanation for this, however, was residual confounding from other unknown poor prognostic features associated with open biopsy, rather than open biopsy itself.

2010-2019: Minimal disease and oncoplastic surgery

As screening mammography became increasing popular in Thailand, the proportion of ductal carcinoma in situ (DCIS) began to rise. CNB findings of DCIS were of some concern as some of these patients actually had invasive cancer. A study from Ramathibodi published in 2012 addressed the upgrading or upstaging rate of CNB-diagnosed DCIS.[34] There were 88 patients diagnosed as having DCIS with or without microinvasion on CNB seen between 2008 – 2010. There were 59 patients having CNB-diagnosed pure DCIS and 19 having DCIS with microinvasion. For those with pure DCIS on CNB, the upstaging rate to macroinvasive cancer (after removal of the whole lesion) was 19% (11/59), and to DCIS with microinvasion, 24% (14/59). The upstaging rate for DCIS with microinvasion to macroinvasive cancer was 34% (10/29). No clinical nor IHC factors were related the upstaging, probably because of the small sample size. Interestingly, if the final diagnosis was pure DCIS, no axillary lymph node metastasis was found, but with microinvasion, lymph node metastasis was detected in

5%. Invasive cancer had 24% axillary node involvement. Thus, SLNB might be omitted for microinvasive cancer if more supporting evidence exists, such as that from the 2005 study from Chiangmai University (see below in the abstracts section).

Non-palpable breast lesions were becoming more common with screening mammography as well. In a study from Chiangmai University Hospital, in 2015, 168 patients with non-palpable BI-RADS (Breast Imaging-Reporting and Data System) category 4 to 5 mammograms underwent image-guided excisions during January 2009 – December 2014.[35] The risks of malignancy in these patients were 20% for those with BI-RADS category 4 (29/145) and 77% for those with BI-RADS category 5 (10/13). Overall 254 lesions were biopsied. Of these, 48 were malignant. DCIS was seen in 58% of all malignant lesions (28/48). DCIS was fast becoming a common breast "cancer" in Thailand, approaching proportions seen in Western countries (a quarter of all breast cancers) at some institutions.

With smaller cancers and low-risk lesions, some of which were detected via screening mammography only, BCT was gaining ground in Thailand once again. In the previous decade, breast reconstruction was probably more common than BCT in Thailand. Now the numbers are reversed in some institutions, and at certain periods BCT constituted 50% of all breast cancer surgery. Oncoplastic surgery, a termed coined in Europe in the 1990's, was the name of an approach to BCS whereby oncologic principles are combined with plastic surgical techniques to aid wide excisions of cancer while maintaining or recreating acceptable cosmesis. After BCS, the ipsilateral breast may be smaller but minimally deformed using some tissue displacement method, or larger or of similar size using volume replacement, or the contralateral breast can be made smaller in a mammoreduction strategy. Once again, surgery for breast cancer was transformed, and the quality of life of the patient who may achieve long term survival became paramount.

A study from Udonthani Cancer Center reported a series of early stage breast cancer patients undergoing BCS with volume replacement using pedicled latissimus dorsi (LD) flap.[36] There were 28 patients who underwent BCS with LD flap volume replacement between 2008 – 2010. A similar group of 22 patients underwent BCS alone in the same period. The most common complication was seroma formation at the donor site area, but there was no flap necrosis or flap loss. After a median follow-up time of 28 and 30 months, there were 1 local recurrence in each group, and 2 distant recurrences in each as well. Thus, with a limited follow-up the oncologic safety was comparable between BCS with and without LD flap reconstruction. The cosmetic outcome was rated excellent by 79% of patients (22/28).

Another type of volume replacement is autologous fat grafting, the subject of a study from Siriraj Hospital published in 2014.[37] In 96 early-stage breast cancer patients who underwent BCS between January 2007 – December 2010, autologous free dermal fat graft (FDFG) was obtained from the patients' lower abdominal wall, and placed into the tumor cavity of the breast after wide excision. This was truly an innovative and elegant idea. The graft was cut from the lower abdomen, including the skin, and de-epithelialized, then shaped to fit the cavity and to maintain normal breast contour. The dermal side was placed on the bared pectoral muscles, so a vascular supply to the graft could be established. Most patients (93%) did not experience graft-related complications. All such complications were graft-related mastitis, requiring graft removal or re-excision in 4 patients (4%). Donor site complications occurred in 10 patients (10%) most of which were seroma formation. The presence of the graft did not delay adjuvant treatment and did not interfere with the detection of recurrent disease. In fact, ipsilateral breast cancer recurrence was found in 5 patients and distant recurrence in 3 after a median follow-up of 45 months. The disease-free survival was 84% at 33 months. Although there were major drawbacks such as the need for two surgical procedures (done simultaneously) at two sites, some significant inflammatory reaction, and graft viability issues, this ingenious method certainly merit more careful study or modifications of technique.

