



Review Article

Experts' Opinions Progress and Trends in the Surgical Management of Breast Cancer in Taiwan

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Abstract

Objective: Radical mastectomy was first described by Halsted almost 130 years ago, and has been applied as a treatment strategy in Taiwan since the middle of the 20th century. However, due to the development of nonsurgical treatment modalities, the management of breast cancer has undergone tremendous change. This study examined Taiwanese publications between 1965 and 2020 to identify trends in the surgical management of breast cancer. **Data Sources:** We searched for papers published by authors from the Taiwan Breast Cancer Society and 18 tertiary referral medical centers in Taiwan. **Study Selection:** After excluding papers completely unrelated to surgery, there were 50 English language articles and 5 Chinese language articles available for historical review. **Results:** This nationwide survey of breast cancer over the past 40 years revealed the following trends in surgical management. (1) As detection rates of early-stage breast cancer increased, the amount of removed breast tissue decreased, with a corresponding reduction in percentage of total mastectomy. (2) Axillary sentinel node biopsy should be routinely performed in early breast cancer rather than axillary lymph node dissection without lymph node metastasis. (3) Since the development of gonadotropin antagonist, bilateral oophorectomy is no longer needed in the early stage in premenopausal population. Further pregnancy is allowed if the cancer is well controlled. (4) Breast reconstruction may be recommended, depending on the patients' preference, after total mastectomy for malignancy. **Conclusion:** Although this review of the literature may not be complete, the trends revealed in our analysis indicate that surgical management of breast cancer has become more patient-friendly, humanistic, and feasible in Taiwan. Currently, breast cancer may not have a poor outcome if the tumor can be detected at an earlier stage.

Keywords: Breast cancer, life quality, reconstruction, sentinel node biopsy

INTRODUCTION

The incidence of breast cancer in Taiwan is increasing, and surgical resection remains a potentially curative modality.^[1-3]

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The concept of total removal of breast cancer tissue to provide a wide safety margin was proposed by Prof. Halsted in 1894.^[4] Radical mastectomy (RM) has since become the gold standard treatment of breast cancer worldwide.^[5-10]

RM involves removal of tissues and organs over the entire anterior chest wall, including whole breast tissue, pectoral muscles, and possibly invaded lymphatic ducts and lymph nodes.^[4] It usually results in an undesirable aesthetic appearance of the chest. Therefore, a lower extent of resection in the surgical treatment for breast cancer was attempted to preserve more tissues and organs of the chest wall, and similar long-term outcomes were achieved. This approach also avoided the complications and other adverse effects caused by RM.^[4-11]

In Taiwan, radical surgeries were also adopted by Taiwanese surgeons in the early 20th century.^[5-7] In 1967, Prof. David Habib, a professor of surgery at Columbia University, New York, USA was invited to be a consultant surgeon at Taipei Veterans General Hospital (VGH), Taipei, Taiwan. He performed breast cancer surgery on Madam Jiang, First Lady of Taiwan, R.O.C.,^[12] and was the first to introduce the concept of hormone receptors in breast cancer in Taiwan. He was critical of studies on breast cancer in Taiwan that he deemed to be “out-of-date” and far behind the level of the developed countries,^[13] and subsequently encouraged and persuaded Taiwanese surgeons to visit the USA for further education and training related to breast cancer management. Hence, Prof. KS Lu, the Head of the Surgical Department at Taipei VGH assigned a young surgeon to receive breast cancer training at Columbia University.

