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Current and Future Strategy for Breast Cancer Treatment at Nagasaki University Hospital

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Breast cancer has emerged as the most frequent malignant neoplasm among Japanese women in recent years, raising awareness in society of the issue of breast cancer, including good screening and therapies. In fact, the establishment of breast cancer screening program with mammography in the United States and Western Europe has contributed to improve the diagnosis of breast cancer at early stage, and proper management, including various options of evidence-based treatment has not only reduced mortality but also enhanced patients' quality of life. However, the mortality rate due to breast cancer in Japan has continued to increase, and the number of patients is also increasing rapidly. It is therefore very urgent to develop a good system of breast care in all medical facilities as well as the provision of a national scheme in Japan. In this report, we review the situations of breast surgery at Nagasaki University Hospital from 1975 to 2004 and current management practices for breast disease, and evaluate the possibility of establishing a better system for breast care at our hospital, which could then act as a core medical institute in Nagasaki.

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Introduction

Although Japan has one of the lowest breast cancer incidence rates in the world, the recent rapid increase in the incidence has made breast cancer the most frequent malignancy among Japanese women.[1,2] The patients of breast cancer in Japan rose from 12,796 in 1975 to 34,307 in 2000, and the number of deaths also increased from 3,262 in 1975 to 9,248 in 2000.[3] This increase in the number of breast cancer patients and the recent social trend of assessing hospitals have encouraged the medical society to develop a unified medical management system of high quality for breast disease and information service to patients. The screening program by mammography as an instrument of state policy has just started recently in Japan and educational campaigns such as the 'pink-ribbon' initiative by patients' groups and volunteers are also on the rise in Japan. In other countries like the United States and those of Western Europe where these programs have already been established for years, they are actually succeeding in reduction of the mortality due to breast cancer, probably as a result of early stage detection and the development of a comprehensive system to treat the disease effectively.[4-7]

Nagasaki University Hospital has treated patients with breast disease for many years. It is a very important task for us to contribute to the provision of good medical services for patients as one of the core medical institutes in Nagasaki. Therefore, a broad review of the old and the current situations regarding breast disease in our hospital is necessary in order to establish an efficient breast care system at

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Nagasaki University Hospital. In particular, breast cancer has caused concern because of a significant increase in incidence and mortality in women during the most productive period of their life, and the need for a comprehensive, good, unified and supportive medical care system in response to the demands appears to be rising. But there exists no integrated collection of statistical data related to breast diseases treated at Nagasaki University Hospital to allow us to review past progress. In addition, the present system of breast care in our hospital should be re-evaluated in order to respond to recent progress in diagnosis and treatment procedures, involving all members from different departments treating such patients.

In this report, we first survey the history of breast disease in our hospital, including the change in the number and the age distribution of cases, and in histological and diagnostic tools from 1975 to 2004, then discuss our system of medical management for patients with breast disease, and propose an ideal future system for effective and safe management.

Subjects and Methods

Subjects

The study subjects were patients with breast disease operated at Nagasaki University Hospital from 1975 to 2004, who were registered in the patient database managed by the Department of Pathology at Nagasaki University Hospital. Information available from the database included patients' ages, operation dates and the final pathological diagnosis, and more than 1,000 patients were retrieved.