Another, similar idea is to use synthetic or biocompatible material to at least partially fill the tumor cavity, which would elicit less inflammatory response and is surgically less invasive. At present, no ideal material is available, but existing materials such as acellular dermal matrix grafts or polypropylene mesh can be used. Prior studies of such materials usually describe attempts to fill the whole cavity, which often induce inflammatory and infectious complications. The more recent idea is to use these materials as a temporary scaffold, to keep the cavity from collapsing and allow surrounding cells to migrate into the cavity and build new tissues. Thus, there is no need to use large quantities of foreign mate-

rial. However, the scaffold hypothesis is without solid supporting evidence (no pun intended), so more study is also needed.

The last refinement of the SLNB technique in the present review is the use of one step nucleic acid amplification (OSNA) assay. An excellent, detailed, and well-written article, from Siriraj Hospital and published in 2014, described a study combining molecular genetic techniques with minimally invasive axillary surgery, two great innovations from the final decades of the 20th century.[38] A sample of 111 SLN's detected using blue dye alone was taken from 62 early-stage breast cancer patients treated between July 2011 – January 2012. The idea behind the use of OSNA was to rapidly detect the presence of metastatic cells in SLN's by using real-time polymerase chain reaction (RT-PCR) techniques to identify tumor-specific genes or gene-related elements in the nodal tissue. In the present study that gene-related element was CK19 mRNA, which could be reverse-transcripted and amplified for detection. The Siriraj study compared OSNA to frozen section examination (and also imprint cytology), using permanent section as gold standard, to determine the relative accuracy of OSNA as an alternative method for intraoperative detection of cancer cells in SLNB specimens.

The SLN's were sectioned at 2 mm intervals, and alternate sections were sent for OSNA and the rest for histopathology. Positive results based on OSNA were defined essentially in terms of CK19 mRNA copy number with a cut-off value. After "discordant analysis" by the authors, the final accuracy measures of OSNA and frozen section examination, relative to permanent section, were: 86% and 93% sensitivity, respectively for OSNA and frozen section, and 93% and 100% specificity, respectively for OSNA and frozen section. It is debatable whether permanent section can be considered a true gold standard in the setting where, in theory, molecular techniques may be more sensitive. Nonetheless, for practical purposes such results are promising for OSNA. With an average reporting time of 47 minutes, OSNA is a viable alternative to intraoperative frozen section examination when the latter is not available. The cost, the need for laboratory space and equipment, and the skills needed to process the tissue and interpret the results will have to be considered. However, OSNA may be used to detect other cancer-related genes of interest, and the consequent research possibilities may make OSNA worth the cost.

As older ideas, techniques and practices are questioned and probed, improvements seem possible. Sometimes that might be the case and sometimes not. But this uncertainty should not detract the clinician-investigator from testing out some of the more interesting, low-risk ideas. An RCT from Surin Hospital was performed to compare the effects of lymphatic ligation versus no ligation in axillary lymph node dissection (ALND), on the occurrence of postoperative seroma.[39] This is an interesting and simple-to-conceive-but-not-to-implement idea. There were 68 breast cancer patients with positive SLNB treated between January 2014 – November 2017 who consented to participate in the study and were randomized to either the lymphatic ligation group or no ligation group (conventional surgery) during ALND. A total of 69 axillae were studied, 34 in the lymphatic ligation group, and 35 in the conventional group. Lymphatic ligation was described in the article but it was difficult to understand how it was actually done or how complete the ligation might be. Two vacuum drains were placed and the drainage was monitored till drain removal, about 2 weeks later (median duration of drainage were 11 days and 15 days for the ligation group and no ligation group, respectively). Total drain volumes were not statistically different between the two groups, though the median value was larger for the no ligation group (785 mL vs. 1,020 mL). Incidences of seroma formation after drain removal were 24% (8/34) and 29% (10/35) for the ligation and no ligation groups, respectively, which were also not statistically different.