Thereafter, the first Taiwanese report on the use of hormone receptors and therapy for breast cancer revealed markedly improved outcomes.^[13] Liu *et al.* used the dextran-coated charcoal method to determine the estrogen receptor (ER) concentration of cancer cell cytosol,^[13,14] and subsequently also measured the concentration of progesterone receptor (PR) in breast cancer cells by a similar method.^[14] Three years later, surgeons at National Taiwan University Hospital also published a paper on the presence of ER and PR in breast cancer cells.^[15]

Numerous articles have described the strategic changes in breast cancer surgery in Taiwan over the past 60 years.^[5-17] However, the improved results in breast cancer treatment cannot be solely attributed to surgery. Advances in various other medical specialties over the past 20 years have also contributed to the improved treatment outcomes of breast cancer^[3,4] including nationwide breast cancer screening programmes,^[2,18] improved diagnostic tools,^[18] surgical equipment,^[6,19] chemotherapy,^[19,20] radiotherapy, hormonal therapies, immune therapies, and target therapies.^[10,20] However, the aim of this review was to analyze the progress and trends of the changes in surgical management for breast cancer in Taiwan over the past 60 years.

At the time of writing (June 2021), there are 18 qualified tertiary referral medical centers in Taiwan, which have been certified by the Ministry of Health and Welfare. Among them, 11 hospitals were built more than 35 years ago (before 1986).

The Taiwan Breast Cancer Society (TBCS) was established in December 1998, and the Taiwan Oncoplastic Breast Surgery Society (TOPBS) was founded in 2016. At the end of 2020, eight experienced surgeons with expertise in breast surgery were elected as chairpersons of the TBCS, and two experts were elected as chairpersons of the TOPBS. These individuals are all working at tertiary medical centers in Taiwan.

In order to observe the historical progress in the surgical management of breast cancer, we searched for studies related to surgical management for breast cancer using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.^[21]

We searched for English articles using PubMed, Google Scholar, Embase, and the Cochrane Library database to identify papers on surgery for breast cancer. The keywords used in the searches were “breast cancer,” “mastectomy,” “sentinel node biopsy,” “breast reconstruction,” and “pregnancy.” Papers by authors from any of the aforementioned 18 tertiary referral medical centers in Taiwan were identified and included in the analysis. Moreover, Google Scholar was used to search for Chinese language articles using similar keywords.

After three expert breast surgeons, CC H, GS L, and CC Whad reviewed these articles, the contents of the articles mentioning surgical treatment of breast cancer were included in this review. Articles which were totally unrelated to surgical treatment for breast cancer or any Chinese language study that was a duplicate of an English language version of the same study were excluded from the analysis. A total of 50 English and five Chinese articles were included in this review [Figure 1].

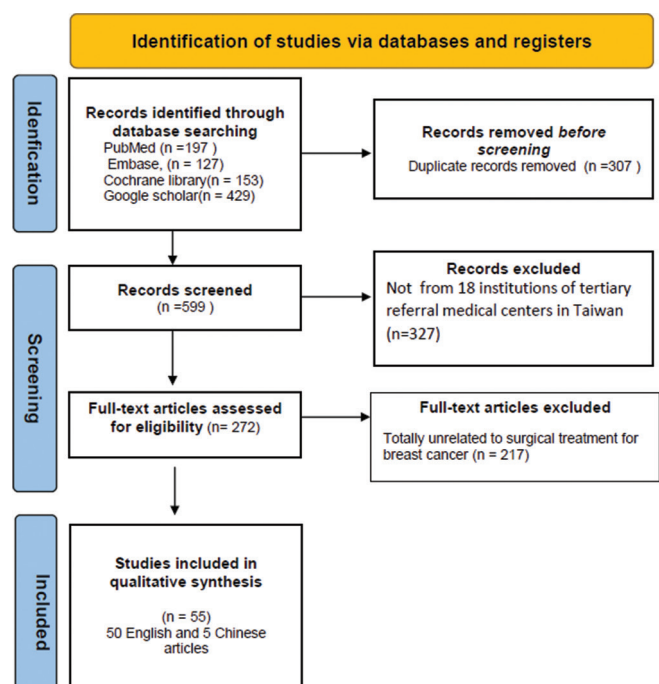


Figure 1: Flow chart of the search methods

THE STRATEGIC CHANGES OF BREAST TISSUE RESECTION EXTENT

Breast tissue is located in the superficial layer of the superficial pectoral fascia [Figure 2]. With the removal of a deep layer of superficial pectoral fascia, the whole breast tissue can be completely removed.

