President's Address

Role of Breast Surgeons in Evolution of the Surgical Management of Breast Cancer

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In breast cancer surgery, there has been a major shift toward less invasive local treatment: from extended or radical mastectomy to modified radical mastectomy, from modified radical mastectomy to breast conserving therapy, and from routine axillary lymph node dissection to sentinel lymph node biopsy. Many breast surgeons have experienced an evolutionary progression of surgical management of breast cancer. However, there is an increasing demand for minimally invasive and non-surgical treatment methods for patients with small breast cancer. Radiofrequency (RF) ablation is the most promising among non-surgical ablation techniques in the treatment of breast cancer, although it is still in the investigative stage. Nevertheless, surgery still plays an integral role in the treatment of breast cancer, because local therapy is important for enhancing survival in the presence of systemic therapy. In clinical practice, surgical oncologists must individualize treatments, selecting a surgical or non-surgical procedure that provides the best local control, does not compromise the chances of cure, and achieves the best cosmetic results.

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Key words: Breast cancer, Breast conserving reconstruction, Sentinel lymph node biopsy, Radiofrequency ablation

Introduction

Breast cancer is a heterogeneous disease. However, a number of randomized clinical trials have demonstrated that variations of local treatment are unlikely to have substantial effects on survival, while systemic therapy can significantly improve survival. The increasing use of screening mammography has enhanced the detection of small, early-stage breast cancer lesions with no nodal metastases. Therefore, the rationale and approach for surgical management of breast cancer have recently undergone major changes in Japan as well as in western countries. Over the

last several decades, there has been a major shift toward less invasive local treatment of breast cancer.

According to a survey of the Japanese Breast Cancer Society (JBCS)¹⁾, breast cancer surgery has changed since 1975 from Halsted's radical mastectomy to modified radical mastectomy with preservation of the pectoralis major muscle. In 1986, breast conservation therapy (BCT) was introduced and by 2003 was performed more frequently than modified radical mastectomy. In 1996, sentinel lymph node (SLN) biopsy was introduced in Japan and 21.5% of breast cancer patients underwent SLN biopsy in 2003 (Fig 1). Thus, BCT has largely replaced mastectomy as the surgical treatment of choice for early-stage breast cancer, and SLN biopsy is accepted as an effective method of assessing axillary nodal status and avoiding unnecessary axillary dissection in patients with node-negative breast cancer. Many breast surgeons have experienced an evolutionary process in the surgical management of breast cancer. In addition, the next step in this continuous evolution is the removal of the primary tumor without any surgery^{2, 3)}. Given the growing

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Abbreviations

JBCS, Japanese Breast Cancer Society; BCT, breast conservation therapy; SLN, sentinel lymph node; AX, axillary lymph nodes; IMN, internal mammary nodes; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CT, computed tomography; MRI, magnetic resonance imaging; RFA, radiofrequency ablation; HIFU, high-intensity focused ultrasound; NADH-diaphorase, nicotinamide adenine dinucleotide-diaphorase

Fig 1. Changing trends in surgical procedures for breast cancer in Japan (Breast Cancer 12 : 1-2, 2004).

Fig 2. En bloc extended radical mastectomy and the location of metastatic internal mammary nodes.

demand from patients for less invasive procedures, minimally invasive techniques are appealing if they can produce local control rates similar to those obtained with wide local excision but with better cosmetic results.

As the presidential address of the 14th Congress of the JBCS, this paper describes my personal progress from extended radical mastectomy to BCT, and then to SLN biopsy and non-surgical ablation of breast cancer.

Extended Radical Mastectomy (1980-1985)

Primary lymphatic drainage of breast cancer is toward the axillary lymph nodes (AX) and internal mammary nodes (IMN). IMN metastases occur in 7-15% of AX-negative and 30-50% of AX-positive

patients. More than 50 years ago, various methods of extended radical mastectomy were developed and performed, but many surgeons were dissatisfied with the results of extended radical mastectomy compared with standard radical mastectomy. In a prospective randomized trial in 1981, Veronesi *et al.*⁴⁾ demonstrated the lack of efficacy of IMN dissection. They reported 10-year overall survival rates of 60.7% and 57.0% in patients treated with radical mastectomy and extended radical mastectomy, respectively. Consequently, extended radical mastectomy has been largely abandoned in many hospitals. Before this trial, other randomized clinical trials comparing modified radical mastectomy with radical mastectomy were conducted and their results also demonstrated that there were no

significant differences in disease-free survival or in overall survival between the two groups^{5, 6)}. Therefore, breast cancer surgery was changed from extended or radical mastectomy to modified radical mastectomy in western countries⁷⁾ as well as in Japan.

