Breast Cancer Handbook

Breast Surgery Department
Japanese Red Cross Medical Center

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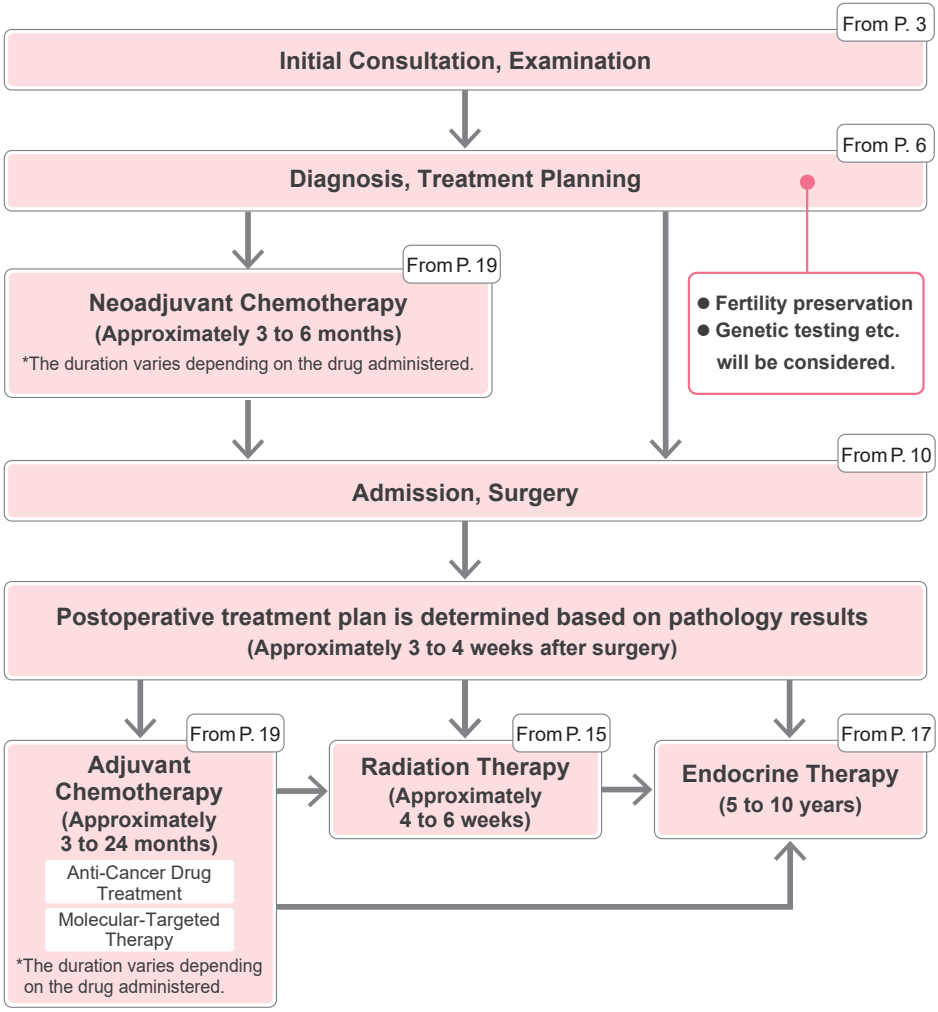
1 Medical Treatment Sequence at Our Center

We strive to swiftly progress from the initial consultation to a diagnosis, making every effort to determine a treatment plan through thorough consultation with the patient.
Breast cancer treatment is an interdisciplinary approach involving the removal of the tumor through local therapies such as “surgery” and “radiation.” Additionally we perform a combination of several treatments to target the seeds of cancer that may have spread throughout the body using “anti-cancer drugs,” “endocrine (hormone),” or “molecular-targeted therapies.” Essentially, we select a treatment tailored to each patient using guidelines based on scientific evidence. Moreover, we consider factors such as the patient’s age, living environment, the presence, or absence of comobidities, and personal preferences, when determining the most suitable treatment.

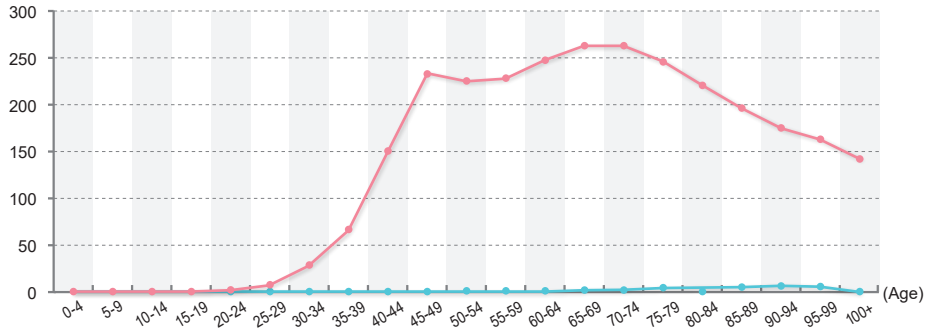


2 Diagnosing Breast Cancer

What is Breast Cancer?

The breast cancer incidence rate in Japan is on the rise, ranking first among all cancers among women. Breast cancer is prevalent among women in their late 40s to 70s, with the risk starting to increase in their 30s, affecting approximately one in nine women. Though rare, it is also seen in men.

2019 Age-Specific Incidence Rates (National Estimate) Per 100,000 people

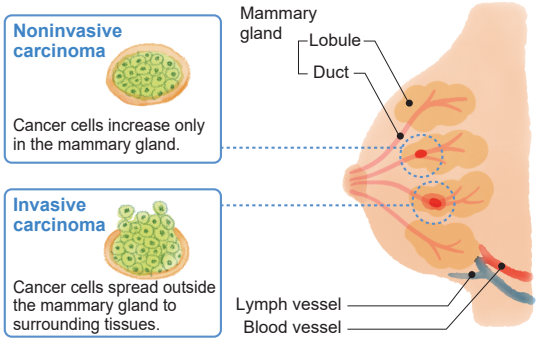


Source: National Cancer Registry Incidence Data

A breast is made up of mammary tissue and fatty tissue. The mammary glands consist of many ducts and lobules.

A condition where cancer cells are present inside a mammary duct and/or lobules is called "**Noninvasive carcinoma**," which does not spread to lymph nodes and other organs.

On the other hand, "**Invasive carcinoma**" is a condition in which cancer cells have broken out of the original lobules and ducts, breaking through and spreading to surrounding tissues. This type of cancer may metastasize to lymph nodes and other organs.



Once breast cancer has metastasized to the axillary lymph nodes (lymph nodes in the armpits), it is likely to spread to the whole body from there. Therefore, determining whether or not the cancer has metastasized to the axillary lymph nodes is crucial in treating breast cancer.

Breast cancer is classified into five stages, from 0 to 4, by whether or not existence of infiltration, how large the tumor is and it has spread into lymph nodes and other organs. In treating breast cancer, it is important to plan the treatment based on various factors, including the cancer's stage, characteristics, and the location of the primary tumor.

Introducing Breast Cancer Screening Tests

The following is the basic breast cancer screening sequence.
If breast cancer is suspected through a breast ultrasound or mammogram, a pathology test is performed to determine if it is breast cancer. After a positive diagnosis, imaging tests are performed to determine the size and extent of the breast cancer and whether or not it has metastasized or not. The order of these tests may vary from person to person.