Modern diagnostic devices for breast disease

Mammographic examinations were performed at Department of Radiology from 1998 using Mammodiagnost 3000 (Philips Medical Systems, Eindhoven, Netherlands). Ultrasonographic examinations were performed using LOGIQ 900 (General Electoric Medical Systems, Milwaukee, WI) by radiologists at Department of Radiology from 1998 to 2002 when they replaced LOGIQ 900 by SDU-2200 (Shimadzu Medical Systems, Kyoto, Japan); breast surgeons at outpatient clinics of breast and endocrine surgery also performed ultrasonographic examinations using Aplio SSA-700A (Toshiba, Tokyo, Japan) since 2002. Breast magnetic resonance (MR) imaging examinations were performed since 1998 on Sigma system (General Electric Medical Systems, Milwaukee, WI) at 1.5 T. All patients were imaged in the prone position using dedicated surface breast coil. Axial images of both breasts and coronal images of the affected breasts were obtained using fat-suppressed T2-weighted fast spin-echo sequence. The following parameters were used: TR/TE=3,000-3100/96-104 (msec/msec); matrix=256×196-224; slice thickness=5-6mm with 1mm gap; two excitations; field of view=30-35 cm for both breasts and 18-24 cm for one single breast. Dynamic contrast-enhanced MR mammography results were obtained using sagittal or coronal views, and three-dimensional fat-suppressed T1-weighted fast spoiled gradient-recalled echo sequences with the following parameters: TR/TE=6.3-9.9/1.7-2.1 (msec/msec); flip angle =20°; matrix=256×256; slice thickness=4-6mm with no intersectional gap; one excitation; field of view=20-25 cm. After one pre-contrast sequence was obtained, Gd-DTPA was administered intravenously as bolus injection using injector at the dose of 0.2 mmol per kg bodyweight, followed by saline flush of 20 mL. Twenty seconds after administration of contrast medium, 4 sequences were carried out at 1 minute intervals. Delayed post-contrast images were obtained, 5 minutes after injection of contrast medium, using three-dimensional fat-suppressed T1-weighted fast spoiled gradient-recalled echo sequences with the following parameters: TR/TE=6.3-9.9/1.7-2.1 (msec/msec); flip angle=20°; matrix=256×256; slice thickness=4-6 mm with no intersectional gap; 2 excitations; field of view=20-25 cm.

Results

Chronological changes in the number of patients with breast disease from 1975 to 2004

Among the cases of breast disease operated on at Nagasaki University Hospital from 1975 to 2004, the number of patients undergoing surgery for benign breast lesions was over 300 cases per 5 years in 1975-1979 and 1980-1984 (Figure 1). This number then steeply decreased in 1990-1994, when the number of benign lesions operated on was around 180, being close to that of malignant breast lesions operated on, and continued decreasing to reach under 100 in 2000-2004. On the other hand, the number of breast cancer patients in each 5-year period was relatively stable from 1975 to 1994 with around 170 cases per 5 years, but increased in 1995-1999 and 2000-2004. The number of breast cancer patients operated on in 2000-2004 at Nagasaki University Hospital exceeded 250, which accounted for 76% of all breast surgeries in the same period.

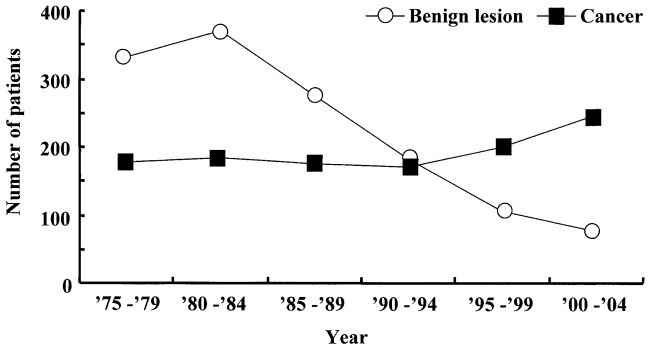

Figure 1. Chronological changes in the number of benign breast lesions and primary breast cancers operated on at Nagasaki University Hospital from 1975 to 2004.

Details of benign breast lesions

The most common benign breast disease indicated for surgery was fibrocystic disease during the whole time period (Figure 2). However,

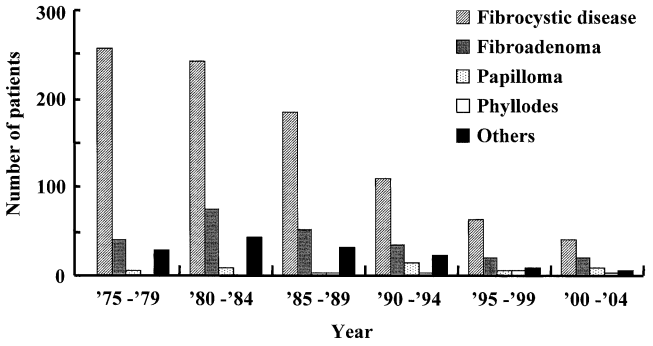

Figure 2. Chronological changes in the number of pathological diagnoses of benign breast lesions removed by surgery at Nagasaki University Hospital from 1975 to 2004.