This was the first properly conducted RCT on the subject of breast cancer to be published in the TJS, and the results should be valid, in principle. Thus, lymphatic ligation, if done correctly, likely has a small effect on the occurrence of seroma. But the current understanding is that serous fluid formation in ALND is mostly from an inflammatory reaction to surgery and not mainly from lymphatic leakage. This trial indirectly supports the latter hypothesis.

There are favorable histological subtypes of breast cancer with good prognosis, and treatment for these cancers should therefore be less aggressive. Recognized favorable subtypes include pure tubular, cribriform and mucinous carcinoma, among others. Papillary cancers, not to be confused with micropapillary cancer, can include tumors with invasive and non-invasive behavior. Encapsulated and solid papillary carcinoma have behaviors similar to that of non-invasive cancer and are recognized as favorable subtypes in all guidelines. But

papillary cancers with invasive features are not generally so recognized. A retrospective study from Ramathibodi Hospital, published in 2019, attempted to define the behavior of papillary cancers, and more specifically invasive papillary cancer.[40] There were 86 patients, with 64 (74%) having invasive papillary cancer. There were no recurrences nor deaths due to cancer after a median follow up of only 22 months. The study concluded that papillary breast cancers, including invasive types as well, might all have favorable prognosis. But this could be so at most only in the short term. Unfortunately, the study was also limited by diagnostic accuracy issues, with questionable diagnosis of invasive papillary cancer in some cases.

Radiotherapy for pN1 (number of positive axillary nodes between 1 to 3 on pathological examination) breast cancers has been on the rise in the past 5 to 6 years. A part of the reason for this trend must be the EBCTCG individual-patient data meta-analysis, published in 2014, supporting favorable long-term (up to 20 years) effects (e.g. increased patient survival) of radiation therapy on mastectomy patients with 1 to 3 positive axillary nodes. This trend is disturbing for several reasons, which we will not dwell on. But a study from Siriraj Hospital published in 2018 was a welcome rebuttal to this trend.[41] The study was a retrospective review of 158 breast cancer patients with tumor size less than 5 cm who had 1 to 3 positive axillary nodes. All were treated between 2000 – 2001, and followed for over 10 years (no exact duration was given). Overall survival and disease-free survival at 15 years were not significantly different between patients receiving or not receiving radiotherapy. However, there was a larger difference in disease-free survival between the two groups for patients with negative hormonal receptor status. Limitations of the study, of course, included the small sample size and the inevitable selection bias. But this result was in keeping with the common sense thinking that low-risk, hormonal positive patients can probably do without radiation therapy. Some of the recent perceived increase in ipsilateral arm lymphedema must at least be attributed to the increased use of radiation therapy, but are these increases justifiable in all cases?

The finding that locoregional therapy can affect long-term survival is in contrast to the predictions of the early dissemination theory of breast cancer. This is not to say that the theory is wrong, but that a more nuanced theory is needed to explain long-term observations. For example, instead of stating that the survival of the breast cancer patient is determined prior to surgery because of the presence of micrometastasis from the very beginning (if systemic treatment were not subsequently given), it is probably more accurate to propose that there might be multiple episodes of microdissemination. One such episode can occur during locoregional treatment failure, with more insidious or longer-term consequences.

The final set of 3 articles deal with reconstructive and oncoplastic surgery, all published in the 40th issue of the TJS (2019). These were all from Ramathibodi Hospital.[42-44] The practice reflected in these articles should represent similar practices elsewhere in Thailand. The first article was about an "in vivo" anatomical study of the deep superior epigastric artery (DSEA), one vital vascular structure to be aware of and preserved when a pedicled TRAM flap is harvested.[42] During hepatobiliary procedures on 7 patients, where upper abdominal incisions needed to be made, an anatomical dissection was carried out during the surgery. Prior informed consent was obtained from all patients. Various danger and safety zones were mapped and correlated with surface markings. It was hoped that this information would be useful in TRAM procedures on future patients. However, pedicled and free TRAM flaps are less frequently used today because of significant complications and morbidity, and difficulties of technique, requiring a steep learning curve. Breast reconstruction after mastectomy is currently dominated by implant-based procedures.