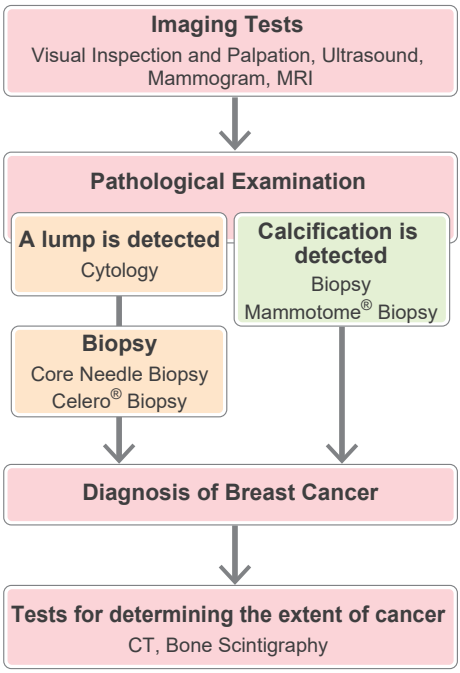
(1) Visual Inspection and Palpation

A physician visually and manually examines the breasts and nipples for any signs of abnormalities. Additionally, the physician checks for swollen lymph nodes in the armpits. If a lump is present, its size, firmness, and the condition of the surrounding edges are also examined.

(2) Mammogram

A mammogram is an X-ray test that captures images of the breast while compressing it as flat and uniform as possible. During the procedure, a technician places the breast between a platform with an X-ray film and a plastic plate. Images are taken from two directions, one vertical and one horizontal. The mammogram sometimes can detect for calcifications that may not be identified using ultrasound.

Breast Cancer Examination Sequence



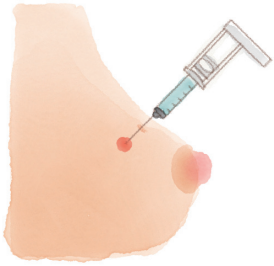
(3) Ultrasound (Echo)

This test exposes the breasts to sound waves, and the reflected waves are transformed into a visual image to identify tumors. Though it does not cause you any pain, it feels cold from the gel applied to the skin. Because a breast ultrasound does not use radiation, it can be performed on pregnant women.

Mammograms and ultrasound differ in what is easily captured, depending on the characteristics of the cancer. For more accurate diagnosis, we generally have you go through both tests.

(4) Cytology

Breast cytology is a test in which a needle is used to extract cells from a lump suspected to be cancerous to be examined under a microscope. It is similar to drawing blood, usually performed without anesthesia. It is a relatively simple, minimally invasive test.



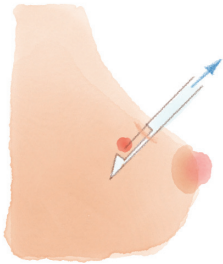
[Cytology]
Cells are obtained in a manner similar to drawing blood.

(5) Biopsy

In a breast biopsy, a sample is extracted with a needle thicker than the one used in cytology, to be examined under a microscope. Because it uses a larger gauge needle, it is performed under local anesthesia. There are two main types of breast biopsies: (a) core needle biopsy (CNB) and (b) vacuum-assisted biopsy (VAB).

(a) Core Needle Biopsy (CNB)

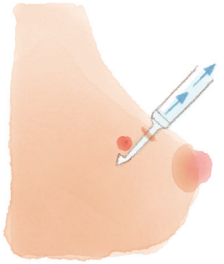
In a core needle biopsy, a needle approximately 2 mm in diameter is used to extract a tissue sample. This procedure is conducted while viewing images from a breast ultrasound to confirm the precise location of the lump. Other than refraining from bathing on the day of your biopsy, there are no specific restrictions.



[Biopsy]
Core needle biopsy:
A sample of tissue is obtained by resecting a small portion.

(b) Vacuum-Assisted Biopsy (VAB)

In a vacuum-assisted biopsy, a needle approximately 4 mm in diameter is inserted to draw a sample of tissue. There are no stitches required because the incision is very small. **Celero® biopsiesare** performed using ultrasound, while **Mammotome® biopsiesare** conducted under X-ray stereotaxis guidance. Because VAB uses a larger gauge needle, your chest area will be covered with a bandage after the procedure, until the next day, to apply pressure on the biopsy site and prevent bleeding.



[Biopsy]
Celero® biopsy/Mammotome® biopsy:
A sample of tissue is obtained by suction.

(6) MRI

An MRI is primarily used to assess the extent of cancer and helps in determining the feasibility of partial mastectomy. During your breast MRI, a contrast agent is administered, and images are captured while you lie on your stomach. MRIs cannot be performed on individuals with tattoos or metallic implants, including pacemakers.

(7) CT scan

A CT scan is performed to assess the size and extent of the breast cancer, and to determine if it has spread to the axillary lymph nodes or other organs outside the breast. Typically, images are captured using a contrast agent.

(8) Bone scintigraphy

A bone scintigraphy test identifies whether or not the cancer has spread to the bones. After injecting a radioactive isotope that has a tendency to accumulate in the bones, images of the bones throughout the body are taken with a special camera.

3 Treating Breast Cancer

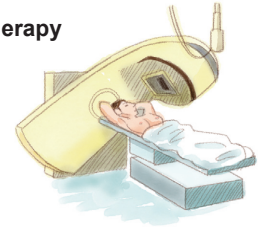
3-1 Introduction

Breast cancer originates in the breast and spreads to organs throughout the body by traveling through the bloodstream or lymphatic system. Therefore, treatment has to be administered not only to the breast but to the entire body.
We combine various appropriate treatment methods based on the characteristics and progression of each patient's cancer. It is beneficial for patients to understand the available treatment methods and the reason behind them, providing them with peace of mind during the treatment process.
Breast cancer treatment is categorized into "**local therapy**" and "**systemic therapy.**" Local therapy focuses on treating the breasts and axillary lymph nodes, while systemic therapy involves administering drugs to address microscopic cancers throughout the body.

Local Therapy

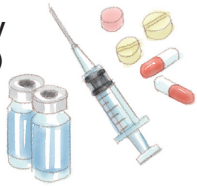
Surgical Therapy

Radiation Therapy



Systemic Therapy

Endocrine Therapy
(Hormonal Therapy)



Chemotherapy
(Anti-Cancer Drugs, Molecular-Targeted Drugs)

In determining which therapy to pursue, various factors must be taken into consideration, including:

- breast tumor size and the presence of axillary lymph node metastasis (**the clinical stage**)
- the characteristics of the breast tumor (**the subtype**)
- the age of the patient
- whether or not the patient wants to conceive
- whether or not the patient has Hereditary Breast and Ovarian Cancer (HBOC) Syndrome (see P. 26 for details)

We aim to engage in thorough discussions with the patients, carefully considering these factors, in order to select a treatment that is most suitable for their individual needs. If you have any questions or preferences in planning your treatment, feel free to discuss them with your physician.

Staging Classification (Stages)

Breast cancer progression is categorized into stages, as outlined in the table below. The stage is determined by factors such as the size and extent of the tumor, the presence of axillary lymph node metastasis, and whether or not it has spread beyond the breast to other organs. The clinical stage is estimated using imaging test results before surgery, and the final staging is determined based on pathology results obtained after surgery.

Clinical Staging of Breast Cancer (UICC TNM classification 8th edition)

Metastasis to other organs	**No sign of metastasis** (M0)				**Metastatic** (M1)
Lymph node metastasis (N) / **Lump Size** (T)	**None** (N0)	**Underarm** (The lump moves) (N1)	**Underarm** (The lump is stationary.) or **Near the breastbone** (N2)	**Underarm and near the breastbone** or **Above and below the collarbone** (N3)	
Noninvasive carcinoma (Tis)	**0**				
No evidence of a lump (T0)		**ⅡA**	**ⅢA**	**ⅢC**	**Ⅳ**
2 cm or less across (T1)	**ⅠA**	**ⅡA**	**ⅢA**	**ⅢC**	
2 to 5 cm across (T2)	**ⅡA**	**ⅡB**	**ⅢA**	**ⅢC**	
Larger than 5 cm across (T3)	**ⅡB**	**ⅢA**	**ⅢA**	**ⅢC**	
Lump of any size (T4) * When the tumor is in the chest wall, when there is edema or ulceration of the skin, or when it is inflammatory breast cancer.	**ⅢB**	**ⅢB**	**ⅢB**	**ⅢC**	

Subtype Classification

Each cancer possesses distinct features, making it crucial to select a drug therapy tailored to the specific characteristics of the cancer cells. Pathological examinations focus on the following items. Breast cancer is then classified into subtypes based on these values, and drug therapy appropriate for each subtype is selected (refer to the “Breast Cancer Subtype Classification” table below).

