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The 457th International Symposium on Therapy

The 457th International Symposium on Therapy was held by the Zoom Webinar on January 19, 2023. Dr. Koichi Ito, Director of the International Medical Society of Japan (IMSJ), presided over the meeting.

Breast cancer frontline

Introductory Message from the Chair

Koichi Ito, MD, PhD
Director, IMSJ

【Discourse】

Discourse:

Rev.Hiroaki Miyoshi
Chief Priest
Hongakuzan Myojuji

Lecture I

Latest trends in breast imaging diagnosis: Personalized screening and role of MRI-guided biopsy

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In Japan, the mortality rate of breast cancer has not decreased, despite mammography-based breast cancer screening having become more widely available. Therefore, the significance of the mammography-based screening has been discussed, and it is now considered necessary to conduct the screening according to the risk of each individual (personalized screening) rather than uniformly applying the same screening procedure for all women in Japan.

In 2016, the results of a randomized controlled trial (J-START) conducted to examine the usefulness of mammographic screening with and without breast ultrasonography in women in their 40s were published in Lancet. The results showed that of the screening methods, (1) 18% (34/184) of breast cancers were detected by mammography alone, and (2) 33% (61/184) of breast cancers were detected by breast ultrasonography alone. In conclusion, mammography alone is not sufficient for breast cancer screening in Japanese women in their 40s. It is an urgent necessary to discuss the indications for adding breast ultrasonography to mammographic screening for early detection of breast cancer.

In 2022, the European Society of Breast Imaging (EUSOBI) reported the following: "EUSOBI recommends such supplemental MRI screening to be offered to women with extremely dense breasts, from age 50 to 70, and at least every 4 years, preferably every 2 to 3 years. MRI can be used as a stand-alone screening technique（without mammography）". The background for this recommendation is based on the findings of a study conducted in 40373 women with extremely dense breasts in 2019. In this study, 16.5 individuals out of 1000 were found to have breast cancer. On the other hand, the results of the J-START study showed that the number of individuals detected by screening to have breast cancer is about 3.2 out of 1000 (117/36752) for mammography and 5.0 out of 1000 (184/36752) for mammography combined with breast ultrasonography. Although there was an increase by about 1.5 times, the fact has become clear that the number of individuals detected is expected to increase only by 2 out of 1000. Therefore,

we wonder if it might actually be useful to introduce ultrasonography for breast screening in Japan in the future.

In Europe and the United States also, breast ultrasonography is not widely accepted as a screening tool, and MRI is recommended for women at high risk. The lifetime risk of 20% or more of developing breast cancer (lifetime risk) is defined as "high-risk". Tools such as the Tyrer-Cuzick model and Gail model are used to evaluate the lifetime risk of breast cancer. In Japan, due to the absence of such assessment tools, it is difficult to immediately adopt the concept of "high risk" cases as in Europe and the U.S. The first step in screening of high-risk women should be MRI screening for hereditary breast and ovarian cancer (HBOC) syndrome. We conducted the research entitled "A study of the usefulness of MRI screening in patients with *BRCA*1/2 pathogenic variants" since 2014. The results showed that the frequency of breast cancer detected by MRI was 9% (2/22). This is the first prospective study in Japan to confirm the usefulness of MRI screening for high-risk women.

MRI screening is used in combination with MRI-guided biopsy for high-risk women. MRI-guided biopsy has been used in Europe and the U.S since 1994. However, in Japan, it began to be covered by the National Health Insurance system only in April 2018, about 11 years after the first MRI-guided biopsy was performed in 2007. According to our data since 2007, the rate of malignancy detected by MRI-guided biopsy is 38% (115/301). Thus, MRI-guided biopsy is considered to be an essential procedure not only in the Western population, but also in the Japanese population.

In April 2020, risk-reducing surgery and breast MRI surveillance began to be covered by the National Health Insurance system for patients with a history of HBOC. As a result, the number of institutions undertaking MRI-guided biopsy has gradually increased, but the examination is still performed at only 13 institutions. Considering the increasing number of individuals that would be expected to undergo MRI screening in the future, it is important to immediately increase the number of institutions that would make MRI-guided biopsy available.