Halsted originally proposed that cancer may invade and spread deeply into the pectoral muscles through the deep fascia and metastasize to the axillary lymphatic ducts or through the internal mammary lymphatic channel into the thoracic cavity.^[4] Cancer may also spread into the upper abdominal rectus muscle sheath, and it can then deeply invade into the intraperitoneal cavity. Lung metastasis can also occur through the subternal lymphatic channels, leading to systemic metastasis.^[22] Halsted, therefore, proposed that RM should be performed by removing all of the breast tissue underlying the pectoral muscles and any possible route of spread (i.e., the lymphatic channels).^[4]

Breast tissue is composed of many lactiferous acini, each consisting of lactiferous lobules and lactiferous ducts.^[22] Therefore, the main breast malignant components are ductal carcinoma and lobular carcinoma.^[23,24] When carcinoma cells are confined to the epithelial layer without penetration of the basement membrane or if there is no metastasis to other organs, this situation is termed “carcinoma *in situ*.”^[24] In contrast, when cancer cells pierce the basement membrane and metastasize to other organs or tissues, the situation is termed “infiltrating (or invasive) carcinoma.”^[23,24] Thus, the main breast carcinomas are “ductal carcinoma *in situ* (DCIS),” “infiltrating ductal carcinoma,” “infiltrating lobular carcinoma,” and “lobular carcinoma *in situ* (LCIS).” However, LCIS is not considered a true malignancy as it has a benign clinical course, although its histological picture is malignant.^[23,24]

Theoretically, DCIS can be totally removed without residual cancer if the surrounding breast tissue can be grossly removed with a narrow safe margin; this procedure is termed “RO

resection.”^[23] The cancer can be “cured” by local tumor resection, without the need for additional procedures.

In contrast, the prognosis of infiltrating breast cancer after RM is not always satisfactory,^[24] and more extensive procedures are recommended. In 1920, some surgeons advocated more extensive surgery for breast cancer to obtain a grossly curative surgery.^[23] The extent of lymphadenectomy was enlarged to the affected side of the neck in the 1940s. Thereafter, further extension to the internal mammary lymphatic chain was suggested in the 1960s.^[25] This procedure was termed “extended RM.”^[25] However, the long-term results of extended RM were dismal in patients with advanced-stage breast cancer.^[24]

More than 4 decades ago, Auchincloss *et al.* demonstrated a “modified RM” (MRM) procedure, which included preservation of the pectoral muscles.^[25] They recommended that to avoid further atrophy of the pectoral muscles after MRM, the pectoral branch of the thoraco-acromion artery should be preserved. The lymphadenectomy procedure is similar to RM.^[26] Patey *et al.* suggested another modified procedure of RM, which involved the preservation of the pectoralis major with removal of the pectoralis minor and a similar extent of lymph node removal to that of RM.^[6] Removal of the pectoralis minor facilitates the clearance of axillary nodes and the lymphatic ducts.^[25]

Although the term “sarcoma” is used, in most cases “cystosarcoma phyllodes” is actually a benign tumor.^[27,28] The tumor can be treated by local tumor excision with a narrow safe margin, without lymph node dissection. However, a malignant phyllodes tumor may occur when the fibrous tissue of the breast becomes malignant.^[27,28] Its behavior is similar to “fibrosarcoma,” and it spreads by a hematogeneous route, rarely by the lymphatic ducts. Therefore, a simple mastectomy with a safe margin is sufficient for this cancer.^[27,28]

Mondor’s disease, another palpable breast mass, is due to thrombophlebitis of the breast blood vessels. It has been well established that this is a benign condition and does not require surgery. Occasionally, it may be accompanied by cancer, but the incidence is very low.^[29]