Breast Cancer Subtype Classification

: Recommended therapies

	Ki67 level	Hormone receptor-positive [1]	Hormone receptor-negative
HER2-negative	Low	Luminal A Endocrine Therapy [2]	Triple-negative Chemotherapy
	High	Luminal B Endocrine therapy + Chemotherapy	
HER2-positive	Any level	Luminal HER2 Endocrine therapy + Chemotherapy + Anti-HER2 therapy	HER2 type Chemotherapy + Anti-HER2 therapy

1) Hormone receptor-positive: When either the estrogen receptor (ER) or progesterone receptor (PgR), or both, are positive.
2) We may consider chemotherapy if there is an elevated risk of recurrence, including metastasis in 4 or more axillary lymph nodes.

● ER (Estrogen Receptor), PgR (Progesterone Receptor)

ER and PgR are two types of hormone receptors, proteins crucial for cancer cell growth. A tumor is considered positive if at least 1% of either receptor is positive. It is considered that the higher the value is more likely effective endocrine (hormone) therapy, the smaller the value is less effective.

● HER2 Protein

The HER2 protein is also involved in cancer cell growth. An IHC (a test method used to detect excess protein expression) score of “0” to “1+” is considered negative, while “3+” is considered positive. For an IHC score of “2+,” additional testing called FISH (a test used to detect gene amplification) is performed to confirm whether it is positive or negative.

● Ki-67 Index

The Ki67 index serves as a marker indicating the cancer's proliferation speed. A higher percentage suggests a faster rate of cell proliferation, with a Ki67 index of 30% generally considered high. However, the interpretation of the Ki67 levels as low or high can vary among institutions. While the Ki67 index is a useful indicator for predicting prognosis, treatment plans are not determined solely based on this measure. The decision to administer chemotherapy is made by comprehensively evaluating malignancy, taking into consideration other indicators in combination with the Ki67 index.

Oncotype DX

Among breast cancers that are hormone receptor-positive but HER2-negative, luminal A type is treated with endocrine therapy, and luminal B type is treated with both endocrine therapy and chemotherapy. When it is unclear which type it is, a test called Oncotype DX (medical insurance treatment) may be suggested.

Oncotype DX is a gene exp ression analysis test using breast cancer specimens, developed by Genomic Health Inc. in the United States. The test can predict the recurrence risk and the potential benefit of chemotherapy in addition to endocrine therapy, providing numerical values. It is useful as one of the materials for judgment whether it is possible to avoid chemotherapy.

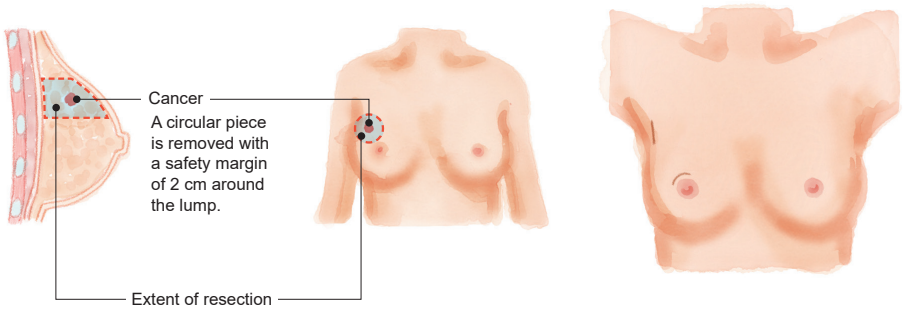
The test is suggested to those we believe will benefit from it and on whom it can be performed. The results will be available 3 to 4 weeks after the test is submitted. Further information about Oncotype DX will be given by your physician during your post-surgery follow-up visit.

3-2 Local Therapy - Surgical Therapy -

In breast cancer surgical therapy, there are two main approaches: partial mastectomy (breast-conserving surgery), which involves removing a part of the breast, and total mastectomy (total breast removal surgery), which involves removing the entire breast while leaving the pectoral muscles in place. Breast reconstruction is an option following total mastectomy.
Surgery on the axillary lymph nodes is also necessary as part of the treatment for breast cancer. The determination of which surgery to conduct is based on factors such as the extent and location of the cancer, breast size, and whether it has spread to the lymph nodes.

Partial Mastectomy (Breast-Conserving Surgery)

In breast-conserving surgery, a circular incision is made around the lump, leaving the nipple and areola intact. This procedure is suitable for lumps with a size of 3 cm or less, taking into account the balance between breast and lump sizes, as well as the location of the lump.
Following surgery, radiation therapy is performed to reduce the risk of cancer recurrence in the remaining breast tissue. However, there is a 3 to 5% chance of local recurrence of cancer in the remaining breast. If cancer is found in the tissue removed as a result of postoperative pathological examination, additional resection may be necessary.
The usual hospitalization is approximately 4 days, during which a drainage tube is placed to collect fluid build-up at the incision area after surgery. It is possible to discharge from the hospital next day after the tube is removed.



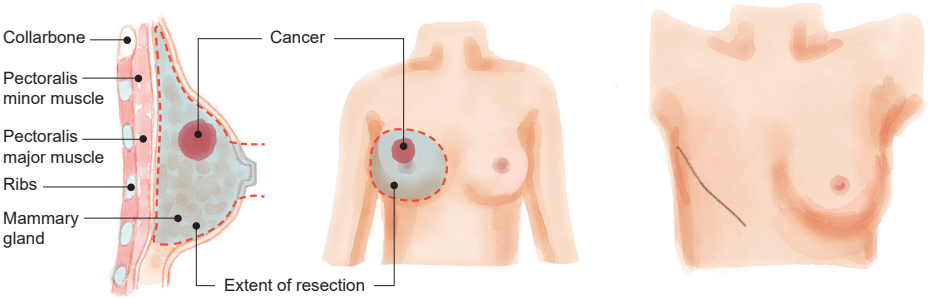
We pursue preserving the aesthetic appearance of the breast.

At our center, we place incisions along the edge of the areola or under the armpit to make the surgical scars less visible. We also make efforts during surgery to minimize the deformation of the breast.

Total Mastectomy (Total Breast Removal Surgery)

Mastectomy is a surgical procedure aimed at removing the entire breast while preserving the pectoralis major and minor muscles beneath it. The skin including the nipple and areola will be removed as well. Total mastectomy is typically recommended in cases where the cancer is widespread, there are two or more lumps in separate parts of the breast, the distance between the nipple and the lump is small, or radiation therapy is not feasible due to reasons such as the presence of collagen vascular disease.

The usual hospitalization period is approximately 10 days, during which a drainage tube is placed to collect fluid build-up at the incision area after surgery. It is possible to discharge from the hospital day after the tube is removed.



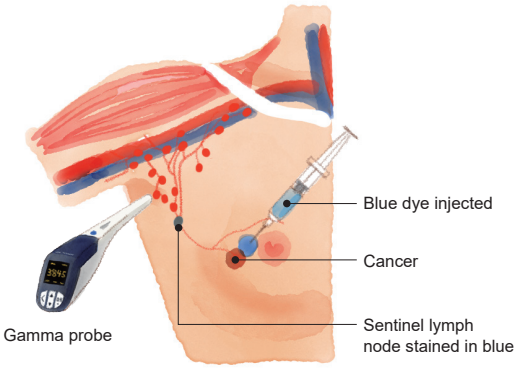
Sentinel Lymph Node Biopsy

Presurgical testing may not definitively indicate whether or not cancer has spread to the lymph nodes in the armpit (axillary lymph nodes). In cases where no apparent metastasis is observed in the axillary lymph nodes, a sentinel lymph node biopsy is performed during surgery to assess the potential spread of cancer.