the number of cases of mammary fibrocystic disease dramatically decreased from 248 in 1975-1979 to only 38 in 2000-2004. Other benign pathological diagnoses included fibroadenoma, papilloma, phyllodes tumor and others such as fat, connective tissue or mammary gland. The number of cases of these benign diseases also decreased with time. In general, the total number of benign breast lesions operated on decreased dramatically from 332 in 1975-1979 to only 76 in 2000-2004.

Recent advances in diagnostic visualization techniques for breast disease before operation

The development and more frequent use of diagnostic procedures for breast disease have improved the sensitivity and accuracy in preoperative diagnosis.

Figures 3 A, B and C show the characteristic features of fibroadenoma, which is a representative benign disease of the breast. Mammography shows a round mass with partially obscured borders containing coarse calcifications (Figure 3 A). Ultrasonography is very useful since it allows us to find very small lesions, and lesions in young patients when diagnosis by mammography is difficult because of high breast density. A well-circumscribed, oval and hypoechoic mass was detected by ultrasonography (Figure 3 B). Fine needle aspiration cytology of the tumor showed no malignancy, suggesting fibroadenoma (Figure 3 C).

Figures 3 D, E, F, G, H and I are from a patient with breast cancer. Mammography shows a high density lesion in dense breast background with enlarged axillary lymph node (Figure 3 D). A solid, lobulated and hypoechoic mass was found with lateral shadow and posterior acoustic enhancement by ultrasonography (Figure 3 E). T1-weighted images show an irregular mass with relative circumscribed border (Figure 3 F). Post-contrast fat-suppressed T1-weighted images show an irregular mass in coronal view (Figure 3 G). Time-signal intensity curve shows a rapid initial increase followed by a plateau (Figure 3 H). Fine needle aspiration cytology of the tumor showed malignant character like high cellularity and marked nuclear overlapping including large nuclei, highly increased nuclear chromatin and mitoses (Figure 3 I).