However, the management of breast cancer patients who are at greater risk of IMN metastases remained controversial in the 1980s^{8, 9)}. Complete resection of the internal mammary lymph nodes (IMN) is not done in conventional extended radical mastectomy. The upper end of the IMN chain is not dissected even in the most aggressive operation described by Urban¹⁰⁾. According to Halsted's theory, there is no justification for leaving viable breast cancer cells in the regional lymphatic system or in the breast in the surgical management of breast cancer. In 1980, we developed a new method of extended radical mastectomy involving en bloc resection of the parasternal portion of the anterior chest wall by sternal splitting between the sternal notch and fourth intercostal space (sternal splitting en bloc extended radical mastectomy)¹¹⁾ (Fig 2a). This is a new approach in keeping with the Halstedian philosophy for operable breast cancer. In fact, metastases in the IMN chain were found not infrequently between the supraclavicular vein and the first rib, an area which would not normally be dissected with Urban's operation¹⁰⁾ (Fig 2b). We performed this type of en bloc extended radical mastectomy in 118 patients between 1980 and 1985 in a clinical trial. The 7-year survival rates were 96% and 68% in IMN-negative patients and IMN-positive patients, respectively¹²⁾. In a retrospective comparative study using multivariate analysis, it was suggested that extended radical mastectomy is advantageous over radical mastectomy, especially for patients with few metastatic axillary lymph nodes¹²⁾.

However, prospective randomized trials comparing en bloc extended radical mastectomy with IMN dissection vs. radical mastectomy alone vs. radical mastectomy with regional radiotherapy in a large number of patients with IMN metastases were required. In 1988, such a prospective randomized trial was conducted at the Tokyo Cancer Institute Hospital [Yoshimoto K: personal communication, 1997]. Of 992 patients with stage I-III breast cancer who underwent IMN biopsy in the first and second intercostal spaces, 181 patients (18%) had IMN metastases. Of these latter

patients, 150 were randomly assigned into one of three groups: radical mastectomy alone (Group 1), radical mastectomy with irradiation of the IMN and supraclavicular lymph nodes (Group 2), or sternal splitting en bloc radical mastectomy with dissection of the IMN and supraclavicular lymph nodes (Group 3). Postoperatively, all patients received six cycles of adjuvant cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy. The 5-year overall survival was 75% for Group 1 patients, 74% for Group 2 patients, and 73% for Group 3 patients. The differences were not statistically significant, regardless of whether the patients were considered collectively or as subgroups. Therefore, it was concluded that IMN dissection and regional radiotherapy provide no survival advantage. Although this result has not yet been published, this is the last trial concerning extended radical mastectomy.

In our series of extended radical mastectomy patients, AX and IMN metastases were recognized as important independent prognostic factors of survival¹³⁻¹⁵⁾. IMN status is a more reliable prognostic factor than DNA ploidy and c-erbB-2 expression¹⁵⁾. The significance of these biological prognostic factors was recognized as being poor. In the Milan trial reported by Veronesi *et al.*⁴⁾, 15 patients treated with radical mastectomy had parasternal recurrence, suggesting that 20% of patients with IMN metastases will develop parasternal recurrence over a 10-year period. Therefore, positive IMN status would be an indication for internal mammary radiotherapy and adjuvant chemotherapy¹⁶⁾. Although IMN dissection has been abandoned in many hospitals, Morrow *et al.*¹⁷⁾ and Veronesi *et al.*¹⁸⁾ have advocated less aggressive IMN biopsy techniques in patients who are at greater risk of IMN metastasis.

Breast-Conserving Treatment (1986~Present)

Breast cancer is a multicentric disease; whole-breast serial sectioning of mastectomy specimens has shown that the frequency of multiple microfoci of breast cancer ranges from 37% to 50%. Therefore, BCT could not be accepted as appropriate treatment before several randomized clinical trials demonstrated that BCT and modified or radical mastectomy yielded similar actuarial survival rates^{19, 20)}. In the NSABP B-06 trial, patients treated with tumorectomy alone suffered local recurrence at a rate of 39%, while the rate was only 10% in patients who underwent tumorectomy plus radio-

Fig 3. Wide excision following a transposition of adipose tissue with the latissimus dorsi muscle pedicle.

therapy. However, this high incidence of local recurrence did not affect survival in this trial. It is apparent that the strategy of surgical management for breast cancer should be based on the evidence obtained in randomized clinical trials. This was the beginning of the departure from Halsted's principle of radical surgery.