The sentinel lymph nodes are the initial lymph nodes within the network of axillary lymph nodes that may be affected by cancer cells. The sentinel lymph node is removed at the outset of the surgery, and a pathological examination is then conducted during the surgery to determine if cancer cells are present in the axillary lymph nodes.

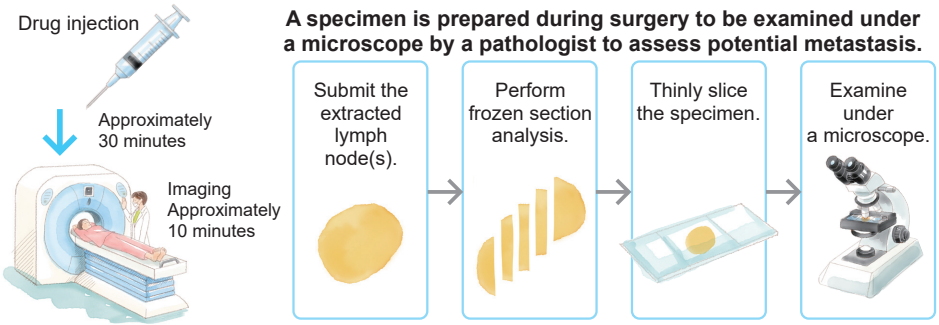
<R.I./Dye Test>

During surgery, sentinel nodes are identified with a gamma probe that can detect 99mTc, a radioactive material injected before surgery. A dye test, involving the intraoperative injection of a blue dye, is also used.



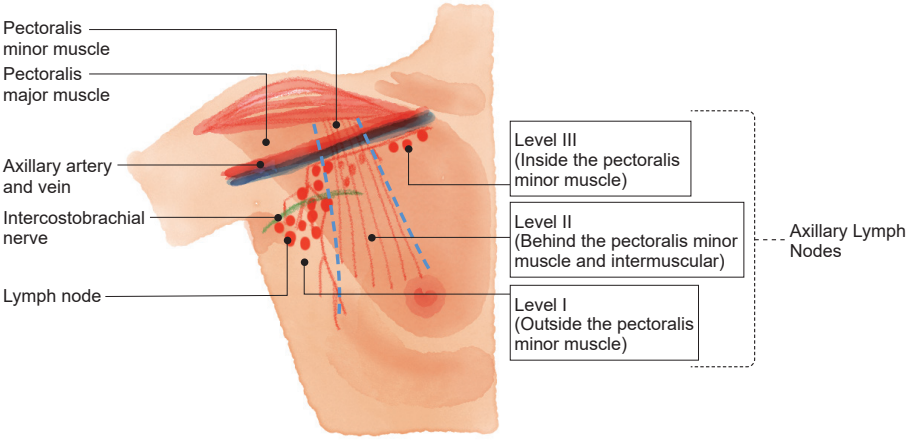
If no cancer cells are detected in the sentinel lymph node, it is assumed that the cancer has not spread to other lymph nodes, and axillary lymph node dissection is typically not performed. Even if cancer cells are found in sentinel lymph nodes, axillary lymph node dissection may not be performed in some cases.

Axillary lymph node may incur aftereffects, including a condition known as lymphedema, which leads to swelling in the hand and arm and abnormal sensations in the armpit, it increases the burden on the patient. Sentinel lymph node biopsy is a critical test because it can alleviate the burden on the patient by avoiding the need for unnecessary axillary lymph node dissection.



Axillary Lymph Node Dissection

Axillary lymph node dissection is a surgical procedure that involves removing lymph nodes embedded in the fat of the armpit as a single mass, typically from level I to level II (see figure below). This procedure may be undertaken when metastasis is identified either in preoperative testing or becomes evident during intraoperative sentinel lymph node biopsy. Complications arising from axillary lymph node dissection may include lymphedema in the arm and tingling sensations in the upper limb. Following axillary lymph node dissection, patients are provided with instructions on preventing lymphedema.



Breast Reconstruction Surgery

Breast reconstruction surgery is used to recreate a breast that has been surgically removed. There are two primary types of breast reconstruction: one uses artificial breast prostheses, and the other is autologous breast reconstruction, which utilizes the patient's own tissue from another part of the body.

We perform breast reconstruction surgery for patients who have undergone total mastectomy (total breast removal). Patients who undergo postoperative radiation therapy may encounter challenges in reconstruction due to the skin becoming weak or becoming difficult to stretch. Your doctor will engage in discussions with you to determine the optimal breast reconstruction method and timing.

Breast reconstruction can be categorized into two timing-based approaches: "primary reconstruction" and "secondary reconstruction." Additionally, the process can be further distinguished by the number of surgeries involved into "one-stage reconstruction" and "two-stage reconstruction." The reconstruction method is tailored to each patient, taking into consideration factors such as their breast cancer condition and personal preferences.

We allow time for the reconstructed breast's position and shape to stabilize before proceeding with nipple and areola reconstruction.

● Primary Reconstruction (Simultaneous Reconstruction)

Primary reconstruction is performed concurrently with breast cancer surgery. By combining breast cancer surgery and reconstruction into one simultaneous procedure, patients experience fewer surgeries compared to secondary reconstruction, reducing the physical and financial burden on the patient.

● Secondary Reconstruction

Delayed reconstruction is performed after a period following breast cancer surgery. It involves more surgeries compared to primary reconstruction. However, as it is done at a later time, the patient can fully focus on breast cancer treatment. People who have undergone breast cancer surgery in the past can also have reconstruction surgery.

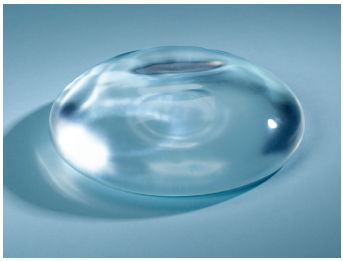
● One-Stage Reconstruction

This process reconstructs the breast in a single procedure using artificial breast (implant) or autologous tissue.

● Two-Stage Reconstruction

This process reconstructs the breast in two separate procedures. In a two-stage reconstruction, the process begins by placing a skin-expanding bag known as a tissue expander beneath the pectoralis major muscle. The skin is stretched by filling the bag with saline solution. Over the course of six months to a year, multiple visits to the doctor are required for the injection of saline solution, allowing for gradual skin expansion. Once the tissue expander has reached a size sufficient for forming a breast shape, the tissue expander is removed, and the breast is reconstructed with an artificial breast (implant) or autologous tissue.

Tissue Expander

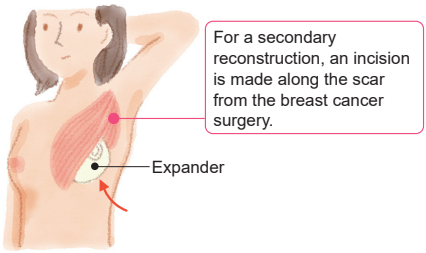


Silicone Breast Implant

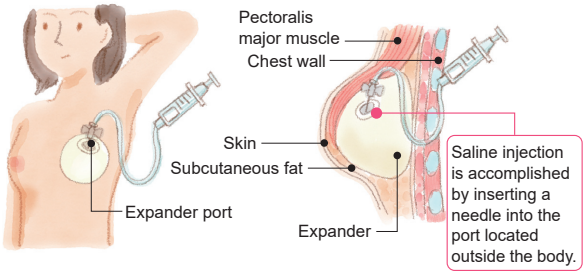
* Source: Allergan Japan Inc.

<Two-Stage Reconstruction Sequence>

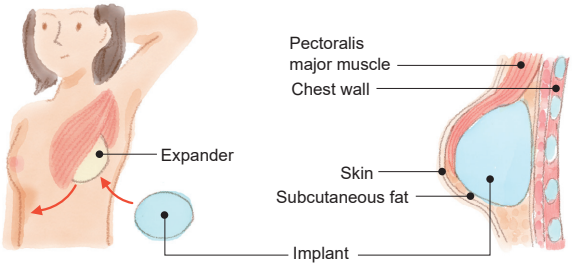
1 Following breast cancer surgery, a tissue expander is inserted.