The second article was about a surgical technique, illustrated with actual cases.[43] The article detailed yet another volume replacement procedure in BCS, this time using local cutaneous rotation flaps. The description was very concise but the highlight was a set of clear, self-explanatory step-by-step photographs in color. The last article was also on a type of BCS oncoplastic procedure, a mammoreduction-based strategy.[44] It reviewed and described in some detail the principles of vertical scar mammoplasty, in the spirit of Lassus and Lejour. Information on the assessment and preparation of the patient, a brief set of operative instructions and the description of the more common operative and postoperative complications were all provided. Also, excellent step-by-step color photographs of actual cases were again included. The appearance of these articles was a sign of the increased popularity of BCT among breast cancer patients, as well as their desire for good cosmetic outcomes.

1980 – 2019: Abstracts from the annual congress of the RCST

In this section we review all the developments thematically, almost as a recapitulation of what was essentially provided in the published articles, but now culled from published abstracts of presentations made during the Annual Congress of the Royal College of Surgeons of Thailand (RCST) within the past 40 years. This is to do justice to the many surgeons and their great institutions whose work also contributed to the development of breast cancer surgery and treatment in Thailand. There were so many interesting accounts that we will confine ourselves to just briefly list some of them. We apologize if some contributions have been left out, not because of lack of importance but because of overlap or lack of information or simply because of inadvertent omission. The main problem with some abstracts is that very little detail is provided, and we did not attempt to determine whether any of these studies was eventually written up and published as a full paper. Some, however, were written up and published in the TJS, and thus are not listed in this section. Here, we use the words "published" and "reported" synonymously, referring to the publication of the abstract in the TJS. The actual public presentation of the corresponding study was usually given a year earlier.

Basic science and tumor markers in breast cancer

A study of the role of dendritic cells in the development of breast cancer published in 2001, from Phramongkutklao Hospital, seemed to show reduced ability of these cells to stimulate T cell proliferation and mixed lymphocyte reaction in breast cancer patients as compared to non-cancer controls. A study from Chulalongkorn Hospital examined the tumor markers CA 15-3 and CEA as predictors of recurrence after breast cancer treatment, published in 2013. Increases in the value of both tumor markers (above a certain cut-off value) were associated with larger tumor size, nodal involvement, and higher cancer stage prior to treatment, but also with recurrence and metastasis after treatment. It was concluded that tumor markers should be used for post-treatment monitoring. In 2013 an abstract was published of a study from Siriraj Hospital determining the relation between vascular endothelial growth factor (VEGF) polymorphism and breast cancer susceptibility and aggressiveness. Genotyping of the VEGF gene was done on 483 breast cancer patients and 524 controls. Two VEGF genotypes were associated with more aggressive cancers as well as higher risk of having breast cancer, and one had higher VEGF mRNA expression, which in turn was also associated with more aggressive cancer. A study from the Thai NCI published in 2014 examined the stem cell markers CD44+/CD24-/ALDH1 in 140 triple negative breast cancers. There were no clear relationships between the presence of these markers and other poor prognostic features. A study from Siriraj Hospital published in 2019 found high expression of prolactin receptor (PRLR) via IHC in breast cancer tissue to be associated with lower overall survival. This study was performed on 237 breast cancer patients and 119 controls, and also found certain PRLR genotype to be associated with poorer survival as well.

Adjuvant systemic therapy in breast cancer

Adjuvant chemotherapy was used in a series of 47 breast cancer patients from the Thai NCI (but the surgery-only group had slightly better 5-yr survival) and a successful use of neoadjuvant chemotherapy was reported from Siriraj Hospital; these were both published in 1985. By 2001, a review of systemic treatment for breast cancer from the UK published as an abstract in the TJS, mentioned the use of vinorelbine, taxanes, and trastuzumab in the treatment of metastatic breast cancer, and even high-dose chemotherapy with bone marrow transplantation (which was deemed of limited use by then). Neoadjuvant chemotherapy was also mentioned as a means to BCT. A case series from Prince of Songkhla University, published in 2004, used letrozole as a second line endocrine therapy for metastatic breast cancer after failure of tamoxifen in 7 patients.