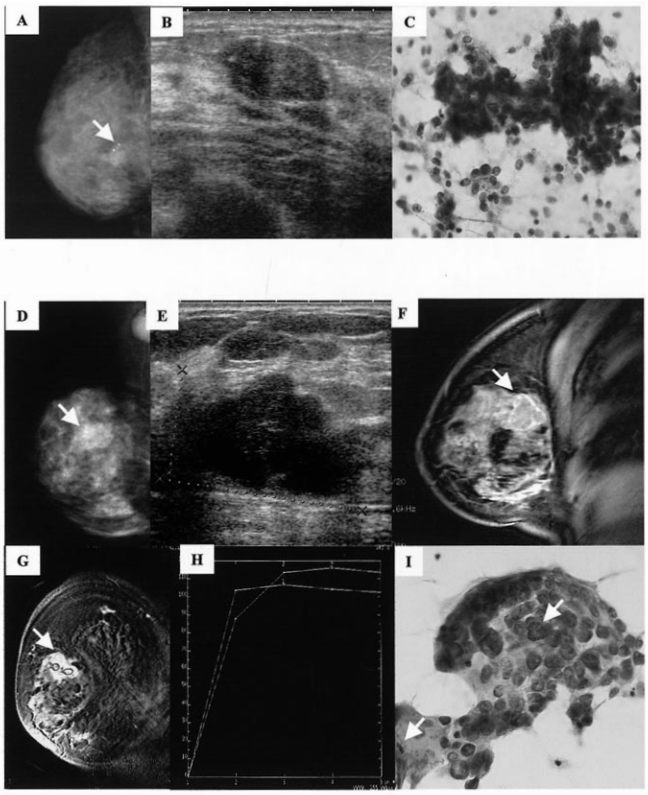

Figure 3. Typical pictures of fibroadenoma (A, B and C) and invasive ductal carcinoma (solid-tubular) (C, D, E, F, G, H and I). **A.** Mammography reveals a mass with coarse calcifications (arrow). **B.** Ultrasonography shows an oval and hypoechoic mass. **C.** The papillary cell cluster shows nuclear overlapping and mild enlar ged of nuclei. There are many degenerated naked nuclei in the background (× 400). **D.** Mammography reveals focal asymmetry lesion without calcifications (arrow). **E.** Markedly hypoechoic, irregular, un-circumscribed mass by ultranosonogrpahy. **F.** MR imaging sagittal view. **G.** MR imaging coronal view. **H.** Time intensity curve. **I.** The cell cluster shows large nuclei with evident difference in size, highly increased nuclear chromatin and large nucleoli. There are two mitoses (arrows) (× 400).

Chronological changes in age distribution in breast cancer patients

Figure 4 shows the age distribution in breast cancer patients for respective 5-year periods from 1975 to 2004. The most common groups in respective periods were aged 45-54 years. In 1975-1979, the proportion of younger patients aged under 35 years and that of older patients aged, over 65 years were both about 10%. The proportion of younger patients aged under 35 years gradually decreased from 1975-1979 to reach 5% in 200-2004, while the proportion of patients aged over 65 years steadily increased from 10% in 1975-1979 to 28% in 2000-2004. In 2000-2004, patients aged 55 years or over assumed about 50% of all cases; 18 patients progressed to distant metastasis and 7 of them died at relatively young age with mean of 51.7 and 49.0 years, respectively (data not shown).

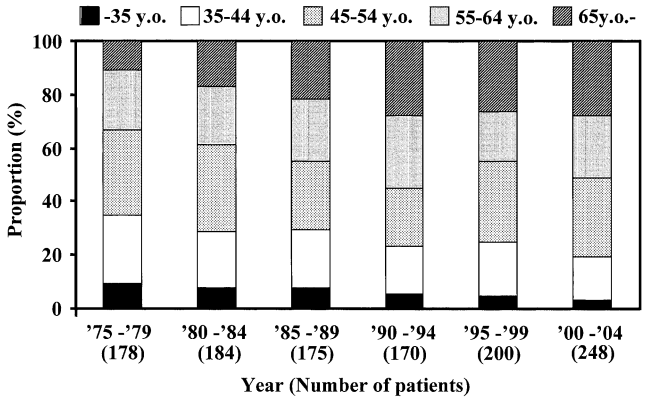

Figure 4. Chronological changes in the age distribution in breast cancer patients from 1975 to 2004.

Discussion

The issues surrounding breast cancer have been changing. Until the 1980s, the most effective treatment for breast cancer was thought to be exhaustive and complete removal of tumor, including axillary lymph nodes and pectoral muscles, which was well known as the Halsted procedure.[8,9] In many Japanese hospitals, almost all patients seen by breast surgeons continued receiving this operation without any further additional treatments or with oral administration of the anti-estrogen tablet, tamoxifen, and/or 5-fluorouracil (5-FU) in the absence of sufficiently consolidate reasons until the 1980s (Figure 5 A); chemotherapy with anticancer agents was performed for metastatic or inoperable breast cancers by infusing a single agent like methotrexate, adriamycin, 5-FU or other agents, following regimens that varied between hospitals (Figure 5 A), and radiotherapy was administered to metastatic sites, usually bone, to reduce the pain (Figure 5 A).