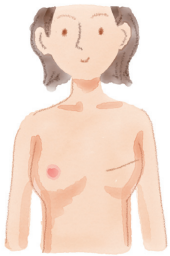
2 Saline solution is injected into the expander.
More solution is added over a period of six months to a year.



3 Once the skin and surrounding tissues have been adequately expanded, an incision is made along the same scar, and the tissue expander is replaced with a breast implant or autologous tissue.



4 The procedure is completed by closing the incision on the breast.

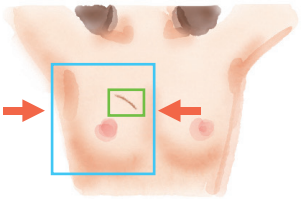


3-3 Local Therapy - Radiation Therapy -

Even when all cancer cells are thought to have been removed by surgery, there remains a risk of undetected cancer cells in the breast or lymph nodes. In such cases, radiation is administered to the breast and lymph node area after surgery. Postoperative radiation therapy is a standard treatment for patients who have undergone a partial mastectomy. Patients who have had a total mastectomy may also receive postoperative radiation therapy if it is deemed necessary based on pathology examination results.
Before beginning radiation therapy, you will undergo an examination by a radiation oncologist to establish your personalized treatment plan. Typically, **you come in for radiation treatment daily for about four to six weeks.** One radiation session finishes in a few minutes, and it is possible to work while at the hospital. In case the chemotherapy is also given after surgery, radiation therapy commences after the completion of chemotherapy. While concurrent administration of endocrine therapy is a possibility, it is advisable to initiate it only after the postoperative wound has fully healed.

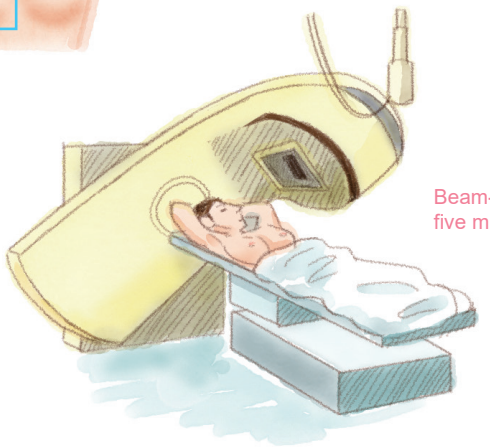
Post-Partial Mastectomy Radiation Therapy

Even when all cancer cells are thought to have been removed by a partial mastectomy (breast-conserving surgery), there remains a risk of undetected cancer cells in the breast or lymph nodes. **It is a standard treatment to use whole breast irradiation (tangential irradiation)** following a partial mastectomy because it has been observed that administering postoperative radiation to the entire breast **reduces the risk of local recurrence by approximately one-third**. If the pathology results of the surgical specimen indicate that cancer cells have reached close to the resection edge, additional irradiation (boost irradiation) may be administered.



Irradiation field
Additional irradiation (boost irradiation) field
Irradiation (opposing bilateral portal irradiation)

Radiation is administered, sparing the lungs, heart, and the other breast.

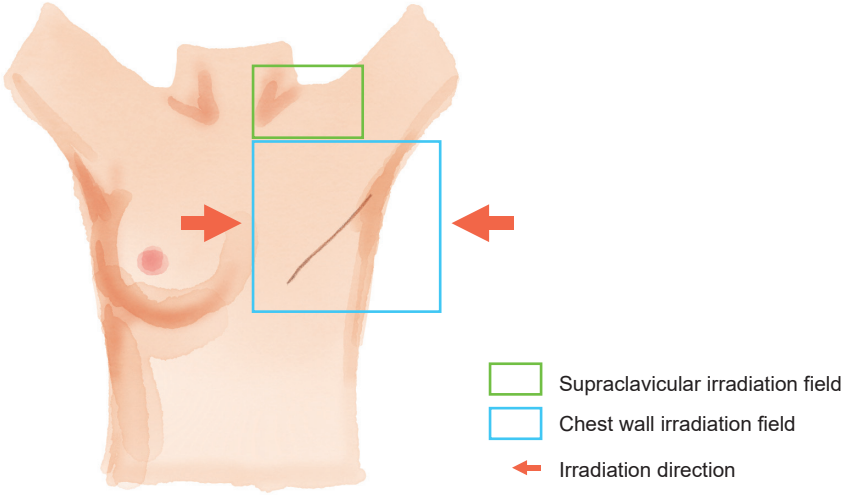


Beam-on time is up to five minutes.

Post-Total Mastectomy Radiation Therapy

Following a total mastectomy (total breast removal), if postoperative pathology results indicate a high risk of cancer recurrence in the chest wall or lymph nodes, radiation therapy may be administered. Radiation therapy is consideredin the following cases:

- Positive axillary lymph nodes (especially when there are four or more positive lymph nodes).
- Positive resective margins.
- Invasion of skin or pectoralis major muscle.



Radiation Therapy Side Effects

- **Dermatitis**

  About two weeks into the course of radiation therapy, the skin may exhibit redness or flakiness. It is advisable to apply moisturizers corresponding to the skin condition. Typically, after the completion of radiation therapy, the skin condition improves over a few months.

- **Radiation Pneumonitis**

  Radiation therapy may induce pneumonia.
  However, the risk of severe radiation pneumonitis is minimized through precise field targeting, ensuring adjacent organs are not harmed.

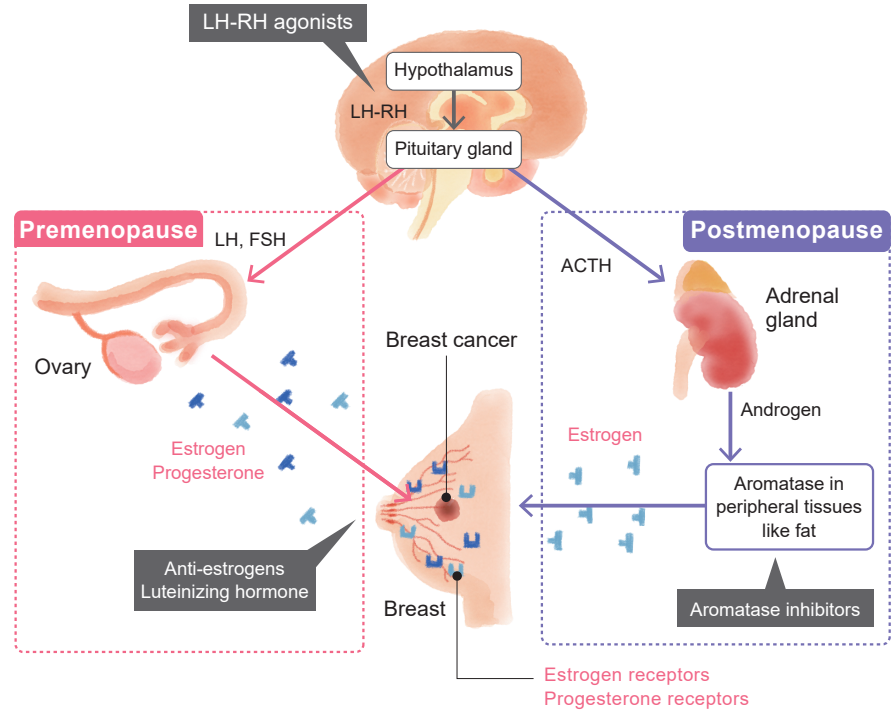
Generally, side effects such as hair loss and nausea are not commonly observed.