Lecture Ⅱ

Recent Strategies for Breast Cancer Therapy ~from diagnosis to treatment~

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Considering the incidence of malignant diseases, breast ranks first among Japanese females, with the number of affected patients growing, especially among females aged ≥40 years. However, breast cancer has the fifth highest mortality rate among malignant diseases, indicating a low mortality rate despite frequency. This can be attributed to improvements in diagnostic techniques, including breast cancer screening, and novel drug therapeutics. Moreover, the extensive role of mammary gland surgery needs to be considered. We report the latest strategies in diagnosis, surgical treatment, perioperative drug therapy, and post-recurrence treatment.

・Breast cancer diagnosis

Breast cancer is a malignant disease with a relatively good prognosis. However, maintaining the quality of life in survivors post-treatment may be challenging. In young breast cancer patients, hereditary breast cancer and fertility-preservation should be considered post-diagnosis. Hereditary breast cancer accounts for approximately 10% of breast cancers, with certain syndromes attributed to multiple genetic abnormalities. Among them, BRCA1/2 gene mutation-induced hereditary breast cancer and ovarian cancer syndrome (HBOC) has a high frequency. From 2020, BRCA1/2 genetic testing will be covered under insurance for patients diagnosed with breast cancer <45 years of age. In patients diagnosed with HBOC preoperatively, contralateral mastectomy, to prevent contralateral breast cancer development, and salpingo-oophorectomy, to prevent ovarian cancer, can be performed simultaneously during breast cancer surgery.

Perioperative drug therapy for breast cancer includes anticancer drug therapy, molecular target drug therapy, and endocrine therapy, with continuous endocrine therapy recommended for ≥5 years. Secondary amenorrhea (infertility) due to anticancer drugs and endocrine therapy needs to be addressed in breast cancer survivors who desire to have children. Therefore, fertility-preservation surgery is widely recommended before initiating drug therapy. Currently, cryopreservation of fertilized/unfertilized eggs or ovarian tissue is recommended in Japan. However, no clear consensus has been established regarding the risk of aging in pregnancy and subtypes due to prolonged standard treatment.

・Surgical treatment

To date, breast-conserving surgery has been the main surgical procedure employed in breast cancer surgery. However, since breast reconstruction surgery has been covered by health insurance since 2013, there has been a growing tendency to perform simultaneous breast reconstruction post-mastectomy. Breast reconstructive techniques include those that utilize artificial materials and those using autologous tissue. Considering

the timing of surgery, primary reconstruction is simultaneously performed with breast cancer surgery, whereas secondary reconstruction is performed after a certain period post-surgery. Selecting the most suitable surgical method is essential, considering factors such as the patient's condition, desires, and body type.

・Perioperative drug therapy

Previously, the purpose of neoadjuvant chemotherapy (NAC) for advanced breast cancer was tumor shrinkage and breast tissue preservation. In 2022, revised guidelines included a 'residual disease-guided approach' after NAC for breast conservation. Breast cancer is broadly classified into four subtypes, with drugs and therapeutic effects markedly differing considering each subtype. Patients who achieve a good therapeutic effect with NAC tend to have a good prognosis. Conversely, postoperative drugs distinct from those that afforded a complete response need to be selected for patients who failed to achieve a complete response. The potential of molecular-targeted drugs and immune-check inhibitors for NAC has been explored, dramatically improving therapeutic effects.

Anticancer drugs, molecular-targeted drugs, and endocrine therapy are selected based on each subtype and risk for postoperative drug therapy. Considering endocrine therapy, continued treatment for 5 years was previously recommended; however, extending therapy for 7 to 10 years has been recommended depending on the risk. The latest guidelines recommend combining cyclin-dependent kinase 4 and 6 inhibitors and anticancer agents, for example, combined with endocrine therapy to treat recurrence. Drug therapy is becoming progressively individualized.

・Treatment after recurrence

Post-breast cancer surgery, recurrence and metastasis are often observed in the bone, liver, and lung. Surgical resection of recurrent lesions remains the first choice, despite poor evidence suggesting an improved prognosis. Drug therapy for each subtype differs, and subtypes occasionally differ between primary and metastatic lesions. Therefore, confirming the subtype by repeat biopsy of the metastatic lesion is recommended before initiating treatment for recurrence. Since 2019, gene panel testing has been covered by health insurance. Treatment options are expected to extend to patients who would experience anyrecurrence after completing recommended treatments.

Currently, more individualized treatment is recommended, from breast cancer diagnosis to treatment for recurrence.