Breast cancer survival, incidence and risk factors

In 1989 the Thai NCI reported, in 107 breast cancer patients, 5-year survival rates of 91%, 83%, 38% and 0% for stages I, II, III and IV disease, respectively, and concluded that MRM was the method of choice for the treatment of operable breast cancer. Siriraj Hospital published in 1993 a study of characteristics of 890 breast cancer patients and their treatment. Symptoms were present (palpable mass) in 77% of patients, with half having palpable axillary node metastasis. Stage II disease was present in 55% of patients, MRM was performed in 88%, and chemotherapy was given in 26%. A case-control study of the effect of hormonal replacement therapy (HRT) on breast cancer risk (623 cases and 679 controls),

from Siriraj Hospital, was published in 2002, and did not show a significant association on a multivariable analysis. From the Prince of Songkhla University, a study was published in 2005 examining the relationship between body mass index and breast cancer survival, but found no such relationship in 1,153 breast cancer patients. Another study from Prince of Songkhla University reported in 2007 found the adjusted breast cancer incidence for Songkhla Province in 2005 to be 24.3 per 100,000, which was the highest of all cancers in women, followed by that of uterine cervical cancer, at 16 per 100,000. The incidence of breast cancer in Thailand has been the highest of all cancers in women since 2001. Younger (<40 years) breast cancer patients (n=298) were compared with older (> 40 years) breast cancer patients (n = 1,062) in terms of 5-year disease-free and overall survival, in yet another study from Prince of Songkhla Hospital, published in 2013. Despite higher proportions of lymphovascular invasion and negative ER status in the tumors of younger patients, all outcomes were similar between the two age groups, with similar types of surgical procedures, types and frequency of adjuvant chemotherapy and hormonal therapy, and similar frequency of radiotherapy being provided to both. Finally, also from Prince of Songkhla University, and published in 2013, 152 node-negative breast cancer patients followed for a median of 52 months tended to have higher recurrence if younger than 50 years with HER2 overexpressed tumors (these results were not statistically significant).

Immunohistochemistry and diagnosis of breast cancer

A study from Chulalongkorn Hospital, published in 1991, compared ER assay results between biopsy and mastectomy specimens from 20 patients and concluded that ER assay from mastectomy specimens was more reliable. Another study from Chulalongkorn Hospital in 1993 evaluated the accuracy of FNAC in the diagnosis of breast cancer in 414 patients with available histological data. The sensitivity was 92% and specificity was 96%. A similar study on the accuracy of FNAC in 78 palpable breast lesions was published in 1999 from Ramathibodi Hospital, with similar conclusions. The usefulness of mammography in breast cancer patients was underscored by the detection of bilateral breast cancer in 6 of 161 patients, all without contralateral breast symptoms, in a study published in 1994 from Samitivej Hospital. A study from Maharaj Nakorn Chiangmai Hospital published in 2000 could not establish any relationship between clinical information, including TNM cancer staging, and hormonal receptor status in 355 breast cancer patients. A similar study from Prince of Songkhla University published in 2003, with a sample of 374 patients, found a positive correlation between hormonal receptor positivity and age, but no association between hormonal receptor status and TNM staging or axillary lymph node status. In 2003 as well, a study of 109 breast cancer patients with known HER2 expression status, examined the latter's association with certain risk factors. This study was from Phramongkutklao Hospital, and the prevalence of HER2 overexpression in the study was found to be 39%, but without any apparent association between HER2 status and any clinical, anatomical, pathological and treatment factors. Another study published in 2008, also from Phramongkutklao Hospital, demonstrated concordance of IHC markers between the primary tumor and metastatic tumor in the axillary nodes in 28 breast cancer patients. In another series of 442 breast cancer cases from the same institution and published in the same issue, HER2 overexpression was now seen in 18% of cases, with the same proportion (18%) of triple negative cancers. Some poor-risk clinical and IHC characteristics were related to these subtypes. A study from Thammasat University published in 2019 estimated the positive predictive values (for breast cancer) of certain patterns of calcifications seen on mammograms in a sample of 62 patients (with 72 lesions) who underwent needle localized excision. It was found that amorphous, fine pleomorphic and fine linear branching calcifications were associated with positive predictive values for breast cancer of 38%, 42% and 33%, respectively.