The broadly held view among oncologic surgeons is that an overly aggressive surgical approach may not be absolutely necessary in patients with early-stage breast cancer.^[3,11,30-32] For example, for a breast cancer measuring <2 cm, the incidence of local tumor infiltration and lymph node metastasis is low.^[24] Therefore, some surgeons treat a small breast cancer (size <2 cm) located at the outer upper quadrant of the breast by quadrantectomy (removal of 1/4 of all breast tissue).^[3,11,30,31] Although a tumor may be located in the inner part of the breast, it has recently been shown that quadrantectomy using oncoplastic techniques^[11] or endoscopy-assisted techniques^[30,31] can be achieved.

As mentioned above, Taiwanese surgeons founded the TOPBS in 2016. In the late 20th century, a small breast cancer could be treated by breast-conserving surgery.^[25,30-32]

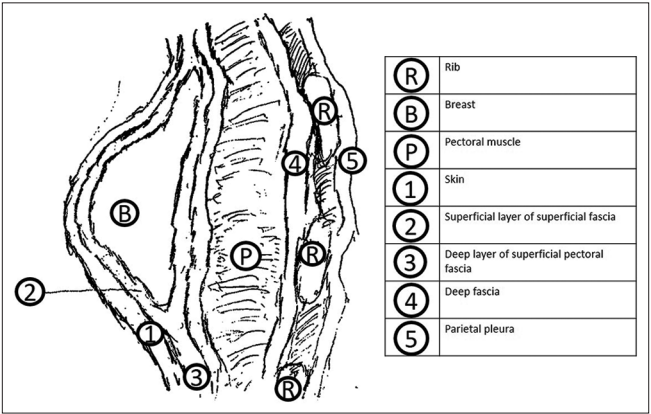


Figure 2: Schematic illustration of a sagittal section of a woman’s anterior chest wall (2 cm lateral to the midclavicular line). B: breast, P: pectoral muscle, R: rib. 1: Skin, 2: Superficial layer of superficial pectoral fascia, 3: Deep layer of superficial pectoral fascia, 4: Deep fascia, 5: Parietal pleura

CONCEPT OF SENTINEL NODE IN BREAST CANCER

The number of metastatic lymph nodes, tumor size, and histological differentiation pattern are independent prognostic factors for breast cancer after surgery.^[24] Liao *et al.* found that the rate of positive metastatic lymph nodes was a factor in breast cancer progression.^[5] These findings suggest the necessity of lymphadenectomy in breast cancer surgery to detect the actual status of lymph node metastasis, especially in the earlier stages (small size tumor without gross lymph node metastasis).

The prognosis of breast cancer is largely related to the status of lymph node metastasis.^[5,7,8,24] Nationwide breast cancer surveillance in Taiwan has led to an increased detection of early-stage breast cancer.^[2,20] Because of the low node metastasis rate of small tumors and the lack of metastasis in a DCIS, an extensive surgical procedure appears to be unnecessary in early-stage breast cancer. In contrast, extensive surgery cannot ensure a “cure” for advanced-stage breast cancer. The sentinel lymph node concept over axillary areas was developed for the staging of breast cancer.

The direction of lymphatic flow of the breast may be similar to the direction of venous return of the axillary vein.^[22,33] Anatomists and pathologists have defined the possible stages of lymph node metastasis in breast cancer. Lymphatic drainage of the breast is mainly via axillary nodes, and lymphatic channels exist along the axillary vein toward the heart and systemic circulation.^[33] Part of the lymphatic flow at the medial side of the breast drains into the ipsilateral internal mammary chain.^[22] Thus, metastasis of lymph nodes and lymphatic ducts in breast cancer is in a similar direction to this lymphatic flow.^[33-42]