We introduced BCT as an alternative to mastectomy in March 1986²¹⁾, while Prof. Ashikari demonstrated breast-conserving surgery at the Tokyo Cancer Institute Hospital in July 1986. Initially, we performed quadrantectomy but subsequently wide excision was performed in most patients. All patients underwent breast radiation therapy after surgery. In a retrospective study, the survival of patients treated with BCT was almost equivalent to those treated with modified radical mastectomy²¹⁾. However, BCT should fulfill two criteria: (a) it should afford the same local control of disease as radical mastectomy, and (b) it should offer clear psychological and cosmetic advantages over mastectomy. The amount of excised breast tissue must be individualized according to the extent of breast cancer to provide local control, but local control and cosmesis are often in conflict. Therefore, in 1990 we developed a novel method of immediate volume replacement using a latissimus dorsi flap with adipose tissue, which can be employed in BCT²²⁻²⁴⁾ (Fig 3). This was the first significant report of the use of volume replacement to prevent deformity, rather than to correct deformity at a later date. Subsequently, Rainsbury *et al.*²⁵⁾ as well as Raja *et al.*²⁶⁾ modified this procedure as latissimus dorsi miniflaps. This represents the beginning of the recent trend

toward the joint "oncoplastic" surgical management of patients with breast cancer. Although Tansini introduced latissimus dorsi myocutaneous flaps in 1894²⁷⁾, it was used as a delayed procedure for correcting the radical mastectomy defect but not for the partial mastectomy defect.

Sentinel Lymph Node Biopsy (1996~Present)

In the 1990s, AX dissection was questioned in patients with early breast cancer, as 75-90% of AX in these cases are disease-free²⁸⁾. Routine AX dissection would expose a large percentage of patients with negative nodes to unnecessary perioperative risk and increased long-term morbidity. The preoperative or intraoperative diagnosis of AX metastases remained a challenge in the management of breast cancer. However, the imaging modalities including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) do not provide accurate information regarding AX metastases²⁸⁾. AX sampling also does not identify a significant percentage of patients with AX metastases²⁹⁾. SLN biopsy has been developed to assess the AX status accurately and to avoid unnecessary AX dissection in breast cancer patients with negative nodes^{30,31)} (Fig 4).

We began a feasibility study of dye-guided SLN biopsy in early 1996³²⁾. This was the first feasibility study of SLN biopsy in Japan. Subsequently, we conducted a multicenter validation study of SLN biopsy consisting of 674 patients with breast cancer at five institutions belonging to the Japanese Breast Cancer Society³³⁾. The SLN was identified in 214 (94%) of 227 patients using the combined dye- and gamma probe-guided methods, while it

Fig 4. Sentinel lymph node and its biopsy by the two mapping procedure.

was identified in 332 (74%) of 447 patients using the dye-guided method alone. The accuracy of SLN biopsy was 96% (522 of 546 cases) and an accuracy of 100% was achieved in patients with tumors less than 1.6 cm in diameter. At the time, this was one of the largest feasibility studies of SLN biopsy for breast cancer worldwide.

The growing demand from patients for less invasive procedures has created considerable incentives for accepting SLN biopsy without AX dissection as standard practice. Since 1999, we have abandoned routine AX dissection in patients with T1-2, N0 disease and negative SLN biopsy results. However, randomized clinical trials comparing SLN biopsy alone with AX dissection are necessary in patients with SLN-negativity before SLN biopsy can replace AX dissection as a standard procedure³⁴. Such trials have been conducted in the USA as well as European countries. A preliminary study has already been reported with excellent results in Italy³⁵. Prof. Krag *et al.* conducted the NSABP B-32 trial in the USA³⁶. The results of ongoing clinical trials involving large number of patients with early breast cancer are eagerly awaited in Japan.

On the other hand, recent developments in SLN biopsy may facilitate selective removal of IMN in patients with breast cancer³⁷. There is renewed interest among radiation oncologists in the prophylactic treatment of the IMN chain because of the success of comprehensive post-

mastectomy radiation therapy in large prospective randomized trials³⁸. In recent years, Veronesi *et al.*³⁹ advocated the necessity of internal mammary SLN biopsy. However, it is difficult to identify internal mammary SLNs by the dye-guided method, because it is performed after resection of the primary tumor. The blue dye travels rapidly through the lymphatic vessels and may not always remain in the IMNs long enough for surgical identification and excision³⁷. On the other hand, internal mammary SLN biopsy is sometimes recommended when either lymphoscintigraphy or the intraoperative gamma probe method suggests internal mammary drainage of isotope. Based on pathological findings following IMN dissection in patients with breast cancer, however, very small lymph nodes are present in the IMN chain. Lymphoscintigraphy or the gamma probe would not allow detection of limited accumulation of isotope in these minute nodes as well as metastatic nodes. In fact, the reported incidences of positive internal mammary SLN are still lower than expected. Thus, internal mammary SLN biopsy is relevant but not practical⁴⁰. More data are needed on the correlation between a hot internal mammary SLN and pathological positivity. Therefore, internal mammary SLN biopsy is still considered to be in the investigative stage.