3-4 Systemic Therapy - Drug Therapy -

Endocrine (Hormone) Therapy

Some breast cancer cells proliferate under the influence of female hormones (estrogen). Endocrine therapy is specifically designed for female hormone-influenced breast cancer. It takes one to three months to take effect. Applying this therapy continuously for a long term (five to ten years) following surgery is expected to be effective in preventing recurrence. The choice of drugs can vary between premenopausal and postmenopausal women due to differences in estrogen production pathways in the body. For premenopausal women, anti-estrogen drugs are used in combination with LH-RH agonists in some cases. For postmenopausal women, anti-estrogens or aromatase inhibitors are used.

Estrogen Production Pathways and Endocrine Therapy Drug Mechanism of Action



LH : luteinizing hormone
LH-RH : luteinizing hormone-releasing hormone
FSH : follicle stimulating hormone
ACTH : adrenocorticotropic hormone

Features and Side Effects of the Main Endocrine Therapy Drugs

Drugs	**LH-RH agonists** **Goserelin** (Brand name: Zoladex®) **Leuprorelin** (Brand name: Leuplin®)	**Anti-estrogens** **Tamoxifen** (Brand name: Nolvadex®) **Toremifene** (Brand name: Fareston®) * Generic versions available	**Aromatase inhibitors** **Anastrozole** (Brand name: Arimidex®) **Exemestane** (Brand name: Aromasin®) **Letrozole** (Brand name: Femara®) * Generic drug available
Mechanism of Action/ Features	● The secretion of estrogen produced in the ovaries and suppresses the growth of cancer cells. ● Applicable to premenopausal women with functional ovaries.	● Suppresses the growth of breast cancer by blocking the estrogen receptors (ER) in cancer cells, keeping estrogen from binding. ● Applicable to both premenopausal and postmenopausal women. In the majority of cases, menstruation does not completely stop (in under 5% of cases). * These are not varian suppression drugs.	● Reduces the secretion of estrogen by suppressing the activity of aromatase, an enzyme necessary to produce estrogen from fat cells. ● Applicable to postmenopausal women whose ovarian function has ceased.
Administration	Subcutaneous injection into the abdominal wall Once every three or six months	Oral, once a day	Oral, once a day
Side effects	● Similar to menopause (including hot flashes, heat sensations, and stiffness in the shoulders)	● Similar to menopause (including hot flashes, heat sensations, and stiffness in the shoulders) ● Increase in vaginal discharge ● Subtle increase in uterine cancer risk among postmenopausal women Routine monitoring for uterine cancer is not recommended. If unusual vaginal bleeding persists for more than one or two weeks, do not ignore, but consult a gynecologis.	● Similar to menopause (including hot flashes, heat sensations, and stiffness in the shoulders) ● Joint pain (stiffness in the handsespecially in the morning) ● Osteoporosis

Chemotherapy

Chemotherapy is a treatment that targets and eliminates cancer cells by administering anti-cancer drugs or molecular-targeted drugs.
There are two types of chemotherapy: “neoadjuvant” and “adjuvant.” Both types are equally effective, and it is recommended to consult your doctor to determine which is more suitable.

At our center, chemotherapy is administered through infusion in the “Chemotherapy Room” on an outpatient basis.
Anti-cancer drugs also temporarily impact normal cells, resulting in side effects. Recent advancements have led to improved strategies to counteract side effects, and our center strives to minimize these effects as much as possible. As you undergo treatment, it is crucial to carefully consider the benefits, side effects, and risks associated with anti-cancer drugs.

Neoadjuvant Chemotherapy (Preoperative Chemotherapy)	**Adjuvant Chemotherapy (Postoperative Chemotherapy)**
● Reducing the tumor size expands the applicability of partial mastectomy, improving the rate of breast conservation, and making initially unresectable tumors smaller and operable. * Even if an effect is observed from neoadjuvant chemotherapy, it does not guarantee the feasibility of partial mastectomy. ● The effect of chemotherapy is confirmed. ● It helps identify which drugs are effective. ● If the expected effect is not observed or if there is tumor progression, proactive measures such as switching drugs or stopping the treatment and accelerating the timeline for surgery will be considered.	● The decision to proceed with adjuvant chemotherapy is made after pathologically examining the surgically removed tissue, taking into account the patient’s preferences. ● If the intravenous administration of chemotherapy (anti-cancer drug therapy) is deemed challenging in older patients, oral anti-cancer drugs may be considered as an alternative. 

Multi-Drug Therapy

Typical anti-cancer drugs used in breast cancer treatment include anthracyclines and taxanes.

Molecular-targeted drugs such as Herceptin® and Perjeta® are also available for HER2-positive breast cancer. Studies have shown the effectiveness of several other drugs, and combining different anti-cancer drugs has been found to enhance overall efficacy as compared to using a single drug. This approach is called “multi-drug therapy.” Multi-drug therapy sessions are often denoted as “EC therapy” or “TC therapy” using the initial letters of the anti-cancer drugs used. In most cases, drugs are administered intravenously.

Major Anti-Cancer Drugs/Molecular-Targeted Drugs

E: Epirubicin (Anthracycline)
A: Adriamycin (Anthracycline)
C: Cyclophosphamide, Oral dosage form (Endoxan®) is also available.
F: 5-Fluorouracil (5-FU), **Oral dosage forms** (S-1, Capecitabine) are also available.
T: Paclitaxel (PTX), Docetaxel (DOC) (Taxenes)
H: Herceptin (HCP)® (Molecular-targeted drug: Trastuzumab)
P: Perjeta® (Molecular-targeted drug: Pertuzumab)
CBDCA: Carboplatin (platinum-based)
Pemb: Pembrolizumab (Keytruda: an immune checkpoint inhibitor)

Drug Holidays

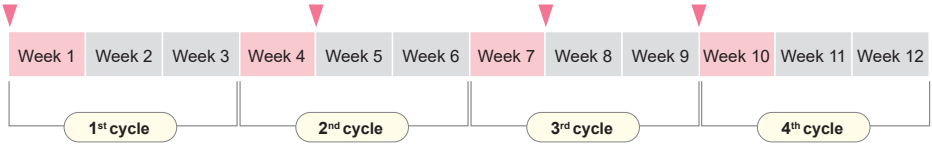
Since anti-cancer drugs cause great damage to the body, they are administered repeatedly with scheduled breaks. Breaks that are too short may hinder the patient's ability to regain physical strength, while breaks that are too long may diminish the effectiveness of the anti-cancer drugs. Therefore, an appropriate break period is pre-determined for each drug. Each treatment interval, including the scheduled break, is called a “cycle.”

Dosing Schedule

Typically, we schedule appointments every 2 to 3 weeks for 4 to 8 infusions, each lasting about 2 to 3 hours (over a period of 3 to 6 months). Depending on the specific anti-cancer drug prescribed, weekly visits may be required. **Detailed information about the drugs and the treatment schedule will be provided during the pre-treatment orientation.**

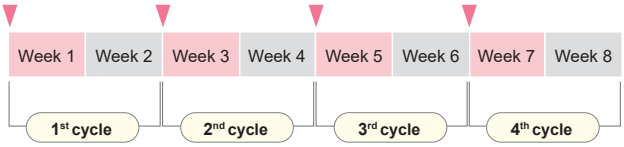
Dosing Schedule Examples

Administering once every three weeks — **Total of 4 cycles** (12 weeks)



Administering once a week for 12 weeks in a row — **Total of 12 administrations** (12 weeks)

Administering once every two weeks — **Total of 4 cycles** (8 weeks)



Side Effects

Typical side effects include myelosuppression (mainly leukopenia), hair loss, nausea, effects on the mucous lining of the gastrointestinal tract (stomatitis and diarrhea), tingling and swelling in the extremities, and nail changes. The severity of these side effects varies from person to person.