Interesting clinical studies and quality of life

An interesting study using a small 3-mm endoscope (ductoscope) to explore the inside of cystic breast lesions, from Vajira Hospital, was published in 2000. There were 4 patients in the study, all of whom underwent the procedure under local anesthesia, and biopsy under direct vision through the scope was done in one patient. An RCT comparing one (axillary drain only) and two drains after MRM in 60 breast cancer patients from Prince of Songkhla University and published in 2001 seemed to show no significant differences between the two groups in terms of drainage volume and occurrence of seroma or hematoma. Another RCT comparing compressive brassiere to conventional (plaster-based) compression

dressing after MRM in 56 patients, form Vajira Hospital and published in 2005, also showed no significant difference in the occurrence of seroma. Quality of life of breast cancer patients who underwent various surgical procedures was measured using validated questionnaires including WHO QOL-BREF and Functional Assessment for Cancer Therapy G and B Questionnaires, which were reported from Vajira Hospital and Siriraj Hospital in 2009. A study using talcum powder (applied to the mastectomy cavity) to reduce drainage after mastectomy was reported in 2014, from Ramathibodi Hospital. In an unreported number of patients randomized to talc or no talc group, it was found that talcum powder did not significantly reduce overall drainage at 2 weeks. A study comparing traditional electrosurgery with a low thermal system (PEAK Plasmablade, Metronic Co.) for dissection during mastectomy was reported in 2018 from Siriraj Hospital. This was an RCT with 50 patients, and no significant differences were found in terms of blood loss, postoperative pain, drainage volume, seroma formation and other complications, between the two groups.

Axillary surgery and SLNB

SLN imprint cytology for intraoperative detection of metastatic cells was reported in 1999 from Siriraj Hospital, in 55 patients. The sensitivity was 82% and specificity was 100% compared to routine H&E. Factors related to SLN identified with isosulfan blue dye alone was also examined. It was found that surgeon experience was the most important factor. A study from Ratchaburi Hospital reported in 2005 showed, in a sample of 16 clinically node-negative breast cancer patients, that SLNB under blue dye alone had a 100% identification rate, and a false negative rate of 6.25% (1/16). A study of 60 breast cancer patients, published in 2005, from Chiangmai University, found T1a tumors (size less than 5 mm) to have no axillary lymph node metastasis (0/2), and hence suggested that axillary surgery for these lesions might be omitted. A comparative study of 112 pathological node negative breast cancer patients who underwent ALND and 85 similar patients who underwent SLNB alone was conducted at Siriraj Hospital and published in 2007. After at least a year of follow up there was 9.8% increase in ipsilateral arm circumference in the ALND group, as compared with 1.2% in the SLNB group. The feasibility of local anesthesia (LA) for SLNB was studied at Ramathibodi Hospital, on 39 breast cancer patients who underwent SLNB under LA, compared with 107 similar patients who underwent SLNB under general anesthesia (GA). The study was published in 2007, and showed similar identification rates and numbers of SLNs removed between the two groups, with similar ratios of positive nodes. No patient in the LA group required GA to complete the procedure. From Phramongkutklao Hospital, in a study reported in 2009, there was comparable accuracy between frozen section and cytological methods of intraoperative detection of SLN metastasis in 166 nodes examined. Statistical predictive models for the presence of metastasis in non-SLNs were developed and published in 2016, from Siriraj Hospital. The area under the ROC curve (AUC) was reported to be between 0.801 to 0.831 in the validation data set. From the same institution, reported in 2018, the addition of tumor load as determined by OSNA was used to create yet another predictive system with a similar AUC. A study from Chulalongkorn Hospital reported in 2018 used a multigene test risk score for disease recurrence (PAM50 ROR) to predict axillary lymph node status in hormone positive, T1 breast cancer patients. There were 34 patients and the AUC was 0.75, and a cut-off value for the score was determined. Finally, in 2018, Prince of Songkhla University reported the use of indocyanine green fluorescent imaging for the detection of SLNs.

Breast conserving surgery and oncoplastic surgery

BCT with ALND was reported in 24 patients from the Thai NCI in 1987 without long-term follow-up; and again in 1989 with 33 stages I to II patients. In a study from Siriraj Hospital, published in 2012, risk factors for recurrence after BCT ("lumpectomy") for DCIS was examined in 135 patients treated between 1999 – 2010. Positive or close surgical margin was the most important risk factor for recurrence. A study from Chulalongkorn Hospital reported in 2017 looked at complications associated with using intraoperative radiation therapy (IORT) to boost the tumor bed in 109 patients undergoing BCS with IORT (Intrabeam System). Complications specific to IORT were not clearly reported. In a study examining residual cancer after BCS, reported in 2017 from Ramathibodi Hospital, in patients with 143 primary breast cancer resections who had secondary surgery as well, residual cancer was found even after free margin excision in as many as 12% (2/25). But conversely, with involved margins, as many as 44% (28/64) did not have any residual cancer. A portable machine with software

for 3-dimensional scanning of intraoperative breast specimens using x-rays was developed by researchers from Prince of Songkhla University in collaboration with the NSDTA, Thailand, reported in 2018. The machine, a prototype ("MiniiScan"), was able to detect lesions and determine resection margins as well as conventional mammography but took a much shorter time.