Table 1. Radiofrequency ablation (RFA) and resection for breast cancer

Authors	No. of patients	Tumor size	RFA equipments generator & electrode probe	Interval between RFA and resection	Histologic examination	No. of complete tumor ablations (%)
<Immediate resection>						
Jeffrey et al [41]	5	4-7 cm	RF-2000 & LeVeen needle	Immediate	H&E and NADH	4 (80)
Izzo et al [42]	26	T1-T2	RF-2000 & LeVeen needle	Immediate	H&E and NADH	25 (96)
Fornage et al [46]	20	T1	RITA-500 & RITA-70 or RITA-1500 & Starburst XL	Immediate	H&E and NADH	19 (95)
Noguchi et al [47]	10	T1	RITA-1500 & Starburst XL	Immediate	H&E and NADH	10 (100)
Total	61					58 (95)
<Delayed resection>						
Elliot et al [43]	1	T1	RITA-1500 & Starburst XL	One month	H&E staining	1 (100)
Burak et al [44]	10	T1	RF-2000 & LeVeen needle	1-3 weeks	H&E staining	9 (90)
Hayashi et al [45]	22	<3.0 cm	RITA-1500 & Starburst XL	1-2 weeks	H&E staining	14 (64)
Total	33					24 (73) *

*: Due to the short interval between RFA and resection, tumor ablation may be underestimated on histological examination with H&E staining.

Fig 5. The principle of breast cancer treatment.

Non-Surgical Ablation: Radiofrequency Ablation (2002–Present)

So-called minimally invasive techniques make percutaneous eradication of breast tumors possible, thus leading to BCT without invasive surgery. This can be achieved with a variety of approaches involving cooling (e.g., cryotherapy) or heating (e.g., focused ultrasound, laser interstitial therapy, microwave, radiofrequency)⁴¹⁾. Currently, the most promising of the noninvasive ablation techniques are radiofrequency ablation (RFA)^{2, 3)} and high-intensity focused ultrasound (HIFU) therapy. RFA treatment for breast cancer has been a subject of investigation in the USA as well as Italy and Japan⁴¹⁻⁴⁷⁾ (Table 1).

In July 2002, we performed RFA treatment with an expandable probe (RITA 500PA; RITA Medical Systems, Mountain View, CA) in 2 patients with small breast cancer lesions. Wide excision and SLN biopsy were performed after

RFA treatment. This is the first pilot study of RFA treatment for small breast cancer in Japan²⁾. Subsequently, we performed a feasibility study of RFA treatment using a 150-W model 1500 generator with a seven-array Starburst XL needle-electrode Model 70 (RITA Medical Systems)⁴⁷⁾. Resected tumors were examined histologically with H&E staining and nicotinamide adenine dinucleotide (NADH)-diaphorase staining. H&E staining revealed a spectrum of changes ranging from necrotic tumor cells to nearly normal-appearing tumor cells, but NADH staining showed no staining of viable cells in any of 10 patients. Thus, RFA treatment is a promising method for local treatment of small breast cancer although patients undergoing RFA treatment should receive adjuvant radiotherapy. However, further studies are needed to determine whether the use of RFA and breast irradiation for local treatment of primary breast cancer may result in local recurrence and can produce survival rates equivalent to those obtainable with conventional BCT. These pilot studies are currently in progress in Japan⁴⁸⁾ as well as the western countries.

Summary

Currently, patients with breast cancer are treated by rational and multidisciplinary approaches involving surgery, radiotherapy, chemotherapy, and hormonal therapy. In breast cancer surgery, however, there has been a major shift toward less

invasive local treatment. Many breast surgeons have experienced an evolutionary progression of the surgical management of breast cancer. It was a long but exciting journey from extended radical mastectomy to BCT and then to SLN biopsy and non-surgical ablation for breast cancer. Nevertheless, surgery still plays an integral role in the treatment of breast cancer, because local therapy is important for enhancing survival in the presence of adjuvant systemic therapy.

In clinical practice, therefore, surgical oncologists must individualize treatments, selecting a surgical procedure that provides the best local control, does not compromise the chances of cure, and achieves the best cosmetic results (Fig 5). In addition, it should be noted that surgical oncologists must retain the primary coordinating role in multidisciplinary approaches to the treatment of breast cancer.

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