On the day of chemotherapy	For several days starting from the day of chemotherapy	For several days to several weeks	For several weeks to several months
Subjective side effects			
Allergic reactions **Infusion reactions***	**Nausea** **Loss of appetite** **Constipation** **Diarrhea** **Tingling** **Fatigue (tiredness)** **Joint and muscle pain**	**Infectious diseases** **Stomatitis** **Skin rashes and dermatitis** **Hair loss**	**Pigmentation changes** **Tingling** **Edema (swelling)** **Nail disorders** **Watery eyes** **Taste disorders** **Decreased heart function**
Side effects for which subjective symptoms are not easily detected			
		Decreased white blood cells (susceptible to infections) **Decreased platelets (susceptible to bleeding)**	**Decreased red blood cells (anemia)**

- The most common side effects of Herceptin® are cardiac dysfunction (in 2 to 4% of patients) and respiratory problems, for which regular cardiac function tests are recommended before and during treatment. Hair loss and nausea are not typically associated with this drugwhen used alone.

* **Infusion reactions:** Approximately 40% of patients may experience fever and chills after the first dose, typically within 24 hours (mostly within 7 to 8 hours), but these symptoms are rare after subsequent doses.

- Major side effects of oral anti-cancer drugs (Xeloda®, TS-1®) include hand-foot syndrome (its symptoms include tingling, burning sensations, peeling of skin on hands and feet,and numbness in hands and feet), loss of appetite, diarrhea, and renal dysfunction.
- Amenorrhea/**fertility preservation**: Premenopausal women experience the absence of menstrual periods due to anti-cancer drug treatment. Many women in their 30s and younger recover from amenorrhea after anti-cancer drug treatment, but depending on their age, they may go into menopause. **If you wish to conceive in the future, please consult your doctor.**

Please help us keep you safe during your chemotherapy.

- Wash your hands and gargle frequently.
- Keep your body clean by taking baths and showers.
- Tooth cavities, ingrown toenails, and festering pimples can easily cause infections, have them treated promptly before starting your chemotherapy.

During your treatment, how about enjoying wigs that you might not get to normally use?

There are chemotherapy nurses and pharmacists in the chemotherapy room who can assist you with any concerns you may have during treatment.
Let's overcome it together.

A nurse and pharmacist will give you another orientation before starting your chemotherapy.

4 After Surgery

Postoperative Follow-Up

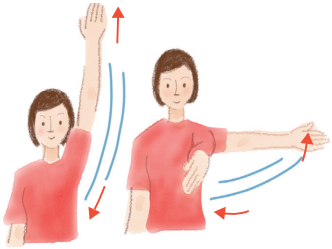
After surgery, your wound area will be checked during outpatient visits. Pathology results will be ready about 3 to 4 weeks after the surgery and will be explained to you in the outpatient clinic. The postoperative treatment plan will be determined based on the pathology results. As breast cancer can recur over time, you will be asked to come in regularly for treatment and recurrence checks for at least 10 years. We conduct the postoperative follow-up in cooperation with our affiliated hospitals. You will visit our hospital once a year while you will receive consultations, prescriptions, and screening throughout the year at the affiliated hospital.

Your Life After Hospital Discharge

After being discharged from the hospital, you may shower or take half-body baths. While you will be capable of self-care upon discharge, make sure to gradually ease back into your everyday life. If you have any concerns or questions, please do not hesitate to address them to our doctors and nurses.

Rehabilitation

After surgery, you may experience difficulty moving your arms or shoulders due to pain or stiffness. In such cases, it is beneficial to start a physical therapy early to gradually improve arm and shoulder mobility. It is important to perform these exercises under the guidance of doctors and nurses without pushing yourself too much.

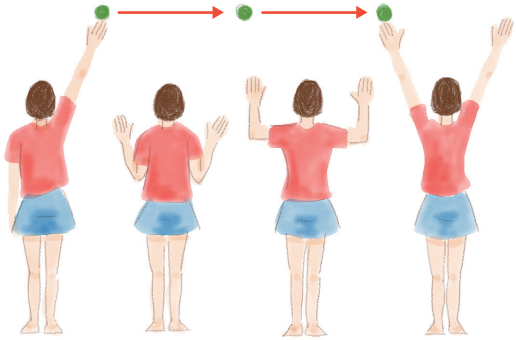


Raising Your Arm

Move the arm on the side of the operated breast forward and to the side at least 90 degrees. If it is difficult to raise the arm, try raising it with both hands clasped together.

Moving Your Shoulder Joint

Raise your elbow to 90 degrees or higher and rotate the shoulder joint.



Climbing the Wall

Extend the arm on the side of the unoperated breast and place a mark at the highest point your hand can reach to make it your target. Stand facing the wall, place both hands at the level of your shoulders, and extend the fingertips along the wall to the target, inhaling. Then, slowly lower your hands to the level of your shoulders, exhaling. Repeat this several times a day and raise the reachable height every per day.

Post-Axillary Lymph Node Dissection Guidelines

30 to 40% of patients who have undergone axillary lymph node dissection may experience lymphedema in the arm on the operated side. It does not necessarily occur in all patients. However, when it occurs, the flow of lymphatic fluid becomes sluggish, and the lymphatic fluid accumulates, leading to swelling in the arm on the operated side.

Our nurse will use a brochure to explain how to prevent this, and how to take care of your arm during your hospitalization and post-discharge appointments. Weight control is crucial in preventing lymphedema. Try to keep your BMI [weight (kg) / height $(m)^2$] at 25 or less.

If necessary, blood pressure measurement, blood sampling, or intravenous infusions can be performed on the arm where axillary lymph node dissection was conducted.

5 Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

In Japan, approximately 5 to 10% of breast cancer cases are considered hereditary, with about half attributed to changes in two genes, *BRCA1* and *BRCA2*. It has become evident that pathological changes in these genes significantly elevate the risk of developing breast and/or ovarian cancer, termed “Hereditary Breast and Ovarian Cancer Syndrome (HBOC).” HBOC affects approximately 1 in 200 to 500 people. Diagnosing HBOC through *BRCA1/BRCA2* genetic testing is valuable for selecting suitable treatment methods for patient and preventive measures a cancer including their family.
Our center offers genetic testing, genetic counseling, and prophylactic breast and ovarian ablation. Testing for hereditary cancers other than HBOC is also available.
You can see more detailed information on HBOC treatment on our center’s Breast Surgery Department website.

BRCA1/2 Genetic Testing

Because genetic testing uses white blood cells, we will collect your blood sample.
If any of the following apply to you, the testing will be covered by medical insurance, and your doctor will provide an explanation of the test. If none of the following apply to you, your medical insurance will not cover the expenses, and you will be responsible for the full amount.

(1) You have developed breast cancer and one of the following applies to you.

- ☐ You were diagnosed with breast cancer at the age of 45 or younger.
- ☐ You were diagnosed with triple-negative breast cancer at the age of 60 or younger.
- ☐ You were diagnosed with two or more primary breast cancers.
- ☐ At least one relative within the third degree has been diagnosed with breast, ovarian, or pancreatic cancer.
- ☐ Male breast cancer

(2) You meet the eligibility criteria for a companion diagnosis to a PARP inhibitor.

(3) You have already been diagnosed with ovarian, fallopian tube, or peritoneal cancer.

Genetic Counseling Department

Genetic counseling is available upon request. There, the characteristics of HBOC and the advantages and disadvantages of the testing will be explained, providing you with better understanding. A family tree will be drawn, and possibilities related to HBOC will be discussed. If you have been diagnosed with HBOC, you will be asked to attend genetic counseling sessions.

Hereditary Breast Cancer Department

If you wish to undergo a *BRCA1/2* test, please talk to your doctor. If you have not been a regular patient at our center, please make an appointment with our Hereditary Breast Cancer Department by phone. If you have a referral letter, you can also schedule an appointment through the Medical Cooperation Division of your regular medical institution.

6 About Our Center

Breast Surgery Department Website

The Department of Breast Surgery provides information about its medical services and staff on its website. We encourage you to visit the website in addition to reviewing this leaflet.

https://www.med.jrc.or.jp/hospital/clinic/tabid/151/Default.aspx

Cancer Consultation Support Center

Our Cancer Support Center offers free in-person or telephone consultations for cancer patients and their families. We recommend utilizing this service.