In the 1990s, hormone therapy was prescribed only for patients with breast cancer tissue showing the presence of estrogen receptors or progesterone receptors,[10] and a number of clinical trials demonstrating the effectiveness of a range of forms of chemotherapy established some uniform regimens combining various anticancer agents used in the adjuvant setting or in metastatic breast cancers.[11-13] The theory depicting breast cancer as a systemic disease from an early stage was popular for a long time, and in fact, many reports revealed that a breast-conserving lumpectomy procedure would not lower the prognosis compared to radical mastectomy.[9,14] Therefore, combination of breast-conserving surgery for relatively small tumors and some adjuvant therapy following the operation has been increasing since the late 1990s (Figure 5 B). Furthermore, use of neo-adjuvant systemic chemotherapy is receiving a lot of attention for cases of far-advanced breast cancer because of the evidence that systemic therapy can help surgeons to perform successful breast-conserving operation by reducing the tumor mass before operation.[15] These conservative operations require extensive pathological examination, where all the resected tissue is cut into blocks and the surgical margin is examined to decide the need for additional therapy and prediction of the prognostic factor, giving reliable evidence of the utility of the treatment to follow. Ultimately, systemic hormone therapy and/or chemotherapy for adjuvant or metastatic breast cancer status are considered on the basis of patient's age, tumor size, hormone receptor status, nodal involvement, nuclear grade, vessel invasion and the status of human epithelial growth factor, receptor type 2 (Figure 5 B). The final decision is usually made through discussions between doctor and patient based on the information about the risks and potential benefits of these treatments. These situations might be beneficial to the patients, but at the same time they often create complex medical scenarios.

These days, patients who visit Nagasaki University Hospital for examination of their breasts are referred to one of the two outpatient clinics of breast and endocrine surgery; one is a part of the Department of Surgical Oncology and the other is a part of the Department of Transplantation and Digestive Surgery. This current situation with two separate breast outpatient clinics might confuse patients and raise doubts as to whether the optimum best management is being

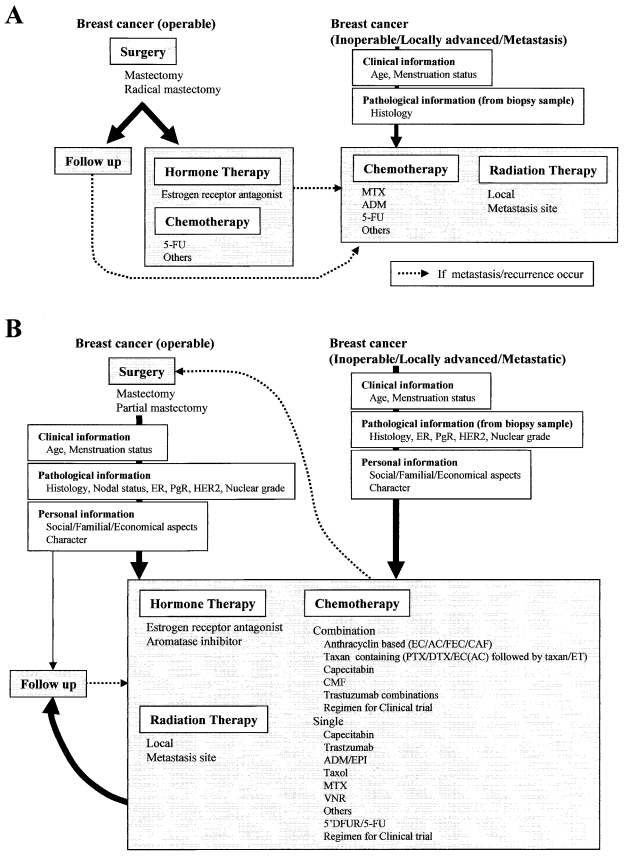

Figure 5. Flow chart showing the treatment course and provision of supporting information for breast cancer patients; the chart compares the range of treatments and their supporting evidence for breast cancer in Nagasaki in the 1980s (A) and in the 2000s (B). ER=estrogen receptor; PgR=progesterone receptor; HER2=human epithelial growth factor, receptor type 2; MTX=methotrexate; ADM=adriamycin; 5-FU=5-fluorouracil; E=epirubicin; C=cyclophosphamide; A=adriamycin; F=fluorouracil; PTX=paclitaxel; DTX=docetaxel; M=methotrexate; EPI=epirubicin; VNR=vinorelbine; 5'DFUR=5'doxifluridine.