The lymph nodes, which are located between the medial border of the latissimus dorsi and the lateral border of the pectoralis minor, have been defined as Level I lymph nodes; the lymph nodes behind the pectoralis minor have been defined as Level II lymph nodes (also called Rotter's nodes), and the lymph nodes from the medial border of the pectoralis minor to the sternoclavicular junction are defined as Level III lymph nodes.^[22] Level III lymph nodes are recognized as “epical nodes,” and they are the highest level lymph nodes to be removed in Haslsted's RM procedure.^[4,6,22] The three levels of lymph nodes are defined as regional lymph nodes by the AJCC-TNM cancer staging system (8th edition).^[43] Lymph node metastasis outside this area is defined as “distant metastasis.”^[43] Usually, the sequence of metastasis is from Level I to III. If a lower-level node has no metastasis but a higher-level node does have metastasis, this is known as “skip metastasis,”^[22,33-43] which is a rare condition in cancer.^[22-24,33,43]

The concept of sentinel nodes was first demonstrated in melanoma of the extremities,^[8,33] and it altered the surgeon's concept of lymphadenectomy extension of breast cancer.^[9,33] Halsted's original demonstration insisted that the territory of lymph nodes below the axillary vein should be totally removed. In a lymphadenectomy procedure of this type, the

thoracodorsal neurovascular bundle and long thoracic nerve should be preserved.^[25] The serratus anterior muscle should also be preserved to avoid causing chest wall deformity.^[25]

If the first station lymph node does not show metastasis, it can be reasonably expected that no further lymphatic metastasis of breast cancer is likely.^[8,33] Radical lymph node dissection for breast cancer may not be necessary in this circumstance. If the first station lymph node tests negative before breast cancer resection, axillary node dissection can be omitted because no lymph node metastasis has occurred.^[8,22,33-42] This first station lymph node is termed the “sentinel lymph node” of breast cancer.^[8,22,33-42]

Hence, detection of the location of the sentinel node is a crucially important issue. In Taiwan, Liu *et al.* injected a radioisotope, technetium 99^m-labeled human albumin around a breast tumor.^[33-36] The lymph node containing the radioisotope can be considered a tracer of the sentinel node. This node can be removed under the guidance of a gamma-detection navigator.^[33-36] Liu's team also found that using a large colloid albumin particle may increase the sentinel node detection rate during surgery.^[34] Hsieh *et al.* analyzed the studies conducted by Liu *et al.* and observed that the incidence of skip metastasis was 7.4% (in their first 91 patients).^[36] With increasing experience, the rates of skip metastasis gradually decreased in their subsequent reports^[8,35] and in other investigations in Taiwan.^[39-42] Using a similar injection method, Chang *et al.* demonstrated that a peritumoral or subareolar injection of radioisotope could achieve a similar success rate of sentinel node detection.^[37] By employing dynamic lymphoscintigraphy, Chen *et al.* in Kaohsiung improved their success rate of sentinel node detection.^[39]

Regarding research conducted by other surgeons in Taiwan, Liu *et al.* used activated carbon particle emulsion as a tracer with a similar sentinel node detection rate. In addition, Yu *et al.* precisely predicted positive metastasis of nonsentinel nodes using a blue dye injection of grossly negative sentinel nodes.^[40] They added intraoperative ultrasonography to enhance the detection rate after neoadjuvant chemotherapy for relatively advanced cancer.^[20] Yu and Liu reviewed seven studies on sentinel node detection rate in Taiwan to analyze the sentinel node biopsy accuracy. The number of patients included in their meta-analysis was 2056, and the accuracy rates ranged from 86.2% to 99%.^[41]

Thus, mapping of sentinel nodes in breast cancer surgery can clearly demonstrate their location. Practically, the pathological diagnosis of sentinel nodes can be obtained from frozen sections by experienced pathologists during surgery.^[36] If the microscopic diagnosis of a sentinel node is negative, further systematic lymphadenectomy procedures can be terminated.^[8,33-42]