Examples of Questions to Ask

- How do I tell my family? How do I tell my children?
- What do I do about my job?
- What is a "second opinion"?
- Tell me about the High-Cost Medical Expense Benefit.
- Tell me about the appearance care program.

Hours: Monday through Friday 9:00 a.m. to 4:30 p.m.
Advance appointments are not required.
Location: Cancer Consultation Support Center on the first floor
Telephone consultations: 03-3400-1311 (Main) *Please ask for "Cancer Consultation."

Event Information

We hold "Cancer-Patientology" seminars on a regular basis.
Please see our website for details.
https://www.med.jrc.or.jp/hospital/tabid/306/Default.aspx

7 Medical Records (for you to fill in)

Preoperative Tests

Date	Test

Preoperative Evaluation

Lump Size (maximum diameter of invasive carcinoma)	cm		
Existence of metastasis to Lymph Node			
Staging Classification (Stages)	cT ( )	cN ( )	cM ( )
	cStage ( )		

Pathological Examination (preoperative)

Tissue Type	Invasive carcinoma	Noninvasive carcinoma	
Nuclear Grade	1	2	3
Estrogen Receptor	%		
Progesterone Receptor	%		
HER2 Protein (Staining)	score 0/1	score 2	score 3
	FISH	Amplification	No Amplification
Ki-67 Index	%		

Neoadjuvant Chemotherapy: Yes / No

Drug To Be Administered	Administration Date	Administration Period
	Number of doses: / Week:	
	Number of doses: / Week:	
	Number of doses: / Week:	

Surgery Schedule

Surgery Date	(Day of week, day, month)
Surgery Type	Partial Mastectomy Total Mastectomy (including skin-sparing mastectomy and nipple-areola-complex sparing mastectomy) Breast Reconstruction (with a tissue expander, implant or autologous tissue) Sentinel Lymph Node Biopsy, Axillary Lymph Node Dissection

Pathological Examination (postoperative) **Preoperative Treatment: Yes / No**

Tissue Type	Invasive carcinoma	Noninvasive carcinoma	
Lump Size (maximum diameter of invasive carcinoma)	cm		
Margin Evaluation	Negative	Positive	
Number of Metastases to Lymph Nodes			
Nuclear Grade	1	2	3
Estrogen Receptor	%		
Progesterone Receptor	%		
HER2 Protein (Staining)	score 0/1	score 2	score 3
	FISH	Amplification	No Amplification
Ki-67 Index	%		
Evaluation of Treatment Effectiveness (Only if there was preoperative treatment)	0 1a 1b 2a 2b 3		
Staging Classification	pT ( )	pN ( )	pM ( )
	pStage ( )		

Postoperative Treatment Plan

Chemotherapy: Yes / No

Drug To Be Administered	Administration Date	Administration Period
	Number of doses: / Week:	
	Number of doses: / Week:	
	Number of doses: / Week:	

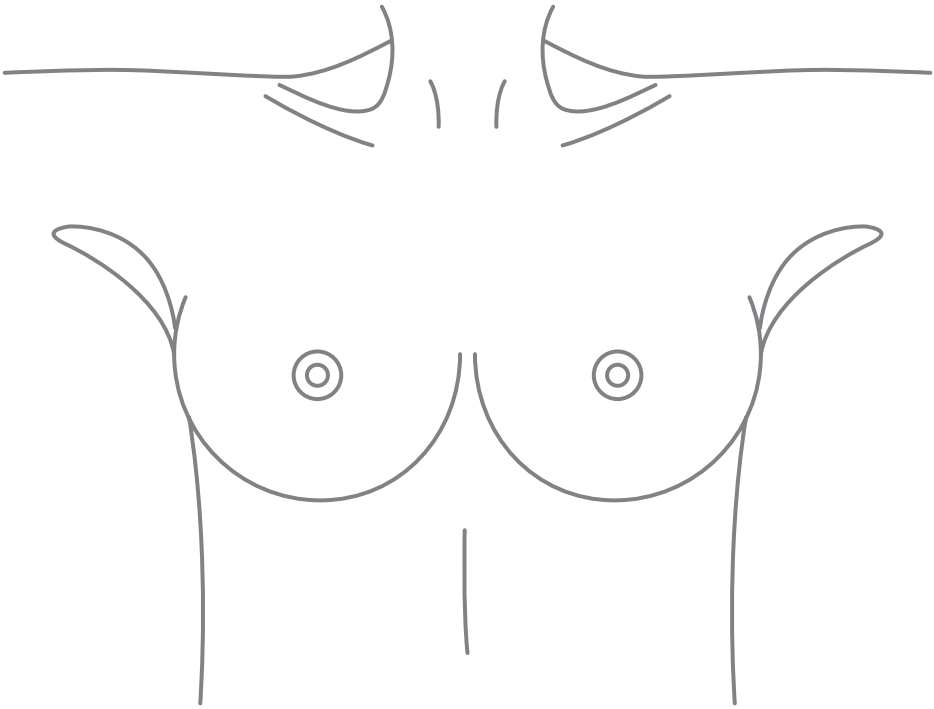
Endocrine Therapy: Yes / No

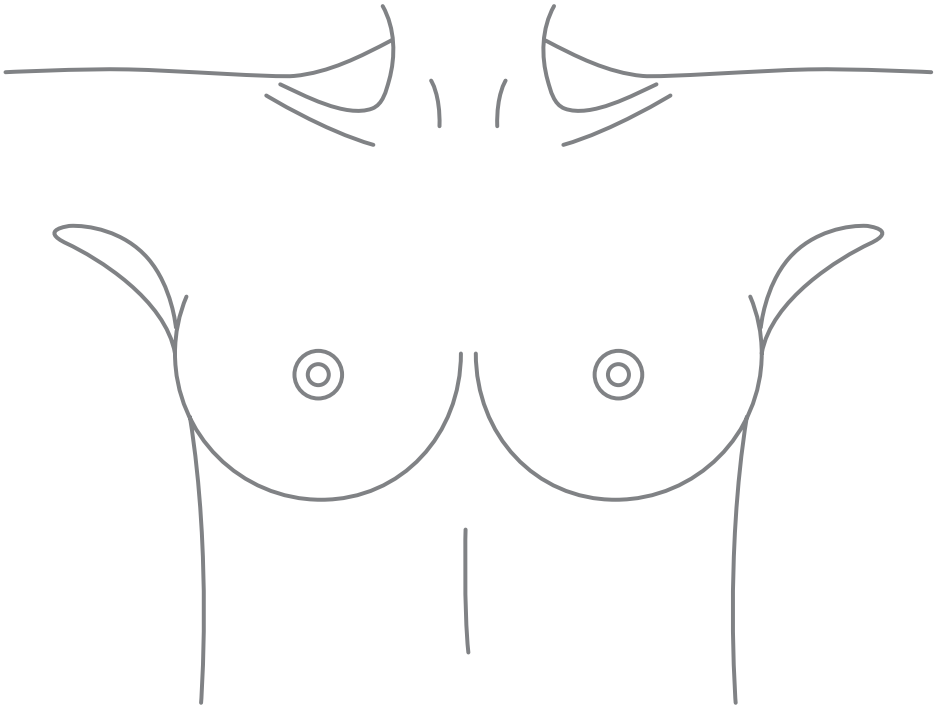
Drug To Be Administered	Administration Start Date	Administration Period

Radiation Therapy: Yes / No (site, number of infusions, durations, boost irradiation, etc.)

Breast Reconstruction / Nipple Areola Complex Sparing

Surgery Type	Surgery Date





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For Those Who Will Undergo Breast Cancer Treatment
http://hospital.luke.ac.jp/guide/24_breast_surgery/index.html

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http://www.marianna-u.ac.jp/breast/03_breast_cancer_i/pdf/20180918_01.pdf

Allergan Japan Inc.
Product Information: Natrelle® Series
https://www.allergan.jp/ja-jp/products/medical-professionals/natrelle

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