Breast reconstruction

A report of a transverse rectus abdominis "island flap" for reconstruction after MRM was published in 1987; this was probably a variation of the pedicled TRAM flap. In 1990, two reports from Siriraj Hospital described the first use of pedicled TRAM flap (in 1987), which was done for reconstruction after chest wall resection in 2 cases; thereafter the TRAM flap was used for immediate reconstruction in 5 patients with stages I to II breast cancer. Also described were 2 patients who underwent delayed reconstruction using the TRAM flap, and a prothesis-based procedure ("tissue expander") was used for immediate reconstruction after mastectomy in 2 further patients. Free TRAM was described for 2 breast cancer patients after mastectomy from Ramathibodi Hospital and was published in 1991. Mammoreduction, based on the inferior dermoglandular pedicle, was used for the contralateral breast in a case of immediate reconstruction for ipsilateral breast cancer, as reported from Siriraj Hospital in 1991. A review of postmastectomy breast reconstruction from Ninewells Hospital in Dundee, Scotland, was published in 2001, in which the dominant reconstruction method was the TRAM flap. A case of Deep Inferior Epigastric Perforator (DIEP) free flap used in a breast cancer patient was reported from Siriraj Hospital in 2001. Extended LD flap as the sole reconstructive modality was reported for 46 lesions in 41 patients in 2007, from Ramathibodi Hospital. Good results with minimal morbidity was observed in the short-term (median follow-up of 8 months). Good short-term results (14 months) for immediate pedicled TRAM flap reconstruction was reported for 14 patients from Ratchaburi Hospital in 2008. A study from Chulalongkorn Hospital reported in 2016 looked at the discrepancy between clinical TNM staging and pathological TNM staging in 87 breast cancer patients who underwent mastectomy with immediate reconstruction. The most marked discrepancy was for N staging, and it was suggested that further preoperative imaging study or cytological diagnosis might be used to reduce the discrepancy to better plan reconstructive procedures. A comparison of complications and recovery after surgery between extended LD and LD with prosthesis for breast reconstruction in 31 breast cancer patients was reported from Ramathibodi Hospital in 2019. Both procedures had similar complication rates but LD with prothesis had slightly faster recovery. Also from the same institution in the same year, 63 breast cancer or high-risk patients who underwent 65 nipple sparing mastectomies with reconstruction were followed for evidence of local regional recurrence. After a mean follow-up of 40 months, 3 patients who had cancer experienced locoregional recurrence, 2 in the regional nodes and one had Paget's disease of the nipple.

2021: Conclusion

We have traveled quite far in the past 40 years. The TJS perspective of breast cancer is unavoidably biased but the view has been incredibly wide. We have seen changes in the theory and practice of breast cancer surgery, the rise of adjuvant therapy including chemotherapy, hormonal therapy, targeted therapy and increased use of radiotherapy. Molecular pathology and diagnostic radiology were also included. We also saw dramatic changes in diagnostic strategies and the approach to prognosis, with more empowerment to patients. There were unfortunately too few contributions from other disciplines, but that is in the nature of the specialty journal. While there were real improvements in all aspects of breast cancer, whether it be more accurate diagnosis, the identification of important prognosticators, the introduction of less invasive and less disfiguring surgery, and the dramatic increase in breast cancer survival as well as the inclusion of patients and their families in the therapeutic process, there are still so many remaining issues that require more thought and creativity for their resolution. The current "theory of breast cancer" is inadequate. Why is breast cancer on the rise? We need better diagnostic technology (better accuracy), more precise surgery and systemic therapy suited for the individual patient and her disease ("precision medicine"). Are we doing too little in certain areas (primary and secondary cancer prevention) or too much in others (overdiagnosis and overtreatment)? Are we overemphasizing the seriousness of some conditions (certain types of DCIS), alarming the public with an iatrogenic rise in cancer incidence and then inadvertently creating a sense of achievement by overtreatment? How will we use proven innovations in

a cost-effective manner in an efficient breast cancer care system? With so many questions to ask and countless ways to answer them, there is always a place to publicize your ideas and we, at the TJS, will be ready and more than happy to consider your contributions. Welcome to the next 40 years of the TJS, at least!

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