According to the concept of radical surgery proposed by Halsted, the lymph nodes in the affected area (anterior chest wall below the axillary vein) should be totally removed.^[4] As

a result of this dissection, the lymphatic flow may become interrupted and stagnate. Lymphedema occurs after a long period following axillary lymph node dissection.^[26,44] The condition of lymphedema will be more severe when radiotherapy is added after RM or MRM.^[3,26] In addition to causing an undesirable aesthetic outcome, the activity of affected upper limbs may also be impaired.^[44] Although some investigators have noted that manual disease procedures may be beneficial, it is difficult to completely relieve edematous symptoms.^[26] Moreover, long-standing lymphedema (usually >10 years) in endothelial cells of the vessel wall of an affected limb may cause degeneration, and when they continue to degenerate, they may even become malignant. Thus, an aggressive malignant tumor, i.e., angiosarcoma may develop.^[44] This cancer is highly lethal and patients do not survive for longer than 3 years, even after limb amputation.^[44]

To reduce the incidence and severity of this lymphedema, a less extensive axillary lymphadenectomy has been recommended. The American Society of Clinical Oncology recommended sentinel node biopsy in 2002. In 2016, the TBCS and the Ministry of Health and Welfare stipulated that the rate of sentinel node biopsy in patients with early breast cancer should approach 100% in tertiary referral medical centers and breast cancer training centers. At present, sentinel node biopsy for grossly negative metastatic lymph nodes is the gold standard in Taiwan.

REDUCTION OF ANTI-ESTROGEN SURGICAL PROCEDURES BY SELECTED ESTROGEN RECEPTOR MODULATOR

It is well known that some sex hormone-dependent malignancies can be treated by hormone deletion procedures.^[10,14,23,24] Previously, bilateral oophorectomy was performed for hormonal deletion in breast cancer therapy. An anti-hormone surgical procedure was first performed by bilateral orchiectomy for male prostate cancer. Thereafter, in order to achieve total hormone ablation, bilateral oophorectomy for premenopausal women with breast cancer and bilateral orchiectomy for male breast cancer were also suggested in breast cancer therapy.^[8,14] For postmenopausal women, some surgeons even perform bilateral adrenalectomy for total depletion of estrogen effects.^[14] However, the side effects of bilateral adrenalectomy are more troublesome.^[4]

The adrenal gland consists of an outer cortex and inner medulla. Histologically, the adrenal cortex consists of three zones: zona granulosa, zona fasciculata, and zona reticularis. These three zones separately secrete hormones: mineralocorticoids, glucocorticoids, and androgens. The adrenal medulla secretes catecholamines (epinephrine and norepinephrine). Androgens may be converted to estrogen through an aromatase.

In addition, hormone therapy of breast cancer can also destroy all estrogen effects from hypophysis, ovaries, and adrenals. Supplementation of hormones other than sex hormones is also problematic. The procedure of bilateral adrenalectomy

is somewhat complex with a higher surgical complication rate. This procedure has virtually been abandoned as an anti-estrogen therapy^[14] since the development of Tamoxifen (a selective ER modulator) in 1977.^[8,45,46] In the late 1990s, another class of more potent anti-estrogen drugs, aromatase inhibitors, and gonadotropin antagonists, has been introduced. Aromatase inhibitors have been applied in postmenopausal ER-positive breast cancer. For premenopausal women, Cheng *et al.*^[47] used goserelin (Zoladex[®]), a gonadotropin antagonist, and chemotherapy for advanced breast cancer in young women. Ovary function can be preserved with the possibility of fertility if the disease is well controlled. A nationwide database managed by Taiwan's National Health Insurance Administration revealed that the rate of bilateral oophorectomy for benign gynecological diseases or nongynecological malignancies was markedly reduced from 22.1% in 2000 ($n = 26419$) to 9.9% in 2010 ($n = 10793$) ($P < 0.0001$).^[48,49]

EARLY BREAST RECONSTRUCTION AFTER TOTAL MASTECTOMY

In consideration of possible local cancer recurrence over the chest wall or the necessity of radiotherapy for advanced stage, breast reconstruction after total mastectomy has usually not been recommended in the past.^[9,14,50,51] The presence of prosthetic material makes early detection of local recurrence more difficult, which would also be a contraindication for breast reconstruction.