achieved at our university hospital. It is indeed inconvenient and inefficient that two outpatient clinics are giving similar services under different management policies. Breast surgeons examine the patients initially, and then evaluate the results of diagnostic procedures such as mammography and ultrasonography, essential tools for diagnosis of breast disease. Furthermore, MR imaging is currently used frequently, because it can characterize the lesion in detail using contrast procedures. Fine needle aspiration cytology or biopsy is carried out before surgery in almost all cases. These improvements in preoperative information provide us with more accurate diagnosis of breast disease before operation and this seems to be the reason for the significant decrease in the number of benign lesions such as mastopathy (fibrocystic disease) operated on at Nagasaki University Hospital in recent years. Recently, information regarding individual patients is discussed at 'Breast & Endocrine meeting' that is held once a week before the operation, which breast surgeons from both groups and a radiologist attend. After operation, adjuvant chemotherapy and/or hormone therapy are considered depending on the final pathological report (Figure 5 B). Neo-adjuvant or adjuvant chemotherapy and hormone therapy are administered to the patients by breast surgeons, depending on the succeeding discussion between a breast surgeon and the patient, since our hospital has not established a department of oncology yet. Radiotherapy to the preserved breast or metastatic sites is performed at the radiology department in our hospital.

The range of possible treatments available for breast cancer, including surgical operation, chemotherapy (neo-adjuvant, adjuvant, metastatic state or clinical trials) and hormone therapy (neo-adjuvant, adjuvant, metastatic state or clinical trials) has become more diverse as an increase in detailed information available on the tumor status which might influence the outcome of therapies. Obviously, the recent increase in the incidence and mortality of breast cancer and much expectations from the society require us to provide higher transparency and unified consensus in the management of each patient at each medical institute. To meet the requirment, the multidisciplinary approach will become more important, enabling doctors to work together and discuss cases in person beyond limitations imposed by the existence of separate specialties and departments. The opportunity to discuss the consensus for the treatment will be required as the multidisciplinary team meeting (MDT meeting) consists of breast surgeons, radiologists, pathologists, oncologists and nurses, both before and after the operation with the intention of providing patients with the best managements (Figure 6). In fact, the holding of MDT meetings is mandatory in the United Kingdom for many malignant diseases.[16,17]

As the main medical institute in Nagasaki, Nagasaki University Hospital has played a role in the proper treatment of a number of patients for a long time. Furthermore, it is also very important to understand the latest trends in breast cancer occurrence and treatment and to provide samples following informed consent to help develop effective new management options for the disease and to get clues for novel treatments in collaboration with research facilities for the future.

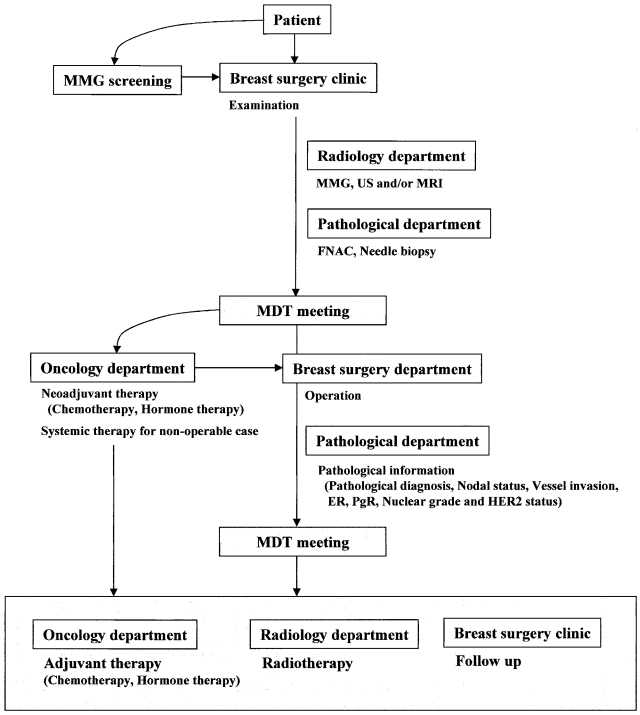

Figure 6. An example of the ideal system for breast care at Nagasaki University Hospital. MMG=mammography; US=ultrasonography; FNAC= fine needle aspiration cytology; MDT=multi disciplinary team.

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