There are two strategies in breast reconstruction, i.e., interval breast reconstruction and immediate reconstruction. Some breast surgeons suggested that reconstruction should only be considered after a long disease-free period of at least 5 years.^[50-53] However, with improvements in hormonal therapy, target agents, and chemotherapy, long-term disease-free survival rates are increasing.^[22,51-54]

When the aforementioned agents are used in adjuvant or neoadjuvant settings, the prognosis of breast cancer also improves.^[54] For cosmetic purposes, early reconstruction issues are increasing in women after mastectomy, especially in younger patients.^[51-53] The use of a pedicle transverse rectus abdominis muscle flap from the patient was the first designed material in breast reconstruction.^[50-52] Within proved prosthetic materials and innovations in surgical techniques developed by plastic surgeons, breast reconstruction has become popular and involves the cooperation of breast surgeons, plastic surgeons, and oncologists.^[53] Therefore, immediate postmastectomy breast reconstruction is now an option in breast cancer management.

ECONOMIC AND SOCIO-PSYCHOLOGICAL PROBLEMS AND LIFE QUALITY OF BREAST CANCER PATIENTS

Because of the outer appearance of the chest wall postmastectomy and the high expense of treatment, fear of cancer and socio-psychological problems in women with

breast cancer are extremely common.^[51-55] The most common psychophysiological problems in female cancer patients are fatigue, insomnia, and pain.^[56] Many measurement systems can be used to estimate the quality of life (QOL) of breast cancer patients. Shi *et al.*^[57] compared the QOL of 172 women who had breast cancer using a cancer QOL questionnaire. They concluded that to improve the QOL after breast cancer surgery, some factors other than the surgery itself should be considered preoperatively and that emotional status as well as postoperative outer appearance are important.^[55] Huang *et al.* used patient symptoms and social support to demonstrate the importance of fertility intention in women of reproductive age with ER-positive breast cancer.^[56] Chao *et al.* confirmed that the QOL of breast cancer patients with bone metastasis improved following the use of zoledronic acid therapy.^[55] Moreover, Tang *et al.* stated that even in terminal breast cancer patients, the use of intensive care units may improve the QOL of terminal care.^[58]

The impacts of emotional stress in breast cancer patients are great.^[11] Patients suffer from surgical stress, the feeling of having lost a body part, and the side effects of adjuvant nonsurgical therapies, in addition to worrying about cancer recurrence and the high cost of the therapies. Taken together, the aforementioned stress or scan leads to considerable psychological distress in cancer patients.^[57] Furthermore, socioeconomic problem scan also contributes to significant psychosomatic issues.^[57,59,60]

In October 1993, the first breast cancer patient society in Taiwan was formed in Taichung City. This society was named “Kai-Hwai Club.” “Kai-Hwai” means “joyful” in English. In this society, the patients may share their experiences of breast cancer treatment, and the goal is to encourage breast cancer patients to help one another solve their emotional problems. This society even communicates with breast cancer patients in other countries. The positive interactions provide psychological support and encouragement for breast cancer patients. Currently, the members of the Kai-Hwai Club number over 1000. Other medical centers in Taiwan have since created similar clubs and societies. By participating in these societies, breast cancer patients derive a variety of benefits, which help to enhance the quality of their postoperative lives.

STUDY LIMITATIONS AND CONCLUSION

In conclusion, the surgical management of breast cancer in Taiwan has shown a number of trends over the past 60 years; today, surgical modalities for the treatment of breast cancer are more patient-friendly, humanistic, and feasible. A diagnosis of breast cancer may no longer have a poor outcome if the tumor can be detected at an earlier stage.

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Conflicts of interest

There are no conflicts of interest.

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